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Pancreatic Cancer

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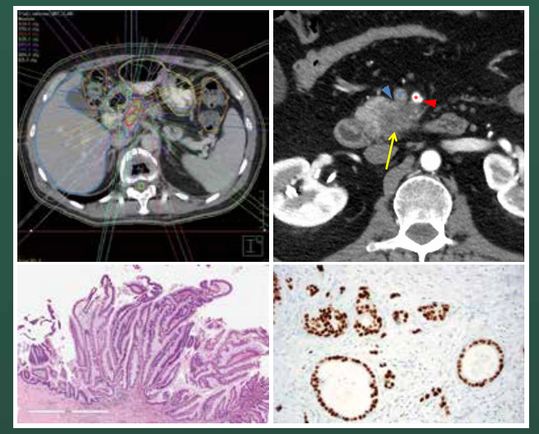

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Pancreatic cancer remains to be a challenge for the health care providers in the world. For the past three decades, we have made few breakthroughs for managing this malignant disease. Unless a breakthrough would be made in the near future, as projected, pancreatic cancer would become the second leading cause of death from cancer diseases in the United States by 2020. This is very likely the sad fact that many other countries in the world would also have to face. However, we are now understanding this disease better, in debt to the basic scientists in the pancreatic cancer research field. Deciphering genomic and epigenetic codes of pancreatic cancer has revealed the molecular pathways underlying the development of pancreatic cancer and also identified potential biomarkers for early diagnosis. Meanwhile, dissecting tumor microenvironment has led to the recognition of the importance of targeting non-neoplastic cells for pancreatic cancer treatment. Nevertheless, metastases remain to be a predominant reason for treatment failure and occur either grossly or microscopically as circulating tumor cells at the time of diagnosis. Thus, the ineffectiveness of pancreatic cancer treatment may be largely attributed to lack of therapies specifically targeting metastases.

The contributions of the clinicians and clinical researches to the field of pancreatic cancer have revolutionized the entire medicine and surgery field. Many chapters of this book have testified the importance of the advancements in the management of pancreatic cancer as landmarks in the history of medicine and surgery. Due to the poor natural history of pancreatic cancer, more recent advancements in pancreatic surgery have focusing on reducing the complication and integrating minimal invasive techniques. Other types of local therapies including stereotactic body radiation and irreversible electroporation have been employed to treat those unresectable pancreatic cancer. However, the role of each of the treatment modalities is quite limited. Thus, a multidisciplinary approach has become a necessity to optimize the management of pancreatic cancer and to avoid an ineffective modality of treatment. This book has highlighted the multidisciplinary concepts essentially in every page.

In summary, this book, contributed by a premium group of pancreatic cancer clinicians and researchers has shed the light on four major points in both clinical management and research development of pancreatic cancer, including making early diagnosis of pancreatic cancer, targeting the tumor microenvironment and metastasis, developing new modalities of systemic therapies such as immune-based therapies, and employing the multidisciplinary approach.

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Preface

The pancreas is one of the most complex organs in the human body, attracting surgeons, gastroenterologists, oncologists, and scientists to better understand its function. The first physicians believed the pancreas was the cradle of the human soul. Since that time our knowledge has grown to understand its critical role in both endocrine and exocrine function. However, when it comes to pancreas cancer the modern clinician and scientist is still perplexed by its complexity. The impact on pancreas cancer survival has lagged behind other cancers. However, in the pursuit of helping our patients there have been great strides in the understanding and management of pancreas cancer. Advancements have been made in discovering the molecular makeup, the role of the immune system, new chemotherapies and even the implementation of new minimally invasive surgical techniques.

The community of pancreatologists has become an international one. This textbook has brought together the pancreas experts of the world to present the most up to date advancements in the management of pancreas cancer. We strive to present a comprehensive approach exploring each stage of the management of pancreas cancer including epidemiology, pathology, diagnostics, treatment and prognosis. The editors hope that this textbook will be serve as important reference material with the newest information for anyone involved in the care and management of patients with pancreas cancer.

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Pancreatic adenocarcinoma is the fourth leading cause of cancer mortality with a 5-year survival approaching only 6% for all stages. Unfortunately, only 20% of pancreas cancers are amenable to surgery at the time of presentation because 50% are metastatic and 30% are locally advanced. Clearly, there is room for improvement in treating this lethal disease.

Given that 80% of patients with pancreas cancer present with advanced disease, one approach to improving survival is earlier detection. Unfortunately, most patients fail to be diagnosed until symptoms have developed which often portends a worse survival. The Identification of pre-cancerous lesions such as intraductal papillary mucinous neoplasm (IPMN) and Mucinous cystic neoplasms (MCN) is one example of early detection. In addition, several centers are currently investigating promising non-invasive screening methods to detect pre-cancerous or early pancreatic cancers.

For resectable tumors, advances in surgical approach over the past four decades have focused on reducing mortality to an acceptable 2% in most high volume centers. However, morbidity rates following pancreatectomy remain quite high. More recently, centers have successfully focused on reducing peri-operative morbidity via the introduction of minimally invasive approaches. It appears that reducing operative morbidity improves the timely use of much needed adjuvant therapy for pancreas cancer, which may eventually translate into an improved survival.

Until recently however, systemic chemotherapy was extremely ineffective. Chemotherapy for pancreas cancer has dramatically changed over the past decade and now is quite effective and better tolerated. As a result of current chemotherapy regimens, more patients with locally advanced tumors are now undergoing conversion therapy and are surgical candidates. In addition, patients with metastatic disease are living twice as long as they did under previous regimens. Current therapeutic regimens now focus on individual tumor biology and genetics with the goal of personalized cancer therapy.

The future is difficult to predict but there is great promise in the treatment of pancreas cancer. Focusing on early detection, improved surgical technique, drug development, and personalized care based on tumor genetics all hold great promise.

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Pancreatic cancer is becoming a common cause of cancer death and is difficult to treat because of late presentation, disease heterogeneity, and treatment resistance. Long-term overall survival remains poor with a 5-year survival rate of 5% and unchanged over the last three decades.

In the era of the precision medicine and minimally invasive surgery, we need a comprehensive book to summarize the current expertise of the management of pancreatic cancer. The goal of this book is to provide the clinician with the most current evidence-based management of pancreatic cancer.

The corresponding authors for this book are all internationally renowned specialists in their fields and bring great insight based on their extensive personal experience. This book covers all aspects of the management of pancreatic cancer and brings the most updated knowledge on the pancreatic cancer from international experts to readers. Besides the epidemiology and pathology of pancreatic cancer, this book really emphasizes the diagnosis and treatment, which includes the surgery, chemotherapy, radiotherapy, and different combined approaches.

The diligent efforts from all authors have provided our readers the state-of-the-art knowledge and clinical expertise. The editors great appreciate their contribution and support.

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Treatment of Pancreatic Cancer

Prognosis of Pancreatic Cancer

Pancreatic cancer incidence and mortality patterns in China, 2011

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Objective: The National Central Cancer Registry (NCCR) collected population-based cancer registration data in 2011 from all cancer registries in China. The incidence and mortality rates for pancreatic cancer were compiled and pancreatic cancer incident new cases and deaths were estimated.

Methods: A total of 234 cancer registries submitted cancer data to NCCR. Data from 177 cancer registries were qualified and compiled for cancer statistics in 2011. Pancreatic cancer cases were extracted and analyzed from the national database. The pooled data were stratified by area (urban/rural), gender and age group (0, 1-4, 5-9, 10-14…85+). Pancreatic cancer incident cases and deaths were estimated using age-specific rates and national population in 2010. The national census in 2000 and Segi's population were used for age-standardized rates.

Results: All 177 cancer registries (77 in urban and 100 in rural areas) covered 175,310,169 populations (98,341,507 in urban and 76,968,662 in rural areas). The morphology verified pancreatic cancer cases (MV%) accounting for 40.52% and 4.33% of pancreatic cancer incident cases were identified through death certifications only (DCO%) with mortality to incidence ratio (M/I) of 0.91. The estimated number of newly diagnosed pancreatic cancer cases and deaths were 80,344 and 72,723 in 2011, respectively. The crude incidence rate was 5.96/100,000 (males 6.57/100,000, females 5.32/100,000). The age-standardized incidence rates by Chinese standard population (ASIRC) and by world standard population (ASIRW) were 4.27/100,000 and 4.23/100,000 respectively, ranking 10th among all cancers. Pancreatic cancer incidence rate and ASIRC were 7.03/100,000 and 4.94/100,000 in urban areas whereas they were 4.84/100,000 and 3.56/100,000 in rural areas. The incidence rate of pancreatic cancer of 33 cancer registries increased from 3.24/100,000 in 2003 to 3.59/100,000 in 2011 with an annual percentage change (APC) of 1.44. The pancreatic cancer mortality rate was 5.40/100,000 (males 5.88/100,000, females 4.89/100,000), ranking 6th among all cancers. The age-standardized mortality rates by Chinese standard population (ASMRC) and by world standard population (ASMRW) were 3.81/100 000 and 3.79/100 000. The pancreatic cancer mortality and ASMRC were 6.47/100,000 and 4.48/100,000 in urban areas, and 4.27/100,000 and 3.08/100,000 in rural areas, respectively. The mortality rates of pancreatic cancer showed an approximately 1.14-fold increase, from 2.85/100,000 in 2003 to 3.26/100,000 in 2011, with an APC of 1.68.

Conclusions: The burden of pancreatic cancer is increasing in China. Identification of high-risk population and adequate treatment and prevention are important.

Keywords: Pancreatic cancer; cancer registry; incidence; mortality; China

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Introduction

Pancreatic cancer is one of the most fatal malignancies with an overall survival rate of only about 5%. Surgery is the most effective therapy to cure this disease, but less than 20% of patients present with early disease onset (1). With the estimated 337,872 new cases and 330,391 deaths, pancreatic cancer is the 12th common cancer and the 7th leading cause of cancer deaths worldwide (2). According to the estimation by the National Central Cancer Registry of China (NCCR), the pancreatic cancer incidence rate was 7.28/100,000 (males 8.24/100,000, females 6.29/100,000), ranking 7th among all cancers in China in 2009. The mortality rate of pancreatic cancer was 6.61/100,000 (males 7.45/100,000, females 5.75/100,000), ranking 6th among all cancer deaths at the same time (3). In the mid of 2014, total 234 registries covering 221 million, accounting for 16.4% of national populations reported registration data of the year 2011 to NCCR. This paper analyzed the pancreatic cancer incident and death status in China in 2011.

Materials and methods

Data source

The NCCR is responsible for cancer data collection, evaluation and publication from local population-based cancer registries. The cancer information was reported to the cancer registries from local hospitals and community health centers, including the Basic Medical Insurances for urban residents and the New-Rural Cooperative Medical System. The Vital Statistical Database was linked with the cancer incidence database for identifying cases with death certificate only (DCO) and follow-up. By June 1, 2014, 234 cancer registries (98 cities and 136 counties) from 31 provinces submitted 2011 data to the NCCR. Data covered about 221,390,275, accounting for 16.43% of whole national population in 2011. Among them, there were 177 population-based cancer registries whose data quality met the quality criteria required by NCCR, distributed in 28 provinces (77 in urban and 100 in rural areas), and covered 175,310,169 population accounting for about 13.01% of the whole Chinese population, including 88,655,668 males and 86, 654,501 females, 98,341,507 in urban and 76,968,662 in rural areas. All cancer cases were classified according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Invasive cases of pancreatic cancer (ICD10: C25) were extracted and analyzed from the overall cancer database.

Population data

The population was estimated based on the fifth National Population Census data [2000] provided by the National Statistics Bureau of China, taking into account of the changes of age composition, gender ratio and the proportion of urban and rural transformation released by the National Bureau of Statistics (http://data.stats.gov.cn/). The national populations in 2011 were stratified by area (urban/rural), gender (male/female) and age groups (0-, 1-4, 5-84 by 5 years, 85+ years). The changes of age-specific death probability were also adjusted when calculating population. Linear changes were assumed in each age group between the fifth and sixth population census.

Quality control

According to "Guideline of Chinese Cancer Registration", we checked the data quality using the inclusion criteria in "Cancer Incidence in Five Continents Volume IX" (4), which was required by the International Association for Cancer Registry (IACR) and the International Agency for Research on Cancer (IARC) (5). We used software including MS-Excel, Statistical Analysis System (SAS) and IARC Tools issued by the IARC/IACR for data check and evaluation. The data were included in the present analysis if they met the following criteria: morphological verification (MV%) higher than 66%, percentage of cancer cases identified with death certification only (DCO%) less than 15%, and mortality to incidence ratio (M/I) between 0.6 and 0.8.

Statistical analysis

Incidence and mortality rates were calculated by area, gender and age groups. The number of new cases and deaths were estimated using the 5-year age-specific cancer incidence/mortality rates and the corresponding populations. The Chinese population in 2000 and World Segi's population were used for age-standardized rates. The cumulative risk of developing or dying from cancer before 75 years of age (in the absence of competing causes of death) was calculated and presented as a percentage. Software including MS-Excel and IARCcrgTools2.05 issued by IARC and IACR was used for data checking and evaluation. SAS software (SAS Institute Inc., Cary, USA) was used to calculate the incidence and mortality rates.

Table 1 The quality control index of pancreatic cancer in China, 2011

Areas	Sex	M/I	MV%	DCO%	UB%
All	Both sexes	0.91	40.52	4.33	0.38
	Male	0.90	41.17	4.44	0.41
	Female	0.93	39.69	4.19	0.35
Urban areas	Both sexes	0.93	41.94	4.39	0.49
	Male	0.91	42.68	4.36	0.54
	Female	0.95	41.01	4.42	0.43
Rural areas	Both sexes	0.88	37.59	4.22	0.16
	Male	0.88	38.13	4.61	0.14
	Female	0.88	36.89	3.71	0.18

M/I, mortality to incidence ratio; MV%, the percentage of cases morphologically verified; DCO%, the percentage of death certificate-only cases; UB%, the proportion of diagnosis of unknown basis.

Results

Quality evaluation

The coverage population of all 177 cancer registries was 175,310,169. Pancreatic cancer M/I ratio in all cancer registry areas was 0.91 (males 0.90 and females 0.93). MV% of pancreatic cancer was 40.52% (males 41.17% and females 39.69%). DCO% was 4.33% (males 4.44% and females 4.19%). Pancreatic cancer M/I ratio in urban areas was 0.93, which was higher than that in rural areas (0.88). Likewise, MV% (41.94%) and DCO% (4.39%) in urban areas was higher than MV% (37.59%) and DCO% (4.22%) in rural areas (*Table 1*).

Incidence rate

In 2011, the crude incidence rate of pancreatic cancer in the registry areas was 5.96/100,000 (6.57/100,000 for males and 5.32/100,000 for females), accounting for 2.38% of all cancers. The age-standardized rates were 4.27/100,000 and 4.23/100,000, respectively, after being standardized by the age structures of Chinese and the world populations. For patients aged 0-74 years, the cumulative incidence rate was 0.50% and aged 35-64 years, and the truncated age-standardized rate (TASR) was 5.68/100,000. In urban areas, the incidence rate was 7.03/100,000 (7.75/100,000 for males and 6.28/100,000 for females), while in rural areas, it was 4.84/100,000 (5.34/100,000 for males and 4.31/100,000 for females). Standardized by the age structures of China and the world, in urban areas, the age-standardized rates were 4.94/100,000 and 4.90/100,000. Both crude incidence rates and age-standardized incidence rates in urban areas were higher than those in rural areas (*Table 2*).

Age-specific incidence rate

The age-specific incidence rate of pancreatic cancer was low before 40 years old, and dramatically increased after then. They reached a peak at the age group of 80- years which were 74.50/100,000 for urban males, while at the age group of 75- years which were 43.44/100,000 for rural males. For urban females, the incidence rate of pancreatic cancer reached a peak at the age group of 85+ years which were 66.18/100,000 in urban areas, whereas at the age group of 80- years in rural areas which were 35.26/100,000 in urban areas.

The age-specific incidence rate of pancreatic cancer among males was higher in urban areas than that in rural areas in all age groups, except for the age group of 35-49 years. For females, it had the same trend except for the age groups of 25-39 years (*Table 3* and *Figure 1*).

Incidence rates of pancreatic cancer from 2003 to 2011

There were 33 registries kept submitting data to NCCR from 2003 to 2011. About incidences of pancreatic cancer, there were fluctuations in the different regions and genders. The incidence rate of pancreatic cancer increased from 3.24/100,000 in 2003 to 3.59/100,000 in 2011 with an annual percentage change (APC) of 1.44 while the APC of males was 1.48. There was no statistically significant in APC of females. In urban areas, the rate was 1.05 times higher in

Table 2 Pancreatic cancer incidence in China, 2011

Areas	Sex	Case No.	Crude rate ($1/10^5$)	Ratio (%)	ASIRC ($1/10^5$)	ASIRW ($1/10^5$)	Cumulative rate 0-74 (%)	TASR 35-64 ($1/10^5$)
All	Both sexes	80,344	5.96	2.38	4.27	4.23	0.50	5.68
	Male	45,385	6.57	2.37	4.99	4.95	0.58	6.87
	Female	34,959	5.32	2.40	3.58	3.55	0.42	4.45
Urban	Both sexes	48,568	7.03	2.69	4.94	4.90	0.57	6.14
	Male	27,339	7.75	2.75	5.77	5.73	0.68	7.51
	Female	21,229	6.28	2.61	4.13	4.09	0.47	4.73
Rural	Both sexes	31,776	4.84	2.03	3.56	3.52	0.42	5.16
	Male	18,046	5.34	1.95	4.15	4.10	0.48	6.17
	Female	13,730	4.31	2.14	2.99	2.96	0.35	4.12

ASIRC, age-standardized incidence rate (using China standard population 2000); ASIRW, age-standardized incidence rate (using World standard population); TASR, truncated age-standardized rate (using World standard population).

Table 3 Age-specific incidence rate of pancreatic cancer in China, 2011 ($1/10^5$)

Age group	All areas			Urban areas			Rural areas		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
All	5.96	6.57	5.32	7.03	7.75	6.28	4.84	5.34	4.31
0-	0.06	0.00	0.12	0.12	0.00	0.27	0.00	0.00	0.00
1-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5-	0.01	0.02	0.00	0.03	0.05	0.00	0.00	0.00	0.00
10-	0.01	0.02	0.00	0.02	0.04	0.00	0.00	0.00	0.00
15-	0.02	0.00	0.03	0.03	0.00	0.07	0.00	0.00	0.00
20-	0.09	0.07	0.11	0.10	0.08	0.13	0.08	0.06	0.09
25-	0.18	0.14	0.22	0.16	0.14	0.17	0.20	0.13	0.28
30-	0.33	0.39	0.28	0.36	0.46	0.26	0.30	0.28	0.32
35-	0.82	0.95	0.69	0.89	0.94	0.84	0.74	0.97	0.49
40-	1.55	1.74	1.35	1.57	1.58	1.55	1.53	1.94	1.11
45-	3.68	4.73	2.58	3.55	4.72	2.29	3.83	4.73	2.92
50-	6.39	7.93	4.77	7.10	8.84	5.25	5.46	6.71	4.16
55-	10.83	13.44	8.17	11.80	14.55	8.97	9.77	12.20	7.28
60-	16.11	18.77	13.40	17.91	21.72	14.07	14.27	15.79	12.71
65-	24.09	28.03	20.16	28.49	34.29	22.86	19.73	22.00	17.41
70-	35.69	40.13	31.38	42.91	48.11	38.09	27.90	31.92	23.82
75-	46.83	53.14	41.28	55.68	61.94	50.17	37.08	43.44	31.47
80-	52.67	59.66	47.16	65.99	74.50	58.86	38.33	42.49	35.26
85+	51.99	59.77	47.46	69.24	74.15	66.18	33.24	42.67	28.15

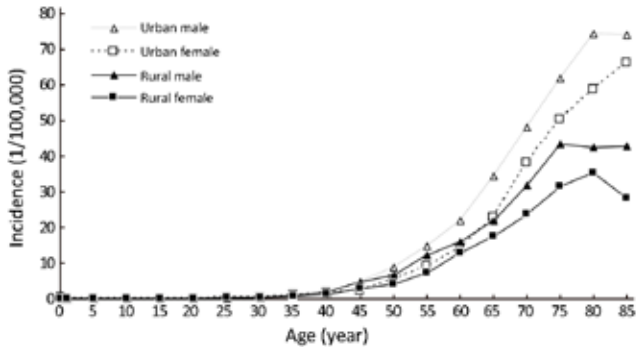

Figure 1 Pancreatic cancer incidence in China, 2011.

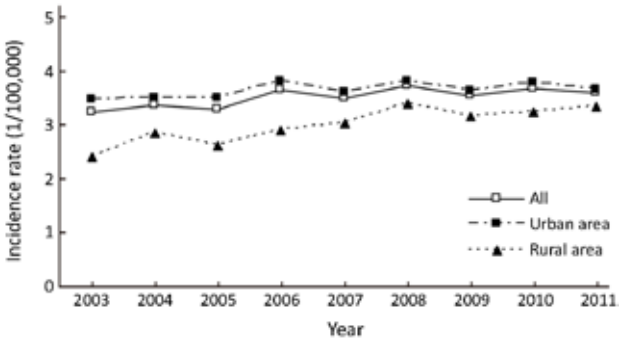

Figure 2 Incidence rates of pancreatic cancer, 2003-2011.

Table 4 Incidence rates of pancreatic cancer, 2003-2011 (1/10^5)

Areas	Sex	2003	2004	2005	2006	2007	2008	2009	2010	2011
All	Both sexes	3.24	3.36	3.29	3.65	3.49	3.74	3.54	3.68	3.59[a]
	Male	3.79	3.95	3.92	4.27	4.05	4.33	4.28	4.37	4.18[b]
	Female	2.73	2.82	2.71	3.07	2.94	3.17	2.85	3.02	3.02
Urban	Both sexes	3.47	3.49	3.49	3.82	3.61	3.81	3.64	3.78	3.64
	Male	4.02	4.09	4.14	4.47	4.12	4.47	4.41	4.48	4.25
	Female	2.95	2.94	2.88	3.22	3.12	3.19	2.91	3.12	3.06
Rural	Both sexes	2.41	2.85	2.62	2.91	3.03	3.40	3.15	3.24	3.35[c]
	Male	2.91	3.35	3.11	3.43	3.80	3.77	3.74	3.88	3.89[d]
	Female	1.94	2.38	2.16	2.45	2.31	3.08	2.59	2.62	2.84[e]

[a-e], from 2003 to 2011, annual percentage changes (APC) of incidence rates were 1.44, 1.48, 3.78, 3.49 and 4.09, respectively.

2011 than that in 2003, but the APC showed no statistically significant in both sexes. Meanwhile, the incidence rate increased 1.39 times from 2003 to 2011 in rural areas with an APC of 3.78 (*Table 4* and *Figure 2*).

Mortality

The crude mortality rate of pancreatic cancer was 5.40/100,000 (5.88/100,000 in males and 4.89/100,000 in females). The China standardized rate was 3.81/100,000, compared with the world standardized rate of 3.79/100,000. The cumulative rate (0-74 years old) was 0.44% and aged 35-64 years, the TASR was 4.74/100,000. The crude mortality rate of pancreatic cancer in urban areas was 6.47/100,000 (7.01/100,000 in males and 5.91/100,000 in females). The age-standardized mortality rates based on the Chinese standard population (ASMRC) and the world standard population (ASMRW) were 4.48/100,000 and 4.47/100,000, respectively. Among patients aged 0-74 years in urban, the cumulative mortality rate was 0.51%, and aged 35-64 years, the TASR was 5.25/100,000. In rural areas, the crude mortality rate was 4.27/100,000 (4.70/100,000 in males and 3.82/100,000 in females). The ASMRC was 3.08/100,000 and the ASMRW was 3.07/100,000. The cumulative mortality (0-74 years) was 0.36%, and aged 35-64 years, the TASR was 4.17/100,000. Urban areas had a higher mortality than rural areas (*Table 5*).

Age-specific mortality rate

The trend in the age-specific mortality rate of pancreatic cancer in urban areas was similar to that in rural areas. The age-specific mortality rate of pancreatic cancer was relatively low in the population younger than 40 years old. There was a dramatic increase in the mortality rate after 50 years old. In urban areas, the age-specific mortality rate of pancreatic cancer reached a peak in the age group of 85+ years whereas it reached a peak at the age group of

Table 5 Pancreatic cancer mortality in China, 2011

Areas	Sex	Case No.	Crude rate ($1/10^5$)	Ratio (%)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Cumulative rate 0-74 (%)	TASR 35-64 ($1/10^5$)
All	Both sexes	72,723	5.40	3.44	3.81	3.79	0.44	4.74
	Male	40,580	5.88	3.01	4.43	4.41	0.51	5.77
	Female	32,143	4.89	4.19	3.21	3.19	0.36	3.67
Urban	Both sexes	44,687	6.47	4.19	4.48	4.47	0.51	5.25
	Male	24,702	7.01	3.68	5.17	5.17	0.59	6.47
	Female	19,985	5.91	5.06	3.80	3.78	0.42	3.99
Rural	Both sexes	28,036	4.27	2.68	3.08	3.07	0.36	4.17
	Male	15,878	4.70	2.35	3.62	3.59	0.42	5.01
	Female	12,158	3.82	3.27	2.57	2.56	0.30	3.31

ASMRC, age-standardized mortality rate (using China standard population 2000); ASMRW, age-standardized mortality rate (using World standard population); TASR, truncated age-standardized rate (using World standard population).

80- years in rural areas.

The age-specific mortality rate of pancreatic cancer among males was higher in urban areas than in rural areas in all age groups, except for the age group of 35-49 years. For females, it had the same trend except for the age groups of 20-29 years (*Table 6* and *Figure 3*).

Mortality rates of pancreatic cancer from 2003 to 2011

The data of 33 cancer registries showed that between 2003 and 2011, the mortality rates of pancreatic cancer had an approximately 1.14-fold increase, from 2.85/100,000 in 2003 to 3.26/100,000 in 2011, with an APC of 1.68. During the period 2003-2011, the mortality rates increased from 3.31/100,000 to 3.71/100,000 in males with an APC of 1.63, and from 2.41/100,000 to 2.83/100,000 in females with an APC of 1.68. The APC showed no statistically significant in urban areas. In rural areas, the APC was 4.09 in both sexes. Moreover, the APC of rural male was 4.32, while the rural females' APC was 3.73 (*Table 7* and *Figure 4*).

Discussion

With poor prognosis, pancreatic cancer is one of malignant tumors with the highest mortality rates worldwide. In the world, approximately 330,391 subjects died from pancreatic cancer per year, making it the 7th leading cause of cancer-related death (2), which is seriously harmful for the health of human beings. Pancreatic cancer has an overall 5-year survival of less than 5% because there are no reliable tests for early diagnosis and no effective therapies for the metastatic form of pancreatic cancer. The only curative treatment for pancreatic cancer is surgical resection which alone can improve 5-year survival to 10%. However, 80% of pancreatic adenocarcinoma is not resectable in the patients with clinical symptoms (6).

This study about pancreatic cancer reported that the incidence of pancreatic cancer was 5.96/100,000, and the mortality rate was 5.40/100,000 in China in 2011. Compared with the data of GLOBOCAN 2012, the male incidence of pancreatic cancer in China (ASIRW 4.50/100,000) was higher than the average level of developing countries (3.30/100,000), but lower than the world (4.90/100,000) and developed countries (8.60/100,000). From 2003 to 2011, the APC incidence and mortality rates of both sexes were 1.44 and 1.68 in China. The APC of male was 1.48. However, there was no statistically significant in APC of females. In urban areas, the APC incidence and mortality rates showed no statistically significant yet. In rural areas, the APC incidence and mortality rates were 3.78 and 4.09 in both sexes.

Pancreatic cancer is related to genetic susceptibility and dietary factors, and closely associated with lifestyles and body status. Genetic risk factors were believed to play a major role. Approximately 10% of pancreatic cancer was estimated to have familial inheritance (7). Analyses of family history of pancreatic cancer including 1,183 cases and 1,205 controls showed that a family history of pancreatic cancer in a parent, sibling or child was associated with increased risk of pancreatic cancer [multivariate-adjusted odds ratios

Table 6 Age-specific mortality of pancreatic cancer in China, 2011 ($1/10^5$)

Age group	All areas			Urban areas			Rural areas		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
All	5.40	5.88	4.89	6.47	7.01	5.91	4.27	4.70	3.82
0-	0.06	0.00	0.12	0.12	0.00	0.27	0.00	0.00	0.00
1-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
20-	0.07	0.06	0.09	0.09	0.10	0.08	0.06	0.03	0.09
25-	0.08	0.08	0.07	0.07	0.10	0.05	0.09	0.07	0.10
30-	0.16	0.18	0.15	0.21	0.23	0.18	0.10	0.10	0.11
35-	0.43	0.60	0.24	0.46	0.58	0.34	0.38	0.63	0.12
40-	1.25	1.43	1.06	1.24	1.39	1.09	1.26	1.49	1.02
45-	2.82	3.49	2.11	2.79	3.37	2.17	2.84	3.64	2.03
50-	5.15	6.53	3.69	5.87	7.65	3.97	4.19	5.03	3.33
55-	9.18	11.32	6.99	9.90	12.19	7.55	8.40	10.37	6.38
60-	14.36	16.95	11.72	16.73	20.38	13.06	11.94	13.49	10.34
65-	20.77	23.86	17.70	24.58	28.52	20.77	17.00	19.37	14.58
70-	32.81	36.86	28.90	39.32	43.99	35.00	25.80	29.51	22.03
75-	43.65	49.40	38.58	53.43	59.47	48.11	32.88	38.32	28.08
80-	57.50	64.30	52.15	71.82	77.34	67.19	42.10	49.22	36.84
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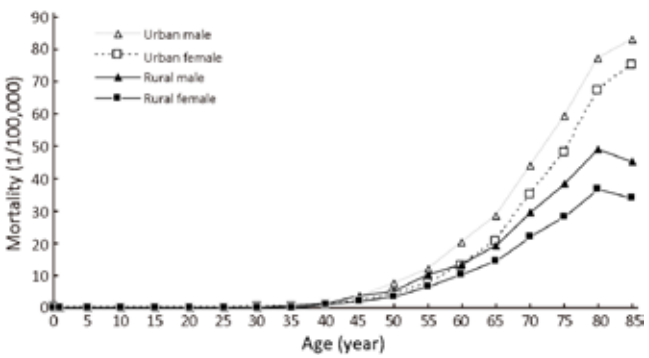

Figure 3 Pancreatic cancer mortality in China, 2011.

(ORs) =1.76; 95% confidence interval (95% CI): 1.19-2.61] (8).

Several studies investigated the relation between diabetes and pancreatic cancer. The proportion of pancreatic cancer patients who also have hyperglycemia or diabetes has previously been under appreciated; new data showed that up to 80% are either hyperglycemic or diabetic and this can be evident in the pre-symptomatic phase (9). Some early studies showed that new-onset diabetes had the strongest association with pancreatic cancer and was largely responsible for the link between diabetes and pancreatic adenocarcinoma (10). Another study found that diabetes was an important risk factor for pancreatic cancer, of which OR was 2.69 (95% CI: 1.51-4.77), which is supported by a veterans system study, where diabetic patients developed pancreatic cancer more easily, compared with non-diabetic patients, resulting in a hazard ratio of 2.17 (95% CI: 1.70-2.77) (11).

Some other factors of body status, including obesity and pressure, were observed to be associated with the pancreatic cancer risk. Obesity has been proposed as additional risk factors for pancreatic cancer. Several studies suggested that obesity could increase the pancreatic cancer risk, which was found to be around 20% higher for obese compared to normal weight individuals (12), although the possibility of confounding cannot be excluded. As to the dietary factors, a study supported fruit consumption to reduce pancreatic cancer risk (OR =1.73 for consumption of 1-2 *vs.* more

Table 7 Mortality rates of pancreatic cancer, 2003-2011 (1/10^5)

Areas	Sex	2003	2004	2005	2006	2007	2008	2009	2010	2011
All	Both sexes	2.85	2.98	2.96	3.35	3.34	3.25	3.23	3.32	3.26[a]
	Male	3.31	3.53	3.53	3.99	3.83	3.77	3.86	4.02	3.71[b]
	Female	2.41	2.48	2.42	2.74	2.87	2.75	2.63	2.65	2.83[c]
Urban	Both sexes	3.04	3.09	3.07	3.51	3.53	3.28	3.28	3.39	3.32
	Male	3.52	3.64	3.66	4.22	3.99	3.80	3.96	4.08	3.75
	Female	2.59	2.58	2.52	2.84	3.09	2.79	2.64	2.75	2.90
Rural	Both sexes	2.11	2.54	2.53	2.60	2.64	3.12	2.98	2.98	3.01[d]
	Male	2.50	3.01	3.02	2.91	3.25	3.69	3.42	3.74	3.55[e]
	Female	1.74	2.09	2.09	2.31	2.09	2.61	2.56	2.25	2.50[f]

[a-f], from 2003 to 2011, annual percentage changes (APC) of mortality rates were 1.68, 1.63, 1.68, 4.09, 4.32 and 3.73, respectively.

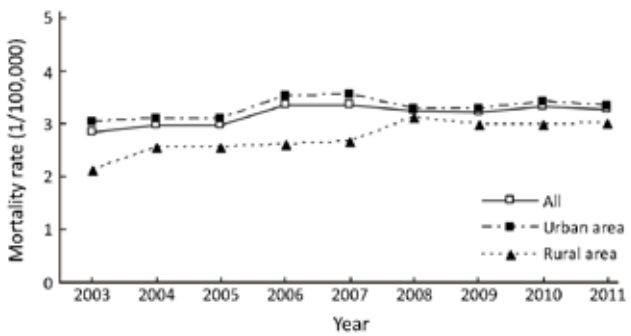

Figure 4 Mortality rates of pancreatic cancer, 2003-2011.

than 3 times/week; 95% CI: 1.05-2.86) and indicated that high consumption of meat was related to an elevated risk (OR =0.59 for consumption of 1-2 *vs.* more than 3 times/week; 95% CI: 0.35-0.97). Tea intake (OR =0.49; 95% CI: 0.30-0.80) was associated with a half reduction in risk of pancreatic cancer. Reduced vegetable consumption (P trend: 0.04) was significant related to pancreatic cancer (13).

Cigarette smoking is the best established risk factor for pancreatic cancer (14,15). In the International Pancreatic Cancer Cohort Consortium nested case-control study (16), which included 1,481 cases and 1,539 controls, the relative risk (RR) was 1.1 (95% CI: 0.9-1.3) for former smokers and 1.8 (95% CI: 1.4-2.3) for current smokers. Significant trends in risk were observed with increased number of cigarettes smoked and duration of exposure, the RR being 1.75 for 30 or more cigarettes smoked per day and 2.1 for 50 or more years of smoking, whereas the RR for those who had quit smoking for >15 years was similar to that of never smokers. A meta-analysis of 82 cohort and case-control studies published between 1950 and 2007 (17) reported a summary RR of pancreatic cancer of 1.7 (95% CI: 1.6-1.9) for current smokers and of 1.2 (95% CI: 1.1-1.3) for former smokers.

When commenting on our results, some limitations must be kept in mind. Data only covered about 16.43% of whole national population in 2011. But it is a true reflection of the malignant situation.

Conclusions

Pancreatic cancer burden is getting serious with the low survival rates. Risk factors, such as smoking, diabetes, obesity and bad dietary habit, maintain high level in Chinese. Pancreatic cancer control strategies, including health education, health promotion, early detection and cancer screening, should be treated as priority in public health.

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Glucose intolerance and the risk of pancreatic cancer

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Abstract: Mortality due to pancreatic cancer is increasing globally in most industrialized countries including Japan. The prognosis of pancreatic cancer is still extremely poor, despite various advances in diagnostic imaging techniques and medical treatment, and the 5-year survival rate remains less than 10%. Early detection of pancreatic cancer is essential for improving outcome, and identifying patients who at high risk is a major concern. Several reported factors can increase the risk of acquiring the genetic mutations that may potentially result in pancreatic cancer. Diabetes has the highest incidence among diseases that may be complicated by pancreatic cancer. In clinical practice, many cases of pancreatic cancer are diagnosed as a result of studies of worsening glycemic control. Glucose intolerance is a pre-diabetic state of hyperglycemia associated with insulin resistance and increased risk of both future diabetes and adverse outcomes. In the future, for early detection and treatment of pancreatic cancer, we believe that it is critical to share consensus with diabetologists, and to perform adequate screening for pancreatic cancer in patients with glucose intolerance.

Keywords: Pancreatic cancer; diabetes; hyperglycemia; insulin resistance

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Introduction

Mortality due to pancreatic cancer is increasing globally in most industrialized countries including Japan, with an estimated 227,000 deaths per year worldwide (1). According to the national statistics of 2011 in Japan, there were 28,829 deaths due to pancreatic cancer, ranking it fifth after lung cancer, gastric cancer, colorectal cancer, and liver cancer (2-4). The prognosis of pancreatic cancer is still extremely poor despite advances in various diagnostic imaging techniques and medical treatment, with a 5-year survival rate of less than 10% (5,6). Early-stage pancreatic cancer is usually clinically silent, and the disease only becomes apparent after the tumor invades into surrounding tissues or metastasizes to distant organs. Early detection of pancreatic cancer is required for improving the outcome, and recognition of high-risk patients is a major issue.

Risk factors for pancreatic cancer

Certain factors can increase the risk of acquiring the genetic mutations that may potentially result in pancreatic cancer (*Table 1*). Risk factors for this malignant disease include cigarette smoking (14-17), family history (7,8,18-21), advancing age, male sex, diabetes mellitus, chronic pancreatitis (12), hereditary pancreatitis (13), obesity (11,22-27), non-O blood group (28,29), a high-fat diet, diets high in meat and low in vegetables, and folate deficiency (1).

Cigarette smoking is one of the biggest risk factors for the development of pancreatic cancer. Heavy smokers have a 2-3-fold increased risk of death due to pancreatic cancer compared with non-smokers.

A family history of pancreatic cancer is also an important risk factor (7,8,18-21); about 3-9% of pancreatic cancer patients have such a family history. Ghadirian *et al*., found that 7.8% of all patients with pancreatic cancer and only 0.6% of controls had a family history of pancreatic cancer, i.e., a 13-fold difference, with no differences in environmental risk factors between the two groups (18). In a meta-analysis of familial risks in pancreatic cancer, Permuth-Wey *et al*. concluded that results from case-

Table 1 Risk factors of pancreatic cancer

Risk factors	Items	Risk	References
Family history	Pancreatic cancer	1.8-13 fold	(1,7)
	Genetic syndromes	2-132 fold	(8)
Complication	Diabetes mellitus	1.8-2.1 fold	(9,10)
	Obesity	3.5 fold	(11)
	Chronic pancreatitis	4-8 fold	(12)
	Hereditary pancreatitis	53 fold	(13)
Favorite item	Cigarette smoking	2-3 fold	(14-17)

Among the risk factors for pancreatic cancer, the ratio is high for those mentioned in the columns.

control [RR =2.82; 95% confidence interval (CI): 1.99-3.66] and cohort (RR =1.62; 95% CI: 1.28-1.97) studies showed a significant increase in pancreatic cancer risk if a relative had been affected, with an overall summary RR =1.80 (95% CI: 1.48-2.12) (8). Familial pancreatic cancer has been defined in most studies as the presence of pancreatic tumors in a pair of first-degree relatives. Prospective analysis of families with this malignant disease shows that first-degree relatives of individuals with familial pancreatic cancer have a 9-fold increased risk of this neoplasm over the general population (18). This risk rises to 32-fold in kindred with three or more first-degree relatives with pancreatic cancer.

Diabetes is a very important risk factor for disease, as described in detail later.

Obesity and being overweight increase the risk of pancreatic cancer significantly. According to a large-scale cohort study performed in Japan (11), men with a BMI of 30 kg/m^2 or more at age 20 years had a 3.5-fold higher risk than men with a normal BMI. Women with a BMI of 27.5-29.9 at the baseline had a ~60% increased risk compared with women with a BMI of 20.0-22.4. In men, weight loss of 5 kg or more between 20 years of age and the baseline age was associated with an increased risk of pancreatic cancer death.

On the other hand, no correlation has been observed between pancreatic cancer and BMI in two other cohort studies (22,23). One report has indicated that the estimated summary RR of pancreatic cancer per 5 kg/m^2 increase in BMI was 1.12 (95% CI: 1.06-1.17) in men and women combined (24). Compared with those with a BMI of 18.5-<25, individuals with a BMI of ≥35 had a 45% greater pancreatic cancer risk (95% CI: 1.04-2.02) (25). Being overweight or obese during early adulthood is associated with a greater risk of pancreatic cancer and a younger age at disease onset (26).

Complex relationship between diabetes and pancreatic cancer

Glucose intolerance is a pre-diabetic state of hyperglycemia associated with insulin resistance and increased risk of future diabetes and adverse outcomes. According to the criteria of the World Health Organization and the American Diabetes Association, glucose intolerance is defined as a two-hour glucose level of 140-199 mg/dL in the 75-gram oral glucose tolerance test.

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar levels. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes, and this leads to serious damage to many body's systems over time, especially the nerves and blood vessels. The classification of glucose metabolism disorders is principally derived from etiology, and includes staging of pathophysiology based on the degree of deficiency of insulin action. These disorders are classified into four groups: (I) type 1 diabetes mellitus; (II) type 2 diabetes mellitus; (III) diabetes mellitus due to other specific mechanisms or diseases; and (IV) gestational diabetes mellitus. Type 1 diabetes is characterized by destruction of pancreatic β-cells. Type 2 diabetes is characterized by combinations of decreased insulin secretion and decreased insulin sensitivity (insulin resistance) (30).

In medical practice, many cases of pancreatic cancer are diagnosed as a result of worsening glycemic control. Diabetes has the highest incidence among diseases that are complicated by pancreatic cancer, with a rate as high as 25.9% according to the pancreatic cancer registry report of 2007 (Committee for Pancreatic Cancer Registry, Japan Pancreas Society) (31). There have been many arguments regarding whether or not diabetes is the cause or result of pancreatic cancer (9,10,32-39); however, details of the molecular biologic mechanism itself have not yet been clarified. Understanding the effect of the pathophysiology of diabetes on the pancreatic duct epithelium is believed to be very important for achieving early detection of pancreatic cancer.

In 1994, the Italian Pancreatic Cancer Study Group published a case control study of 720 patients with pancreatic cancer. This study concluded that the increased prevalence of diabetes mellitus in these patients was likely

Table 2 Important studies regarding diabetes and the risk of pancreatic cancer

Reference	Studies	Summary RR (95% CI)
Ben *et al*. [2011]	35 cohort studies	1,94 (1.66-2.27)
Donghui Li *et al*. [2011]	3 case-control studies	1.8 (1.5-2.1)
Huxley R *et al*. [2005]	36 studies	1.82 (1.66-1.89)
Jee SH *et al*. [2005]	Cohort study	1.29 (1.22-1.37)
Gapstu S M *et al*. [2000]	Cohort study	2.15 (1.22-3.80)
Everhart *et al*. [1995]	20 studies	2.1 (1.1-2.7)
Gullo L *et al*. [1994]	Case control study	3.04 (2.21-4.17)

These are representative articles reporting the relationship between diabetes and the risk of pancreatic cancer. There are also strong clinical, epidemiological, and experimental evidences suggesting pancreatic cancer relates to diabetes.

related to the diabetes caused by the tumor (34).

Mizuno *et al*. reported a retrospective study of 540 pancreatic cancer patients that showed that the prevalence of diabetes in different stages of pancreatic cancer was 45%, of which more than half were less than 2 years in duration (35). Their data showed that even though the prognosis of pancreatic cancer patients complicated by diabetes was the same as that of patients without diabetes, outcome and survival were better if they were diagnosed in association with diabetes alone (median survival time: 20.2 months), compared to patients diagnosed on the basis of symptoms such as pain, jaundice, and/or appetite loss (10.2 months, $P<0.01$).

There is also strong clinical, epidemiological, and experimental evidence that pancreatic cancer causes diabetes (*Table 2*). Hyperglycemia and diabetes mellitus occur in approximately 85% of patients with pancreatic cancer, diabetes being present in 45-67% of patients with pancreatic cancer, depending on how the presence of diabetes is ascertained. The majority (approximately 75%) of diabetes in patients with pancreatic cancer is new-onset (i.e., less than 3 years in duration). New-onset diabetes often resolves when the cancer is resected (36).

Huxley *et al*. performed a meta-analysis of 9,220 cases of pancreatic cancer in 36 reports published between 1966 and 2005 (19 cohort studies and 17 case-control studies). They reported that the relative risk of developing pancreatic cancer in diabetes patients was 1.82 (95% CI: 1.66-1.89) (9). Everhart *et al*., performed a meta-analysis of 20 reports published between 1975 and 1994 (9 cohort studies and 11 case-control studies) of patients suffering from diabetes from one year or more prior to diagnosis of pancreatic cancer in which the relative risk of pancreatic cancer was appropriately calculated. They reported that the relative risk of pancreatic cancer in diabetes patients was 2.1 (95% CI: 1.1-2.7) (10). Moreover, Gapstur *et al*. extracted 35,640 men and women (average age: 40 years) and performed a 25-year prospective study of the relationship between the blood glucose level at one hour in the 50-g oral glucose tolerance test (OGTT) and the onset of pancreatic cancer. They reported that the relative risk of pancreatic cancer was 1.65 (95% CI: 1.05-2.60) in the group with a mild blood glucose increase of 120-159 mg/dL, 1.60 (95% CI: 0.95-2.70) in the group with a glucose level of 160-199 mg/dL, and 2.15 (95% CI: 1.22-3.80) in the group with a glucose level of 200 mg/dL or more compared with control cases in which the blood glucose level at one hour was 119 mg/dL or less. There was a significant relationship between the increase in blood glucose and the onset of pancreatic cancer (37).

The complex relationship between the two diseases has been the subject of numerous clinical, epidemiological, and experimental studies. Epidemiologic studies have suggested that long-standing type 2 diabetes is a modest risk factor for the development of pancreatic cancer. Meta-analysis of multiple cohort and case control studies has shown that the risk of pancreatic cancer in patients who have had diabetes for more than 5 years is 1.5- to 2-fold higher. This is not fully explained by risk factors such as obesity that are shared between the two diseases (38).

Possible mechanism of carcinogenesis in obesity and diabetes

Previous reports have indicated that hyperinsulinemia (40), insulin resistance (41) and insulin-like growth factor (IGF) gene polymorphisms (42) affect the onset of pancreatic cancer.

Insulin analogs and stimulators of insulin secretion used for treatment of diabetes increase the risk of pancreatic cancer, whereas metformin reduces the onset and death rate of pancreatic cancer (43).

It has been reported that a high insulin level promotes the growth of human pancreatic cancer cell lines (44,45),

and that hyperglycemia and a high fatty acid level promote the growth of pancreatic cancer cells (46).

Butler *et al.* classified 45 autopsied samples of pancreas tissue from patients into 4 groups depending on BMI and the presence of type 2 diabetes, then histologically compared and investigated the proliferation of pancreatic duct epithelium using Ki67 immunostaining (47). They found that the Ki67 positivity rate in the pancreatic duct epithelium was significantly (4-fold) higher in the diabetic group with BMI <25 than in the non-diabetic group with BMI <25, while the Ki67 positivity rate was approximately 10-fold higher in the non-diabetic group with BMI >27, and 14.3-fold higher in the diabetic group with BMI >27. These results suggest that the proliferation of pancreatic duct epithelium is accelerated in diabetic and obese patients. Accordingly, it is surmised that hyperglycemia due to diabetes is involved in the accelerated proliferation of pancreatic duct epithelium, and that furthermore, hyperinsulinemia, which is observed in insulin-resistant obese patients, is also involved in the accelerated proliferation of pancreatic duct epithelial cells.

Recent findings from both epidemiologic investigations and experimental systems suggest that metformin, a hypoglycemic agent used in the management of diabetes, may be a potential chemopreventive agent for pancreatic cancer. Two epidemiologic investigations in patients with type II diabetes found that patients taking metformin had a reduced risk of cancer (48,49). These results were significant both before and after adjusting for BMI. Evans *et al.*, reported that metformin use among 11,876 diabetic patients, including 923 cancer cases, was associated with a 21% reduced risk for all types of malignancies, and a dose-response relationship was observed. Currie *et al.*, reported that 2,109 of 62,809 diabetic patients developed cancer. Compared with patients treated with metformin monotherapy, those treated with sulfonylurea and insulin had 1.36- and 1.42-fold higher risks of cancer, respectively.

Li *et al.*, compared and investigated the treatment regimen of diabetes and the pancreatic carcinogenesis rate, and found that while insulin analog and insulin secretagogue respectively increased the risk of pancreatic cancer onset in diabetic patients by approximately 4.99- and 2.52-fold, metformin, which is an insulin resistance-improving drug that does not increase the insulin concentration in blood, reduced the risk of pancreatic cancer by 62%, and even when metformin treatment was continued for 5 years or longer (50). Metformin is known to have a direct effect on the activation of AMP-activated protein kinase (AMPK), and mediates cell proliferation and apoptosis via p53 and p27kip1. Furthermore, protein synthesis and cell growth are inhibited due to inhibition of the mammalian target of rapamycin (mTOR) (51). Yang *et al.*, reported that the molecular mechanism involved in cell proliferation via AMPK and mTOR is involved in the carcinogenesis of pancreatic cancer against a background of diabetes (52). As is evident from these reports, it is believed that various molecular mechanisms are involved in the increased cell proliferation due to hyperglycemia and hyperinsulinemia, and that clarifying these mechanisms will lead to the future prevention and treatment of pancreatic cancer.

In addition, one of the possible mechanisms of carcinogenesis resulting from obesity and diabetes is oxidative stress. In a study of the mechanism of oxidative stress in diabetics, Giardino *et al.* cultured vascular endothelial cells in the presence of a high sugar concentration and found that reactive oxygen species (ROS) did not increase in the culture medium, whereas in the cells oxidative stress increased due to diabetes, rather than an increase in ROS (53). Moreover, Nishikawa *et al.* investigated the involvement of the mitochondrial electron transport system as a source of intracellular ROS production in diabetes, and found that the generation of mitochondria-mediated ROS played a major role in the expression of intracellular metabolic disorder due to high glucose (54). Furthermore, it has been reported that the ROS generated in this manner damage the genomic DNA involved in cell proliferation in various ways, and may be involved in carcinogenesis (55). It is believed that hyperglycemia damages the DNA of pancreatic duct epithelia through oxidative stress, leading to the onset of pancreatic cancer. In this way, it is considered that hyperglycemia and hyperinsulinemia due to diabetes, obesity and glucose intolerance are involved in accelerated cell proliferation in the pancreatic duct epithelium cell. Various molecular mechanisms are involved in carcinogenesis due to hyperglycemia and hyperinsulinemia, and clarification of these mechanisms will lead to methods for prevention and treatment of pancreatic cancer (*Figure 1*).

Conclusions

In the future, for early detection and treatment of pancreatic cancer, we believe that it is critical to share consensus with diabetologists, and perform adequate screening for pancreatic cancer in patients with glucose intolerance. As described above, it is important to consider the relationship

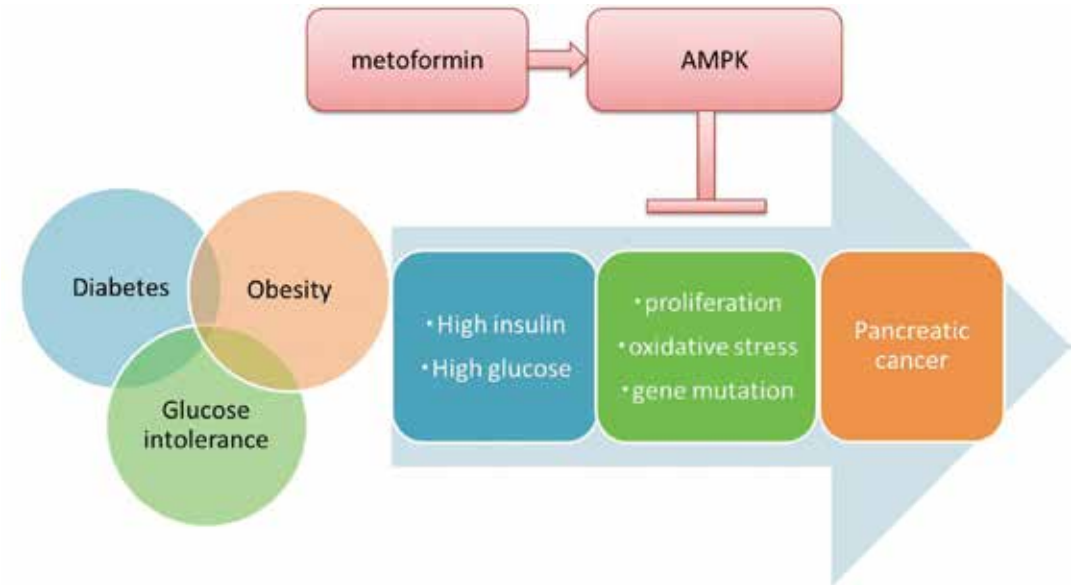

Figure 1 Possible mechanism of carcinogenesis in obesity and diabetes. Hyperglycemia and hyperinsulinemia due to diabetes, obesity and glucose intolerance are believed to be involved in the accelerated proliferation of pancreatic duct epithelial cells. Various molecular mechanisms are involved in carcinogenesis due to hyperglycemia and hyperinsulinemia, and clarification of these mechanisms will lead to methods for prevention and treatment of pancreatic cancer.

of diabetes with pancreatic cancer, and to bear in mind that diabetes is an important factor for early detection of pancreatic cancer. However, pancreatic cancer screening for all diabetes patients is inefficient, because diabetic morbidity is very high. Therefore the determination of specific risk factors and an appropriate time point for screening in diabetes patients is required.

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Pancreatic adenocarcinoma pathology: changing "landscape"

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Abstract: Pancreatic cancer is a devastating disease. At time of diagnosis the disease is usually advanced and only a minority of patients are eligible for surgical resection. The overall 5-year survival is 6%. However, survival of patients with early stage pancreatic cancer is significantly better. To improve the prognosis of patients with pancreatic cancer, it is essential to diagnose and treat pancreatic cancer in the earliest stage. Prevention of pancreatic cancer by treating noninvasive precursor lesions just before they invade tissues can potentially lead to even better outcomes. Pancreatic carcinogenesis results from a stepwise progression in which accumulating genetic alterations drive neoplastic progression in well-defined precursor lesions, ultimately giving rise to an invasive adenocarcinoma. A thorough understanding of the genetic changes that drive pancreatic carcinogenesis can lead to identification of biomarkers for early detection and targets for therapy. Recent next-generation sequencing (NGS) studies have shed new light on our understanding of the natural history of pancreatic cancer and the precursor lesions that give rise to these cancers. Importantly, there is a significant window of opportunity for early detection and treatment between the first genetic alteration in a cell in the pancreas and development of full-blown pancreatic cancer. The current views on the pathology and genetics of pancreatic carcinogenesis that evolved from studies of pancreatic cancer and its precursor lesions are discussed in this review.

Keywords: Pancreatic cancer; genetics; precursor lesions; pancreatic intraepithelial neoplasia (PanIN); intraductal papillary mucinous neoplasm (IPMN)

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with an extremely poor prognosis. The overall 5-year survival rate is 6%. The median survival varies from almost 2 years for patients with local and resectable disease, to only a few months for patients with advanced metastatic disease. Unfortunately, the vast majority of patients present at an advanced inoperable stage, whereas only about 20% of patients have localized disease that is amenable for surgery (1). To improve prognosis for patients with PDAC, it is essential to diagnose and treat the disease in the earliest stages, ideally even before a full blown invasive PDAC is established, by treating precursor lesions (2).

A growing body of evidence has helped establish that invasive PDAC develops from well-defined noninvasive precursor lesions (3). The most common precursor to invasive PDAC, pancreatic intraepithelial neoplasia (PanIN), is microscopic (3). In addition to this microscopic lesion, there are two macroscopically discernible cystic precursor lesions in the pancreas (4). These cystic precursor lesions are intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) (4).

In addition to morphologic characterization of pancreatic carcinogenesis, our understanding of the genetic alterations that drive carcinogenesis has increased dramatically over the last decades. In particular, recent advancements in sequencing technologies have immensely deepened our understanding of the genetics of PDAC (5-9). Whereas earlier studies have focused on the major driver genes

involved in invasive PDAC, more recent studies using next-generation sequencing (NGS) have produced a more complete understanding of the genetics of PDAC, its variants, and its precursor lesions. Mathematical modeling of genetic data suggests that the genetic evolution of PDAC takes almost 12 years from the earliest genetic alteration in a precursor lesion to the development of a full-blown invasive cancer (10). Thus there is an almost 12-year window of opportunity to prevent PDAC from even developing if we can identify and treat noninvasive precursor lesions. In addition, the genes targeted in pancreatic neoplasms may serve as future biomarkers in the genetic diagnosis of PDAC and its precursors (7,8). This review article discusses the pathology and the current knowledge of genetics of PDAC and its precursor lesions PanIN, IPMN and MCN.

Genetics of invasive PDAC and its precursor lesions

Genetics of invasive PDAC

Invasive PDAC is one of the best understood tumors at the genetic level (5-7,10,11). Invasive PDACs are genetically very complex, with wide-spread chromosome abnormalities, numerous losses and gains of large segments of DNA, and on average more than 60 exomic alterations in each cancer (12,13). The genes most commonly targeted in PDAC are *KRAS*, *CDKN2A*, *TP53* and *SMAD4*. In addition, several less commonly mutated genes, including *MLL3*, *SMAD3*, *FBXW7* and *ARID1A* have been identified. Germline mutations in *BRCA2* and *CDKN2A*, and less frequently in *BRCA1*, *PALB2* and *ATM* have been identified in a small subset of patients with familial PDAC (14-16). In addition, patients with Lynch syndrome (caused by germline mutation in one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6* or *PMS2*) and Peutz-Jeghers syndrome (PJS) (caused by germline mutation of the *STK11* gene) are at increased risk of PDAC (17,18).

Importantly, despite the relatively large number of genes targeted in PDAC, genetic alterations in PDAC have been shown to involve several core cellular signaling pathways and processes (*Table 1*).These include chromatin modification (*EPC1* and *ARID2*), DNA damage repair (*TP53*, *ATM*, *PALB2* and *BRCA2*) and other mechanisms (*ZIM2*, *MAP2K4*, *NALCN*, *SLC16A4* and *MAGEA6*) (6). In addition, a recent study has also suggested that genes described traditionally as embryonic regulators of axon guidance, particularly signaling trough slit ligands and roundabout receptors (SLIT/ROBO), may also be targeted in pancreatic cancer (5). Most PDACs harbor a mutation in a gene in each core pathway, but the specific gene mutated in a given pathway can differ among different PDACs. Therapeutic targeting of one or more of these pathways may thus be more effective than targeting of a specific genetic alteration.

With the advances in sequencing technologies, the genetic alterations in PDAC can now be studied at unprecedented levels, providing insights into the disease in ways that simply were not possible a decade ago. For example, comparisons of the genetic alterations in metastases to the primary tumors from which they arose provided insight into the length of time it takes for metastases to develop. Yachida *et al.* found that the genetic alterations in metastatic PDACs are surprisingly similar to those in matched primary tumors (7). By investigating whether mutations identified in the index metastasis were present or absent in multiple additional samples from the primary tumor they identified two categories of mutations. First, mutations present in all samples from a given patient were considered "founder mutations", which were likely established in the noninvasive precursor lesion that gave rise to the invasive PDAC. Founder mutations included mutations in the major genes known to be involved in pancreatic carcinogenesis (i.e., *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*). Mutations that were only present in a subset of the samples from each patient were considered "progressor mutations". Progressor mutations occurred later than founder mutations and represent subclonal evolution beyond the parental clone. Of interest, Yachida *et al.* found that clonal populations that give rise to distant metastases were represented within the primary carcinoma, but these clones were genetically evolved from the original parental, nonmetastatic clone. Thus, genetic heterogeneity of metastases reflects the heterogeneity within the primary carcinoma. Extending this observation further using quantitative analyses of the timing of the genetic evolution of PDAC, Yachida and colleagues calculated that almost 12 years pass between the initiating mutation and the birth of the nonmetastatic invasive PDAC. Five more years are required for the acquisition of metastatic ability and the average patient dies 2 years thereafter (7). Compared to the traditional view on PDAC as a very rapidly progressing disease that is almost instantaneously metastatic, these studies revealed that genetic evolution and growth of PDAC resembles that of other tumor types and that there is a wide window of opportunity for early detection and treatment (10).

Table 1 Core signaling pathways in pancreatic ductal adenocarcinoma

Regulatory process or pathway	Representative altered genes
Invasion	*ADAM11, ADAM12, ADAM19, ADAM5220, ADAMTS15, DPP6, MEP1A, PCSK6, APG4A, PRSS23*
TGFβ signaling	*TGFBR2, BMPR2, SMAD4, SMAD3*
KRAS signaling	*KRAS, MAP2K4, RASGRP3*
JNK signaling	*MAP4K3, TNF, ATF2, NFATC3*
Integrin signaling	*ITGA4, ITGA9, ITGA11, LAMA1, LAMA4, LAMA5, FN1, ILK*
Wnt signaling	*MYC, PPP2R3A, WNT9A, MAP2, TSC2, GATA6, TCF4, RNF43**
Hedgehog signaling	*TBX5, SOX3, LRP2, GLI1, GLI3, BOC, BMPR2, CREBBP*
Control of G1/S phase transition	*CDKN2A, FBXW7, CHD1, APC2*
Apoptosis	*CASP10, VCP, CAD, HIP1*
DNA damage control	*ERCC4, ERCC6, EP300, RANBP2, TP53, ATM, PALB2, BRCA1, BRCA2#*
Small GTPase signaling	*AGHGEF7, ARHGEF9, CDC42BPA, DEPDC2, PLCB3, PLCB4, RP1, PLXNB1, PRKCG*
Homophilic cell adhesion	*CDH1, CDH10, CDH2, CDH7, FAT, PCDH15, PCDH17, PCDH18, PCDH9, PCDHB16, PCDHB2, PCDHGA1, PCDHGA11, PCDHGC4*
Chromatin regulation	*ARID1A, EPC1, ARID2*
Axon guidance	*ROBO1, ROBO2, SLIT2, SEMA3A, SEMA3E, SEMA5A, EPHA5, EPHA7*

*, *RNF43* is mutated in a subset of MCNs and IPMNs (8). See text; #, *ATM*, *PALB2*, *BRCA1* and *BRCA2* are mutated in hereditary pancreatic cancer and less frequently in sporadic PDAC (14-16). See text. Adapted from Jones *et al*. (6) and Biankin *et al*. (5).

Pancreatic intraepithelial neoplasia (PanIN)

The vast majority of PDACs are believed to arise from PanIN (3,19). PanINs are small microscopic lesions that are <5 mm. They are composed of a flat or papillary neoplastic epithelium. Three grades of dysplasia can distinguished in PanIN lesions (*Figure 1*). PanIN-1A and PanIN-1B have low-grade dysplasia. They are characterized by tall columnar cells with basally located small round-to-oval nuclei and abundant supranuclear mucin. PanIN-1A has flat epithelium, whereas PanIn-1B is characterized by papillary or micropapillary architecture. PanIN-2 is considered intermediate-grade dysplasia and shows mostly papillary epithelium with mild to moderate cytological atypia. PanIN-3 is considered high-grade dysplasia (carcinoma *in situ*) and characterized by usually papillary or micropapillary proliferations of cells with significant cytological atypia (19). Of note, PanINs are often surrounded by lobular parenchymal atrophy which, when multifocal, can be detected by endoscopic ultrasound and may serve as a biomarker in patients at high-risk for PDAC (20).

PanIN lesions are common in the pancreas. For example, Konstantinidis and colleagues found PanINs in 153 (26%) of 584 pancreata surgically resected for a reason other than PDAC. Most of these lesions were PanIN-1 (50% of pancreata with PanIN) and PanIN-2 (41% of pancreata with PanIN), whereas PanIN-3 was only present in 13 cases (8% of pancreata with PanIN) (21). By contrast PanIN-3 has been reported to be present in 30-50% of pancreata with an invasive PDAC (19). Moreover, the number of PanINs, in particular those with high-grade dysplasia, is higher in patients with a strong family history of PDAC compared to patients with a PDAC but no family history of the disease (22).

Genetic studies support the hypothesis that PanINs can be a precursor to invasive pancreatic cancer, and have shown that the increasing morphologic grades of dysplasia in PanIN are accompanied by the accumulation of genetic alterations (*Figure 1*) (3). Telomere shortening and activating mutations in the *KRAS* oncogene are the most common alterations in low-grade PanIN lesions (23-25). Studies in genetically modified mouse models have shown that *KRAS* mutations can initiate PanIN development (26), and deep sequencing using NGS techniques have shown that *KRAS* mutations are present in >90% of all PanIN lesions, even those with low-grade dysplasia. These deep sequencing studies suggest a gradual expansion of the *KRAS*-mutant clone during PanIN progression (24). It appears that *KRAS* mutation alone provides only a modest selective advantage

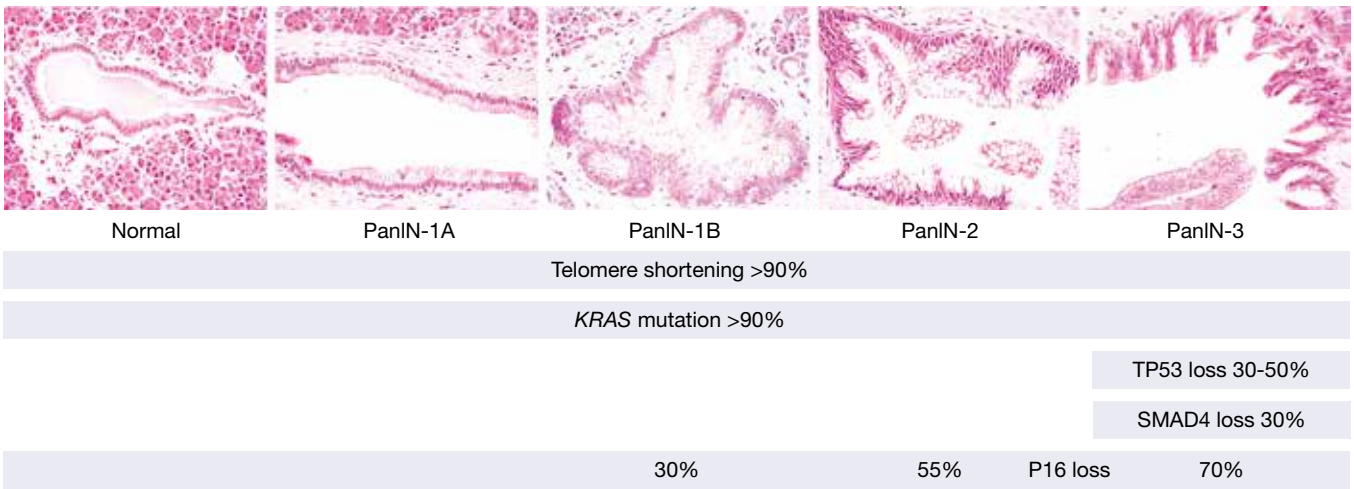

Figure 1 PanIN progression model of pancreatic cancer. Each step in the progression from normal epithelium to low-grade PanIN, and on to high-grade PanIN is accompanied by accumulating genetic alterations. From left to right: a normal pancreatic duct is lined by cuboidal to low-columnar epithelium with amphophilic cytoplasm. PanIN-1A shows flat epithelial lining with tall columnar cells with basally located nuclei and abundant supranuclear mucin. PanIN-1B identical to PanIN-1A except for a papillary, micropapillary, or basally pseudostratified architecture in PanIN-1B. PanIN-2 demonstrates full-thickness pseudostratification of nuclei with mild-to-moderate cytologic abnormalities. PanIN-3 is characterized by complete loss of polarity, budding of cellular tufts into the duct lumen, and significant nuclear pleomorphism. PanIN, pancreatic intraepithelial neoplasia.

over neighboring cells and that additional genetic or epigenetic events are needed for neoplastic progression (24).

A subset of PanINs (10%) harbors a *GNAS* mutation, a recently discovered oncogene mutated in about 60% of IPMNs (9,24). Interestingly, in some PanINs a *GNAS* mutation is the only mutation and in other PanINs the *GNAS* mutation seems to have occurred earlier than the *KRAS* mutation. Some of these PanIN lesions with a *GNAS* mutation may progress to IPMNs, as Matthaei and colleagues found that 33% of lesions with a size between PanINs and IPMNs (the so called incipient IPMNs) harbor *GNAS* mutations (27). Together these data suggest that *GNAS* mutations in PanIN may drive the lesion towards the IPMN pathway, although specificity of *GNAS* mutations for the IPMN pathway needs further confirmation.

The other genes targeted in invasive PDAC, including *CDKN2A/P16*, *TP53* and *SMAD4*, are also altered in PanIN lesions, supporting the hypothesis that PanINs are a precursor to invasive PDAC (3,28-30). These genetic alterations appear to occur after telomere shortening and *KRAS* gene mutations, as they are usually not found in low-grade PanINs, but instead are found in higher-grade PanIN lesions.

Some of the genetic changes in PanINs appear to be associated with progression (24). For example, loss of *P16* protein expression, a marker for genetic inactivation of *CDKN2A/P16*, correlates with increasing PanIN grade (30% of PanIN-1A/B, 55% of PanIN-2, and 70% of PanIN-3 lost *P16* expression) (28,31).This finding suggests that loss of *P16* may be more important for progression of PanIN than for initiation (3,24). Late genetic events that almost exclusively occur in PanIN-3 are inactivation of *TP53* and *SMAD4*, which are found in 30-50% of PanIN-3 lesions (29,30).

In addition to genetic changes, epigenetic alterations also play a role in PanIN progression. Hypermethylation of the promoters of tumor suppressor genes can be seen in low-grade PanIN lesions and they increase with grade of dysplasia (32). Promoter hypermethylation of *CDKN2A/P16* is responsible for a third of *P16* silencing, whereas homozygous deletions and intragenic mutation coupled with loss of heterozygosity (LOH) account for the remaining two-thirds (31). Many microRNAs are aberrantly expressed in PanINs and some of these are likely to be important in pancreatic carcinogenesis. Expression of some microRNAs, such as miR-196b, appears specific for high-grade lesions (PanIN-3 and PDAC) (24).

The genetic alterations, if any, that are crucial for transition from high-grade PanIN (*in situ* carcinoma) to an invasive carcinoma are still largely unknown. Direct

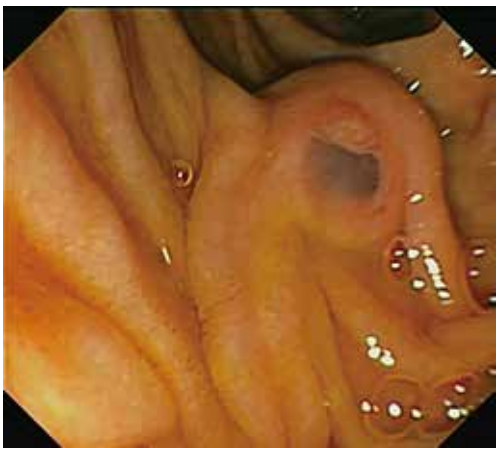

Figure 2 Endoscopic picture of a bulging ampulla of Vater with extruding thick mucin in a patient with an IPMN, sometimes referred to as "fish-eye" ampulla, and virtually pathognomonic of IPMN. IPMN, intraductal papillary mucinous neoplasm.

comparative sequencing of a precursor lesion and the associated invasive carcinoma can greatly increase our knowledge of the genetic changes that drive this transition. However, it is almost impossible to identity the exact PanIN that gave rise to the PDAC since much of the pancreas is usually overgrown by the PDAC once the tumor is resected. Also distinction between PanIN-3 adjacent to PDAC and the process of "cancerization of a pancreatic duct" by a PDAC can be difficult (19). Despite these difficulties, Murphy and colleagues tried to address the mechanisms that control progression to invasion by exome sequencing of 10 PDACs and 15 adjacent PanIN-2 and PanIN-3 lesions (33). PanINs and invasive carcinomas appeared to harbor similar numbers of mutations. There was a trend towards fewer mutations in PanIN-2 (average of 30 mutations) compared to the invasive carcinomas (average 50 mutations), but, surprisingly, PanIN-3 showed on average more mutations (63 mutations). In total, 66% of mutations were common to the invasive carcinoma and the adjacent PanIN, 10% of mutations were only present in the invasive carcinoma, and 25% of the mutations were only present in the PanIN lesions. When individual PanIN lesions were analyzed, genetic overlap between PanIN and adjacent invasive carcinoma ranged from 34% to 96%, but >50% commonality of mutations was present in 10 of the 15 PanIN lesions (33). The very high commonality between PanIN and invasive carcinoma in a few cases may represent very recent genetic divergence, but also raises the concern that a lesion is actually ductal spread of the adjacent invasive cancer instead of a true PanIN-3 lesion.

A number of clinical studies of PanIN lesions have been performed in parallel to the previously mentioned genetic studies, and the clinical significance of PanIN lesions in different settings is now being understood. PanIN at a resection margin does not affect survival in patients who have a resection for invasive PDAC. This is likely because the patients with invasive cancer and a PanIN at a margin are likely to die from their invasive PDAC long before the residual PanIN has time to progress to an invasive cancer (34). Although the data are not so strong, Konstantinidis and colleagues investigated the significance of incidentally discovered PanIN in pancreatic resections for reasons other than PDAC (21). They found that presence of PanIN-1 or 2 in the resection margin or PanIN of any grade anywhere in the pancreas did not result in an appreciable cancer risk in the pancreatic remnant after resection (21). Follow-up of patients in this study was relatively short [median 3 years (range, 0.5-11 years)] compared to the time needed for PDAC development (11,21).

Intraductal papillary mucinous neoplasm (IPMN)

IPMNs are epithelial mucin-producing tumors that arise within the larger pancreatic ducts. At endoscopy a so-called "fish-eye" ampulla of Vater, i.e., a bulging ampulla with extruding mucin, can be seen and is almost diagnostic for IPMN (*Figure 2*). IPMNs are by definition >5 mm in diameter, and they typically are characterized by papillary proliferations that dilate the existing duct infrastructure. IPMNs are usually found in the head of the pancreas, but they can involve any portion of the pancreas and some involve the entire length of the gland (35,36). IPMNs are very common, and studies of asymptomatic individuals who undergo a CT scan have revealed that close to 3% of asymptomatic individuals have pancreatic cysts, approximately 25% of which is consistent with an IPMN (35,37,38). The prevalence of IPMN is equal in men and women; the majority of patients are diagnosed around 60 years of age (4).

IPMNs can macroscopically be categorized in three groups: 10-35% arises in the main pancreatic duct (MD), 40-65% in a branch duct (BD), and 15-40% involves both the main and BDs (mixed type) (39-44). These numbers vary greatly from study to study, but the pattern of duct involvement does guide therapy. For example, examination

Table 2 International consensus guidelines for surgical resection of pancreatic cysts according to Tanaka *et al.* (36)

Main duct IPMN	Surgical resection is strongly recommended for all surgically fit patients. If the margin is positive for high-grade dysplasia, additional resection should be attempted to obtain at least moderate-grade dysplasia. However, MPD dilation of 5-9 mm should be considered as one of the "worrisome features", similar to the case for BD-IPMN, with a recommendation of evaluation but no immediate resection. To date, there have been no consistent predictive factors for malignancy in MD-IPMN, including the degree of MPD dilation, presence of symptoms, or mural nodules
BD IPMN	Any of the following high-risk stigmata of malignancy present? • Obstructive jaundice in a patient with cystic lesion of the head of the pancreas • Enhancing solid component within cyst • Main pancreatic duct >10 mm in size ❖ Consider resection if clinically appropriate Are any of the following worrisome features present? • Pancreatitis[a] • Cyst >3 cm • Thickened/enhancing cyst walls • Main duct size 5-9 mm • Nonenhancing mural nodule • Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy ❖ Perform endoscopic ultrasound, and if any of these features are present: • Definite mural nodule[b] • Main duct features suspicious for involvement[c] • Cytology: suspicious or positive for malignancy ❖ Consider resection if clinically appropriate
MCN	Surgical resection is recommended for all surgically fit patients. Observation may be considered in elderly frail patients. In patients with MCNs of <4 cm without mural nodules, parenchyma-sparing resections (i.e., middle pancreatectomy) and distal pancreatectomy with spleen preservation as well as laparoscopic procedures should be considered

[a], pancreatitis may be an indication for surgery for relief of symptoms; [b], differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue; [c], presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is inconclusive; BD, branch duct; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm.

of resected IPMNs has shown that 62% of MD and 58% of mixed type IPMNs have high-grade dysplasia, and that 44% of MD and 45% of mixed type IPMNs have an associated invasive carcinoma (36). In contrast, only 24% of BD-IPMNs have high-grade dysplasia, and 17% an associated invasive carcinoma (36). Risk assessment and decision-making on which IPMNs to resect and which IPMNs can be safely followed is based on these percentages. However, relying solely on MD *vs.* BD in decision making can be treacherous as a recent study of 512 IPMNs found that 30% of suspected BD-IPMNs (67/233) had histological involvement of the main pancreatic duct not evident in preoperative imaging (44). Importantly, the misdiagnosed BD-IPMNs had significantly more high-grade dysplasia and were more likely to harbor an associated carcinoma than histologically pure BD-IPMNs (44).

In order to address the complexities of managing patients with an IPMN, consensus guidelines for the management of IPMN and MCN were established in 2012. These guidelines advise that most IPMNs that involve the MD should be surgically resected because of their high rate of malignancy, whereas surgical indications for BD-IPMNs include the presence of "high-risk stigmata" such as mural nodules and symptomatology (*Table 2*) (36). If there are

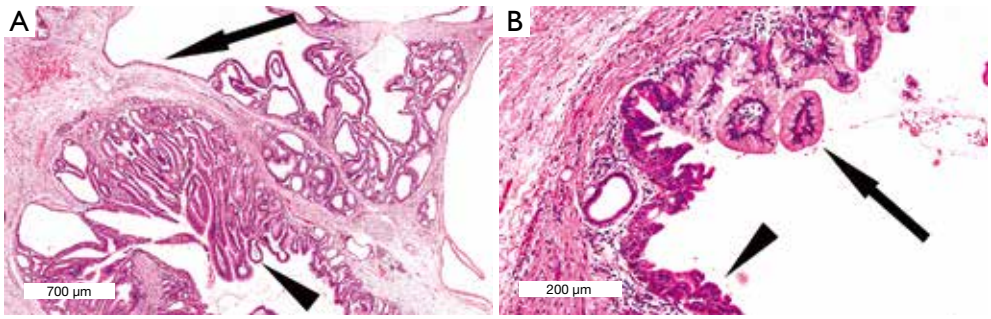

Figure 3 (A) Gastric-foveolar type IPMN with areas with low-grade (arrow) and intermediate-grade dysplasia (arrowhead); (B) gastric-foveolar type IPMN with transition from intermediate-grade dysplasia (arrow) to high-grade dysplasia (arrowhead). IPMN, intraductal papillary mucinous neoplasm.

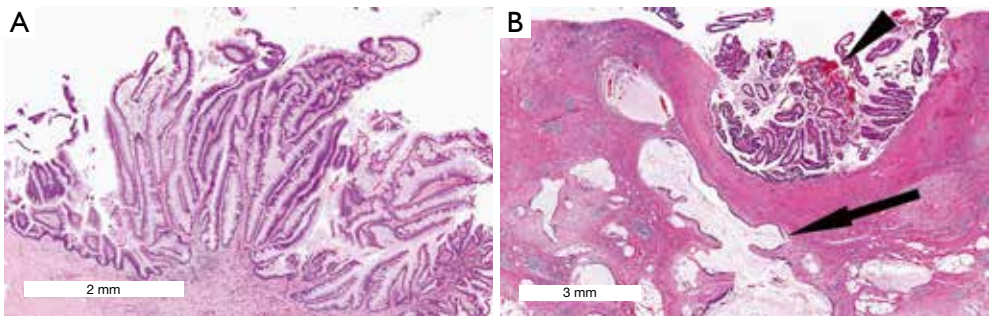

Figure 4 (A) Intestinal type IPMN with intermediate-grade dysplasia; (B) mucinous adenocarcinoma (arrow) arising from an intestinal type IPMN (arrowhead). IPMN, intraductal papillary mucinous neoplasm.

only so-called "worrisome features" (defined in *Table 2*), further diagnostic workup is advised. A recent study showed that "high-risk stigmata" had a good correlation with malignancy, but "worrisome features" did not (45). Clearly, development of additional biomarkers that can be used to predict presence of high-grade dysplasia or invasive growth has great potential to improve clinical decision-making (4).

Histologically, IPMNs can be categorized as gastric-foveolar, intestinal, pancreatobiliary, or oncocytic type based on the direction of differentiation of the neoplastic epithelium as defined by histology and immunolabeling (46,47). In addition, intraductal tubulopapillary neoplasms (ITPN) are recognized as an intraductal neoplasm distinct from IPMNs; however, these lesions are rare, and their precise relationship to the other IPMN subtypes remains to be defined. Most BD-IPMNs have gastric-foveolar histology, whereas intestinal, pancreatobiliary, and oncocytic histologies are seen more often in the main duct type IPMNs. The histologic directions of differentiation in IPMNs have clinical implications and therefore deserve a more detailed discussion.

Gastric-foveolar IPMNs are lined by epithelium resembling foveolar epithelium of the gastric mucosa (*Figure 3*). The neoplastic epithelial cells have apical mucin with small basally oriented nuclei. The epithelium is usually flat and composed of a single layer of cells, although the neoplastic epithelium can form papillae. Mitoses are rare and most lesions have low-grade dysplasia, although intermediate-/high-grade dysplasia is present in 10% (48). Immunohistochemically the neoplastic epithelium expresses MUC5AC and MUC6, but does not express MUC1 and MUC2 (47). MUC4 is expressed in lesions with higher grades of dysplasia (49). Gastric-foveolar IPMNs can be mixed with pancreatobiliary and intestinal type epithelium. Associated invasive carcinomas are rare, but when present tend to be ductal adenocarcinomas.

Intestinal IPMNs resemble villous adenomas of the gastrointestinal tract (*Figure 4*). Long papillae, lined by mucin-secreting neoplastic epithelial cells, protrude from the cyst wall. The neoplastic cells have elongated

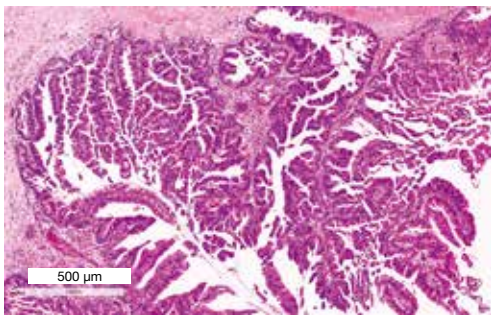

Figure 5 Pancreatobiliary type IPMN with high-grade dysplasia. IPMN, intraductal papillary mucinous neoplasm.

nuclei and can be pseudostratified. Intestinal IPMNs usually have moderate- to high-grade dysplasia (46). Immunohistochemically the neoplastic cells strongly express MUC2 and MUC5AC, but do not express MUC1. MUC6 is focally expressed in some cases (50). Some also express MUC4 (49). CDX2, a marker of intestinal differentiation, is also expressed in this subtype (47). Associated invasive carcinomas arising from intestinal IPMNs are typically colloid carcinomas (mucinous noncystic adenocarcinomas) with a similar mucin profile (51), but can also be ductal adenocarcinomas or mixed ductal/colloid carcinomas (52).

Pancreatobiliary IPMNs are usually high-grade lesions with complex architecture with cribriforming papillae and bridging (*Figure 5*). The neoplastic cells are cuboidal and have atypical round nuclei with clearly visible nucleoli. Lower-grade dysplasia is rare but when present is characterized by mild atypia with hyperchromasia and enlarged nuclei (46). The neoplastic cells express MUC1, MUC5AC and some also express MUC6. MUC2 is not expressed. Associated invasive carcinomas usually are ductal adenocarcinomas, with the same mucin expression pattern (47,51,53).

Oncocytic IPMNs, also known as intraductal oncocytic papillary neoplasms (IOPNs), are morphologically the most complex lesions, and have intricate branched papillae with cribriform formations and solid cell nests. They almost always harbor high-grade dysplasia (*Figure 6*). The cells have abundant eosinophilic cytoplasm, but can have intracellular mucin and intraepithelial mucin pools. MUC1 and MUC6 are expressed by the neoplastic cells. Incidentally goblet cells may be seen expressing MUC2 and MUC5AC. When present, an associated invasive carcinoma is usually the rare oncocytic carcinoma. Although only a small number of cases have been reported this may represent a true subtype based on distinct histology and genetics (54).

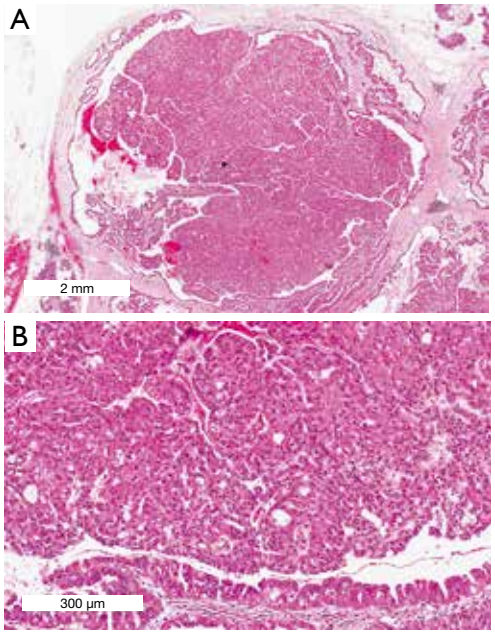

Figure 6 Oncocytic type IPMN with high-grade dysplasia. (A) Overview; (B) detail. IPMN, intraductal papillary mucinous neoplasm.

ITPN are the most recently recognized pancreatic intraductal neoplasm and, as mentioned above, may represent a separate entity from IPMN. A predominant tubulopapillary growth of cuboidal neoplastic cells in the affected duct combined with a more solid architecture with minimal cytoplasmic mucin and frequent necrotic foci define this neoplasm (*Figure 7*). ITPNs often have an overall cribriform appearance. The lesions are always high-grade. MUC6 is expressed in all cells and MUC1 is expressed focally. MUC2 and MUC5AC are negative (55).

IPMN subtypes have been categorized based on their histologic and morphologic features. Although there are clear differences, many IPMNs show mixed histologic features suggesting that these phenotypes do not represent completely distinct underlying pathways. For instance, intestinal and pancreatobiliary IPMNs can both harbor areas with gastric differentiation, and it has been suggested that the low-grade gastric-foveolar type is a common precursor to other types of IPMNs (47).

IPMNs can be a precursor to invasive PDAC. Although IPMNs show many of the genetic alterations involved in PanIN and classic invasive PDAC, such as *KRAS*, *TP53*, *SMAD4*, *CDKN2A/P16* (3,6), some genetic alterations, such as activating *GNAS* mutations and inactivating

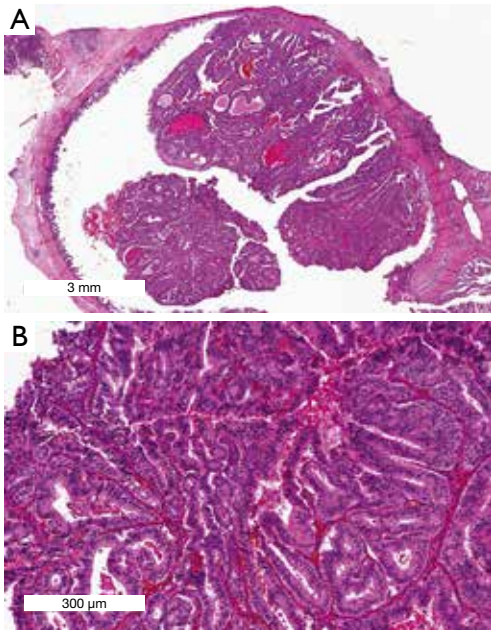

Figure 7 Intraductal tubulopapillary neoplasm with high-grade dysplasia. (A) Overview; (B) detail.

RNF43 mutations, seem to be more specific for the IPMN precursor pathway (8,9).

Wu *et al.* sequenced the exomes of eight IPMNs and found that IPMNs contain an average of 26±12 somatic mutations (8). The genes most frequently targeted in IPMNs appear to be *KRAS*, *GNAS*, *CDKN2A/P16*, *RNF43*, *TP53*, and *SMAD4*. In a large follow-up study in which 51 cancer genes were sequenced in 48 IPMNs, Amato and colleagues found that virtually all IPMNs (>90%) harbor a *KRAS* and/or *GNAS* mutation, and that *CDKN2A/P16*, *RNF43*, *TP53*, *BRAF*, and *SMAD4* are less commonly targeted (56). *KRAS* mutations appear to be early events, as close to 90% of low-grade and intermediate-grade IPMNs harbor a *KRAS* mutation (9). Both intestinal and pancreatobiliary type IPMNs harbor *KRAS* mutations, while *GNAS* mutations appear to be more common in intestinal type IPMNs (9,56,57). Of interest, *KRAS* and *BRAF* mutations have not been reported in ITPN (58). Interestingly, *in vitro* research in pancreatic ductal cells found that mutated *GNAS* may extensively alter gene expression, including expression of mucin genes through the interaction with MAPK and PI3K pathways. Extensively altered expression of MUC2 and MUC5AC in different cell lines suggested a role in morphologic and histologic presentation (59).

As >95% of IPMNs show either a *KRAS* or *GNAS* mutation, it is possible that all IPMNs are initiated by a mutation in either one of these genes. Recently an IPMN with associated carcinoma was reported in a patient with McCune-Albright syndrome (post-zygotic noninherited activating *GNAS* mutations), further establishing the causal role of *GNAS* in pancreatic tumorigenesis (60).

The targeting of *RNF43* tumor suppressor gene in IPMNs is of interest because the protein product of this gene plays an important role in the Wnt/β-catenin pathway (8,56). *RNF43* is a transmembrane E3 ligase that down-regulates the Wnt pathway by removing Wnt receptors from the cell surface in intestinal stem cells (61). While further research on the role of *RNF43* in IPMN is needed, newer therapies targeting the Wnt/β-catenin pathway may be applicable to IPMN associated invasive PDACs with an *RNF43* mutation (62,63).

Another gene that is frequently inactivated in IPMNs is *CDKN2A/P16*. Homozygous deletions, intragenic mutations coupled with LOH and epigenetic alterations can inactivate *CDKN2A/P16* (31). LOH at 9p was seen in 10% of low-grade, 20% of intermediate-grade, and 33% of high-grade IPMNs, and 100% of invasive PDACs (64). Loss of *P16* is thus a marker for progression to high-grade dysplasia/invasive carcinoma. A recent study found *CDKN2A/P16* mutations in about 5% of IPMNs by NGS, but showed loss of expression in the same tissue in 0% of low-grade, 25% of intermediate-grade, 30% of high-grade, and 50% of invasive IPMNs, suggesting an important role for inactivation by epigenetic mechanisms coupled with LOH (56).

TP53 is mutated late in IPMN progression (56). Mutation of *TP53* leads to protein inactivation and typically to the abnormal accumulation of the protein product in the neoplastic cells, reflected by very strong immunostaining for the *TP53* protein (*Figure 8*). Alternatively, completely absent immunostaining indicates a stop codon mutation coupled with LOH (65). *TP53* expression is usually normal in low-grade IPMNs, but *TP53* expression is altered in a third of intermediate-grade IPMNs and close to half of high-grade IPMNs (66). The tumor suppressor gene *SMAD4* is also inactivated late in IPMN progression. Although inactivated in 55% of invasive PDACs, *SMAD4* is rarely inactivated in low- or intermediate-grade IPMNs. *SMAD4* can be inactivated by homozygous deletion or by intragenic mutations coupled with LOH. Wilentz *et al.* (29) reported loss of immunohistochemical expression of the *SMAD4* protein is a marker for inactivation of the *SMAD4*

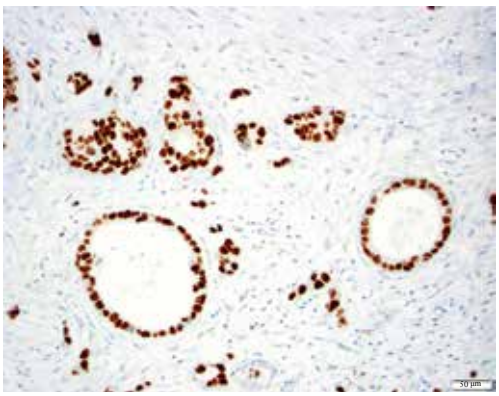

Figure 8 *TP53* immunohistochemistry showing strong aberrant expression of *TP53* consistent with somatic *TP53* mutation in a pancreatic ductal adenocarcinoma. A somatic mutation of *TP53* was confirmed in this case.

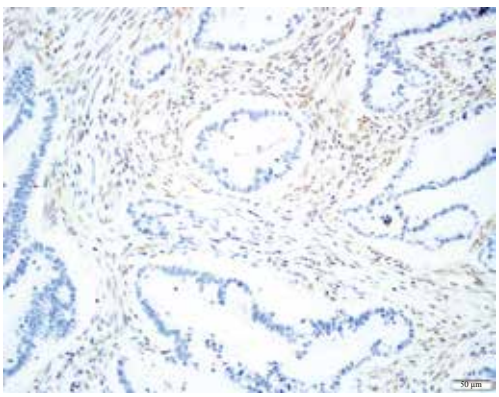

Figure 9 SMAD4 immunohistochemistry showing loss of SMAD4 expression in a pancreatic ductal adenocarcinoma. Note the normal expression in surrounding stromal cells compared to negativity in tumor cells.

gene (*Figure 9*). *SMAD4* expression was shown to be normal in IPMNs with low-, intermediate- and high-grade dysplasia, while 3 of 4 IPMN associated invasive carcinomas showed loss of *SMAD4* (67). Other studies showed similar results, with retained expression of *SMAD4* in non-invasive IPMNs but loss of *SMAD4* in 3-16% of IPMN associated invasive carcinomas. Iacobuzio-Donahue *et al.* reported that all 19 colloid carcinomas arising from an IPMN had normal expression of *SMAD4*, whereas weak staining was seen in 5 of 9 invasive ductal adenocarcinomas arising from an IPMN, suggesting a link of *SMAD4* loss with ductal differentiation (68).

Phosphatidylinositol-3 kinases (PI3K) are lipid-kinases that play a role in proliferation, differentiation, survival, and several other cellular functions. *PIK3CA* is an oncogene that activates the AKT pathway and is mutated in 10% of intermediate- and high-grade IPMNs, and this genetic targeting of *PIK3CA* seems to be another late event in the progression of IPMNs (69). *PIK3CA* was mutated 3 of 11 (37%) ITPNs, which also had overall significantly higher expression of phosphorylated AKT than the control group IPMNs, suggesting that this pathway may be a driver of ITPN development (58). LOH of *PTEN*, another tumor suppressor gene in the AKT pathway, has been reported in 0% low-grade, 30% intermediate-grade, and 40% high-grade IPMNs. Weak or absent *PTEN* expression in 30% of IPMNs was also significantly associated with higher nuclear grade, but further studies are needed to evaluate clinical value of *PTEN* in IPMNs (70). Intriguingly, alterations in the PI3K pathway do not occur commonly in PDACs, pointing to this pathway's unique importance in IPMNs (5).

STK11, a tumor suppressor gene encoding for the serine threonine protein LKB1, is mutated in the germline of patients with the PJS. PJS is known to cause a 132-fold increase in risk of invasive PDAC and some of these invasive cancers arise from IPMNs (71). Mutations in *STK11* are seen in 5% of nonPJS IPMNs (72).

The expression of human telomerase reverse transcriptase (hTERT) and of Sonic hedgehog (Shh) is increased in IPMNs with higher grade of dysplasia, most significantly in progression from intermediate- to high-grade IPMNs (73,74). The loss of expression of the tumor suppressor gene *BRG1* has also been association with progression in IPMNs (75). Changes in the expression of some genes in IPMNs are driven by genetic alterations, while in other tumors gene expression changes are produced by epigenetic DNA modifications, microRNAs, post-translational protein modifications, and possible feedback mechanisms. For example, >90% of IPMNs show at least one aberrantly methylated tumor suppressor gene promoter site (76). Genes that have been reported to be methylated in IPMNs included *CDKN2A/P16*, *TP73*, *APC*, *hMLH1*, *MGMT*, and *E-Cadherin* (76). Significantly more genes are methylated in IPMNs with high-grade dysplasia than in IPMNs with low-grade dysplasia. Moreover, some genes may be selectively methylated in high-grade lesions, which may be useful in the clinical management of IPMNs (32,76,77). MicroRNAs are also aberrantly expressed in IPMNs (78). Both MiR-21 and miR-155 are up-regulated in invasive carcinomas associated with IPMNs compared to noninvasive IPMNs

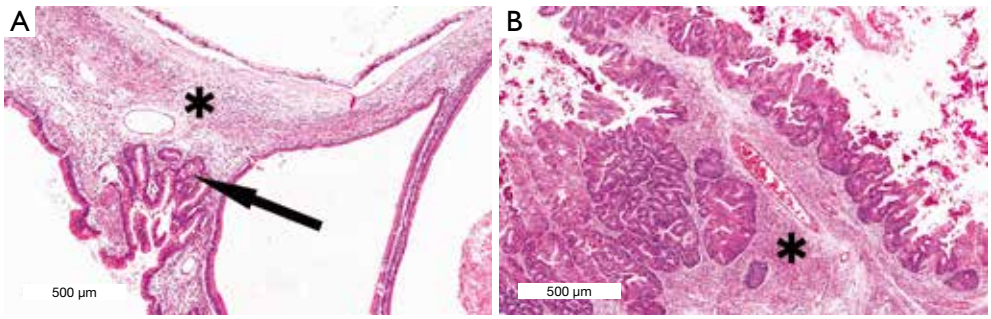

Figure 10 (A) Mucinous cystic neoplasm with low- to intermediate-grade dysplasia and focal goblet cells (arrow). Note the cellular ovarian-type stroma (asterix); (B) mucinous cystic neoplasm with high-grade dysplasia and typical ovarian-type stroma (asterix).

and normal tissue, suggesting a role for these microRNAs in carcinogenesis (79,80). These microRNAs regulate key tumor suppressor pathways: miR-21 represses several genes including *PTEN* (81), and miR-155 represses *TP53INP1* (80). Downregulation of microRNA MiR-101 has also been shown in progression of IPMNs. MiR-101 can silence *EZH2* expression in IPMN (82), and in IPMNs *EZH2* expression has an inverse correlation in expression with the tumor suppressor CDKN1B/p27. *EZH2* might transcriptionally silence CDKN1B/p27 and is also known to methylate the protein histone 3 at lysine 27 (83).

It has also been suggested that the pattern of expression of certain microRNAs can be used as a marker of different IPMN subtypes. MiR-196a expression is associated with intestinal IPMN (84) and miR-200c, miR-141, miR-216 could be used to mark dysplastic progression in IPMN-tissue (85), and cyst fluid (86). MicroRNAs can also be detected in serum and can have discriminating diagnostic applications (87). Other diagnostic approaches for early diagnosis of high-grade/invasive IPMN may be detection of *TP53* and/or *SMAD4* mutations in pancreatic juice or cyst fluid (88), circulating tumor cells (89), mRNA binding proteins (90), ubiquitin and thymosin-β4 in EUS FNA (91), and monoclonal antibodies (92).

Thus, a number of genetic, histological and clinical studies have defined the molecular basis for the development of IPMNs which in turn suggests novel molecular biomarkers and novel therapeutic approaches for these neoplasms.

Mucinous cystic neoplasm (MCN)

MCN is the least common of the precursor lesions that can give rise to invasive PDAC. MCNs occur almost exclusively women and usually in the tail of the pancreas. MCNs are cyst forming neoplasms, and characteristically the cysts do not communicate with the pancreatic duct system. By definition, MCNs contain a characteristic ovarian-type stroma (*Figure 10*). One theory on the pathogenesis of MCNs argues that they are the result of ectopic gonadal mesenchyme that is incorporated in the pancreas during the fourth and fifth weeks of embryogenesis as a result of the close proximity of the left primordial gonad to the dorsal pancreatic anlage which gives rise to the pancreatic body and tail. This could also explain MCNs at the contralateral side in the hepatobiliary tract (93,94). However, because this cannot explain the rare occurrence of MCN in male patients, an alternative theory has been put forth which suggests that neoplastic epithelial cells of MCNs induce ovarian stromal differentiation in cells that are normally present in the pancreas (95).

MCNs account for approximately 8% of all resected cystic lesions of the pancreas (96,97). Small MCNs (<3 cm) are usually incidental findings, whereas larger MCNs may produce nonspecific complaints such as abdominal discomfort and the sensation of a mass in the epigastric region. Surgical resection is recommended for all surgically fit patients (*Table 2*). Up to one-third of resected MCNs have an associated invasive carcinoma, although more recent studies report lower percentages (5-15%), likely due to the fact that smaller low-grade MCNs are being detected incidentally in patients imaged for other reasons (98-100). Invasive adenocarcinomas arising in MCNs usually resemble a common PDAC but can also have a mucinous histology. Because invasive carcinoma can arise very focally in an MCN, when MCNs are resected they should be sampled extensively, if not completely, by the examining pathologist (99). Patients with a surgically resected noninvasive MCN are cured after the resection. The 5-year survival rate for patients with an MCN with an associated invasive carcinoma is about 50-60%, depending

on the extent of invasion (96).

Grossly, in contrast to IPMNs, MCNs do not communicate with the pancreatic ductal system. Most MCNs form large (average size 10 cm) multilocular lesions containing thick mucin, or sometimes mucin tinged by hemorrhage. Lesions with low-grade dysplasia usually have a smooth and glistering internal surface, whereas lesions with high-grade dysplasia are lined by epithelium with papillary projections. MCNs with an associated invasive carcinoma are often large and multilocular and contain papillary projections or mural nodules (96,101).

Microscopically, the cysts of MCNs are lined by a columnar mucin-producing neoplastic epithelium. By definition, they also have an ovarian-type stroma consisting of densely packed spindle cells with round to elongated nuclei and a small amount of cytoplasm (*Figure 10*). The stromal cells express inhibin, estrogen and progesterone receptors, as well as vimentin, smooth-muscle actin, and desmin. In some lesions the stroma may become fibrotic and hypocellular and be more difficult to recognize. The epithelial lining of the cysts consists of mucin-producing tall columnar epithelial cells with pseudopyloric, gastric-foveolar, small-intestinal or large-intestinal differentiation. Squamous differentiation is only rarely seen (95). The epithelial cells express cytokeratins 7, 8, 18, and 19, the gastric type mucin MUC5A, and pancreatic type mucin DUPAN-2 and CA19-9, whereas scattered goblet-like cells express the intestinal MUC2. MUC1 expression is observed in most ductal adenocarcinoma arising from MCN, but is negative in the associated noninvasive components (102). The degree of dysplasia in MCN can vary greatly and change abruptly from minimal to severe or even focal invasive growth. The highest degree of dysplasia present in an MCN determines the classification of the lesions as MCN with low-grade, intermediate-grade, or high-grade dysplasia (95). The vast majority (70-80%) of MCNs are low-grade (98,100).

MCNs is less well-characterized at the genetic level than are PanINs and IPMNs. However, recent whole-exome sequencing of carefully microdissected MCNs has revealed that the neoplastic epithelium has an average of 16±7.6 somatic mutations and relatively few allelic losses (8). *KRAS* is the most frequently mutated gene in MCN. Using Sanger sequencing *KRAS* mutations have been found in 25% (7/27) of MCNs with low-grade dysplasia, 40% (5/13) of MCNs with intermediate-grade dysplasia, and 90% (8/9) of MCNs with high-grade dysplasia or invasive carcinoma. Mutations in *TP53* are a relatively late event occurring only in areas with high-grade dysplasia or an associated invasive carcinoma (103). Whole-exome sequencing identified *RNF43* mutations in 3 of the 8 MCNs examined (8). Loss of *SMAD4* is a late event in neoplastic progression of MCN and found in associated invasive adenocarcinomas but not typically in noninvasive components of MCNs (104). Rarely *PIK3CA* gene mutations are found in MCN, but these seem confined to those with high-grade dysplasia (105). Hypermethylation of *P14* and *P16* has been reported in about 15% of non-invasive MCNs (106).

Global gene expression profiling identified a number of genes that are up-regulated in the epithelium of MCNs, including *S100*, *PSCA*, *C-MYC*, *STK6/STK15*, *cathepsin E*, *TCF4*, and *pepsinogen C*. In addition, activation of the Notch pathway was shown in the epithelial component by the demonstration of overexpression of Jagged1 and the downstream Notch pathway member Hes1. Overexpression of steroidogenic acute regulatory (STAR) protein and estrogen receptor 1 (ESR1) occurs in the stroma (107).

Conclusions

PDAC is a deadly disease. The key to reducing deaths from PDAC is to detect pancreatic neoplasia at a very early and still curable stage or, even better, to detect and treat precursor lesions before they transform into incurable invasive cancers. PDAC develops from several histologically and genetically distinct precursor lesions providing an opportunity for early detection and prevention (2). Moreover, genetic studies have suggested that the window of opportunity to diagnose and treat a precursor lesions is almost 12 years (10).

While the genes that are recurrently mutated in PDAC and in precursor lesions (such as *KRAS*, *GNAS*, *TP53*, *CDKN2A/P16*, *SMAD4*) are prime targets for early detection efforts, some of the genes that are less commonly mutated (such as *ATM*, *BRCA2*, and *RNF43*) are potentially more therapeutically targetable. Moreover, therapeutic targeting of one or more core signaling pathways involved in PDAC instead of a specific genetic alteration may be important to circumvent genetic heterogeneity of PDAC.

Although progress in the therapy of patients with PDAC is invaluable, early detection and prevention of PDAC are likely to be more effective to decrease mortality (2). Today biomarkers can be assessed in cyst fluid aspirated by fine needle aspiration or in secreted pancreatic juice collected in the duodenum (9,88,108,109). Recent studies revealed genetic alterations in pancreatic cyst fluid that can

discriminate between a completely harmless cyst such as serous cyst adenoma and a premalignant cyst such as IPMN and MCN (8). However, the ultimate goal is to identify those patients with a high-grade precursor lesion and/or early invasive PDAC (88). Those patients would benefit from a surgical resection, whereas patients with lesions with only low-grade dysplasia could be safely followed without surgery. Such definitive biomarkers are not yet available, but further dissection of the genetic progression of PDAC precursor lesions will hopefully lead to the identification of biomarkers that indicate high-grade dysplasia or transition to invasive growth. Ultimately this will lead to better risk stratification of patients with pancreatic cancer precursor lesions and patients at increased risk of PDAC. Newer gene-based tests have the potential to greatly aid in clinical decision-making and the selection of patients who would benefit from surgical treatment, while on the other hand patients with low-risk lesions could be spared from an operation.

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The role of epithelial-mesenchymal transition in pancreatic cancer

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Abstract: Pancreatic cancer is the fourth leading cause of cancer related death in the US. Despite the advances in medical and surgical treatment, the 5-year survival rate for such cancer is only approximately 5% when considering all stages of disease. The lethal nature of pancreatic cancer stems from its high metastatic potential to the lymphatic system and distant organs. Lack of effective chemotherapies, which is believed to be due to drug-resistance, also contributes to the high mortality of pancreatic cancer. Recent evidence suggests that epithelial-mesenchymal transition of pancreatic cancer cells contributes to the development of drug resistance and an increase in invasiveness. Future strategies that specifically target against epithelial-mesenchymal transition phenotype could potentially reduce tumoral drug resistance and invasiveness and hence prolong the survival of patients with pancreatic cancer.

Keywords: Pancreatic cancer; epithelial-mesenchy mal transition; cancer stem cell

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Introduction

Pancreatic cancer (PC) is the tenth cause of new cancer cases and the fourth leading cause of cancer related death in the US, with an estimated 43,140 new cases and 36,800 deaths in 2010 (1). Despite the advances in surgical and medical treatment, the 5-year survival rate for PC is only approximately 5% when considering all stages of disease (1). Without a specific diagnostic marker and being asymptomatic in early stage, PC is often diagnosed at an advanced/late stage when only palliative measures can be offered, which can only partially explain its observed poor prognosis (2). The 5-year survival rate of PC remains low at only 10-25% for those with locoregional disease due to local recurrence and/or distant metastasis after curative surgery (3). The lethal nature of PC therefore stems from its high metastatic potential to the lymphatic system and distant organs. In addition, lack of effective chemotherapies, which is believed to be due to drug-resistance, also contributes to the high mortality of patients diagnosed with PC (4). Recent evidence suggests that epithelial-mesenchymal transition (EMT) of PC cells contributes to the development of drug resistance (5).

EMT plays crucial roles in the formation of the body plan and in the differentiation of tissues and organs. During EMT, epithelial cells undergo profound phenotypic changes such as loss of cell-cell adhesion, loss of cell polarity, and acquisition of migratory and invasive properties (6). EMT not only occurs during embryonic development or as a physiological response to injury, but is also an important element in cancer progression through a variety of mechanisms. EMT endows cells with migratory and invasive properties, induces stem cell properties, prevents apoptosis and senescence, induces resistance to conventional chemotherapy, and contributes to immunosuppression (6).

To support the role of EMT in PC progression, several reports have shown the increased expression of EMT markers such as N-cadherin (7), transcription factors including Snail, Slug and Twist (8), fibronectin (9), and vimentin (9,10) in surgically resected PC specimens but not in the normal noncancerous pancreatic tissue. In addition, the presence of EMT in PC is often associated

with undifferentiated phenotype and overall poor survival compared to the tumors without EMT (9,10). As mentioned previously, EMT contributes to drug resistance in cancer cells probably through induction of the formation of cancer stem cells (CSCs) or stem-like cells (4,11). This concept is supported by the findings of the increased expression of stem cell markers in drug-resistant PC cells (12-14).

In this concise review, we will summarize the current knowledge regarding the mechanisms and implications of EMT in PC.

Molecular mechanisms of EMT

EMT is a process by which epithelial cells lose their polarity and are converted to a mesenchymal phenotype. EMT has been considered as the critical event inducing morphogenetic changes during embryonic development, organ fibrosis and tumor metastasis. Phenotypic changes of EMT include the downregulation of epithelial markers (e.g., E-cadherin, desmoplakin and plakoglobin) and upregulation of mesenchymal markers (e.g., vimentin, fibronectin and α-smooth muscle actin) (6,15,16). A variety of transcriptional factors, including Snail, Slug, Twist, Zeb1, SIP1, and E47, were shown to induce EMT through repression of E-cadherin transcription (17-22). In addition to transcriptional repression, other mechanisms can also repress E-cadherin expression. A previous study reported that promoter hypermethylation was associated with E-cadherin repression and induction of EMT (23). Recent evidences highlight the role of chromatin modification in E-cadherin repression. Snail interacts with histone deacetylase 1 (HDAC1)-histone deacetylase 2 (HDAC2), AJUBA-protein arginine methyltransferase 5 (PRMT5), or polycomb repressive complex 2 (PRC2) to repress E-cadherin expression (24-26). We recently demonstrated that regulation of the polycomb repressive complex 1 (PRC1) protein Bmi1 by Twist1 is essential in Twist1-induced suppression of E-cadherin (27).

Hypoxia is an important microenvironmental factor for triggering metastasis during cancer progression. Recent studies showed that hypoxia-inducible factor 1 and 2 (HIF-1α and HIF-2α) induces the expression and coordinates the interplay of EMT regulators. HIF-1α regulates the expression of EMT regulators such as Snail, Zeb1, SIP1 either directly or indirectly (28,29). We prev iously demonstrated the direct regulation of Twist1 by HIF-1α, suggesting the critical role of hypoxia in the induction of EMT (30). HIF-2α has also been shown to regulate Twist1 expression (31). The results from these studies suggest the critical role of intratumoral hypoxia in the induction of EMT through either HIF-1α or HIF-2α or both.

Accumulating evidences suggest that cells can acquire stem-like properties during induction of EMT (32,33). This finding provides a crucial link between the acquisition of metastatic traits and tumor-initiating capability in cancer cells undergoing EMT. To support this theory, we previously demonstrated the direct regulation of the stemness gene Bmi1 by Twist1. Twist1 and Bmi1 act cooperatively to repress E-cadherin and p16INK4A, leading to the induction of EMT and stem-like properties of cancer cells. A recent report showed that Bmi1 is induced by another EMT regulator Zeb1 through regulation of the miR-200 family in pancreatic cancer cells (34). It indicates that the polycomb repressive protein Bmi1 may play a central role in the induction of EMT and stemness in pancreatic cancers.

Pancreatic CSCs

Based on the CSC theory, a tumor contains a heterogeneous population of mature cancer cells and a small number of CSCs. These CSCs, similar to their normal counterparts, have the ability to self-renewal and undergo multilineage differentiation (35). Most of the CSCs are identified by their specific cell surface markers. Pancreatic CSCs have been identified based on the expression of CD24, CD44, and epithelial-specific antigen (ESA). These cells represent only 0.5% to 1% of all PC cells but have at least 100-fold greater tumorinitiating potential than the majority of the tumor cells that are negative for these markers. More importantly, tumors derived from $CD24^+ CD44^+ ESA^+$ PC cells have been shown to be able to copy the phenotypic diversity characterized in the original tumor (36,37). Different populations of pancreatic CSCs have also been reported based on their expression of CD133 and CXCR4 (38) and a ldehyde dehydrogena se (ALDH) (39). Little overlap existed between the $ALDH^+$ and $CD24^+ CD44^+$ cell population despite the fact that they had a similar tumor formation capacity *in vivo* (39). It is conceivable that multiple phenotypically distinct cell populations are clonogenic in an individual tumor. Alternatively, it is possible that the phenotype of CSCs changes in response to cellular activation status, interactions with the external microenvironment, or disease stage. Another possibility is that these different CSC populations are interrelated by a retained hierarchical arrangement in which the expression

of each specific marker is restricted to a specific cellular compartment, which is reminiscent of the structured relationship between long- and short-term stem cells and progenitors in normal hematopoiesis (39).

EMT, Pancreatic CSCs, and drug resistance

Existing therapies for patients with cancer are largely against differentiated tumor cells, while sparing the relative quiescent CSCs (35). This paradigm can plausibly explain the commonly seen relapse after debulking chemotherapy due to the persistence of CSCs. The possible mechanisms underlying drug resistance in CSCs include the expression of energy-requiring transporters, the resistance to druginduced apoptosis, and an active DNA-repair capacity (40). Du *et al.* (14) reported that chemoradiation-resistant PC cells acquired characteristics of CSCs and have high expression of anti-apoptotic protein bcl-2 and apoptosis inhibitory protein survivin. In another study, Hong *et al.* (41) reported that an ATP-binding cassette (ABC) transporter, ABCB1 (MDR1), was significantly augmented during the acquisition of drug resistance to gemcitabine. Pancreatic CSCs have been shown to be resistant to gemcitabine, the most commonly used chemotherapeutic agent for PC, in multiple studies (12,14,38,41,42). Treatment with gemcitabine can therefore enrich the CSC population likely through selection process that eventually leads to treatment failure (12,38,42). Emerging evidence suggests that Hedgehog pathway is important to CSC signaling (43). To support the critical role of pancreatic CSCs in the development of drug resistance, combined treatment with gemcitabine and cyclopamine, a small molecule smoothened antagonist, not only induced tumor regression but also decreased in CSC markers and Hedgehog signaling (42). In addition, ABC transporter inhibitor verapamil resensitized drug-resistant CSCs to gemcitabine in a dosedependent manner (41).

Accumulating evidence suggests that EMT is important in cancer progression conceivably through commencing stem cell properties to cancer cells (4,6,11). Several studies have reported that pancreatic CSCs also possess mesenchymal features (12-14,39,44-46). During the EMT, mesenchymal cells are characterized by decreased expression of epithelial marker E-cadherin and increased expression of genes that encode members of the Snail family of transcriptional repressors (8,39). Rasheed *et al.* (39) reported that the expression of CDH1 that encodes for E-cadherin and of SNAI2 that encodes for Slug was decreased up to 5-fold and increased up to 51-fold, respectively, in ALDH+ CSCs compared with unsorted tumor cells (39). Both Shah *et al.* (12) and Du *et al.* (14) reported that drug-resistant CSCs have decreased expression of E-cadherin and increased expression of vimentin, which are features of EMT. Transforming growth factor-β (TGF-β) is a regulator of many types of physiological and pathological EMT (11). When incubated in the presence of TGF-β, the side population (SP) cells, a CSC enriched fraction from PC cell line, changed their shape into mesenchymal-like appearance including spindle shaped assembly. This alteration was associated with significant reduction of E-cadherin expression level and induction of the expression of Snail and matrix metalloproteinase-2. When incubated in the absence of TGF-β, these cells restored epithelial-like appearance and the expression of E-cadherin. These results suggest that SP cells from PC possess superior potentials of phenotypic switch, i.e., EMT and mesenchymal-epithelial transition (MET) (44).

Reversal of EMT phenotype has been shown to restore drug sensitivity (5,46). Arumugam *et al.* (5) reported an inverse correlation between E-cadherin and Zeb-1, a transcriptional suppressor of E-cadherin, correlated closely with resistance to gemcitabine, 5-fluorouracil, and cisplatin. Silencing Zeb-1 in the mesenchymal PC lines not only increased the expression of E-cadherin but also restored drug sensitivity. They suggested that Zeb-1 and other regulators of EMT may maintain drug resistance in human PC cells (5). In another study, Li *et al.* (46) reported that the expression of several microRNAs (miRNA) including miR-200 were significantly down-regulated in gemcitabineresistant PC cells. Emerging evidence has demonstrated the critical role of miRNA in various biological and pathological processes including EMT. These cells showed EMT characteristics such as elongated fibroblastoid morphology, lower expression of E-cadherin, and higher expression of vimentin and Zeb-1. By restoring the expression of miR-200, the expression of Zeb-1, Slug, and vimentin was down-regulated in the drug-resistant cells. These cells also showed reversal of EMT phenotype leading to epithelial morphology and had increased sensitivity to gemcitabine (46).

In summary, the current available treatment for cancer may select for drug resistant CSCs. Pancreatic CSCs could acquire drug resistance through EMT. Strategies target CSCs and/or EMT could potentially overcome the drug resistance problem during chemotherapy.

EMT and PC progression

As mentioned previously (9,10), the presence of EMT in PC is often associated with undifferentiated

phenotype and overall poor survival compared to the tumors without EMT. EMT may not only induce drug resistance in CSCs but also increase tumorigenicity both in vitro and *in vivo*, migratory ability and invasiveness of PC cells (4,12-14,39,44,45). MUC1, a transmembrane mucin glycoprotein, has been shown to be associated with the most invasive forms of PC (47). Roy *et al.* (47) reported that overexpression of MUC1 in PC cells triggered the molecular process of EMT, which translated to increased invasiveness and metastasis. MUC1+ cells gained mesenchymal markers such as Slug, Snail and vimentin and lost E-cadherin expression. Furthermore, genes associated with metastasis and angiogenesis such as vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-2, 3, and 9 were significantly increased in MUC1+ cells (47). MMPs have been implicated in facilitating the invasion and metastasis of PC (48). Bone morphogenetic proteins (BMPs) was reported to be able to induce EMT in PC cells, which resulted in an increase in invasiveness of the cells, in part through increased expression and activity of MMP-2 (49). In another study, overexpression of Slug significantly increased invasion and metastasis of PC cells through upregulation and activation of MMP-9 (50).

EMT is a dynamic process and is triggered by stimuli coming from extracellular matrix microenvironment and many secreted soluble factors. Among the many signaling pathways involved in this process, Wnt, TGF-β, Hedgehog, Notch, and nuclear factor-κB (NF-κB) signaling pathways are critical for EMT induction (51). Gordon et al (52) reported that loss of type III TGF-β receptor expression increased motility and invasiveness associated with EMT during PC progression. Wang *et al.* (45) reported that Notch-2 and its ligand, Jagged-1, were highly upregulated in gemcitabine-resistant PC cells. The finding is consistent with the role of the Notch signaling pathway in the acquisition of EMT phenotype. Down-regulation of Notch signaling pathway not only decreased invasive behavior of the drug-resistant cells but also led to partial reversal of the EMT phenotype, resulting in the MET, which was associated with decreased expression of vimentin, Zeb-1, Slug, Snail, and NF-κB (45). Their findings therefore provide a direct evidence of the association between EMT and PC invasiveness. In a recent study, Haque *et al.* (53) reported that Cyr61/CCN1 signaling is critical for EMT and promotes pancreatic carcinogenesis. Cyr61 (cysteinerich 61) is a member of the CCN family of growth factors that includes CTGF, NOV, WISP-1, WISP-2 and WISP-3. Cyr61 is known to link cell surface and extracellular matrix and plays important roles on cell adhesion, proliferation, migration, differentiation, and angiogenesis during normal developmental and pathological processes (54). Cyr61 expression was detected in the early PC precursor lesions and its expression intensified with disease progression. Upon Cyr61 silencing, the aggressive behaviors of PC were reduced by obliterating interlinking events such as reversing EMT, blocking the expression of stem-cell-like traits and inhibiting migration. In contrast, addition of Cyr61 augmented EMT and stemness features in relatively less aggressive PC cells (53).

Taken together, PC with EMT features has more aggressive behaviors and is associated with poor patient survival. Multiple proteins and signaling pathways are involved in this process. Reversal of EMT phenotype could potentially reduce PC invasiveness and hence prevent metastasis.

Conclusion

Accumulating evidences suggest that EMT plays important roles in PC progression through several plausible mechanisms. PC cells may acquire stemness properties and become drug resistant during undergoing EMT. PC with EMT features is more aggressive and is associated with poor patient survival. Future strategies that specifically target against EMT phenotype could potentially reduce tumoral drug resistance and invasiveness and hence prolong the survival of patients with PC.

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Histamine regulation of pancreatitis and pancreatic cancer: a review of recent findings

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Abstract: The pancreas is a dynamic organ that performs a multitude of functions within the body. Diseases that target the pancreas, like pancreatitis and pancreatic cancer, are devastating and often fatal to the suffering patient. Histamine and histamine receptors (H1-H4HRs) have been found to play a critical role in biliary diseases. Accordingly, the biliary tract and the pancreas share similarities with regards to morphological, phenotypical and functional features and disease progression, studies related the role of H1-H4HRs in pancreatic diseases are important. In this review, we have highlighted the role that histamine, histidine decarboxylase (HDC), histamine receptors and mast cells (the main source of histamine in the body) play during both pancreatitis and pancreatic cancer. The objective of the review is to demonstrate that histamine and histamine signaling may be a potential therapeutic avenue towards treatment strategies for pancreatic diseases.

Keywords: Histamine; pancreas; pancreatitis; pancreatic cancer

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Introduction

Pancreas

The pancreas plays a key role in humans serving as both an endocrine and exocrine gland in the digestive system (1). The pancreas extends across the abdomen, and has an enlarged head region as well as a tail portion. Located behind the stomach and partially connected to the duodenum, the pancreas acts to aid in digestion as well as adjusting gastrointestinal hormone levels. The exocrine portion of the pancreas utilizes zymogens and bicarbonate in order to assist in digestion and neutralization, respectively (2). As to be expected, the endocrine pancreas aids in regulating hormone levels to allow for metabolic homeostasis.

Comprising part of the small intestinal tract, the pancreas is made up of different epithelial cell types, which have very specific functions. Various genes have been associated with the formation and regulation of the pancreas such as Sox 9, Neurog3, and Ptf1a (1). The exocrine region of the pancreas is composed of duct cells and acinar cells which function to produce zymogens (2). Duct cells deliver zymogens and bicarbonate for activation in the duodenum, and subsequently digestion of food (2). In the endocrine portion of the pancreas there are large collections of epithelial cells called islets of Langerhans (3). The islets of Langerhans contain several types of hormone-secreting cells including α, β, γ, ε, and pancreatic polypeptide-secreting cells (3). β cells have received much attention in research because these cells produce insulin, and are implicated various forms of diabetes (3). *Figure 1* depicts a cartoon schematic of the pancreas, pancreatic cells and surrounding organs (open

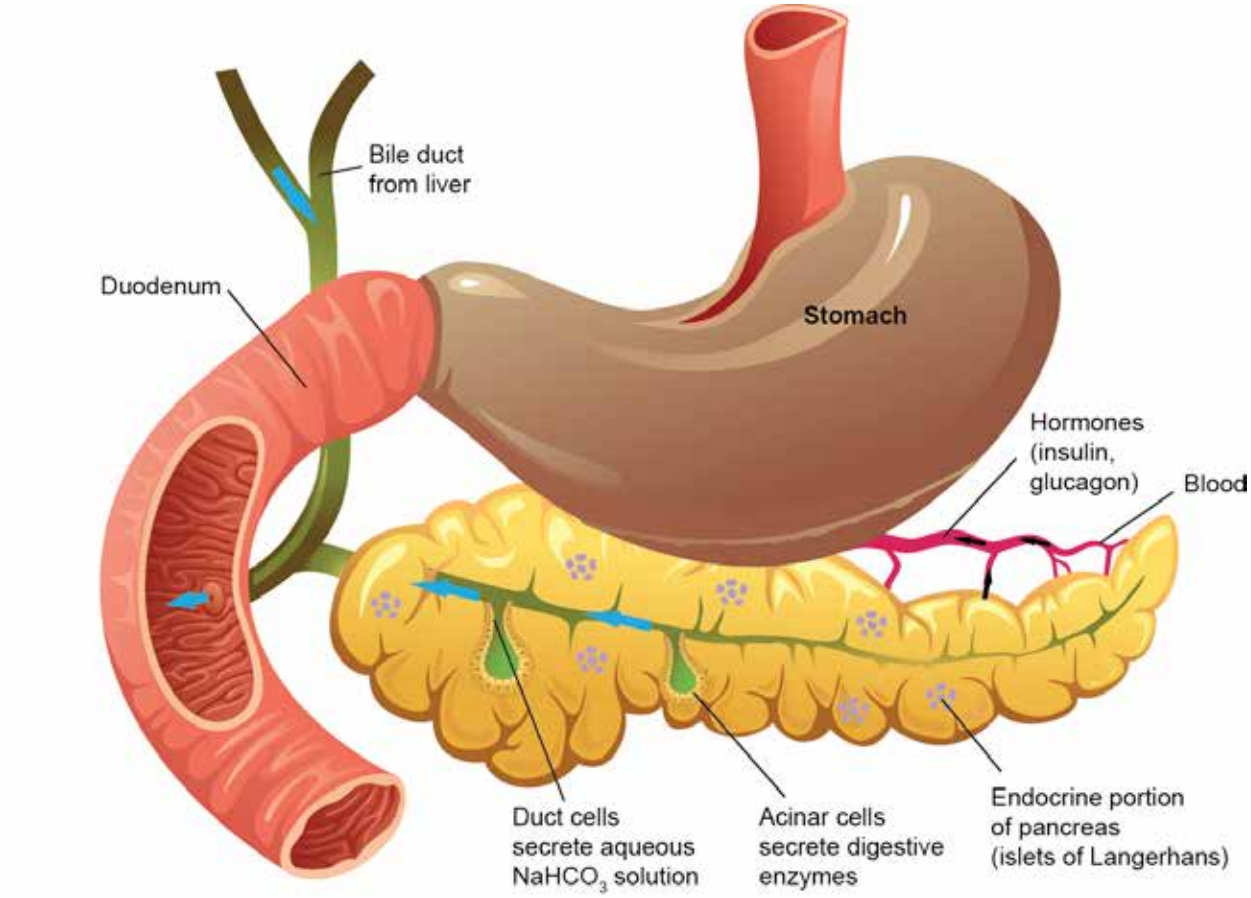

Figure 1 A cartoon depiction of the pancreas and surrounding organs (open access, no copyright).

access, no copyright).

Pancreatitis

There exist two divisions of pancreatitis: acute and chronic, with autoimmune pancreatitis falling under the chronic distinction (4). Pancreatitis can arise due to damage of the pancreas, infection, as a result of alcoholism and smoking or due to genetic mechanisms (2). Acute pancreatitis is diagnosed in 210,000 Americans every year, and can range from mild to lethal in severity, with 20% of cases resulting in death caused by necrotizing disease (5). The condition is caused by the pancreas using its own proteases to digest itself. It remains unknown whether or not trypsin and cholecystokinin are directly responsible for this autodigestive damage (6). Acute pancreatitis results in symptoms of epigastric pain, vomiting, and nausea, along with markedly increased amylase and lipase levels (6). To determine the prognosis, the systemic inflammatory response (SIRS) and the Bedside Index for Severity of Acute Pancreatitis (BISAP) tests are employed (5). Currently, there are not many treatments to combat the disease itself, but supportive treatments such as fluid resuscitation, and enteral feeding help to maintain health in the patient (5).

Chronic pancreatitis typically originates from acute pancreatitis although not all patients continue on to develop chronic pancreatitis. This recurrent form of pancreatitis is marked by fibrosis, loss of islet and acinar cells in the pancreas, and inflammation (7). Patients who develop acute pancreatitis by smoking or consuming alcohol are more likely to develop the chronic form of pancreatitis (7). Diagnosing chronic pancreatitis can be attained through various imaging tests (MRI, EUS, CT), and patients typically present with great abdominal pain similar to that of acute pancreatitis (7). Like acute pancreatitis, treating and managing chronic pancreatitis is very difficult; Many

times even after therapy, patients still retain symptoms (7). In order to manage chronic pancreatitis, abstinence from alcohol, pancreatic enzymes, analgesics, or sometimes narcotics and opioids are employed (7).

Autoimmune pancreatitis typically presents in middle-aged and elderly males, accompanied with obstructive jaundice, diabetes mellitus, and epigastric discomfort (8). Three criteria are used to diagnose autoimmune pancreatitis; Enlargement of the pancreas and narrowing of the main pancreatic duct, elevated levels of autoantibodies, and lymphoplasmacytic infiltration and fibrosis (8). Although rare, it has also been found that autoimmune pancreatitis can be misdiagnosed as, or found in conjunction with pancreatic cancer. These findings make it rather difficult for clinicians to determine the true diagnosis of the patient, so tests to differentiate the conditions must be used (4).

Pancreatic cancer

According to the American Cancer Society, in 2013, there will be 45,220 cases of pancreatic cancer diagnosed in US, with 38,460 dying of this devastating cancer (9). Pancreatic cancer remains one of the deadliest cancer types, with a five-year survival rate of about 5% (10). Pancreatic cancer is notorious for being asymptomatic, which then allows the disease a greater ability to metastasize to other organs before it is ever diagnosed. This particular type of cancer arises due to several factors, including environmental, genetic, and pathological causes (11). Specifically, a history of smoking, increased body mass index, family history of pancreatic cancer, alcoholism, pancreatitis, and diabetes mellitus are all factors, which increase the risk of obtaining pancreatic cancer (10). There are various forms of pancreatic cancer, which affect both the endocrine and exocrine pancreas systems. The most common cancerous tumor in the pancreas is invasive ductal adenocarcinoma, and typically retains the title of pancreatic cancer (11). Neuroendocrine tumors in the pancreas may also arise, but are much less prevalent (12). Neuroendocrine tumors result due to an excess in pancreatic hormone levels, and treatment must be established to correct the excess in that particular hormone, as well as possibly identifying the presence of an inherited disease that caused this excess (12). Currently, due to the asymptomatic nature of pancreatic cancer, early diagnosis remains a challenge. However, once the diagnosis is made, patients typically undergo various treatments such as chemotherapy, chemoradiotherapy, possibly surgical resection of the tumor, as well as other supportive therapies (4,9,10,12).

Histamine

The biogenic monoamine histamine is one of the most intensely studied molecules in the biological system (13). Histamine is known to induce broad spectrum of biological activities including cell proliferation, differentiation, regulation of gastrointestinal function, and modulation of immune responses (13). Histamine is a low molecular weight amine synthesized exclusively by L-HDC that is expressed in numerous cells throughout the body including gastric-mucosa, parietal, and mast cells (14). After histamine is formed by HDC it is rapidly stored or degraded (15).

Histamine exerts its biological effects by interacting with four G protein-coupled (GPCR) receptors, i.e., H1HR, H2HR, H3HR, and H4HR (15). Activating or inhibiting the HRs triggers downstream signaling pathways to elicit immune-modulatory and pro-inflammatory cellular responses (15). H1HRs main signal is induced by ligand binding and activation of phospholipase C-generating inositol 1, 4, 5-triphosphate and 1, 2-diacylglycerol (DAG) leading to increased cytosolic Ca^{2+} (13,16,17). The H2HR is coupled to adenylate cyclase and to phosphoinositide secondary messenger system via separate GTP-dependent mechanisms (18,19). Histamine is a strong stimulant of cAMP accumulation in many cells, and H2HR-dependent signaling of histamine is typically mediated through cAMP (18,19). In contrast, H3HR activation triggers inhibition of cAMP formation, accumulation of Ca^{2+} and stimulation of mitogen-activated protein kinase (MAPK) (20,21). H4HR is expressed in many areas of the body including intestinal tissue, basophils, and mast cells (13,22). Similar to H3HR, H4HR signaling mechanisms triggers an inhibition of adenylyl cyclase and downstream of cAMP response elements as well as activation of MAPK (22,23). *Figure 2* depicts the generally acknowledged signaling of the histamine/histamine receptor axis [used with permission from Shahid, *et al.*, "Histamine, Histamine Receptors, and Their Role in Immunomodulation: An Updated Systematic Review" *The Open Immunology Journal*, *2009;2:9-41 (open access journal)*].

The role of histamine during biliary damage and biliary cancer has been extensively studied (14,15,17,18,20,21,23). Because the biliary tract and pancreas share similar pathological, phenotypical and biological features (24) it is likely that histamine, the histamine receptors and the synthesis of histamine by HDC are all important in

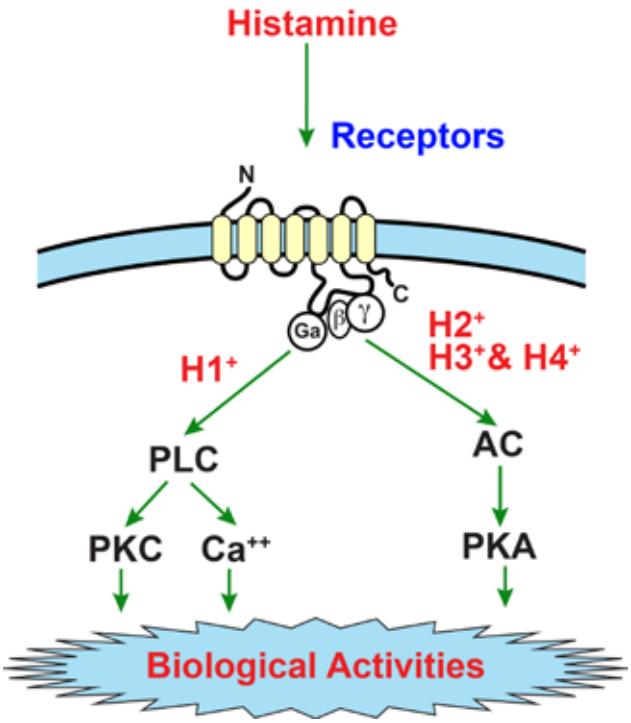

Figure 2 The classical binding sites of histamine and their main signaling pathways such as AC (adenylate cyclase/cyclic AMP), PKC (protein kinase C), PKA (protein kinase A), PLC (phospholipase C), H1+ or H2+ (stimulation via H1 or H2 receptor), H3- & H4- (inhibition via H3 and H4 receptors). Used with permission from Shahid *et al.*, "Histamine, Histamine Receptors, and Their Role in Immunomodulation: An Updated Systematic Review" *The Open Immunology Journal, 2009;2:9-41 (open access journal).*

the regulation of pancreatic diseases like pancreatitis and pancreatic carcinoma.

Histamine and pancreatitis

As stated above, while most cases of acute pancreatitis are non-progressive, recurrent episodes may lead to chronic pancreatitis, which is also a very challenging disease (25). As the pathophysiological causes of acute and chronic pancreatitis gradually become revealed to us, it is hopeful that their treatments will become more successful. However, the biological basis of pain and the mechanisms underlying the pathogenesis of acute and chronic pancreatitis is still poorly understood (26-28). Recent findings indicate that the activation of granulocytes and macrophages in pancreatitis results in the release of a number of cytokines and inflammatory mediators and an important inflammatory mediator, the mast cell, secretes histamine as well as other chemotactic molecules and inflammation activators (29-31). Mast cells have been implicated in the pathogenesis of pain in other conditions and some have hypothesized that mast cells and histamine secretion play a role in the pain of chronic pancreatitis, which is characterized by mononuclear inflammatory cell infiltration (27,32-34). Interestingly, it has been shown that humans with painful chronic pancreatitis have an increased number of pancreatic mast cells compared to those with painless chronic pancreatitis (27).

Because histamine is produced predominantly by mast cells, it is important to consider studies involving mast cell activation and pancreatitis to analyze the resultant effects of histamine during the course of this threatening disease. It has also been argued that increased circulating histamine levels worsen distant organ injury, especially if derived from pancreatic mast cells in cases of acute and chronic pancreatitis (28,35,36). In an attempt to study the activation of pancreatic mast cells and the effects of mast cell inhibition on the activation of peritoneal and alveolar macrophages during acute pancreatitis, a recent study suggested that pancreatic mast cells are significant triggers of local and SIRS in the early phases of acute pancreatitis (37). These authors confirmed that pancreatitis resulted in increased levels of circulating histamine in plasma in both the pancreas and lung. The inhibition of mast cell degranulation with cromolyn sodium also resulted in a reduction in pancreatic myeloperoxidase (MPO) activity, indicating that this treatment reduced pancreatic inflammation (37). Several mediators released by mast cells, including histamine are increased shortly after (a few minutes) the induction of pancreatitis in their experimental models. In addition to this, administration of mast cell inhibitors results in a reduction of the local and SIRS and prevents changes in endothelial cells and vascular permeability (37). As histamine has been confirmed to be a potent vasodilator, histamine may possibly be an important factor to study in increased vascular permeability in pancreatic inflammation (28,38). There is a very large population of mast cells that resides in the periacinar space, pancreatic interstitium and mesentery and these mast cells degranulate early in acute pancreatitis (39). In three models of necrotizing disease, local increases were noted of mast-cell mediators, histamine being one of them (39). In addition, water immersion-induced stress was shown to result in the conversion of hyperstimulation mild pancreatitis into necrohaemorrhagic disease, similarly to when histamine or dimethyl PGE2 were added in a duct

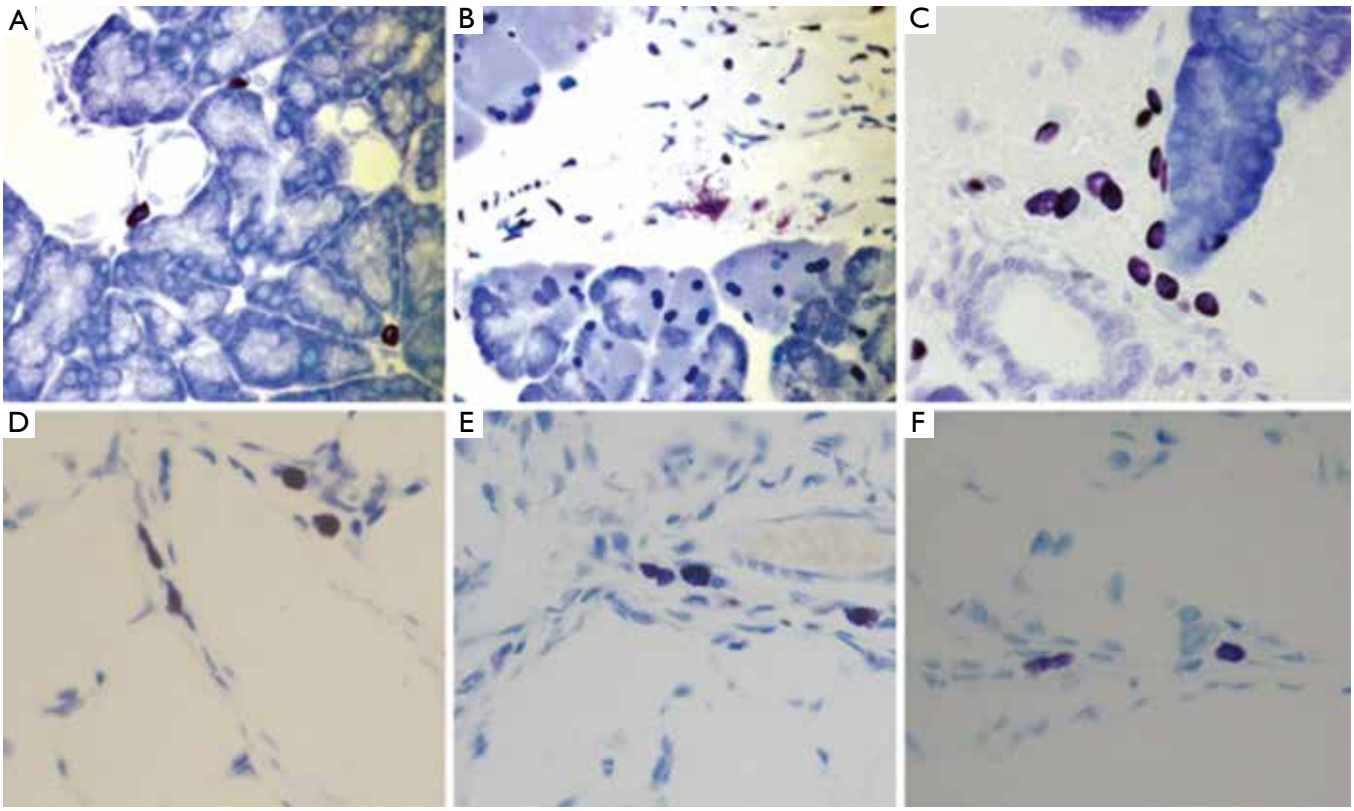

Figure 3 Immunohistochemistry for mast cells (marked by toluidine blue, 40×) in the pancreas (A-C) and lung (D-F) after induction of pancreatitis (B and E) and after cromolyn treatment (C and F). Degranulating mast cells were observed in the pancreas after pancreatitis induction (B) and cromolyn treatment inhibited mast cell degranulation (Used with permission from *World Journal of Gastroenterology* "Pancreatic and pulmonary mast cells activation during experimental acute pancreatitis" 2010;16:3411-7).

hyperpermeability model of mild pancreatitis (40). A similar pattern of increase in plasma histamine has been recorded in pancreatitis models upon exposure to water immersion stress (40,41). As acute pancreatitis can be fatal when it advances to systemic inflammation and multi-organ failure, Kempuraj *et al.*, desired to study a mouse model of pancreatic duct ligation-induced acute pancreatitis that is associated with systemic inflammation and substantial mortality (28). These authors found using an Enzyme-Linked Immunosorbant Assay (ELISA) for *in vivo* mouse duct ligation-induced acute pancreatitis models, plasma histamine concentrations were increased. In concurrence with these findings, it has also been speculated that increased circulating histamine levels originating from activated pancreatic mast cells are implicated in the development of acute lung injury during acute pancreatitis (28,35,36). Zhao *et al.*, demonstrates that pancreatitis-associated lung injury is an early-occurring and severe complication that involves a number of inflammatory cells and their products in the initiation and progress of the condition (36). While higher plasma levels of histamine were determined, the intraperitoneal administration of cromolyn (a mast cell stabilizer) reduced pancreatitis-induced systemic increase of histamine after one hour. Cromolyn was also found to prevent pancreatitis-induced pulmonary endothelial barrier dysfunction after 6 hours (36). The authors hypothesize that mast cells and histamine may play an important role in the activation of leukocytes during the initiation of pancreatitis-associated lung injury by altering phenotypes of adhesion molecules (36). *Figure 3* shows immunohistochemistry for mast cells (marked by toluidine blue) in the pancreas and lung after induction of pancreatitis (B and E) and after cromolyn treatment (C and F). Degranulating mast cells were observed in the pancreas after pancreatitis induction (B) and cromolyn treatment inhibited mast cell degranulation (Reused with permission from *World Journal of Gastroenterology* "Pancreatic and pulmonary mast cells activation during experimental acute pancreatitis" 2010;16:3411-7).

In clinical trials, controlling histamine levels by way of receptor inhibition or mast cell stabilization has yielded mixed results. In a retrospective analysis of pancreatic exocrine insufficiency (PEI), Sander-Struckmeier *et al.*, aimed to determine whether the efficacy of pancrealipase/pancreatin may be affected by the concomitant use of proton pump inhibitors (PPIs)/histamine-2 receptor antagonists (H2RAs) (42). PEI, which is a deficiency or absence of digestive enzyme secretion in the duodenum, is associated with many pancreatic disorders such as cystic fibrosis and chronic pancreatitis. Analyzed data from a number of clinical trials in patients having PEI indicates that the efficacy of pancrelipase/pancreatin is not affected by concomitant PPI/H2RA use and concurs with the treatment guidelines' recommendation that acid suppression is not routinely mandated with pancreatic enzyme replacement therapy (42). Early administration of protease inhibitors has commonly been employed for the therapy of acute pancreatitis in Japan. Kohsaki *et al.*, state that a number of clinical trials have failed to show the clinical effects of protease inhibitors and H2 receptor antagonist during the treatment of acute pancreatitis and these authors argue that well-organized clinical studies should be undertaken to assess the relative therapeutic value of these agents for acute pancreatitis (43). However, according to Abdel Aziz *et al.*, non-enteric-coated enzyme preparations along with acid suppression (histamine-2 blockers or PPIs) have at least a modest effectiveness in treating pain caused by chronic pancreatitis and may be worth a trial in patients with less advanced disease diagnosis (44). Clearly, more work needs to be performed to fully understand the role of histamine and histamine receptors (H1-H4HRs) on the treatment strategies of pancreatitis.

Histamine and pancreatic cancers

Pancreatic cancer is the leading cause of cancer-related deaths worldwide due to its aggressive nature (45). For this reason, it is of great importance that we ascertain the interrelations of pancreatic cancer and discover new therapeutics to help combat this devastating disease. HDC, which converts histidine to histamine, has been an important area of study recently due to histamine's known ability to accelerate cancerous cells into cell cycle arrest (45). In normal pancreatic islet cells, HDC is predominantly found in glucagon cells, but in pancreatic tumors, HDC was found in all types of islet cells: glucagon-, insulin-, somatostatin-, pancreatic polypeptide- and serotonin-producing enterochromaffin cells (46). Over expression of HDC has been demonstrated in various pancreatic cancer cells, but one study found that 79% (19/24) of the evaluated pancreatic tumors showed HDC expression (46,47). Based on this study, we can define HDC as an indicator of endocrine differentiation and, therefore, a potential diagnostic tool in pancreatic cancer (46).

Various other studies have been performed to evaluate how histamine carries out cellular proliferation via its G-protein coupled histamine receptors (H1-H4HR). Previous research performed on the PANC-1 cell line, which is derived from human pancreatic carcinoma and contains a mutated $_{p}53$, demonstrated that these cells over express H1HR and H2HR (45). These PANC-1 cells can also secrete histamine into the extracellular medium where it can act as an autocrine or paracrine growth factor to regulate cellular proliferation through the binding of H1 and H2 histamine receptors (45,48). When bound to H1HR, histamine has been shown to induce PANC-1 proliferation by up regulating nerve growth factor (NGF) secretion and mRNA expression (49). These effects can be negated by pyrilamine, the H1HR antagonist, which further proves the increased proliferative effect of histamine (49). Histamine or an agonist binding to H1HR has also proven to influence PANC-1 cells into metastasis due to a decrease in cellular adhesion; which is associated with an increase in matrix metalloprotease 2 (MMP2) activity (48,50). In contrast, when H1HR and H2HR were blocked using specific receptor antagonists there was an increase in adhesion and, therefore, a decrease in cellular motility (48). Activation of H2HR in PANC-1 cells tends to have the opposite effect of H1HR activation. A study by Cricco *et al.*, states that H2HR activation, through the binding of histamine, generates partial cellular differentiation of the PANC-1 cell line and stimulates cAMP production to inhibit proliferation (45). Bcl-2, an anti-apoptotic regulator protein, may be involved in this regulation of cAMP (45). This H2HR activation also inhibited PANC-1 cell growth by moving the cells into G_0/G_1 phase arrest (45). Furthermore, the expression of proliferating cell nuclear antigen (PCNA) and Bax, a pro-apoptotic factor, were decreased through H2HR modulation (45,51). Additional research done on the various histamine receptors has proven that H3HR stimulation increases cellular proliferation by regulating the cell cycle, but that H4HR stimulation diminishes pancreatic tumor growth (52,53). The pathological and biological functions of H3HR and H4HR activation

in pancreatic tumors are vague and require further investigation in order to be clearly defined.

Currently, mast cells have been of great interest in the studies of pancreatic cancer as well (54). Mast cells are ubiquitous and found throughout all tissues of the human body and contain many cytoplasmic granules that, when stimulated, are able to release considerable quantities of histamine into the surrounding microenvironment (54). Mast cells have other roles, but their release of histamine is what draws them into the interest of this review. In general, mast cell infiltration is increased in cases of pancreatic cancer when compared to normal pancreatic tissue (55). This same study demonstrated how PANC-1 cells, when in the presence of mast cell conditioned media, were accompanied with an influx of mast cells; Which leads to increased pancreatic cancer cell migration, proliferation, and invasion (55). Conversely, this infiltration did not have an effect on normal pancreatic tissues (55). This increase in mast cell number can be an indicator of higher-grade pancreatic adenocarcinoma and, therefore, can be correlated with poorer prognosis for the patient (54,55). The exact pathological and physiological role of mast cells and histamine secretion in pancreatic carcinoma is unclear and requires further research.

Clinical studies in pancreatic cancer

Currently, 5-6% of pancreatic cancer patients with non-resectable disease have an estimated survival rate of 5-year, but chemotherapy resistant patients have a median survival time of <6 months (56,57). Due to its poor prognosis and aggressive nature pancreatic cancer has prompted many research facilities to perform clinical trials to help determine a productive treatment method for this disease. For the past 10-15 years the main form of chemotherapy treatment for advanced and metastatic cancer was the use of gemcitabine, an anti-metabolite (56). Generally, gemcitabine is a favorable treatment in patients that have a poor performance status (56). Five recent clinical trials tested the efficacy of gemcitabine by administering it to different sets of patients; four trials administered it as a fixed dose rate of 10 mg/m^2/min, while one trial administered it as a standard infusion rate over 30 minutes (56,58-61). The data from all five of these trials gave a median response rate (RR) of 23%, a median progression-free survival (PFS) of 4 months, and an overall survival (OS) of 6 months (56).

Research has suggested that there may be a survival benefit in first-line treatment when erlotinib, a tyrosine kinase inhibitor, is combined with gemcitabine (56,62). One trial treated patients in a 1:1 ratio with either a combination of erlotinib and gemcitabine or gemcitabine together with a placebo (62). The results from this study concluded that OS was significantly prolonged with the erlotinib/gemcitabine treatment compared to gemcitabine with the placebo (6.24 *vs.* 5.91 months, respectively) (62). Overall first-year survival was also greater with the combined treatment (23% *vs.* 17%), but there tended to be more adverse side effects with the combined treatment (erlotinib and gemcitabine) when compared to gemcitabine with the placebo (62).

Other studies have suggested the use of gemcitabine in conjunction with platinum agents as a potential treatment in the first-line setting of advanced pancreatic cancer (56,63-65). When analyzing the results from gemcitabine with platinum agents there tended to be an improvement in RR and PFS (P=0.006 and 0.059, respectively), but no significant improvement in OS (P=0.1) when compared to other methods of treatment (56). Gemcitabine is not the only compound that has been suggested to be used with platinum agents. Some research has suggested the use of the pyrimidine analog, 5-fluoruracil (5-FU) with platinum agents as well (56). Recently, 8 trials studied the effectiveness of 5-FU with oxiplatin, a platinum based alkylating agent, and 2 trials tested 5-FU with cisplatin, a platinum containing drug that cross-links DNA (56,62,66-72). When analyzing the data from these 8 clinical trials, the 5-FU combined with a platinum agent had a median PFS of 2.9 months and a median OS of 5.7 months (56,62,66-72). When compared to the treatments stated earlier, it seems as if the combination of 5-FU with platinum containing agents is less efficient in terms of survival benefit (56).

Future studies and concluding statement

Throughout this article we have aimed to highlight the characteristics of pancreatitis, pancreatic cancer, and histamine's role in the progression and development of these diseases. When viewing current literature that discusses the involvement of histamine in various forms of pancreatitis we can see that histamine and mast cell secretion tightly regulate inflammation, which can ultimately lead to endothelial cell destruction. Being able to block this pro-inflammatory signaling pathway via mast cell degranulation inhibition may decrease the damaging effects that histamine is able to enact on the pancreas. Histamine has also been labeled as a vasodilator in pancreatitis, but its

exact function in this area requires further investigation. In terms of clinical trials, some work on the treatment of acute pancreatitis using protease inhibitors and an H2 receptor antagonist were ineffective in terms of prevention and replacement therapy, but were successful in relieving pain in early developed acute pancreatitis. Clinical trials on histamine influence in pancreatitis are few and far between and thus require additional studies. Histamine's regulation of pancreatic cancer is more convoluted and confusing than it is in pancreatitis in general. When working through its H1HR and H3HR receptors histamine has demonstrated pro-proliferative and metastatic abilities in the PANC-1 cell line, but when bound to H2HR or H4HR histamine has proven to be anti-proliferative through G_0/G_1 cell cycle arrest, the diminishment of tumor growth, and generation of partial cellular differentiation. Recent clinical trials on pancreatic cancer have been valuable in terms of generating treatment options that successfully help to prolong life, but no current trials have been performed with histamine-, mast cell-, or histamine receptor-related therapies. For this reason, clinical studies on the manipulation of histamine through various signaling molecules, such as mast cells, HDC, and H1-H4HR, need to be developed to help determine if this area of study could be beneficial to the lives of future patients. The future of histamine in prevention, diagnosis and therapy of pancreatic diseases is unknown and open to evaluation and experimentation.

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Imaging preoperatively for pancreatic adenocarcinoma

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Abstract: Pancreatic cancer is a highly lethal malignancy which is increasing in incidence and mortality. The fourth leading cause of cancer death in the U.S., pancreatic cancer is projected to become the second leading cause of cancer death by 2020. Patients with pancreatic cancer have an abysmal 5-year survival of 6%, and 90% of these patients eventually die from the disease. This is in large part due to the commonly advanced stage of disease at the time of diagnosis. Currently, the only potentially curative therapy for pancreatic carcinoma is complete surgical resection. Patients who undergo incomplete resection with residual disease have similar survival rates to those patients with metastatic disease and should be spared this relatively morbid surgery. Thus, the key to impacting prognosis is the detection of smaller and earlier stage lesions, and the key to optimal management is accurately determining which patients have potentially resectable surgery and which patients would not benefit from surgery. Cross-sectional imaging plays an essential role in both the diagnosis and appropriate staging of pancreatic carcinoma. The diagnosis and staging of pancreatic adenocarcinoma is performed with cross-sectional imaging. Multi-detector computed tomography (MDCT) is the most commonly used, best-validated imaging modality for the diagnosis and staging of pancreatic cancer. Modern contrast-enhanced magnetic resonance imaging (MRI) has been demonstrated to be equivalent to MDCT in detection and staging of pancreatic cancer. Endoscopic ultrasound (EUS) is very sensitive for detecting pancreatic masses; however, due to limitations in adequate overall abdominal staging, it is generally used in addition to or after MDCT. Transabdominal ultrasound and positron emission tomography/computed tomography (PET/CT) have limited roles in the diagnosis and staging of pancreatic cancer. Preoperative imaging is used to characterize patients as having resectable disease, borderline resectable disease, locally advanced disease (unresectable) and metastatic disease (unresectable). As the definitions of borderline resectable and unresectable may vary from institution to institution and within institutions, it is essential to accurately assess and describe the factors relevant to staging including: local extent of tumor, vascular involvement, lymph node involvement and distant metastatic disease. To facilitate this, standardized reporting templates for pancreatic ductal adenocarcinoma have been created and published. Structured reporting for pancreatic cancer has been reported to provide superior evaluation of pancreatic cancer, facilitate surgical planning, and increase surgeons' confidence about tumor resectability.

Keywords: Pancreatic cancer; staging; multi-detector computed tomography (MDCT); magnetic resonance imaging (MRI)

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Introduction

Pancreatic cancer is a highly lethal malignancy which is increasing in incidence and mortality (1,2). Pancreatic adenocarcinoma, the most aggressive form, accounts for 85-95% of all pancreatic malignancies (3). It is estimated that there will be 46,420 new cases of pancreatic cancer diagnosed and 39,590 deaths from pancreatic cancer in the U.S. in 2014 (4). Approximately 90% of patients diagnosed with pancreatic cancer eventually die from the disease (5). Currently, pancreatic cancer is the fourth leading cause of cancer death

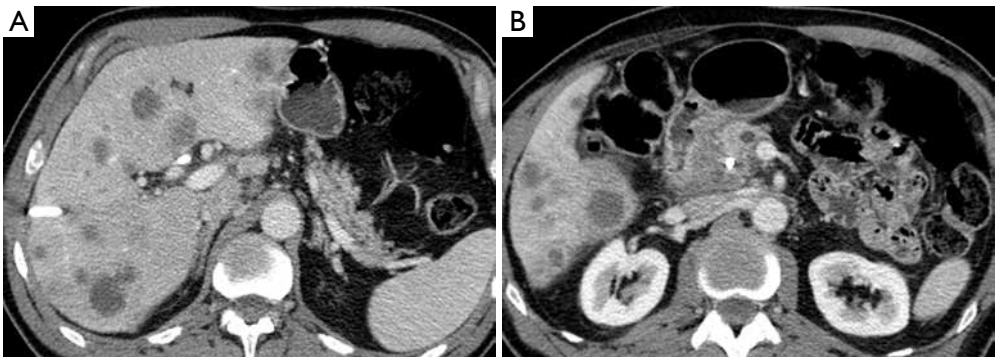

Figure 1 A 58-year-old man with stage IV pancreatic adenocarcinoma at presentation. (A) Portal venous phase 5 mm axial MDCT image through the pancreatic body and tail reveals slight dilation of the main pancreatic duct and numerous liver metastases; (B) at a more caudal level, the hypovascular mass in the right aspect of the uncinate process and additional hepatic metastases are noted, note the high density plastic biliary stent and the moderately dilated main pancreatic duct (both seen in cross section). MDCT, multi-detector computed tomography.

in the U.S.; however, it is projected to become the second leading cause of cancer death in the U.S. by 2020 (2).

Survival with pancreatic cancer is dismal with only a 6% 5-year survival (2). This is in large part due to the commonly advanced stage of disease at the time of diagnosis (*Figure 1*). The most common presenting symptoms of pancreatic cancer (i.e., abdominal pain, weight loss, anorexia and asthenia) are nonspecific and no effective screening tool to detect early asymptomatic patients is available (6).

Currently, the only potentially curative therapy for pancreatic carcinoma is complete surgical resection. However, this therapy is limited to patients whose tumors can be resected with negative pathologic margins (R0 resection) and do not have metastatic disease. Unfortunately, 53% of patients have distant metastatic disease at the time of diagnosis and only 15-20% of patients have potentially resectable disease at the time of diagnosis (2,7). Of those patients deemed resectable prior to surgery, 14-30% of these patients are found to be unresectable at the time of surgery (8,9). Patients who undergo incomplete resection with residual microscopic (R1) or macroscopic (R2) disease have similar survival rates to those patients with metastatic disease and should be spared this relatively morbid surgery (10). Thus, the key to optimal management is accurately determining which patients have potentially resectable surgery and which patients would not benefit from surgery. Cross-sectional imaging plays an essential role in both diagnosing and appropriately staging pancreatic carcinoma (11).

Initial diagnosis

The diagnosis of a solid pancreatic mass is made with cross-sectional imaging modalities including, transabdominal ultrasound, endoscopic ultrasound (EUS), multi-detector computed tomography (MDCT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT).

Ultrasound

Transabdominal ultrasound

The initial workup of typical symptoms of pancreatic cancer, including upper abdominal pain and jaundice, often starts with transabdominal ultrasound. While ultrasound is readily available, inexpensive, and does not use ionizing radiation, it is not an ideal screening tool for detection of pancreatic masses due to its relatively low sensitivity (11,12). This is in part due to high operator dependence as the sensitivity for detection of pancreatic masses has been reported from 67-90% (13). The pancreas in often not well visualized in obese patients and can be significantly obscured by shadowing bowel gas in both obese and non-obese patients. When pancreatic adenocarcinoma is identified via ultrasound, it is typically a hypoechoic hypovascular mass (*Figure 2*) with irregular margins. In the absence of a discrete visualized mass, secondary signs of pancreatic cancer including pancreatic duct (PD) dilatation (>2-3 mm) and contour abnormalities can be seen, suggestive of an underlying mass, thus warranting further investigation.

Endoscopic ultrasound (EUS)

EUS is the dominant endoscopic technique used for the diagnosis and evaluation of pancreatic masses (12). High resolution imaging of the pancreas can be achieved by

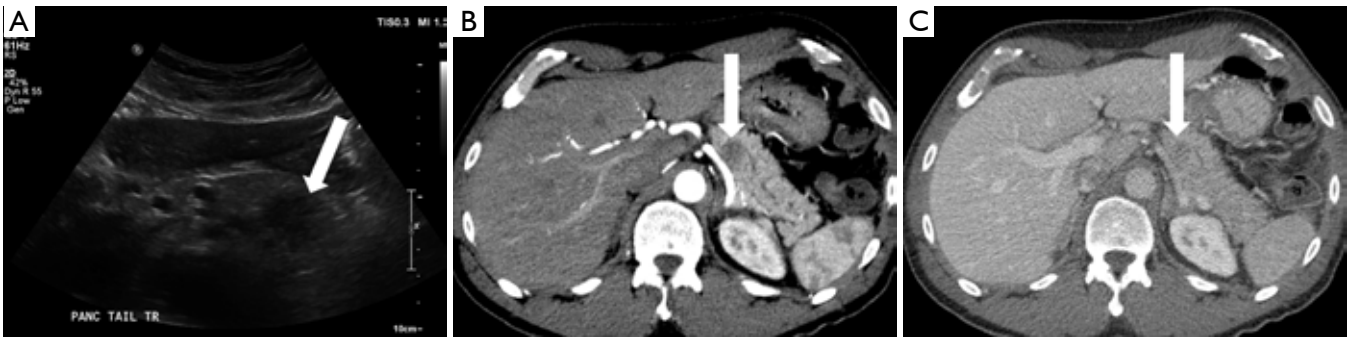

Figure 2 A 50-year-old man who underwent abdominal sonography for abdominal pain. (A) Transabdominal sonographic transverse image through the pancreatic body and tail in the upper abdomen shows a poorly marginated hypoechoic lesion (arrow); same patient, multiphasic MDCT the next week demonstrates that the small mass in the posterior pancreatic body and the upstream main pancreatic duct are much better seen on the pancreatic parenchymal phase 2.5 mm axial image (arrow on B) acquired at 35 s after the initiation of IV contrast medium compared to the portal venous phase image (arrow on C) acquired at 70 s. MDCT, multi-detector computed tomography.

placing a high frequency probe in close proximity to the pancreas (14). EUS is highly sensitive for the detection of pancreatic masses (sensitivities reported as high as 93-100%) and has a negative predictive value approaching 100%, particularly when used in conjunction with fine needle aspiration (FNA) (13). EUS is useful for the detection of small masses (<2-3 cm) which may be occult on other imaging modalities and for patients with indeterminate findings on prior imaging (15-17). The National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma state that patients who do not have a pancreatic mass visualized on cross-sectional imaging should undergo further evaluation with EUS and/or endoscopic retrograde cholangiopancreatography (ERCP) as clinically indicated (18). Another advantage of EUS is that pancreatic masses can be detected and characterized without the use of intravenous contrast, which is of particular use for patients with renal dysfunction or other contraindications to intravenous contrast. The typical appearance of pancreatic adenocarcinoma with EUS is a heterogeneous hypoechoic solid mass with irregular borders; however, this appearance is not specific for adenocarcinoma.

EUS is an invasive procedure; however, it is generally safe, and has reported procedural complication rates as low as 1.1-3% (19). The most commonly reported complications are bleeding (1-4%), pancreatitis (1-2%), perforation (0.03%) and tumor seeding of the biopsy tract (20). Peritoneal tumor seeding with EUS-FNA is a rare complication and occurs less frequently with EUS-FNA than with percutaneous biopsy (21). The major limitation of EUS that impacts patient care and management decision making is the inability to stage disease beyond the pancreas, thus it is generally used in addition to or after MDCT.

Multi-detector computed tomography (MDCT)

MDCT is widely available and the most commonly used, best-validated imaging modality for the evaluation of a patient with a suspected pancreatic mass (11,18). The reported sensitivity of MDCT for the detection of pancreatic adenocarcinoma is as high as 89-97% (22). The sensitivity for detecting small masses (≤1.5 cm) is lower and has been reported to be 67% (23). The typical appearance of pancreatic adenocarcinoma on MDCT is an ill-defined mass which is hypoenhancing relative to the avidly-enhancing non-tumoral pancreatic parenchyma (*Figure 3*). Eleven to twenty-seven percent of adenocarcinomas are isoenhancing to the pancreatic parenchyma and are occult on CT, particularly when small (24-26). In these cases, secondary signs of a pancreatic mass such as abrupt cutoff of the PD with upstream dilatation (*Figure 4*), mass effect, and contour abnormality may be present (27). Approximately 10% of pancreatic adenocarcinomas do not appear as a focal mass but as diffuse gland enlargement/involvement (28).

Pancreas CT protocols can vary somewhat from institution to institution but typically are multiphasic with thin-section imaging (≤3 mm) and with multi-planar reconstructed (MPR) images (coronal and/or sagittal planes). Post-contrast imaging must include the pancreatic parenchymal phase which is a late arterial phase acquired after a delay of 35-50 s and a portal venous phase which is acquired after a delay of 60-90 s (29,30). The pancreatic parenchymal phase is

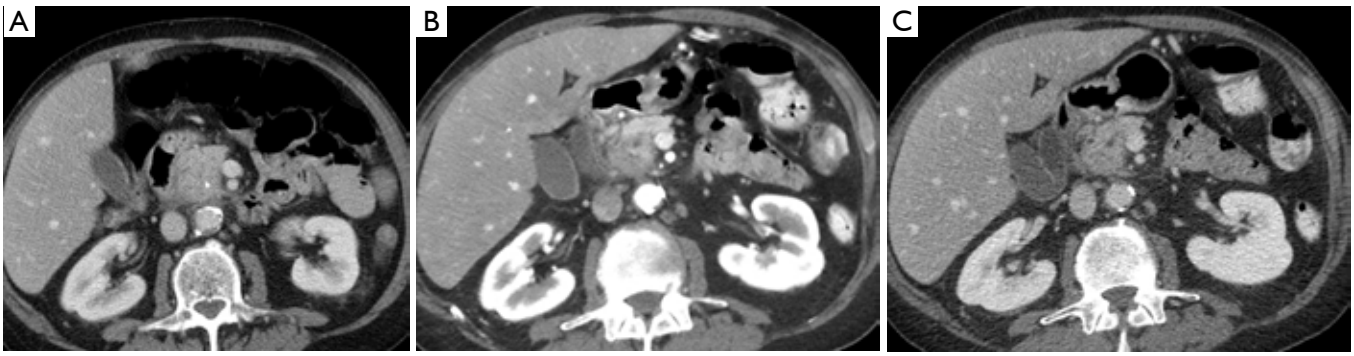

Figure 3 A 60-year-old man who presented to the emergency department with nausea and abdominal pain was found to have possible pancreatic head mass. (A) Portal venous phase 5 mm axial image demonstrates fullness in the pancreatic head, but a mass is not clearly discernable. A multiphasic MDCT examination was performed specifically to evaluate potential pancreatic mass; (B) pancreatic parenchymal phase 2.5 mm axial image better demonstrate the margins of the hypovascular mass in the posterior head region compared to either the initial emergency department CT or (C) the 5 mm portal venous phase image obtained as part of the multiphasic pancreatic scan. MDCT, multi-detector computed tomography.

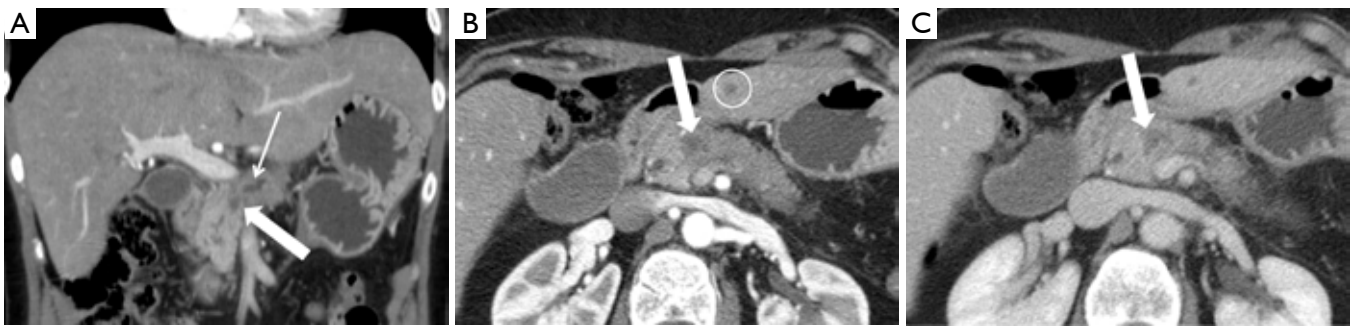

Figure 4 A 63-year-old woman with small pancreatic adenocarcinoma and upstream main pancreatic duct dilation. (A) Coronal reformatted 3 mm MDCT portal venous phase image demonstrates the dilated main pancreatic duct (small arrow) leading in to the 1.0 cm ductal adenocarcinoma (large arrow) in the pancreatic neck region. Note the slightly diminished enhancement of the gland in the body and tail region; the tiny tumor is better depicted on the pancreatic parenchymal phase 2.5 mm axial image (B); compared to the portal venous phase image (C) and appears resectable from a vascular standpoint; however, there is a small metastasis present in the lateral segment of the left lobe of the liver (circle on B). MDCT, multi-detector computed tomography.

timed for peak parenchymal enhancement to maximize the difference in enhancement of the hypoenhancing adenocarcinoma and background pancreas in order to increase conspicuity of the mass (31,32) (*Figure 2*). This phase allows for adequate evaluation for the relationship of the mass with adjacent arterial structures which is essential for staging (31,32). The portal venous phase of imaging provides optimal evaluation for involvement of adjacent veins (mesenteric, portal and splenic) and for the presence of metastatic disease, particularly in the liver (30). However, despite optimal imaging, small metastatic lesions in the liver can be missed on CT resulting in unresectable disease being found at surgery (33).

MPR images are typically included in a pancreas protocol CT as they have been shown to improve evaluation of local extension of tumor and evaluation for vascular involvement (34,35). Curved planar reformatted (CPR) images (*Figure 5*) are also often included as they have been shown to increase lesion detection and improve evaluation of vascular involvement (36,37).

Dual-energy CT (DECT) (*Figure 6*) is a novel imaging method which utilizes X-ray beams at two different energy levels to increase image contrast on intravenous contrast-enhanced CT images. This is possible because the viewing energies can approach the K-edge of iodine, and the differences in Hounsfield units (HU—CT measure of

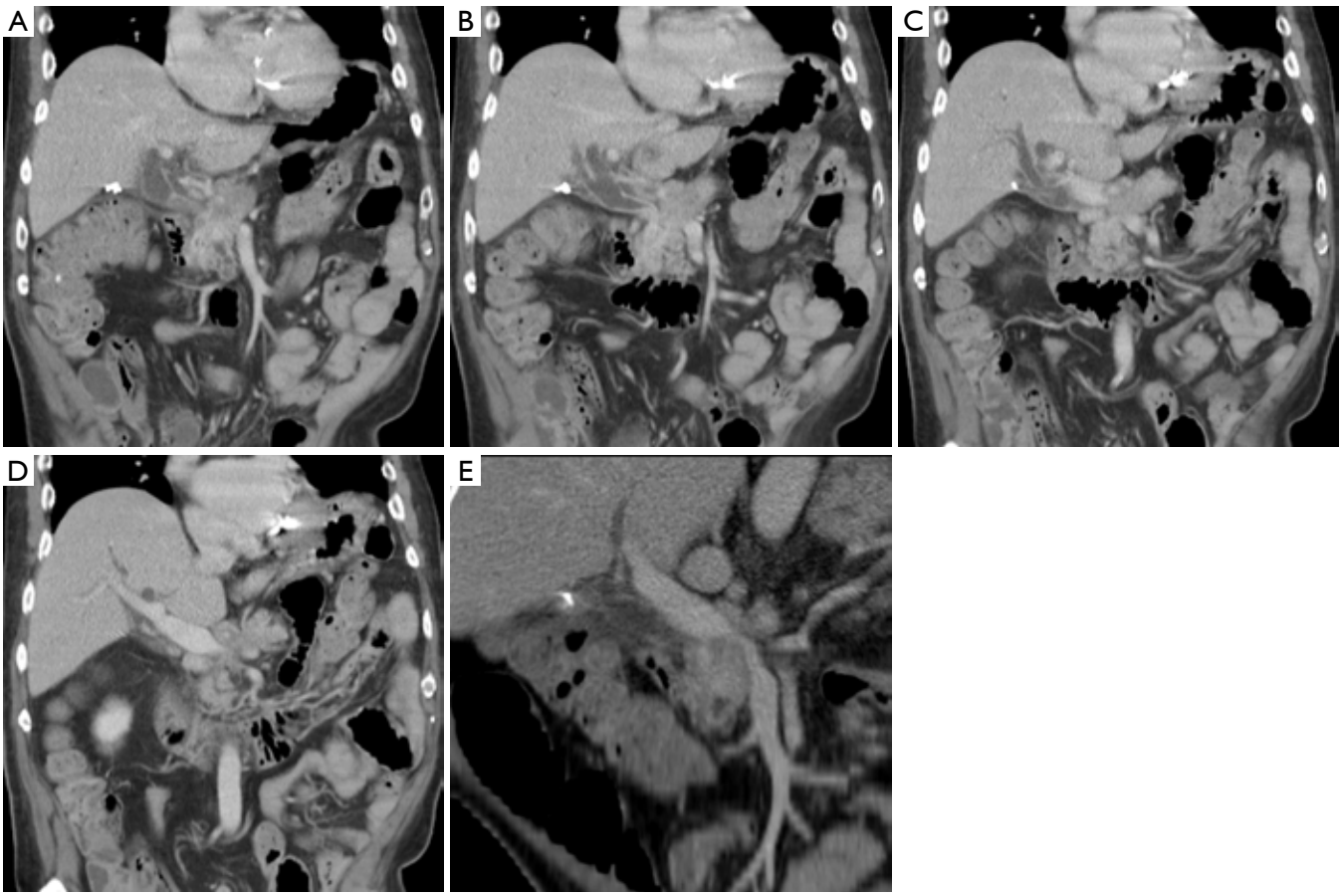

Figure 5 A 69-year-old man with a narrowed superior mesenteric vein. (A-D) Successive coronal reformatted images progressing from anterior to posterior demonstrate narrowing of the portal confluence by the hypovascular pancreatic adenocarcinoma in the superior head region, much better depicted, particularly from the standpoint of length of vein involved, on the curved multiplanar reformatted image (E). The axis of this image is aligned with the long axis of the portal vein.

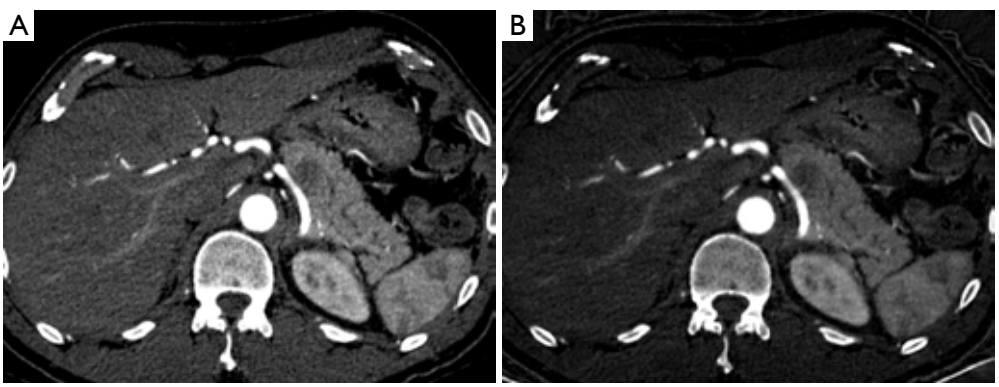

Figure 6 Dual energy MDCT in a 50-year-old man with a small resectable pancreatic ductal adenocarcinoma in the body region (same patient as *Figure 2*). (A) Low viewing energy (52 keV) axial 2.5 mm image and (B) iodine material density 2.5 mm image demonstrate increased conspicuity of the lesion and its relationship to the adjacent splenic artery (compare to *Figure 2B* and *2C*). MDCT, multi-detector computed tomography.

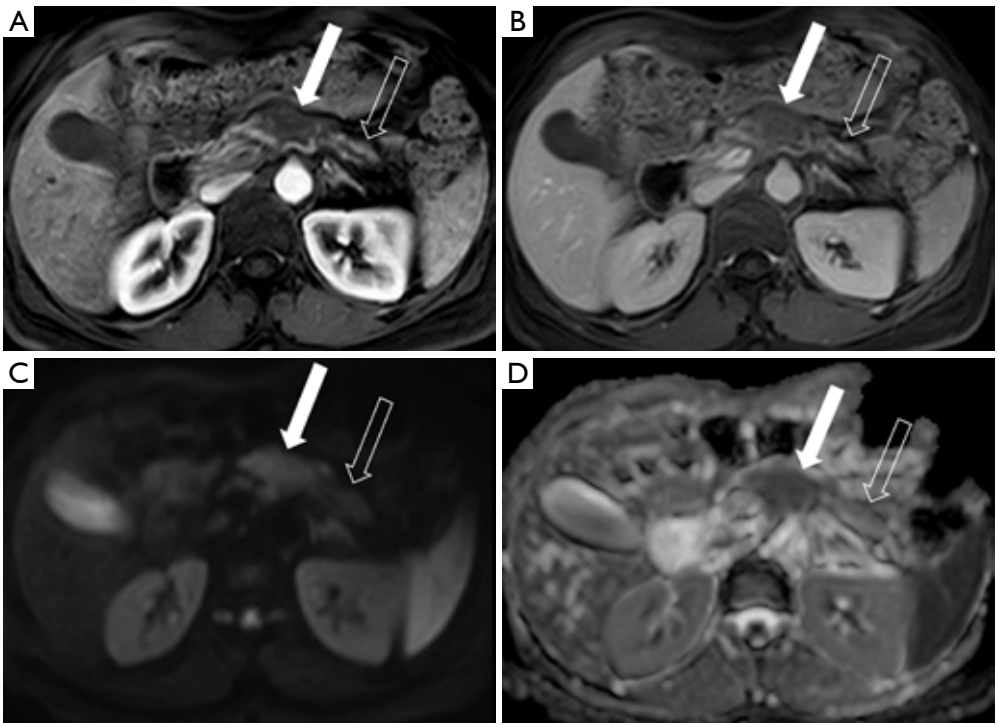

Figure 7 A 49-year-old woman who underwent upper abdominal MRI to evaluate an incidental hepatic lesion detected on abdominal ultrasound obtained for abdominal pain. (A) Pancreatic parenchymal; and (B) portal venous phase 5 mm axial images well depict the 3.0 cm mass (solid arrows) in the pancreatic body. Note the upstream glandular atrophy and main pancreatic duct dilation (open arrows); the lesion is seen as high (bright) signal on the diffusion weighted image (arrow on C); and is confirmed to have restricted diffusion on the ADC map (arrow on D). MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient.

density or linear attenuation coefficient of tissue) between tumoral and non-tumoral tissue increases. DECT also allows generation of iodine images from the same CT acquisition; these images have high contrast to noise ratios, thus enhancing lesion conspicuity. This advance is important for imaging small pancreatic cancers which tend to be isoattenuating or near isoattenuating to the remainder of the pancreas. Early studies have shown an improvement in lesion detection for patients with pancreatic adenocarcinoma (38-41). Staging can also be improved by review of iodine images and generation of CT angiograms from low energy or iodine datasets (41). It is important to note that dual energy CT techniques are relatively radiation dose neutral examinations, and do not result in significantly increased radiation exposures for patients compared to standard single energy CT (42).

Magnetic resonance imaging (MRI)

Modern contrast-enhanced MRI has been demonstrated to be equivalent to MDCT in detection and staging pancreatic cancer (43,44). With its superior contrast resolution, MRI provides increased lesion conspicuity and may be better than CT at detecting small cancers (44-46). MRI is particularly useful for the detection and characterization of pancreatic masses that are isoenhancing to the pancreatic parenchyma and not directly seen on CT (25). A limitation of MRI in the detection of pancreatic adenocarcinoma is the susceptibility of MRI to significant degradation by respiratory motion artifact. This is of particular concern when using gadoxetate disodium contrast as it has been associated with increased motion artifact on arterial-phase imaging, which is often critical for detecting these cancers (47,48). The typical appearance of pancreatic adenocarcinoma on MRI is an ill-defined T1 hypointense, T2 hypointense, relatively hypoenhancing mass. Adenocarcinomas usually demonstrate restricted diffusion on diffusion weighted imaging (*Figure* 7), which may allow for increased detection of tumors even in the unenhanced state (49).

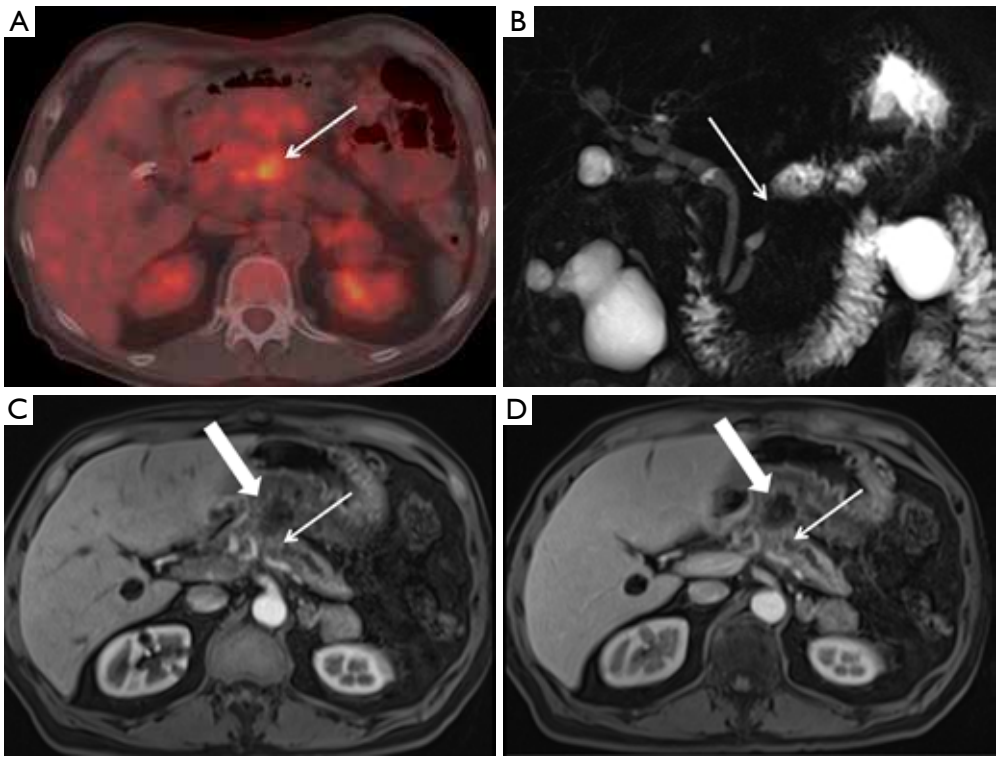

Figure 8 A 75-year-old man with SMV occlusion and locally advanced pancreatic cancer who underwent PET/CT. (A) Axial PET/CT image through the pancreatic body and neck regions reveals an FDG-avid lesion in the midline (arrow). No distant metastatic lesions were detected, but there is abnormal, less FDG avid activity extending toward the gastric antrum; (B) MRCP image demonstrates focal narrowing of the main pancreatic duct (arrow) in the region of the mass, with upstream dilation in the body and tail; (C) pancreatic parenchymal phase 5 mm axial image; and (D) portal venous phase 5 mm axial image demonstrate the abrupt duct cut off by the small pancreatic mass (small arrows), with an inflammatory collection extending towards the stomach. SMV, superior mesenteric vein; PET/CT, positron emission tomography/computed tomography; FDG, fluorodeoxyglucose; MRCP, magnetic resonance cholangiopancreatography.

PET & PET/CT

PET and PET/CT are not routinely used for the initial diagnosis of cancer in patients with clinical suspicion for pancreatic adenocarcinoma. PET/CT is more sensitive for the detection of pancreatic cancer than PET alone (50). The sensitivity and specificity of PET/CT in diagnosing pancreatic carcinoma has been reported to be 89% and 88%, respectively (51). PET/CT may be more sensitive for the diagnosis of pancreatic carcinoma than conventional MDCT and MRI (51). Multiple studies have demonstrated that PET/CT is more sensitive than standard cross-sectional imaging for detecting distant metastatic disease (52,53). Contrast-enhanced PET/CT has also been shown to improve detection of distant metastatic disease when compared with non-contrast PET/CT (54). The typical appearance of pancreatic carcinoma on PET/CT is a focal fluorodeoxyglucose (FDG)-avid mass with CT or MRI characteristics as previously described (*Figure 8*).

The role of PET/CT in the initial diagnosis and staging is evolving and not well defined at this time. The NCCN clinical practice guidelines acknowledge the utility of PET/CT in staging pancreatic adenocarcinoma but state that PET/CT is not a substitute for high-quality contrast-enhanced CT but can be used in conjunction with a pancreas-protocol CT as indicated (18).

Staging

Cross-sectional imaging plays an essential role in the staging of pancreatic adenocarcinoma and thus determining the most appropriate therapy for patients. MDCT is the most widely used and validated modality for the staging of

Table 1 TNM pancreatic cancer staging (AJCC)

Stage	Definition
Primary tumor (T)	
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor limited to pancreas, ≤2 cm
T2	Tumor limited to pancreas, >2 cm
T3	Extension into peripancreatic tissues (excluding arteries)
T4	Tumor involves celiac axis or superior mesenteric artery
Regional lymph nodes (N)	
Nx	Regional lymph nodes not assessed
N0	No metastatic regional lymph nodes
N1	Metastatic regional lymph nodes
Distant metastasis (M)	
M0	No distant metastatic disease
M1	Distant metastatic disease

AJCC, American Joint Committee on Cancer.

pancreatic adenocarcinoma; however, MRI is an equivalent alternative to MDCT for staging. The NCCN practice guidelines recommend that imaging for staging should be done with specialized pancreatic CT or MRI while the consensus statement by the International Study Group of Pancreatic Surgery (ISGPS) recommends evaluation with specialized pancreatic CT (55,56). The decision to use MDCT or MRI should be based on availability, local practice, and local experience/expertise.

Preoperative imaging is used to characterize patients as having resectable disease, borderline resectable disease, locally advanced disease (unresectable without distant metastatic disease) and metastatic disease (unresectable). Borderline resectable disease refers to locally advanced pancreatic adenocarcinoma with involvement of the mesentericoportal veins or local arteries that is in between routinely resectable disease and definitely unresectable disease (56). The exact definitions of borderline resectable and unresectable disease have evolved over recent years and still vary from institution to institution and between different societies. Therefore, it is critical that accurate assessment and reporting of the local extent of disease and the presence and absence of lymph node and distant metastatic disease is performed for optimal management.

The staging system that is most commonly used by clinicians is the TNM staging system maintained by the American Joint Committee on Cancer (AJCC) (57). This system evaluates local extent of the primary tumor, lymph node involvement, and presence of distant metastatic disease to classify disease and give prognosis (*Table 1*) (58). The resectability of a tumor is dependent on its location in the pancreas, involvement of local arteries (celiac, superior mesenteric, and hepatic) and veins (superior mesenteric and portal), lymph node involvement, and presence of distant metastatic disease. A step-wise approach to assessment of resectability is utilized in our practice and includes: (I) location of the primary tumor and relation to surrounding organs; (II) evaluation of distant metastatic disease (most commonly in the liver and peritoneum); (III) involvement of the peripancreatic arteries; (IV) involvement of the peripancreatic veins, with description that can allow the surgeon to prepare for potential vein graft; (V) extrapancreatic perineural spread of tumor to the celiac region. If stage IV disease is identified in the liver, a critical analysis of the peripancreatic vessel involvement is not necessary.

Tumor location

Approximately 60-70% of pancreatic cancers involve the pancreatic head (3,59). Pancreatic head cancers are defined as those arising to the right of the superior mesenteric–portal vein confluence (58). Approximately 10-20% of pancreatic cancers are in the body and 5-10% are in the tail. Cancers between the mesenteric-portal vein confluence and left lateral margin of the aorta are in the body and those lateral to the aorta are in the tail (58). The location of the tumor determines whether the patient would be treated with a pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy. The size of the tumor is also important, as it contributes to the T stage and could be important for determining response to the therapy on subsequent studies (60).

Location of the tumor is also important as it determines the route of local spread of disease. With pancreatic adenocarcinoma, there can be direct invasion (*Figure 9*) of adjacent structures (e.g., duodenum, stomach, adrenal gland, kidney, and colon); however, this does not make disease for a patient unresectable, if this extension can be otherwise adequately and safely resected (61). One route of direct tumor spread that is of particular importance for tumors of the head and uncinate process is perineural invasion (retrograde extension of disease along the neural fascicles of the neurovascular bundles), as it is indicative of a

very poor prognosis (62). Perineural invasion (*Figure 10*) is extremely common with pancreatic carcinomas of the head and uncinate process, being reported in up to 53-100% of cases, and often results in positive resection margins at surgery (63). Adenocarcinomas of the pancreatic head typically spread along the plexus pancreaticus capitalis 1 (PPC1) or gastroduodenal artery (GDA) plexus (if in the dorsal aspect of the head). This can be seen on MDCT as direct contiguous extension of tumor soft tissue extending posterior to the portal vein to along the medial upper margin of the uncinate process or along the GDA to the common hepatic artery (CHA), respectively (63). Adenocarcinomas of the uncinate process typically extend along the PPC2. This can be seen on MDCT as direct contiguous tumor soft tissue extending along the posteroinferior pancreaticoduodenal artery (PIPDA) up to and along the superior mesenteric artery (SMA) (63,64). Note is made that tumor can also extend along this pathway to involve the mesenteric root (63).

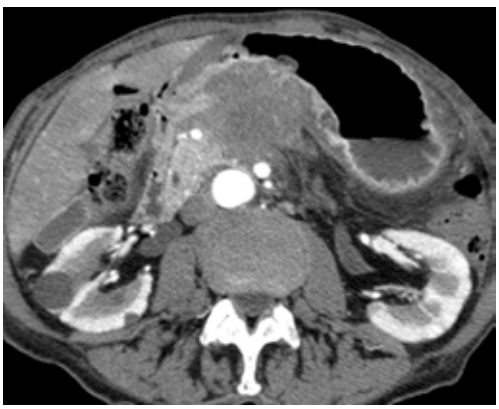

Figure 9 An 85-year-old woman with locally invasive pancreatic adenocarcinoma. Pancreatic parenchymal phase axial image demonstrates the low attenuation hypodense mass in the pancreatic neck/body extending through the posterior antral wall and disrupting the enhancing gastric mucosa.

Vascular involvement with tumor

Determining vascular involvement is the most important component of determining the resectability of a borderline or locally advanced pancreatic adenocarcinoma. Evaluation of the celiac artery, SMA, CHA, superior mesenteric vein (SMV), and portal vein are essential for accurate staging and determining subsequent therapy. Encasement (>180° circumferential contact) of a vessel by tumor (*Figure 11*) is an imaging sign of vascular invasion with a sensitivity of 84% and specificity of 98% (65). Abutment (≤180° circumferential contact) of a vessel with tumor (*Figure 12*) is not considered a sensitive sign of vessel invasion (65). Addition findings suggestive of vessel invasion are tumor causing vessel deformity (tear-drop configuration) or narrowing (regardless of degree of contact), vessel irregularity, direct invasion into a vessel, and thrombosis (3,66). Note that the degree of vascular contact is best evaluated perpendicular to the long axis of the vessel (*Figure 13*), so, for example, the SMA and SMV should be assessed on axial images, while a coronal or sagittal reformatted image might better demonstrate involvement of the portal vein and CHA. These imaging signs of vessel invasion were selected to maximize specificity (at the expense of sensitivity) to ensure that patients with clearly unresectable disease did not undergo an unnecessary surgery and to minimize the number of patients with potentially resectable disease being denied surgery.

The exact definition of borderline resectability and unresectability of locally advanced pancreatic cancer is vague,

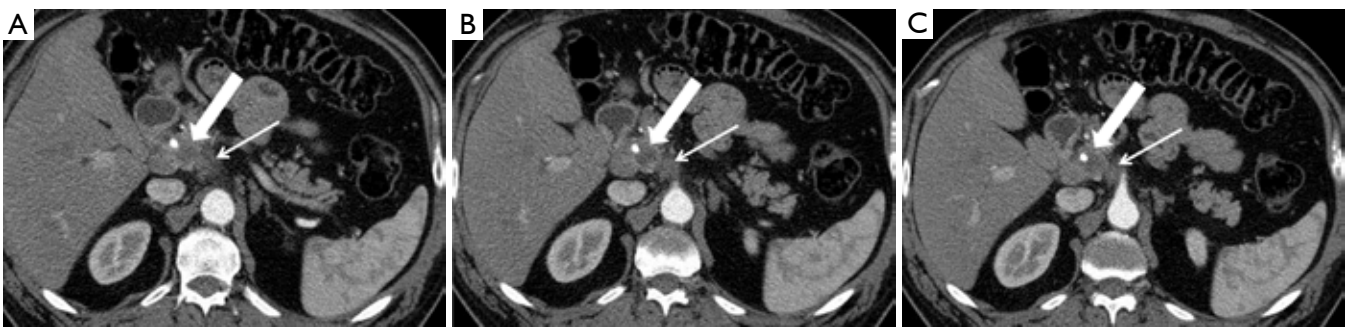

Figure 10 A 61-year-old man with small pancreatic cancer and perineural spread to the celiac ganglion. (A-C) Successively caudal pancreatic parenchymal phase 2.5 mm axial images demonstrate the hypovascular mass in the medial pancreatic head extending posteriorly along the plexus pancreaticus capitalis 1 and abutting the right margin of the celiac trunk. This patient received neoadjuvant therapy.

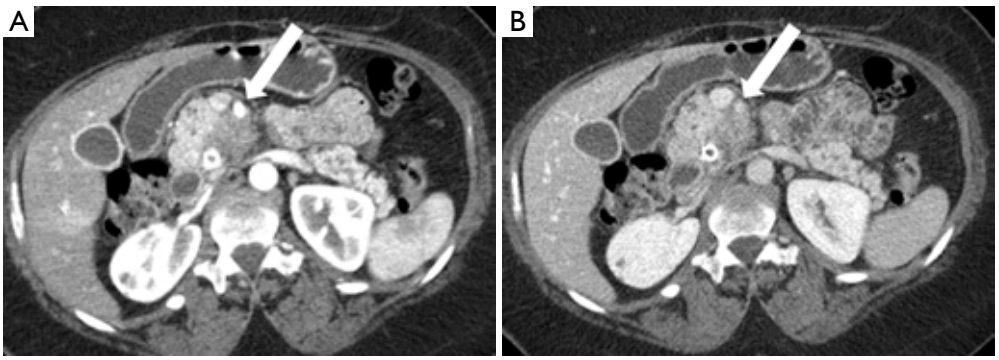

Figure 11 A 55-year-old woman with SMA encasement. (A) Pancreatic parenchymal phase 2.5 mm axial image depicts the relationship of the hypovascular mass in the medial pancreatic head to the SMA (arrow) where there is ≥180° contact indicating encasement; note that this relationship is better seen on this phase of IV contrast administration compared to (B) the portal venous phase 5 mm axial image. SMA, superior mesenteric artery.

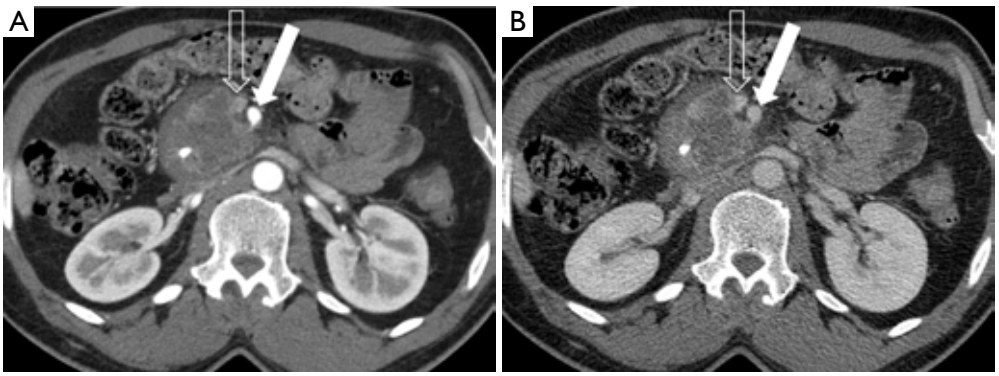

Figure 12 A 52-year-old man with SMA abutment. (A) Pancreatic parenchymal phase 2.5 mm axial image demonstrates contact of the large mass in the pancreatic head with <90° of the SMA (arrow); the SMV (open arrow) is not well evaluated in this phase of contrast, but is better seen on (B) the portal venous phase 5 mm image, where approximately 180° contact is present with slight straightening of the right lateral SMV (open arrow) wall indicating involvement/invasion. SMA, superior mesenteric artery; SMV, superior mesenteric vein.

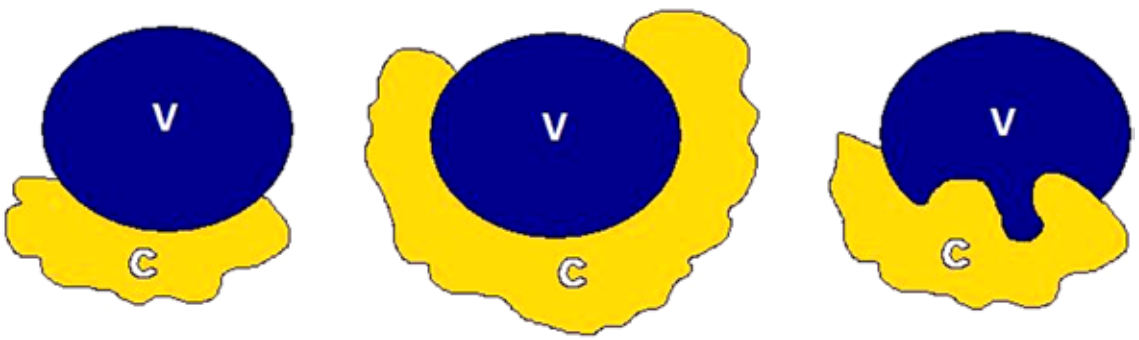

Figure 13 Cartoon depiction of vascular involvement. (A) Abutment of the C with the V; (B) encasement; and (C) involvement/invasion with teardrop deformity. C, cancer; V, vessel.

Table 2 Different definitions of borderline resectable pancreatic cancer

Anatomy	NCCN 2014	AHPBA/SSAT/SSO	MD Anderson Cancer Center	ISGPS	ACTO
Superior mesenteric vein/portal vein	Involvement with distortion/narrowing and/or occlusion amenable to reconstruction	Abutment, encasement, or short-segment occlusion amenable to reconstruction	Short-segment occlusion amenable to reconstruction	Involvement with distortion/narrowing and/or occlusion amenable to reconstruction	Tumor-vessel interface ≥180° and/or occlusion amenable to reconstruction
Superior mesenteric artery	Abutment (≤180°)	Abutment (≤180°)	Abutment (≤180°)	Abutment (≤180°)	Tumor-vessel interface <180°
Common hepatic artery	Abutment or short-segment encasement	Abutment or short-segment encasement	Short segment encasement/ abutment	Abutment or short-segment encasement	Short-segment tumor-vessel interface (any degree) amenable to reconstruction
Celiac artery	No abutment or encasement	No abutment/ encasement	No abutment or encasement	No abutment or encasement	Tumor-vessel interface <180°

NCCN, National Comprehensive Cancer Network; AHPBA/SSAT/SSO, American Hepato-Pancreato-Biliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology; ISGPS, International Study Group of Pancreatic Surgery; ACTO, Alliance for Clinical Trials in Oncology.

controversial, and varies from institution to institution (67). Differences in imaging practices and interpretation, local surgical skill, and local experience contribute to these varying definitions. Tumors with no evidence of metastatic disease, no definite involvement (abutment or encasement) of the SMV or portal vein, and clear fat planes around the celiac artery, hepatic artery and SMA are considered clearly resectable as per the consensus statements by the NCCN and by the American Hepato-Panceato-Biliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO)/Gastrointestinal Symposium Steering Committee (GSSC)/University of Texas M. D. Anderson Cancer Center (MDACC) (68,69). Note is made that isolated tumor involvement of the pancreaticoduodenal artery does not constitute borderline resectability or unresectability, as this vessel is routinely resected as part of a Whipple procedure.

The MDACC published a classification system for the resectability of pancreatic cancer in 2006 (70). Subsequent consensus guideline statements regarding borderline resectable cancer have been published by the NCCN, the AHPBA/SSAT/SSO/MDACC, and the ISGPS (18,56,68,70,71). The Alliance for Clinical Trials in Oncology (ACTO) has recently published their own definition of borderline resectable disease (67). These are summarized in *Table 2*. Findings that are not directly related to vascular invasion but otherwise affect surgical planning are extension of the tumor along the CHA to the origins of the right and left hepatic arteries, extension of tumor along the SMA to the first branch, and extension of tumor along the SMV to the most proximal draining vein (72).

Accurate restaging of vascular involvement following preoperative neoadjuvant therapy of borderline resectable pancreatic cancers is difficult and somewhat controversial. Neoadjuvant-therapy-induced regional changes decrease the sensitivity of CT for detecting disease resectability (71). Katz *et al.* demonstrated that while only 0.8% of patients demonstrated downstaging to resectable disease on imaging, 66% of patients were found to be resectable at surgery (73). The ISGPS consensus statement recommends that if neoadjuvant therapy is administered, an exploratory laparotomy with attempted resection should be considered in the absence of disease progression (distant metastasis) on subsequent imaging (56).

In addition to vascular involvement with tumor, relevant variant vascular anatomy is also important to identify and report when determining resectability. For example, multiple jejunal branches inserting high on the SMV near the portal confluence can make vascular resection/reconstruction difficult (74). Arterial variants that can preclude resection include a replaced hepatic artery arising from the SMA (which is involved with tumor) and a low origin of the CHA from the celiac axis with an aberrant course inferior to the portal vein (74).

Nodal disease

Although cross-sectional imaging is not particularly sensitive for the detection of lymph node involvement with pancreatic cancer, MDCT is generally considered the modality of choice. Abnormal appearing region lymph nodes (>1 cm in short axis diameter, rounded morphology, or cystic appearance) that are in the surgical bed are considered nodal metastasis and are generally not a contraindication to surgery; however, if confirmed at surgery, adjuvant chemotherapy is indicated. For cancers in the pancreatic head/neck, this includes lymph nodes along the celiac axis and in the peripancreatic and periportal regions and for cancers in the body/tail this includes lymph nodes along the CHA, celiac axis, splenic artery and splenic hilum. Lymph node involvement outside of the surgical bed is considered distant metastatic disease and is a contraindication for surgery. Therefore, a description of the location of abnormal appearing lymph nodes is the most important aspect of nodal evaluation for staging.

Distant metastatic disease

Distant metastatic disease most commonly occurs in the liver, peritoneum, lungs and bones. As previously stated, lymph node metastases outside of the surgical field are considered distant metastases. The presence of distant metastatic disease makes the primary lesion unresectable. Note that if a patient is scanned initially with a standard abdominal portal venous phase MDCT, and liver metastases along with a primary pancreatic adenocarcinoma are clearly evident, a repeat multiphasic CT is not required to further evaluate, and follow up imaging can also be single portal venous phase. The majority of patients found to have unresectable disease at surgery despite the appearance of resectable disease on state of the art multiphasic MDCT preoperative imaging are due to small metastatic lesions in the liver and peritoneum. Evaluation for hepatic metastatic disease is most often performed with MDCT or MRI; however, MRI is more sensitive for the detection of small metastatic lesions (75). Furthermore, MRI provides better specificity in characterizing indeterminate liver lesions (43), and MRI is often used for further evaluation when MDCT demonstrates indeterminate liver lesions. None of the imaging modalities are sensitive for the detection or early peritoneal disease. Peritoneal thickening/nodularity and/or ascites not otherwise explained should be considered suspicious for metastatic disease. Although PET/CT has been reported to be more sensitive for the detection of distant metastatic disease, the cost-effectiveness has not been proven, and PET/CT is not routinely used in staging (76).

Structured reporting

As imaging plays an essential role in determining the appropriate management of patients with pancreatic adenocarcinoma, an accurate, complete, and concise report is needed to ensure that the pertinent findings are relayed to the referring clinicians. Structured reports have been shown to not only be equally efficient and accurate in conveying information to referring clinicians as free-style reports, they have been shown to be more accepted and preferred by both radiologists and clinicians (77-79). A standardized reporting template for pancreatic ductal adenocarcinoma has been published as a consensus statement of the Society of Abdominal Radiology (SAR) and the American Pancreatic Association (APA) (72). Structured reporting for pancreatic cancer has been reported to provide superior evaluation of pancreatic cancer, facilitate surgical planning, and increase surgeons' confidence about tumor resectability (80).

Conclusions

Detection and accurate staging of pancreatic carcinoma utilizing abdominal cross sectional state of the art imaging is essential to providing optimal therapy for patients. While specialized pancreatic MDCT is the most commonly used and best-validated modality for diagnosing and staging, MRI is an equally sensitive alternative. A complete and accurate assessment of the primary tumor, its relationship to/involvement of neighboring structures (particularly vascular structures) and distant metastatic disease is required for accurate characterization of disease as resectable, borderline resectable and unresectable. Structured reporting is a good tool for reporting pancreatic adenocarcinoma and has been shown to improve evaluation and surgeons' confidence in the report.

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Imaging of pancreatic cancer: an overview

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Abstract: Pancreatic cancer (PaCa) is the fourth leading cause of cancer-related death in the United States. The median size of pancreatic adenocarcinoma at the time of diagnosis is about 31 mm and has not changed significantly in last three decades despite major advances in imaging technology that can help diagnose increasingly smaller tumors. This is largely because patients are asymptomatic till late in course of pancreatic cancer or have nonspecific symptoms. Increased awareness of pancreatic cancer amongst the clinicians and knowledge of the available imaging modalities and their optimal use in evaluation of patients suspected to have pancreatic cancer can potentially help in diagnosing more early stage tumors. Another major challenge in the management of patients with pancreatic cancer involves reliable determination of resectability. Only about 10% of pancreatic adenocarcinomas are resectable at the time of diagnosis and would potentially benefit from a R0 surgical resection. The final determination of resectability cannot be made until late during surgical resection. Failure to identify unresectable tumor pre-operatively can result in considerable morbidity and mortality due to an unnecessary surgery. In this review, we review the relative advantages and shortcomings of imaging modalities available for evaluation of patients with suspected pancreatic cancer and for preoperative determination of resectability.

Keywords: Pancreatic cancer; ultrasound; computed tomography; magnetic resonance imaging; endoscopic ultrasound guided fine needle aspiration

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Introduction

Pancreatic cancer (PaCa) is the fourth leading cause of cancer-related death in the United States. In 2010, there were over 43,000 estimated new cases of PaCa and over 36,000 deaths attributed to it in the United States (1). The estimated lifetime risk of developing PaCa is about 1 in 71 (1.41%) (2). The disease is rare before age 45 but incidence rises rapidly after that and peaks in the seventh decade of life. The major risk factors include smoking (3), hereditary predisposition to PaCa itself or to multiple cancers (4) and to a lesser degree, chronic pancreatitis (5). PaCa does not exhibit early symptoms and initial symptoms are often nonspecific. Classical presentation of PaCa (painless jaundice) is present in only 13-18% of the patients and is often accompanied by pruritus, acholic stools dark urine, and weight loss (6). Abdominal pain is present in 80-85% of patients with locally advanced or advanced disease. Acute pancreatitis and new onset diabetes mellitus can often be the initial presentations of PaCa (7,8).

In up to 75% of the cases, the tumor is located within pancreatic head mostly sparing the uncinate process. Tumors in the pancreatic head often present early with biliary obstruction. However, tumors in the body and tail can remain asymptomatic till late in disease stage. Surgical resection is the standard of care for treatment but only but <10% of patients with pancreatic tumors have resectable tumors at the time of presentation. The criteria for unresectability include infiltration of superior mesenteric artery (SMA) and/or celiac artery or the presence of distant metastasis including metastatic celiac or mediastinal lymph nodes. The size of pancreatic tumor is a major determinant

of resectability and up to 83% of tumors ≤20 mm are resectable compared to only 7% of tumors >30 mm in size (9). The 5-year survival rate in patients with resectable tumors can be as high as 20-25% and compares favorably with patients with unresectable tumor, very few of whom survive 5 years after diagnosis. Imaging techniques currently used for diagnosis and preoperative staging of pancreatic cancer include abdominal ultrasound (US), contrast-enhanced computed tomography(CT), magnetic resonance imaging (MRI), MR cholangiopancreatography (MRCP) and invasive imaging modalities like endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS).

Imaging modalities

Abdominal ultrasound (US)

Abdominal ultrasound (US) is widely available, noninvasive, relatively inexpensive imaging modality without contrast associated adverse effects. It is usually performed to rule out choledocholithiasis and look for biliary dilation in patients who present with jaundice and abdominal pain. The real world accuracy of conventional US for diagnosing pancreatic tumors is 50% to 70% (10). The results of US are highly operator dependant. In addition, body habitus (adipose tissue), overlying bowel gas and patient discomfort can limit the use of US in evaluating the pancreas. If an initial US excludes choledocholithiasis in a patient with signs and symptoms to suggest a pancreatic etiology, CT or MRI is commonly used for further evaluation.

Computerized tomography (CT)

Computerized tomography (CT) is the initial comprehensive imaging done in patients with suspected PaCa. Since the past decade, advances in CT technology have improved its accuracy in diagnosing and tumor staging of PaCa.

Non-contrast CT

Ideally, use of non-contrast CT to evaluate pancreas is limited to patients with renal failure or allergic reactions to iodinated contrast agent used. As the pancreatic tumors are hypovascular and can be visualized only with contrast imaging, non-contrast CT scans have poor sensitivity and specificity for pancreatic tumors and hence cannot be relied on to make a diagnosis.

CT with Intravenous (IV) contrast

Multidetector CT (MDCT) provides very thin slice cuts, higher image resolution and faster image acquisition. This technique allows better visualization of the pancreatic adenocarcinoma in relation to the SMA, celiac axis, superior mesenteric vein (SMV), and portal vein as greater parenchymal, arterial, and portal venous enhancement is achieved when imaging the pancreas with MDCT. This can potentially aid in early detection and accurate staging of pancreatic carcinoma (11,12). MDCT with intravenous contrast is, therefore, generally considered as the imaging procedure of choice for initial evaluation of most patients suspected to have pancreatic cancer (13). It has reported sensitivity between 76-92% for diagnosing pancreatic cancer (14-18). Pancreatic ductal adenocarcinoma is hypovascular and therefore enhances poorly compared to the surrounding pancreatic parenchyma in the early phase of dynamic CT and gradually enhances with delayed images. As a result, on contrast enhanced CT, pancreatic adenocarcinoma is typically seen as a hypoattenuating area but may occasionally be isoattenuating to the surrounding normal parenchyma thereby leading to misdiagnosis. Prokesch et al have reported that indirect signs such as mass effect on the pancreatic parenchyma, atrophic distal parenchyma, and abrupt cut off of the pancreatic duct PD dilation (interrupted duct sign) are important and should be considered as indicators of tumors when mass cannot be clearly identified on CT (19). Multiple studies have reported extrahepatic biliary dilation and/or PD dilation (double duct sign) as findings suggestive of PaCa (20). It is also important to be aware of changes to the parenchyma caused by chronic pancreatitis as they can closely mimic the changes due to PaCa and may lead to misdiagnosis. Contrast enhanced MDCT can be used to evaluate local extension, invasion of adjacent vascular structures and surgical resectability with an accuracy of 80% to 90% (21). However for pre-operative staging, it is limited in detecting liver metastases and early lymph node metastasis (22,23). The absolute contra-indications of contrast CT are in patients with renal failure and contrast allergy.

Pancreatic protocol CT (CT angiography)

Preoperative staging and assessment of resectability is usually performed using pancreatic protocol CT or CT angiography. CT angiography is done by bolus administration of iodinated nonionic contrast with imaging done in arterial and venous phases after intravenous injection of contrast. The arterial phase of enhancement,

which corresponds to the first 30 seconds after the start of the contrast injection, provides excellent opacification of the celiac axis, superior mesenteric artery, and peripancreatic arteries. The portal venous phase, which is obtained at 60 to 70 seconds after the start of the contrast injection, provides better enhancement of the superior mesenteric vein, splenic and portal veins as well as the pancreas itself and any liver metastases that may be present. Even though pancreatic protocol CT is widely regarded to be superior to non-pancreatic protocol contrast MDCT for determining resectability, there is currently insufficient direct evidence to support this.

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP)

Magnetic resonance imaging (MRI) can be used in imaging for PaCa in patients with equivocal findings at ultrasound or MDCT. MRI examination of the pancreas is done with intravenous administration of contrast material and gadolinium is the most commonly used agent. PaCa is hypointense on gadolinium-enhanced T1- weighted images in the pancreatic and venous phases because it is hypovascular with abundant fibrous stroma compared to the pancreatic parenchyma. Tumors appear isointense on delayed images because of slow wash-in of contrast medium. MRI is commonly used to detect PaCa when a mass lesion is not identifiable on CT scan. There is however no significant diagnostic advantage of MRI over contrast- enhanced CT (sensitivity of 86% on CT *vs.* 84% on MRI) (24). Combining the two tests does not improve upon what is achieved with one test alone. MRI is better at characterizing cystic lesions of the pancreas and can provide some indirect radiological evidence to aid in diagnosis of pancreatic cancer. The choice of MRI or CT usually depends upon available local expertise and the clinician's comfort with one or the other radio-imaging technique. It is contraindicated in patients with metal in the body (e.g.: pacemakers, implants) and contrast allergy.

Magnetic resonance cholangiopancreatography (MRCP) is a useful adjunct to other radiographic diagnostic techniques and may emerge as the preoperative imaging procedure of choice for patients with suspected PaCa. MRCP uses magnetic resonance technology to create a three dimensional image of the pancreaticobiliary tree, liver parenchyma, and vascular structures. MRCP is better than CT for defining the anatomy of the biliary tree and pancreatic duct, has the capability to evaluate the bile ducts both above and below a stricture, and can also identify intrahepatic mass lesions. It is reportedly as sensitive as ERCP in detecting pancreatic cancers and unlike conventional ERCP, does not require contrast material to be administered into the ductal system (25). Thus, the morbidity associated with endoscopic procedures and contrast administration is avoided. Although MRCP has not yet completely replaced ERCP in patients with suspected pancreatic cancer in all centers, it is routinely used in patients with high grade stenosis of the gastric outlet or proximal duodenum or in those with certain post-surgical anatomy (e.g., Billroth II, Roux-en Y biliary bypass), which make the biliary ductal system difficult to access by ERCP (26). Chronic pancreatitis can be difficult to differentiate from pancreatic adenocarcinoma on MRI since both show low signal intensity on T1-weighted images and both may be associated with pancreatic and/or biliary ductal obstruction. Dynamic gadolinium-enhanced MRI cannot differentiate chronic pancreatitis and PaCa on the basis of degree and time of enhancement (27). MRCP images may be more helpful in distinguishing between chronic pancreatitis and pancreatic adenocarcinoma especially if the duct-penetrating sign signifying a non-obstructed main pancreatic duct is present (28).

Positron emission tomography (PET) imaging

Positron emission tomography (PET) scanning with the tracer 18-fluorodeoxyglucose (FDG) relies upon functional activity to differentiate metabolically active proliferative lesions such as cancers, most of which are FDG-avid lesion such as cancers from benign lesions, most of which do not accumulate FDG with the exception of inflammatory lesions such as chronic pancreatitis. The utility of PET in the diagnostic and staging evaluation of suspected PaCa remains uncertain and there is still no consensus on whether PET provides information beyond that obtained by contrast-enhanced CT (29). As PET imaging is usually performed after the initial CT, the sensitivity and specificity of PET varied depending on the CT result. Sensitivity and specificity after a positive CT was 92% (87% to 95%) and 68% (51% to 81%); after a negative CT, the corresponding values were 73% (50% to 88%) and 86% (75% to 93%). Elevated serum blood glucose levels increase the number of false negative PET scans. Data published on the use of PET scans in PaCa are conflicting. Some studies suggest that PET is useful for identifying metastatic disease that is missed by CT (30),

while others reported that PET often misses small volume metastases within the peritoneum and elsewhere, including the liver (31).

More recent studies have investigated the value of integrated PET/CT, which has better spatial resolution as compared to PET scans. In one case series, the sensitivity and specificity of PET/CT for the diagnosis of PaCa compared with CT alone was 89% versus 93% and 69% versus 21% respectively (32). PET/CT is also superior to conventional imaging (MDCT, CT angiography, EUS) used for tumor staging and detection of distant metastases (sensitivity and specificity rates were 89 versus 56 and 100 versus 95 percent, respectively). A major limitation of this study was that the CT component of PET/CT was performed without the use of intravenous contrast material. When compared to MDCT with contrast, currently available data does not show that PET or integrated PET/ CT provide any additional information. Further studies are needed to evaluate the role of PET for diagnosis and staging especially in patients with a negative or indeterminate MDCT.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

Endoscopic Retrograde Cholangiopancreatography (ERCP) is used for diagnosis and palliation in patients with known or suspected pancreatobiliary malignancies. During an ERCP, cannula is passed from the endoscope into the pancreatic or biliary ducts. Contrast dye is injected through the cannula into the ducts and the biliary and pancreatic ductal systems are visualized flouroscopically. In contrast to other imaging modalities, tissue diagnosis of the involved ducts may be achieved using needle aspiration, brush cytology, and forceps biopsy. Brush cytology has 35-70% sensitivity and 90% specificity (33). Triple sampling using brush cytology, FNA and forceps biopsy of biliary stricture during ERCP improves the sensitivity for diagnosing cancer to 77% (34). ERCP and brushing of biliary stricture has better diagnostic accuracy for cholangiocarcinoma (about 80%) compared to pancreatic carcinoma (35). ERCP has a limited role in staging of pancreatic and biliary cancers.

Palliation of biliar y obstruction in patients with pancreatic and biliary cancer may be performed with biliary stent placement with ERCP or a surgical bypass. The available evidence does not indicate a major advantage to either alternative, so the choice may be made depending on clinical availability and patient or practitioner preference. ERCP is a widely available imaging modality and this modality may be preferable to surgery in some cases due to lower overall resource utilization and shorter hospitalization. The role of ERCP in biliary drainage prior to surgery for potentially resectable pancreatic cancers is currently debated and should be individualized based on specific clinical situation. However, the vast majority of patients with PaCa has an unresectable or borderline resectable tumor requiring chemotherapy ± radiation and would benefit from an ERCP for biliary drainage. Acute Pancreatitis is a side effect encountered after ERCP in 5-7% of the patients. Gastrointestinal bleeding, perforation, infection and sore throat are other less common complications of ERCP.

Endoscopic Ultrasound Guided Fine Needle Aspiration (EUS/EUS-FNA)

EUS/EUS-FNA is used for definitive diagnosis of PaCa or in patients with suspected cancer not diagnosed by conventional imaging. EUS examinations are usually performed using radial echoendoscope initially and whenever a suspicious 'mass' lesion is identified during the EUS exam, fine needle aspiration (FNA) is performed using a linear echoendoscope. Fine needle passes are made using a EUS-FNA needle in the same sitting. The cytology specimens are usually stained by the Diff-Quik and Papanicoulou method (Pap smear) and sample is collected for cell blocks. The final diagnosis is based on examination of the Pap smears and the cell blocks using standard cytologic criteria (36). Special cytology stains are used as indicated to diagnose neuroendocrine tumors. The sensitivity of EUS-FNA for diagnosing pancreatic cancer has ranged from 80-95% in various published studies (37-39). The performance characteristics of EUS-FNA for diagnosing PaCa seem to be inf luenced by presence of obstructive jaundice at initial clinical presentation and presence of underlying chronic pancreatitis. In patients without obstructive jaundice, the diagnostic accuracy of EUS-FNA is very high (98.3%) and is not significantly influenced by presence of underlying chronic pancreatitis. However, in patients presenting with obstructive jaundice, the sensitivity (92.0%) and accuracy (92.5%) of EUS-FNA for diagnosing malignancy is significantly lower especially so in patients with chronic pancreatitis (40). Absence of an identifiable mass lesion on EUS rules out PaCa with almost 100% certainty in the hands of experienced endosonographers (41). The accuracy of EUS-FNA for PaCa diagnosis can be further improved with use of adjunctive immunostaining in slides obtained by smearing

EUS-FNA specimens (42). EUS is helpful in further evaluation of patients with non-specific and subtle findings suggestive of PaCa on CT and MRI imaging. We had earlier reported in non-jaundiced patients with "enlarged head of pancreas" or "dilated PD with or without a dilated CBD" on CT/MRI, a pancreatic malignancy was present in 9.0% of patients and EUS-FNA diagnosed cancer in these patients with 99.1% accuracy (43).

EUS probably has a role in preoperative staging of PaCa for determining resectability. Portal vein and splenic vein invasion are visualized better with EUS. However, tumor involvement of SMA and SMV is not reliably determined by EUS. In published studies , EUS has a T-stage accuracy of 78-94% and N-stage accuracy of 64-82% (44-49). However, the presence of biliary stent at the time of EUS examination reduced the T-stage accuracy to 72% (50). EUS also plays a role in identification and biopsy of metastatic peripancreatic, celiac and mediastinal lymph nodes for tumor involvement. Ahmed *et al.*, questioned the role of EUS for T-staging and found its accuracy between 49% and 69% in two different studies (51,52). With recent advances in CT and MRI technology and the ability to perform image reconstruction, very detailed evaluation of vascular infiltration by tumors is nowpossible. EUS imaging probably has an adjunctive role in T-staging of pancreatic tumors. However, due to its ability to reliably identify lymph nodal metastasis in celiac and mediastinal lymph nodes, EUSFNA can prove to be beneficial in pre-operative assessment of resectability (53,54). The main limitation of EUS is its operator dependence and limited availability of expert endosonographers for accurate reporting. EUS carries a 0.1-1% risk of pancreatitis. As with any invasive procedure, complications like bleeding, tear, anesthetic complications can occur but are rare.

In conclusion, MDCT is the preferred initial imaging modality in patients with clinical suspicion for pancreatic cancer. The role of MRI for use in pancreatic cancer diagnosis is evolving and is currently used interchangeably with MDCT for this purpose. MRCP seems promising in differentiating pancreatic cancer from chronic pancreatitis. PET scans can provide information on occult metastasis but its clinical benefit is not established. EUS is the most accurate examination for diagnosing pancreatic cancer and can be a useful adjunct to CT/MRI in determining resectability of pancreatic cancer. EUS/EUS-FNA can also provide a definite determination about the presence of pancreatic cancer in patients with non-specific findings suggestive of cancer on conventional imaging.

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Endoscopic ultrasonography for pancreatic cancer: current and future perspectives

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Abstract: A suspected pancreatic lesion can be a difficult challenge for the clinician. In the last years we have witnessed tumultuous technological improvements of the radiological and nuclear medicine imaging. Taking this into account, we will try to delineate the new role of endoscopic ultrasound (EUS) in pancreatic imaging and to place it in a shareable diagnostic and staging algorithm of pancreatic cancer (PC). To date the most accurate imaging techniques for the PC remain contrast-enhanced computed tomography (CT) and EUS. The latter has the highest accuracy in detecting small lesions, in assessing tumor size and lymph nodes involvement, but helical CT or an up-to-date magnetic resonance imaging (MRI) must be the first choice in patients with a suspected pancreatic lesion. After this first step there is place for EUS as a second diagnostic level in several cases: negative results on CT/MRI scans and persistent strong clinical suspicion of PC, doubtful results on CT/MRI scans or need for cyto-histological confirmation. In the near future there will be great opportunities for the development of diagnostic and therapeutic EUS and pancreatic pathology could be the best testing bench.

Keywords: Endoscopic ultrasound; pancreatic cancer; multidetector helical computed tomography; fine-needle aspiration; pancreatic cyst; neuroendocrine tumor

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Introduction

One of the most important task of pancreatic endoscopic ultrasound (EUS) remains diagnosis and staging of pancreatic cancer (PC), the most deadly of all gastrointestinal (GI) malignancies, the fourth leading cause of cancer-related deaths in the United States, with a very poor prognosis. The 5-years survival rate is less than 5% (1). PC is a major health problem for several reasons: aggressive behaviour of the tumor, relative frequency that appears to be increasing, approximately 30,000 new cases in 2002 and about 32,000 in 2004 were diagnosed in the United States (1). Unluckily, most patients present late in the history of their disease with advanced cancer either locally or with metastatic spread (2). Even though surgery represents the only chance for cure, at the time of diagnosis only 10% to 25% (in the more optimistic series) of PC patients will be amenable to potentially curative resection (3) and in this case the prognosis remains dismal (4). This is demonstrated by a 5-year survival not above 20% after surgical resection (5). Furthermore, if we consider the high costs of major pancreatic surgery not only in terms of money but also morbidity and mortality even in the most experienced surgical hands (6,7), it is clear that all efforts must be oriented towards the need of an early diagnosis and to reliably identify patients who really can benefit from major surgical intervention. A study indeed found that a complete resection with negative margins can be achieved in almost half of patients with suspicion of locoregional PC, when state-of-the-art preoperative

imaging was used (8).

Pancreatic tumors have always represented a complex dilemma for clinicians and diagnostic imaging and, currently, there is no consensus on the optimal preoperative imaging modality for diagnosis and staging assessment of patients with suspected or proved locoregional PC. This brought us during the years to a complex range of diagnostic proposals.

Three steps are crucial in clinical practice: first you must find the lesion (detection), secondly you must make a differential diagnosis between benign and malignant pancreatic masses and once the diagnosis of PC is established you need the most accurate preoperative staging to select patients that can benefit from curative resections. Modern imaging techniques such as transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and EUS are less invasive and less costly than surgery. For years EUS has been claimed to be the best currently available technique for imaging the pancreas, but in the last ten years we have witnessed tumultuous and galloping technological improvements of the radiological and nuclear imaging techniques. Taking into account the rapid increase in the sensitivity and accuracy of these new technologies, in a narrative review we analyzed current and future perspectives of EUS in the mangement of PC.

Other important and challenging tasks of pancreatic EUS are represented by:

(I) the differential diagnosis of solid pancreatic masses (auto-immune pancreatitis, chronic pancreatitis, solid-cystic dystrophy of the duodenal wall, neuroendocrine tumor, pancreatic metastasis);

(II) differential diagnosis and surveillance of pancreatic cystic lesions;

(III) detection, diagnosis and staging of neuroendocrine tumors (NETs) of the duodenopancreatic area;

(IV) diagnosis of parenchymal and ductal changes of chronic pancreatitis (CP);

(V) the setting of idiopathic acute pancreatitis (AP) in order to define an aetiology, to identify patients that can take advantage of an endoscopic treatment (endoscopic retrograde cholangiopancreatography or ERCP) and to predict severity of the AP.

To identify all publications considered appropriate to discuss this issue, a MEDLINE search of all studies published from 1965 to 2012 was conducted. The final date of the MEDLINE search was November 25, 2012. The following medical subject headings were used: pancreatic cancer, pancreatic cyst, neuroendocrine tumor, endoscopic ultrasound, echoendoscopy, EUS, fine-needle aspiration, and FNA. The search was also performed using reference lists from published articles. The titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles.

The challenge of EUS

EUS is one of the most important innovations that have occurred in GI endoscopy during the last 30 years. This technique has been introduced in the early 1980s (9), just to overcome difficulties in visualization of the pancreas on transabdominal US. It has been for many years a mere imaging modality, but the development of new electronic instruments with linear or sector scanner allowed the visualization in the echografic field of a needle coming out from the operative channel of the echoendoscope so guiding the needle in the target lesion both within and outside the GI wall. So we witnessed in the early 1990s at the birth of interventional EUS, both diagnostic and therapeutic.

For many years EUS has been advocated as the best available technique for imaging the pancreas and the extra-hepatic biliary tree. High resolution images of the main pancreatic duct and surrounding parenchyma can be achieved and structures as small as 2-3 mm can be distinguished thanks to the small distance between the transducer and the gland, that allows to use higher frequency probes, from 7.5 to 20 MHz, with lower penetration depth but more elevated spatial resolution (10). EUS, compared with transabdominal US, CT and MRI, has a superior parenchymal resolution, that gives reason for the results of several studies establishing the higher sensitivity of EUS (98%) in the diagnosis of PC in comparison to all the other imaging modalities, i.e., US (75%), CT (80%), even with pancreatic protocols, angiography (89%) and so on (11,12). The results of EUS were even better in small tumors, less than 3 cm, where sensitivity of US and CT decreased to only 29% (11). However, the introduction of multidetector helical CT (MDHCT) has today revolutionized the field of pancreatic imaging and "has created a new dimension of temporal and spatial resolution" reaching a sensitivity of 97-100% and a non-resectability prediction near to 100% (13). Also MRI, developed in the early 1990s, has known great improvement in technology and softwares in the last ten years, with the addition of magnetic resonance cholangiopancreatography (MRCP) and MR angiography. The reported sensitivity of MRI ranges from 83% to 87% with a specificity from 81% to 100%. Given the increasing sensitivity of MDHCT and the high cost of MRI, the latter to date should not be considered the first choice in PC diagnosis and staging,

even though MRI may be useful in the detection and characterization of non-contour-deforming pancreatic masses and it is more sensitive than CT in the detection and characterization of small liver metastases and peritoneal and omental metastases (10,14).

In the last ten years EUS had to bear the weight of the rapidly evolving technology of radiological imaging modalities and finally also the advent and the evolution of nuclear imaging such as positron emission tomography (PET) (15) and the integrated approach PET/CT, aimed to overcome the major disadvantage of PET scan, that is the limited anatomical information (16).

In short, the development of modern imaging modalities have limited or almost annulled the advantages of EUS in terms of sensitivity, accuracy for T and N staging, prediction of resectability (i.e., detection of vascular infiltration) in the preoperative evaluation of PC. Multiple published studies with discordant results compared EUS and CT or other imaging modalities in the diagnosis or detection, staging and prediction of resectability of suspected or known PC (12). For example in the study of Schwarz *et al.* the diagnosis of periampullary tumors could be achieved with high sensitivity by EUS (97%) and spiral CT (90%) (17). For small tumors the most sensitive method remains EUS, which correctly predicted all lesions <2 cm. When comparing accuracy rates for resectability, EUS was the leading modality, but the difference with spiral CT was not significant. In a systematic review, comparing EUS and CT for the preoperative evaluation of PC, the authors concluded that literature is heterogeneous in study design, quality and results (18). There are many methodologic limitations that potentially affect the validity. Overall, EUS is superior to CT for detection of PC, for T staging and for vascular invasion of the spleno-portal confluence. The two tests appear to be equivalent for N staging, overall vascular invasion and resectability assessment. The optimal preoperative imaging modality for the staging and assessment of resectability of PC remains undetermined. Prospective studies with state-of-the-art imaging are needed to further evaluate the role of EUS and CT in PC. In this challenge EUS has been mainly supported by the advent of interventional EUS (EUS-guided fine-needle aspiration or EUS-FNA). In contrast to the very high sensitivity previously shown, specificity of EUS is limited, especially when inflammatory changes are present. The ability to perform EUS-FNA may overcome some of the specificity problems encountered with EUS in distinguishing benign from malignant lesions, allowing an improvement of EUS accuracy, mainly as a result of enhanced specificity, without loosing too much in sensitivity (12). To tell the truth also the negative predictive value of 100% for EUS in pancreatic tumors must be in some way mitigated: in a multicenter retrospective study were identified 20 cases of pancreatic neoplasms missed by nine experienced endosonographers. Factors that caused a false-negative EUS result included chronic pancreatitis, a diffusely infiltrating carcinoma, a prominent ventral/dorsal split and a recent (<4 weeks) episode of AP. The authors suggested that if a high clinical suspicion of PC persists after a negative EUS, a repeated examination after 2-3 months may be useful for detecting an occult pancreatic neoplasm (19).

Anyway we should refrain from the idea that investigations only exist to compete with one another, but instead we should accept that different technologies often provide complementary information which ultimately result in optimum patient care. An overriding principle of care should be that patients should first undergo the least invasive, harmful and most widely available investigation. Moreover we must consider that EUS can not define distant metastases, it is still not universally available and highly operator dependent. So spiral CT or better MDHCT must today be the initial study of choice in patients with a suspected pancreatic lesion.

Current role of EUS in pancreatic cancer diagnosis

Starting from the above mentioned concepts we will propose a diagnostic algorithm in case of a suspected PC, trying to place EUS in shareable and evidence-based positions inside this algorithm. As already mentioned, in case of a clinical suspicion of PC, the initial study should be performed with a spiral or multidetector CT: if there is a PC with distant (hepatic for instance) metastases, there is no place for EUS. CT scan can be negative for pancreatic pathology: in this case we must search for other causes accounting for patient's symptoms, but if the suspicion of pancreatic disease remains strong we must proceed to EUS: if endosonography depicts a pancreatic lesion, we can biopsy it (EUS-FNA) or just refer the patient to the surgeon or propose a follow-up of the detected lesion, if EUS diagnosis leans towards a benign process. If pancreatic EUS is negative we can reasonably exclude a pancreatic disease. This is why EUS is the test with the best negative predictive value for the pancreas that approaches 100% (19).

Second scenario: the CT scan shows some doubtful pancreatic changes or inconclusive imaging such as small (<2 cm) masses, fullness, enlargement or prominence of the

gland. The clinical significance of these indeterminate CT findings is not established, however in a clinical setting with a proper suspicion of PC they are very worrisome. Also in this case EUS is indicated and again we can rely on its high negative predictive value (20), with the possibility of real-time EUS-guided FNA that has been demonstrated useful for overcome EUS specificity problems in the differential diagnosis between malignancy and inflammation (20,21).

Third scenario: CT imaging is positive for PC. Contrast-enhanced MDHCT is highly accurate for the assessment of PC staging and resectability (22) and we can be facing a resectable tumor or not. In the first case the patient can go straight to surgery, even if some authors, in order to most reliably identify patients who might really benefit from major surgical intervention, recommend EUS to be performed as second staging modality (10,23). A cost minimization analysis strengthened the sequential strategy, MDHCT followed by EUS, in potentially resectable cancers (22). If both methods confirm resectability the patient is referred to the surgeon and there is general agreement between experts and literature that FNA is not necessary for resectable cancers. Anyway in some cases one can argue that not all pancreatic tumors are ductal adenocarcinomas: endocrine neoplasias, lymphomas, solid-papillary tumors, metastatic cancer, such as metastases from breast, kidney, adrenal gland and so on can be found in the pancreas and they may have varying prognostic outcomes and may require different treatment approaches. In this case, if there is any imaging or clinical doubt about the nature of the mass, FNA could be advisable even in the presence of a resectable pancreatic mass. On the other hand if MDHCT shows a non-resectable pancreatic tumor, histological or cytopathological confirmation is needed in order to address the patient to protocols of palliative radio- or chemo-therapy (10,24). In very few cases is also described that EUS can recover the patient for surgery demonstrating that MDHCT overstaged the tumor.

When do we need cytological or histological diagnosis?

There is only one answer to this question: when the obtained information can change patient management. So we need cyto-pathological confirmation:

(I) in patients with unresectable pancreatic masses or anyway not eligible for surgery prior to start palliative radio- or chemo-therapy (this is the main indication for pathological confirmation in PC) (10,24);

(II) when we have some justified doubts that the resectable pancreatic mass is not a ductal adenocarcinoma but a different type of tumor amenable to different therapeutic strategies (25);

(III) when the patient or sometimes also the surgeon wish to have a cytopathogical confirmation of cancer before engaging in a major surgical intervention;

(IV) in the differential diagnosis between carcinoma and mass forming pancreatitis.

The differentiation between a malignant and an inflammatory tumor especially in a setting of CP is very challenging. This is one of the main limitations of EUS, which is also observed with all other imaging modalities. It restricts the value of EUS for one of the most frequent differential diagnostic dilemmas in pancreatic diseases. The positive predictive value of EUS for PC in patients with concurrent CP was only 60% (26). In this case histological confirmation may be of outstanding value, but also EUS-FNA showed some limitations in presence of CP, in particular a lower sensitivity in comparison to patients without chronic inflammation (73.9% *vs.* 91.3%, P=0.02) (27). The authors suggest some tips for improving the yield of pancreatic mass EUS-guided FNA in the setting of CP: multiple FNA passes, repeated procedures, on-site cytologic interpretation, sampling of suspicious non-pancreatic lesions, such as lymph nodes or liver lesions, use of core-biopsy needles, the cooperation of an experienced pancreatic cytologist. The impact of an expert cytopathologist on diagnosis and treatment of pancreatic lesions in current clinical practice is well demonstrated: in a series of 106 EUS-FNA sensitivity increased from 72% to 89% due to the cytopathologist experience (28). In this difficult challenge EUS can be assisted by new technological advances such as contrast-enhanced (CE) imaging that increased sensitivity and specificity of EUS in discriminating between focal pancreatitis and PC, from 73% to 91% and from 83% to 93%, respectively (29). Another new tool that could demonstrate to be useful in this setting is EUS elastography. Allowing the visualization of tissue elasticity distribution it could help in the differential diagnosis of focal pancreatic masses or in the differentiation of benign and malignant lymph nodes or various solid tumors. Possibly it will help EUS-FNA in targeting less fibrous areas inside the lesion of interest (30). It uses a hue color map (red-green-blue) to display the stiffness of the tissue (31,32): recent data with quantitative, second-generation EUS elastography, demonstrate its usefulness for differential diagnosis of solid pancreatic masses, allowing for a quantitative and objective assessment of tissue stiffness, which indicates the malignant or benign nature of the pancreatic lesion. A good reproducibility of the results was

proven (32).

How to obtain samples for cytopathological or histological confirmation in pancreatic masses

Non surgical pancreatic cyto-histological samples can be obtained either endoscopically by means of EUS or ERCP guidance or percutaneously by CT or US guidance. ERCP-directed brush cytology has a low sensitivity between 33% and 57% and a specificity between 97-100% (33-35). Even adding ERCP-directed biopsies the sensitivity does not exceed 70% (34,35). In a prospective study, Rosch *et al.* compared ERCP-guided brush cytology, ERCP-directed biopsies and EUS-FNA for diagnosis of biliary strictures. Biliary stenoses of undeterminate origin remained a difficult challenge, but EUS-guided FNA has been demonstrated superior to ERCP-guided techniques for pancreatic lesions (43% *vs.* 36%) (36). Percutaneous FNA or core biopsy of the pancreas via CT and transabdominal US has a success rate of 65% to 95% for detecting malignancy (37-40) and it is considered safe, with a mortality rate for abdominal biopsies of 1:1,000 (38,41). The development of instruments with electronic linear o sector scanners, equipped with color Doppler technology permitted FNA for cytology specimens guided by means of EUS. We performed a systematic review and a meta-analysis of the literature in order to evaluate the accuracy of EUS-FNA in the diagnosis of cancer in solid pancreatic masses (42): counting atypical results as positive, we found a sensitivity of 0.88 (95% CI: 0.847-0.929) and a specificity of 0.960 (95% CI: 0.922-0.998); counting atypical results as negative, sensitivity was 0.812 (95% CI: 0.750-0.874) and specificity 1. The updated data literature confirms that EUS-FNA is highly accurate in diagnosis of cancer in solid pancreatic masses (43,44). The most weighted factors affecting the accuracy are on-site cytopathological evaluation and lesion size (44). A recent Japanese study reported that with four needle passes, in absence of on-site cytology, it can be obtained a sensitivity of 93% and a specificity of 100% in the cytopathological diagnosis of solid pancreatic lesions (45). During the last ten years EUS-FNA was established as a low risk diagnostic tool in PC. The complication rate of EUS-FNA is considered to be very low, ranging between 0.3% and 1.6% (20,46-48). Controversy has arisen about the preferred method of choice to obtain pancreatic diagnostic tissue: the percutaneous approach with CT/US guidance or the EUS-guided endoscopic one. To our knowledge, till now there are only retrospective studies (49,50) and one prospective, randomized study (51) comparing the performance of percutaneous CT/US-guided FNA with EUS-guided FNA in pancreatic lesions. A retrospective analysis suggested that the sensitivity of CT-FNA was superior to EUS-FNA (71% *vs.* 42%) (49), while another retrospective study found an equivalent accuracy between EUS-FNA, CT/US-FNA and surgical biopsies (50). In the only prospective, randomized, crossover trial EUS-FNA resulted numerically, though not quite statistically, superior to CT/US FNA for the diagnosis of PC (51).

So why should we choose EUS-guided sampling instead of CT/US-FNA? Indeed some arguments in favour of this choice exist and can be summarized as follow:

(I) the ability to sample lesions (including lymph nodes) too small to be identified by other methods;
(II) concern about cutaneous and peritoneal seeding: a study from Micames *et al.* showed lower frequency of peritoneal seeding in patients with PC diagnosed by EUS-FNA *vs.* percutaneous FNA (52); a shorter needle path, the use of smaller needles and the ability to biopsy the lesion through a segment of the GI wall, which becomes part of the resected specimen, in case of surgery, can minimize the risk of needle-tract seeding;
(III) the possibility of targeting more confidently small lesions adjacent to vessels, using the color Doppler capability or lesions located in seats difficult to be reached percutaneously;
(IV) the provision of sometimes remarkable additional diagnostic and staging information through the EUS examination;
(V) there are some initial data about the superior cost-effectiveness of EUS-guided FNA in the evaluation of pancreatic head adenocarcinoma compared with CT-FNA and surgery (53).

Finally, the true strength of EUS in a patient with suspected PC is the possibility to offer a really "all inclusive" service; it can in a single step:

(I) detect the lesion (diagnosis);
(II) assess the local extent and vascular invasion of the tumor (staging and resectability assessment);
(III) if the tumor is deemed unresectable, biopsy the lesion for cytopathological confirmation (EUS-FNA);
(IV) if the patient is symptomatic, treat the pain (coeliac plexus neurolysis) or even the jaundice (EUS-guided biliary drainage) (palliative treatment).

At our institution as well as in other centers all around the world we are witnessing a clear trend toward increasing referrals for pancreatic EUS-FNA with a parallel decrease

in referrals for percutaneous FNA. EUS-FNA is perceived by physicians to be superior to CT/US-FNA and is already the preferred choice in some realities (23,51).

Current role of EUS in the differential diagnosis and surveillance of pancreatic cystic lesions

EUS can help us in detecting some morphological changes characteristic for malignancy, like thick wall, thick septations, macroseptations, mural nodules, presence of mass, but can also supply information on the surrounding pancreatic tissue and pancreatic duct anatomy, suggestive for CP or can define the communication of the cystic lesion with the pancreatic duct (54). Current literature data tell us that the EUS accuracy for differentiating malignant *vs.* non-malignant in this clinical setting ranged from 43% to 93%, with an interobserver agreement of 50% (55,56), pancreatic duct anatomy is best visible by secretin MRCP. Thus, EUS alone is not sufficient for clinical decision making, but EUS role today is no more limited to imaging alone: EUS-FNA can give some help in the characterization of pancreatic cystic lesions. EUS-FNA may provide more information: cytology and viscosity, amylase level, CEA and molecular analysis on the aspirated fluid (56-59). It is a relatively safe procedure with a complication rate of 2.2% (mostly pancreatitis) (60,61). By means of EUS-FNA we can localize the cystic lesion, define its morphology, direct the needle to the cystic wall, mural nodules, debris, septations or associated mass. In this respect we can use various needles (25, 22, 19 gauge needle or Trucut needle), one to 3 passes and we must give the patient prophylactic antibiotics. Resuming current literature data (56-59), today we know that in the aspirated fluid the interpretation of parameters should be as reported below:

(I) CEA levels;
(i) <5 ng/mL: serous cystadenoma or pseudocyst;
(ii) >800 ng/mL: mucinous cystic adenoma (MCA) or cancer;
(iii) CEA is the most accurate marker for differentiating mucinous from non-mucinous cysts but it cannot distinguish intraductal papillary mucinous neoplasm (IPMN) from MCA or benign from malignant mucinous cyst.
(II) High amylase;
(i) Pseudocyst and IPMN;

Furthermore we know that cytology is quite insensitive for both diagnosis and detection of malignancy and "EUS-FNA-Surgical Correlation" accuracy ranged between 55% and 97%.

About biochemical analyses on the aspirated cystic fluid new tools and possibilities are represented by immuno-molecular analysis (K-ras, p53, mucins pattern, telomerase, PCNA, VEGF, MMP-7 and so on) (62). We published that high levels of chromogranin A in the aspirated fluid can help in the diagnosis of neuroendocrine pancreatic cystic tumor (63). Data from US (64,65), Spain (66,67) and our group (68) seem to demonstrate that cytology samples obtained by echobrush had superior diagnostic yield compared to EUS-FNA and cytology brushings are more likely to provide an adequate mucinous epithelium specimen than standard FNA, but be careful about possible serious complications, reported with the echobrush, from 0% to 22.7%, i.e., acute pancreatitis, severe bleeding, minor bleeding, self-limited abdominal pain or minor abdominal disconfort. Also 1 death is reported in one series (66). A cost-effective analysis for asymptomatic incidental solitary cystic pancreatic tumors demonstrated that risk stratification of malignant potential by EUS-FNA and cyst-fluid analysis was most effective (69).

In conclusion, in defining the nature of a pancreatic cystic lesion CT, MRI and EUS morphology may not be enough, EUS-FNA may be of some help, combining cytology, CEA and amylase levels in the aspirated fluid. Trucut biopsy is feasible but today we don't have any data about the role of the new pro-core needle. We know that the echobrush is feasible, it can give us some better result compared to standard FNA, but complication risks must be considered. For the initial setup EUS and secretin MRCP are the best. Management decision should be individualized based on surgical candidacy, expertise and life expectancy. MRCP +/- EUS are the best for follow-up (70).

Current role of EUS in detection, diagnosis and staging of neuroendocrine tumors of the duodenopancreatic area

NETs of the duodeno-pancreatic area pose various problems in terms of diagnosis, detection, staging and treatment. Correct preoperative diagnosis, detection and staging are mandatory in these cases, to select treatment options, type of surgical intervention and to optimize the curative approach itself, limiting time and complexity of surgical intervention, thus contributing to an improvement in results of surgery. In this clinical scenario the main endoscopic technique is represented by EUS. In the past, the only endoscopic procedure that had a role in the diagnosis of NETs of the pancreas was the ERCP, which today has completely lost any diagnostic role (replaced by magnetic

resonance cholangiography and by EUS), but it has kept an exclusively operative space when drainage of the biliary tree or the pancreatic ductal system is necessary. The EUS characteristics of pancreatic NETs are in most cases represented by a homogeneous echo-pattern, often hypoechogenic, rarely non- homogeneous, with cystic or calcified areas, whilst margins are clear in over 84% of patients, sometimes having a hypoechogenic border (71). In several studies, albeit with small numbers due to the rarity of the disease, EUS demonstrated high sensitivity and specificity in diagnosing NETs of the pancreatic-duodenal area, with correct detection between 57% and 89% (71-74). Sensitivity is between 80% and 90% for tumors discovered in the pancreas, whilst it drops to 30-50% for lesions located outside the pancreas, mainly gastrinomas of the duodenal wall. The most sensitive technique for detecting these latter lesions remains intraoperative endoscopic transillumination (approximate 83%) and duodenectomy can increase sensitivity by a further 15% (75). Even though it is an extremely operator-dependent procedure and its diffusion is not completely adequate, EUS has proven to be an accurate means of preoperatively detecting small NETs of the pancreas, it is the most sensitive preoperative detection and staging technique in this clinical field and it should be used at an early diagnostic stage, as it has also proven to be cost-effective (less expensive, time saving, reduced morbidity compared with other more invasive procedures).

It must be said, however, that advancement of radiologic techniques over the last few years, especially the MDHCT, but also MRI, in terms of software and hardware, has been enormous and in the more recent comparative studies between EUS and multi-phase spiral CT the difference in sensitivity between the two methods, for example in localizing pancreatic insulinomas, would appear to be reset to zero, even though there are few comparative data reported in the literature to prove this. It can therefore be asserted that the most efficient tool for detecting insulinomas of the pancreas is a combined imaging protocol that consists of both MDHCT and EUS (76,77).

Preoperative detection of gastrinomas continues to be a problem, mainly because over the years they have often been reported as having an extrapancreatic site (up to 50% of cases). The pancreatic localization is not, as previously believed, almost exclusively in the head (the so-called gastrinoma triangle), but they are increasingly detected in the body/tail of the pancreas. Lesions located in the duodenal wall are smaller than those in the pancreas (9.6 *vs.* 28.7 mm). There are no data in the literature to confirm that spiral CT for gastrinomas has filled the sensitivity gap of EUS, as occurred for insulinomas. The EUS sensitivity for the detection of pancreatic gastrinomas is between 75% and 94%, for peripancreatic lymph nodes it is between 58% and 82%, whilst it drops to 11-50% for gastrinomas of the duodenal wall (77). Problems return again in the MEN-1 syndrome, where many tumors are small in size (1.1 cm) and they are often multiple (median 3.3 lesions/patient). In this clinical setting an EUS follow-up carried out for 8 years on 13 MEN-1 patients, revealed the onset of pancreatic tumors in 11 cases (78). It would seem that an aggressive screening programme with EUS in these patients, leading to early surgical treatment, could improve prognosis (79-81), but there is no agreement in the literature. Nevertheless, various papers demonstrated the efficacy of EUS in detecting and following small endocrine tumors of the pancreas in asymptomatic patients with MEN-1 syndrome (78-81).

The electronic linear scanning instruments introduced in the 1990s, made it possible to perform EUS-guided FNA, with increased EUS specificity for example in the diagnosis of pancreatic carcinoma and metastatic lymph node involvement (20). Some papers have been published demonstrating the usefulness of EUS-guided FNA also for the diagnosis of functioning NETs of the pancreas (80) and functioning and non-functioning NETs (82-88). As for pancreatic carcinoma, the superiority of EUS-FNA versus CT-FNA has been also demonstrated for pancreatic NETs (88). The possibility to predict biologic behaviour and outcome by means of molecular biology techniques applied to the EUS-FNA cell sample has also been described. This approach allows to limit the number of false positive findings of the morphologic EUS test alone, which may be due to intra- or peri-pancreatic lymph nodes or splenosis nodules. A methylene blue tattoo can be made with EUS-guided injection on a small NET of the pancreas in order to facilitate intraoperative localization. Both linear and radial new generation electronic EUS scopes enable application of pulsed colour and power Doppler functions, more recently associated with the use of ultrasound contrast media. These techniques can help in localization and differential diagnosis of small hypervascular pancreatic nodules (89).

A look in the near future

IntraDuctal UltraSound (IDUS) and 3-Dimensional IDUS will perhaps add something to the already high performances of EUS in diagnosis and staging of biliary and pancreatic

diseases (90). A new frontier in diagnosis and therapy could be opened by a new technique, named Endoscopic Ultrasound Retrograde CholangioPancreatography (EURCP) (91), that with some needed technological advances will allow us to put together in the same instrument the diagnostic accuracy of EUS and EUS-FNA with the therapeutic possibilities of ERCP and EUS. With such an instrument in experienced hands we can predict that the benefits to the patients and the health care system will be substantial. Today EUS is following the same way as endoscopy, i.e., to cross the bridge between a mere diagnostic technique and a therapeutic modality. In this view EUS can guide or better will guide in the near future a number of therapeutic procedures, such as ablative techniques (92,93), injection therapies (94,95), creation of digestive anastomoses (96,97). Regrettably these new techniques have progressed very slowly till now for several reasons (small number of operative endosonographers, very little incentive by manufacturers to put substantial resources into EUS and accessories development because the market is too small, the competition of CT, MRI and vascular interventional radiology).

Conclusions

To date the most accurate imaging techniques for the pancreas remain CE MDHCT and EUS. They provide the most cost-effective and accurate modalities for diagnosis and staging of most cases of pancreatic diseases. CE spiral CT or better MDHCT must today be the initial study of choice in patients with suspected PC. It has replaced digital subtraction angiography for evaluation of vascular infiltration and has similar or higher accuracy than EUS in assessing locoregional extension and vascular involvement. EUS has the highest accuracy in detecting small lesions, in assessing tumor size and lymph nodes involvement. After CE spiral CT or MDHCT or MRI as the first diagnostic tool, it remains the need of EUS as a second step in several cases: negative results on CT/MRI scans and persistent strong clinical suspicion of PC, doubtful results on CT or MRI scans, need for cyto-histological confirmation. However it remains true that the choice of diagnostic and staging modalities varies among different centers depending on the local availability of the high-end imaging techniques and operators expertise. As far as the evolution of EUS-guided therapeutic procedures is concerned, to our view, there will be in the near future great opportunities for the development of diagnostic and therapeutic EUS and pancreatic pathology will be the best testing bench for the new era of EUS.

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Delayed diagnosis of pancreatic cancer reported as more common in a population of North African young adults

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Background: Pancreatic cancer is one of the most challenging tumor entities worldwide, characterized as a highly aggressive disease with dismal overall prognosis and an incidence rate equaling mortality rate.

Objective: In order to have an update about pancreatic cancer incidence and evolution in North Africa, we conducted an epidemiological analytical retrospective study at the level of three Algerian regions: Sidi-bel-Abbes, Oran and Tlemcen along the last eight years [2006-2013].

Methods: We performed a retrospective hospital-based study in which we analyzed the records of 160 pancreatic cancer patients registered, evaluated and treated in a Northern African region; at the level of hospital centers of the three western Algerian regions from 2006 to 2013.

Results: Along the period of study, 160 patients were diagnosed with pancreatic cancer; with a mean age of 66.2 years, and a sex ratio of 1.65; other parameters such as a medical history smoking and alcoholism history, tumor site; histological type as well as the stage of diagnosis were also enrolled in the study. Our statistical analyses reported a very significant correlation between patients who belonged to the age group of 21-40 years and the advanced stage of diagnosis (basing on TNM classification) with P=0.02.

Conclusions: Pancreatic cancer is increasingly diagnosed in young adults at an advanced stage in North African regions.

Keywords: Pancreatic cancer; young adults; delayed diagnosis; North Africa

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Introduction

Pancreatic cancer is one of the most challenging tumor entities worldwide, characterized as a highly aggressive disease with dismal overall prognosis and an incidence rate equaling mortality rate (1,2). Less developed regions have low rates of pancreatic cancer (2.4), it is relatively rare in Africa and Asia (3,4). However and despite all medical research efforts; it ranks as the fourth deadliest cancer in the United States after cancers of the lung, colon, and breast. In 2013, an estimated 45,220 newly diagnosed of pancreatic cancer and 38,460 deaths were expected in the US (5).

The main reason could be the difficulty of its diagnosis since no specific cost-effective screening tests can easily and reliably find early-stage pancreatic cancer in people who have no symptoms of the disease. This means it is often not found until later stages when the cancer can no longer be removed with surgery and has spread from the pancreas to other parts of the body (6). In fact, the Surveillance, Epidemiology, and End Results (SEER) database also shows that for every 12.2 patients diagnosed per 100,000, 10.9 will die from pancreatic cancer, despite the best efforts of researchers and clinicians to improve survival outcomes in patients (7).

In order to have an update about pancreatic incidence and evolution in western Algeria, we conducted an epidemiological analytical retrospective study at the level of three western Algerian regions: Sidi-bel-Abbes, Oran and

Tlemcen along the the last 8 years [2006-2013].

Patients and methods

The population

This hospital based study was carried out respectively at the level of Surgery Departments of the University Hospitals of Sidi-bel-Abbes and Tlemcen as well as the Pathology Department of the Military Hospital of Oran (HMRUO) where patients' data were collected routinely. In the current epidemiological retrospective study we analyzed patients' records basing on different parameters such as: age, gender, medical history, smoking history, as well as TNM histopathological classification. A total sample of 160 patients aged between 16-96 years was diagnosed with pancreatic cancer between 2006 and 2013.

The statistical analysis

Concerning the statistical analytical study, the raw data were summarized using rates and cross-tabulations. Associations between categorical parameters were tested using Pearson's chi-squared test (χ^2) test. Results were presented using P value; the level of its significance was limited by the rate of 5%. All data were processed and analyzed via SPSS 20.0 (Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL, USA. August 2011).

Results

Of 160 patient records were included in our survey, 105 (65.6%) were male and 55 (34.8%) were female. There was an overall male predominance with the male to female ratio of 1.9 (*Table 1*). The median age at the diagnosis was 62.2 with a minimum age of 16 years and maximum of 96 years.

More than the half of our patients were aged between 61-80 years old (57.5%) followed respectively by the age groups of 41-60 (21.2%), the more than 80 (13.7%); 21-40 (6.87%) and finally patients aged less than 20 (0.62%) (*Table 1*).

The site of the tumor was in the head of the pancreas in 90% of cases, in the body of the pancreas in 5.62% of cases, and in the tail of the pancreas in 4.3% of cases (*Table 1*).

The proportion of patients with a history of cigarette smoking was 32.5%; all the smokers were male patients; similar results were also reported for history of alcohol; where only males were alcoholics (20.6%) (*Table 1*).

Table 1 Patients medical features

Characteristics	Number of cases	Percentage (%)
Sex (n=160)		
Male	105	65.62
Female	55	34.38
Sex ratio	–	1.9
Age (years)		
<20	1	0.62
21-40	11	
41-60	34	21.25
61-80	92	57.5
>80	22	13.75
Smoking history		
Male smoker	52	32.5
Female smoker	0	0
Male non-smoker	24	15
Female non-smoker	55	34.38
Not mentioned	29	18.12
Alcohol history		
Alcoholism (only males)	33	20.6
Not mentioned	52	32.5
Symptoms and signs		
Jaundice	148	92.5
Abdominal pain	152	95
Right hypocondrium pain	145	90.6
Vomiting and nausea	138	86.3
Weight loss	140	87.5
Dark urine	102	63.75
Pruritus	105	65.6
Tumour site		
Head of the pancreas	144	90
Body of the pancreas	9	5.63
Tail of the pancreas	7	4.37
Histopathology		
Well differentiated adenocarcinoma	72	45
Moderately differentiated adenocarcinoma	33	20.62
Poorly to moderately differentiated adenocarcinoma	30	18.75
Infiltrant adenocarcinoma	10	6.25
Poorly differentiated carcinoma	7	4.37
Non differentiated carcinoma	5	3.12
Not mentioned	3	1.89

Table 1 illustrates as well the following histological types: 20% moderately differentiated adenocarcinomas; 45% well differentiated adenocarcinomas; 6% infiltrant adenocarcinomas; 3% non-differentiated carcinomas; 4% poorly differentiated carcinomas and 18% poorly to moderately differentiated adenocarcinomas.

The majority of our patients complained from the following symptoms: abdominal pain (95%); jaundice (92%); right hypocondrium pain (90%); vomiting and nausea (86%); weight loss (87%); dark urine (63%); pruritus (65%); acholic stools (57%) (*Table 1*).

Table 2 demonstrates the most common diseases recorded in medical history of our studied population which were respectively: high blood pressure (20.6%); type 2 diabetes (15%) and type 1 diabetes (13%).

Table 2 Patients' medical history

Medical history	Number of cases	Percentage (%)
High blood pressure	33	20.6
Males	20	12.5
Females	13	8.1
Type 1 diabetes	22	13.7
Males	16	10
Females	6	3.7
Type 2 diabetes	25	15.6
Males	16	10
Females	9	5.6
Nothing to report	80	50
Males	53	33.1
Females	27	16.8

Table 3 illustrates the different proportions of diagnosis stages of our patients. A total of 26.2% were diagnosed at M1 stage; followed respectively by T4 stage (21.8%); T3 (21.2%); T2 (13.2%); N1 (10.6%); T1 (4.3%) and Tis (1.8%).

In order to deepen our investigation, we performed a statistical analytical study by which we studied possible association between patient's age group and the stage of diagnosis (TNM classification) via Pearson's chi-squared test. Our statistical analyses reported a significant association between patients aged between 21-40 years and the stage of diagnosis with P=0.02 i.e., (P>0.05); however any significant association was reported between the other age groups and the stage of diagnosis (*Table 3*).

Discussion

The present survey is one of the very few surveys who studied the profile of pancreatic cancer in North Africa in general and Algeria in particular.

With a sex-ratio of 1.9 our investigation confirmed once more that men are more likely to develop pancreatic cancer than women. These results matched with many other previous investigations as those of Schiffman *et al.* (8).

Our results showed that 32% of our patients were cigarette smokers, and 20% were alcoholics; which could represent a risk factor for developing a pancreatic cancer since several published reports showed that smokers had about a 2-fold increased risk, compared to nonsmokers (9,10).

We noticed also that most of our patients complained from Jaundice; right hypochondrium pain and abdominal pain; which proves that pancreatic cancer is a silent disease, as reported in many other findings stated that pancreatic cancer symptoms do not manifest early and initial symptoms

Table 3 Association between age and TNM histopathological classification

Characteristics	Tis (%)	T1 (%)	T2 (%)	T3 (%)	T4 (%)	N1 (%)	M1 (%)	P value
Age (years)								
<20	–	0	0	0	0	0	1 (0.6)	–
21-40	–	0	1 (0.6)	3 (1.9)	2 (1.25)	1 (0.6)	4 (2.5)	0.027
41-60	1 (0.6)	1 (0.6)	6 (3.7)	7 (4.3)	5 (3.1)	6 (3.7)	8 (5.0)	0.928
61-80	1 (0.6)	3 (1.9)	12 (7.5)	21 (13.1)	21 (13.1)	9 (5.6)	25 (15.6)	0.733
>80	1 (0.6)	3 (1.9)	3 (1.9)	3 (1.9)	7 (4.3)	1 (0.6)	4 (2.5)	0.521
Total	3 (1.8)	7 (4.3)	22 (13.7)	34 (21.2)	35 (21.8)	17 (10.6)	42 (26.2)	

P, statistical significance.

are often nonspecific (11). Concerning tumors' location, most of them were located in the head of the pancreas (90%), followed respectively by cancer of the neck and the tail of the pancreas which represented a tiny minority. The study of Kalser *et al.* demonstrated as well that more than two thirds of pancreatic cancers occur in the head of the pancreas (12).

Diabetes mellitus was associated and pointed in several investigations as possible risk factor for pancreatic cancer (10); which concord to our findings since 30% of our studied population presented type 1 and type 2 of diabetes (*Table 2*).

Our survey demonstrated an increasing frequency of pancreatic cancer with the advanced age of patients since most of them were aged between 61 and 80 years old, these results agree with those of Shibata's *et al.* who concluded that this could be due to the dietary habits of the patients (13).

In the other hand; the current investigation confirmed indeed the rarity of pancreatic cancer in young adults; since only 7% of our population suffered from it, which agrees with the results of Perez *et al.* who found that the incidence of identified pancreatic carcinomas in patients under the age of 30 was only about 0.46/million (14). Same conclusion for Lüttges *et al.* who evaluated the incidence of pancreatic ductal adenocarcinomas in patients aged of 40 years old and was approximately equal to 0.3%, and the incidence in patients aged of 20 years was only about 0.1% (15).

However, despite the low rate of our patients (7%) belonging to that young age group; 36.36% of them were diagnosed at M1 stage which represented the majority. Concordant with our results those of Brand *et al.* who found that pancreatic cancer is increasingly diagnosed in the younger at an advanced stage (16). Berry *et al.* stated that nearly 50% of patients aged between 16 and 54 with pancreatic cancer are more likely than those who are older to be diagnosed at a stage when the disease is incurable, because of poor awareness, misdiagnosis and care delays (17).

Some authors confirm that pancreatic cancer is frequently diagnosed at an advanced stage, possibly because of the tumor biology showing an aggressive behavior and symptoms often being non-specific mainly in the young (18); Gulliford *et al.* reported as well that patients with some less common cancers such as pancreatic cancer were more likely to require three visits or more to their primary care physician before they were referred to a specialist (19). What we have to emphasis as well is the status of Algeria as a third world country, thus it's undeniable that lack of healthcare centers, high prices of drugs, cancer therapies, medical checkups as well as the low socioeconomic level of Algerian citizen are all major factors which may have a direct impact on that fatal disease survival chances.

Since most of our patients had pancreatic adenocarcinomas (*Table 1*) presented in late stage at the time of diagnosis; their prognosis was pretty poor; with a 1-year survival rate of 20% and a 5-year survival rate of less than 5%: as explained the survey of Kuvshinoff *et al.* (20). The only hope of long-term survival is if curative resection can be undertaken; however, since pancreatic cancer patients seldom exhibit disease-specific symptoms until late in the course of the disease, very few patients (<15-20%) have resectable disease by the time the diagnosis is made (21,22). While complete surgical resection may lead to long-term survival in approximately 25% of patients, only 15% are actually resectable (20).

It is therefore essential to distinguish all kinds of tumor from other pancreatic neoplasms particularly adenocarcinoma for which the prognosis is extremely poor as stated above (23). Surgery for pancreatic cancer is probably the most demanding and risky operative procedure in abdominal surgery (24). Nevertheless the huge lack of pathology laboratories and cancer research centers in Algeria and third world countries have a main negative impact on the precision and quality of the diagnosis.

Seelig *et al.* reported that in a young patient with advanced disease, resection may give a weak but valuable increase of survival. In fact, metastatic pancreatic cancer could become overt when the point of no return has already been passed as it could be the case in the presence of positive interaortocaval lymph nodes, or metastatic cancer will be detected during operation despite negative imaging results preoperatively (25). Picozzi *et al.* affirmed that despite R0 resection, long-term survival does not exceed 25% even in the most experienced pancreatic centers may prove that carcinoma of the pancreas is a systemic disease. Further improvement of survival can only be achieved by adjuvant treatment (26).

Our survey showed clearly that young adults who suffered from pancreatic cancer in general; and cancer of the head of pancreas in particular; are unfortunately diagnosed at a very late stage in Western Algeria; when the likelihood of recovery is poor and patients have no other choice than to accept their ongoing symptoms.

Conclusions

Young adults are often seen to be healthier than older ones. Lack of awareness, socio-cultural habits and carelessness

could be fatal for patients who suffer from pancreatic cancer; awareness should be increased among healthcare professionals and mainly among third world countries' citizen. The earlier the diagnosis is made, the better are chances for the patient's survival.

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Pancreatic cancer surgery: past, present, and future

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Abstract: The history of pancreatic cancer surgery, though fraught with failure and setbacks, is punctuated by periods of incremental progress dependent upon the state of the art and the mettle of the surgeons daring enough to attempt it. Surgical anesthesia and the aseptic techniques developed during the latter half of the 19th century were instrumental in establishing a viable setting for pancreatic surgery to develop. Together, they allowed for bolder interventions and improved survival through the post-operative period. Surgical management began with palliative procedures to address biliary obstruction in advanced disease. By the turn of the century, surgical pioneers such as Alessandro Codivilla and Walther Kausch were demonstrating the technical feasibility of pancreatic head resections and applying principles learned from palliation to perform complicated anatomical reconstructions. Allen O. Whipple, the namesake of the pancreaticoduodenectomy (PD), was the first to take a systematic approach to refining the procedure. Perhaps his greatest contribution was sparking a renewed interest in the surgical management of periampullary cancers and engendering a community of surgeons who advanced the field through their collective efforts. Though the work of Whipple and his contemporaries legitimized PD as an accepted surgical option, it was the establishment of high-volume centers of excellence and a multidisciplinary approach in the later decades of the 20th century that made it a viable surgical option. Today, pancreatic surgeons are experimenting with minimally invasive surgical techniques, expanding indications for resection, and investigating new methods for screening and early detection. In the future, the effective management of pancreatic cancer will depend upon our ability to reliably detect the earliest cancers and precursor lesions to allow for truly curative resections.

Keywords: Whipple; pancreaticoduodenectomy (PD); pancreatic cancer; pancreatic ductal adenocarcinoma (PDAC); surgical history; history of pancreatic cancer; Codivilla; Kausch; William Halsted; John Cameron

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the 4th leading cause of cancer deaths in the United States with 2015 projections estimating 49,000 new cases, 41,000 new deaths, and a 5-year relative survival rate of only 7% (1). For those afflicted with this terrible disease, surgery remains the only hope for cure. Unfortunately, only 15-20% of patients are candidates for surgery at the time of diagnosis and among these, median postoperative survival is <20 months with a 5-year survival of only 20% (2). However, it was not long ago that pancreatic resections were thought to be impossible and more recently still that perioperative mortality rates approached 30%. Today, pancreaticoduodenectomy (PD) is the most common procedure performed for pancreatic cancer and it is carried out routinely at high-volume centers with mortality rates <2%. It has taken over a century of persistence by pioneering surgeons, each building upon the achievements of the previous, to arrive at this point (*Table 1*). Thanks to their efforts, the focus has now shifted from surviving the operation to surviving the cancer and the field of pancreatic surgery is evolving to reflect that. Though the operations themselves are likely to remain largely the same, the future of pancreatic surgery lies in how, when, and in whom we perform them.

From barbers and bloodletters: the rise of surgery in the 19th century

Prior to the 19th century, the pancreas and some accounts of its disease had already been described, but abdominal surgery was uncommon and discouraged since merely entering the abdomen was almost uniformly fatal (16). Surgery was in its infancy and its practitioners, considered on par with craftsmen and artisans, held much lower social standing than their university-trained physician counterparts (17). In Europe, they aligned themselves in guilds with barbers and received training through apprenticeships. These barber-surgeons applied their

Table 1 Landmark pancreatic resections

Year	Surgeon	Place	Procedure	Notes
1882	Friedrich Trendelenburg (3)	Bonn, Germany	DP and splenectomy	First anatomical solid tumor resection
1898	Alessandro Codivilla (4)	Imola, Italy	One-stage partial PD	First attempted radical PD, unsuccessful
1898	William Halsted (5)	Baltimore, USA	Transduodenal excision	First local periampullary tumor excision
1909	Walther Kausch (6)	Berlin, Germany	Two-stage partial PD	First successful partial PD
1914	Georg Hirschel (7)	Heidelberg, Germany	One-stage partial PD	First successful one-stage partial PD
1929	Roscoe Graham (8)	Toronto, Canada	Enucleation	First neuroendocrine tumor resection
1934	Allen Whipple (9)	New York, USA	Two-stage PD	First anatomical PD (ampullary carcinoma)
1937	Alexander Brunschwig (10)	New York, USA	Two-stage PD	First anatomical PD for PDAC
1940	Allen Whipple (11)	New York, USA	One-stage anatomic PD	First one-stage anatomical PD
1942	Kenneth Watson (12)	Surrey, UK	Two-stage PPPD	First PPPD
1978	Traverso & Longmire (13)	Los Angeles, USA	One-stage PPPD	Reintroduction and popularization of PPPD
1994	Gagner & Pomp (14)	Montreal, Canada	Laparoscopic PD	First laparoscopic pancreatic resection
2003	Giulianotti *et al*. (15)	Grosseto, Italy	Robot-assisted lap PD	First robotic pancreatic resection

DP, distal pancreatectomy; PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; PPPD, pylorus-preserving pancreaticoduodenectomy.

broad skill with knives and razors to a range of minor external procedures (as opposed to the "internal medicine" practiced by physicians) such as lancing abscesses, excising skin lesions, and removing foreign bodies in addition to the more mundane, but steady occupations of cutting hair, shaving, and bloodletting (16).

At the dawn of the 19th century, while surgeons were still shedding their artisan roots, major surgical interventions were still relatively rare. The extraordinary pain combined with high mortality rates from postoperative infections relegated surgery to a last resort measure and emphasized speed and simplicity over technique (16). This would soon change with the revolutionary advent of anesthesia in the 1840s followed by growing adherence to Listerism in the later half of the century. These advances catalyzed the field's transformation from a tradecraft into a true medical science capable of the complex abdominal surgery required to intervene upon the pancreas.

Ether anesthesia was first used in 1842 by a rural surgeon from Georgia named Crawford W. Long (18), but the technique was popularized by William T. G. Morton after his famous demonstration at Massachusetts General Hospital in 1846 (19,20). Absent the limitations imposed by patient discomfort, surgeons were free to dispense with slashing speed in favor of meticulousness and procedures became increasingly sophisticated. Unfortunately, these technical achievements were overshadowed by an abysmal mortality rate of over 50% for major operations (21,22). The overwhelming majority of these deaths resulted from the postoperative wound infections that developed in up to 80% of cases. At the time, the germ theory of disease was not widely accepted and surgeons did not recognize a need for cleaning instruments, hands, or even operative sites prior to surgery.

In 1867, inspired by Louis Pasteur's experiments with fermentation, Joseph Lister published the first of his pioneering works on surgical antisepsis (23,24). He suggested that wound infection resulted from airborne contamination by ubiquitous "atmospheric germs" and recommended the use of carbolic acid in wound dressings to kill any contaminating organisms before they could cause disease. Over the next 40 years, Listerian antiseptic techniques gradually evolved into the more scientific and comprehensive principles of surgical asepsis, which sought to prevent infection by excluding bacteria altogether from the operative field (21). By the first decade of the 20th century, surgeons had assimilated most of the familiar surgical accouterments and rituals of modern aseptic technique, which led to a dramatic decline in postoperative mortality rates. German-trained New York physician Carl Beck reported in 1895 that antisepsis, followed by asepsis, had decreased amputation associated mortality at the University Hospital in Munich from an excess of 60% to just 2% (22).

The building blocks of pancreatic surgery

Cancer of the pancreas: defining the problem

In his 1761 publication *The Seats and Causes of Diseases*, Italian anatomist Giovanni Battista Morgagni [1682-1771] reported several cases of pancreatic "scirrhus," which many consider to be the earliest recorded accounts of PDAC (25). However, lack of a microscopic evaluation and the ambiguous terminology of the day make it impossible to know whether his descriptions represent genuine PDAC or merely chronic pancreatitis. Additional reports begin to appear in the literature by around 1820, but perhaps the most reliable early accounts of PDAC were published in 1858 by Jacob M. Da Costa (26). His compilation of 37 cases, including the first microscopic diagnosis, helped to legitimize PDAC as a true disease entity, which even by that time had not been firmly established (27). Despite the mounting evidence confirming the existence of PDAC, efforts directed at surgical intervention were slow to develop. According to the famous Polish surgeon Johann von Mikulicz-Radecki [1850-1905], the delay in progress resulted from three seemingly insurmountable barriers that led to a *noli me tangere* stance toward pancreatic surgery (28). First, the anatomical location of the pancreas made it "exceedingly difficult" to access using the surgical techniques and resources available in the 19th century. Second, diagnosis of PDAC was very difficult and usually made at a late stage when disease was already unresectable. Finally, the significant morbidity of pancreatic surgery often proved fatal due to limitations in perioperative care including the lack of intravenous fluids, nutritional support, and infection control.

Surgical palliation: evolution of the bilioenteric bypass

Following the advent of surgical anesthesia and antisepsis, abdominal procedures became more frequent as surgeons were suddenly able to intervene upon previously nonsurgical diseases. It was during this period of rapid surgical discovery that many of the building blocks of modern pancreatic surgery were first developed. Notable among these is the bilioenteric bypass, which has its origins in the management of benign biliary disease before its application to malignant obstructive processes. Because the pancreas remained off limits to all but the most intrepid surgeons, palliative biliary bypass became the first form of surgical management for PDAC.

James Marion Sims [1813-1883], an American surgeon from South Carolina, performed the first planned cholecystostomy in 1878 (29). His patient was a 45-year-old woman with long-standing jaundice and a large right upper quadrant mass that he presumed to be "dropsy" of the gallbladder (gallbladder hydrops) from obstructive cholelithiasis. After noting temporary symptom relief with gallbladder aspiration, Sims decided to create a permanent fistula to allow for continuous external decompression. Under antiseptic technique, he incised the gallbladder, removed a total of 60 gallstones, and sutured the cut edges to the abdominal wall. Afterwards, the patient reportedly experienced "*immediate relief of pain, itching, nausea, [and] vomiting*" (29). Unfortunately, she died abruptly on post-operative day 8 from a gastrointestinal hemorrhage related to her obstructive coagulopathy. Nevertheless, Sims considered the procedure a success in principle and justified by the fact that "*death is absolutely certain in every case where the gall-ducts are mechanically obstructed, unless an outlet be obtained*." Furthermore, in acknowledgement of the changing times, Sims commented that the procedure was also "*a triumph for Listerism; for the post-mortem showed there was not the least trace of peritonitis or other untoward complication to be found as the direct result of the operation*".

Two years later in 1880, Alexander von Winiwarter [1848-1917] attempted the first bilioenteric bypass by performing an anastomosis between the gallbladder and colon (30). A series of anastomotic complications ensued, but eventually he was able to revise the original bypass to a functioning cholecystojejunostomy. In 1887, two surgeons independently adapted von Winiwarter's procedure for palliation in the setting of malignancy when they performed the first planned, one-stage cholecystojejunostomies. The first was performed by the Russian surgeon Nestor Dmitrievic Monastyrski for a periampullary tumor, followed a month later by Swiss surgeon Otto Kappeler for PDAC (31).

Over time, the procedure would continue to undergo revisions and modifications, but the most significant for the evolution of pancreatic surgery came when Ambrose Monprofit performed the first Roux-en-Y cholecystojejunostomy in 1904 (32). Using an adaptation of Cesar Roux's recently described gastrojejunostomy-en-Y technique, he fashioned a defunctionalized limb of jejunum to serve as a conduit for restoring biliodigestive continuity (33). A similar Roux-en-Y configuration with a cholecystojejunostomy biliary reconstruction would later serve as the backbone for Whipple's revised two-stage PD (34).

Figure 1 Alessandro Codivilla [1861-1912]. Courtesy of Archivio Storico, Universita de Bologna, Italy.

The first pancreatic resections for cancer

Distal pancreatectomy (DP)

In his 1886 monograph, *The Surgery of the Pancreas*, preeminent American surgeon Nicolas Senn [1844-1908] wrote, "*the most favorable conditions for extirpation are presented if the disease is primarily located in the tail of the pancreas*" (35). Like other surgeons of the day, Senn recognized that compared to the head of the pancreas, the body and tail were more easily accessible and amenable to resection without the need for pancreatic, biliary, or gastrointestinal reconstruction. Moreover, bleeding was less of a concern because there were fewer major vascular structures in this region (apart from the splenic vessels) and tumors were less likely to cause obstructive jaundice with its attendant coagulopathy.

Based on these factors, it is no surprise that the first anatomical resection for a solid tumor of the pancreas was a DP, performed by Friedrich Trendelenburg [1844-1924] in 1882. Over the course of a 1.5-hour procedure, he resected a massive spindle cell carcinoma *en bloc* with the tail of the pancreas from which it arose (3). The procedure was complicated by an intraoperative splenic injury and necessitated splenectomy. Despite a postoperative course complicated by wound infection and worsening malnutrition, the patient insisted on being discharged from the hospital and reportedly died at home a few weeks later from acute respiratory failure. Unfortunately, details are scarce and no autopsy was performed to determine the specific cause of death (36,37).

Despite the patient's poor outcome, Trendelenburg's procedure successfully demonstrated the technical feasibility of a major pancreatic resection and marks the birth of pancreatic cancer surgery. Nevertheless, the burgeoning field remained slow to progress and over the span of more than 2 decades between 1882 to 1905, only 24 distal pancreatectomies were performed by 21 different surgeons (including Trendelenburg) (36,37).

Early attempts at pancreatic head resection

By the turn of the century, reports of pancreatic head resections for solid tumors finally began to emerge, but these were mostly limited resections like Giuseppe Ruggi's enucleation in 1889 (38) and Domenico Biondi's duodenum-sparing partial head resection in 1894 (39). One glaring exception is the unique case of Italian surgeon Alessandro Codivilla (1861-1912, *Figure 1*), who ambitiously attempted the first recorded partial PD in 1898 (4). Interestingly, Codivilla is best known for his career and contributions in the field of orthopedic surgery, but the early focus of his career, prior to appointment as professor of orthopedics, was in abdominal procedures with particular expertise in gastric surgery (4).

On exploration, Codivilla encountered an "epithelioma of the head of the pancreas" that he would have preferred to enucleate, but because it was adherent to the duodenum he decided in favor of an *en bloc* resection of the pancreatic head, distal stomach, proximal duodenum, and distal common bile duct. His reconstruction consisted of a Roux-en-Y gastrojejunostomy [described by Roux just 1 year prior (33)] with cholecystojejunostomy over Murphy buttons. While there is admittedly no discussion of Codivilla's management of the pancreatic stump in the sparse documentation of the procedure, he most likely ligated it based on the typical practice of the day for distal resections and his own writings on the subject of pancreatic surgery (4). Postoperatively, the patient developed continuous drainage of serous fluid from the surgical wound followed by "milky clots" suggestive of a pancreatic fistula. The patient subsequently developed intractable diarrhea and "died of cachexia on the 21st day" (4,36).

Just 5 days after Codivilla's procedure, William Stewart Halsted [1852-1922, *Figure 2*] performed the first successful resection of a periampullary cancer at the Johns Hopkins

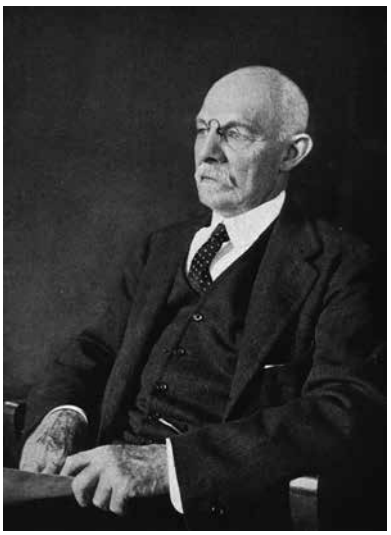

Figure 2 William Stewart Halsted [1852-1922]. Photograph by John H. Stockdale. Courtesy of the U.S. National Library of Medicine.

Hospital (5). Through a transduodenal approach, he resected *en bloc* a large wedge-shaped portion of duodenum surrounding the papillary growth with short segments of the adjacent pancreatic and common bile ducts. The ducts were then reimplanted into the duodenum by incorporating them into the primary closure of the duodenal defect. The patient survived the procedure, but ultimately died later that year from complications related to local recurrence of her cancer.

Kausch: the first successful PD

In the years following the landmark procedures by Codivilla and Halsted, a succession of discoveries paved the way for what was to be the first successful PD. The first was Theodor Kocher's popularization of a method for duodenal mobilization in 1903 (40) followed by its successful application to pancreatic surgery by Pierre Duval in 1906 (41). The "Kocher maneuver" overcame Mikulicz's first barrier by significantly improving surgical access to the pancreas.

In 1907, Abel Desjardins published a theoretical blueprint for a one-stage PD that included the first description of a pancreaticoenterostomy reconstruction (42,43). A year later, Louis Sauve outlined a similar procedure, but advocated for two-stages and externalization of the pancreatic remnant to form a controlled pancreatic fistula (41,42). In both cases, the authors based their reports on cadaveric dissections without ever performing them in a living person.

The American surgeon Robert Coffey built upon these contributions with his 1909 results from a series of experimental pancreaticoenterostomies performed in dogs (44). Coffey obtained his best outcomes by invaginating the pancreatic stump into a draining limb of bowel in an end-to-end fashion, surrounding the cut edge of pancreas with a protective collar of inverted, peritoneum-covered bowel.

In the same year that Coffey reported his results, German surgeon Walther Kausch [1867-1928] drew upon the cumulative knowledge gained over the preceding 11 years to perform the first successful partial PD in a patient with ampullary cancer (6). Due to severe malnutrition and obstructive jaundice, Kausch elected to perform the procedure in two stages to minimize the surgical risk. In the first, he restored biliary outflow with a loop cholecystojejunostomy and Braun anastomosis over Murphy buttons. Two months later, Kausch completed the procedure by performing an *en bloc* distal gastrectomy, proximal duodenectomy, and partial pancreatic head resection followed by a loop gastrojejunostomy and end-to-end pancreaticoduodenostomy in a manner similar to Coffey's canine procedure. The patient lived an additional 9 months in good condition before ultimately dying of cholangitis.

In the 2 decades following Kausch's procedure, there were just two additional reports of successful pancreaticoduodenal resections (7,45). Although the technical aspects of the procedure had improved greatly, diagnosis and perioperative care (two of the Mikulicz barriers to PDAC surgery) were slower to progress. Without the ability to diagnose cancer effectively at an earlier stage, surgeons were often forced to abort procedures due to advanced disease encountered upon exploration. Moreover, the inherent risks of the surgery and the limited resources available for managing even the uncomplicated cases meant that in many instances, palliative procedures had better survival than attempts at curative resection. As a result, many surgeons had abandoned efforts at resecting cancers in the head of the pancreas and periampullary cancers were resected through the largely unsuccessful transduodenal approach.

The turning point for pancreatic surgery came in 1927, just 5 years after the landmark discovery of insulin by Banting and Best (46), when Wilder and colleagues reported the first insulin-secreting tumor of the pancreas (47). Two years later, Roscoe Graham performed the first curative resection for

an insulinoma by enucleation, thereby demonstrating the existence of a diagnosable pancreatic neoplasm amenable to surgical intervention (8).

From Whipple to Cameron: the modernization of pancreatic cancer surgery

The success of pancreatic resections for neuroendocrine tumors renewed interest in pancreatic surgery, particularly in the newly appointed Surgeon-in-Chief at Columbia-Presbyterian Medical Center in New York, Allen Oldfather Whipple (1881-1963, *Figure 3*). At the time, he was struggling with the transduodenal approach for periampullary cancers and viewed the successes with neuroendocrine tumors as an opportunity to revive more radical resection techniques for "*attacking the problem of malignancy of the pancreas and peri-ampular region*." (9). In 1935, he published his landmark manuscript entitled *Treatment of Carcinoma of the Ampulla of Vater*, wherein he presented a two-stage technique for the radical resection of periampullary cancers consisting of cholecystogastrostomy and posterior loop gastrojejunostomy followed by partial duodenectomy, partial pancreatic head resection, and pancreatic stump occlusion (*Figure 4*) (9,48). Shortly thereafter, he revised the first stage to a Roux-en-Y cholecystojejunostomy (and later choledochojejunostomy) after it became apparent that the reflux of acidic gastric contents through the cholecystogastrostomy resulted in cholangitis and anastomotic stricture (*Figure 5*) (34,49). After Whipple's report on PD for ampullary tumors, Alexander Brunschig became the first to apply the procedure successfully to PDAC in 1937 (10).

Figure 3 Allen Oldfather Whipple [1881-1963]. Courtesy of Archives & Special Collections, Columbia University Health Sciences Library.

In 1940, Whipple performed the first successful one-stage PD as an unplanned, but masterfully improvised procedure on a patient believed to have gastric cancer. After transecting the midportion of the stomach, Whipple was "astonished and chagrined" to find that the tumor

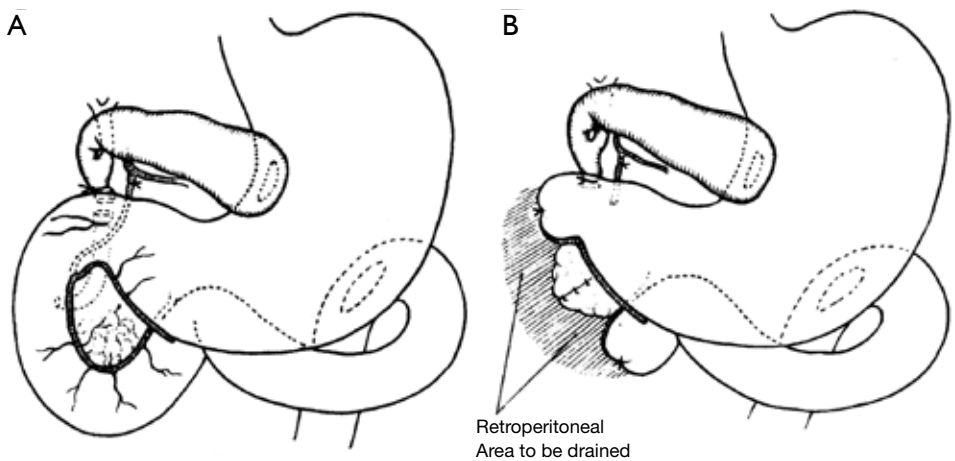

Figure 4 Two-stage pancreaticoduodenectomy as described by Allen O. Whipple in his original 1935 publication. (A) Common bile duct ligation, cholecystogastrostomy, and posterior loop gastrojejunostomy; (B) partial duodenectomy (parts 2 & 3), partial pancreatic head resection using a V-shaped incision, suture ligation of main pancreatic duct, approximation and closure of V-shaped defect in pancreatic remnant. Adapted from reference (9), with permission from Wolters Kluwer Health Inc.

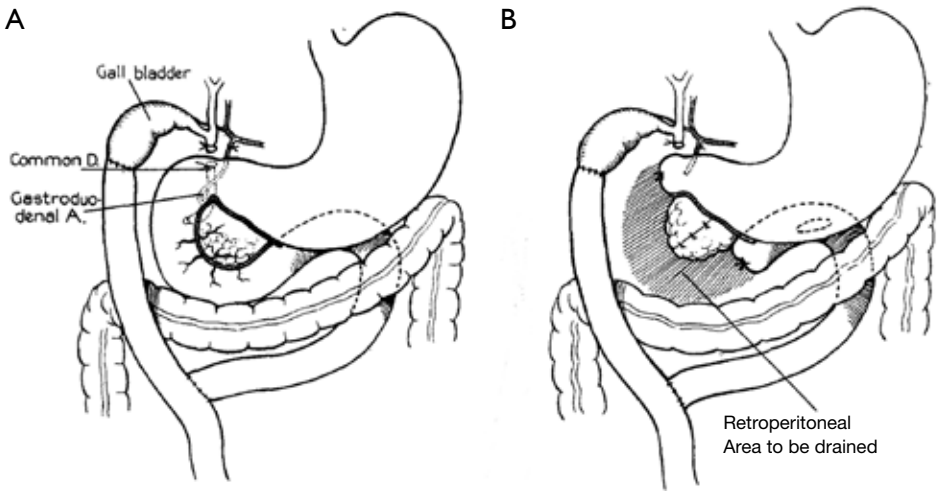

Figure 5 Revised Roux-en-Y pancreaticoduodenectomy as described by Allen O. Whipple in 1938. (A) Stage 1: ligation of the common bile duct followed by Roux-en-Y cholecystojejunostomy (later choledochojejunostomy); (B) stage 2: posterior gastrojejunostomy with partial duodenectomy, partial pancreatic head resection, and pancreatic duct occlusion in the same manner as the original procedure. Adapted from reference (34), with permission from Elsevier.

was actually located in the head of the pancreas (11). However, because the patient was not jaundiced, he felt comfortable proceeding with an impromptu conversion to a one-stage PD. To accomplish this, he expanded the usual *en bloc* resection to include the distal stomach, the entire duodenum, and the pancreatic head followed by loop gastrojejunostomy and choledochojejunostomy (*Figure 6*) (50,51). The patient recovered uneventfully and although pathology revealed a non-functioning islet cell carcinoma, she lived an additional 9 years before succumbing to metastatic disease. Later that same year, Verne Hunt (52) in Los Angeles and Ridgway Trimble (53) in Baltimore independently performed successful one-stage pancreaticoduodenectomies as well.

Whipple had previously stressed the importance of a staged procedure to minimize the bleeding risk from prolonged biliary obstruction. Serendipitously, 1940 was also the year that vitamin K became widely available for clinical use. When combined with bile salts, it effectively reversed the coagulopathy caused by prolonged biliary obstruction. This, along with the increased availability of intraoperative blood transfusions, obviated the need for staging the operation and the one-stage procedure became the operation of choice in most patients (54).

Another of Whipple's tenets from his early experience with PD was the avoidance of a pancreatic anastomosis in favor of stump occlusion to avoid serious anastomosis-related complications. However, by the early 1940s, several surgeons were successfully employing pancreaticoenterostomies and animal studies were demonstrating rapid epithelialization of pancreatic anastomoses within 24-48 hours. By 1942, Whipple had also incorporated an end-to-side pancreaticojejunostomy using a duct-to-mucosa technique (54). Going forward, Whipple described his procedure thus:

"*(I) At least two days of vitamin K and bile salts therapy; (II) the distal half of the stomach, the entire duodenum, the terminal portion of the common duct and the head of the pancreas were removed en masse; (III) a vertical limb of the jejunum, starting at the duodenojejunal junction, was brought up through a rent in the mesocolon, behind the colon, with the following anastomoses in sequence: (i) a choledochojejunostomy, end-to-end; (ii) an anastomosis between the pancreatic duct and the wall of the jejunal opening the size of the pancreatic duct, followed by the tacking of the stump of the resected pancreas to the wall of the jejunum; (iii) an end-to-side gastrojejunostomy. A sump drain in the bed of the duodenum was used. Silk technic was employed throughout.*" (11).

The "Whipple procedure" remained the standard resection technique for cancers involving the head of the pancreas until Traverso and Longmire reintroduced the concept of pylorus preservation in 1978 to reduce the incidence of postgastrectomy syndrome and marginal ulceration (13). Pylorus-preserving pancreaticoduodenectomy (PPPD)

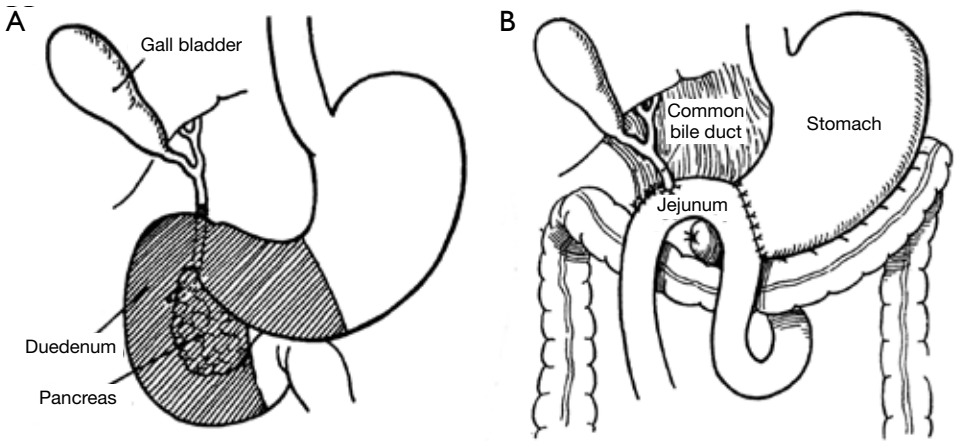

Figure 6 First one-stage radical pancreaticoduodenectomy as described by Allen O. Whipple in 1945. (A) Shaded area illustrates the anatomical region to be resected (partial gastrectomy, total duodenectomy, pancreatic head resection, common bile duct ligation and transection); (B) reconstruction with antecolic gastrojejunostomy and choledochojejunostomy. Pancreaticojejunostomy was added in 1942. Adapted from reference (50), with permission from Wolters Kluwer Health Inc.

was originally described by Kenneth Watson in 1944 and consisted of a resection similar to Whipple's original two-stage procedure with reconstruction via end-to-end duodenojejunostomy rather than loop gastrojejunostomy (12). Traverso and Longmire's PPPD, which employed an end-to-side duodenojejunostomy, later gained popularity because of its simplified procedure, reduced operative times, and the perception that it reduced gastrectomy-related complications by preserving the stomach and pyloric sphincter mechanism. Alternatively, many believed that the more limited resection and lymphadenectomy risked leaving behind microscopic disease and that an intact sphincter increased the incidence of delayed gastric emptying (55,56). Over the years, there has been a great deal of controversy over which is the superior technique and studies comparing the two have been inconsistent and contradictory. According to a recent systematic review and meta-analysis of randomized, controlled trials comparing PPPD to classical PD, PPPD is associated with decreased blood loss and operative time, but the two procedures are otherwise equivalent in terms of mortality, morbidity, and survival (57).

Improving surgical outcomes

At the end of his career, Whipple had performed a total of 37 pancreaticoduodenectomies with a total mortality rate of approximately 33% (31). However, in contrast to the monumental progress of the 1930s and 1940s, the next 30 years were marked by failure to improve upon Whipple's original results with reported mortality rates ranging from 20-40%, morbidity between 40-60%, and 5-year survival rates of less than 5% for PDAC (58,59). Complications ranged from post-operative hemorrhage, sepsis, intra-abdominal abscesses, delayed gastric emptying, and fistulae, all of which were usually attributed to the "Achilles' heel" of the procedure, leakage at the pancreatic anastomosis.

During the 1960s and 1970s, the excessive mortality and lack of long-term survival led some surgeons to question whether PD should be abandoned altogether in the treatment of PDAC. In some instances, it was argued, palliative bypass alone resulted in better quality of life and longer survival (60,61). Concurrently, new pathological data were emerging to suggest that PDAC was often a multifocal disease, meaning that standard partial resections likely left disease behind in the pancreatic remnant (62-64). These factors led many in the field to advocate for total pancreatectomy (TP) over PD because it eliminated the need for the troublesome pancreatic anastomosis and addressed the issue of tumor multicentricity by providing a more oncologically radical resection. However, enthusiasm over the procedure was soon tempered as emerging studies showed that the theoretical benefits of TP had not borne out in practice. Specifically, it did not confer any survival benefit compared to partial resection, but guaranteed the additional morbidity of brittle diabetes and complete exocrine pancreatic insufficiency (65,66). Shortly

Figure 7 John Lemuel Cameron, former Chairman of the Johns Hopkins Department of Surgery [1984-2003]. Oil on canvas portrait by Peter Egeli. Reprinted with permission.

thereafter, TP was generally abandoned for all but a few rare indications, such as large tumors traversing surgical boundaries.

Outcomes following PD for PDAC finally began to improve in the 1980s when several institutions reported mortality rates of <5% (67-70). This was attributed to the growing trend in centralization of care at high volume centers where surgeons specialized in pancreatic surgery. Johns Hopkins, under the leadership of John L. Cameron (*Figure* 7), was a leading force behind this progress and serves as the first example of the benefit of regionalization of pancreatic surgery to a high-volume institution. Between 1984 and 1995, Johns Hopkins Hospital increased its share of Maryland PDs from 21% to 59% of the total statewide volume. This was accompanied by a decline in unadjusted mortality from 3.2% [1984-1987] to 1% [1992-1995] at Johns Hopkins compared to a decline from 19.5% to 12.4% at low volume Maryland centers over the same timeframe (71). Linear regression modeling demonstrated that for every 1% increase in the hospital's market share of PDs, the relative risk of in-hospital mortality decreased by 5% with 61% of the total observed reduction in statewide mortality attributable to regionalization. Furthermore, although mortality decreased at low volume centers as well, the relative risk increased from 4.4% to 12.6%.

The centralization of pancreatic surgery in Maryland developed out of the concerted effort to improve outcomes in PDAC. The initial successes of the Johns Hopkins group generated increasing referrals, which in turn fueled more progress. Between 1970 and 2006, 1,423 consecutive PDs were performed for PDAC at the Johns Hopkins Hospital, 80% of which were performed by just 3 surgeons and 93% by just 11 surgeons (72). During this period, case volume increased from approximately 2 to over 120 cases per year while mortality declined from 30% to 1%. As a result of this growth, the surgeons acquired increasing technical proficiency, which translated into shorter operative times and decreased intraoperative blood losses (72,73). The mounting experience at Johns Hopkins and several other developing high-volume centers allowed for the standardization of diagnostic workups, technical operative details, and postoperative management strategies into treatment algorithms and critical pathways (71).

Current trends and future directions

The safety with which pancreatic resections are now performed has led to several changes in the practice of pancreatic cancer surgery. The first major change pertains to the expanding demographic of who we operate on. Today, surgical indications are expanding to include a broader range of patients, including those with borderline resectable (BLR) cancers and those with benign precursor lesions such as intraductal papillary mucinous neoplasms (IPMNs) (74,75). Another evolving change is the manner in which we perform surgery. As our technological capabilities continue to progress, some surgeons have adopted minimally invasive alternatives to open surgery using laparoscopic and robotic techniques. The ultimate goal of these minimally invasive approaches is to maximize candidacy for adjuvant therapy and minimize the delay in its delivery by decreasing postoperative complications. However, the future of pancreatic cancer surgery and the key to attaining a truly curative outcome lies in the timely resection of disease before it has an opportunity to metastasize. This will ultimately depend on developing new and creative ways of screening for and diagnosing disease in its earliest forms.

Locally advanced and borderline resectable (BLR) disease

In contemporary practice, high-resolution tri-phasic CT imaging with three-dimensional (3-D) reconstruction is the best initial diagnostic imaging modality for PDAC. It addition to diagnosing the presence of disease, it is also the best means of determining whether it is amenable to

surgical resection by evaluating for presence of metastases and involvement of major vascular structures, including the celiac axis, superior mesenteric artery (SMA), hepatic artery, superior mesenteric vein (SMV), and portal vein (PV) (76). As imaging technology has improved, it has significantly reduced the need for staging laparoscopies and the incidence of nontherapeutic laparotomies (77).

Only 15-20% of patients newly diagnosed with PDAC present with resectable disease. The majority of these patients are found to have metastases (stage IV), while another 30% have stage III disease as defined by some degree of major vessel involvement. Stage III PDAC is further divided into locally advanced unresectable pancreatic cancer (LAPC) and BLR pancreatic cancer (78). Surgically unresectable cancers are those that demonstrate metastatic spread, mesenteric or celiac arterial encasement (>180 vessel involvement), and non-reconstructable involvement of the SMV/PV (often marked by complete occlusion and extensive collateralization of flow) (79). While there is currently no single, standardized definition of BLR disease, it generally depends on whether the involved vascular structures are amenable to achieving an R0 (microscopically margin negative) resection. From a technical standpoint, resection and reconstruction of the SMV/PV can be performed safely in selected patients when performed by experienced surgeons at high-volume centers (80,81). Following *en bloc* vascular resection, there is no difference in disease-specific survival when compared to standard resection.

A neoadjuvant approach is most commonly applied to patients with BLR PDAC in an attempt to improve the chance of a margin-negative resection and control micrometastatic disease. In one recent study evaluating induction FOLFIRINOX [5-fluorouracil (5-FU), oxaliplatin, irinotecan, and leucovorin] therapy in LAPC, 85% of 47 patients underwent successful resection upon surgical exploration and 92% of these resulted in an R0 resection (82). Similar results have been demonstrated in small studies evaluating different neoadjuvant regimens as well (83,84).

Prophylactic surgery for benign precursors

IPMNs are relatively common macroscopic lesions of the pancreas known to be benign precursors to invasive PDAC. Like the microscopic pancreatic intraepithelial neoplasia (PanIN) lesions, IPMNs are believed to progress to PDAC through a series of genetic and morphological changes accumulated over time. Since they can be identified on imaging, they offer a unique opportunity for early detection and prevention of PDAC through surgical resection. The importance of prophylactic resection is highlighted by 5-year survival rates after resection ranging from 77-100% in patients with noninvasive lesions compared to 34-62% in patients found to have an associated invasive carcinoma (85). Guidelines currently recommend surgical resection for all main-duct IPMNs and any branch-ducts IPMNs meeting resection criteria based on specific high-risk features (85).

A trend toward minimally invasive surgery (MIS)

One of the most notable changes occurring in contemporary pancreatic cancer surgery is the trend toward MIS. MIS is currently the standard approach for many procedures such as cholecystectomy and appendectomy because it has been shown to decrease length of stay and surgical site infection rates while improving pain control and wound cosmesis (86,87). These outcomes have been replicated in more complicated abdominal and thoracic procedures as well, demonstrating that a high degree of manual dexterity can be achieved using laparoscopy. Despite early resistance stemming from concerns over safety, increased cost, and inferior oncological outcomes compared with open pancreatectomy, minimally invasive pancreatic resections are now becoming more commonplace due to the favorable results of several large studies.

Laparoscopic pancreatectomy

The first laparoscopic anatomical resection was a PD performed in 1994 by Gagner and Pomp for chronic pancreatitis (14). However, since that time there has been a much broader experience with laparoscopic DP owing to its lack of anastomoses and lesser risk of hemorrhage. To date, several studies have evaluated laparoscopic DP with splenectomy and found it to be safe and effective with morbidity and mortality rates similar to the open procedure (88-92). Moreover, there has been no decrease in long-term survival or differences in margin status, suggesting that the minimally invasive approach achieves at least an equivalent oncologic resection as the open approach (88).

The benefits of laparoscopic DP over open surgery are the same as for other procedures, including significant decreases in operative times, transfusion requirements, narcotic administration, and length of stay (88-90). Also, a metastatic evaluation of the entire abdomen can be performed at the

beginning of the procedure, which can then be aborted if needed without risking any significant morbidity or mortality.

Laparoscopic PD has been more slow to develop owing to its high degree of technical difficulty, significant learning curve, and increased operative times (93,94). However, several studies have shown that when performed by experienced surgeons at specialized high-volume centers, laparoscopic PD is safe with similar morbidity or mortality as the open procedure. Specifically, there have been no reports of increased post-operative hemorrhage, delayed gastric emptying, or pancreatic fistulae as many initially feared would be the case (95-97). Furthermore, as with distal resections, oncologic outcomes are similar with no significant differences in margin status or overall survival (95-97). One study even demonstrated a statistically significant improvement in progression-free survival, though this did not carry over into overall survival (98). The benefits of laparoscopic PD are similar to those seen with laparoscopic DP and include decreased wound infection rates, transfusion requirements, and length of total hospital and intensive care unit (ICU) stay, which offset the increased cost of laparoscopic surgery (95,96,99,100).

Robotic-assisted pancreatectomy

In recent years, robotic-assisted surgery has become an increasingly popular technique in many surgical subspecialties, but only recently has been applied to pancreatic surgery. It has several technical advantages over laparoscopy including high definition 3-D visualization with up to 10× magnification, instrumentation with 7 degrees of freedom (compared to 5 for laparoscopy), tremor filtering and motion scaling for improved precision, and an ergonomic console design that minimizes muscle fatigue (101). Together, these features allow the surgeon to more closely recapitulate the technique of an open procedure, making for an easier transition to MIS compared to laparoscopy.

Though still in its infancy, robotic-assisted pancreatectomy in the form of PD, central pancreatectomy, DP, and TP have all already been described in the literature for the treatment of pancreatic adenocarcinoma (15,102). Although most series are limited to a small number of patients at select high-volume centers, they show no difference in morbidity or mortality when compared to the open approach (102-104). The largest series of 250 consecutive robotic pancreatectomies, the majority of which were for pancreatic adenocarcinoma, reported a 0.8% and 2.0% 30- and 90-day mortality, respectively (102). These rates are comparable to open and laparoscopic approaches at high-volume institutions. Additionally, conversion to an open procedure was required in only 6% of patients and overall post-operative morbidity was low. A smaller series of 134 patients undergoing robotic-assisted pancreatectomy showed similar low rates of post-operative morbidity and mortality (15). There is also literature to suggest that the robotic approach achieves better oncological resections with higher rates of negative resection margins and better lymph node yield compared to laparoscopic techniques (105).

So far, the limited experience with minimally invasive pancreatic resections has demonstrated a great deal of promise in delivering at least equivalent oncologic resections with the added benefits of speedier recovery and fewer wound-related complications. The importance of this in the larger scheme of management is the potential to increase the number of patients who qualify for adjuvant therapy and to decrease the time interval between surgery and receiving that therapy (101).

Early detection: the future of pancreatic cancer surgery

Despite all of the resources available to modern medicine today, contemporary surgeons continue to struggle with one of the same barriers Mikulicz described over a century ago; namely, the inability to diagnose PDAC early enough to make a difference (28). Pancreatic tumors are located deep within the retroperitoneum and may grow quite large before causing symptoms, at which point 80-85% of patients already have advanced unresectable disease (76). However, recent studies using mathematical models of clonal evolution within the primary tumor indicate that it may take up to 7 years for a cancer to acquire metastatic potential (106-108). If true, this offers a generous window within which an earlier diagnosis and curative resection may be obtained. In order to exploit this latency period, strategies must be developed to reliably identify and stratify at-risk populations likely to be harboring these early stage cancers. Studies have already successfully demonstrated this principle for some high-risk groups in whom magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) were used to detect asymptomatic pancreatic lesions in up to 42% of participants (109). In 2013, the International Cancer of the Pancreas Screening (CAPS) Consortium published their screening recommendations, which focused primarily on family history and specific genetic alterations as criteria for identifying high-risk screening populations (110). However, this only covers

a fraction of PDAC cases, meaning additional work is required to develop a more comprehensive strategy for identifying a broader range of high-risk patients.

New methods for screening and diagnosis will also have to be developed since many of these early cancers are likely to be too small for detection on imaging. In recent years, a great deal of research has been invested in the discovery of reliable diagnostic biomarkers for PDAC. By 2009, one study determined that over 2,500 gene products had already been suggested for this role (111). The most extensively studied of these is the sialylated blood group antigen CA19-9, which has proven utility in evaluating prognosis and recurrence, but is a poor diagnostic screening tool (112). Likewise, none of the other candidates have been applied to meaningful clinical roles in the diagnosis of PDAC either. Still, with the improving sensitivity, increasing availability, and declining cost of high-throughput sequencing technologies, there is hope on the horizon (113). A recent study by our group used next-generation sequencing to rapidly and reliably detect driver mutations from fine needle aspirates (FNA) of pancreatic cancers, while other studies have successfully detected mutant alleles such as *KRAS* and *p53* in their serum (114-116). These studies were conducted in known, usually advanced cases of PDAC, but they effectively illustrate proof of principle. Even if early cancers and precursor lesions do not spill enough DNA into the bloodstream for detection, studies have also characterized benign pancreatic lesions by sequencing pancreatic juice and cyst fluid (117-119). Together, these results raise the possibility of using targeted deep sequencing as a viable screening method in high-risk patients. Furthermore, there is also promising research investigating new class of potential biomarkers such as circulating tumor cells, monoclonal antibodies, and miRNAs (120-122).

Summary

Pancreatic cancer is a highly lethal disease for which surgical resection offers the only hope for cure. Pancreatic resection for PDAC requires complex operations that have become safe and routine only within the past 3 decades. Our arrival at this point was made possible by the innovation and persistence of intrepid surgeons together with critical advances in related fields, such as the development of anesthesia, the germ theory of disease, and the discovery of vitamin K. Following the period of technical refinements initiated by Whipple, the contemporary era in pancreatic surgery was ushered in by the migration of care to high-volume centers of excellence. These institutions obtained improved outcomes by concentrating resources and experience, optimizing diagnostic and treatment algorithms, and effectively coordinating multidisciplinary care. Today, the field continues to evolve with the advent of minimally invasive resection techniques and the ongoing expansion of surgical indications. However, just as Mikulicz described over a century ago, the potential for a surgical cure is too often thwarted by our inability to reliably diagnose PDAC at its earliest stages. What remains for the next generation of surgeons and scientists is the development of effective methods for screening and early detection, which will dramatically increase the rate of truly curative resections.

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Footnote

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Current surgical management of pancreatic cancer

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Abstract: En bloc resection is the treatment of choice for localized pancreatic cancer. While the perioperative mortality associated with resection is low, it still carries a significant morbidity rate of up to 50% in certain high-risk subsets of patients. With advances in perioperative care, radical resection with inclusion of adjacent vascular structure to achieve negative margin status can be performed with comparable mortality and morbidity in high-volume centers. Early results with the use of minimally invasive technique in pancreatic surgery are promising. Recent data on perioperative care to decrease morbidity with pancreatic surgery will also be discussed.

Keywords: Pancreaticodoudenectomy; distal pancreatectomy; laparoscopic pancreatic surgery

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Introduction

Worldwide, over 200,000 people die annually of pancreatic cancer. In the United States, pancreatic cancer is the 4th leading cause of cancer death, and in Europe it is the 6th (1). Great majority of patients present with locally advanced or metastatic disease (2). Surgical resection remains the only potentially curative intervention for select patients who present with localized disease. In 1912, Walter Kausch reported the first successful resection of duodenum and a portion of the pancreas for periampullary tumor (3). In 1935, Whipple redefined the procedure as a two stage operation consisting of gastric and biliary bypass in the first stage followed by pancreaticoduodenectomy (4,5). In 1978, Traverso and Longmire introduced the pylorus preserving pancreaticoduodenectomy (6). During the 1960s, many centers reported operative mortality following pancreaticoduodenectomy to be 20-40%, with postoperative morbidity at 40-60% (7). With advances in surgical techniques and perioperative care, the mortality rates associated with the procedure has reduced to less than 5%, while morbidity rate approached 40% even in highvolume centers (8-11).

Approximately 15-20% of patients initially diagnosed with pancreatic caner are amenable to resection (12,13). Great majority of pancreatic cancer (90%) are ductal in origin located predominantly in the head (>75%) (14). Unresectable lesions are those involving SMA or celiac axis (T4) or those with distant metastases (M1). Controversy exists regarding the definition of borderline resectable lesions. Generally, tumor abutment of visceral arteries or short-segment occlusion of the superior mesenteric vein is considered anatomically borderline resectable lesion (15). Recent Consensus Conference sponsored by Americas HepatoPancreatoBiliary Association, Society for the Surgery of Alimentary Tract, and Society of Surgical Oncology provided a more precise definition for clinical trial design and literature comparison (16) : (I) tumorassociated deformity of the superior mesenteric vein (SMV) or portal vein (PV) (*Figure 1*); (II) abutment of the SMV or PV≥180°; (III) short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction; (IV) short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction (*Figure 2*); and (V) abutment of the superior mesenteric artery (<180°). Outcome following resection is influenced by R0 resection (10,11,17), nodal involvement (10,11), histologic grade (11,18), elevated CA19-9 levels (18-20), high Body Mass Index (21), and operative blood loss (17,22).

Operative techniques for head of pancreas cancer include

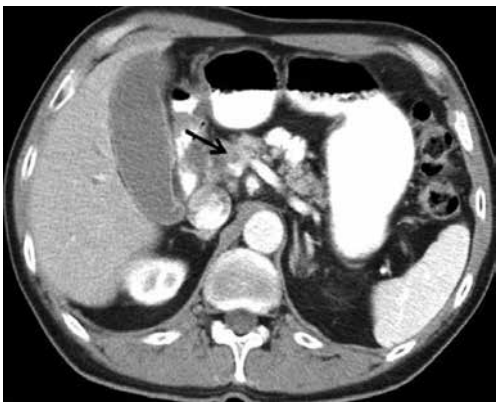

Figure 1 Arrow points toward the deformity of superior mesenteric vein by tumor.

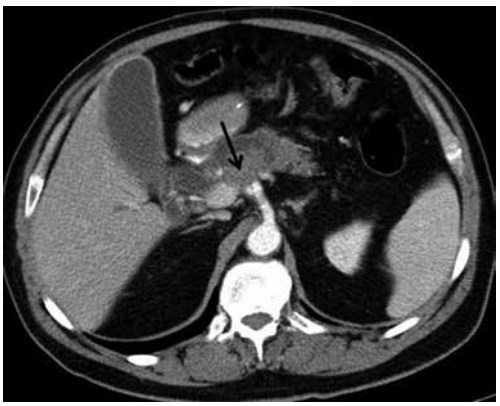

Figure 2 Arrow points toward the deformity of portal vein and abutment of tumor on the common hepatic artery.

the standard pancreaticoduodenectomy (Whipple procedure) and pylorus-preserving pancreaticoduodenectomy. Extended retroperitoneal lymphadenectomy and superior mesenteric vein and/or portal vein resection have recently been evaluated for maximal surgical clearance of disease. The type of pancreatic anastomosis has also been examined, including pancreaticojejunostomy versus pancreaticogastrostomy. Several institutions have repor ted their results for laparoscopic pancreatic resection with comparable results to open resection. Various post operative strategies have been evaluated for reduction of post-operative complication rates, including the use of octreotide (somatostatin analogue), pancreatic enzyme replacement therapy, erythromycin and nutritional support. The purpose of this article is to review the preoperative, operative, and post operative management strategies in the treatment of pancreatic cancer.

Determination of resectability

Paramount to the decision for performing pancreaticoduodenectomy is the accurate identification of patients who have resectable disease. Various imaging modalities are available to accurately stage a patient with pancreatic cancer, including CT, PET/CT, ERCP, endoscopic ultrasound, mesenteric angiography, and MRCP. CT scan has been the main imaging modality for determination of resectability. With advances in medical imaging and improvement in the resolution capability, the role of diagnostic laparoscopy is now limited in the initial evaluation of resectability. In a recent study of 298 patients, Mayo *et al.* reported 87% resection rate in this cohort where CT was performed in 98% of the study patients, EUS in 32%, and laparoscopy in 29% (23). In the laparoscopy group, 27% had findings that precluded resection. In a recent review of their experience at Memorial Sloan-Kettering Cancer Center, White *et al.* reported an yield of diagnostic laparoscopy of 14% overall, but only with 8% yield in patients with in-house pre-operative imaging versus 17% with external imaging (24). The same group proposed a judicious use of diagnostic laparoscopy with the combination of pre-operative CA19-9 as a stratification factor to consider laparoscopy in those with resectable disease on imaging and elevated CA19-9 level (25).

Preoperative biliary drainage

Because of the predominant location of pancreatic cancer in the head of pancreas, obtructive jaundice is a common presenting symptom. Several cohort studies have been published regarding the detrimental effect of pre-operative biliary instrumentation/stenting on the post-operative course with higher infectious complications in the stented group (26-31). No difference in survival was observed. However, others have reported no impact on post-operative complications with pre-operative biliary drainage (32,33) In a recent multicenter randomized trial comparing early surgery versus preoperative biliary drainage followed by surgery, 202 patients were enrolled. The rates of serious complications were 39% (37 of 96 patients) in the earlysurgery group and 74% (75 of 106 patients) in the biliarydrainage group ($P<0.001$) (34). A follow-up report from the same trial showed that there was a significant delay in time to surgery (1 week versus 5 weeks).

However, the delay did not influence survival (35). While there is an increase in overall infectious complications following surgery in the stented group, the detrimental effect of pre-operative biliary stenting is likely limited to those with subsequent bacterial colonization of the biliary tree from stent placement (36). Jagannath *et al.* found no difference in post-operative complications between the un-complicated pre-operative stent group compared with unstented group. The adverse outcome was associated with positive intraoperative bile culture. Further adding to the controversy of pre-operative biliary stenting, while high pre-operative bilirubin was associated with worse survival outcome, resolution of jaundice following pre-operative biliary stenting appeared to counter the adverse survival effect of bilirubinemia (37). Thus, pre-operative biliary drainage should be used judiciously in symptomatic patients.

Operative considerations

Pancreaticoduodenectomy

The traditional pancreaticoduodenectomy (PD) consists of resection of the pancreatic head, duodenum, distal common bile duct, gallbladder, and gastric antrum (4,5). A more recent modification of this procedure involves preservation of the pylorus and gastric antrum, referred to as the pylorus preserving pancreaticoduodenectomy (PPPD) (6). Resection is then followed by re-establishing gastrointestinal continuity. The jejunum is typically used for each anastomosis, consisting of pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy or duodenojejunostomy in the case of PPPD. During the 1960s and 1970s, mortality associated with PD approached 25%. Over the past 3 decades, experience performing PD has increased with associated decrease in perioperative mortality rate to less than 5% (38-41). However, it is still a technically challenging procedure with significant perioperative morbidity. Cameron reported his personal series of 1000 PD performed over a span of 34 years with 1% perioperative mortality (41). Perioperative morbidity was observed in 41% of the cohort including delayed gastric emptying (18%), pancreatic fistula (12%), wound infection (7%), intra-abdominal abscess (6%), cardiac event (3%), pancreatitis (2%), bile leak (2%), pneumonia (2%), hemobilia (2%), and reoperation in 2.7%. To minimize postoperative morbidity, various strategies for reconstruction have been under intense investigation. The predominant controversy regarding standard PD versus PPPD or pancreaticojejunostomy versus pancreaticogastrostomy reconstruction has been extensively studied (42-44). No significant superiority of one variant of PD over another has been convincingly demonstrated. Surgeon's experience with the specific variant of PD appeared to be the determining factor in achieving optimal surgical outcome.

Distal pancreatectomy

Distal pancreatectomy is the standard procedure for cancer of the body or tail of pancreas. It entails the resection of distal portion of pancreas extending from the left of the superior mesenteric vein/portal vein axis to the tail with en bloc resection of surrounding lymphatic tissue. Spleen is conventionally removed with the procedure. Spleensparing distal pancreatectomy (Warshaw operation) can be performed safely without increase in complication rate, operative time or in-hospital stay (45). While cancer of the body and tail tends to present at an advanced stage due to the lack of early symptoms and tends not to be amenable to complete resection on presentation, there is no survival difference when compared with cancer of the head of pancreas stage by stage (46,47).

Laparoscopic pancreatic resection

With the publication of COST trial, minimally invasive surgical approach has been evaluated in increasing frequency for cancer resection (48). For the surgical management of pancreatic neoplasm, laparoscopic distal pancreatectomy (LDP) is rapidly becoming the surgical procedure of choice in place of open distal pancreatectomy (ODP) for tumor of the body/tail of pancreas. While several groups have published their results with LDP, the majority of the publication did not specifically address the oncologic outcome following LDP for pancreatic cancer (49-59). Overall, when compared with ODP, LDP is associated with a longer operative time, less blood loss, and shorter length of stay. Conversion rate from laparoscopic approach to open varies between 0 to 30%. In their institutional experience, Baker *et al.* noted a lower number of lymph nodes harvested in 27 LDP patients (mean=5) compared with 85 ODP patients (mean=9) (57). Kooby *et al.* performed a matched analysis of 23 LDP patients with 189 ODP patients from a database with pooled data from 9 academic centers (58). There was no difference in positive margin rates, number of lymph nodes examined, or overall survival in patients

Table 1 Select Literature on Laparoscopic PD

	N	Conversion rate (%)	Mean OR Time (min)	Mean Blood Loss (mL)	Mean Length of Stay (d)	Overall Morbidity (%)	Mortality (%)	Positive Margins (%)
Gagner (61)	10	40	510	NR	22	50	0	0
Dulucq (62)	25	12	287	107	16	32	4	0
Palanivelu (63)	42	0	370	65	10	NR	2	0
Pugliese (64)	19	32	461	180	18	37	0	0
Cho (65)	15	0	338	445	16	27	0	0
Kendrick (66)	62	0	368	240	7	42	2	11

with pancreatic cancer. Jayaraman *et al.* reviewed their results of 343 distal pancreatectomies over a 7-year study period at Memorial Sloan-Kettering Cancer Center: 107 were attempted laparoscopically and 236 ODP (59). The conversion rate was 30%. Similar complication rates were observed in both groups. They also observed significantly less blood loss, longer operative times, and shorter hospital stays in favor of LDP group. The number of lymph nodes examined (LDP =7 *vs.* ODP =7) and margin positivity (LDP =3% *vs.* ODP =4%) were similar between both groups. They observed a higher conversion rate in patients with larger tumor, higher BMI, and tumor proximity to celiac axis. No survival data were provided. Based on these data, LDP appeared to be an appropriate oncologic surgical approach in select patients with cancer of the body/tail of pancreas.

Laparoscopic pancreaticoduodenectomy (LPD) was first described by Gagner and Pomp in 1994 (60). Due to the complexity of the operation and lack of apparent advantages, reports regarding LPD contained case reports and small series. Series containing 10 or more successful LPD are listed in *Table 1*. While these reports demonstrated the safety and feasibility of performing LPD, larger prospective trials are needed to further define the advantage, if any, of LPD.

Role of extended retroperitoneal lymphadenectomy

Nodal status is a significant prognostic variable in pancreatic cancer. The number of nodes involved with metastases, the ratio of lymph node involvement, and the minimum number of lymph nodes examined had all been shown to have prognostic significance (67-69). Because of the importance of nodal staging, extended lymphadenectomy (EL) during pancreaticoduodenectomy was proposed to improve the surgical outcome of pancreatic cancer patients. The definition of EL is not uni form. Commonly EL refer red to the dissect ion of additional lymph nodes along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery and laterally to the renal hila with circumferential clearance of the celiac trunk (70). While several groups from Japan had reported favorable outcome following EL during pancreaticoduodenectomy (71-73), multiple randomized trials had not demonstrated an improvement in overall survival following EL (70,74-76). Yeo *et al.* also observed a significantly higher complication rate associated with the radical surgery group (43%) compared with the standard pancreaticoduodenectomy group (29%) (74). Higher rates of delayed gastric emptying and pancreatic fistula and longer hospital stay were observed in the radical surgery group. The higher morbidity associated with EL was also reported in a meta-analysis on standard versus radical pancreaticoduodenectomy (77). The authors also did not find a difference in survival between the standard versus radical pancreaticoduodenectomy.

Portal vein and superior mesenteric vein resection

Because achieving an R0 resection had prognostic significance for patient outcome, vascular resection during PD had been evaluated. The great majority of vascular resection during PD involved portal vein and superior mesenteric vein resection and reconstruction. Yekebes *et al.* reported equivalent perioperative morbidity and mortality between the standard PD group and the group with vascular resection (78). The median survival was 15 months in patients with histopathologic proven vascular invasion and 16 months in those without (P=0.86). Riedeger and colleagues also reported similar results with regard to portal vein/superior mesenteric vein resection (79). In their study cohort of 222 pancreaticoduodenectomy patients,

53 required portal vein and/or superior mesenteric vein resection while 169 did not. There was no significant difference in morbidity or mortality between the two groups. Kanoeka and colleagues demonstrated that the length of portal vein/superior mesenteric vein (PV/SMV) resected had an inverse correlation with survival (80). PV/SMV resections that are <3 cm were associated with a 5-year survival rate of 39% *vs.* 4% for resections that are ≥3 cm in length (P=0.017). Chua and Saxena performed a systematic review of published reports on extended pancreaticoduodenectomy with vascular resection (81). Twenty-eight retrospective studies were included in the review comprising of 1 458 patients. The median R0 resection rate was 75% (range, 14-100%). The median mortality rate was 4% (range, 0-17%). Based on the reports from high-volume centers (>20 pancreaticoduodenectomy/year), the median survival associated with extended pancreaticoduodenectomy with vascular resection was 15 months (range, 9-23 months). Therefore, in select patient where R0 resection can be achieved, PV/SMV resection/reconstruction can be performed with comparable morbidity and survival outcome to standard pancreaticoduodenectomy.

Post operative considerations

While the perioperative mortality for pancreaticoduodenectomy has dropped to 5% in recent times due to advances in surgical techniques, the morbidity rate remains high at 40%. Pancreatic fistula remains the most serious complication after pancreaticoduodenectomy and occurs in up to 20% of patients. Other major complications include delayed gastric emptying and hemorrhage. In an effort to identify independent risk factors for post operative morbidity, Adam and colleagues prospectively studied 301 patients who underwent pancreatic head resections (82). Three pre-operative risk factors were found to independently correlate with increased complication rate: presence of portal vein/splenic vein thrombosis or hypertension, elevated pre-operative creatinine, and the absence of pre-operative biliary drainage. In contrast, other studies (including a prospective randomized controlled trial) have reported a statistically significantly higher complication rate for patients undergoing pre-operative biliary drainage (26-31,34). Patients undergoing operation after 1998 were also noted to have fewer complications, suggesting that increased experience and improved patient selection has led to improvement in perioperative care. The requirement for resection of additional organs also correlated with a higher complication rate.

Patient's age and its impact on morbidity, mortality, and survival have been intensely investigated (83-87). The majority of studies used age 70 or 80 as the cutoff. In their systematic review of literature, Riall *et al.* found that higher morbidity and/or mortality was observed in the elderly population (87). Makary *et al.* reviewed their single institutional experience with 2,698 patients undergoing pancreaticoduodenectomy over a 35-year period (83). When compared to the younger group (<80), patients in the 80-89 group had statistically significant higher morbidity and mortality rates (P<0.05). Haigh *et al.* identified 2 610 patients undergoing pancreaticoduodenectomy from 1/2005 through 12/2007 in the American College of Surgeons National Surgical Quality Improvement Program database (88). Elderly patients (>70 years old) had a higher likelihood of developing at least 1 morbidity compared with that of younger patients (40.7% *vs.* 34.0%; P=0.01). Furthermore, elderly patients had a higher perioperative mortality rate compared with that of younger patients (4.3% *vs.* 1.7%; P=0.01).

The efficacy of octreotide, a somatostatin analogoue, in decreasing complication associated with pancreatic resection is controversial. The rationale for using octreotide is that it can decrease pancreatic enzyme secretion thereby decreasing the rate of pancreatic fistula formation (89). Multiple randomized multicenter trials comparing octreotide or vaprotide, another somatostatin analogue, to placebo in patients undergoing pancreatic resection have been performed (89-97). The use of somatostatin analogues did not impact mortality in patients undergoing pancreatic resection. While some studies demonstrated a statistically significantly decrease in the development of pancreatic leak/stula with the use of somatostatin analogue, others showed no difference.

Delayed gastric emptying is another leading cause of morbidity in patients undergoing pancreaticoduodenectomy (98). The occurrence of delayed gastric emptying resulted in prolonged nasogastric tube decompression, initiation of enteral or parenteral nutrition, and prolonged hospital stay. The pathogenesis of delayed gastric emptying has been attributed to decrease gastric motility secondary to decreased levels of motilin (99). Motilin induces contractions of intestinal smooth muscles, initiates phase III of the gastric migrating motor complex, and improves gastric emptying in patients with diabetic gastroparesis (100,101). Yeo and colleagues performed a prospective randomized trial evaluating the effects of erythromycin

on delayed gastric emptying in patients undergoing pancreaticoduodenectomy, randomizing 118 patients to erythromycin lactobionate 200 mg every 6 hours or saline. The erythromycin group had reduced incidence of delayed gastric emptying (19% *vs.* 30%), need for nasogastric tube re-insertion (6 *vs.* 15 patients, P<0.05), and retention of liquids and solids on radionucleotide gastric emptying study (P<0.01) (102). Thus, the use of erythromycin can reduce the occurrence of delayed gastric emptying after pancreaticoduodenectomy.

Patients with pancreatic cancer who are deemed candidates for curative resection are frequently malnourished pre-operatively (103,104). Serum albumin level is a significant prognostic indicator of post operative mortality. Winter and colleagues categorized patients into 3 groups based on pre-operative serum albumin level (>3.5, 2.6-3.5, <2.6). Post operative mortality was 7% in the group with lowest serum albumin level compared with 3% for the intermediate group, and 0.9% for the >3.5 group (105). Okabayashi and colleagues evaluated the benef it of early post operative enteral nutrition (EPEN) *vs.* late post operative enteral nutrition (LPEN) in pat ients undergoing pancreat icoduodenectomy (106). Twenty-three patients received TPN followed by the initiation of oral intake during the late post operative period (LPEN group). Sixteen patients were initiated on enteral feeds via jejunostomy tube on post-operative day 1 (EPEN group). The EPEN group had significantly lower rate of post-operative pancreatic fistula and shorter length of hospital stay. Brennan and colleagues performed a prospective randomized trial in patients undergoing major pancreatic resection, comparing patients receiving parenteral nutrition with patients who did not (107). They found that the group receiving parenteral nutrition had significantly higher complication rate with increased rate of intra-abdominal infection and longer duration of hospitalizaion.

Continuous infusion of nutrients has been demonstrated to cause a delay in gastric emptying. Elevated levels of cholecystokinin (CCK) is a known cause of delayed gastric emptying (108,109). Van Berge Henegouwen and others performed a prospective randomized study comparing continuous (CON) feeding protocol (1,500 kCal/24 hrs) with cyclic (CYC) feeding protocol (1,125 kCal/18 hr) (110). They found that patients in the CYC group were able to tolerate a normal diet sooner than the CON group. The length of hospital stay was shorter in the CYC group. Levels of CCK were lower in the CYC group, suggesting that lower levels of CCK plays a role in reducing delayed gastric emptying.

Enteral nutrition formulas containing immunomodulating agents (arginine, RNA, Omega-3 fatty acids) have been investigated in patients undergoing cancer surgery. Braga and colleagues performed a prospective randomized double blind clinical trial comparing standard enteral feeds with enteral feeds enriched with arginine, RNA, and Omega-3 fatty acids post operatively in patients undergoing curative resection for neoplasms of the colorectum, stomach, or pancreas (111). Patients receiving immunomodulating agents had a statistically significant decrease in post operative infection rate and length of post operative stay. The use of probiotics has been shown to stabilize the intestinal barrier, increase intestinal motility, and enhance the innate immune system. Rayes and colleagues performed a randomized double blind study in 80 patients undergoing pylorus preserving pancreaticoduodenectomy. One group received early post-operative enteral feeds with lactobacillus, and the other group received placebo (112). The incidence of post operative infections was significantly lower in the group receiving lactobacillus compared with placebo group(12.5% *vs.* 40% P=0.005).

Conclusion

While resection of pancreatic cancer can be performed with low perioperative mortality, the associated perioperative morbidity can be significant. Recent advances in surgical instrumentation have made wide spread adoption of laparoscopic distal pancreatectomy possible. Similar to experience in other cancer types, the initial oncologic outcome with laparoscopic distal pancreatectomy appear comparable to open distal pancreatectomy. The advantage of minimally invasive surgery in terms of less blood loss and shorter hospital stay was also observed. The advances in surgical techniques also allow more aggressive surgical resection to be performed with acceptable perioperative mortality and morbidity. With the advances in systemic treatment of pancreatic cancer, the ability to achieve negative resection margin will improve the outcome of patients with this aggressive disease.

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Surgical treatment of pancreatic head cancer: concept revolutions and arguments

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Abstract: As we have a deeper and more thorough understanding of the biological behavior of pancreatic head cancer, surgical treatment concepts of this lethal disease are changing all the time. Meanwhile, numerous arguments emerge. Thus, we will probe into the focuses and arguments in the surgical treatment of pancreatic head cancer in this article, including the scope of lymphadenectomy, total mesopancreas excision (TMpE), vascular resection, minimally invasive pancreaticoduodenectomy (PD), palliative resection, surgery for recurrent disease and surgery for primary pancreatic cancer and liver metastasis.

Keywords: Surgical treatment; pancreatic head cancer

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Introduction

Radical resection is a fundamental way to gain long-time survival for the patients with pancreatic cancer. Progresses in surgical techniques and operation methods greatly reduce the perioperative complication rate and mortality. However, the overall survival time does not improve. With a better knowledge of the biological behavior of pancreatic cancer, the concepts of pancreatic surgical treatment have changed. Surgeons have spared no effort to explore the surgical treatment of pancreatic cancer, struggling to make some breakthroughs. Although we have achieved some progress, arguments are going and will never demise.

Lymphadenectomy of pancreatic head carcinoma

Extended lymphadenectomy (ELND) is based on the following theories: adenocarcinoma of the head of the pancreas frequently metastasize to lymph nodes that are beyond the confines of the conventional pancreaticoduodenectomy (PD). Whipple procedure usually leaves out lymph nodes circumferentially from hepatic hilum, celiac trunk (CT) and abdominal aorta, as well as peripancreatic soft tissue, leading to poor prognosis of patients. Arguments about the value of ELND have never ended, and people's understanding of this issue differs in different periods. Regional pancreatectomy was first reported by Fortner in 1973. In the following 10 to 20 years, most retrospective studies in European, America and Japan confirmed that ELND was superior to conventional PD. However, clinical randomized controlled trials carried out in recent 10 years make people to re-recognize the value of ELND. Four prospective, randomized trials comprising some 424 patients and one meta-analysis showed that ELND appears to convey no survival benefit, and may be associated with several complications such as severe diarrhea and delayed gastric emptying postoperatively, which may due to circumferential clearance of the superior mesenteric vessels with severance of parasympathetic nerve fibers (1).

So far, people have not reached an agreement with the scope of lymphadenectomy of the pancreatic head carcinoma. The National Comprehensive Cancer Network (NCCN) practice guidelines suggest that outside of a clinical trial, ELND should not be considered as a routine part of the Whipple procedure. And PD with standard lymphadenectomy is the operation of choice (2). And according to new classification of pancreatic carcinoma of Japan Pancreas Society (JPS) [2003] (3), the removal should entail the second order nodes (N2), which include peripancreatic lymph nodes, and lymphatic tissue circumferentially from the hepatoduodenal ligament, hepatic artery and the right side of superior mesenteric artery (SMA).

Total mesopancreas excision (TMpE)

Mesopancreas was first recognized by German scholars Gockel and colleagues (4) in 2007, which refers to the perineural lymphatic layer located dorsally to the pancreas and reaching beyond the mesenteric vessels. Mesopancreas is a critical structure associated with incomplete removal and local recurrence of tumor (5), and TMpE gives clinicians a total new understanding of the R0 resection of pancreatic head carcinoma.

Adham *et al.* (6) described the concept of "the mesopancreas triangle" for the first time, and thus characterized the surgical scope of TMpE accordingly. "The mesopancreas triangle" has anatomical boundaries that are represented by a base lying on the posterior surface of the superior mesenteric vein (SMV) and portal vein (PV), a summit lying on the anterior surface of the aorta between CT and SMA origin, and is limited on each side by the right semicircumferences of the CT and SMA plexus. Kawabata *et al*. (7) then proposed the concept of "total mesopancreatoduodenum excision (tMPDe)" on the basis of the above theory. When performing tMPDe, lymphadenectomy with the left side of SMA together with mesopancreas resection is necessary to achieve a complete clearance of the retroperitoneal resection margin. Wu *et al*. extended the concept of mesopancreas further. Uncinate process and pancreatic head divide the mesopancreas into anterior and posterior parts, and the latter has a different surgical scope from "the mesopancreas triangle". Take the inferior mesenteric artery (IMA) as the lower boundary, and clear the connective tissue circumferentially from the IMA. Take the summit lying from anterior of abdominal aorta proximally to two centimeters distant from the initial of CT as the upper boundary of the dorsal mesopancreas, and clear the connective tissue circumferentially from the CT; take the left vena genitalis as the left posterior boundary, and SMV as the left anterior boundary.

There are still a lot of controversies about TMpE. The most obvious question is does "mesopancreas" do exist? No anatomical textbook has mentioned the presence of "mesopancreas" before. And Agrawal *et al*. (8) dissected

20 fresh adult cadavers, but failed to find any fibrous or fascia enveloping the so called "mesopancreas", neither macroscopically nor microscopically. Thus, it is believed that there does not exist a "mesopancreas" structure in anatomy. Nevertheless, "mesopancreas" plays an important role in the assessment of PD and the prognosis of pancreatic head carcinoma. Studies showed that R0 rate of TMpE was significantly higher, when compared with conventional PD (93% *vs*. 60%) (7). Another question is that is TMpE another kind of regional lymphadenectomy? Although the scopes of lymphadenectomy of TMpE and conventional PD are partly overlapping, each has its own emphasis. Lymphadenectomy focus on clearance of regional lymph nodes, while TMpE attempts to clear all of the soft tissue including nerves, capillaries and lymph nodes; since pancreatic cancer has the tendency of perineural and vessel invasion, clearance of the peripancreatic nerve plexus can significantly improve the radical rate of pancreatic cancer and relieve the intractable pain resulting from the invasion of plexus (9). Furthermore, the latest guidelines make a recommendation that lymphadenectomy should be as far as N2 when performing PD (2), but TMpE always involves N16 (namely lymph nodes circumferentially from abdominal aorta), which seems to go against the current guidelines. The final question is can TMpE benefit patients? Several aspects of TMpE, such as the median operative time and blood loss, perioperative complications rate, mortality and median length of hospital stay, are comparable to other operative methods of pancreatic head carcinoma (6). And TMpE can improve the R0 resection rate. As for median overall survival time, there is not any follow-up data so far. So large scale, randomized controlled trials are needed to clarify the value of TMpE in the future.

Vascular resection

Pancreatic cancer involving adjacent great vessels was once treated as a surgical contraindication. However, with the development of operative skills, narcotic progresses and intensive care medicine, SMV/PV resection and reconstruction at the time of PD has gain positive popularity. A UK multicenter (nine high-volume UK centers) retrospective cohort study comparing 1,588 patients with resectable pancreatic cancer showed that the perioperative mortality did not show significant difference between PD with vascular resection (PDVR), conventional PD and surgical bypass (SB). Both PD and PDVR groups had greater complication rates than the SB group, but with no difference between PD and PDVR. Overall survival between PD and PDVR groups is similar, but significantly better compared with SB (10). If it is difficult to achieve a negative margin when performing vascular resection (like intensive portal invasion), or distal vascular branches are too many for surgeons to accomplish vascular reconstruction, give up surgical treatment in time!

Arterial resection at the time of PD is technically safe and feasible. Whereas, involving CT and SMA is an indication of intensive infiltration into the surrounding structures. Thus, even if the involved artery is resected meanwhile, there is still high rate of margin positive retroperitoneal resection, and the complication rate will increase significantly. Hence, most scholars do not advocate arterial resection and reconstruction. Since vascular resection and reconstruction at the time of PD requires complex operative procedures and has a high complication rate, operations should be carried out by skilled surgical team in high-volume centers. What's more, only the patients who achieve R0 resection can benefit from the surgery.

Minimally invasive PD

Since Gagner and colleagues reported the first case of laparoscopic PD in the world in 1994 (11), an increasing number of surgeons from high-volume clinical centers showed extremely high passion for minimally invasive surgeries (MIS), including Robot-assisted PD and laparoscopic PD. Laparoscopic PD strictly follows the radical care principle throughout the operation. It can assistant the operator to clearly expose PV and SMV, and search for peripancreatic lymph nodes and those circumferentially from abdominal vessels by locally magnifying visual field. But procedures such as dissension of uncinate process of pancreas and reconstruction of digestive tract require exquisite skills, thus only surgeons with abundant experiences at laparoscopy and open surgery can give those surgeries. Vinci robot-assisted surgeries have several advantages, such as more flexible laparoscopic needle holders and superior visualization of the three-dimensional (3D) operative field, which help it gain popularities among clinicians. Unfortunately, expensive cost hinders the spread and wide use of Vinci robot-assisted surgeries in a short time.

A recent meta-analysis (12) was consisted of six studies that included 542 patients (169 MIS and 373 open). This study showed that MIS was associated with a reduction in intraoperative blood loss, significantly higher retrieval

of lymph nodes, significantly lower R1/R2 resection rate, and significantly reduced hospital stay. Postoperative complications rates were comparable, but longer operative times and significantly smaller tumor size were noticed in the MIS group. Although this meta-analysis showed encouraging consequences, there existed great bias. For example, all of the studies included were retrospective and mainly focused on operative and perioperative outcomes, but long-term oncologic results were unavailable, and there were no multicenter studies. Consequently, before randomized controlled trials or prospective cohort studies prove the equivalent or superior of MIS to the open surgery, minimally invasive PD cannot be considered as a routine application.

Palliative resection

In general, people show negative attitude towards palliative resection. Lavu *et al*. (13) found that compared with the patients who underwent palliative surgical bypass (PB), those underwent margin positive PD had a slightly longer length of hospital stay and a significantly reduced median survival time. Gillen *et al*. (14) carried out a systematic review and meta-analysis of four studies. These studies made a comparison between palliative R2 resection and PB procedures. Results showed that compared with PB procedures, palliative R2 resection would lead to a significantly higher complication rate and mortality, as well as significantly longer operative time and hospital stays. Therefore, palliative R2 resection cannot be recommended. And for those with local oppression and obstruction in advanced stage, PB is a standard of care.

Nonetheless, preoperative evaluation of pancreatic cancer for resectability has some limitations, for one can only give an exact judgment after resecting the neck of pancreas during the surgery. And for those involving CT or SMA, R1 or R2 resection is the exclusive option. Therefore, we should make a careful preoperative evaluation of the resectability of tumor, and try hard to avoid R2 resection. Meanwhile, we should not go too far, because over-conservation may wrongly exclude the candidates for regional extended resection or vascular resection.

Surgery for recurrent disease

A total of 80% patients will experience local recurrence in 2 years following resection, and surgical treatment for recurrent disease has never reached an agreement. First of all, severe postoperative adhesions will increase the complexity as well as the complication rate of secondary operation. Secondly, a large number of tumor recurrences are located close to the CT and SMA therefore not resectable. Finally, it is unclear if secondary surgery can increase the median survival time. Recent studies support the concept of surgical exploration and resection of the local recurrent disease (15) for the following reasons: (I) surgical resection of the recurrence combined with intraoperative radiotherapy of the tumor bed will help to reduce the risk of another recurrence at the resection site; (II) in case of local irresectability, intraoperative radiation can be performed with a palliative intention in terms of tumor reduction and pain control (15); (III) resection of the recurrence may increase the median survival time. A study confirmed that there was a tendency of increased median survival in the group of patients undergoing resection of the recurrence (17.0 months) compared with the bypass group (9.4 months), although this difference was not significant. In addition, patients with a prolonged interval (>9 months) from resection to recurrence were more likely to benefit from resection compared with those with recurrence within 9 months (median survival 7.4 *vs*. 17.0 months, P=0.004). Consequently, for patients with recurrence beyond 9 months following operation, secondary surgery can be considered (16).

Surgery for primary pancreatic cancer and liver metastasis

Pancreatic cancer with liver metastasis is seen as a surgical contraindication, but some case reports and small studies indicated that surgical treatment may benefit part patients. Michalski *et al*. (17) performed a systemic review of the literature and identified 103 cases with pancreatic and liver metastasis. Compared with the patients underwent PD without metastasis resection, those underwent PD and hepatectomy had a significantly longer median survival time (11.4 *vs*. 5.9 months, P=0.038), and the complication rate and mortality is 24.1-26% and 0-4.3%, respectively. They proposed that experienced pancreatic surgical centers can chose patients with M1 diseases as the candidates for surgery. However, it cannot be ignored that pancreatic cancer is a systemic disease, and tumor cells probably have spread to other organs in patients with liver metastasis, which adds difficulties to R0 resection. And large, prospective studies are needed to further confirm the value of this kind of treatment.

As a conclusion, with a deeper and more thorough

understanding of the biological behavior of pancreatic cancer, our surgical treatment concepts of this lethal disease are changing all the time. However, because of the lack of effective and powerful evidence-based evidences, it is difficult to achieve an agreement in a short time. The revolution of the surgery of pancreatic cancer will progress among endless debates.

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Footnote

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Pancreatic cancer surgery and nutrition management: a review of the current literature

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Abstract: Surgery remains the only curative treatment for pancreaticobiliary tumors. These patients typically present in a malnourished state. Various screening tools have been employed to help with preoperative risk stratification. Examples include the subjective global assessment (SGA), malnutrition universal screening tool (MUST), and nutritional risk index (NRI). Adequate studies have not been performed to determine if perioperative interventions, based on nutrition risk assessment, result in less morbidity and mortality. The routine use of gastric decompression with nasogastric sump tubes may be unnecessary following elective pancreatic resections. Instead, placement should be selective and employed on a case-by-case basis. A wide variety of feeding modalities are available, oral nutrition being the most effective. Artificial nutrition may be provided by temporary nasal tube (nasogastric, nasojejunal, or combined nasogastrojejunal tube) or surgically placed tube [gastrostomy (GT), jejunostomy (JT), gastrojejunostomy tubes (GJT)], and intravenously (parenteral nutrition, PN). The optimal tube for enteral feeding cannot be determined based on current data. Each is associated with a specific set of complications. Dual lumen tubes may be useful in the presence of delayed gastric emptying (DGE) as the stomach may be decompressed while feeds are delivered to the jejunum. However, all feeding tubes placed in the small intestine, except direct jejunostomies, commonly dislodge and retroflex into the stomach. Jejunostomies are associated with less frequent, but more serious complications. These include intestinal torsion and bowel necrosis. PN is associated with septic, metabolic, and access-related complications and should be the feeding strategy of last-resort. Enteral feeds are clearly preferred over parental nutrition. A sound understanding of perioperative nutrition may improve patient outcomes. Patients undergoing pancreatic cancer surgery should undergo multidisciplinary nutrition screening and intervention, and the surgical/oncological team should include nutrition professionals in managing these patients in the perioperative period.

Keywords: Complications; enteral feeding tubes; nutrition; pancreatic cancer surgery

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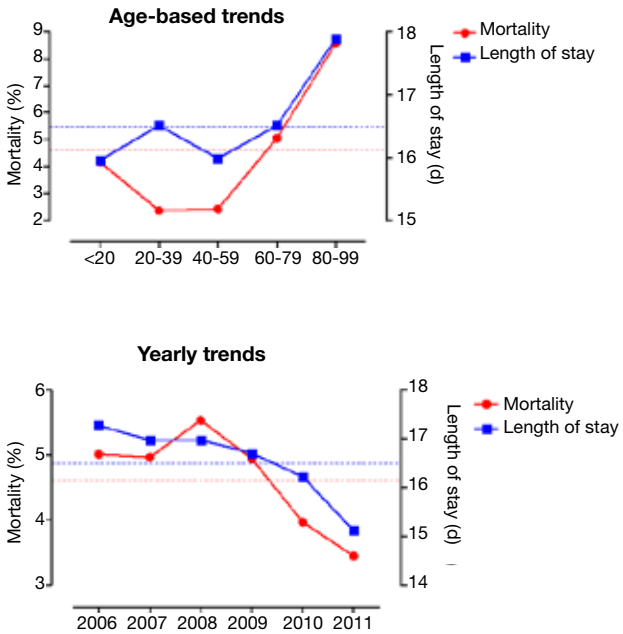
Introduction

Pancreatic cancer is the 4th leading cause of cancer death in the United States, despite being the 12th most incident cancer. Complete surgical resection is the only therapy with the possibility of long-term survival. The first large series of 41 patients undergoing pancreaticoduodenectomy (PD), or Whipple procedure, was reported in 1941 (1). The mortality rate was 29%. Most of the improved survival achieved over the past 3 decades has been related to improved perioperative management, and earlier recognition and treatment of post-operative morbidity. Mortality rates are currently <5% at high-volume pancreatic surgery centers (2,3). In fact, mortality rates have remained relatively low in the United States over the last decade (*Figure 1*) (4).

Despite significant improvement in mortality, morbidity remains high, ranging from 30-60% in some reports (3,5,6). Risk stratification and decreasing morbidity are essential to improving outcomes following a procedure with such high morbidity at baseline. The most serious complication remains development of a pancreatic fistula (PF), which can occur in 20% of patients (3,6,7). Sequelae of PFs include deep-space surgical site infections (SSIs) and sepsis, which can be associated with mortality rates of 40% (8). In a series of 132 patients undergoing pancreatic surgery, Sierzega *et al.* demonstrated an association between malnutrition and PF (9). On multivariable analyses, the only factor significantly predicting PF was a nutritional risk index (NRI) score of 100 or less (OR =8.12, 95% CI: 1.06-22.30; P<0.05). Schnelldorfer *et al.* found that patients with a low serum albumin undergoing surgery for chronic pancreatitis were at greater risk of developing a PF (P=0.04) (10). With a post-operative 20-25% 5-year survival, any time lost to morbidity that can be prevented needs to be further understood and addressed.

Malnutrition, a medical condition caused by improper or insufficient diet, has been determined to be an independent risk factor for morbidity and mortality in patients undergoing surgical procedures. This includes increased incidence of superficial and deep SSIs, sepsis, impaired wound healing, failure of ventilator weaning, pneumonia, renal insufficiency, cardiac and neurologic events, re-admission, length of stay and overall costs (11-15). This leads to a vicious cycle, as complications are detrimental to the nutritional state of the patient.

The operative field for pancreatectomy is at the intersection of the digestive system. The flow of food, hormonal stimulation, enzyme release and digestive vasculature are affected by the location of the malignancy



The left y-axis represents the mortality rates, the right y-axis represents the mean length of stay, and the x-axis corresponds to the year or age. The dashed lines represent the overall means.

Figure 1 Population-based trends following pancreaticoduodenectomy from California, Florida, and New York.

and the operative reconstruction. Patients with pancreatic carcinoma present with a high frequency of malnutrition-related signs and symptoms at the time of diagnosis, including weight loss (85%), anorexia (83%), abdominal pain (79%), epigastric pain (71%), nausea (51%), diarrhea (44%), vomiting (33%), and steatorrhea (25%) (16). A moderate to severe risk of malnutrition was identified in 52-88% of patients who underwent pancreatic resection for cancer (13). Yet there is scant data to optimally nourish patients in the perioperative period despite the recognized malnourished state and associated increased morbidity and mortality.

Malnutrition has been documented to be an independent risk factor in surgical outcomes for nearly 80 years, thus identifying patients at risk prior to surgery may be critical to improving outcomes (13,17). Patients should be screened for nutritional risk, and nutritional intervention should be provided early in treatment to optimize outcomes. Early identification and intervention has been shown to reduce morbidity, length of stay, and admission costs in hospitalized patients (17-19). The following is a review of available literature regarding pancreatic cancer surgery and

perioperative nutritional considerations and strategies.

Methods

A systematic search was performed using PubMed for studies published through May 26, 2014. Search terms used were 'pylorous preserving PD or pancreatic resection or pancreatectomy or Whipple or pancreatic surgery or duodenal preserving pancreatic head resection' and 'nutrition or feeding or nasogastric or nasojejunal or gastrojejunostomy or jejunostomy', restricted to title, abstract or keywords. We sought articles with level I evidence whenever possible; however, the majority of the literature was comprised of level II or greater evidence. Systematic reviews, meta-analyses, randomized and observational cohort studies were included. Opinion papers, case reports, and animal studies were excluded for this review. Perioperative, as used in this manuscript, encompasses the period from diagnosis, through surgery, to full recovery with oral intake. Management of acute and chronic pancreatitis was not included.

Preoperative nutrition assessment

In general, malignancies predispose patients to preoperative malnutrition. Proper screening for malnutrition can help identify patients at increased risk for perioperative morbidity. Unfortunately, the terminology surrounding malnutrition remains quite confusing. Manifestations of disease-related catabolism are often indistinguishable from those related to starvation, and patients with malnutrition may not be well fed calorically. That is, patients may lack a diet filled with nutrients and protein despite being capable of efficiently metabolizing the available sources of nutrition. Various screening tools have been developed and validated for identifying patients at risk of malnutrition, including the subjective global assessment (SGA), malnutrition universal screening tool (MUST), and NRI (20) (*Table 1*). These tools, in conjunction with certain anthropometric measurements, such as body mass index (BMI) and laboratory markers of nutrition, such as albumin and prealbumin, can help guide preoperative strategies to improve patient nutrition. Though significant weight loss is considered a reliable indicator, malnutrition is far more complex. Even patients with a high BMI may be at considerable risk of malnutrition (13,21,22).

The SGA requires a physical examination by a health professional (21). Therefore, time constraints and ease of use may be barriers. The patient-generated SGA (PG-SGA) was developed for the oncology population and includes questions to be filled out by the patient in addition to the physical examination and has been shown to effectively identify malnutrition (22,23). Recently, the abridged PG-SGA (aPG-SGA) was found to be an effective tool at identifying cancer cachexia and predicting outcomes including risk for chemotherapy intolerance and life expectancy (24). The MUST and NRS-2002 have been validated for use in hospitalized patients with high sensitivity and specificity for predicting postoperative morbidity (23,25-28). The NRI failed to detect surgical or oncology patients at high risk for malnutrition (25,26) but was found to be an independent factor in predicting SSI after PD (27). Using ≥5% weight loss during the 6 months prior to surgery was found to be as reliable as SGA, MUST, and NRS-2002, whereas low BMI alone was shown to be an unreliable measure of malnutrition (23,25,26). Using BMI as a single measure to assess malnutrition risk amongst patients with pancreatic cancer would overlook as many as 21-24% of patients who were classified as overweight or obese by the World Health Organization, as high BMI may reflect an excess of certain nutrients or nutrients in wrong proportions (29).

Only one study has compared these measures to evaluate the prevalence and effect of malnutrition on postoperative morbidity for patients undergoing resection of pancreatic cancer (13). On its own, weight loss of ≥5% preadmission over the preceding three to six months was related to an increased risk of SSI and increased length of stay. The MUST and NRI showed excellent agreement with regards to overall morbidity, SSI rate, and length of hospital stay, while MUST and SGA had excellent agreement regarding SSI rate (13). Nevertheless, this was a retrospective review.

Preoperative serum markers

Albumin is an acute phase protein which decreases during periods of inflammation, trauma, and injury. It has long been known that albumin is not reflective of the adequacy of a patient's intake (30). However, hypoalbuminemia is strongly associated with poor postoperative outcomes, such as mortality and infection following gastrointestinal surgery (31). Amongst patients undergoing resection for pancreatic adenocarcinoma (n=268), preoperative hypoalbuminemia (<4 g/dL) was associated with an increase in postoperative complications (40.3% versus 25.5%; P<0.05), as cited in the retrospective review by Kanda and colleagues (17).

C-reactive protein (CRP) is an acute phase protein which

Table 1 Screening tools

Screen	Clinical parameters	Score/results
SGA	Questionnaire: weight loss, changes in dietary intake, gastrointestinal symptoms, functional capacity Physical examination: muscle, subcutaneous fat, sacral and ankle edema, ascites Clinician's overall judgment	Stage A, well-nourished; stage B, moderate or suspected malnutrition; stage C, severe malnutrition
PG-SGA	Weight loss Condition and age Metabolic stress Physical examination	Stage A, well-nourished; stage B, moderate or suspected malnutrition; stage C, severe malnutrition
aPG-SGA	Weight and weight change Food intake Symptoms Activities and functions	Score 0-1, no nutrition problem; score 2-8, increasing nutrition problem; score ≥9, critical need for improved symptom management and/or nutrition intervention
MUST	BMI Weight loss Presence of acute disease	0, low risk; 1, medium risk; 2, high risk
NRI	Serum albumin level Ratio of actual to usual weight	>100.0, no risk; 97.5-100.0, low risk; 83.5-97.5, medium risk; ≤83.5, high risk
NRS-2002	Age adjustment (≥70 years) Nutritional score: weight loss, changes in food intake, BMI, general condition Severity of disease score	Pt rescreened if score <3 (absent, mild, or moderate risk); nutrition care plan initiated if score ≥3 (severe risk)

SGA, subjective global assessment; PG-SGA, patient-generated subjective assessment; aPG-SGA, abridged patient-generated subjective assessment; MUST, malnutrition universal screening tool; NRI, nutritional risk index; NRS, nutritional risk screening; BMI, body mass index.

Table 2 Glasgow prognostic score (23)

Biochemical measurements	Score
CRP ≤10 mg/L and albumin ≥3.5 g/dL	0
CRP ≤10 mg/L and albumin <3.5 g/dL	0
CRP >10 mg/L	1
CRP >10 mg/L and albumin <3.5 g/dL	2

CRP, C-reactive protein.

also increases during periods of inflammation, trauma, and injury. Elevated preoperative CRP have been associated with a worse prognosis for various cancers (32,33). Patients with an elevated preoperative CRP (>10 mg/L) had a significantly shorter survival (8.3 versus 18.2 months; P<0.05) than patients with lower CRP levels (≤10 mg/L) in one series of 65 patients (34). The majority of this data is based on retrospective reviews.

It is clear that systemic inflammation is associated with increased weight loss, functional decline, loss of lean tissue, and overall poor prognosis (35). The Glasgow prognostic score (GPS) measures both albumin and CRP. It has been shown to be a reliable prognostic indicator for survival in various cancers, independent of tumor stage, including patients undergoing palliative resection for advanced pancreatic cancer (36). The GPS (*Table 2*) may be useful in identifying patients at high risk for malnutrition.

Preoperative counseling

The Enhanced Recovery After Surgery (ERAS) Society has evaluated various preoperative and intraoperative measures that may influence postoperative outcomes following pancreatic surgery (37). One of those preoperative

measures was the effect of proper preoperative counseling, including meeting with a specialist in nutrition. Although evidence specific to pancreatic surgery is lacking, there is strong support for this approach. The use of preoperative multidisciplinary counseling has been used with success in other surgical specialties including colorectal, bariatric and transplant surgery (38,39).

Perioperative nutrition

Malnourishment before and prolonged fasting after major abdominal surgery are significant risk factors for adverse outcomes (40-42). The role of perioperative nutrition in malnourished patients has been studied to some extent in other forms of gastrointestinal malignancies. In a prospective randomized controlled trial by Wu and colleagues [2006] 468 patients with moderate to severe malnutrition (as defined by the clinician) with gastric, colon, or rectal cancer were randomly divided to receive a standard oral nutrition (control group) preoperatively or parenteral or enteral nutrition for 8 to 10 days preoperatively (study group) (43). The mortality and complication rates were significantly lower in the study group (2.1% *vs.* 6.0%, P=0.003 and 18.3% *vs.* 33.5%, P=0.012, respectively). The most frequent complication in all groups was infection related to debilitation and/or immobility. Septic complications were not significantly different between the two groups, nor between those patients receiving parenteral versus enteral nutrition (P>0.05). There remains considerable debate on how best to nourish patients prior to pancreatic surgery, as well as in the postoperative period. There does not appear to be benefits to providing supplemental nutrition to well-nourished patients in the pre-operative period. And in a small randomized controlled trial of well-nourished patients undergoing PD or esophagectomy enterally fed immediately post-operatively versus initiation on post-operative day 6, the early fed group unexpectedly had a greater decrement in respiratory mechanics as measured by vital capacity and FEV_1. Other measurements of strength, fatigue, weight and anastomotic leak were not significantly different between the two groups, and the authors concluded that immediate postoperative enteral feeding should not be used in well-nourished patients routinely (44).

Oral feeding

Various reports have studied the efficacy of early oral feeding strategies following pancreatic surgery. According to the ERAS Society recommendations, routine use of preoperative enteral nutrition is not indicated (37). However, there is low-level evidence suggesting preoperative supplemental nutrition may be indicated in the malnourished patient. The European Society for Clinical Nutrition and Metabolism (ESPEN) more strongly supports preoperative nutritional support for 10-14 days in patients at severe nutritional risk, even if surgery needs to be delayed. ESPEN defined severe risk by the presence of at least one of the following criteria: weight loss >10-15% within 6 months, BMI <18.5 kg/m^2, SGA grade C, serum albumin <3 g/dL (45).

Routine use of postoperative enteral tube feeding is not indicated and patients should be started on a normal, oral diet, with a gradual increase over 3 to 4 days. There is soft evidence referenced in ERAS recommendations that fast-track oral feeding strategies result in less delayed gastric emptying (DGE) than normal oral feeding strategies. ESPEN guidelines also support early initiation of normal food within 24 hours after major gastrointestinal surgery. Again ESPEN more strongly argues for simultaneous enteral nutrition supplied beyond anastomoses in patients that cannot achieve >60% of their nutritional needs within 10 days and/or with obvious under nutrition at the time of surgery (45).

The discrepancy between ERAS and ESPEN guidelines recognizes that most patients are incapable of attaining their nutritional goals *per os* in the post-operative period. In Bozzetti's letter [2013], the discrepancies between planned feeding schedules and intake outcomes are pointed out in studies of patients undergoing pancreatectomy (46-53). In response, Lassen and associates point out that some of the literature supporting the ESPEN approach also suffers qualitatively and that enteral tubes are not risk free (54).

A recent ERAS study of 115 patients undergoing PD by Braga and associates aimed to start liquids on post-operative day 1 and solids on post-operative day 2 in the ERAS group, versus post-operative day 3 and post-operative day 4, respectively, in the historical control group. These objectives were achieved in 55% of patients for oral liquid targets and 53% for solid food targets. Low compliance with ERAS targets was related to rate and severity of complications. For example, of the 60 patients with poor compliance to early oral feeding, nearly 72% had post-operative complications (55).

Oral feeding strategies remain the preferred modality following pancreatic surgery. In a meta-analysis by Gerritsen and colleagues [2013], mean length of stay was shortest in the oral diet (15 days) and gastrojejunostomy

(GJT) (15 days) groups compared to the jejunostomy (JT) (19 days), parenteral nutrition (PN) (20 days), and nasojejunal tube (NJT) (25 days) groups (56). Even when assessing the efficacy of early fast-track feeding strategies, various reports failed to show an improvement in length of stay (57-59). According to Gerritsen and colleagues [2013], the mean time to resumption of a normal diet was fastest in the oral group (6 days), compared to the NJT (8 days), PN (11 days), JT (12 days), and GJT (14 days) groups (56). An estimated 49.4% of patients experienced a complication in the oral feeding group, which was only higher than the JT group (43.8%). The nature of the complications was not included in the report. Mortality rates ranged from 1.8% in the NJT group to 4.4% in the oral group, to 5.4% in the PN group. The incidence of DGE and PF were 14.1% and 7.7%, respectively, in the oral feeding group. Again it should be noted that this was an observational analysis and not a prospective study. Martignoni *et al*. found no difference in mean reported weight loss during the hospital stay when comparing oral feeding to enteral nutrition groups (3.8 *vs*. 4.4 kg; P>0.05) (58). However, this too was a retrospective study.

Allowing patients to eat at will postoperatively has been supported by various surgical subspecialties, including colorectal and bariatric surgery (60,61). In a prospective randomized controlled trial from multiple institutions, Lassen and colleagues randomized patients to enteral tube feeding (needle catheter jejunostomy tube) (N=227) or food at will (N=220) following upper gastrointestinal surgery, (e.g., gastrectomies, pancreatic surgery, hepatic resections, biliary surgery, esophagectomies) (62). A total of 18.4% (n=82) of subjects underwent a Whipple. There were significantly less major complications in the food at will group (100 in 220 patients) compared to the enteral tube feeding group (165 in 227 patients) (P=0.01). There was no significant difference in reoperation rate (P=0.50), thirty-day mortality (P=0.83), or total mortality within the trial period (P=0.36) between the two groups. Adjusting for presence or lack of an upper gastrointestinal anastomosis did not result in any significant difference between the two groups, including anastomotic leak rate, major infectious complication or percent of patients with a major complication. Mean time to flatus was significantly shorter in the food at will group (2.6 *vs*. 3 days, P=0.01); time to first bowel movement was not significantly different (P=0.11). Mean length of stay was significantly shorter in the food at will group (13.5 *vs*. 16.7 days, P=0.046). The overall enteral feeding tube complication rate was 7.2% and the reoperation rate caused by the catheter was 1.3%.

Parenteral nutrition

PN provides a means of nourishment for patients in whom oral or enteral nutrition is not possible or practical. The appropriate selection of patients for use of PN is important because it causes more harm than benefit in patients who can tolerate enteral nutrition or who are not malnourished. According to ASPEN and ESPEN guidelines, PN is generally regarded to be appropriate and beneficial in the post-surgical period in undernourished patients in whom enteral nutrition is not feasible or tolerated within 7-10 days of their procedure. PN is associated with an increased risk of bloodstream infection (especially fungemia), independent of and in addition to the risk of central venous catheterization alone, as well as decreased likelihood of earlier live discharge from the intensive care unit postoperatively (63-67). PN is also associated with the development of metabolic complications, including refeeding syndrome, hyperglycemia, and serum electrolyte abnormalities. It is important to recognize that some of the historical limitations of PN were related to inappropriate formulations heavy in carbohydrate calories, high volume preparations, poor concomitant glycemic control and hyperalimentation. PN can be a life saving form of nutritional supplementation when appropriately used and formulated to meet the needs of individual patients, alone or in combination with enteral or *per os* nutrition (64).

Authors have attempted to demonstrate a role for routine PN in post PD patients. Despite early enthusiasm for PN, oral nutrition has consistently been shown to be safer and more effective than PN with respect to occurrence of post-operative complications (including infection, PF and DGE) and length of stay (57,68). In a prospective randomized controlled trial by Klek and colleagues [2011], 167 malnourished cancer patients were randomly assigned to receive either enteral or parenteral and standard or immunomodulating nutrition for 14 days before undergoing surgery to assess the effect on postoperative complications (69). Malnutrition was defined by the ESPEN criteria presented earlier (45). The authors found that immunomodulating enteral feeds in malnourished patients significantly decreased overall morbidity (P=0.01), infectious complications (P=0.04), mortality (P=0.03), and length of stay (P=0.006) compared to standard enteral feeding. Immunomodulation made no significant difference in the PN arm with respect to morbidity, mortality, or length

of stay (P>0.05). In cases of prolonged gastrointestinal dysfunction where enteral feeding strategies are not possible, PN should be given until caloric requirements are met *per os*.

PN has also been suggested as a potential tool in the conservative management of PF; however, other feeding modalities have proven more effective. Klek *et al*. [2011] performed a prospective randomized controlled trial of 78 patients with PFs randomized to either EN or PN (70). At 30 days, the PF closure rate was 60% in the EN group compared to 37% in the PN group (P=0.04). The median time to closure in the EN group was 27 days, while the median time was not reached at the conclusion of the study for the PN group (P=0.047). The only two factors associated with PF closure were EN [OR =6.136, 95% confidence interval (CI): 1.204-41.623; P=0.04] and initial fistula output ≤200 cc/day (OR =12.701; 95% CI: 9.102-47.241; P<0.001). It should be noted that DGE can be well managed with distal feeding tubes, so PN should not be necessary in these patients.

Enteral nutrition

EN via a tube passed through the nose or abdominal wall provides a means of supplementing *per os* intake or ensuring adequate nutrient intake when *per os* feeding is not practical, with fewer severe risks than PN. When compared to PN in the general surgical literature, EN has been shown to lead to reduced infections, decreased mortality, shorter length of stay, and to be more cost effective (71-73). In the absence of gastrointestinal dysfunction, the evidence supports the use of EN over PN when *per os* nutrition is not possible. However, many questions remain with respect to timing, site of tube feeding, oral *vs*. tube feeds, and type of formula. This decision-making process is further complicated by the relatively common occurrence of DGE post-operatively in the pancreatic surgery cohort. The complexity of these decisions requires PD patients be cared for by a multidisciplinary team, including nutrition professionals.

More recent publications endorse the benefit of different enteral nutrition routes. Zhu *et al*. demonstrated the superiority of NJT to JT with respect to complications and length of hospital stay in a randomized, controlled clinical study (74). Gerritsen and colleagues [2012] after their systematic analyses reported their own experience with NJ, JT and PN (75). In this review, NJT feeding (44 patients) was compared to JT feeding (48 patients) and PN (37 patients). There was no difference in time to resumption of oral intake between NJT feeding (median 13 days), JT feeding (16 days) and PN (14 days) (P=0.15). Abu-Hilal *et al*. found that NJT feeds following pancreatic surgery led to resumption of a normal diet faster than GJT or JT feeds (median 10 *vs*. 14 *vs*. 14 days, respectively; P=0.02) (76). In the meta-analysis by Gerritsen *et al*. [2013], there was no difference in length of stay between the three groups (P=0.35). The time to resumption of a normal diet was longest in the GJT group (mean 14 days), 12 days in the JT group, and shortest in the oral diet group (mean 6 days) (56).

Scaife and colleagues attempted to retrospectively identify risk factors that predict the need for enteral feeding tubes, and found a number of factors that may help predict those that will require assistance post-operatively (77). Patients were categorized according to the presence or absence of the following ten NSQIP preoperative risk factors, including preoperative dependent functional status; presence of chronic obstructive pulmonary disease (COPD); advanced age; male gender; elevated creatinine; leukocytosis; steroid use; bleeding disorders; hypoalbuminemia; and increased BMI. The most important single predictor in terms of feeding tube need was age ≥80 years (P=0.035). There were no complications related to feeding tube placement, regardless of timing of placement. Of the 56 feeding tube placed intraoperatively, 16.1% required replacement for clogging, inadvertent removal, and premature removal. They also estimated a benefit in terms of cost by prospectively implementing a strategy of inserting feeding tubes at the time of operation, dependent on the presence of these pre-operative risk factors. In a theoretical population of 100 patients, there was a cost savings of US $4,050.

In the majority of cases patients should be allowed to eat at will. Enteral feeding strategies, while superior to PN, should only be employed selectively and tubes should not be routinely inserted. PN should be utilized only when other forms of enteral nutrition are not possible. Following these strategies should decrease length of stay by allowing quicker resumption of *per os* nutrition, which may additionally minimize costs.

Perioperative enteral tubes

The role of enteral tubes has been highly debated and fairly surgeon specific. The specific evidence favoring an optimal decompression and feeding strategy following pancreatic surgery is lacking. *Table 3* compares four different feeding modalities. We describe the role of perioperative nasogastric tube decompression as well as perioperative feeding enteral

Table 3 Feeding modality

Enteral access	Pros	Cons
Nasojejunal tube	Non-invasive enteral strategy	Dislodgement
	Early enteral feeding	Occlusion
		Discomfort
Gastrojejunal tube	Ability to vent and feed via single tube	Dislodgement
	Improved patient comfort	Occlusion
		Malfunction of gastric port
Jejunal tube	Early enteral feeding	Bowel strangulation
		Volvulus
		Leakage
Parenteral nutrition	Ability to feed in the setting of ileus or mechanical obstruction	Increased costs
		Infectious complications

tubes following pancreatic surgery.

Draining (sump) nasogastric tubes

Placement of draining NGT to prevent gastric distension, emesis, anastomotic leaks, and decrease time to return of bowel function following pancreatic cancer surgery has been considered standard practice (78). Recent data, suggests that NGT decompression may be unnecessary following pancreatic surgery. In a retrospective cohort study Fisher *et al*. described a series of 100 consecutive patients undergoing pancreatic surgery, with 50 patients having the NGT removed once patients demonstrated adequate bowel function (NGT group) and 50 patients having the NGT removed immediately postoperatively (no NGT group) (79). The mortality and morbidity rates were similar between the NGT and No NGT groups (0% *vs*. 2%, respectively; P=1.0 and 44% *vs*. 44%, respectively; P=1.0), as was the time to return of bowel function (median 5 *vs*. 5 days, respectively; P=0.81). The incidence of biliary anastomotic leaks was 0% in both groups. The PF rates were 6% in the NGT group and 10% in the no NGT group (P=0.72). Furthermore, length of stay was not significantly different between the two groups (median 7 in both groups; P=0.30). There were no complications from NGT insertion postoperatively (2 in the NGT group *vs*. 4 in the no NGT group; P=0.68).

In another observational cohort study of 250 patients [125 patients in each group (routine NGT & selective NGT)] undergoing PD, the authors concluded routine use of NGTs may be unnecessary (80). Selective NGT placement referred to those tubes placed when clinically indicated, such as for prolonged endotracheal intubation. The overall morbidity was not significantly different between the routine NGT and selective NGT groups (81.6% *vs*. 80.8%, respectively; P=NS). On multivariate analysis, routine use of NGT was an independent risk factor for DGE [hazard ratio (HR) =8.56; P=0.03]. Moreover, overall length of stay was significantly shorter in the selective NGT group compared to the routine NGT group (median 6 *vs*. 7 days, respectively; P<0.0001). Finally, return of bowel function was significantly shorter in the Selective NGT group (median 4 *vs*. 5 days, respectively; P<0.0001).

Gastrojejunostomy tubes

GJT are routinely placed at some institutions following pancreatic surgery. The benefits include the ability to feed distal to the area of resection, while also maintaining the ability to vent the stomach through the gastrostomy port. As mentioned, the incidence of DGE ranges from 6% to 45% following any pancreatic surgery (56,81,82). In a study by Mack and colleagues, 36 patients were randomized to GJT placement (20 patients) or standard NGT placement (16 patients) following PD to assess the impact on development of DGE (59). The overall complication rate was not significantly different between the GJT and NGT groups (20% *vs*. 25%, respectively; P=NS). The incidence of gastroparesis was 0% in the GJT group *vs*. 25% in the NGT group (P=0.03). Moreover, the duration of gastric decompression was significantly shorter in the GJT group compared to the NGT group (mean 5.3 *vs*. 9.5 days, respectively; P=0.02). Length of stay was significantly shorter in the GJT group (median 11.5 *vs*. 14 days, respectively; P=0.01). Finally, overall hospital charges were significantly

less in the GJT group compared to the NGT group (mean US $52,589 *vs.* $82,151, respectively; P=0.04).

Though randomized, this study was limited by non-standardization of gastric decompression, route and type of nutritional supplementation in the control groups

Nasojejunal tubes

NJT feeding emerged as a feeding modality as a result of perceived complications related to JT and PN. Gerritsen and colleagues [2012] retrospectively reviewed a series of 129 patients undergoing PD over 10 years (75). Overall morbidity rates were not significantly different between the 3 groups (NJT 84% *vs.* JT 92% *vs.* PN 92%, respectively; P=0.49). However, tube related morbidity was highest in the NJT group (41%) compared to the JT (23%) and PN (16%) groups (P=0.03). The most frequent tube-related complication in the NJT group was dislodgement (34%), while the JT was the only group requiring return to the operating room for complications related to the tube (6%). There was a trend toward significance in tube-related morbidity between the NJT and JT groups (P=0.06). There was one tube-related mortality in the JT group, compared to none in the NJT and PN groups; however, this was not statistically significant (P=1.0). There was no difference in the rate of DGE in NJT (34%), JT (50%), and PN (40%) groups (P=0.30). Moreover, there was no difference in length of stay between NJT (median 17 days), JT (19 days), and PN (16 days) groups (P=0.83). The authors concluded that none of the feeding strategies was superior to the other.

Jejunostomy tubes

JT feeding has historically been employed in pancreatic cancer surgery to initiate early enteral nutrition in a relatively malnourished patient. Several studies have evaluated the efficacy and complications associated with JT placement and feeding. In the study by Gerritsen *et al.* [2012], the most serious complications occurred in the JT group, including four tube-related relaparotomies and one tube-related mortality (75). Complications specific to JTs included mechanical bowel obstructions and leakage. As reported in a large retrospective review of 2,022 patients by Myers and colleagues, certain life-threatening complications have been reported with the use of JTs, including torsion and bowel necrosis at an estimated rate of 0.4% of patients (83). Overall tube-related complications occurred in 1.5% of patients with the most common complications being either occlusion or dislodgement in 0.7% of patients. The intra-abdominal infection rate was reported to be 0.8%. Gerritsen *et al.* [2012] found JTs to have the lowest wound infection rate (6%) compared to the NJT group (16%) and PN group (30%) (P=0.02) (75). Interestingly, in the systematic review by Gerritsen and colleagues [2013], the JT group had the lowest mean overall morbidity rate at 43.8% (56).

Pancreatic fistula

PF is one of the most serious complications following pancreatic cancer surgery. The definition varies widely in the literature, although two of the most common definitions include >10 cc/day of amylase rich fluid after postoperative day 3 or continued drainage of amylase rich fluid after postoperative day 20 as defined by the international study group on pancreatic fistula (ISGPF) (84). Schmidt *et al.* evaluated various risk factors for the development of PF following PD in a series of 510 patients (85). A total of 46 PFs developed postoperatively. Interestingly, the use of mechanical bowel preparation was found to be protective against development of a PF (6% *vs.* 19%, P<0.02). On multivariate analysis, risk factors for PF formation included invaginated pancreatico-jejunostomies (OR =3.30, P=0.01) and closed suction drainage (OR =2.24, P=0.05). Factors protective against PF formation included pancreatitis (OR =0.22, P=0.05) and preoperative endoscopic biliary stenting (OR =0.34, P=0.05). As expected in this series, patients with PFs were more likely to develop septic complications, longer hospitalizations, and a higher incidence of reoperations.

Methods to treat PF from a nutritional standpoint have been previously discussed. Although both EN and PN have been used to assist in closure of PFs, EN is clearly superior with a shorter median time to closure than PN (70). The only predictors of closure were EN and initial fistula output ≤200 cc/day.

Future endeavors

The evolution of pancreatic surgery over the last three decades has led to significant improvements in morbidity and mortality. Improving patients' perioperative nutritional status is a realistic target to further improve outcomes and quality of life. Many questions remain. For example, what is the best measure of malnutrition in patients with pancreatic cancer and what parameters should be used to signal the optimal time for surgery in the malnourished patient?

What should be the duration of preoperative nutrition in the malnourished patient, and should it be *per os* or via a tube? Are NJT feeds in fact superior to other forms of postoperative enteric alimentation following pancreatic cancer surgery? Is there potentially a role in placing a gastric stimulator or performing a sleeve gastrectomy at the time of surgery in patients with either known gastroparesis or those at significantly increased risk of developing DGE? Does enzyme replacement play a role during the perioperative period? Do any interventions short of returning the patient to balanced nutrition result in decreased morbidity and mortality? These questions will help further our understanding of the impact of nutrition on this patient population; this requires a commitment from the field, as these questions are unlikely to be resolved by individual centers. Defining feed strategies and categorizing success and failure after pancreatic surgery should be considered by the International Study Group of Pancreatic Surgery.

Conclusions

Nutrition plays an integral role in pancreatic cancer surgery, not only preoperatively, but also in the postoperative period. A multidisciplinary approach to assess preoperative nutrition helps determine which patients may require additional support in the perioperative period. We believe oral feeding at will remains the best approach based on available randomized control trials and observational studies in pancreatic surgery, and literature from other surgical disciplines. This approach provides nourishment and hydration, though has not been clearly demonstrated to provide balanced nutrition. Enteral feeding tubes should be used in select cases. The choice of feeding tube should be the NJT if possible, as the major morbidity profile is the least. There does not appear to be benefits from routine use of NGTs for decompression. PN should be reserved for patients in whom it is not possible to obtain enteral access for feeding. Mitigating postoperative complications, including DGE and PF, remain of utmost importance to maximize outcomes in patients undergoing pancreatic surgery. Future endeavors should focus on better identifying those patients who might benefit from perioperative supplementation of nutrition, which specific enteral feeding route, and the timing of placement.

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Preoperative therapies for resectable and borderline resectable pancreatic cancer

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Abstract: In the era of multidetector high quality CT imaging, it is feasible and critical to use objective criteria to define resectable pancreatic cancer. This allows accurate pretreatment staging and the development of stage-specific therapy. Tumors of borderline resectability have emerged as a distinct subset and the definition has been expanded in the last few years. Borderline resectable tumors are defined as those with tumor abutment of <180 degrees (<50%) of the SMA or celiac axis, short segment abutment or encasement of the common hepatic artery typically at the gastroduodenal artery origin, SMVPV abutment with impingement and narrowing or segmental venous occlusion with sufficient venous flow above and below the occlusion to allow an option for venous reconstruction. Most of the patients whose cancer meet these CT criteria are candidates for preoperative systemic chemotherapy followed by chemoradiation since they are at a high risk for margin positive resection with upfront surgery. Patients whose imaging studies show radiographic stability or regression proceed to pancreaticoduodenectomy (or pancreatectomy) and this may require vascular resection and reconstruction. Prospective biomarker and functional imaging enriched studies are warranted to determine the best overall treatment strategy for these patients.

Keywords: Pancreatic cancer; borderline resectable tumors; preoperative therapies

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Introduction

Pancreatic cancer presents as a locally advanced or metastatic cancer in most patients and only about 20-25% of patients present with a potentially resectable cancer. Even in these patients, the 5-year survival rate after a successful pancreaticoduodenectomy (PD) or pancreatectomy is approximately 15-20% (1). Patients who undergo a margin positive resection (R2 or R1) do poorly and their survival is similar to those with locally advanced disease (2-5). Given the systemic nature of pancreatic adenocarcinoma, and the morbidity involved with surgery, it is essential to clearly determine the resectability status at the time of initial staging evaluation. This is best accomplished by a computerized tomography (CT) scan optimized for pancreatic imaging (6). Based on this high quality CT imaging, pancreatic tumors are classified as resectable, locally advanced or metastatic. Tumors of "borderline resectability" are emerging as a distinct subset of pancreatic tumors and do not easily fit the traditional categories of resectable or locally advanced pancreatic cancers (7,8). It is important to make this distinction because these presentations tend to confound the results of clinical trials and misguide treating physicians – i.e. in the absence of objective criteria for preoperative staging, some patients with borderline resectable pancreatic cancer will be treated as if they have resectable cancer (with an increased risk of margin positive resection) while others will be treated as having locally advanced disease (and suggest 'dramatic' downstaging and operability). These patients are poor candidates for upfront PD given the high rate of margin positive resection and in selected patients; preoperative therapy can achieve an R0 resection surgery.

This helps select appropriate patients for surgery who

have the greatest likelihood of a favorable postoperative outcome. This allows the appropriate candidates suited for surgery to proceed with PD. This article reviews the definition of borderline resectable tumors and provides a framework for preoperative therapeutic options of patients with resectable and borderline resectable pancreatic cancers.

Preoperative staging criteria and the changing paradigm

A multidetector computerized tomography (MDCT) with 3-dimensional reconstruction is the best modality to determine local tumor resectability except for its low sensitivity for low-volume hepatic or peritoneal metastases (in ~20% of patients, CT occult metastatic disease is found on laparoscopy or exploration) (9-11). Whenever possible, it is helpful to perform a CT scan prior to biliary decompression procedures since post-procedure pancreatitis, if it occurs, may obliterate the vascular planes and preclude accurate assessment of the extent of disease. Endoscopic ultrasound (EUS) has a higher sensitivity compared to a CT scan to detect small tumors and is indicated in selected patients especially those who are candidates for preoperative therapy.

The American Joint Committee on Cancer (AJCC) TNM (Tumor, Nodes, Metastasis) staging for pancreatic cancer was revised in 2002 (6th edition), to reflect the fact local tumor resectability can be determined by high quality CT imaging and these criteria are unchanged in the latest AJCC edition (12). Based on the AJCC criteria, patients with stages 3 and 4 pancreatic adenocarcinoma are considered to have unresectable disease. Criteria for resectability include the absence of tumor extension to the celiac artery (CA) and superior mesenteric artery (SMA), a patent superior mesenteric vein (SMV) and portal vein (PV), and no distant metastases. Locally advanced, surgically unresectable tumors are defined as those that encase the adjacent arteries (celiac axis, SMA, common hepatic artery) or that occlude the SMV, PV, or SMPV conf luence. With sophisticated imaging, there is a paradigm shift and a growing category of borderline resectability and the attempt to standardize the definition of borderline resectable pancreatic cancer is work in progress, being modified with time.

Borderline resectable criteria: NCCN, MDACC and AHPBA guidelines

Even though there is some consistency in the AJCC definitions of resectability, these become blur red when describing borderline resectable pancreatic adenocarcinoma. At the University of Texas M.D. Anderson Cancer Center (MDACC), patients with (anatomic) borderline resectable pancreatic cancer were originally defined to include those whose tumors exhibit: shortsegment encasement of the hepatic artery which is amenable to resection and reconstruction without evidence of tumor extension to the celiac axis; abutment of the SMA to involve less than or equal to 180 degrees of the circumference of the artery; or short-segment occlusion of the SMV, PV, or SMPV conf luence with a suitable option for vascular reconstruction due to a normal SMV below, and PV above the area of tumor involvement (7). Since then the criteria have been extended to include additional patients where the surgery could prove to be technically challenging. The American hepato-pancreatico-biliary (AHPBA) association consensus conference on pancreatic cancer [2009] expanded the venous involvement criteria to allow tumor abutment of the SMV/PV with or without impingment and narrowing of the lumen (in addition to venous encasement or short segment occlusion). NCCN has adopted some of these AHPBA guidelines in its most recent version [2.2011] and allows SMV/portal vein abutment with impingment and narrowing of the lumen (13-16). The criteria for arterial involvement (SMA and hepatic artery) are clear and similar across the board.

The above definitions describe the anatomic subset of borderline resectability that deal only with tumorvessel orientation (referred to as type A). Katz and colleagues have described two additional subsets, types B and C, which attempt to define additional criteria for borderline resectability beyond the imaging based principles (17). Most physicians encounter patients with operable pancreatic cancer who are not quite ready for immediate surgery and require extra time off to sort out host or tumor related concerns. Some of these patients have subtle indeterminate subcentimeter liver lesions or peritoneal/omental nodules that are suspicious for metastatic disease they are too small to proceed with a diagnostic FNA-biopsy or additional imaging tests (PET-CT or MRI). These patients fit the MDACC type B definition of borderline resectable pancreatic cancer. Type B patients may have had a technically resectable or a borderline resectable primary tumor as defined on CT images. Another subset of patients is those who have associated medical comorbidities that need time to evaluate or a reversible borderline per formance status (typically ECOG 3). Good examples of

these presentation is a patient who has a small asymptomatic pulmonary embolism on routine imaging or a patient with a low prealbumin and decline in nutrition and performance status in the presence of obstructive jaundice and cholangitis though progress is noted after biliary decompression and a close eye on nutritional supplementation. This subset const itutes Type C category (and patients in this category may also have had a radiographic potentially resectable or a borderline resectable primary tumor).

Rationale for preoperative therapy in patients with resectable and borderline resectable (types A, B, C) pancreatic cancer

The rationale for delivering preoperative therapy in early pancreatic cancer includes potential for down staging in order to maximize the chances for an R0/R1 resection, using this approach to gauge the cancer's biology and allow appropriate candidates suited for surgery to proceed with PD, treat micrometastatic disease early, and lastly, deliver "adjuvant" therapy in a preoperative setting when it is better tolerated. This has been studied at several institutions in a phase II setting (18-22). Our group has completed two gemcitabine based chemoradiation trials in patients with potentially resectable pancreatic cancer (18,21). In the 176 patients from both trials (Gem-XRT and Gem-Cis-XRT) isolated tumor progression at the time of preoperative restaging was rare with the rate of local tumor progression precluding surgery 0.6% (1 of 176 patients). We have used a similar preoperative strategy for borderline resectable pancreatic cancer with the exception that therpay lasts longer prior to planned PD (the original dataset of 176 patients did not include any patients with MDACC criteria for borderline resectability). Since patients with borderline resectable pancreatic cancer (type A) are at a high risk for margin positive resection and poor survival, these patients are ideal candidates for a prolonged course of preoperative therapy.

Treatment schema

After reviewing the patient's pancreas protocol CT scan in a multidisciplinary conference with radiologists and surgical, medical and radiation oncologists, patients' cancers are categorized as borderline resectable types A, B, C or a combination of these. Most patients are candidates for initial gemcitabine based systemic therapy for 2-4 months. Patients with an ECOG PS of 0-1 are considered for combination chemotherapy, often with gemcitabine and a platinum agent. A restaging CT scan is reviewed after approximately 8 weeks of systemic therapy and patients with radiographic response or a biochemical response in the presence of stable disease are candidates for more systemic therapy followed by chemoradiation or may proceed to chemoradiation. After a break of 4-6 weeks from their radiation therapy, patients who continue to show disease stability or response are candidates for surgery. Gemcitabine or capecitabine are the common radiation sensitizers used in this setting. After a break of 4-6 weeks from their radiation therapy, patients who continue to show disease stability or response are candidates for surgery.

Given the high rate of systemic relapse in patients with resected pancreatic cancer, the "best" systemic therapy available may be applicable in the neoadjuvant setting in selected patients. The recent phase 3 study published by Conroy and colleagues reports on FOLFIRINOX superiority over gemcitabine in the treatment of metastatic pancreatic cancer and has gathered interest (23). 342 patients with a PS of 0 or 1 were randomly assigned to receive FOLFIRINOX or gemcitabine. Six months of chemotherapy were recommended in both groups in patients who had a response. The primary end point was overall survival. The median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group [hazard ratio for death, 0.57; 95% confidence interval (CI), 0.45 to 0.73; P<0.001]. Median progression-free sur vival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (P<0.001). The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). The authors concluded that FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status. There has been some interest from cooperative groups and single institutions to propose FOLFIRINOX based systemic therapy followed by chemoradiation for patients with upfront unresectable (but borderline criteria) pancreatic cancer to potentially maximize their chance of resectability and improve survival after preoperative therapy. Though, it is important to note that beside an excellent PS, >50% of patients in the FOLFIRINOX study had pancreatic tail tumors and the triple drug regimen was not without toxicity (especially in patients with biliary stents/ those prone to cholangitis).

Katz and colleagues have published the largest to date retrospective report of 160 patients with borderline

resectable pancreatic cancer (from a prospective database, 1999-2006) (17). Of these, 125 (78%) received preoperative therapy with mostly chemotherapy followed by chemoradiation and 66 (41%) underwent PD. Twenty seven percent (18 of 66) required vascular resections and in 94% of the patients this was an R0 resection. The median survival was 40 months for patients who underwent preoperative therapy followed by surgery and 13 months for patients who did not undergo PD (P<0.001). Interestingly, the percent change in CA 19-9 over the course of preoperative therapy was associated with overall survival. When compared to patients who had a >50% decrease in serum CA 19-9, patients with an increase in serum CA 19-9 had a greater than 2-fold risk of death [(HR =2.4, P=0.02, 95 % CI 1.2, 4.9)]. In practice, the radiographic stability (or response), patient' s tolerability to therapy and performance status as well as the CA 19-9 trend is factored into making a therapy decision. Prospective data on the role of CA 19-9 as a predictive marker is needed before we consider using it as a part of the 'resectability criteria' in treated patients.

Understandably, there is an inherent selection bias given that the prolonged course of therapy which selects for better tumor biology, though the role of radiation in this setting needs further evaluation. When our systemic agents and biomarker based techniques to select patients improve, it will provide additional justification for the need for prolonged therapy prior to locoregional options.

Barriers to preoperative therapy for borderline resectable cancer

It is mandatory for patients with resectable or borderline resectable pancreatic cancer to proceed with a cytologic diagnosis of adenocarcinoma (via EUS-guided FNA biopsy) prior to initiating preoperative therapy (16). On rare occasion, this can lead to pancreatitis. In the preoperative therapy setting, when the duration of therapy exceeds 8 weeks, patients with plastic stents are at risk for stent occlusion and cholangitis (especially in the radiation phase). In a clinical trial of 79 patients undergoing chemotherapy with Gemcitabine in combination with Cisplatin followed by Gemcitabine based chemoradiation, at least one stent exchange was necessary in 46 (75%) of the 61 patients who entered the protocol with a plastic biliary stent and selfexpandable metal stents which ultimately were placed in 36 (46%) of 79 patients (18,21).

Biomarker based selection and sequencing of preoperative therapies: Are we there yet?

A significant challenge to the management of pancreatic cancer (PC) patients is resistance to a broad range of therapies. There is an emerging consensus that poor intratumoral drug levels may be related to high stromal density, hypoperfusion, and/or drug transport/metabolism within the tumor (24). These factors have been evaluated in animal models but not understood in patients. e.g., gemcitabine, the standard first-line therapy for advanced disease and a drug used in our preoperative management is an incompletely understood drug with little data demonstrating levels of gemcitabine (dFdC) or its active metabolite within human tissue or evaluating factors affecting penetration or lack of activity in many patients. We have some emerging biomarker data, albeit of retrospective nature (from prospective trials) and we need to exploit this information to generate new knowledge and plan elegant next-generation studies (*Figure 1*). A few of these are discussed below:

Human equilibrative nucleoside transporter (hENT1) protein

The hNET-1 transports gemcitabine into cells (25,26). Farrell and colleagues studied the predictive value of hENT1 levels in patients from RTOG9704, a large prospective randomized adjuvant treatment trial comparing gemcitabine to 5-fluorouracil (5FU) as systemic therapy in patients getting 5FU based chemoradiation (27,28). In this study, 538 patients were assigned randomly, after surgical resection, to either gemcitabine or 5 FU. HENT1 immunohistochemistry was performed on 229 tissue microarrays and scored as having no staining, low staining, or high staining. HENT1 expression was associated with overall survival in a univariate (P=0.02) and multivariate model in the gemcitabine arm (P=0.004) and hENT1 expression was not associated with survival in the 5FU arm. The authors concluded that this report supports preclinical data and that hENT1 is relevant predictive marker of benefit from gemcitabine in patients with resected pancreatic cancer. Prospective trials in the neoadjuvant and

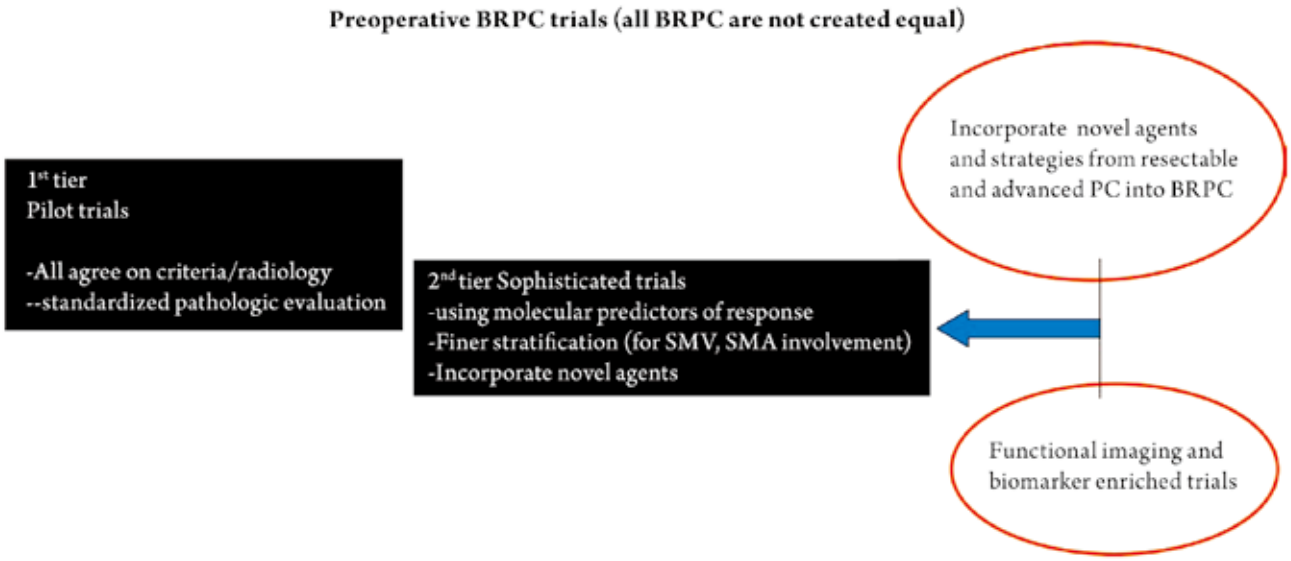

Figure 1 Schema for borderline resectable pancreatic cancer trials: looking ahead. BRPC: borderline resectable pancreatic cancer; SMV: superior mesenteric vein; SMA: superior mesenteric artery; PC: pancreatic cancer.

adjuvant setting are warranted to understand its utility as a predictive biomarker.

Gemcitabine single nucleotide polymorphisms

Okazaki and colleagues evaluated 17 single nucleotide polymorphisms (SNPs) of gemcitabine metabolism genes, including CDA, dCK, DCTD, RRM1, hCNT1, hCNT2, hCNT3, and hENT1 genes in 154 patients with potentially resectable pancreatic adenocarcinoma who were enrolled in clinical trials at the UTMDACC from February 1999 to January 2006 (29,30). Patients received neoadjuvant concurrent gemcitabine and radiation therapy with or without gemcitabine-cisplatin induction therapy. They found that none of the 17 SNPs, individually, had a significant association with OS. A combined genotype effect on OS was observed. Patients carrying 0 to 1 (n=43), 2 to 3 (n=77), or 4 to 6 (n=30) variant alleles had median survival time of 31.5, 21.4, and 17.5 months, respectively. The hazard ratio of dying was 1.71 (95% confidence interval, 1.06-2.76) and 3.16 (95% confidence interval, 1.77-5.63) for patients carrying two to three or four to six at-risk genotypes (P=0.028 and P<0.001), respectively, after adjusting for clinical predictors. Four SNPs mainly, CDA C111T, dCK C-1205T, dCK A9846G, and hCNT3 A25G had a significant association with neutropenia toxicity (individually and combined). The authors concluded that these observations suggest that polymorphic variations of drug metabolic genes may be associated with toxicity of gemcitabine-based therapy and OS of patients with resectable pancreatic cancer.

Rapid autopsy based DPC4 data

Recent rapid autopsy data presented by Dr. Iacobuzio-Donahue and colleagues suggest that pancreatic cancers can present with distinct genetic subtypes with different patterns of failure (31). In their study, patients with DPC4 intact tumors were more likely to die of locally destructive disease (30% of patients) and those with DPC4 mutated tumors with a distant widespread metastatic disease (70%). These distinct patterns of failure (locally destructive versus metastatic) were unrelated to clinical stage at presentation, treatment history, and histopathologic features. There is significant interest in understanding if this data holds true in patients being treated (prospectively) and eventually use this information to guide therapy based on subgroups of patients (locally destructive or wildly metastatic phenotypes). The feasibility of determining DPC4 status on diagnostic cytology specimens was tested recently in patients with locally advanced pancreatic cancer using immunohistochemical staining though patient numbers were small and additional validation studies are warranted (32).

Summary

Preoperative management of pancreatic cancer is an important and evolving field especially with the enlarging definition of borderline resectability. Clearly this effort needs a multidisciplinary working group of surgeons, radiation and medical oncologists, gastroenterologists, radiologists and a pathologist committed to research-driven patient care and is best suited to a high volume center with surgical expertise in vascular resections and interposition grafting. Currently, we lack functional imaging or biomarker based knowledge that can reliably provide data that suggests or predicts response to therapy. This is important going forward since it may have an impact on sequencing of therapies (chemotherapy, chemoradiation) and can help select patients for specific therapies and for surgery.

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Management of periampullary adenocarcinoma by pancreaticoduodenectomy at a regional teaching hospital

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Background: Periampullary adenocarcinoma (PA) includes: pancreatic, duodenal and ampullary adenocarcinoma; and cholangiocarcinoma. Pancreaticoduodenectomy (PD) is required for cure of PA. Previous studies demonstrated the likelihood of cure increases when a microscopically negative (R0) margin is achieved. Clearance of the superior mesenteric artery (SMA) margin has been identified as the most critical margin in PD. Some authors have emphasized the importance of certain techniques to clear the SMA margin. Neither the degree to which these techniques have been incorporated nor their impact on margin status and survival has been described. We hypothesized that use of techniques focusing on clearing the SMA margin would result in higher R0 resection rates and improved survival after PD in patients with PA.

Methods: A retrospective study was performed on patients from 1/1/1985 until 7/31/2007. Data on patient demographics, clinical presentation, preoperative treatment, operative technique, margins, and postoperative outcomes were collected. Ninety-three patients were identified for inclusion in the study. Three approximately equal groups were created for analysis.

Results: The overall survival (OS) for the entire cohort was 19 months and was not different among the groups studied. Margins were microscopically negative in 81% of cases. The percentage of node-positive cases increased during the time period, as did the number of lymph nodes (LNs) examined (P=0.017). The use of pylorus-preserving PD decreased (P=0.001) while resection of the superior mesenteric/portal vein (SMV/PV) increased during the study period. We observed an increase in descriptions of the clearance of the anterior aspect of the aorta and inferior vena cava (IVC), dissection to the right side of the SMA, dissection to the origin of the SMA and intra-operative identification of the SMA margin. Dissecting to the SMA did not change the likelihood of achieving an R0 margin. OS was improved after R0 resections (R0: 21 months *vs.* R1/2: 10 months) but this difference was not statistically significant (P=0.099). There was no association between margin status and OS. Changes in the pathology reporting of margins were observed, with statistically significant increases in the percentage of cases in which the SMA, common bile duct and pancreatic neck margins were separately reported. However, the SMA margin was separately reported in only 26% of pathology reports.

Conclusions: The operative techniques used in PD at this institution have changed over time. The increasing frequency of dissection to the SMA and identification of the SMA margin by both surgeon and pathologist suggest an increased attention to the SMA margin. This shift did not result in significant improvements in survival or margin status, but it is consistent with the recognition of the importance of the SMA margin. Our analysis has also identified areas of potential improvement in the ways in which operative and pathology reports for PD are generated.

Keywords: Pancreaticoduodenectomy (PD); adenocarcinoma; lymph nodes (LNs); margin status

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Introduction

Periampullary adenocarcinoma (PA) is a term encompassing four epithelial malignancies: carcinoma of the head of the pancreas (HOP), duodenal carcinoma, ampullary carcinoma and cholangiocarcinoma involving the distal common bile duct (1,2). Because of the similarities in location and natural history among these malignancies, and because a precise, preoperative diagnosis is sometimes elusive, these tumors are approached in the same way. In the setting of non-metastatic disease, surgical resection by pancreaticoduodenectomy (PD) offers the only chance for cure (2-7).

Even after resection under optimal conditions, however, recurrence is the rule (2,8). The poor prognosis of these diseases has been thoroughly analyzed and several poor prognostic factors have been identified one of the most important observations is that periampullary carcinoma prognosis is closely related to the clinical stage (9). The categories of clinical stage (*Table 1*) defined by Fisher *et al.* and Warshaw *et al.* (10,11) are well known to surgeons familiar with PD. Surgical cure is rare in locally advanced lesions, hence the modifier "unresectable". An opportunity for surgical cure does exist in lesions deemed to be resectable or borderline-resectable (11). The rationale for this clinical staging scheme hinges on the importance of the pathologic status of the surgical margins and the recognition of the impact of margin status on prognosis (6,7,9,10,12). Others have observed that patients left with a positive margin (R1 or R2) after PD for cancer of the HOP experienced a median survival that was similar to patients with localized (non-metastatic) disease who did not undergo resection, while those with grossly and microscopically negative (R0) margins after PD enjoyed an apparent survival advantage (3,13).

These data have led to the following principles: (I) when attempting to resect periampullary carcinoma, the goal should be to achieve an R0 resection (11); and (II) proper patient selection and operative technique are crucial to the effort of achieving negative margins (4-7,14-17).

Wolff *et al.* emphasized the importance of both high quality, multi-phasic CT examination in patient selection and the surgical clearance of the superior mesenteric artery (SMA) margin to achieving negative margins (18). These principles have represented a paradigm shift in the care of patients with periampullary carcinoma. It is unclear how widely these practices have been incorporated into direct patient management or what impact they have had on the success of margin clearance and overall survival (OS) in pancreatic cancer. We hypothesized that: (I) patients who had undergone operative clearance of the SMA margin by dissection along the right lateral wall of the SMA would be more likely to have had an R0 resection than patients who did not undergo this SMA dissection; and that (II) this improvement in R0 resection rates would result in an improvement in OS. In order to explore this hypothesis, we performed a single-institution, retrospective study of consecutive patients who underwent PD for periamplullary carcinoma to determine margin status and the impact of margin status on OS of patients in the cohort.

Table 1 Demographics

Variables	1985-1998 (N=32) [%]	1999-2003 (N=33) [%]	2004-2007 (N=28) [%]
Gender			
Male	16 [50]	22 [67]	20 [71]
Female	16 [50]	11 [33]	8 [29]
Age			
Mean	64	64	62
Race			
Caucasian	22 [69]	26 [79]	22 [79]
Black	6 [19]	5 [15]	2 [7]
Hispanic	1 [3]	2 [6]	1 [4]
Other/unknown	3 [9]	1 [3]	2 [7]
Presentation			
Abdominal pain	11 [34]	14 [42]	12 [43]
Back pain	1 [3]	0 [0]	1 [4]
Light stools	8 [25]	10 [30]	7 [25]
Elevated LFTs	3 [9]	6 [18]	5 [18]
GI bleed	0 [0]	0 [0]	3 [11]
Jaundice	24 [75]	24 [73]	21 [75]
Pururitis	5 [16]	7 [21]	3 [11]
Weight loss	18 [56]	15 [46]	8 [29]
Dark urine	6 [19]	11 [33]	8 [29]
Types of cancer			
Pancreatic	19 [59]	23 [70]	15 [54]
Ampullary	7 [22]	6 [18]	11 [39]
Bile duct	1 [3]	1 [3]	2 [7]
Duodenal	4 [13]	3 [9]	0 [0]
Unknown	1 [3]	0 [0]	0 [0]
Pre-op therapy			
Neoadjuvant	1 [3]	1 [3]	1 [4]
Sphincterotomy	5 [16]	7 [21]	7 [25]
Stent	15 [47]	15 [45]	14 [50]

Table 2 LN status and number examined

Variables	1985-1998 (N=32) [%]	1999-2003 (N=33) [%]	2004-2007 (N=28) [%]
LN status			
Neg	20 [63]	17 [52]	11 [39]
Pos	10 [31]	16 [48]	17 [61]
1-2 pos	6 [19]	9 [27]	10 [36]
>2 pos	4 [13]	7 [21]	7 [25]
Unknown	2 [6]	0 [0]	0 [0]
LN examined			
1-10	23 [72]	20 [61]	5 [18]
11-20	4 [13]	10 [30]	10 [36]
>20	1 [3]	3 [9]	13 [46]
Unknown	4 [13]	0 [0]	0 [0]

LN, lymph node; Neg, negative; Pos, positive.

Table 3 Margin status

Variables	1985-1998 (N=32) [%]	1999-2003 (N=33) [%]	2004-2007 (N=28) [%]
Margin status			
Neg	30 [3]	24 [72]	21 [75]
Pos	1 [94]	9 [27]	7 [25]
Unknown	1 [1]	0 [0]	0 [0]
Margins reported			
Pancreatic	21 [66]	31 [94]	27 [96]
Pancreatic duct	3 [9]	1 [3]	6 [21]
Duodenal	19 [59]	22 [67]	18 [64]
Uncinate process	1 [3]	2 [6]	1 [4]
Gastric	2 [6]	11 [33]	23 [82]
Biliary	0 [0]	3 [9]	1 [4]
Common bile duct	12 [38]	24 [73]	27 [96]
Portal vein	4 [13]	5 [15]	0 [0]
Retroperitoneal	0 [0]	7 [21]	17 [61]
Splenic artery	0 [0]	1 [3]	0 [0]
Radial	0 [0]	3 [9]	3 [11]
Bowel	2 [6]	6 [18]	6 [21]

Neg, negative; Pos, positive.

Methods

We performed a retrospective review of our in-house tumor registry to identify patients who underwent a PD for PA between January 1, 1985 and July 31, 2007. Eligibility criteria consisted of patients with a histologic diagnosis of adenocarcinoma of the HOP, ampulla, duodenum, or bile-duct, collectively called ampullary adenocarcinoma. A list of 509 eligible patients diagnosed with pancreatic cancer during the period of the study was initially identified. Patients who had not undergone a PD for their adenocarcinoma were eliminated, resulting in a final list of 93 patients for study. From a review of the medical records, we developed a custom database (Filemaker Pro, Filemaker, Inc.), which included pertinent demographic and clinical information.

In addition, pathology reports (Copath, Mysis, Inc.) were reviewed to determine the status of the common bile duct, pancreatic neck and SMA margins. Operative reports (Netaccess) were reviewed to determine which of the following operative maneuvers were performed: conventional PD, pylorus-sparing PD, or resection of SMV/PV. The impact of the various surgical maneuvers on margin status was examined using Fisher's exact test.

We also analyzed the changes in operative techniques that occurred over time using the Chi-squared test for trend. The impact of margin status on OS was examined using the Kaplan-Meier method and log rank testing. P values less than or equal to 0.05 were considered statistically significant.

Results

A total of 93 patients were identified for inclusion in the study. For purposes of statistical analysis, the cohort was divided into early [1985-1998], middle [1999-2003] and late [2004-2007] groups.

The study population between the groups was relatively stable in that gender, age, race, modes of presentation, types of cancer and types of preoperative therapy were not significantly different when compared among the three time periods (*Table 1*). Over the course of the study, with 98% (n=91) of the patients having nodal status evaluated, there was an increase in the relative proportion of lymph node (LN) positive tumors identified, with the positive nodal status increasing along with the number of LNs examined (*Table 2*). Over this same time period, the 30-day and in-house operative mortality decreased from 15.6% in the early group to 4% in the late group (19,20).

Overall, 18% (n=17) of cases were classified as having involved margins (*Table 3*). In the early group, only 3% (n=1) of cases had positive margins while in the latter two groups the margins were positive in about a quarter of cases [1999-2003, 27% (n=9); 2004-2007, 25% (n=7)]. However, no statistically significant association between margin status

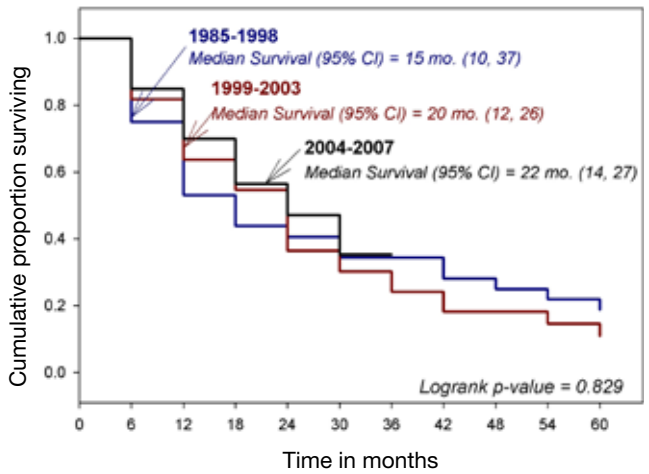

Figure 1 Overall survival (OS).

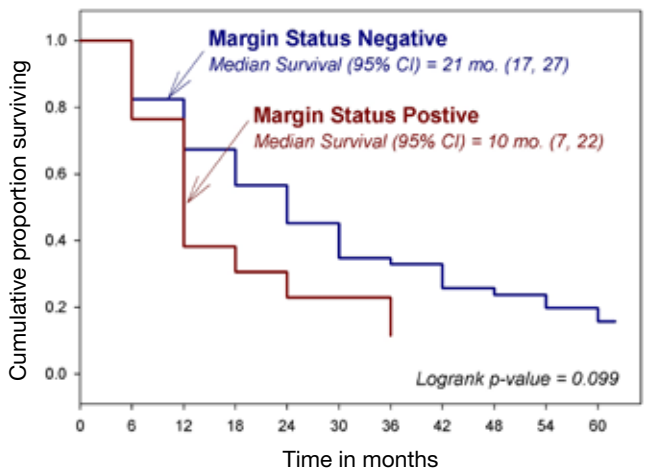

Figure 2 Survival with margin status.

and any operative maneuver could be identified. Specifically, the likelihood of obtaining a negative margin was not increased among patients in whom the SMA dissection was described when compared to those patients in whom this dissection was not described.

The median OS for the entire cohort was 19 months, with an estimated 5-year OS of 18% (*Figure 1*). Survival did not vary by time period, margin status, or the performance of an SMA dissection (*Figure 2*).

In contradiction to the apparent stability of our patient population, there were significant changes in the types of operations performed over the study time period. Pylorus-preserving resection declined during the study from 38% of cases early on to 0% in the late group, while resection

Table 4 Surgical interventions

Surgical interventions	1985-1998 (N=32) [%]	1999-2003 (N=33) [%]	2004-2007 (N=28) [%]
Operation			
Conventional Whipple	17 [53]	28 [85]	28 [100]
Pylorus-sparing Whipple	12 [38]	3 [9]	0 [0]
Resection of SMV/PV	1 [3]	2 [6]	6 [21]
Unknown	3 [9]	2 [6]	0 [0]
Techniques during Whipple			
Retroperitoneal palpation	2 [6]	2 [6]	0 [0]
Comment on mass	22 [69]	22 [67]	14 [50]
Kocher maneuver	24 [75]	25 [76]	28 [100]
Clearance of tissue ant to IVC/aorta	2 [6]	8 [24]	8 [29]
Dissection to origin of SMA	0 [0]	2 [6]	5 [18]
Dissection to right side of SMA	3 [9]	16 [48]	21 [75]
Complete mobilization of SMV/PV	5 [16]	11 [33]	8 [29]
Pancreas excised off SMPV surface	21 [66]	21 [63]	23 [82]
Intra-operative LN biopsy	18 [56]	12 [36]	8 [29]
Intra-operative periampullary biopsy	7 [22]	9 [27]	3 [11]
Intro-operative Id of RP margin	3 [9]	18 [54]	22 [79]
Comment on R status	2 [6]	4 [12]	6 [21]

SMV, resection of the superior mesenteric; PV, portal vein; IVC, inferior vena cava; LN, lymph node.

of the superior mesenteric and/or the portal vein (SMV/PV) actually increased during the time period, accounting for about 1 in 5 cases in the late group (*Table 4*). In addition, intra-operative techniques such as intro-operative LN and periampullary biopsies decreased during this time period (56-29% and 22-11%, respectively), other techniques such as dissection of the SMA (both origin and right side) and intraoperative identification of the RP margin steadily increased (0-18%; 3-21%; 3-79%, respectively; *Table 4*). Dissection along the right side of the SMA was more

Table 5 Overall changes in Whipple techniques from 1985-2007 (summary)

Increased with time	P value	Decreased with time	P value	No change (P=0.05)
Resection of SMV/PV	0.029	Pylorus-sparing PD	<0.001	Complete mobilization of SMV/PV
Clearance of tissue ant to IVC/aorta	0.049	Intra-operative LN biopsy	0.005	Comment on ± mass RP margin
Dissection of origin of SMA	0.015	Comment on ± mass	0.042	Positive pathologic RP margin
Dissection of right side of SMA	<0.001			
Intra-operative identification of RP margin	<0.001			
Pathologic RP margin separately reported	<0.001			

SMV, resection of the superior mesenteric; PV, portal vein; PD, pancreaticoduodenectomy; IVC, inferior vena cava.

common as time went on as was intra-operative identification and marking of the SMA margin. Finally, we observed that the three margins of interest—the common bile duct, pancreatic neck and SMA margins—were reported more frequently as time went on (*Figure 1*). The CBD margin was reported in only 38% of cases during the early time period but in 96% of cases by the end of the study period. Reporting of the pancreatic neck margin increased as well, from 66% to 96 % of cases. The most dramatic change was seen in SMA margin reporting. In the early group, no pathology report made specific mention of this margin, but in the middle and late groups 21% and 61% of reports, respectively, made separate mention of the SMA margin. Overall, the summary of changes in the treatment of PD from 1995-2007 at our institution can be seen in *Table 5*.

Discussion

Although PD is a requisite part of the curative treatment for periampullary carcinoma (9), the low cure rates after surgery alone (3,9,21) and the potential morbidity and mortality of the procedure (1,22) make proper patient selection and conduct of the operation important aspects in the care these patients. Since clearance of the surgical margins is associated with a survival advantage (9,10,23), both the patient selection process and operative techniques should be aimed at optimizing the likelihood of achieving an R0 margin status. In spite of general agreement on the importance of proper patient selection and operative techniques (16,17,24), few studies have attempted to describe the extent to which the selection process and crucial operative techniques have been incorporated into clinical practice or correlate these techniques with margin status.

In the current study, we were unable to demonstrate that focused surgical attention to the SMA margin was associated with improvements in OS or with higher R0 resection rates. This lack of an association between SMA margin and OS likely stems from multiple factors; first, close attention to the SMA margin appeared to be a rather late-developing phenomenon. It is possible that the low rate of positive margins observed during the early time period represents an underestimation of the true rate. Such an underestimation is plausible in light of our observation that the key margins were reported in a minority of early patients. Considering this differential in margin reporting, our observation of higher rates of margin positive resections in the middle and late groups is not surprising. One could argue that the increased attention paid to the margins by the surgeons resulted in a closer assessment of the margins by the pathologists. And, in fact, the increased marking of the SMA margin by the surgeon coincided with the increased identification of it by the pathologist, thus supporting this argument. Certainly, it has been recognized that retrospective assessment of margins is difficult and that real time orientation of the specimen and identification of the margins is required for an accurate assessment of the margins. In any case, the potential misclassification of margin status in the early group might have masked any advantage provided by dissection along the SMA that took place in the middle and late groups.

Another potential explanation for the lack of association between SMA dissection and OS/R0 resection rates is a shift in the complexity of the patients over the course of the study. The increases in node positive disease and portal vein resections that we observed in the middle and late periods suggest that these patients were likely a higher risk group with more aggressive tumor biology. These indicators of aggressive biology would be expected to be associated with a higher risk of microscopically positive margin involvement (25). In addition, the average number of cases per year in each cohort, which increased from about two per year in the early group to eight per year in the late,

also suggests that the patients in the early group might have been a more highly selected patient population and could have represented the lowest risk patients presenting during that time period (19,20). If such differences in disease biology did exist, the patients in the early group would be expected to do better than those in the middle and late groups. Therefore, any advantage derived from SMA dissection in the middle and late groups might not have been evident.

Another potential shortcoming of our analysis is the sole focus on operative technique. Certainly, while we believe that operative technique is an important determinant of margin status, we also recognize that it is not the only factor that has an impact. A more sophisticated, multivariate analysis of the factors that are associated with margin status was not possible due to the size of our study. And, in fact, the modest size of our cohort suggests the potential for a type 2 error due to inadequate power.

An alternate explanation for the lack of association between operative technique and margin status is that the operative reports might not accurately represent what was actually done. Since this was a retrospective study, we were forced to rely on the operative reports to define the surgical maneuvers employed. It is possible that similar operative techniques were performed by surgeons throughout the study period but merely reported differently over time. The convergence of the operative data and the pathologic data, however, make that unlikely.

Finally, we have to acknowledge that the lack of an association between margin status and technique and margin status and survival could be because no such association exists. Although our data cannot refute this possibility directly, the weight of previous studies and the opinion of pancreatic cancer experts both support a link between these factors (2,9,25). In spite of the fact that our study failed to add to that evidence, it has given us insight into the past and current status of pancreatic surgery and the pathologic assessment of PD specimens at our institution.

We now understand that there have been changes in the conduct of PD over the years within our study [1987-2007]. Pylorus-preserving PD is on the decline while portal vein resections have become more common. The importance of this change in operative technique is not clear, but it seems unlikely that the switch away from pylorus preservation would have a cause-and-effect relationship with the higher rates of positive margins we observed throughout the study. A more plausible explanation for the increase in margin positivity is the combination of more aggressive disease biology and a more thorough, and therefore accurate, assessment of the surgical margins. Our finding that reporting of surgical margins improved over time and that, specifically, attention to the SMA margin has grown (5,10,25), supports this theory.

In spite of the fact that the current study failed to confirm our main hypothesis, we did gain valuable insight about the management of PD and the pathologic assessment these specimens at our institution.

Future quality improvement efforts planned at our institution will implement standardized operative templates that would require a surgeon to indicate, in the affirmative or negative, whether a particular part of the procedure was performed. In addition, intra-operative interaction between surgeon and pathologist to orient the specimen and identify the crucial margins of interest will be strongly encouraged. Prospective recording and reporting of these activities could serve as surrogate indicators for quality of care, not unlike the requirement for surgeons participating in ACOSOG-Z5041 to obtain intra-operative photographs of the SMA and SMV/PV to document appropriate clearance of these margins. These surrogate quality indicators might be an especially useful adjunct in evaluating pancreatic surgery programs with more moderate volumes, since estimates of survival and operative complications in such programs are susceptible to wide variation after only a few adverse events and, thus, can be somewhat imprecise, with wide confidence intervals. Finally, introduction of synoptic pathology reports that require separate reporting of the margins is now required by the most recent iteration of the CAP guidelines (26).

Prospective recording of operative details, real-time, in-person communication between surgeon and pathologist, and standardization of the pathology report to include critical information should increase our ability to verify whether proper surgical techniques are employed on a consistent basis and, ultimately, to correlate the use of these techniques with important outcomes. We believe these changes are necessary to provide optimal care to patients with PA. By implementing them, pancreatic surgery programs will signal their interest in this process to those involved in efforts to develop strategies for the regionalization of care of such complex clinical problems.

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Robotic pancreaticoduodenectomy for pancreatic adenocarcinoma: role in 2014 and beyond

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Abstract: Minimally invasive surgery (MIS) for pancreatic adenocarcinoma has found new avenues for performing pancreaticoduodenectomy (PD) procedures, a historically technically challenging operation. Multiple studies have found laparoscopic PD to be safe, with equivalent oncologic outcomes as compared to open PD. In addition, several series have described potential benefits to minimally invasive PD including fewer postoperative complications, shorter hospital length of stay, and decreased postoperative pain. Yet, despite these promising initial results, laparoscopic PDs have not become widely adopted by the surgical community. In fact, the vast majority of pancreatic resections performed in the United States are still performed in an open fashion, and there are only a handful of surgeons who actually perform purely laparoscopic PDs. On the other hand, robotic assisted surgery offers many technical advantages over laparoscopic surgery including high-definition, 3-D optics, enhanced suturing ability, and more degrees of freedom of movement by means of fully-wristed instruments. Similar to laparoscopic PD, there are now several case series that have demonstrated the feasibility and safety of robotic PD with seemingly equivalent short-term oncologic outcomes as compared to open technique. In addition, having the surgeon seated for the procedure with padded arm-rests, there is an ergonomic advantage of robotics over both open and laparoscopic approaches, where one has to stand up for prolonged periods of time. Future technologic innovations will likely focus on enhanced robotic capabilities to improve ease of use in the operating room. Last but not least, robotic assisted surgery training will continue to be a part of surgical education curriculum ensuring the increased use of this technology by future generations of surgeons.

Keywords: Whipple; minimally invasive surgery (MIS); pancreatic adenocarcinoma; innovation; operative technique

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Introduction

Surgery remains a key component of treatment for resectable pancreatic adenocarcinoma. Pancreaticoduodenectomy (PD), or Whipple procedure, for pancreatic head and uncinate process lesions has historically been one of the most difficult abdominal surgical operations and has garnered a well-deserved reputation in by both the medical and lay communities as a risky operation. These challenges include but are not limited to the location of the pancreas in the retroperitoneum, the proximity to major vascular structures, and the unforgiving nature of required anastomoses for functional preservation (1). Mortality rates have dropped dramatically over the past several decades with improvements in preoperative care, intraoperative surgical techniques and instrumentation, as well as post-operative care. One should note that despite improvement in pancreatic fistulae rates, they have not disappeared completely. It is often the improved management of the post-operative complications that has helped drop the

mortality rates.

There has been growing academic interest in the relationship between hospital and surgeon volume and their effect on morbidity, mortality, and oncologic outcomes. There is little doubt that with the current healthcare climate and trends in centralization of care into large healthcare systems that this effect will continue for pancreatic and other high risk surgeries (2,3). There is, however, another growing academic focus on improving outcomes following major pancreatic resection through minimally invasive surgical approaches. Indeed, there has already been widespread adoption of both laparoscopic and robotic resections for cancers of the left pancreas to the point that many believe these approaches should become the standard of care (4). Yet, the demanding technical requirements of performing a minimally invasive PD have proven a very steep hill to climb for most. The pancreatic and biliary anastomosis requires meticulous and precise suturing skills that are not easily mastered. Bleeding from structures such as the superior mesenteric vein can be catastrophic if not handled and repaired with delicacy and efficiency. Robotic PD offers the opportunity to overcome several technical challenges associated with laparoscopic PD, while maintaining the benefits of minimally invasive surgery (MIS). Herein, we review the published literature regarding laparoscopic and robotic PD and our institutional series of robotic PD procedures.

Laparoscopic PD

Minimally invasive PD was first reported by laparoscopic approach in 1994 by surgeons Gagner and Pomp (5) who performed a single, purely laparoscopic procedure. Additional reports of laparoscopic PD in porcine animal models concluded more information on the feasibility and safety of this procedure (6,7). In the ensuing two decades, there are only a few fairly small case series of laparoscopic PD demonstrating the safety and feasibility of this surgical technique (8-15). In 2011, a review of 27 published articles regarding laparoscopic PD concluded similar morbidity and mortality rates as compared to open PD (16). Further case series concluded oncologic outcomes comparable to open PD in terms of consistent negative margin resection rates and lymph node retrieval (10,15,16). It should be noted that almost none of these series demonstrated any superiority in terms of morbidity, mortality, or oncologic outcomes. Actually, most of them had significantly higher rates of pancreatic fistulae and longer operative times than open techniques. It is therefore, not a tremendous surprise that most surgeons have been reluctant to adopt the technique of laparoscopic PD for either benign or malignant disease processes.

Most likely, the low number of published laparoscopic PD procedures is reflective of the inherent complexity of the operation. Many authors describe a difficult learning curve for successfully completing laparoscopic PD (13). Modifications to laparoscopic PD have been performed to attempt to overcome some of the challenges associated with the procedure. These include a combined approach with mini-laparotomy to facilitate skeletonization of the hepato-duodenal ligament and reconstruction (17). Inherently though, the laparoscopic platform has several limitations including non-articulated instruments, lack of depth perception due to two dimensional imaging and constricted intra-abdominal space. These factors make complex pancreatic operations, which are already difficult by their nature, even more complex (1). Even more advanced procedures such as laparoscopic major vascular resection combined with laparoscopic PD have been described, but as the authors note, this technique requires extensive experience with laparoscopy and experience with open major vascular resection in order to be performed safely (18,19). These challenges when combined together have ushered the way for new technological advancements to improve upon the existing minimally invasive surgical technology.

Robotic PD

Robotic surgery may offer many advantages over laparoscopic surgery including articulation of instruments with almost 540° of motion, elimination of surgeon tremor and binocular enhanced three dimensional vision (20). In addition, there are several ergonomic benefits afforded to the surgeon which likely decrease fatigue in the operating room (21), while the enhanced optic and motion capabilities lead to the more accurate movements needed for resection and suturing of delicate tissues. Simply sitting instead of standing for long periods of time, typical of performing a PD, will no doubt benefit the surgeon and possibly lead to better performance. Magnification and depth perception both allow the surgeon to utilize sutures that would be nearly impossible to use with standard laparoscopy. Sutures such as a 6-0 polypropylene on a BV-1 needle are commonly used during robotic Whipple procedures at our institution. These attributes allow the surgeon to overcome many of the

Table 1 Largest reported case series of robotic PDs published to date

Author	Year	Country	Study type	No. of patients	Malignancy [%]	Comparison (No. of patients compared)
Buchs (26)	2011	USA	Prospective, case-matched study	44	33 [75]	Open PD [39]
Chalikonda (27)	2012	USA	Prospective, case-matched study	30	14 [46.7]	Open PD [30]
Zhou (28)	2011	China	Prospective, case matched study	8	8 [100]	Open PD [8]
Giulianotti (22)	2010	USA	Retrospective, case series	20	20 [100]	None
Zeh (29)	2012	USA	Retrospective, case series	50	37 [74]	None
Boggi (30)	2013	Italy	Retrospective, case series	34	22 [64.7]	None
Lai (31)	2012	China	Retrospective, case series	20	15 [75]	Open PD [67]
Narula (24)	2010	USA	Retrospective, case series	5	1 [20]	None

PD, pancreaticoduodenectomy.

Table 2 Operative details from the largest reported case series of robotic PDs published to date

Author	Operative time (min)	EBL (mL)	Margin negative resection rate (%)	No. of lymph nodes collected	Hospital LOS (days)	Complications
Buchs (26)	444±93.5	387±334	41 (93.2)	16.8	13	No difference in complication rates
Chalikonda (27)	476.2	485.8	30 (100.0)	13.2	9.79	Decreased postoperative morbidity following RAPD
Zhou (28)	718±186	153±43	87.5	–	16.4±4.1	Complications were lower with RAPD
Giulianotti (22)	421	394	91.7	14	12.5	No comparison to open
Zeh (29)	568	350	89	18	10.0	–
Boggi (30)	597	220	100	32	–	No comparison to open
Lai (31)	491.5	247	73.3	10	–	No difference in complications
Narula (24)	420	–	100	16	9.6	–

–, information not collected or not available. PD, pancreaticoduodenectomy; EBL, estimated blood loss; LOS, length of stay; RAPD, robotic assisted PD.

insufficiencies associated with classic laparoscopic surgery, making challenging minimally invasive pancreatic surgeries more feasible.

In the past decade, several groups have successfully performed robotic assisted major pancreatic resections, but the literature shows that they have been slow to expand (20,22-24). The first large series of robotic pancreatic procedures was published by Giulianotti *et al*. in 2010. This study included 60 robotic PD demonstrating the safety and feasibility of the procedure (22). Unfortunately, this series included procedures where the pancreatic remnant was not anastomosed but rather injected with fibrin glue and oversewn (almost 50%). This was followed by a case series of 132 robotic PD procedures by Zeh and Moser, published in 2013, again concluding the safety and feasibility of robotic technology as compared to laparoscopic and open platforms, with low incidence of conversion (25). It did, however, demonstrate a relatively higher rate of pancreatic fistulae than one might expect from the same or similar high-volume institution for open PDs. Furthermore, they did not find any significant difference in the length of stay. In addition, operative times were significantly higher. *Table 1* highlights the largest reported case series of robotic PDs published to date. Operative details including procedure time and estimated blood loss are reported in *Table 2*, along with details regarding margin status and lymph node

retrieval for operations performed for malignancy. For centers reporting length of stay, mean hospital length of stay ranged from 9.8-16.4 days.

When compared to open PD, several case series have reported similar postoperative morbidity and complication rates following robotic PD (26,28,31). One comparison study noted a significantly lower postoperative complication rate following robotic PD (25% *vs.* 75%, P=0.05) (28). As reported by Chalikonda *et al.*, patients who underwent robotic PD had a significantly shorter length of stay when compared to open PD (9.79 *vs.* 13.26 days, P=0.043) (27). In addition, procedure related oncologic surgical outcomes appear to be equivalent when comparing robotic to open PD, in terms of resection margin negative rates and number of lymph nodes harvested at the time of surgery (27,28,32). In fact, one series notes an improvement in mean lymph node retrieval rate with robotic assisted PD as compared to open (16.8 *vs.* 11, P=0.02) (26). This is not to claim that removing more lymph nodes necessarily results in better long-term oncologic outcomes, but it does negate any belief that a minimally invasive approach is inferior to open.

Rates of postoperative pancreatic fistula following robotic PD remain mixed in reports from the literature. From the initial Giulianotti *et al.* series of robotic pancreatic resections, there was an increased rate of postoperative pancreatic fistula (31.6%) (22). They hypothesized that with improvement in technique and more experience with microsurgery reconstructions, rate of postoperative pancreatic fistula would decline. Lai and colleagues also report a high postoperative pancreatic fistula rate of 35%, but they were all managed conservatively and without need for reoperation (31). Other series however, have noted no difference in postoperative pancreatic fistula rates (27). Finally, robotic PD has been found to be safe in older populations (age >70) with similar rates of morbidity, mortality and outcomes as compared to a younger cohort, thereby precluding age as a contraindication for robotic PD (33).

Two major review series of robotic assisted pancreatic surgery have been published to date. Zhang *et al.* summarize comparisons of open to robotic pancreatectomy in their 2013 article and conclude through meta-analysis that the procedure is safe with lower associated positive margin rate. Their analysis supports no difference in postoperative pancreatic fistula rate or mortality (34). A second review on robotic pancreas surgery concludes that this approach lead to advantages which may include decreased postoperative pain and blood loss, fewer complications and decreased hospital length of stay with faster recovery (21). These promising findings have led many surgeons to take on even more complex robotic assisted pancreatic resections including extended pancreatectomy with vascular resection for locally advanced pancreatic adenocarcinoma (35).

Robotic assisted HPB surgery—institutional experience

Carolinas Medical Center is a 1,000-bed academic affiliated medical center located in Charlotte, NC. The institution serves as a major referral center for the central and western regions of both North and South Carolina. It is a high volume center for both pancreatic and hepatic resections, (greater than 150 each, annually). Robotic surgery is routinely used at our institution for a variety of general, urologic and gynecologic procedures. The senior author, JBM, who had already been performing robotic HPB procedures at another institution since 2006, initiated the program at CMC in 2008. Over the course of 7 years, we have significantly expanded our experience and have moved beyond the learning curve to a robust practice of liver, pancreas, and biliary operations for both benign and malignant conditions. In particular, our experience with robotic PD has grown significantly with an increasing number of procedures performed each year. Last year the senior author performed 96 robotic HPB procedures. Of note, since program initiation back in 2008, the senior author has performed over 200 open PDs and 150 of other (non-HPB) robotic foregut operations, accentuating the importance of being an experienced HPB and robotic surgeon, before embarking on performing robotic PDs.

In our previous work, we described the learning curve to perform robotic liver, biliary and pancreatic procedures (36). This included a time period of utilizing the robot to perform portions of the dissection for PD with planned conversion to an open procedure for the reconstruction phase. During the robotic surgery learning curve, we became increasingly more comfortable with the reconstructive phase of the operation and significantly more efficient. Now, we routinely perform the entirety of the PD procedure using robotic surgery. As highlighted in our previous work, several robotic HPB procedures during the learning phase were converted to laparoscopy or hand-assisted laparoscopy (36). This is reflective of the challenges encountered with robotic surgery. With the accumulating surgeon's experience in using robot technology, conversion to laparoscopy, hand assist laparoscopy or open surgery is

fairly infrequent.

Robotic assisted Whipple—operative technique

The DaVinci Si robot (Intuitive Surgical, Sunnyvale, CA) is used to perform all robotic PD's at Carolinas Medical Center. Our technique has continually evolved over time and is often modified for individual patient characteristics. The patient is placed in the supine position. Pneumoperitoneum is obtained with a Veress needle at the umbilicus and subsequently upsized to a 12 mm port. Three additional robotic 8 mm cannulae, as well as one additional 12 mm camera port (in the right mid-clavicular line) are placed under direct vision. The umbilical trocar site serves as the assistant port during most of the resection portion of the procedure. Upon initial entry, the abdominal cavity is inspected for evidence of metastatic disease, and the round ligament is taken down and preserved for a vascularized pedicle flap as is our institutional experience and routinely performed in open PD. The gallbladder is commonly sutured to the anterior abdominal wall in order to expose the porta hepatis without the need for a Nathanson retractor, which is used in cases where the patient's gallbladder has previously been removed. The inferior border of the distal gastric antrum and proximal duodenum is mobilized with care to avoid injury to the distal gastric antrum or the pylorus. The right gastric and right gastroepiploic vessels are dissected, sealed, and divided using the robotic bipolar vessel-sealing device. The proximal duodenum is divided distal to the pylorus using a laparoscopic 60 mm stapler device, and the stomach is placed into the left upper quadrant for reconstruction later. The hepatic flexure of the colon is taken down to expose the duodenum. A Kocher maneuver is performed and the ligament of Treitz is mobilized to allow the duodenum to move freely into the right upper quadrant. The common hepatic artery is dissected out and a portal and celiac lymphadenectomy is performed. Intraoperative ultrasound is always performed to confirm the vascular anatomy of the porta hepatis. The gastroduodenal artery is identified, ligated, clipped and divided. The inferior border of the pancreas and the neck are dissected out and mobilized. A tunnel is created underneath the neck the pancreas, on top of the superior mesenteric and portal vein all the way to the superior aspect of the pancreas. An umbilical tape is passed underneath the pancreas. At this point, the neck of the pancreas is transected using the robotic monopolar scissors coupled with saline irrigation to minimize charring of the tissue, a technique which has been previously described (37).

The small bowel is transected about 20 cm distal to the ligament of Treitz. The small bowel mesentery is ligated with a robotic vessel sealing device up towards the base of the uncinate process. Finally, the uncinate process is mobilized away from the superior mesenteric vein and the superior mesenteric artery. The common hepatic duct is then transected just above the cystic duct takeoff. The entire specimen is then placed into a specimen retrieval bag and removed from the abdominal cavity from the slightly enlarged umbilical trocar site. The latter site is partially closed using interrupted sutures around the 12 mm trocar. Then, the camera is moved to this location for the reconstruction phase of the procedure.

For the reconstruction phase of the procedure, the stapled end of the jejunum is brought alongside the transected surface of the pancreas, typically thru a window made in the transverse colonic mesentery. A two layer, end-to-side pancreaticojejunostomy is performed, nearly identical to our open technique. The posterior layer is performed using 5-0 monofilament suture in a running fashion to approximate the capsule of the pancreas with a seromuscular jejunal layer. A small enterotomy (matching the diameter of the pancreatic duct) is created in the jejunum with the electrocautery scissors and a duct-to-mucosal anastomosis is performed using interrupted 6-0 monofilament sutures, typically over a small 8 or 5 French pediatric feeding tube. The anterior layer is completed using an additional 5-0 running monofilament suture. The entire anastomosis is wrapped using the round ligament pedicle flap.

The hepaticojejunostomy is performed approximately 10-15 cm downstream from the pancreaticojejunostomy using a 4-0 or 5-0 monofilament sutures in a running or interrupted fashion, depending on the size of the duct. Finally, an antecolic duodenojejunostomy is performed approximately 50 cm from the biliary anastomosis using absorbable monofilament suture in a running fashion. A single closed suction drain is placed in the right upper quadrant close to the bile duct and the pancreatic anastomosis. All the port sites are closed appropriately.

Evaluation of institutional experience

In order to evaluate our experience with robotic PD, we have recently performed a retrospective cohort analysis of all robotic PD procedures performed at our institution between August 1, 2012 and August 31, 2014, with approval from the Institutional Review Board at Carolinas Medical

Table 3 Patients' demographics, tumor characteristics and oncologic resection quality parameters

Variable	Open (N=49) (%)	Robotic (N=27) (%)	P value
Age* (years)	62.1±12.9	63.6±9.8	0.59
BMI* (kg/m^2)	26.7±5.5	26.8±4.3	0.93
Male	22 (44.9)	14 (51.9)	0.56
Malignant etiology	40 (81.6)	22 (81.5)	0.61
Tumor size* (cm)	3.6±2.5	3.0±1.2	0.29
Positive margin	14 (36.8)	6 (26.1)	0.39
Positive lymph nodes present	30 (81.1)	15 (62.5)	0.11
No. of positive lymph nodes* (N)	2.6±2.6	2.3±2.9	0.69

*, mean values.

Table 4 Primary and secondary endpoints of the comparison between open and robotic PD procedures

Variable	Open, N=49 (%)	Robotic, N=27 (%)	P value
Estimated blood loss (mL)*	866.8±931.5	466.7±452.3	0.042
Operative time (min)*	391.1±141.8	527.4±87.7	0.001
Hospital length of stay (days)*	11.5±7.1	10.1±5.8	0.398
30-day complications	33 (67.4)	11 (40.7)	0.008
Delayed gastric emptying	15	4	0.043
Surgical Site Infections	13	1	0.001
Pancreatic fistula	6	2	0.061
Hospital length of stay (days)*	11.5±7.1	10.1±5.8	0.398
ICU length of stay (days)*	2.9±3.2	1.5±1.2	0.048
30-day readmissions (%)	14 (29.8)	6 (22.2)	0.480
Death (%)	2 (4.1)	0 (0)	0.410

Continuous parameters are described by mean value and standard deviation. Categorical parameters are described by absolute numbers and percentages. *, mean values. PD, pancreaticoduodenectomy.

Center. Study data were collected and managed using REDCap electronic data tools hosted at our institution (38). Variables collected included, but not limited to, patient demographics, operative techniques, oncologic resection quality parameters, morbidity and mortality. A total of 32 patients underwent robotic PD by one, experienced robotic HPB surgeon (JBM), during the reported time period. The intention was to complete the procedure in a completely robotic fashion. Prior to this time period, the senior author had performed segments of a small series of PD's with planned conversions to open, in order to better study the technical and logistical factors of performing robotic PDs, while minimizing impact on the patient and the operating room in terms of length of procedure. A total of 27 robotic PD performed at our institution were completed without conversion. The remaining five patients (15.6%) required conversion to an open procedure secondary to need for portal or superior mesenteric vein resection. These patients were analyzed as a unique subset. Results from robotic cohort were compared to a contemporaneous series of open PD performed during the same time frame by the four fellowship-trained hepatobiliary surgeons within the CMC HPB Surgery department, and includes the open PDs from the one robotic surgeon (JBM). There were no differences in patient characteristics including age, BMI, sex, or malignant etiology (*Table 3*). Tumor size, rates of positive margin and number of positive lymph nodes were no different between groups.

Primary and secondary endpoints are depicted in *Table 4*. Overall estimated blood loss was significantly lower with robotic PD (866.8 *vs.* 466.7 mL, P=0.042), however,

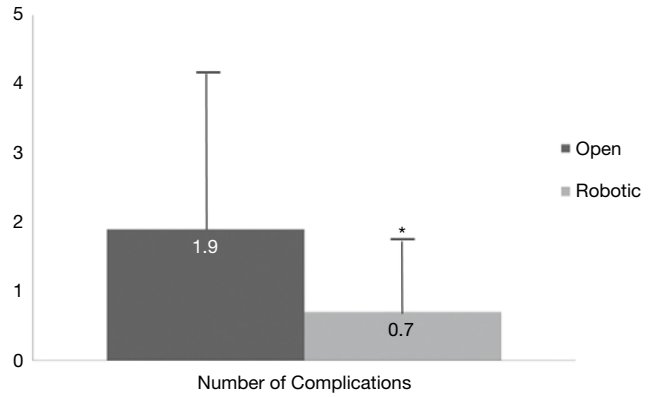

Figure 1 Overall complications. The number of complications, including, but not limited to, delayed gastric emptying, surgical site infection and pancreatic anastomosis leak rate was lower in the robotic group (P=0.008).

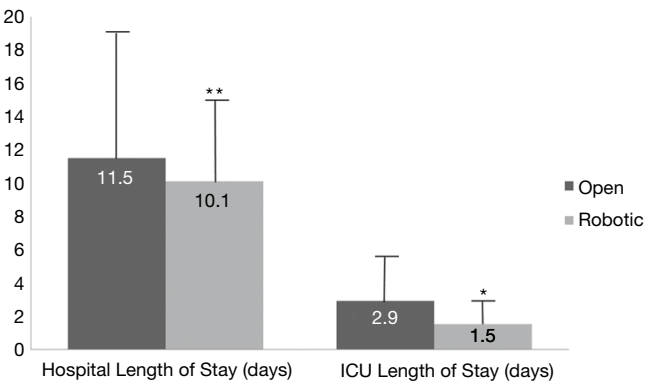

Figure 2 Length of stay. There was significant difference in ICU length of stay between the open and robotic PD group, in favor of the latter. There was a trend for shorter hospital length of stay in robotic group. However, for this observation there is potential for type II error, given the small sample size of the groups. *, P=0.398; **, P=0.048. PD, pancreaticoduodenectomy.

operative time was longer (391.1 *vs.* 527.4 min, P=0.001). Analysis of 30-day postoperative complications (*Figure 1*) revealed significantly fewer complications in the robotic group (P=0.08). Delayed gastric emptying was the most commonly encountered postoperative complication and it was significantly less in the robotic group (30.6% in open *vs.* 14.4% in robotic PD, P=0.043). There were fewer surgical site infections in the robotic group (26.5% in open *vs.* 3.7% in robotic PD, P=0.001). Perhaps the most striking finding was the lower rate of pancreatic fistula compared to open (12% *vs.* 7.4%, P=0.061) in this series, which is the lowest of any published series to date. Actually, if a few more patients were enrolled to the robotic PD group, statistical significance would have been reached (type II error). Mean intensive care unit length of stay was significantly less following robotic PD (2.9 *vs.* 1.5 days, P=0.048) and mean hospital length of stay was decreased by 1.5 days (P=0.398) (*Figure 2*). While hospital length of stay was not significantly different in this analysis, it, again, might represent a type II error (*Figure 2*). There were no deaths within 90 days following robotic PD and there were two deaths following open PD. Overall, our analysis indicates a trend toward many significant benefits associated with robotic PD, including fewer complications and shorter length of stay.

Robotic pancreatectomy: 2015 and beyond

As robotic technology continues to improve and become less expensive and more widely adopted, we will likely see increasing utilization for complex hepatobiliary and pancreatic procedures. Historically, minimally invasive surgical techniques are initially applied to benign disease processes and/or low-grade neoplasms. Subsequently, they are applied to malignant diseases in order to demonstrate similar effectiveness of minimally invasive and open procedures. This appears to be true for pancreatic and peri-ampullary malignancies, including adenocarcinoma, thus far as more surgeons are using a robotic-assisted approach for pancreatic cancer management (28,29). Future reports regarding long-term oncologic effectiveness are still needed to confirm at least equivalency between open and robotic PD.

It is likely that surgeons performing robotic procedures will continue to embrace more challenging pancreatic procedures including vascular resections associated with extended pancreatectomy (35). This has certainly been the senior author's experience. Simply stated, "the more you do, the more you do." Early reports are emerging for the use of robotic surgery for total pancreatectomy coupled with autologous islet cell transplantation (39-41), a procedure that historically has been performed by open laparotomy. In addition, robotic instrumentation, both hardware (the actual tools) as well as software, will continue to improve providing access to better equipment, affording better visualization and leading to increased ease of use.

Key to expansion of minimally invasive surgical techniques is access to education and training with new technology. Surgical resident and fellow education for

robotic surgery is rapidly expanding in the United States and will no doubt become a requisite component, as it has already done so in both urology and gynecology. The reality is that residents in urology or gynecology who complete their training without robotics are at a significant disadvantage to those who have completed comprehensive robotic training (42). The majority of general surgical residents today will at least have some exposure to robotic surgery during their training (42). More institutions are adopting specialized instruction, educational curriculum, and specific surgical rotations which focus on robotic surgery, indicating the expanding presence of this new technology in formal surgical education (43). The addition of specialized technology, including surgeon instructor consoles, will make it easier to mentor trainees regarding the specifics of robotic assisted surgery and it will hopefully allow them to overcome the learning curve associated with this technology in less time (44).

Finally, disadvantages to robotic surgery include the lack of haptic feedback and cost of equipment purchase and maintenance (45). Increased procedure related costs for robotic pancreatic surgery have been previously described (30,46). This is reflective of both extended time in the operating room, disposables and fixed intraoperative charges. Through retrospective institutional review we have analyzed the associated procedure-related costs comparing robotic PD to open PD. Our findings indicate that while operative charges were significantly higher with robotic PD ($48,857.06 *vs*. $35,665.34 USD, P=0.009), once inpatient hospital charge and follow-up visit charges were incorporated into total costs associated with robotic PD procedure, there was no significant difference in overall cost ($176,931.50 *vs*. $182,552.68, P=0.69). We anticipate that future investigations will continue to demonstrate the long-term negligible cost difference between open and robotic procedures due to shorter hospital length of stay and fewer postoperative complications.

Conclusions

Robotic PD for pancreatic adenocarcinoma represents the latest iteration of minimally invasive oncologic surgery. Multiple reported series have found this procedure to be safe and technically feasible. The literature to date supports decreased morbidity associated with robotic PD as compared to open PD, particularly in relevance to wound associated complications and hospital length of stay. Long terms studies are still needed to demonstrate the overall equivalent oncologic outcomes. We anticipate that the future of robotic surgery will find an increasing role for complex abdominal operations, particularly for PD procedures, especially as we incorporate robotic assisted surgery training into current surgical education curriculum.

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Laparoscopic distal pancreatectomy for adenocarcinoma: safe and reasonable?

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Abstract: As a result of technological advances during the past two decades, surgeons now use minimally invasive surgery (MIS) approaches to pancreatic resection more frequently, yet the role of these approaches for pancreatic ductal adenocarcinoma resections remains uncertain, given the aggressive nature of this malignancy. Although there are no controlled trials comparing MIS technique to open surgical technique, laparoscopic distal pancreatectomy for pancreatic adenocarcinoma is performed with increasing frequency. Data from retrospective studies suggest that perioperative complication profiles between open and laparoscopic distal pancreatectomy are similar, with perhaps lower blood loss and fewer wound infections in the MIS group. Concerning oncologic outcomes, there appear to be no differences in the rate of achieving negative margins or in the number of lymph nodes (LNs) resected when compared to open surgery. There are limited recurrence and survival data on laparoscopic compared to open distal pancreatectomy for pancreatic adenocarcinoma, but in the few studies that assess long term outcomes, recurrence rates and survival outcomes appear similar. Recent studies show that though laparoscopic distal pancreatectomy entails a greater operative cost, the associated shorter length of hospital stay leads to decreased overall cost compared to open procedures. Multiple new technologies are emerging to improve resection of pancreatic cancer. Robotic pancreatectomy is feasible, but there are limited data on robotic resection of pancreatic adenocarcinoma, and outcomes appear similar to laparoscopic approaches. Additionally fluorescence-guided surgery represents a new technology on the horizon that could improve oncologic outcomes after resection of pancreatic adenocarcinoma, though published data thus far are limited to animal models. Overall, MIS distal pancreatectomy appears to be a safe and reasonable approach to treating selected patients with pancreatic ductal adenocarcinoma, though additional studies of long-term oncologic outcomes are merited. We review existing data on MIS distal pancreatectomy for pancreatic ductal adenocarcinoma.

Keywords: Laparoscopy; adenocarcinoma; pancreatic neoplasm; distal pancreatectomy; outcomes

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Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related mortality in men and women in the United States. In 2014, it is estimated that there will be 46,420 new cases and 39,590 deaths due to this disease (1). Surgical resection remains the only potentially curative therapy, and several randomized trials support administration of adjuvant chemotherapy or chemoradiation to improve survival outcomes (2-6). Preoperative chemotherapy with or without radiotherapy is recommended for patients with borderline resectable pancreatic adenocarcinoma, albeit no randomized data exist (7).

Distal pancreatic adenocarcinomas of the body or tail of the pancreas comprise only 20-25% of all diagnosed pancreatic adenocarcinomas (8). While more proximal periampullary tumors typically present with jaundice, malabsorption, and pancreatitis, distal tumors are usually

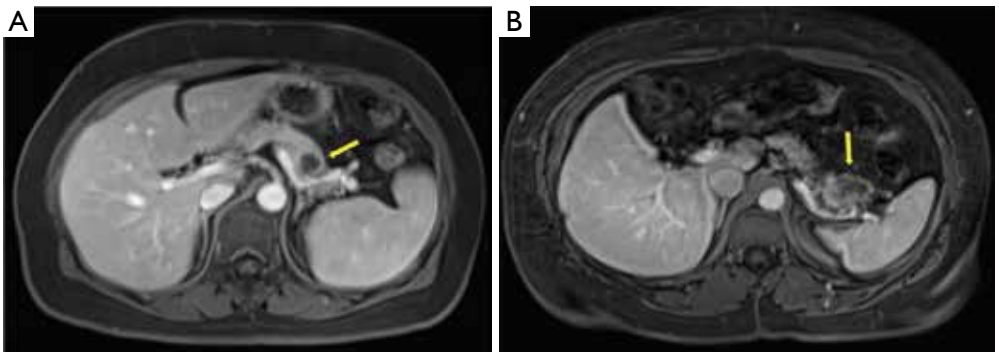

Figure 1 (A,B) Cross-sectional imaging of pancreatic adenocarcinoma of the distal pancreas.

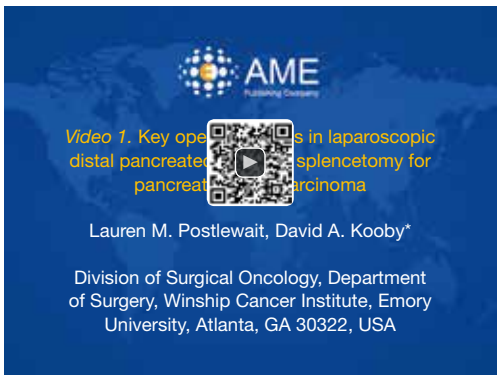

Figure 2 Key operative steps in laparoscopic distal pancreatectomy and splencetomy for pancreatic adenocarcinoma (23). Available online: http://www.asvide.com/articles/506

associated with vague symptoms including weight loss and abdominal pain (8); consequently, distal cancers present at later stages than proximal cancers and are more likely to be metastatic or locally unresectable at the time of diagnosis (9).

The surgical approach to pancreatic resection for adenocarcinoma is dependent on the location of the tumor along the length of the pancreas. While pancreaticoduodenectomy (Kausch-Whipple procedure) is used to treat select patients with cancers of the pancreatic head, neck, and uncinate process, the operative approach for patients with early stage pancreatic cancer of the body and tail is the distal (or left) pancreatectomy (3). *Figure 1* shows cross sectional images of pancreatic ductal adenocarcinoma requiring distal pancreatectomy. Distal pancreatectomy for adenocarcinoma is not commonly performed given the typically advanced stage of presentation of this disease. In an analysis of the Surveillance Epidemiology and End Results (SEER) database from 2003-2009, only 81 distal pancreatectomies for adenocarcinoma were performed on average each year in the United States (10), limiting the ability to study this patient population in a randomized fashion.

Over the last few decades, laparoscopic surgery has been adopted and is considered the standard approach for resection for many retroperitoneal and abdominal organs (11-15). The adoption of laparoscopic pancreatectomy by the surgical community has been slower to occur secondary to concerns of the technical difficulty and risk of complication; however, since the first series of laparoscopic distal pancreatectomies in 1996, these concerns have been addressed in multiple studies that have supported the safety and benefits of laparoscopic pancreatic surgery (16-20). This review examines patient outcomes after laparoscopic distal pancreatectomy for adenocarcinoma with a focus on the short and long term oncologic outcomes.

Surgical technique

The approaches to laparoscopic distal pancreatectomy are well described elsewhere (21,22), and key operative steps of this technique are shown in *Figure 2*. Variations of the technique will be discussed, such as: patient positioning, use of hand access ports, the role of splenic preservation, direction and extent of dissection, and role of robotics (which will be covered in a separate section). *Figure 3* shows intraoperative images of laparoscopic distal pancreatectomy for adenocarcinoma, and pancreatosplenectomy specimens are demonstrated in *Figure 4*.

Patients are typically positioned either in supine or lazy right lateral decubitus position depending on tumor location and surgeon preference. The advantages of supine position are ease of set up, clearer airway access for anesthesia, and ability to access the pancreatic head and

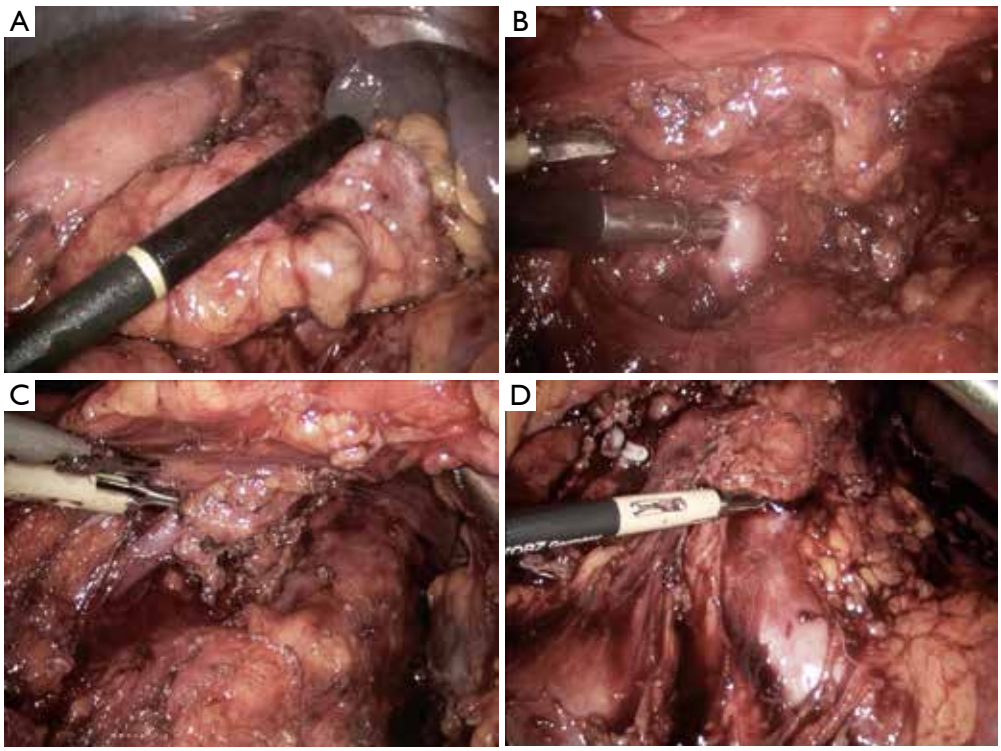

Figure 3 Intraoperative images of laparoscopic distal pancreatectomy for adenocarcinoma illustrating (A) the ultrasound probe over the pancreatic tail tumor; (B) the dissection of the splenic artery; (C) the dissection of the splenic vein; and (D) the splenic artery stump, left renal vein, and left adrenal vein after resection of the specimen.

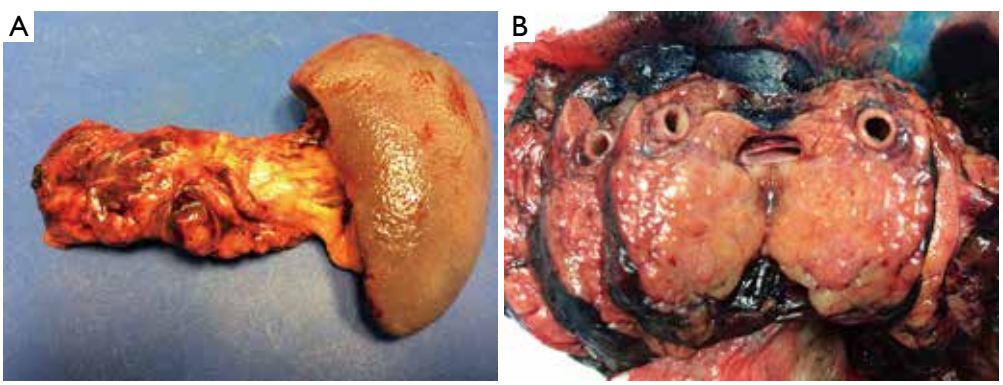

Figure 4 (A) Typical pancreatosplenectomy specimen from distal pancreatectomy for adenocarcinoma; (B) distal pancreatectomy specimen showing a section through the tumor of the pancreatic tail.

neck if necessary for tumors extending to this location. The benefits of the lateral position include gravity retraction of the stomach and spleen, more direct visualization of the body and tail of the pancreas, and superior surgeon ergonomics and comfort (24).

In the laparoscopic hand-access technique, an abdominal port is placed through which the surgeon's hand can access the peritoneal cavity during the laparoscopic procedure. Others have described the technical details of laparoscopic hand-assist distal pancreatectomy (18,25,26). Potential advantages to a hand-access approach include preserving the surgeon's ability of direct palpation of the

tumor and anatomy, ease of removal of larger malignant specimens through the hand port, use of manual dissection, and opportunity to apply direct pressure in the case of bleeding. The largest comparative trial of hand access (n=61) compared to total laparoscopic (n=72) distal pancreatectomies is from the authors' institution (27). Though patients who underwent total laparoscopic procedures had shorter hospital stays (5.3±1.7 *vs.* 6.8±5.5 days; P=0.032), there was a trend that total laparoscopic procedures had higher rates of conversion to open procedure compared to hand assist (8.5% *vs.* 3.3%; P=0.21). In the same study, it was found that the hand-access approach was used less frequently in recent cases of laparoscopic distal pancreatectomy compared to earlier cases at a single intuition (25.6% *vs.* 68.1%; P<0.001) (27). Despite this temporal shift, the hand assist approach still plays an important role in more challenging cases of resection of larger tumors, tumors with increased surrounding inflammation, and in obese patients.

Another option in the laparoscopic approach to distal pancreatectomy is splenic preservation. This can be accomplished through preservation of the splenic vasculature or en bloc resection of the splenic vasculature with preservation of the short gastric vessels to supply the spleen, known as the Warshaw technique (28), although splenic function following this approach is not validated. Multiple studies have addressed the value of splenic preservation with regards to perioperative morbidity and mortality with no clear consensus on recommendations for benign disease (29-31). For patients with malignant disease, vessel-preserving splenic preservation may compromise radial resection margins, as residual pancreatic tissue likely remains following dissection; thus, splenic preservation is not recommended for these patients by the authors.

During a typical open distal pancreatectomy, surgeons mobilize the spleen and dissect under the pancreatic tail and proceed towards the pancreatic neck in a left to right direction, or lateral-to-medial approach, as the operating team is looking down on the target organ. The laparoscopic view is antero-caudal, lending itself to dissection under the gland and a medial-to-lateral approach giving the surgeon access to the splenic vessels first (24). No head to head comparison of these approaches exists.

Radical antegrade modular pancreatosplenectomy (RAMPS) represents an alternate surgical approach to distal pancreatectomy. In this procedure, first described in the context of an open approach in 2003, the surgeon performs the dissection of the pancreas from right to left taking a wider margin where possible, to include the lymphatic tissue surrounding the celiac axis, Gerota's fascia of the left kidney, and the left adrenal gland when necessary (32). In proceeding with the dissection in this manner, it was hypothesized that one could achieve an improved oncologic resection with a higher likelihood of obtaining negative tangential (mobilization) margins (89%; n=32), increased rates of R0 (microscopically negative) resections (81%; n=32), an improved N1 dissection [mean lymph node (LN) count =18], and a five-year overall survival similar to that of patients undergoing pancreaticoduodenectomy for adenocarcinoma (35.5%) (33,34). Later, the RAMPS technique was adapted for laparoscopic surgery and is an option in the laparoscopic resection of distal pancreatic adenocarcinoma (17).

As RAMPS is designed in part to improve tangential surgical margin clearance, one must consider the true value of the R0 resection, for which current data are conflicting. In a recent study comparing survival outcomes in patients who underwent RAMPS (n=38) to those who had traditional distal pancreatosplenectomies (n=54), Park *et al.* found that RAMPS was not independently associated with overall survival (HR: 1.502; 95% CI: 0.796-2.834; P=0.209) (35). Jamieson *et al.* analyzed outcomes of 148 cases of classic or pylorus-preserving pancreatoduodenectomies for pancreatic adenocarcinoma stratifying by margin status (36). Distinguishing between transection margins and tangential or mobilization margins, the study revealed that patients with R1 mobilization (tangential) margins had the same survival as patients with R0 resections (P=0.52), while R1 transection margins were independently associated with shorter survival (HR: 2.76; 95% CI: 2.12-3.91) (36). This suggested that while R0 transection margins were related to survival, the status of the mobilization margin was not; however, a meta-analysis of randomized controlled trials examining outcomes related to adjuvant therapy after pancreatic resection for pancreatic adenocarcinoma found that margin status, in general, was not an independent predictor of survival (R1: HR 1.10; 95% CI: 0.94-1.29; P=0.24) (37). Though this study challenged the value of negative resection margins, surgical doctrine currently recommends R0 resection, and the RAMPS approach can increase R0 rates.

Patient selection

In surgical planning, multiple factors must be considered in choosing candidates for laparoscopic distal pancreatectomy.

These include medical comorbidities, size of the tumor, adjacent organ involvement, and major vascular involvement. Differences between patient populations undergoing laparoscopic and open distal pancreatectomy were considered in a multi-institutional retrospective study from the Central Pancreas Consortium (CPC; representing a collaboration of academic US institutions with high volumes of pancreatic surgery) (38). In this study of patients who underwent distal pancreatectomy for all pathologies between 1999 and 2008, 439 patients underwent open-approach procedures while 254 patients had a laparoscopic procedure. There was no difference in age (>65 years: 30% *vs.* 31%; P=NS) or ASA class (>2: 54% *vs.* 49%; P=NS). Additionally, patients had similar BMIs (>27: 45% *vs.* 51%; P=NS). Open procedures were more frequently done for pancreatic adenocarcinoma (29% *vs.* 9%; P<0.001) and larger tumors (>3.5 cm: 58% *vs.* 40%; P<0.001) with longer postoperative specimens (>8.5 cm: 59% *vs.* 46%; P=0.002) and more frequent splenectomy (90% *vs.* 66%; P<0.001). For laparoscopic distal pancreatectomy, no assessed preoperative factor increased the risk of major complication or pancreatic fistula (38).

A study from the authors' institution compared patient populations undergoing laparoscopic distal pancreatectomy in the context of early experience and recent experience (27). One hundred thirty two patients over 11 years were divided into groups of 66 based on timing of resection representing the early and present experience of the institution. Eleven of these patients had pancreatic adenocarcinoma. There was no observed difference between the temporal groups in age, sex, and obesity rate. In more recent cases, patients had a higher rate of comorbidities (Charleston comorbidity score ≥3: 40.9% *vs.* 16.7%; P=0.003). There were increased tumors in the body and neck in the more recent experience (74.2% *vs.* 26.3%; P<0.001). Additionally, a trend was appreciated in increased mean size of tumors in the recent experience (4.0±2.8 *vs.* 3.3±1.5 cm; P=0.09). Despite the increase in more proximal tumors and increased comorbidities in the recent cohort undergoing laparoscopic distal pancreatectomy, there were no differences in perioperative complications rates between early and recent experience, thereby suggesting that this technique has acceptable morbidity in these higher risk patients (27).

The CPC studied patients who underwent laparoscopic distal pancreatectomy to create a risk score to predict development of post-operative complications (39). The preoperative factor that independently correlated with major complications and major pancreatic fistulas (class B or C) was increased BMI (>27: HR 3.27, 95% CI: 1.16-9.60, P<0.05; HR 6.49, 95% CI: 1.79-23.50, P<0.01). Other risk factors included length of pancreas specimen >8 cm and estimated blood loss >150 mL. The increased risk from higher BMI can be helpful in counseling patients pre-operatively (39). Conversely, Boutros *et al*. found that unselected patients undergoing laparoscopic distal pancreatectomy had similar outcomes to selected patients, implying that selection criteria for laparoscopic approach could be expanded (40).

Outcomes after laparoscopic distal pancreatectomy for adenocarcinoma

Open distal pancreatectomy has long been considered the standard approach to resection of distal pancreatic ductal adenocarcinoma with acceptable morbidity and a perioperative mortality of less than 1% (30). As advanced MIS techniques develop, a laparoscopic approach to managing pancreatic cancer is now an option. There are limited data comparing laparoscopic and open distal pancreatectomy for adenocarcinoma (*Table 1*). Here, we explore the postoperative outcomes as well as the short-term (nodes and margins) and long-term (recurrence and survival) oncologic outcomes after laparoscopic resection of distal pancreatic ductal adenocarcinoma.

Postoperative surgical outcomes of laparoscopic resection

The first studies to report postoperative outcomes after laparoscopic resections of pancreatic ductal adenocarcinoma had small samples sizes with no comparative element. In a retrospective, multi-centered European trial in 2005, 127 patients who underwent laparoscopic resection for pancreatic neoplasms were studied (19). Twenty-four patients underwent distal pancreatectomy with splenectomy, and only 3 patients had pancreatic adenocarcinoma on pathology. The conversion rate for the entire patient population was 14%, and there were no perioperative deaths. With laparoscopic distal pancreatectomy and splenectomy, the mean OR time was 195 minutes, and 27% of patients had postoperative pancreatic complications. Patients who underwent a laparoscopic procedure had shorter hospital stay compared to those where the procedure was converted to open (7 *vs.* 11 days; P<0.0021) (19). In 2006, in a single institution study of 16 patients in the US undergoing laparoscopic hand-assisted distal pancreatectomy, only one patient had adenocarcinoma. This patient had an

Table 1 Published studies comparing open with laparoscopic distal pancreatectomy for adenocarcinoma

Study	Total cases		Conversions	Mean estimated blood loss (mL)		Complication rate (%)		Peri-operative mortality (%)		Mean tumor size (cm)		Positive margin (%)		Mean number of harvested lymph nodes		Overall survival	
	Open	Lap		Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap
Kooby *et al*. (41) [2010][a]	189	23	4	790*	422*	–	–	0.9	0	4.5	3.5	27	26	12.5	13.8	16 months[b,c]	16 months[b,c]
Magge *et al*. (42) [2013]	34	28	5	570*	290*	50	39	0	0	4.5	3.7	12	14	12[c]	11[c]	–	HR: 1.11 CI: 0.47-2.62
Rehman *et al*. (43) [2013]	14	8	0	650	306	42	37	0	0	3.2	2.2	14	12	14[c]	16[c]	3 year: 74%	3 year: 82%
Hu *et al*. (44) [2014]	23	11	0	150[c]	100[c]	–	–	0	0	3.1	2.8	0	0	16.1	14.8	54 months[c]	42 months[c]

[a], multi-institutional; [b], case-controlled data; [c], median value reported; –, data not available; *, P<0.05; Lap, laparoscopic.

operative time of 224 minutes with 1,250 mL of estimated blood loss. Post-operatively, the patient tolerated a general diet in 3 days and was discharged on post-operative day 4 without complication (18). Though these data suggest that laparoscopy could be performed for pancreatic adenocarcinoma resection in the distal pancreas, they fail to offer comparison between the laparoscopic approach and the standard open approach.

One of the first case-controlled comparative trials of laparoscopic versus open distal pancreatectomies was conducted in 2006 (45). In this study, 15 laparoscopic procedures were matched to 15 open procedures. Three of the 15 laparoscopic procedures were converted to open secondary to bleeding and retroperitoneal tumor adherence; these three cases represented the only pancreatic adenocarcinomas included. At that time the authors concluded that their results were unclear as to whether resection of distal pancreatic adenocarcinoma was "consistently feasible with the laparoscopic approach" (45).

In 2008 the CPC published the largest comparative trail to that date (16). This study of 667 patients who underwent distal pancreatectomy between 2002 and 2006 included 159 (24%) attempted laparoscopic resections with mixed pathologies. Twenty (13%) laparoscopic procedures were converted to open. Importantly, 150 patients had pancreatic adenocarcinoma in this study. Resections for pancreatic adenocarcinoma were performed open more frequently than laparoscopically in this population (26% *vs*. 10%; P<0.001). Cohorts were matched by age, ASA, tumor size, length of resected specimen, and pathology for open (n=200) or laparoscopic (n=142) resection. There was no difference in OR time (216 *vs*. 230 minutes; P=0.3), development of major pancreatic fistula (18% *vs*. 11%; P=0.1), major complication (17% *vs*. 10%; P=0.08), or 30-day mortality (1% *vs*. 0%; P=0.040). Open procedures had higher estimated blood loss (588 *vs*. 357 mL, P<0.01), increased wound infections (15% *vs*. 5%; P=0.004), increased need for drain placement post-operatively (15% *vs*. 6% P=0.02) and longer hospital stay (9.0 *vs*. 5.9 days; P<0.01). Laparoscopic resection was independently associated with shorter hospital stays (HR 0.33; CI: 0.19-0.56; P<0.01). From this study, it became clear that laparoscopic distal pancreatectomy is not only feasible, but it could also offer additional benefits as compared to the open approach; yet, the question of oncologic outcomes after laparoscopic resection remained (16).

Short term oncologic outcomes of laparoscopic resection

Resection margins

Though debated, one of the oncologic goals of resection in pancreatic adenocarcinoma is achieving microscopically negative margins (R0). Some small non-comparative studies have shown that laparoscopic resection can frequently achieve R0 resections for pancreatic adenocarcinoma (93-100%) (19,46,47). Multiple comparative studies have found that laparoscopic and open procedures have similar rates of R0 margins on final pathology (74-97% *vs*. 73-96%; P=NS)

(16,41,43,48). The CPC studied 212 patients with resected pancreatic adenocarcinoma and matched open (n=70) and laparoscopic (n=23) resections by age, ASA, and tumor size. They found no difference in positive margin (R1) rates (34% *vs.* 26%; P=0.61) (41). Few studies have found that laparoscopic margins are more likely to be negative than in open procedures, but DiNorcia *et al.* report in their series of distal pancreatectomies with mixed pathology that the laparoscopic approach was associated with decreased R1 resections (2.8% *vs.* 13%; P=0.01); however, the malignancies reported include neuroendocrine tumors and pancreatic adenocarcinoma. Additionally, patients who had procedures that were converted to open were analyzed in the open group, and the groups were not matched such that adverse pathologic factors that could have increased the risk of R1 margins were not considered (31).

In a study by Fernandez-Cruz *et al.*, laparoscopic RAMPS for pancreatic adenocarcinoma was evaluated (17). As discussed previously, the RAMPS approach to distal pancreatectomy potentially offers increased rates of R0 resections with negative tangential margins. Of 13 attempted laparoscopic RAMPS in this study, 3 procedures were converted to open secondary to adhesions to the diaphragm and invasion of the colon. In the 10 RAMPS cases that proceeded laparoscopically, an R0 resection was achieved in 90%, whereas in the converted cases, the R0 rate was only 33%, suggesting that an R1 resection in these patients was associated with more invasive or adherent disease (17). This study does not offer comparison to the open technique. Other small studies of highly selected patients undergoing minimally invasive RAMPS for malignancy in the pancreatic tail reported R0 tangential and transectional margins in 100% of cases (49,50). Yet these patients who had R0 resections were highly selected only to include tumors that were confined to the pancreas, did not invade adjacent organs, and did not approximate the celiac axis (50). Therefore, in highly selected patient populations, MIS RAMPS can offer excellent resection margins.

LN harvest

Current data suggest that a minimum of 12 LNs should be harvested for resections of pancreatic adenocarcinoma based on single institution and SEER data (51,52). If fewer that 12 LNs are resected, the likelihood of underestimating the nodal stage becomes greater. Therefore, patients with fewer than 12 LNs resected who seemingly have N0 disease have shorter median overall survival than N0 patients with greater than 12 LNs resected secondary to occult nodal metastases (16 *vs.* 23 months; P<0.001) (52).

In the aforementioned non-comparative study of patients undergoing laparoscopic RAMPS, the mean LN harvest was 14.5 (6-20 range) for the ten laparoscopic distal pancreatectomies for pancreatic adenocarcinoma (17). Most studies comparing the number of LNs in laparoscopic and open cases found no significant differences in the number of LNs harvested (31,41,43,48,53). In a matched comparative study of distal pancreatectomies for pancreatic adenocarcinoma, the CPC found similar numbers of LNs for open compared to laparoscopic cases (12.3±8.3 *vs.* 14.0±8.6; P=0.46) (41). One single institution study of distal pancreatic resection for mixed pathology reported fewer LNs in the laparoscopic group (mean: 4 *vs.* 10; P=0.04); however, the laparoscopic cohort had fewer patients with pancreatic adenocarcinoma (4.1% *vs.* 21%; P<0.01), which could have influenced the surgeon's operative approach to nodal resection (54).

Long-term oncologic outcomes of laparoscopic resection

Few studies offer long-term data on patients after laparoscopic distal pancreatectomy for pancreatic adenocarcinoma. Below, the results from these few studies on recurrence and survival are summarized.

Data are scarce on recurrence of pancreatic adenocarcinoma after laparoscopic resection, and comparative data are limited. Most of our insights into recurrence outcomes originate from non-comparative studies. In 2005, Mabrut *et al.* conducted a multi-institutional European study of laparoscopic distal pancreatectomies that included 16 patients with a pancreatic malignancy, 4 of which were pancreatic adenocarcinoma (19). During the median 15-month follow up, 23% of patients with malignant tumors had a recurrence. Notably, no patients had evidence of trochar site recurrences (19). The following year, D'Angelica *et al.* reported a series of laparoscopic hand-assisted distal pancreatectomies, one of which was for adenocarcinoma (18). This patient presented six months post-operatively with liver metastases but no local recurrence (18). Larger comparative trials that report recurrence data are warranted.

In the study by Fernandez-Cruz of laparoscopic RAMPS, 3 of 10 patients died within a year with local recurrence and liver metastases with a median survival of 14 months (17). All patients who underwent laparoscopic RAMPS received adjuvant chemotherapy three weeks post-operatively (17). In a more recent study of patients undergoing laparoscopic distal pancreatectomy for adenocarcinoma, the median

Table 2 Cost-comparisons of open and laparoscopic distal pancreatectomies

Study	Total cases		Mean operative cost		Mean length of stay (days)		Mean total cost of care	
	Open	Lap	Open	Lap	Open	Lap	Open	Lap
Eom *et al*. (55) [2008]	167	31	–	–	13.5*	11.5*	$3,401*	$4,884*
Abu *et al*. (56) [2012]	16	35	£5,231*	£6,039*	11[a,*]	7[a,*]	£15,324	£10,587
Fox *et al*. (57) [2012]	76	42	$4,510[a]	$4,655[a]	7[a,*]	5[a,*]	$13,656[a,*]	$10,842[a,*]
Limongelli *et al*. (58) [2012]	29	16	€1,989*	€2,889*	8.8*	6.4*	€10,944	€9,603
Rutz *et al*. (59) [2014]	45	70	$4,900*	$5,756*	6	5	$13,900	$10,480

[a], median value reported instead of mean. –, data not available; *, P<0.05; Lap, laparoscopic.

survival after resection was 19 months (n=29) (47). In an unmatched single institution study of patients undergoing laparoscopic (n=8) or open (n=14) distal pancreatectomy for pancreatic adenocarcinoma, there was no difference in 3 year overall survival rates (82% *vs*. 74%; P=0.89) (43). The CPC reported a 16 month median survival after both laparoscopic (n=23) and open (n=70) approaches in matched cohorts (P=0.71) (41). The evidence to date suggests that the recurrence and survival outcomes of laparoscopic distal pancreatectomy for adenocarcinoma are similar to those of open procedures.

Cost outcomes

In evaluating comparative value of surgical techniques, cost must be considered. There are limited financial data on outcomes specific to pancreatic adenocarcinoma pathology after laparoscopic resection; therefore, the data on laparoscopic distal pancreatectomy including resection for all pathology are here reported and are summarized in *Table 2*.

A single institution Korean study in 2008 found that the total cost (operating room charges and hospitalization cost) for laparoscopic (n=31) distal pancreatectomies was more expensive than that of the open [167] approach ($4,884.2±1,845.1 *vs*. $3,401.4±1,247.5; P<0.001) (55). Subsequent studies in Britain and Italy in 2012 showed that though the operating room cost of laparoscopic distal pancreatectomy is higher than open (£6,039/€2,889 *vs*. £5,231/€1,989; P<0.05), decreased length of hospital stay after laparoscopic procedures (6.3-7 *vs*. 8.8-11 days; P<0.01) led to equivalent total hospital costs (£10,587/€9,603 *vs*. £15,324/€10,944; P=0.2) (56,58). Two recent North American studies reported that laparoscopic distal pancreatectomy was less expensive than open distal pancreatectomy in overall hospital cost (57,59). In a study from the author's institution, 115 patients who underwent uncomplicated distal pancreatectomies from 2009-2013 were assessed (laparoscopic: n=70; open: n=45) (59). Nineteen of these patients had pancreatic adenocarcinoma (laparoscopic: 16%; open: 18%). Again, the operating room cost was higher for patients undergoing laparoscopic procedures ($5,756 *vs*. $4,900; P=0.02), but the shorter length of stay after laparoscopy (5.2 *vs*. 7.7 days; P=0.01) led to decreased total variable costs ($10,480 *vs*. $13,900; P=0.06) (59). These studies show that laparoscopic distal pancreatectomy is a financially reasonable approach to resection. Future goals are aimed towards reducing intraoperative costs further.

Robotic approach to resection of distal pancreatic adenocarcinoma

Rates of robotic surgery have been increasing since its advent over a decade ago (60). Much like laparoscopic surgery initially, there are barriers to the universal adoption of this new approach including overall expense, a steep learning curve, and lack of tactile feedback to the operator. Yet, robotic surgery offers three-dimensional optics, increased freedom of motion, precision, and improved ergonomics for the surgeon (60-62). Consequently, robotic surgery is becoming widespread and versatile.

The surgical approach to robotic conventional distal pancreatectomy with splenectomy and the RAMPS procedure has been well described elsewhere (63-65). One of the first reports of robotics used in pancreatic surgery came from Italy in 2003 (66). In this study, 5 patients underwent robotic distal pancreatectomy, 3 of whom had pancreatic adenocarcinoma. The operating room time was 270 minutes. The mean length of stay was 11 days.

One patient had a complication of a pancreatic leak (20%), and there were no post-operative mortalities (66). A similar study from 2010 of 43 patients who underwent distal pancreatectomy by the same author had similar postoperative outcomes: pancreatic leak 20.9% and postoperative mortality of 1.5% (64). Choi *et al*. report on a case series of 4 patients who underwent robotic RAMPS for pancreatic adenocarcinoma in which 100% had R0 margins with a median LN count of 8.5 (range, 2-23) (65). Multiple other cases of robotic distal pancreatectomy and splenectomy have been reported (63,67-72). The results of these studies suggested that robotic distal pancreatectomy could be a feasible approach but were lacking in detailed oncologic and comparative data.

In a study comparing rates of splenic preservation in robotic distal pancreatectomy (n=20) and laparoscopic distal pancreatectomy (n=25), the success of spleen preservation was higher in the robotic group (95% *vs*. 64%, P=0.027) (68); however, in the case of pancreatic adenocarcinoma, splenic preservation is not recommended. A recent single-institution US study compared consecutive robotic resections (n=30) to an earlier cohort of laparoscopic (n=94) distal pancreatectomies (73). There were no differences in length of hospital stay, pancreatic fistula formation, rate of blood transfusion, or readmission between the two groups. The study included 27 cases of pancreatic adenocarcinoma representing 43% of the robotic and 15% of the laparoscopic patients (P<0.05). For the pancreatic adenocarcinoma cases, the rate of R1 resections was lower in the robotic group (0% *vs*. 36%; P<0.05), and the robotic procedure yielded more LNs (19 *vs*. 9; P<0.01) (73). Though this study offers promising short-term oncologic results, studies on long-term outcomes are warranted.

Data from a single institutional study suggest that robotic surgery may further shorten hospital length of stay, resulting in lower total hospital cost compared to open and laparoscopic approaches (LOS: 4 *vs*. 8 *vs*. 6 days, P<0.05; $10,588 *vs*. $16,059 *vs*. $12,986, P<0.05) (74). Though this offers insight into a single hospital's experience, it does not reflect financial outcomes universally or the monetary investment in the robotic technology and its upkeep. Further studies are needed.

Not enough data exist to evaluate the safety and long-term outcomes of robotic distal pancreatectomy for pancreatic adenocarcinoma. The robotic approach to distal pancreatectomy does offer the advantage of increasing the surgeon's ability to preserve the spleen, yet this is contraindicated in the case of pancreatic adenocarcinoma. Therefore, at this time, robotic surgery for distal pancreatic adenocarcinoma does not offer a definitive benefit.

Fluorescence-guided intraoperative tumor localization

Another emerging technology in oncologic surgery is fluorescence-guided tumor localization to aid in complete tumor resection. In this technique, tumor-specific fluorescent particles are administered to the patient that bind tumor. These particles can then be visualized or detected with an instrument, which allows surgeons to more easily distinguish between cancer cells and normal tissue during resection. In mouse models of pancreatic cancer, this technique has allowed for improved margins of resection, decreased local and distant recurrence, and longer disease-free survival after open and laparoscopic resections (75,76). In another study of a mouse model, a fluorescence-detecting device showed promise for use in the inspection of surgical margins for residual disease, which could increase rates of attaining negative margins (77). This technology could represent the next step to improving treatment of pancreatic cancer in open and laparoscopic resections.

Conclusions

Over the last two decades, laparoscopic distal pancreatectomy for pancreatic adenocarcinoma has become more common, though there are no randomized trials comparing this technique to open surgical technique. Data primarily from retrospective studies suggest that post-operative complication rates between open and laparoscopic distal pancreatectomies are similar. In exploring short-term oncologic outcomes after laparoscopic resection of distal pancreatic adenocarcinoma, there are no differences in the rate of achieving negative margins or in the number of LNs resected when compared to open surgery. There are limited recurrence and survival data on laparoscopic compared to open distal pancreatectomy for pancreatic adenocarcinoma, but in the few studies that assess long term outcomes, recurrence rates and survival outcomes appear similar; the need for randomized trials remains. Most recent studies have suggested that though laparoscopic distal pancreatectomy incurs a greater operative cost, the associated shorter length of hospital stay leads to decreased overall cost compared to open procedures.

Multiple new technologies are emerging to improve treatment of pancreatic cancer. Robotic pancreatectomy

is feasible, but there are limited data on resection of pancreatic adenocarcinoma, and outcomes appear similar to laparoscopic approaches. Additionally fluorescence-guided surgery represents a new technology on the horizon that could improve oncologic outcomes after resection of pancreatic adenocarcinoma. Overall, laparoscopic distal pancreatectomy appears safe and reasonable, though additional studies of long-term oncologic outcomes are merited.

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Can pancreaticoduodenectomy performed at a comprehensive community cancer center have comparable results as major tertiary center?

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Background: Pancreatic resection is a definitive treatment modality for pancreatic neoplasm. Pancreaticoduodenectomy (PD) is the primary procedure for tumor arising from head of pancreas. Prognosis is overwhelmingly poor despite adequate resection. We maintained a prospective database covering years 2001 to 2010. Outcome data is analyzed and compared with those from tertiary centers.

Methods: Sixty-two patients with various histology were included. Pylorus preserving pancreaticoduodenectomy (PPPD), classic pancreaticoduodenectomy, and subtotal pancreatectomy were procedures performed. Three patients had portal venorrhaphy performed to obtain clinically negative margin. Forty six patients had malignancy on final pathologic analysis.

Results: The average age of patients was 63. Mean preoperative CA19-9 for exocrine pancreatic malignancies was higher than for more benign lesions. There was a decrease in operative time during this period. Blood transfusion was uncommon. There was very few pancreatic leak among the patients. Two bile leaks were identified, one controlled with the drainage tube and the other one required repeat surgery. The primary reason for the prolonged hospitalization was gastric ileus. For patients without a gastrostomy tube, nasogastric tube was kept in until gastric ileus resolved. 30 days mortality rate was calculated at 4.8. Mean survival time during our follow up was 30.6 months. Comparing to published literature, present series' mortality, morbidity, and survival are similar. Five year survival was 39%.

Conclusion: Despite overall poor outcome for patients with pancreatic and biliary malignancies, we conclude that surgery can be performed in community hospitals with special interest in treating pancreatic disorder, offering patients equivalent survival and quality of life as those operated in tertiary centers.

Keywords: Pancreaticoduodenectomy for pancreatic cancer; surgical outcome; community hospital

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Introduction

With about 44,000 new cases and about 37,600 cancer deaths in 2011, pancreatic cancer ranks fourth among cancerrelated deaths in the United States. It is the second leading cause of death due to gastrointestinal tract neoplasm. It is one of the few cancers whose survival has not improved over the past 40 years (1).

Pancreatic cancer affects more commonly elderly, and less than 20% of patients present with localized, potentially curable tumors (2). The average life expectancy after diagnosis with metastatic disease is three to six months. Average five year survival is 6%. Seventy-five percent of patients die within first year of diagnosis. Pancreatic cancer has the highest death rate of all major cancers (3).

Symptoms of pancreatic cancer depend on the location, as well as on the stage of the disease. Significant number of tumors develops in the head of the pancreas and usually led to cholestasis, abdominal discomfort and nausea.

Table 1 Patient sex characteristic

Year	Sex		Total
Frequency Row Pct	F	M	
≤2004	13	10	23
	56.52%	43.48%	
≥2005	22	17	39
	56.41%	43.59%	
Total	35	27	62

P=1.0; Fisher's exact test was used to exam the association between two factors.

Table 2 ASA characteristic

Year	ASA		Total
Frequency Row Pct	2	3	
≤2004	9	14	23
	39.13%	60.87%	
≥2005	9	28	37
	24.32%	75.68%	
Total	18	42	60
Frequency Missing = 2			

P=0.25; Fisher's exact test was used to exam the association between two factors

Obstruction of the pancreatic duct may lead to pancreatitis. Most patients have systemic manifestations of the disease such as asthenia, anorexia, and weight loss. Less common manifestations include venous thrombosis, liverdysfunction, gastric obstruction, and depression (4-6).

Pancreaticoduodectomy (PD) is the most commonly performed surgery in patients with pancreatic cancer as 75% of tumors are located at head of pancreas. First successful pancreatic head resection was described by Walter Kausch in 1912, and later modified by Allen O Whipple in 1935 as two stage procedure whereby diversion was followed by definitive resection (7,8).

Method

In Appleton, Wisconsin, a community hospital cancer center was established in 2001. Patients underwent PD were followed from 2001 to 2010, 62 PD's were performed during this time interval by a surgical team with interest in gastrointestinal oncology. The results were compared with a large series of similar surgery performed elsewhere in the United States (9). The retrospective analysis of the database was approved by the local Institutional Review Board of ThedaCare Hospitals.

SAS 9.2 statistical sof tware was used to perform statistical analysis. Student t-test was used to test the mean difference between two groups of patients. Fisher's exact test was used to examine the association between two factors in a table. Kaplan Meier survival curves were used to estimate survival.

A total of 62 patients (female 35, male 27) with histologyproven pancreatic cancer, ampullary carcinoma and other histological types, including benign histological entities, were included in the study (*Tables 1 and 2*). To query on the difference in outcome between the early and later time interval, we arbitrarily analyzed patients operated before and after year 2005.

Pylorus preserving pancreaticoduodenectomy (PPPD) was performed in forty one patients; twenty patients had traditional PD and one patient with subtotal pancreatectomy. Clinical pathway was adapted and utilized uniformly in the later period. Three patients had portal venorrhaphy due to tumor adherence to the portal vein. Forty six patients had malignant diagnoses, whereas sixteen patients had benign histology. One case had dual histology (ductal carcinoma and neuroendocrine tumor).

Table 3 Histology of pancreatic mass	
Benign neoplasm (16)	Carcinoma (46)
Pseudotumor (3)	Pancreatic ductal carcinoma (26)
IPMN (2)	Cholangiocarcinoma (5)
Mucinous cystadenoma (1)	Neuroendocrine carcinoma (2)
Chronic pancreatitis (6)	Ampullary carcinoma (4)
Benign adenomatosous hyperplasia (1)	Lymphoma (2)
Duodenal bleeding (2)	Renal cell carcinoma (1)
Adenoma (1)	Duodenal carcinoma (4)
	Leiomyosarcoma (1)
	Multiple histologies - ductal and neuroendocrine carcinoma (1)

Table 4 Erythromycin use by year

Year	Erythromycin		Total
Frequency Row Pct	n	y	
≤2004	6	17	23
	26.09%	73.91%	
≥2005	1	37	38
	2.63%	97.37%	
Total	7	54	61
	Missing Data = 1		
P=0.0094.			

Final pathology showed pancreatic adenocarcinoma, cholangiocarcinoma, adenoma, lymphoma, ampullary carcinoma, duodenum carcinoma, leiomyosarcom, isolated metastatic carcinoma to pancreas, and neuroendocrine tumor. Benign histological diagnoses included, pancreatitis, IPMN, pseudotumor, and adenomatous hyperplasia (*Table 3*).

Majority of patients presented with jaundice, weight loss and abdominal pain. All of the patients had computed tomography scan done as part of their evaluation. Endoscopic retrograde cholangiopancreatography (ERCP) was performed for patients with symptoms related to bile duct obstruction. Preoperative biliary stents were placed at the discretion of the endoscopist, with relief of jaundice being the primary intent.

Mean age of patients was 63 years, with ages ranging from 39 to 78 years. Ethnicity among the patients included 34 Caucasians, 3 Asians, 5 Hispanics, and 13 patients of unknown origin.

Clinical data

Average operative time was 385 minutes for surgeries performed before 2005 and 348 minutes for surgeries performed after 2005. Comparing procedures performed pre- and post- 2005, length of hospital stay was shorter (nearly reaching statistical significance) adjusted for gender, age, and ASA (P=0.06). Average length of stay for all patients was 16.1 days (range 0-87 days), mean ICU stay was 3 days (range 1-63 days). Among the covariates examined, only erythromycin use (as motility agent) changed significantly: there was a substantial increase in its usage (P=0.009). Erythromycin was ordered for 17 (73.91%) patients out of 23 surgeries performed before 2005 and 97.4% of patients received Erythromycin after the surgery (*Table 4*).

Blood transfusion was given to 15 patients requiring blood product. Mean preoperative CA19-9 for exocrine pancreatic malignancies was 638, whereas for benign lesions

Table 5 Descriptive statistics for continuous variables by year of surgery

Year	N	Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P* vs. ≤ 2004
≤2004	23	Age	23	64.33	10.01	67.48	43.03	77.96	
		LOS	22	19.05	16.04	15.00	8.00	87.00	
		OR_time	23	6.39	1.11	6.12	4.75	8.75	
		ICU_LOS	23	1.00	0.00	1.00	1.00	1.00	
		Crystalloids	23	4995.65	2010.54	5000.00	2000.00	9700.00	
		Colloids	23	413.04	333.45	500.00	0.00	1100.00	
		Blood	23	732.61	464.56	700.00	0.00	2400.00	
≥2005	39	Age	39	62.43	10.61	65.32	36.00	77.06	0.49
		LOS	39	13.18	7.86	12.00	0.00	40.00	0.06
		OR_time	37	5.81	1.68	5.35	2.02	11.50	0.15
		ICU_LOS	37	1.00	0.00	1.00	1.00	1.00	–
		Crystalloid	37	4918.92	2980.20	4600.00	0.00	16000.00	0.91
		Colloid	37	337.84	387.37	250.00	0.00	1500.00	0.44
		Blood	37	784.46	1303.09	500.00	0.00	8000.00	0.86

*Student T-test has been used to test the mean difference between two groups of patients. LOS = length of stay, OR_time=operating time from making incision to closure of skin, ICU_LOS=intensive care unit length of stay, Blood=blood transfusion given in mL.

Table 6 Post surgical complications

prolonged gastric ileus	18
respiratory failure	3
renal failure	3
wound infection/dehiscence	2
DVT	2
incisonal hernia	2
bowel leak	2
severe anemia	1
liver abscess	1
UGI bleeding	1
atrial fibrillation	1
coagulopathy	1
C-difficile collitis	1
acidosis	1
tension pneumothorax	1
re-operation	1

and endocrine tumors it was 122 (*Table 5*).

There were three perioperative deaths due to ischemic bowel and severe acidosis, equivalent to thirty day mortality rate of 4.8%. Major causes of 30 day postoperative death in our study were small bowel necrosis (ii) and disseminated intravascular coagulopathy (i). There was one pancreatic leak in our patient population. Two bile leaks were identified, one controlled with the drainage tube and one required laparotomy to repair the leak. Average length of stay was 15 days. The primary reason for prolonged hospitalization was gastric ileus. For patients without a gastrostomy tube, nasogastric tube was kept in until gastric ileus resolved.

Respiratory failure and renal failure occurred in 4.8% of patients. Wound infection, DVT, and incisional hernia each comprises 3.2% of our patient population (*Table 6*).

To date, 45% of our patients (N=28) have died, with two patients from causes unrelated to carcinoma. Mean survival during our study period was 30.6 months for all 62 individuals (*Tables 7 and 8*). Three year survival for patients with pancreatic cancer and carcinoma of non pancreas

Table 7 Overall survival in 30 days, 1,3, and 5years

Time (month)	Survival	Survival Standard Error	Lower (95% CI)	Upper (95% CI)
1	0.9032	0.0375	0.79721	0.95532
12	0.7308	0.0578	0.59788	0.82590
36	0.5681	0.0713	0.41737	0.69352
60	0.4519	0.0831	0.28647	0.60367

Table 8 Comparison with the Cameron et al (9) study

Time (month)	Preset Series		Survival (Cameron *et al.*)	P
	Survival	SE		
1	90%	4%	99%	0.021
12	73%	6%	64%	0.116
36	57%	7%	27%	<0.0001
60	45%	8%	18%	0.001

Table 9 ASA classifcation of present study population

ASA	Frequency	Percent	Cumulative frequency	Cumulative percent
missing	13	20.97	13	20.97
non cancer	16	25.81	29	46.77
1/2	22	35.48	51	82.26
3/4	11	17.74	62	100.00

origin were 39% and 66%, respectively.

In our series of patients, 47.9% had metastatic disease in regional lymph nodes. 14.2% had positive margins. For patients without lymph node metastasis and negative margin, survival was 75%, 47%, and 47% at 12, 36 and 60 months post surgery, respectively. Patients with lymph node metastasis had 5 years survival rate of 39% whereas those without lymph node involvement had 5-year survival of 48%. Majority of the patients were of fered adjuvant chemoradiation therapy based on tumor size greater than 2 cm or if lymph node metastasis was present. Overall 5-year survival in this patient population was 39% (*Figure 1*). Stage of cancer does not appear to have an impact on survival. Stages I/II had 5-year survival of 36%, and stages III/IV patients had survival of 34% (*Figure 2*).

Discussion

Our results were produced in a comprehensive community cancer center accredited by the American College of Surgeons Commission on Cancer. Multidisciplinary discussions were held during regularly scheduled tumor conferences. Many of the services providing diagnostic and therapeutic work up are readily available within the medical complex. Specialists with interest in gastrointestinal oncology participate in discussion forums to formulate treatment plans for each patient. Treatment progress notes are made available shortly after each encounter with the patient with an electronic medical record system.

There are numerous publications demonstrating an improvement of outcome after PD in high volume medical

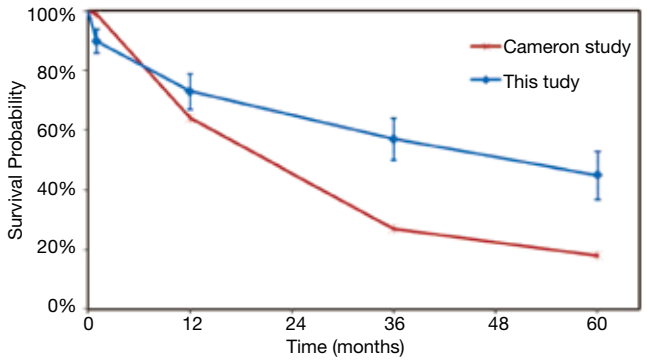

Figure 1 Comparison of survival data.

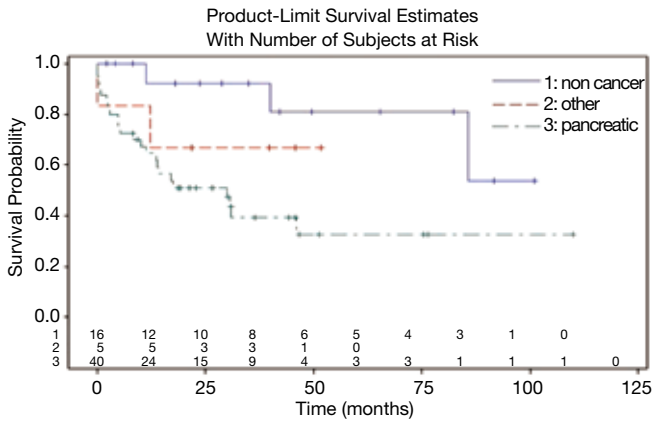

Figure 2 Survival of patients stratied by diagnosisa.

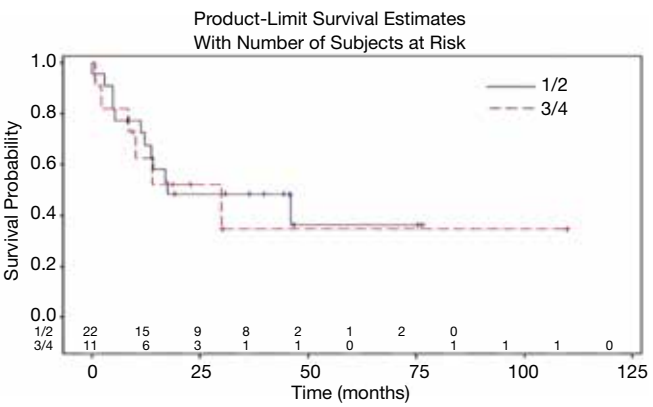

Figure 3 Survival analyzed with respect to ASA score.

centers (10-13). Surgeon volume alone also significantly decreases mortality for complex procedures (14). An analysis of high volume centers has shown that there is a significant variability in mortality (0.7% to 7.7%) and, with other variables analyzed, demonstrates that the variability cannot be explained by hospital volume alone (15). Surgeon experience is an important determinant of overall morbidity. In the same study, it was concluded that experienced surgeons (those who have performed more than fifty PD) have equivalent results whether they are high volume surgeons (some performing more than 20 PD per year) or low volume surgeons (16).

In the literature, five year survival for pancreatic cancer patients treated with PD ranged from 3% in the early series to 20% in more recent publications (16-18). In our series, 5-year overall survival for patients treated for carcinoma was 39%.

We have chosen a single institution series from Johns Hopkins with one thousand consecutive PD to compare the results between the two institutions. Mortality, morbidity, and survivals are similar (19,20).

The learning curve in pancreatic surgery suggested that after 60 PD's, there are improved outcomes of estimated blood loss, operative time, length of stay, and margin status—factors which have been associated with overall outcome (21). The results presented in this study are consistent with the conclusions presented by published literature.

The benefits of regionalization of complex surgery were demonstrated in a number of studies. Benefits of a high volume center include a decrease in mortality and cost and the ability to perform prospective randomized trials and to provide surgical training (22,23).

One of the goals of this study is to determine if we can provide excellent care to patients diagnosed with periampullary tumors. The closest medical center with pancreaticobiliary service to our center is approximately 90 miles. Given the choice for location of service, an overwhelming majority of patients preferred not to travel long distances. Having a pancreaticobiliary service in our encatchment area serves to facilitate treatment as well as to allow patient's family members easier access to the treating medical center.

There has been a dramatic improvement of surgical care in treating periampullary tumors over the last two decades. Anesthetic and perioperative care during the duration of our study have made the greatest contribution to decreasing perioperative mortality. The development of clinical pathways also has contributed to optimizing the outcome (24).

There are limitations to a single institutional series such as ours. Patient population is not large. Because of the small number of patients, meaningful statistical analysis is difficult to derive. Morbidity, mortality, and long term outcomes (cancer specific survival, overall survival) nevertheless have utility in assessing a cancer program. The data presented here gives support to continuing the pancreaticobiliary program at our institution.

Our results ref lect the dedication of specialists with interest in treating pancreaticobiliary disorders. We assert that hospital volume alone cannot be the sole determinant of outcome. It is our belief that surgeon volume combined with a multidisciplinary approach and excellent ancillary support provide an excellent prediction of survival as demonstrated in this study of patients with pancreatic and biliary malignancies.

The factors contributing to improved survival for patients diagnosed with periampullary tumors are numerous. Improved perioperative critical care and improved surgical care decrease operating time. Advances in adjunctive therapies contribute to improved survival. It is through these novel therapies that we will see further improvement in survival rates (25).

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Outcomes of resected pancreatic cancer in patients age ≥70

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Objective: To determine outcomes of patients ≥70 years with resected pancreatic cancer.

Methods: A study was conducted to identify pancreatic cancer patients ≥70 years who underwent surgery for pancreatic carcinoma from 2000 to 2012. Patients were excluded if they had neoadjuvant therapy. The primary endpoint was overall survival (OS).

Results: We identified 112 patients with a median follow-up of surviving patients of 36 months. The median patient age was 77 years. The median and 5 year OS was 20.5 months and 19%, respectively. Univariate analysis (UVA) showed a significant correlation for increased mortality with N1 (P=0.03) as well as post-op CA19-9 >90 (P<0.001), with a trend towards decreased mortality with adjuvant chemoradiation (P=0.08). Multivariate analysis (MVA) showed a statistically significant increased mortality associated with N1 (P=0.008), post-op CA19-9 >90 (P=0.002), while adjuvant chemoradiation (P=0.04) was associated with decreased mortality.

Conclusions: These data show that in patients ≥70, nodal status, post-op CA19-9, and adjuvant chemoradiation, were associated with OS. The data suggests that outcomes of patients ≥70 years who undergo upfront surgical resection are not inferior to younger patients.

Keywords: Pancreatic cancer; surgery; elderly; adjuvant therapy; chemoradiation

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Introduction

Pancreatic cancer remains the fourth leading cause of cancer-associated deaths in the United States (1,2). Despite advancements in multi-modality therapy pancreatic cancer remains extraordinarily lethal with a 5-year overall survival (OS) of approximately 5% (1,3). Furthermore in the United States the incidence of pancreatic cancer has continued to increase since the 1930s (4). There are greater than 43,000 cases diagnosed annually in the United States, with a large proportion dying of their disease (5).

The current accepted standard of care for resectable pancreatic cancer remains resection followed by adjuvant therapy consisting of chemotherapy. The use of post-operative radiotherapy (PORT) continues to be a topic of controversy (6). Several studies have shown an increase in OS compared to surgery alone (7-9), whereas others have shown no benefit (10-12).

In the United States the elderly population has continued to grow with a 30% increase from 2000 to 2010 (13). Additionally, the average life span has increased secondary to advancements in public health, nutrition, early detection of diseases, and continued medical progress. This increase in average life expectancy as well as advancements in cancer screening has led to a growing number of cancer diagnoses in the elderly (14).

Pancreatic cancer tends to occur at an older age, with relatively rare occurrence before the age of 45 and a sharp increase in its incidence thereafter (4). Incidence of the disease increases with advancing age, with an incidence of

29 per 100,000 in patients aged 60-64 and 91 per 100,000 in patients aged 80-84 years (15). In the United States the median age for patients diagnosed with pancreatic cancer is 72 (16). Increasing age is a well-known risk factor for the development of pancreatic cancer (17,18). In fact, approximately two-thirds of cases are diagnosed in patients greater than 65 years old (4,15). As such, more elderly patients are being diagnosed with pancreatic cancer and being considered for multi-disciplinary treatment (19). However, elderly cancer patients remain underrepresented in many clinical studies, with age greater than 70 years as a frequent exclusion criterion (20,21). As such the question remains as to whether these data can be extrapolated to the elderly population. The aim of this study was to determine the outcomes of age ≥70 patients with resected pancreatic cancer at our institution.

Materials and methods

Patients

An analysis of pancreatic cancer patients ≥70 years who underwent upfront surgical resection for pancreatic carcinoma from 2000 to 2012 was conducted to determine outcomes. Patients were excluded if they had M1 disease, lack of surgical resection, use of neoadjuvant therapy, or age <70, and unusual histologies including lymphoma, cystadenoma, intraductal palpillary mucinous neoplasm, signet ring cell carcinoma, neuroendocrine tumors, islet cell tumors such as gastrinoma, insulinoma, glucagonoma and VIPoma.

Treatment

Surgery

Patients with pancreatic head tumors underwent pancreaticoduodenectomy with or without a pylorus-sparing procedure. A minority of patients with pancreatic body or tail tumors underwent pancreaticoduodenectomy, complete pancreatectomy, or partial pancreatectomy with or without splenectomy, and/or vein resection/repair depending on the size and location of the tumor with respect to regional organs and vasculature.

Adjuvant therapy

Following surgery, patients received chemoradiation with or without neoadjuvant or adjuvant chemotherapy, chemotherapy alone, or no adjuvant therapy. Adjuvant therapy was initiated within 4 months from the time of surgery in all cases.

Patients treated with chemotherapy alone received single-agent gemcitabine. Patients treated with chemotherapy followed by radiation were treated in a similar fashion to the radiation therapy oncology group (RTOG) 9,704 protocol with 1 month of gemcitabine followed by concurrent chemoradiation with continuous infusion 5-FU or gemcitabine, followed by adjuvant gemcitabine. Patients treated with chemoradiation alone received concurrent radiation with 5-FU or gemcitabine. The median radiation dose was 50 Gy (range, 43.2-63 Gy) in 180 to 200 cGy daily fractions for a median of 28 fractions (range, 24-35 fractions) to the pancreatic tumor bed and regional lymphatics; a minority of patients received a boost to the tumor bed (median 0 Gy; range, 0-14.4 Gy).

Statistical analysis

The primary endpoint was OS, defined as the interval from surgery to date of death. Statistical analysis was performed using SPSS® version 21.0 (IBM®, Chicago, IL, USA). Progression-free survival (PFS) was also analyzed and defined as the interval from surgery to first recurrence or death. Continuous variables were compared using both Wilcoxon rank sum test and the Kruskal Wallis test as appropriate. Pearson's Chi-square test was used to compare categorical variables. Actuarial rates of OS were calculated using the Kaplan-Meier method and the log-rank test. A Cox multivariate model was performed for OS, including all clinical, histopathologic, and treatment variables. Continuous variables for inclusion in the multivariate model were split at clinically meaningful cut-points; post-operative CA19-9 level was split at <90 and ≥90. All statistical tests were two-sided and an α (type I) error <0.05 was considered statistically significant.

Results

Patient characteristics are shown in *Table 1*. A total of 112 patients age ≥70 who underwent upfront pancreatic resection were analyzed with a median follow-up of surviving patients of 36 months. The median patient age was 77 years and the majority of patients presented with advanced disease and received adjuvant treatment.

Postoperative complications are presented in *Table 2*. The most common complications were pancreatic leak (14.3%) and wound infection (12.5%). Postoperative 30, 60,

Table 1 Patient characteristics

Variable	Level	Age ≥70 y; N (%)
Gender	Male	59 (52.7)
	Female	53 (47.3)
Site	Head	87 (77.7)
	Body	7 (6.3)
	Tail	18 (16.1)
Days from diagnosis to surgery	≤30	83 (74.1)
	>30	29 (25.9)
Median path tumor size (cm, range)		3.0 (0.5, 8.5)
Pathologic tumor stage	T1/2	24 (21.4)
	T3/4	88 (78.6)
Median nodes positive (range)		1 (0, 25)
Median nodes removed (range)		11 (0, 49)
Pathologic nodal stage	N0	49 (43.8)
	N1	63 (56.3)
Tumor grade	Well	12 (10.7)
	Moderate	75 (67.0)
	Poor	18 (16.1)
	Unknown	7 (6.3)
Surgical margins	Negative	94 (83.9)
	Positive	18 (16.1)
Post-op CA19-9 >90	No	64 (57.1)
	Yes	19 (17.0)
	Unknown	29 (25.9)
Adjuvant treatment	None	34 (30.4)
	Chemoradiation	53 (47.3)
	Chemotherapy	25 (22.3)

Table 2 Post-operative complications

Post-op complications	N (%)
Pancreatic leak	16 (14.3)
Gastrojejunostomy leak	1 (0.9)
Atrial fibrillation	6 (5.4)
Pulmonary embolus	2 (1.8)
Abscess	2 (1.8)
Wound infection	14 (12.5)
Wound dehiscence	1 (0.9)
Anastomotic bleed	4 (3.6)
Stricture	1 (0.9)
Enterocutaneous fistula	0 (0)
SMA clot with bowel necrosis	1 (0.9)
Peritonitis	3 (2.7)
30 day mortality	3 (2.7)
60 day mortality	4 (3.6)
90 day mortality	5 (4.5)

SMA, superior mesenteric artery.

and 90 day mortality was 2.7%, 3.6%, and 4.5%.

Figure 1 shows the OS and PFS Kaplan Meier curves for the patients included in this analysis. The median, 3 and 5 year OS was 20.5 months, 36%, and 19% respectively (*Figure 1A*). The median, 3 and 5 year PFS was 14.6 months, 24%, and 17% respectively (*Figure 1B*).

Table 3 illustrates the univariate analysis (UVA) and multivariate analysis (MVA) for OS. On UVA, increased mortality was associated with N1 status [hazard ratio (HR) 1.64: 1.05-2.56; P=0.03], post-operative CA19-9 >90 (HR 2.78: 1.56-4.93; P<0.001). There was a trend towards decreased mortality associated with adjuvant treatment with chemoradiation (HR 0.64: 0.39-1.05; P=0.08). On MVA, increased mortality was associated with N1 status (HR 1.91: 1.19-3.07; P=0.008) and postop CA19-9 >90 (HR 2.68: 1.45-4.94; P=0.002), while decreased mortality was significantly associated with adjuvant chemoradiation (HR 0.5: 0.26-0.95; P=0.04). Interestingly, there was no correlation associated with adjuvant chemotherapy alone. Age, tumor stage, interval from diagnosis to surgery, margin status, tumor site, and gender were not prognositic on UVA or MVA.

Discussion

This is one of the first studies to document outcomes and prognostic factors in patients ≥70 with pancreatic cancer treated with upfront resection with or without adjuvant therapy. Interestingly, adjuvant chemoradiation was associated with decreased mortality on MVA, whereas adjuvant chemotherapy was not prognostic. On both UVA and MVA, patients with N1 disease and post-operative CA19-9 >90 were prognostic for increased mortality.

The elderly population continues to remain underrepresented in clinical literature, representing only 25-30% of study participants (20). Secondary to this dearth of data there has been recent interest in defining the roles of different therapies in the elderly with pancreatic cancer.

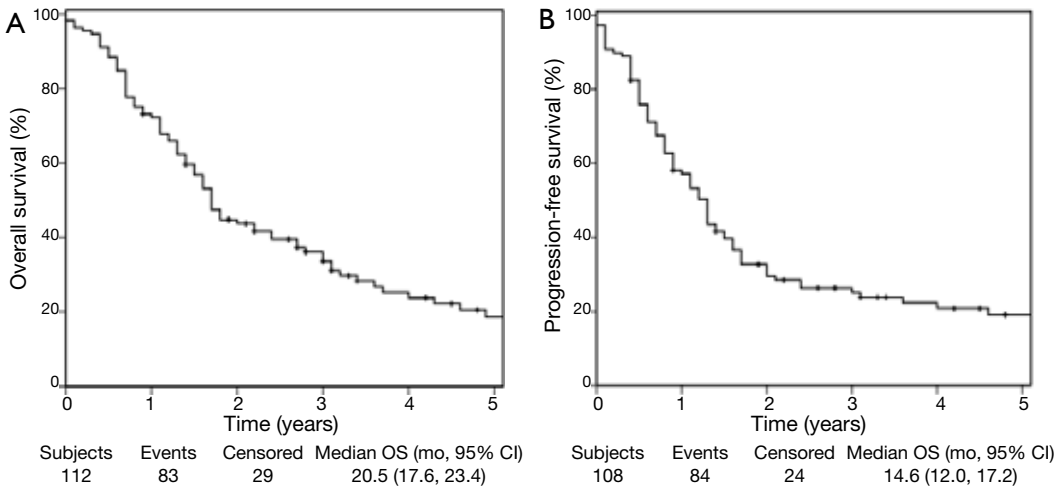

Figure 1 Kaplan-Meier survival curve of (A) overall survival (OS); (B) progression-free survival (PFS).

Table 3 Univariate and multivariate analysis for overall survival

Variable	Level	Median OS (m)	UV HR (95% CI)	P value	MV HR (95% CI)	P value
Age*			1.02 (0.98, 1.07)	0.37	1.01 (0.96, 1.06)	0.76
Gender	Male	20.5	Ref			
	Female	19.9	0.92 (0.60-1.41)	0.70	0.86 (0.55, 1.36)	0.53
Diagnosis to surgery (days)	≤30	19.8	Ref			
	>30	21.9	0.93 (0.57-1.51)	0.76	0.85 (0.48, 1.49)	0.57
Tumor site	Head	20.8	Ref			
	Body	65.9	0.54 (0.20, 1.50)	0.24	1.03 (0.32, 3.35)	0.96
	Tail	15.6	1.26 (0.70, 2.24)	0.44	1.62 (0.84, 3.13)	0.15
Tumor grade	Well	28.9	Ref			
	Moderate	18.7	1.24 (0.63, 2.45)	0.53	1.13 (0.52, 2.47)	0.75
	Poor	19.1	1.17 (0.51, 2.69)	0.71	1.04 (0.42, 2.62)	0.93
	Unknown	48.2	0.66 (0.23, 1.94)	0.45	0.52 (0.14, 2.01)	0.35
Pathologic tumor stage	T1/2	19.8	Ref			
	T3/4	20.8	1.19 (0.70-2.02)	0.53	1.27 (0.67, 2.41)	0.47
Pathologic nodal status	N0	28.8	Ref			
	N1	18.2	1.64 (1.05-2.56)	0.03	1.91 (1.19, 3.07)	0.008
Surgical margins	Negative	19.9	Ref			
	Positive	21.1	0.75 (0.40-1.42)	0.38	0.94 (0.46, 1.93)	0.87
Post-op CA19-9	≤90	26.4	Ref			
	>90	10.1	2.78 (1.56-4.93)	<0.001	2.68 (1.45, 4.94)	0.002
	Unknown	20.5	1.31 (0.79-2.17)	0.29	1.13 (0.64, 1.98)	0.68
Adjuvant treatment	None	15.6	Ref			
	Chemoradiation	21.1	0.64 (0.39-1.05)	0.08	0.50 (0.26, 0.95)	0.04
	Chemotherapy	20.5	1.05 (0.58-1.90)	0.87	0.67 (0.33, 1.33)	0.25

*, continuous variable; OS, overall survival; m, months; HR, hazard ratio; CI, confidence interval; UV, univariate; MV, multivariate; Ref, reference (HR 1.00).

A retrospective study by Sehgal *et al.* (n=16,694) reported the rates of chemotherapy delivered and associated survival in different age groups in all patients with pancreatic cancer from the Cancer Information Resource files registry (4). They found that elderly patients with pancreatic cancer receive treatment less frequently than younger patients. Additionally, median OS was significantly less in the age >70 group (4.21 *vs.* 7.07 months and 7.89 months for age >70, 51-70, and ≤50 years respectively), however these patients were shown to have a comparable or better survival benefit from chemotherapy. In their UVA, age >70 was not prognostic for OS. This study also showed an OS benefit in all patients treated with radiotherapy (HR 0.47, P<0.001). Our results are in general agreement with this study, suggesting that elderly patients with pancreatic cancer do derive a benefit from treatment, specifically chemoradiotherapy (CRT).

There continues to be controversy regarding the role of PORT in resected pancreatic cancer patients (6). Several trials have shown benefit from the used of PORT in pancreatic cancer. In Gastrointestinal Tumor Study Group (GITSG) 9,173 (n=43) patients who had undergone curative resection were randomized to observation or CRT with 40 Gy split course radiation and concurrent 5-fluorouracil (5-FU) chemotherapy (9). The median survival in the CRT arm was significantly improved compared to the observation arm (20 *vs.* 11 months, P=0.035). Additionally, the 2-year survival rates were significantly improved with CRT *vs.* the observation group (42% *vs.* 15%; P=0.035). This initial study has led to adjuvant CRT being adopted in the United States. The European Organisation for Research and Treatment of Cancer (EORTC)-40,891 (n=218) phase III study sought to confirm these results and as such randomized patients with resected pancreatic cancer or periampullary cancer to observation or 5-FU based CRT (12). The initial data showed no difference in median survival between the two groups, (19 *vs.* 24.5 months; P=0.208). However, further subgroup analysis of just pancreatic tumor showed use of adjuvant CRT improved 2-year OS (23% *vs.* 37%; P=0.049) (22).

While these studies support the use of PORT in the treatment of pancreatic cancer there are additional data that do not support its use. The European Organisation for Research and Treatment of Cancer (ESPAC)-1 trial (n=541) compared observation, chemotherapy alone or CRT (11). They reported that adjuvant CRT worsened the median survival compared to those who did not receive CRT (16 *vs.* 18 months) as well as reported an inferior 2-year survival (29% *vs.* 49%; P=0.05). However, this study has been widely criticized for lack of quality assurance and the split-course treatment techniques. The study allowed radiation oncologists to choose their dose with a range of 40-60 Gy. Moreover, only 53% of patients enrolled in the study were included in the final analysis. Lastly the physician was able to choose how the patient was randomized and prescribe chemotherapy or "background" CRT.

While the previously mentioned trials included elderly patients, but did not specifically analyze this population, there have been two other trials that have specifically examined the elderly population. Miyamoto *et al.* examined pancreatic cancer patients age ≥75 (n=42) treated with CRT as adjuvant or definitive therapy (23). Median OS for the patients that received surgery followed by CRT was 20.6 months *vs.* 8.6 months for CRT as definitive therapy. Importantly, they showed that in this elderly population outcomes after CRT were similar to historic controls, although many patients experienced substantial treatment-related toxicity. Another study, Horowitz *et al.* from Johns Hopkins analyzed 655 patients from their prospectively collected database of patients who underwent resection and 5-FU based CRT (n=313) or no adjuvant treatment (n=342) (24). They showed that the 2-year survival for elderly patients receiving adjuvant CRT was significantly greater than those who received surgery alone (49% *vs.* 31.6%; P=0.013); however, the 5-year survival in both groups was similar (11.7% *vs.* 19.8% respectively; P=0.310). Upon MVA adjuvant CRT had protective effect with respect to 2-year survival [relative risk (RR) 0.59; P=0.44].

Our study differs from the aforementioned studies in the fact that we examined patients who underwent upfront surgical resection followed by no treatment, chemotherapy, and CRT. The study by Horowitz *et al.* compared surgery alone to CRT, and the Miyamoto *et al.* study compared only CRT as an adjuvant therapy to CRT as definitive therapy. While these differences do exist it appears that our data is in general agreement that elderly patients with pancreatic cancer benefit from treatment, specifically chemoradiation in the adjuvant setting.

Our study does present several inherent limitations based on the fact that this is a retrospective analysis, a time period spanning 12 years, including that fact that patient selection may influence survival. Overall, our study suggests that elderly patients with resected pancreatic cancer benefit from therapy and specifically that adjuvant CRT, however, conclusion drawn from this analysis are hypothesis generating and not definitive.

Conclusions

Our study begins to define prognostic variables associated with OS in elderly patients, a group that continues to be underrepresented in clinical research. Our data shows an increase in OS in patients that were treated with adjuvant CRT but not chemotherapy alone.

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Pancreatic fistula and postoperative pancreatitis after pancreatoduodenectomy for pancreatic cancer

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Abstract: The most serious complication after pancreatoduodenectomy (PD) is pancreatic fistula (PF) type C, either as a consequence or independently from postoperative pancreatitis (PP). Differentiating between these two types of complications is often very difficult, if not impossible. The most significant factor in early diagnosis of PP after PD is an abrupt change in clinical status. In our retrospective study we also observed significantly higher levels of serum concentrations of CRP and AMS comparing to PF without PP. Based on our findings, CT scan is not beneficial in the early diagnosis of PP. Meantime PF type C is indication to operative revision with mostly drainage procedure which is obviously not much technically demanding, there are no definite guidelines on how to proceed in PP. Therefore the surgeon's experience determines not only whether PP will be diagnosed early enough and will be differentiated from PF without PP, but also whether a completion pancreatectomy will be performed in indicated cases.

Keywords: Pancreatoduodenectomy (PD); pancreatic fistula (PF); postoperative pancreatitis (PP); drainage; total pancreatectomy

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Introduction

Pancreatoduodenectomy (PD) has its indication of radical intent in the treatment of periampulary malignant tumors as cephalopancreatic neoplasia, distal cholangiocarcinoma or ampuloma. PD managing to provide a 5-year survival of 31.4% for tumors diagnosed in stage I and only 2.8% for stage IV with a median of 24.1 and 4.5 months respectively (1). In patients with unresectable adenocarcinoma 5-year survival reach only 0.6% for stage IV with a median survival of 2.5 months and 3.8% for stage I with a median of 6.8 months. Radical resection is the only chance for patients with this tumor. Unfortunately only 15-20% of them are suitable for it.

Mortality of this type of resection has intermediate risk to compare to total pancreatectomy with highest and to distal pancreatectomy with lowest risk. Retrospective review from a prominent high volume cancer center revealed 30-day mortality rates of 4.9% in the 1980s, 1.5% in the 1990s and 1.3% in the 2000s (2). By the Nationwide Inpatient Sample for 1994-1999 Birkmeyer *et al*. demonstrated wide variation in perioperative mortality based on hospital volume: 17.6% for low volume compared to 3.8% for high volume (3).

Complications after PD affect a large part of patients and include a variety of clinical entities—internal (as pneumonia, cardiovascular events, infection and others) as well as surgical [bleeding, pancreatic fistula (PF), postoperative pancreatitis (PP), infection-sepsis and others]. The high rate of complications is due to multiple factors as comorbidity, technical complexity of the operation, frail patient population and remains as high as 31-60% (4).

The aim of this review is to present the occurrence of PF and PP, the possibilities of their differentiation and some aspects of treatment after PD as well as to present some aspects of the possibilities to differentiate PH and PP in our retrospective study.

Table 1 New classification of pancreatic anastomosis failure (9)

Grade	Classification
1	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions. Allowed therapeutic regimens include: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade of complication applies to patients with fistula whose only change in management other than use of allowed drugs in maintenance of the drain until the fistula has dried up
2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and total parenteral nutrition are also included
3	Requiring surgical, endoscopic, or radiologic (invasive) intervention
3a	Intervention not under general anesthesia
3b	Intervention under general anesthesia
4	Life-threatening complication (including CNS complications) requiring IC/ICU management
4a	Single organ dysfunction (including dialysis)
4b	Multiorgan dysfunction
5	Death of a patient with PAF

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit; PAF, pancreatic anastomosis failure.

Pancreatic fistula (PF)

PF is the most feared complication after PD, being considered the "Achilles' heel" of this procedure (5). In spite of previous studies with outstanding results with almost no need for reoperation (6), actual rate of PF grade "C"—severe—(7) requiring operative re-intervention varies between 5% and 20% with mortality rate nearly 40% (8).

Definition

There is no universally accepted definition of PF. Most of them rely on amylase content of the effluent from intraabdominal drain. International study group of PF (ISGPF) organized by Bassi *et al.* (7) extended definition to standardizing of postoperative treatment by the adoption and by the modification the definition based on clinical impact on the patient hospital course and the outcome and graded PF into A, B, C. The grading was based on nine clinical criteria: patient's condition, use of specific treatment, US and/or CT findings, persistent drainage >3 weeks, reoperation, signs of infection, sepsis, readmissions and death. Strasberg *et al.* proposed intraabdominal collection with hemorrhage and peritonitis are also the result of PF (9) (*Table 1*).

Risk factors for PF

Multivariate logistic regression analysis showed that none of the general risk factors as age, gender, history of jaundice, preoperative nutrition, type of resection and the length of postoperative stay seemed to be associated with PH (10,11). Two intraoperative risk factors—pancreatic duct size and parenchyma texture of the remnant pancreas—were found to be significantly associated with PF. Pancreatic duct size >3 mm means only 4.88% of PF, and 38.1% in pancreatic duct size <3 mm respectively. PH rate was less than 3% in hard pancreatic tissue meanwhile in soft tissue reached more than 32%. French multicentric retrospective survey on PD for ductal adenocarcinoma found that a soft pancreatic parenchyma, the absence of preoperative diabetes, pancreaticojejunostomy and low volume centers were independent risk factors for PF (12). Although anastomotic technique was not a significant factor, PH rate was much less in cases of duct-to-mucosa pancreaticojejunostomy (10,13,14). On the other hand PH risk score for prediction of clinically-relevant PH after PD reflected intraoperative blood loss (13). There are other factors apart from technical consideration, of which increased intraoperative blood loss—more advanced stages of disease requiring portal or superior mesenteric vein resection, patient obesity, jaundice associated coagulopathy and others (11).

Moreover careful consideration should be given to the larger pancreatic stumps, wide pancreatic remnant mobilization, and the duct decentralization on the stump in anteroposterior axis (15).

Preventive measures

Occlusion of pancreatic duct

To prevent complications following PD especially the development of PF various techniques of managing the pancreatic remnant have been proposed (11). Occlusion of the pancreatic duct (chemical occlusion or simple duct ligation) compared with pancreaticojejunostomy there is no significant difference found in the postoperative complications, mortality and exocrine insufficiency. Moreover there were significantly more patients with diabetes mellitus in the duct occlusion group. So there is no evidence to show that pancreaticojejunostomy can be replaced by pancreatic duct occlusion (16).

Pancreaticogastrostomy

Four RCTs comparing pancreaticogastrostomy to pancreaticojejunostomy have failed to show any significant difference regarding to PF ratio, postoperative complications or mortality (17-20). The type of anastomotic fashion plays no role for the risk of PF. Results of one RCT has showed significantly lower rate and severity of PF after pancreaticogastrostomy compared to pancreaticojejunostomy (21). A prospective RCT by Bassi *et al.* revealed no significant difference in PF ratio between duct-to-mucosa anastomosis and single layer end-to-side pancreaticojejunostomy (22). The use of isolated Roux-en-Y pancreaticojejunostomy cannot prevent the development of PF formation (20,23).

Total pancreatectomy

Total pancreatectomy allows not only more extensive lympfadenectomy and decreases the risk of positive resection margins but also obviates a leak from pancreatic anastomosis. This type of procedures is however associated with the development of diabetes mellitus, decreasing of immunity and loss of pancreatic exocrine function. So indication for total pancreatectomy is not corresponding to routine treatment of localized ductal adenocarcinoma of the head of pancreas (24).

Based on the current evidence it is unclear whether drainage of pancreatic duct with a stent (internal or external) can reduce PF rate (25,26).

Pharmacologic prevention

There were optimistic results of the multicentric study regarding to the role of Octreotide in the prevention of postoperative complications following pancreatic resection from the 90's showing reducing of the occurrence of the typical postoperative complications (27). Current single-center, randomized, double-blind trial of perioperative subcutaneous pasireotide in patients undergoing either PD or distal pancreatectomy showed similar results. Authors presented that the perioperative treatment with pasireotide decreased the rate of clinically significant postoperative PF, leak, or abscess (28).

According to the actual literature the administration of Octreotide by principle is not recommended but only in the case of low consistency pancreatic parenchyma or when intraoperative handling of the pancreatic stump is more aggressive (10). Somatostatin administration may have reduced the pancreas edema, protected the normal tissues and improved the anastomosis quality, but on a daily basis, the abdominal drainage fluid is not affected without any difference between preoperative and postoperative use (29). Moreover there is no statistical difference in the incidence of PF between the patients who received the prophylactic use of octreotide after surgery and the patients who did not somatostatin therapy (30).

Drain removal and other preventions

There is no standard regarding to the best time when the intraabdominal drain should be removed. The most surgeons indicate drainage removal once the output of amylase-rich fluid is low (31). Until now, there has been no consensus on the optimal timing of the removal of prophylactic drainage after pancreatic surgery in general. The similar situation is associated with poor or no agreement to the type of nutrition, use of antibiotics, imaging strategy and hospital discharge (32).

Treatment approaches

The current treatment depends on the grade of PF. It is noteworthy that 70% of PH resolves spontaneously (33). The best strategy for the management of PF is still highly debated. Actual rate of PF grade C requiring a relaparotomy varies between 5-20% even in experienced center with mortality rate as high as 39% (4,8). Different strategies include both preservation of the pancreatic remnant and a completion pancreatectomy (34). Pancreatectomy avoids further PF but leads to complete pancreatic insufficiency and to "brittle" diabetes (35). Preserving approach—debridement and drainage of the pancreatic region or resection the dehiscent jejunal loop followed by the occlusion of the main pancreatic duct—is technically easier

and has the advantage of maintaining pancreatic function but on the other hand leads to the risk of a persistent PH. Balzano *et al*. presented better results with completion pancreatectomy with splenectomy in the case of PH grade C with autologous islet transplantation reducing the metabolic consequences of total pancreatectomy (36). Moreover there is experience with other methods—the conversion to pancreaticogastrostomy and the bridging stent technique but without evidence whether drainage of the pancreatic duct with a stent can reduce PF rate after PD (37). Finally there is also the experience with resection of dehiscent jejunal loop and drainage of pancreatic region followed by gastrofistulostomy (38).

Acute postoperative pancreatitis (PP)

PP is a less frequent but very serious surgical complication with often fatal results. It is most often seen following surgery on the pancreas itself, but in rare cases has also been described after surgical procedures on organs very distant from the pancreas. The occurrence of PP according to Carter from 1956 depends upon the following condition (39): mechanical injury direct to the pancreas and especially to the pancreatic ducts, vascular conditions, spasm of the sphincter of Oddi and stagnation of duodenal contents.

The incidence of PP reported in the literature is approximately 8-10%, following PD ranges from 1.9-50% (40). But to analyze PP ratio by literature is difficult: PP is mostly not evaluated as a separate complication of PD but in the range of PH (40). Contrary to acute pancreatitis with 5-15% mortality, the mortality of PP is more than 30% (41).

Diagnosis

PP is clinically defined as abdominal pain which develops during the postoperative course with a concurrent two- to three-fold increase in the levels of specific pancreatic enzymes in the blood. A non-standard postoperative course accompanied by pain, distension of the abdominal muscles, prolonged paralytic ileus and cloudy, often brownish, discharge from the drains may signify developing PP (26,42,43). Evaluation may however be complicated by the development of benign postoperative hyperamylasemia and the subjective perception of postoperative pain. Clinical symptoms may be hidden, especially if the patient remains under analgosedation, or even on artificial lung ventilation, after a long operation with greater blood loss. The first warning sign of the development of PP may be progressive circulatory instability, especially in patients with replenished blood supply (26). Early diagnosis of PP based on clinical and laboratory results is very difficult from standard currently performed examinations, as is the evaluation of preoperative findings during reoperation, especially after a longer interval from the primary operation.

Nonetheless a similar condition may also be caused by other postoperative complications. In a study by Wilson *et al*. (44) which clinically evaluated the postoperative course PP was only diagnosed at autopsy in 10 of 11 cases. Operative findings on revision also do not always correlate with the results of laboratory and imaging examinations.

Pancreatic leak from PJA or PGA and peripancreatic abscess may be clinical signs of PP. They may however also develop due to technical error during sewing of the anastomosis, where edge necrosis may occur in an otherwise undisturbed glandular parenchyma. During surgical revision in a postoperatively changed terrain, pathological changes in the remaining pancreas and its surroundings are often difficult to evaluate due to signs of superficial tissue digestion and the presence of necrosis, which develop due to digestion by activated pancreatic juice. Postoperative changes in cases of PF may easily be misinterpreted for signs of PP and vice-versa.

Regarding laboratory analysis, in addition to values of amylase, lipase and trypsin levels, Büchler *et al*. also favors analysis of CRP and calcium levels (45). In recent years, diagnosis of PP has most often been reliant on CRP level along with the result of spiral contrast CT examination, where necrotic changes in the parenchyma are evaluated according to the Balthazar classification (46). In accordance with current literary findings, CRP levels best reflect the development and course of the disease. In contrast, CT examination performed prior to surgical revision has not shown to be beneficial in terms of evaluating changes in the pancreatic gland.

Treatment approaches

PJA disconnection and drainage procedures during surgical revision after PD in cases of PP are usually insufficient and do not lead to a better prognosis. An appropriate, although risky, solution during early revision with suspicion of PP is a completion pancreatectomy with splenectomy. However, after late revisions in an operating field devastated by pancreatitis, the mortality of patients after completion pancreatectomy nears 100%, according to most authors (47,48). Is it desirable to proceed with the completion

pancreatectomy soon after the primary procedure (34)? However to perform a completion pancreatectomy in a patient with PF type C may be an unwarranted procedure, unjustifiably risky with subsequent significant worsening of quality of life. Early diagnosis of PP may therefore be a key moment in the treatment of PH type C in patients after PD.

Base on the current literature, very few firm statements can be made: the criteria for drain removal, imaging strategy and timing of hospital discharge in patients with PF remain unclear (31). In the case of PP after PD treatment strategy is unclear yet and available standard is lacking.

Our own experience

We retrospectively evaluated the postoperative clinical course, and radiological and laboratory data of 7/160 patients underwent PD in the period of 2007-2011 in our institution for ductal adenocarcinoma of the head of pancreas and died during primary hospitalization because of PF type C with autopsy findings of PP in four cases (49). We compared this group of 4 (2.5%) patients to the group of 10 (6.25%) patients with only a pancreatic leak type C and 12 (7.5%) patients with an uncomplicated clinical course. None of the patients with PP survived. We found significantly higher levels of serum pancreatic amylase on the 1st postoperative day (POD) in 3 of these patients compared to the other groups. Significantly increasing levels of CRP during the first five POD were observed in 75% of these patients. Retrospectively analyzed contrast CT scans up to the 5th POD did not show PP. Only one patient had findings of PP type E according to Balthazar on CT scan performed on the 9th POD.

Results commentary

A basic aim of our study was to confirm or rule out a diagnosis of PP in the interval from the primary surgical procedure to the surgical revision, with respect to our standard type of surgical procedure (disconnection and closure of the feature stump and peripancreatic drainage). Our retrospective evaluation showed that we were mistaken in almost half of the patients. Subsequent decision to perform a disconnection of the pancreatojejunostomy with drainage of the resected area with planned external PF did not reflect the current view on treatment of this complication. This error, in both diagnosis and type of surgical revision, has also been presented by other authors, who came to very similar conclusions based on retrospective analyses (50,51). Completion pancreatectomy can be of significant benefit when performed as soon as possible after diagnosis of potentially fatal PP (52). The longer the interval between primary operation and surgical revision, the lower the chance of performing completion pancreatectomy without endangering the life of the patient. Due to the gradual postoperative development of inflammatory peripancreatic infiltrate, the procedure becomes intolerable for the patient. In any case, the decision to perform completion pancreatectomy is very difficult for the surgeon.

In our set of patients who died in direct association with a serious postoperative pancreatic leak from the pancreaticojejunostomy, PP occurred in 4 out of 7 cases (57%) based on autopsy histological findings. All of these patients were suspected of having PP based on macroscopic findings during revision surgery.

If we retrospectively evaluate our patient group and our reaction to the obtained values—markers—of PP, it is necessary to state that we rather underestimated the increasing values and was of the opinion that the values reflect developing pancreatic leak and that we have time and will observe the patient. We evidently missed the opportunity to perform early surgical revision and remove the remaining pancreas.

Another discovery was the evaluation of the postoperative finding on the remaining pancreas. We attributed superficial necroses to developing PP; autopsy findings, however, did not confirm PP. Evidently these were superficial changes caused by digestion of pancreatic tissue by activated pancreatic juice from PJA dehiscence. In accordance with other authors, we do not consider feature soft biopsy to be of value.

Prior CT examinations did not describe structural changes in the pancreas in any of the four cases of autopsy-confirmed PP, not even on retrospective evaluation.

The results of our retrospective study confirmed the following:

(I) An abrupt increase in values of serum amylase and CRP from the 1st POD to 5th POD is indicative of the development of PP following PD for ductal adenocarcinoma;
(II) CT examination may not be beneficial in diagnosing this complication;
(III) When life-threatening PP is diagnosed, a completion pancreatectomy is recommended. The decision depends on the surgeon's experience;
(IV) In some patients, PP may not be confirmed on biopsy or autopsy; changes on the remaining pancreas may only be superficial, caused by digestion of activated pancreatic juice leaking from dehiscence of the pancreaticojejunostomy.

Cost of pancreatic fistula (PF)

Patients who experience any complications after pancreatic surgery are associated with a three-fold increase in costs over those without complications (53). It is of note that one of the most serious postoperative surgical complications is PF type C either as a consequence or independently from PP. The hospital stay of these patients is significantly longer than that of patients without PF (53). A median total cost of the treatment depends on the type of PF: A, B and C—100%, 170%, 620% respectively. There is no significant difference in total cost between patients without PF and with PF type A (54).

Conclusions

The most serious complication after PD is PF type C, either as a consequence or independently from PP. Differentiating between these two types of complications is difficult. Meantime PF type C is indication to operative revision with mostly drainage procedure which is obviously not much technically demanding, there are no definite guidelines on how to proceed in PP. Therefore the surgeon's experience determines not only whether PP will be diagnosed early enough and will be differentiated from PF without PP, but also whether a completion pancreatectomy will be performed in indicated cases.

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Laparoscopic pancreaticoduodenectomy: a descriptive and comparative review

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Abstract: Laparoscopic pancreaticoduodenectomy (LPD) is an extremely challenging surgery. First described in 1994, it has been slow to gain in popularity. Recently, however, we have seen an increase in the number of centers performing this operation, including our own institution, as well as an increase in the quantity of published data. The purpose of this review is to describe the current status of LPD as described in the literature. We performed a literature search in the PubMed database using MeSH terms "laparoscopy" and "pancreaticoduodenectomy". We then identified articles in the English language with over 20 patients that focused on LPD only. Review articles were excluded and only one article per institution was used for descriptive analysis in order to avoid overlap. There were a total of eight articles meeting review criteria, consisting of 492 patients. On descriptive analysis we found that percent of LPD due to high-grade malignancy averaged 47% over all articles. Average operative time was 452 minutes, blood loss 369 cc's, pancreatic leak rate 15%, delayed gastric emptying 8.6%, length of hospital stay 9.4 days, and short term mortality 2.3%. Comparison studies between open pancreaticoduodenectomy (OPD) and LPD suggested decreased blood loss, longer operative time, similar post-operative complication rate, decreased pain, and shorter hospital length of stay for LPD. There was also increased number of lymph nodes harvested and similar margin free resections with LPD in the majority of studies. LPD is a safe surgery, providing many of the advantages typically associated with laparoscopic procedures. We expect this operation to continue to gain in popularity as well as be offered in increasingly more complex cases. In future studies, it will be beneficial to look further at the oncologic outcome data of LPD including survival.

Keywords: Laparoscopic; laparoscopy; pancreaticoduodenectomy; whipple; review; laparoscopic *vs*. open

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Introduction

Pancreatic cancer is the 12th most common cancer in the world, with 338,000 new cases diagnosed in 2012 (1). In the United States in 2014, it affected over 46,000 people resulting in a mortality 39,590 individuals (2). The treatment—pancreaticoduodenectomy (PD) has seen improved perioperative outcomes and complication rates over the last few decades (3-6). Nevertheless, it continues to be a morbid operation with complications ranging from 24-59% (7-9). Laparoscopic surgery reduces surgical morbidity in various operations, however laparoscopic pancreaticoduodenectomy (LPD) is a relatively new procedure which lacks a clear consensus regarding its benefits (10-14). Although the first published case was described in 1994, it has been slow to gain popularity (15). This is likely in part due to the challenging technical aspect of the procedure including the retroperitoneal location of the pancreas, close vicinity to the superior mesenteric artery and vein, portal vein and hepatic arteries and the technical difficulty of three anastamosis. In recent years, however, we have seen an increasing number of studies examining LPD. Initial research evaluated feasibility and outcomes, assessing whether LPD could be done with adequate safety (16-23). The question then moved from is LPD safe to how does it compare to the open approach? Will it appreciate the same benefits of other laparoscopic surgeries? Partially enabled by higher volumes at specialized centers, studies began comparing LPD with open pancreaticoduodenectomy (OPD). Although there are a handful of pancreaticoduodenectomy review articles evaluating LPD in the literature, many include papers with limited sample sizes and case reports. Our goal with this review was to examine the larger sampled articles available and evaluate the present state of LPD.

Methods

A literature search was performed in the PubMed database using MeSH terms "laparoscopy" and "pancreaticoduodenectomy". The final search was completed on February 20, 2015 and revealed 180 articles. We identified only those in English involving total LPD with over 20 patients in the study. Irrelevant articles, review articles, those with less than 20 patients, laparoscopic

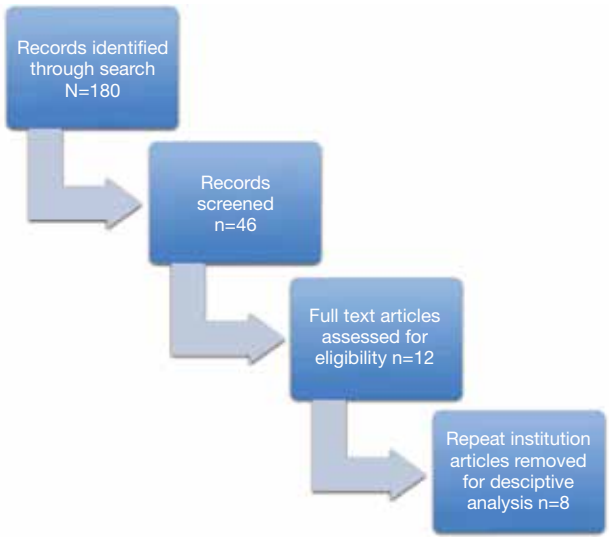

Figure 1 Literature search.

Table 1 Articles reporting on 20 or more laparoscopic pancreaticoduodenectomies

Author	Year	Number of cases	Country
Asbun	2012	268	USA
Croome	2014	322	USA
Speicher	2014	56	USA
Song	2015	2,192	Korea
Palanivelu	2009	75	India
Mesleh	2013	123	USA
Honda	2013	26	Japan
Corcione	2013	22	Italy

assist, robotic, and hybrid focused studies were excluded. Those involving colon, spleen, biliary resections, porcine models, and articles published prior to 2005 were also excluded from the study. Two researchers (JM and AP) worked through these criteria independently and identified 12 studies deemed suitable. For our descriptive analysis we used only one article per institution when multiple publications originated from a single center to avoid overlap. In these instances we chose the most recent article. Following this exclusion, we were left with eight articles. See *Figure 1*.

In the literature review, both descriptive and comparative studies were found. We extracted technical, perioperative and intraoperative data. This included conversion rate, operative time, and intraoperative blood loss. We also collected information on hospital length of stay, pancreatic leak, delayed gastric emptying, post-operative bleeding, abscess formation and short term mortality. Oncologic data including proportion of patients with invasive malignancy, number of lymph nodes removed, and margin status was also recorded. Five-year overall survival was not available in most studies and the diversity of malignant etiologies in patients made this more difficult to interpret collectively. In our descriptive analysis, we used a weighted average to calculate our various rates based on the number of subjects in each study.

Results

Descriptive analysis

A total of eight articles were included that met our inclusion and exclusion criteria. Year of publication ranged from 2009 to 2015. There were a total of 492 patients who underwent LPD included in our review. All of the studies were retrospective. Three studies were purely descriptive in nature and the remaining five articles compared laparoscopic and OPD. Regarding article country of origin there were 4 from USA, 1 from Korea, 1 from India, 1 from Japan, and 1 from Italy (19,24-30). See *Table 1*.

Purpose for PD ranged from treatment of benign and low-grade malignancies to high-grade malignancies such as pancreatic ductal adenocarcinoma, ampullary adenocarcinoma, cholangiocarcinoma, and metastatic renal cell carcinoma. The percent of LPD for high-grade malignancy in studies reviewed ranged from 10.1% to 100%, with an average of 47% over all cases.

Although documented in only four articles, rate of laparoscopic pylorus preserving pancreaticoduodenectomy was found to be the technique of choice in 63% of cases, ranging from 0 to 100% per article. Additionally, five studies discussed pancreatic duct anastomosis technique, of which four used an end to side anastomosis, and one used both end-to-end and end-to-side technique. Conversion rate to open was noted in 7 of the 8 articles. The average rate of conversion ranged from 0-15%, with an average over all cases of 13%. Average operating time among patients undergoing LPD was 452 minutes, ranging from 357 to 551 minutes. There did appear to be a significant improvement in operating time depending on the experience of the surgeon. Average blood loss for LPD was 369 cc's, ranging from 74 to 592 cc's. This also improved considerably based on surgeon experience.

Table 2 Descriptive data of laparoscopic pancreaticoduodenectomy

Author	Malignant etiology (%)	Conversion rate (%)	Operative time (min)	Blood loss (cc)	Hospital stay (days)	Pancreatic leak (%)	Delayed gastric emptying (%)	Short-term mortality (%)
Asbun	64	15	541	195	8	16.7	11.3	5.7
Croome	100	7	379.4	492.4	6	11	9	2
Speicher	NR	0	381	200	8.5	16	NR	4
Song	10.1	NR	480.4	592	14.1	29.9	3.2	0
Palanivelu	96	0	357	74	8.2	6.7	NR	1.3
Mesleh	79	10	551	NR	7	9	13	NR
Honda	46	2	519	303	NR	23	11.5	0
Corcione	100	2	450	NR	20	27	NR	4.5

NR, not recorded.

Pancreatic leak information was available in all eight papers, and ranged from 6.7% to 29.9% of cases per article. The average pancreatic leak proportion was 15%. Over all, the average delayed gastric emptying rate was 8.6%, ranging from 3.2% to 13% over included studies. The average length of hospital stay for LPD patients was 9.4 days, ranging from 6 to 20 days per article. This data was reported in 7 of the 8 articles. Finally, short-term mortality, defined as all cause mortality less than 100 days from surgery, was 2.3% over all studies. See *Table 2*.

Although survival data was rarely available and difficult to interpret with varying malignant etiologies, we did record two surrogates for oncologic outcomes—number of LNs removed and margin free resection. Firstly, the average number of lymph nodes removed was recorded in 6 of the 8 articles, ranging from 14 to 23.4 nodes. Margin free resection ranged from 77% to 100% and was available in six studies.

This data, although not directly comparing LPD to OPD, does show that LPD is safe and feasible with acceptable outcomes. Descriptive studies such as these have led to more acceptance in the surgical community of this complex laparoscopic surgery. One hindrance to the utilization of more surgeons performing this technique is likely the technical difficulty and the lack of formalization of education in this technique. Interestingly, some studies have specifically looked at this learning process with encouraging findings.

Learning curve

A number of the studies we include in our review address the learning curve required for LPD with promising findings. Surgeons performing LPD do indeed improve significantly over time, with decreased operative times, blood loss, pancreatic leak rates, and length of hospital stay. For example, Kim *et al*. (22), in a study of 100 consecutive cases of laparoscopic pylorus preserving pancreaticoduodenectomy performed by the same surgeon found that when they divided these patients into three chronological periods, there were significant outcome improvements. For example, operative times went from 9.8 hours in period one to 6.6 hours in period three. Length of hospital stay went from 20.4 to 11.5 days, and complication rate (including pancreatic fistula, ileus, bleeding, delayed gastric emptying) went from 33.3% to 17.6% in period one and three, respectively. A study by Speicher *et al*. (28) divided LPD into three cohorts of ten patients (last cohort had six patients) based on order performed, and found that operative time as well as blood loss decreased. Additionally, they proposed a staged learning process, with separate performance measures that progressed in difficulty as the operator's skill improved. These authors found the learning curve for LPD involved a slow difficult beginning phase, a precipitous acceleration in improvement phase, and finally a plateau phase with slow but continued improvement over time. Finally, Song *et al*. (24) performed a matched cohort analysis comparing LPD *vs*. OPD. They found that when dividing their LPD patients into early and late groups consisting of 47 and 50 patients respectively, the late group had significantly shorter operative times (399.4 *vs*. 566.5 minutes, P<0.001), less EBL (503 *vs*. 685 cc's, P=0.018), and shorter length of hospital stay (11.2 *vs*. 17.3 days, P<0.001).

Although these improvements may be intuitive as surgeons move along the learning curve, the significant

progress observed by these authors, including the decreased rate of complications is encouraging. With appropriate guidance, we expect more surgeons to move to LPD.

Open vs. LPD

As initial studies have showed the feasibility and safety of LPD, more recent studies are directly comparing OPD to LPD. In our review, we found 6 articles that met our inclusion and exclusion criteria that compared these surgeries. Articles were published between 2012 and 2015, and were all retrospective in nature. Study subjects ranged from 56 to 680 individuals per study, and five papers originated from the USA. The remaining study was from Korea. We will examine these on a study-by-study basis in order of publication.

In 2012 Asbun *et al*. (25) published an article in JACS which compared 215 OPD with 53 LPD that underwent surgery between 2005 and 2011. These cohorts were well matched for gender, comorbidities, ASA score, BMI, and age. Authors state selection criteria was based mainly on patient preference and not clinical factors, although if major vascular resection was required or the abdomen was expected to be hostile either open or laparoscopic with a low threshold to convert to open was performed (these patients were analyzed on a non-intention to treat fashion). They found that the LPD group had less intraoperative blood loss (1,032 *vs*. 195 cc's, P<0.001), PRBC transfusions (4.7 *vs*. 0.64 U, P<0.001), decreased ICU stay (3 *vs*. 1.1 days, P<0.001), and overall hospital stay (12.4 *vs*. 8 days, P<0.001). LPD patients did have increased operative time (401 *vs*. 541 minutes, P<0.001). Rate of complications, including pancreatic leak rate and delayed gastric emptying, were similar between the groups. In terms of oncologic data, numbers of lymph nodes removed as well as lymph node ratio were better for the LPD group (16.84 *vs*. 23.44, P<0.001 and 0.241 *vs*. 0.159, P=0.0072, respectively). Furthermore, margin status, number of patients utilizing adjuvant chemotherapy, and time to start adjuvant treatment was similar between groups. This article demonstrates possible benefits of the laparoscopic procedure over open. The finding of an improved LN resection with LPD is very interesting. However, as patients requiring major vascular resection and those with hostile abdomens were more likely to be in the open group, there is potential for selection bias that affected the results in favor of the LPD group.

Mesleh *et al*. (30) published an article 2013 which addressed the issue of cost of OPD *vs*. LPD. Their study included 48 OPD and 75 LPD who underwent operation between 2009 and 2012. Patients appear matched on demographic data and difficulty of the operation. There were ten patients requiring conversion to open. Analysis was completed on an intention to treat basis. Authors extracted cost information, divided into "admission" and "surgical" cost. They found that while "surgical" cost was higher for the laparoscopic group, "admission" cost was greater for the open group. The increased "surgical" cost was tied to the longer OR time as well as more expensive surgical equipment. On the other hand, "admission" cost was less for the laparoscopic group. These differences in part cancelled each other out and overall cost (converted from dollars to "units" for this publication) was similar between OPD *vs*. LPD groups (154 *vs*. 173 units, P=0.5). As a side note, the authors also found that the LPD group had increased lymph node retrieval as well as decreased blood loss compared to OPD. Although these cost findings may not be generalizable to other institutions, this is an important article as it shows LPD may not actually be more expensive overall, which is a common assumption. Furthermore, as the learning curve improves, surgical cost of LPD should decrease with operative times.

One criticism of many comparison studies is that there is inherent bias in favor laparoscopic approaches, as the more difficult resections are reserved for the open surgeries. In 2014, Croome *et al*. (31) in part addressed this issue by comparing only LPD *vs*. OPD with comparable vascular resections. Their study included 58 OPD and 31 LPD cases, all requiring major vascular resections. Patients were similar in demographic data with the exception that the LPD group was significantly older (63.6 *vs*. 69.5 years, P=0.01). There was no difference in the distribution or difficulty of vessels requiring resection between groups. Operative time was similar between the OPD *vs*. LPD groups (465 *vs*. 465 minutes, P>0.99), although clamp time was greater in the laparoscopic group (25.1 *vs*. 46.8 minutes, P<0.001). As seen previously, blood loss was less in the laparoscopic group (1,452.1 *vs*. 841.8 cc's, P<0.001) as well as length of hospital stay (9 *vs*. 6 days, P=0.006). In terms of oncologic data, LPD group had more lymph nodes harvested (15.9 *vs*. 20 nodes, P=0.01), and greater R0 resection (75.9 *vs*. 93.5%, P=0.038). These improved oncologic variables did not translate to improved survival, as intention-to-treat analysis using Kaplan-Meier survival estimates were similar (P=0.14). In-hospital

30-day mortality was similar between groups as well (P=0.96). Although these authors admittedly have advanced technical expertise in LPD, the fact that they have similar and in some cases improved results even in the context of difficult laparoscopic cases involving major vascular resections underlines the future possibilities of LPD. Furthermore, the improved oncologic data begs the question—is there potential for a survival benefit with the laparoscopic approach?

In an attempt to answer this, Croome *et al*. (27) performed another study looking specifically at patients undergoing PD for pancreatic ductal adenocarcinoma (PDA) only, and compared open *vs*. laparoscopic surgery to assess whether there were oncologic differences. They compared 214 OPD and 108 LPD patients who underwent surgery from 2008 to 2013. They not only compared the typical perioperative variables, but also looked at proportion of patients undergoing chemotherapy, time to start chemotherapy, and delay of chemotherapy. Firstly, they found similar operative times, tumor characteristics, margin status, number of nodes resected, and perioperative complications (including pancreatic fistula, delayed gastric emptying, short term mortality) between groups. LPD was associated with decreased blood loss (866.7 *vs*. 492.4 cc's, P<0.001), blood transfusion (33% *vs*. 19%, P=0.01), and length of hospital stay (9 *vs*. 6 days, P<0.001). By looking solely at patients with PDA, the authors were able to more precisely compare oncologic outcomes between LPD and OPD groups. Interestingly, they found that not only was time to adjuvant therapy less for the LPD group (59 *vs*. 48 days, P<0.001), but delay beyond 8 weeks and number not receiving treatment (or delay beyond 3 months) was also less for the LPD group (41% *vs*. 27%, P=0.01 and 12% *vs*. 5%, P=0.04, respectively). In their survival analysis, they found that progression free survival was superior in the LPD group compared to the OPD (P=0.02) but overall survival was similar (P=0.12). Although no overall survival difference was appreciated, the fact that progression free survival improved is encouraging. Further studies should be done with larger sample size to further analyze survival.

A study by Speicher *et al*. (28), as discussed previously, primarily studied the learning curve for LPD. However, they also compared LPD *vs*. OPD. Their overall findings were consistent with most other studies, in that LPD was associated with less blood loss, higher lymph node harvest, and similar post op morbidity. They found that the early laparoscopic cases had worse outcomes compared to open, but over time these variables improved substantially and overall results were as stated.

Finally, the most recent article, published by Song *et al*. (24) in 2015 comprised 576 OPD and 104 LPD after exclusions. They performed a matched analysis with the benign and low-grade malignancy patients that consisted of 93 OPD controls and 93 LPD cases. Exclusion criteria for the LPD group were vascular involvement, severe pancreatitis, trauma or injury, and history of major abdominal surgery. They also analyzed patients with carcinoma in a separate analysis, comprising 483 OPD and 11 LPD patients. Exclusion criteria were similar for matched analysis but also included patients with severe cardiopulmonary morbidity. Results found that in the matched comparison, LPD had longer operative times (347.9 *vs*. 482.5 minutes, P<0.001), similar blood loss (570 *vs*. 609 cc's, P=0.5), shorter length of hospital stay (19.2 *vs*. 14.3 days, P<0.001), and decreased analgesic injection requirement. Major complications, including pancreatic fistula and delayed gastric emptying were similar. In terms of the oncologic outcomes for those patients with high-grade malignancy, they found no difference in lymph nodes removed or 5-year overall survival. Margins were also similar.

Comparison of LPD and OPD suggest that although the laparoscopic approach has increased operative times, complication rate and mortality are similar. Additionally blood loss, length of hospital stay, and oncologic outcomes appear better in most studies. Although many of these papers had similar demographic characteristics between groups, selection bias favoring LPD continues to be a problem. Many studies excluded patients with vascular involvement or higher risk surgical candidates. It is promising, however, that when surgical difficulty was similar, as shown by Croome *et al*., the LPD group continued to have good outcomes. Although a randomized controlled trial is needed to best evaluate differences between these groups it would be quite difficult to set up, especially as many LPD are done at centers specializing in this procedure with patients going to them specifically for laparoscopic surgery. However, as further studies are performed the evidence illustrating the benefits of LPD will likely strengthen. Furthermore, it will be an important topic in future research to evaluate how LPD affects oncologic outcomes, especially survival. Any meaningful improvement in survival would be a great advancement in the treatment in periampullary cancer.

Conclusions

LPD is a safe operation that provides many of the benefits

associated with laparoscopic surgery. We expect the prevalence of this operation will continue to grow in the future and will also likely be utilized in increasingly more difficult cases. Future studies should minimize selection bias and also focus on further evaluating oncologic outcome differences between LPD and OPD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Surgery for oligometastasis of pancreatic cancer

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Abstract: The incidence of pancreatic adenocarcinoma (PDAC) has steadily increased over the past several decades. The majority of PDAC patients will present with distant metastases, limiting surgical management in this population. Hepatectomy and pulmonary metastasectomy (PM) has been well established for colorectal cancer patients with isolated, resectable hepatic or pulmonary metastatic disease. Recent advancements in effective systemic therapy for PDAC have led to the selection of certain patients where metastectomy may be potentially indicated. However, the indication for resection of oligometastases in PDAC is not well defined. This review will discuss the current literature on the surgical management of metastatic disease for PDAC with a specific focus on surgical resection for isolated hepatic and pulmonary metastases.

Keywords: Pancreatic cancer (PC); oligometastasis; hepatic metastasis; pulmonary metastasis; surgical management

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Introduction

Pancreatic adenocarcinoma (PDAC) is a highly aggressive malignancy with one of the worst prognoses among gastrointestinal tumors. The American Cancer Society estimates that approximately 48,960 patients will be diagnosed with PDAC in 2015 with more than 40,560 deaths due to the disease (1). The median 5-year survival is only 6%, likely a result of the tumor's invasiveness and propensity towards metastases (2). The majority of patients will have distant metastases discovered by imaging at the time of diagnosis or in the operating room during attempted pancreatic resection (3). The liver is the most common location of distant metastasis in PDAC based on autopsy studies, followed by the peritoneum, lung and pleura, bones, and adrenal glands (4-8). However, distant metastases of PDAC has reported in almost every organ, including the brain and leptomeninges, diaphragm, gallbladder, heart and pericardium, small and large intestines, kidneys, ovaries and uterus, seminal vesicles, skin, stomach, spleen, testis, thyroid gland, urinary bladder, and orbit (5,7-17). Once PDAC has metastasized to distant organs, prognosis is dismal with an overall 5-year survival of only 1% (18,19).

The most effective treatment for PDAC is surgical resection, but patients with distant metastases are considered unresectable based upon National Comprehensive Cancer Network (NCCN) and National Cancer Institute (NCI) treatment guidelines (20,21). Therefore, unlike other malignancies, synchronous metastasectomy of PDAC is rarely performed in current clinical practice when distant disease is found. However, in some patients, distant metastases are not discovered until surgery despite a thorough pre-operative workup with negative imaging. In these situations, an extended resection could be advocated in select patients despite the fact that oligometastases are already present. The goal in this situation is to achieve total resection of all tumor with a microscopically negative (R0) resection margin, one of the most important factors contributing to increased long-term survival for patients with PDAC (22,23). However, little information exists about the value of synchronous metastasectomy together with pancreatectomy in patients with PDAC, particularly with regards to survival.

Hepatic metastasis of pancreatic cancer (PC)

The liver is the most common initial location of distant recurrence (24) in part because it is the first major organ reached by portal venous blood draining from the pancreas or lymphatic spread. With improvements in computed tomography (CT) imaging and three-dimensional reconstruction techniques, the ability of preoperative imaging to identify metastatic PDAC has increased dramatically over the last few decades. Approximately 50% of new PDAC cases are found to have distant metastases at diagnosis (3), and only 10-20% are surgical candidates at presentation (20,25-28). Currently, PDAC patients with stage IV disease on diagnostic imaging are referred for systemic adjuvant therapy and pancreatic resection is not routinely considered. Several large randomized control trials have demonstrated increased overall survival (OS) in patients with metastatic PDAC who undergo treatment with either gemcitabine-based chemotherapy or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) (29,30). However, the literature suggests that

up to 12% of occult liver metastasis are only discovered at the time of explorative laparotomy, often due to limitations in the ability of pre-operative imaging to detect small (<5 mm) liver and peritoneal metastases (31,32). Treatment in such patients is met with great controversy and is a challenge for surgeons, especially when occult liver metastases are found concomitantly in a patient with a locally resectable pancreatic tumor. This creates a difficult decision about whether to perform a palliative bypass or the intended pancreatic resection. If pancreatectomy is chosen, similar controversy remains about whether to leave the liver metastases in situ or to perform the intended pancreatectomy together with a synchronous hepatectomy.

Hepatectomy for liver metastatic disease

Due to advancements in surgical technique and improvements in perioperative management, pancreatic resection can be performed with relatively low rates of morbidity and mortality. Many high volume surgical centers have reported in-hospital mortality rates of less than 5%, with a few selected centers reporting no operative mortality after pancreaticoduodenectomy (33-37). Pancreatic resection has been offered to a greater number of patients in recent years, in part due to the use of vascular reconstruction at high volume surgical centers for patients with tumor invasion into the portal vein or superior mesenteric artery. Vascular resection with reconstruction is performed in order to increase the likelihood of obtaining an R0 surgical margin, and studies have demonstrated improvement in OS with this technique (37-42). In this background, a discussion on whether to expand resection in the case of incidental synchronous liver metastases may be appropriate.

Several large randomized trials have shown the benefit of chemoradiation therapy (CRT) on OS after surgical resection of PDAC (43,44). Specifically, improved survival has been demonstrated in patients with tumor diameter <20 mm or early pT stage by TNM staging (45,46). Patients with resectable hepatic metastases that remain stable or decrease in size with neoadjuvant chemotherapy could theoretically be selected for simultaneous liver resection and pancreatectomy given favorable tumor biology and a propensity towards improved survival. In addition, resection of oligometastases could potentially benefit the patient by reducing tumor burden prior to adjuvant systemic therapy. Therefore, in selected patients, pancreatectomy combined with liver resection and systemic therapy may provide a chance for cure. Although surgery is critical to the curative therapeutic paradigm, recent improvements in survival have been largely due to more effective systemic therapy, highlighting the importance of a multidisciplinary treatment approach in these patients (47) (*Figure 1*).

Hepatectomy is common for resectable colorectal and neuroendocrine liver metastases. Most surgical centers have reported 5-year survival rates ranging from 40% to 58% for colorectal liver metastases (48-54) and up to 76% for neuroendocrine metastases (55-57) after resection. As a result of improved survival, the criteria for resectability of colorectal liver metastases has been significantly expanded over the course of the last decade and resection, when possible, has become standard of care in these patients (58). Although various complications such as bile leak, hemorrhage, and hepatic abscess have been reported after liver resection for colorectal cancer metastases (59), these can usually be managed non-operatively and without added mortality. Numerous studies have suggested that hepatic resection for colorectal liver metastases and neuroendocrine metastases is safe and effective, and liver resection in these patients is now well established. In contrast, hepatectomy for PDAC liver metastases is extremely controversial. The data for resection of PDAC liver metastasis are not well established, and the available literature is limited to surgery in a small number of extremely selected patients. Additionally, it is unclear from these studies how many patients received neoadjuvant chemotherapy prior to metastatectomy. Establishing hepatectomy for PDAC liver metastasis will only be justified if an improvement in survival and/or quality of life without an increase in surgery-related morbidity and mortality can be demonstrated. Currently, there is little information on outcomes after pancreatectomy for PDAC in patients with metastatic disease, making an objective conclusion difficult to achieve and a treatment guideline difficult to formulate.

Current literature has shown that pancreatectomy with synchronous hepatic metastasectomy can be performed safely without a significant increase in perioperative morbidity and mortality (60-64) (*Table 1*). However, the potential benefit on long-term survival is less clear (62,68). Singh *et al*. (62) demonstrated that the resection of a solitary liver metastasis can be safely performed together with pancreaticoduodenectomy. However, whether OS improved was not definitively proven. In this study, three PDAC patients underwent synchronous metastasectomy and pancreaticoduodenectomy and died at 7, 14 and 18 months post-operatively. de Jong *et al*. (63) examined 40 patients who underwent surgery with curative intent [resection and/

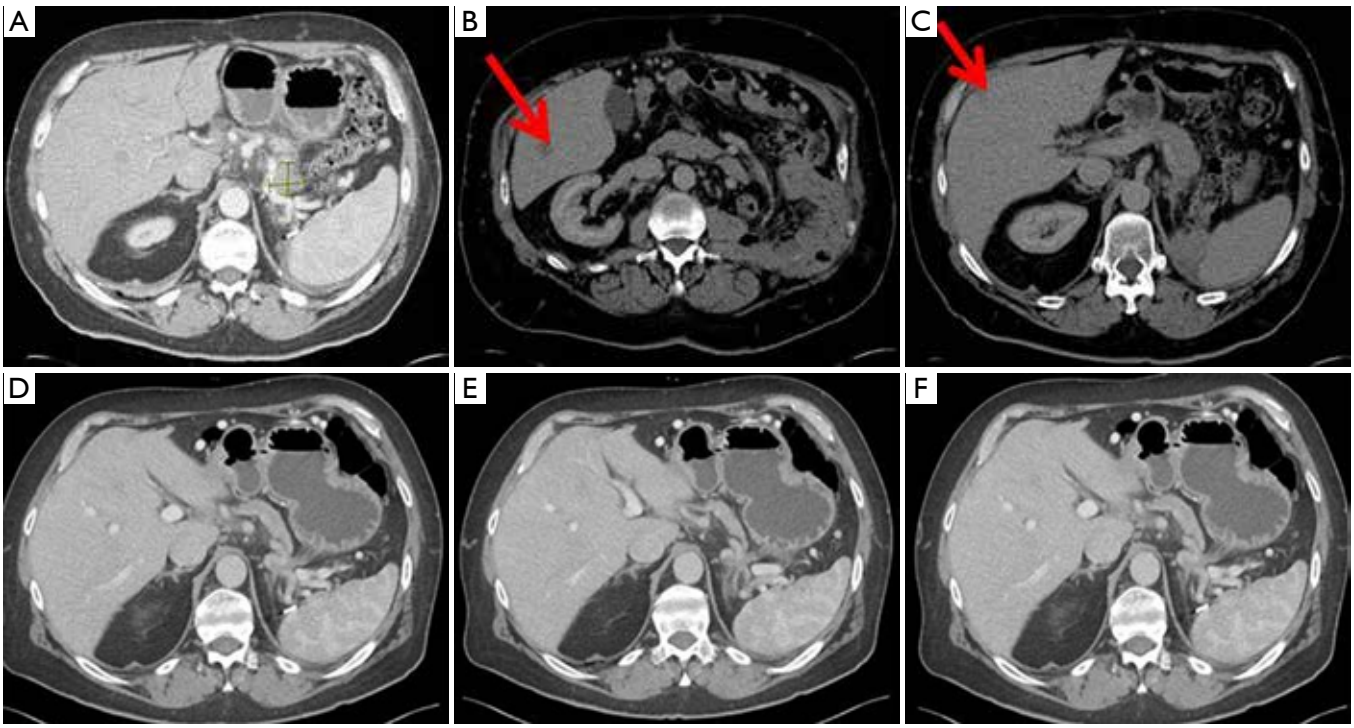

Figure 1 A 66-year-old man diagnosed with biopsy proven oligometastatic pancreas cancer in 2012. CT demonstrates (A) biopsy proven pancreas primary tumor; (B) biopsy proven liver metastasis; (C) 2nd liver metastasis. Patient was treated with gemcitabine and abraxane followed by 5-FU, leucovorin, oxaliplatin, and irinotecan. Twenty-four months after diagnosis, CT demonstrated significant radiologic response in (D) pancreas primary; (E) liver metastasis; and (F) 2nd liver metastasis. Surgical resection of pancreas and liver lesions demonstrated complete pathologic response in all three sites and patient currently has no evidence of disease 6 months post resection and 30 months after diagnosis. CT, computed tomography; 5-FU, 5-fluorouracil.

Table 1 Summary of recent studies of PC liver metastatic patients for pancreatectomy with hepatectomy

First author	Year	PC patient (n)	Hepatic resection	Morbidity (%)	Perioperative mortality (%)	1-year OS (%)	3-year OS (%)	5-year OS (%)	Median OS (months)
Klempnauer (65)	1996	20	S or M	N/A	4.3	41.0	N/A	N/A	8.3
Takada (66)	1997	11	S	N/A	N/A	N/A	N/A	N/A	6
Adam (67)	2006	40	S or M	N/A	N/A	N/A	N/A	25.0	20
Gleisner (68)	2007	17	S	45.5	9.1	N/A	6.7	0	5.9
Shrikhande (69)	2007	11	S	24.1	0	58.9	N/A	N/A	11.4
Singh (62)	2010	3	S	N/A	0	N/A	N/A	N/A	N/A
de Jong (63)	2010	20	S or M	N/A	1.0	N/A	8.0	N/A	13
Seelig (70)	2010	14	S	45.0	0	43.0	17.0	N/A	11
Klein (64)	2012	22	S	18.0	0	N/A	5.0	0	7.6

PC, pancreatic cancer; OS, overall survival; S, synchronous hepatectomy with pancreatectomy; M, metachronous hepatectomy with pancreatectomy; N/A, not applicable.

or radiofrequency ablation (RFA)] for periampullary liver metastases. Among the 40 patients in the study, 20 patients had a tumor that originated in the pancreas, only four of which underwent neoadjuvant chemotherapy. Additionally, 27 of the 40 patients presented with synchronous metastatic disease while the other 13 had metachronous metastatic disease, although metastatic disease at presentation did not affect median survival (synchronous *vs.* metachronous, 16 *vs.* 19 months; P=0.55). Surgery consisted of resection only (n=31; 78%), RFA only (n=8; 20%) or resection plus RFA (n=1; 2%). In the 32 patients, the extent of hepatic resection was a wedge resection (n=22; 69%), segmentectomy (n=6; 25%), and hemihepatectomy (n=4, 10%). The median survival of patients with a pancreaticobiliary tumor was 13 months with overall 3-year survival of 8%. Klein *et al.* (64) reported an overall median survival in PDAC patients with hepatic metastases of 228 days (±298.0) after resection, with a two-year survival of 5% (one patient). This included 22 PDAC patients who underwent synchronous, liver-directed therapy either with liver segmentectomy (7 patients, 32%) or enucleation of the hepatic metastases (15 patients, 68%). No patient achieved five-year survival after hepatic resection. All patients received adjuvant therapy with gemcitabine, but it is unclear which patients may have also received neoadjuvant chemotherapy. Gleisner *et al.* (68) reported that the median OS of periampullary or PDAC patients who underwent hepatic resection of synchronous metastasis was not different from the OS of matched patients who underwent palliative bypass (5.9 *vs.* 5.6 months; P=0.46). This study included 17 (77.3%) PDAC patients and the majority of patients (86.4%) had a solitary hepatic metastasis, with a median size of 0.6 cm. Hepatic resection included a wedge resection in 20 patients (90%), a segmentectomy in one patient (4.5%), and a hemi-hepatectomy in one patient (4.5%). Only six of the PDAC patients received adjuvant chemotherapy. Finally, Takada *et al.* (66) noted no improvement in OS in addition to higher surgical morbidity and mortality in patients undergoing pancreatoduodenectomy with synchronous partial liver resection.

Alternatively, several publications have demonstrated improved long-term survival after the successful resection of a pancreatic lesion and hepatic metastases (64,71-73). Adam *et al.* (67) reported 5-year survival rates upwards of 25% and a median survival of 20 months for patients who underwent hepatic resection of metastatic lesions from pancreatic primary tumors. The subset of patients with PDAC had a 5-year survival of 20%, which is comparable to patients with resectable PDAC without metastases. Klempnauer *et al.* (65) reported a median survival of 8.3 months after synchronous liver and pancreatic resection and 5.8 months after metachronous hepatic resection. One-year survival rates were 41% after synchronous resection and 40% after metachronous resection of hepatic metastases of pancreatic (n=20) or ampullary (n=2) carcinomas. Shrikhande *et al.* (69) suggested that pancreatic resections with simultaneous liver resection for metastatic disease can be performed with acceptable safety in highly selected patients. Of the 11 PDAC patients with liver metastasis, those who underwent pancreatectomy with synchronous hepatectomy had significantly longer median survival than the patients who underwent exploratory laparotomy without any resection (11.4 *vs.* 5.9 months, P=0.038). Of note, the patients included in this study were considered to be in good overall health with an ASA grade of III or better, had only one or two isolated liver metastases, and a high probability of an R0 resection. Only one patient in the study received neoadjuvant therapy, while the majority received adjuvant chemotherapy. Given the strict inclusion criteria, the authors suggested that resection of liver metastases in PDAC patients, although safe in this series, cannot be generally recommended until further controlled trials are conducted.

Although the studies on the surgical management of PDAC liver metastasis were all single institution retrospective a study involving a small number of patients without well-defined indications for resection, the data suggests that hepatic resection is safe and may be appropriate for highly selected PDAC patients. Survival data at this time is mixed and a prospective study is needed to determine the exact benefit, if any, the resection of hepatic metastasis will have on OS. Furthermore, the use of neoadjuvant and adjuvant CRT should be standardized in these patients to prolong survival and avoid confounding results. At this time, resection of PDAC liver metastases should only be considered in patients who are in overall good general health without significant comorbidities. It should be recommended that patients undergo neoadjuvant chemotherapy with an assessment by imaging for stability or decrease in the size and number of metastases prior to hepatic resection. In order to preserve vascular inflow and outflow as well as biliary drainage and preserve an adequate future liver remnant (45), wedge resection, segmentectomy or hemihepatectomy may be considered for these selected patients. Until it is determined which patient population will achieve the greatest benefits with metastastectomy,

pancreatic resection with hepatectomy should be cautiously considered only in selected PDAC patients with limited liver metastases in whom surgery is considered.

Ablation techniques for PDAC liver metastasis

Ablation techniques have become widely used in the treatment of hepatic metastases, including RFA, microwave, laser, cryoablation, and irreversible electroporation. Ablation can be performed using an open, laparoscopic, or percutaneous image-guided approach. Within the past several decades, numerous publications on ablation therapy techniques for liver metastases have demonstrated the effectiveness and safety of this therapy (74-79). These techniques are currently used to treat colorectal cancer liver metastasis in selected patients (33,80-84), and have been proposed as an alternative to hepatectomy in patients with limited hepatic involvement or with solitary liver metastasis (79,83,84). Simo *et al*. (79) reported that laparoscopic RFA of resectable colorectal liver metastases is associated with low perioperative morbidity and mortality with comparable long-term survival to hepatic resection in carefully selected patients. This was especially true in patients where the hepatic metastases were smaller than 3 cm and no tumors were within 1 cm of central biliary structures.

RFA has also been shown to be beneficial in the treatment of liver metastases from pancreatic neuroendocrine tumors, especially to control symptoms and optimize quality of life (85,86). However, there are differing opinions about the utility of RFA for unresectable PDAC. Girelli *et al.* (87) reported that RFA of a locally advanced PC is feasible and relatively well tolerated. Moreover, RFA in parallel to palliative therapy may provide a survival benefit, especially for stage III patients with unresectable PDAC (88). Alternatively, Pezzilli *et al.* (89) concluded that although RFA is a feasible technique, its safety and long-term results are disappointing for unresectable PDAC. Few studies have specifically analyzed the outcomes of ablation techniques for PDAC liver metastasis. Therefore, further research is needed to determine the benefit of ablation techniques as therapeutic options for the isolated liver metastases in PDAC patients.

Pulmonary metastasis of pancreatic cancer (PC)

The lung is another common site for distant metastasis in PDAC patients (6,8). Most notably, recurrence to the lung after initial primary tumor resection is associated with the most long-term survivors of at least 5 years for any patient with metastatic PDAC (24). Although pulmonary metastasectomy (PM) has been shown to provide a survival benefit for colorectal cancer patients with lung metastases (90-94), an evaluation of PM for PDAC is limited. At our institution, a retrospective study of PM for isolated PC metastases by Arnaoutakis *et al*. (95) reported that PM for isolated PDAC lung metastases is safe and effective. Compared to the non-PM patients, the median OS of PM patients was significantly improved (52 *vs*. 22 months, P=0.04). Additionally, there was a trend in favor of PM for post-relapse survival. Patients undergoing PM had a median survival after relapse of 18.6 months, compared with only 7.5 months for non-PM patients. It is important to note that the patients in this study were highly selected and had a good biologic tumor character identified by a favorable response to systemic therapy. In addition, patients undergoing PM had a relatively long interval between initial pancreatectomy and pulmonary relapses. No studies to date have been published with regards to simultaneous PM and pancreatic resection, and further analysis of treatment in patients with synchronous lung metastases is needed for PDAC.

The successful outcomes of patients undergoing PM after pancreatectomy indicate that the complete resection of the primary tumor and lung metastases is possible with favorable outcomes. PM should be performed for isolated lung metastases after resection for PDAC in patients with an acceptable performance status with tumors exhibiting a favorable response to systemic therapy. Furthermore, RFA can be considered for the treatment of PDAC pulmonary metastases in patients that have contraindications for surgery, although further analysis is needed (74).

Conclusions

Recent improvements in operative management of PDAC have reduced perioperative morbidity and mortality in patients undergoing pancreatectomy, and subsequently have led to increased 5-year survival. While the majority of PDAC patients will present with metastatic disease and will not be operative candidates, in certain situations, metastasectomy may be beneficial and warrants further investigation. However, resection of metastatic pancreas cancer should be approached with extreme caution, knowing that the data is extremely limited. As systemic therapy for PDAC improves, appropriate selection of patients may lead to more aggressive surgical approaches, similar

to the current paradigm for metastatic colorectal cancer. In current practice, metastasectomy for solitary hepatic or pulmonary metastases of PDAC should be considered only when (I) a negative surgical (R0) resection can be achieved by pancreatectomy; (II) the PDAC has responded to neoadjuvant systemic therapy; (III) the oligometastases are resectable; (IV) the patient is in overall good general health with limited comorbidities. When applied in these situations, surgery may be considered for these selected patients with the primary goal of improving long-term survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Current status and future direction of chemotherapy for pancreatic cancer

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Introduction

Pancreatic carcinoma is a disease with a dismal prognosis; the 5-year survival rate of patients diagnosed with this cancer remains less than 5% (1). Since it is difficult to diagnose pancreatic cancer at an early stage, 70-80% patients with pancreatic cancer have unresectable disease, including locally advanced or distant metastatic disease, at diagnosis. Pancreatic cancer is currently the fifth leading cause of cancer-related mortality in Japan, with an estimated 28,017 deaths occurring from the disease in 2010 (2).

Pancreatic cancer is clinically classified to three stages, namely, resectable, unresectable locally advanced, and metastatic, regarding treatment strategy. According to the TNM classification by the UICC, resectable disease corresponds mostly to Stage I and II and in some cases, to Stage III, unresectable locally advanced disease corresponds to Stage III, and metastatic disease corresponds to Stage IV. The treatment strategy differs by the clinical stage, and it is important to determine the clinical stage in each pancreatic cancer patient to select the most appropriate treatment method.

For more than 10 years, ever since a phase III study revealed survival benefit of gemcitabine as compared to fluorouracil therapy (3), gemcitabine has been widely used as the standard chemotherapy for unresectable pancreatic cancer. After gemcitabine chemotherapy became established as the standard therapy, many newer agents have been investigated for the treatment of unresectable pancreatic cancer, and some promising treatments have been developed. Furthermore, chemotherapy is also applied as adjuvant therapy after surgery and combined with radiotherapy for locally advanced disease.

Chemotherapy for unresectable pancreatic cancer

Gemcitabine has become established as the standard treatment for patients with unresectable pancreatic cancer, improving the patient survival as compared to fluorouracil (*Table 1*) (3). However, the anticancer activity of this drug is only modest; the reported response rate is around 10% and the median overall survival (OS) is 6 to 7 months in patients with unresectable pancreatic cancer treated with gemcitabine. Thus, the prognosis of these patients remains poor, and development of more effective treatments for pancreatic cancer is urgently needed.

S-1. which consists of tegafur, gimeracil and oteracil potassium, has been developed for pancreatic cancer in Japan. Tegafur is a prodrug of fluorouracil, and gimeracil is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for the degradation of fluorouracil, which allows efficacious concentrations of fluorouracil to be maintained in the plasma and tumor tissues. Oteracil potassium, a competitive inhibitor of orotate phosphoribosyltransferase (OPRT), inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, and reduces the serious gastrointestinal toxicity of fluorouracil. A phase II study of S-1 demonstrated promising activity against pancreatic cancer; the response rate was 37.5%, median time to progression (TTP) was 3.7 months, median OS was 9.2 months (7). Furthermore, it was expected that S-1 administered combined with gemcitabine (GS therapy) might be more effective, and several phase II studies of GS therapy have been conducted. In a reported multi-institutional study of GS therapy, the response rate was 44%, the median progression-free survival (PFS) was 5.9 months, and the median OS was

Table 1 Randomized clinical trials for unresectable pancreatic cancer which demonstrated statistically significantly positive results

Regimen	n	Response	Median OS (months)	%1-year survival	hazard ratio (95%CI)	P-value	Author [Year]
Fluorouracil	63	0	4.41	2.0%	-	0.0025	Burris HA III *et al.* [1997] (3)
Gemcitabine	63	5.4%	5.65	18.0%	-		
Gemcitabine	284	6.9%	5.9	17.0%	-	0.038	Moore MJ *et al.* [2005] (4)
Gemcitabine/erlotinib	285	8.2%	6.2	23.0%	0.82 (0.69-0.99)		
Gemcitabine	277	13.3%	8.8	35.4%	-	-	Ioka T *et al.* [2011] (5)
S-1	280	21.0%	9.7	38.7%	0.96 (0.78-1.18)	<0.001*	
Gemcitabine/S-1	275	29.3%	10.1	40.7%	0.88 (0.71-1.08)	0.15	
Gemcitabine	171	9.4%	6.8	20.6%	0.57 (0.45-0.73)	<0.001	Conroy T *et al.* [2011] (6)
FOLFIRINOX	171	31.6%	11.1	48.4%			

*, non-inferiority; OS, overall survival; %1-year survival, one-year survival rate

10.1 months (8).

Thus, S-1 or GS therapy was expected to replace gemcitabine as the standard therapy for unresectable pancreatic cancer, and a phase III study was conducted comparing S-1 or GS therapy with gemcitabine alone (5). The primary endpoint was OS, and the superiority of GS therapy and the non-inferiority of S-1 were examined. It was expected that the median OS would be 7.5 months in the gemcitabine group, 8.0 months in the S-1 group, and 10.5 months in the GS group. The subjects were chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer. Patients were randomly assigned to receive only gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle), only S-1 (80/100/120 mg/day according to body surface area on days 1 to 28 of a 42-day cycle), or gemcitabine plus S-1 (gemcitabine 1,000 mg/m^2 on days 1 and 8 plus S-1 60/80/100 mg/day on days 1 to 14 of a 21-day cycle). In the total of 834 enrolled patients, median OS was 8.8 months in the gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the GS group. The non-inferiority of S-1 to gemcitabine was demonstrated [hazard ratio, 0.96; 97.5% confidence interval (CI), 0.78 to 1.18; P<0.001 for non-inferiority], while the superiority of gemcitabine plus S-1 was not proven (hazard ratio, 0.88; 97.5% CI, 0.71 to 1.08; P=0.15) (*Table 1*) (5). Both treatments were generally well-tolerated, although hematologic and gastrointestinal toxicities were more severe in the GS group than in the gemcitabine group. As a result, at present S-1 monotherapy is accepted as an alternative treatment option for unresectable pancreatic cancer in Japan.

Although many gemcitabine-based combination regimens have been evaluated, a statistically significant survival benefit as compared to gemcitabine alone was obtained only for erlotinib combined with gemcitabine in a phase III study (the PA. 3 study) (4). Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor and is used in the treatment of various types of solid tumors, especially lung cancer. In the PA.3 study, erlotinib plus gemcitabine therapy reduced the risk of death by 18% as compared to treatment with gemcitabine alone (hazard ratio 0.82; 95% CI, 0.69-0.99; P=0.038), with a median OS of 6.24 versus 5.91 months, respectively (*Table 1*) (4). As a result, combination therapy with gemcitabine plus erlotinib came to be recognized as one of the standard treatments for unresectable pancreatic cancer. In Japan, a phase II study was conducted to examine the feasibility and efficacy of gemcitabine plus erlotinib therapy in Japanese patients, and 107 patients were enrolled (9). The most common adverse events were skin rash, including acneiform dermatitis and anorexia. While interstitial lung disease-like events were of grave concern and were reported in nine patients (8.5%), all of the patients recovered or improved. The median OS and median PFS were 9.23 and 3.48 months, respectively. In Japanese patients with unresectable pancreatic cancer, erlotinib plus gemcitabine therapy showed acceptable toxicity and promising efficacy that were not inferior to the results reported from western patients.

As a chemotherapeutic regimen not including gemcitabine, FOLFIRINOX, consisting of oxaliplatin, irinotecan, fluorouracil and leucovorin, was investigated for advanced pancreatic cancer in France. A phase III study comparing FOLFIRINOX with gemcitabine demonstrated significant survival benefit of FOLFIRINOX as compared to gemcitabine in patients with metastatic pancreatic cancer (*Table 1*) (6). FOLFIRINOX was associated with a higher incidence of toxicity; in particular, febrile neutropenia was observed in 5.4% patients in the FOLFIRINOX group and 1.2%

Table 2 Recent clinical trials of chemotherapy or chemoradiotherapy for locally advanced pancreatic cancer

Radiotherapy	Chemotherapy	n	Median OS (month)	Author [year]
-	Gemcitabine	50	15	Ishii H *et al.* [2010] (14)
60 Gy	Fluorouracil/cisplatin	59	8.6	Chauffert B *et al.* [2008] (15)
-	Gemcitabine	60	13	
50.4 Gy	Gemcitabine	34	11.1	Loehrer Sr PJ *et al.* [2011] (16)
-	Gemcitabine	37	9.2	
50.4 Gy	S-1	61	16.2	Ikeda M *et al.* [2012] (17)

OS, overall survival; % 1-year survival, one-year survival rate

patients in the gemcitabine group. Based on these results, FOLFIRINOX is considered as a first-line option for metastatic pancreatic cancer as a standard care, however, appropriate selection of candidates is necessary, such as patients with a good performance status, of younger age and having no risk of cholangitis. In Japan, a small phase II study of FOLFIRINOX is currently under investigation to examine the feasibility in Japanese patients, because irinotecan is used 180 mg/m^2 in this regimen, whereas only use at 150 mg/m^2 or less is approved for various types of cancers in Japan.

A another promising new chemotherapy regimen is a combination of gemcitabine plus *nab*-paclitaxel. This combination yielded promising results in a phase I/II study; the response rate was 48% and the median OS was 12.2 months in patients with metastatic pancreatic cancer (10). This study also suggested that Stromal Secreted Protein Acidic and Rich in Cysteine (SPARC) expression may be an important marker of early activity of gemcitabine plus *nab*-paclitaxel in patients with advanced pancreatic cancer. A phase III study comparing gemcitabine plus *nab*-paclitaxel with gemcitabine alone is currently under investigation in the USA.

Treatment strategy for unresectable locally advanced pancreatic cancer

Randomized controlled trials (RCTs) conducted by Moertel *et al.* and the Gastrointestinal Tumor Study Group (GITSG) have shown the survival benefit of chemoradiotherapy with fluorouracil as compared to radiation alone in patients with locally advanced pancreatic cancer (11,12). Chemoradiotherapy with concurrent external-beam radiotherapy (EBRT) and systemic fluorouracil chemotherapy has become a standard treatment. Various intensive radiotherapy and/or chemotherapy schedules have been investigated in clinical trials in efforts to improve the efficacy and increase the survival rates. According to the EBM-based clinical guidelines for pancreatic cancer published by the Japan Pancreas Society, chemoradiotherapy is effective for locally advanced disease and is recommended as one of the treatment options (13).

On the other hand, since gemcitabine has been applied to unresectable pancreatic cancer including locally advanced disease, the efficacy of gemcitabine in respect of survival has been reported to be comparable to that of chemoradiotherapy. In the guidelines for pancreatic cancer published by the Japan Pancreas Society, chemotherapy with gemcitabine alone is also recommended as a treatment option for patients with unresectable locally advanced pancreatic cancer (13). We first conducted a phase II study of gemcitabine alone to examine its efficacy and safety in patients with locally advanced disease of the JCOG 0506 study (14). This study was conducted to be foreseeing a phase III trial comparing gemcitabine monotherapy with chemoradiotherapy, to establish the most promising treatment for locally advanced pancreatic cancer. The primary endpoint of this study was the 1-year survival rate. Fifty patients were enrolled from January 2006 to February 2007, and the results revealed a median OS of 15.0 months and 1-year survival rate of 64.0% (*Table 2*) (14), which significantly exceeded expectations. The toxicities were generally mild and the drug was well-tolerated. Furthermore, a RCT of gemcitabine *vs.* conventional chemoradiotherapy with fluorouracil plus cisplatin failed to show any survival benefit of chemoradiotherapy (*Table 2*) (15). Based on these results, gemcitabine monotherapy has come to be regarded as the provisional standard therapy.

A clinical trial conducted in the USA comparing gemcitabine plus radiotherapy *vs.* gemcitabine alone in patients with locally advanced pancreatic cancer reported that the OS was superior in the combined treatment group as compared to the gemcitabine alone group (*Table 2*) (16). Furthermore, chemoradiotherapy using S-1 exhibited promising efficacy in a phase II study conducted in Japan; the median OS was 16.2 months (17). There is a possibility

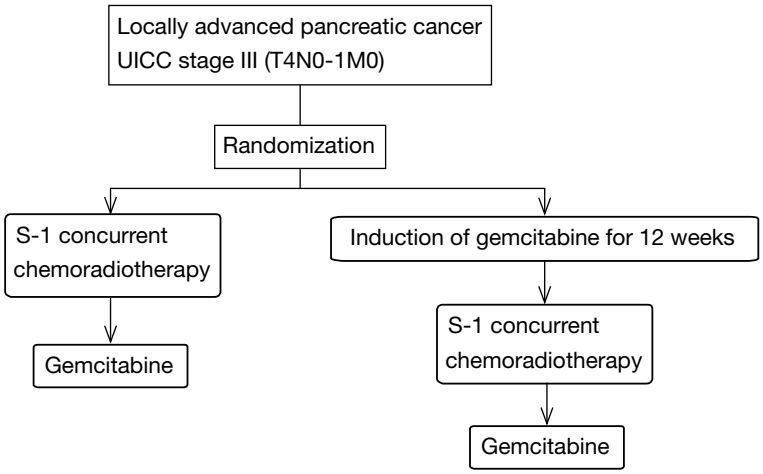

Figure 1 Study design of the JCOG 1106 study, which is a randomized phase II study comparing induction chemotherapy with gemcitabine followed by S-1 chemoradiotherapy with S-1 chemoradiotherapy without prior induction chemotherapy (18). Gemcitabine, 1,000 mg/m^2 d1, 8, 15, repeated every 4 weeks; S-1, 80 mg/m^2/day on the day of irradiation.

that new methods of chemoradiotherapy might improve the survival, especially prolonged survival of more than 2 years. Thus, in order to develop more promising new chemoradiotherapies, we conducted a randomized phase II study of two chemoradiotherapeutic methods; one consisting of S-1 chemoradiotherapy and maintenance therapy with gemcitabine, and the other consisting of induction gemcitabine chemotherapy for 3 months followed by S-1 chemoradiotherapy and maintenance therapy with gemcitabine (JCOG1106) (18).

The JCOG1106 study is a multi-institutional open-label randomized phase II study to evaluate the efficacy of induction chemotherapy of gemcitabine in combination with S-1 chemoradiotherapy and select a candidate in phase III study comparing with gemcitabine alone (*Figure 1*) (18). The primary endpoint is OS, and we shall select the treatment method providing the better survival between the two for use in a subsequent phase III study. The one-year survival rate of the two treatments would be expected to be more than 60% at least, because that of patients administered gemcitabine monotherapy in the JCOG 0506 study was 64%. The sample size is 100 patients and this study is currently under investigation.

Adjuvant therapy after surgery

Several RCTs have been conducted to assess the efficacy of postoperative adjuvant chemotherapy. The ESPAC-01 study demonstrated the survival advantage of fluorouracil-based adjuvant chemotherapy (19). Adjuvant therapy with gemcitabine produced significant prolongation of the disease-free survival (DFS); in the CONKO-01 study, the median DFS was 13.4 months in the gemcitabine group and 6.9 months in the surgery alone group (P<0.001) (20). The survival advantage of adjuvant gemcitabine therapy was also demonstrated by the final results of this study (*Table 3*) (24). Furthermore, the ESPAC-03 study was conducted to examine the efficacy and safety of gemcitabine as adjuvant chemotherapy as compared to fluorouracil plus folinic acid. The study revealed no difference in the survival between the two treatments, and gemcitabine was found to be less toxic than fluorouracil plus folinic acid (26). Thus, gemcitabine was established as a postoperative adjuvant chemotherapy in patients with resectable pancreatic cancer.

In Japan, although RCTs of fluorouracil plus mitomycin C and fluorouracil plus cisplatin have been conducted, neither of these regimens showed any survival benefit (22,23). Subsequently, a RCT of the efficacy/toxicity of adjuvant chemotherapy using gemcitabine was conducted (25). Although the number of patients was smaller, the results were similar to those of the CONKO-01 and ESPAC-03 studies (*Table 3*). Based on these results, gemcitabine treatment also came to be recommended as postoperative adjuvant chemotherapy in Japan (13). Two large RCTs of adjuvant chemotherapy with gemcitabine are currently in progress. One is a non-inferiority study comparing S-1 with gemcitabine (the JASPAC-01 study), and the other is a superiority study comparing gemcitabine plus S-1 with

Table 3 Postoperative adjuvant chemotherapy for pancreatic cancer

Arm	N	Median OS (months)	5-year survival	P-value	Author [year]
Observation	31	11	8%	0.02	Bakkevold KE *et al.* [1993] (21)
Doxorubicin/fluorouracil/mitomycin C	30	24	4%		
Observation	77	13	18.0%	NS	Takada T *et al.* [2002] (22)
Fluorouracil/mitomycin C	81	13	11.5%		
No chemoradiation	144	17.9	20%	0.05	Neoptolemos JP *et al.* [2004] (19)
Chemoradiation	145	15.9	10%		
No chemotherapy	142	15.5	8%	0.009	
Chemotherapy	147	20.1	21%		
Observation	44	15.8	14.9%	0.94	Kosuge T *et al.* [2006] (23)
Fluorouracil/cisplatin	45	12.5	26.4%		
Observation	175	20.2	9%	0.005	Neuhaus P *et al.* [2008] (24)
Gemcitabine	179	22.8	21%		
Observation	60	18.4	10.6%	0.19	Ueno H *et al.* [2009] (25)
Gemcitabine	58	22.3	23.9%		
Fluorouracil/folinic acid	551	23.0	-	0.39	Neoptolemos JP *et al.* [2009] (26)
Gemcitabine	537	23.6	-		

OS, overall survival; 5-year survival, 5-year survival rate

gemcitabine alone (the JSAP-04). Recently, the news of an interim analysis that the JASPAC-01 study demonstrated the non-inferiority of S-1 has been released.

Future direction

In pancreatic cancer, major advances have been made in relation to the establishment of standard treatments in recent years. However, the survival of patients with pancreatic cancer still remains dismal. Although administration of many molecular-targeted agents in combination with gemcitabine have been investigated, none of the agents, except erlotinib, showed efficacy. In order to develop more molecular-targeted agents, it is important to find unique biomarkers or driver mutations for carcinogenesis or progression of pancreatic cancer.

Various intensive regimens such as FOLFIRINOX and gemcitabine plus *nab*-paclitaxel have been developed. New molecular-targeted agents are also expected to be introduced for pancreatic cancer. It would be important to identify patients that would benefit from these regimens based on clinical information about the patient and biomarkers from the point of view of establishment of an individualized treatment strategies.

In recent years, many clinical trials have investigated new chemotherapy regimens for patients with metastatic pancreatic cancer as distinct from patients with locally advanced disease, because of the differences in the characteristics and prognosis of patients with metastatic and locally advanced disease. A new chemotherapeutic regimen can be accurately evaluated only in patients with metastatic disease. On the other hand, in patients with locally advanced disease, intensive chemotherapy or chemoradiotherapy may be useful for down-staging the tumor and make the patient suitable for surgical resection.

Although currently, surgery remains the only potentially curative treatment for pancreatic cancer, most patients develop recurrence. Survival benefit of adjuvant chemotherapy was demonstrated, however, the prognosis of patients with advanced disease stages such as stage II and III is still poor. The efficacy of neoadjuvant therapy has been examined for these patients (27-30). Various neoadjuvant therapies have recently been investigated, and RCTs are needed to confirm the efficacy and safety of neoadjuvant therapy.

Since a large number of patients is required to confirm the survival benefit in RCTs, it is difficult to conduct these trials in a single country. Many clinical trials using new agents are conducted as global studies or Asian studies including Japan. Global cooperation in multinational trials is essential to achieve the goal.

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Role of gemcitabine as second-line therapy after progression on FOLFIRINOX in advanced pancreatic cancer: a retrospective analysis

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Background: Cancer of the exocrine pancreas is a highly lethal malignancy. Surgical resection is the only potentially curative treatment. Unfortunately, because of the late presentation, the majority have either locally advanced cancer at initial diagnosis. Systemic chemotherapy provides benefit to patients with advanced pancreatic cancer, improving disease-related symptoms and survival when compared to best supportive care alone. Based on fase III study, FOLFIRINOX regimen became the standard first-line treatment. But, the optimal management strategy for patients who fail initial FOLFIRINOX is undefined. Despite the lack of clinical trials that report the real benefit of gemcitabine in patients with advanced exocrine pancreatic cancer as second line treatment. We aim at reporting our experience with this regimen.

Methods: Patients with advanced exocrine pancreatic cancer who received gemcitabine (1.000 mg/m^2 on days 1, 8 and 15 every 4 weeks) until disease progression, as second-line therapy at our institution were retrospectively evaluated. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method.

Results: A total of 20 patients were reviewed. Median age was 57 years (range, 43-74 years), and 55% were older than 60 years. Most patients were male (80%), had metastatic disease (60%), and ECOG performance status of 0 or 1 (65%). PFS and OS were 2.0 (95% CI, 1.2-2.8) and 5.7 months (95% CI, 3.9-7.4), respectively. There were no deaths due to the treatment.

Conclusions: In this study, gemcitabine was a reasonable second-line treatment option for patients with advanced pancreatic adenocarcinoma and good ECOG performance status. Phase III trials are urgently needed comparing gemcitabine versus best supportive of care (BSC) can evaluate the real benefit of this chemotherapy after progression on FOLFIRINOX.

Keywords: Pancreatic adenocarcinoma; gemcitabine; second-line; retrospective analysis

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Introduction

Pancreatic adenocarcinoma is a highly lethal cancer, being responsible for about 266,000 deaths per year worldwide. It represents the eighth cancer-related death in men and the ninth in women (1,2). Surgery is the only potentially curative treatment. However, due to the delayed diagnosis of pancreatic cancer, surgery is feasible in only 15% to 20% of patients and, even after resection, the prognosis is very poor.

Systemic chemotherapy offers benefit for advanced pancreatic cancer, improving symptoms and overall survival (OS) when compared to best supportive of care (BSC) (3).

Until recently, first-line therapy was gemcitabine-based chemotherapy, with a median OS of 5 to 6 months (3). Based on the phase III PRODIGE 4 trial, which compared FOLFIRINOX (a combination of 5-fluorouracil, oxaliplatin and irinotecan) to gemcitabine as first-line therapy in 342 patients with metastatic disease, FOLFIRINOX showed higher progression-free survival (PFS) and OS. Therefore, FOLFIRINOX became the standard first-line therapy in patients with good performance status (4).

Although recent advances have improved outcomes in the first-line therapy of metastatic pancreatic cancer, all patients will eventually develop disease progression. Treatment options in subsequent lines are limited and there is no standard of care in this setting. Despite the lack of clinical trials reporting the benefit after first-line therapy, gemcitabine-based chemotherapy has been routinely used as second-line therapy in most centers for patients who fail FOLFIRINOX. Based on the growing need to understand the real benefit of gemcitabine as second-line therapy in patients previously treated with FOLFIRINOX, we aim at showing our retrospective experience with gemcitabine as second-line therapy after progression on FOLFIRINOX.

Methods

Patients

Patients diagnosed with advanced pancreatic adenocarcinoma treated with gemcitabine as second-line therapy after progression on first-line FOLFIRINOX at São José Hospital (Beneficência Portuguesa de São Paulo, Brazil) from January 2011 to July 2014 were eligible for analysis. Patients who received at least one cycle of gemcitabine were included. Medical records were retrospectively reviewed after approval by the hospital Research and Ethics Committee.

Eligibility criteria for this retrospective review included histologic diagnosis of metastatic pancreatic adenocarcinoma, progression of disease on FOLFIRINOX as first-line therapy and use of at least once cycle of gemcitabine as second line therapy. Data collection was concluded in September 2014. Gemcitabine-related side effects were not evaluated in this study.

Treatment

Gemcitabine was administered intravenously (IV) at a dose of 1,000 mg/m^2 on days 1, 8 and 15 every 4 weeks until disease progression. Imaging evaluation was performed with computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography scan (CT/PET scan), at the discretion of the attending physician. Imaging tests were analyzed by radiologists at our institution according to response evaluation criteria in solid tumors.

Statistical analysis

Demographic and clinical characteristics were summarized by medians and frequencies, as appropriate. The primary end-point was PFS, defined as the time interval between gemcitabine beginning and time of disease progression based on imaging studies or death, whichever occurred first. OS was defined as the time interval between gemcitabine beginning and time of death or last follow-up. PFS and OS were estimated by Kaplan-Meier method. SPSS for Windows version 22.0 was used for data analysis (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

Thirty-five patients were initially eligible for this study. Twenty out of those 35 patients received at least one complete cycle of gemcitabine and qualified for the study. Patients' characteristics are listed in *Table 1*. Median age was 57 years (range, 43-74 years), and 55% were older than 60 years. Most patients were male (80%), had metastatic disease (60%), and ECOG performance status of 0 or 1 (65%). All patients were treated with FOLFIRINOX as first-line therapy. Only three patients had received prior gemcitabine as adjuvant therapy after surgery.

Treatment

Median time on gemcitabine as second-line therapy was 8 weeks, ranging from 1 to 8 cycles. Posology and dose reductions due to toxicity occurred at each oncologist's discretion. Most patients (90%) received a dose of 1,000 mg/m^2, and 2 patients (10%) received 800 mg/m^2 on days 1, 8 and 15 every 4 weeks. All patients (100%) discontinued treatment due to either disease progression or death.

Efficacy

Median PFS and OS were 2.0 months (95% CI, 1.2-2.8)

Table 1 Patient characteristics

Patient characteristics	N (N=20)	%
Age (years)		
Median	57	
Range	43-74	
Sex		
Female	4	20
Male	16	80
Performance status		
ECOG 0	4	20
ECOG 1	9	45
ECOG 2	7	35
Received adjuvant gemcitabine		
Yes	3	15
No	17	85
Received surgery for localized disease		
Yes	6	30
No	14	70
At the beginning of folfirinox		
Locally advanced disease	8	40
Metastatic disease	12	60
Time in months that was treated with folfirinox, including rechallenge		
Median	24	
Variation	1-36	

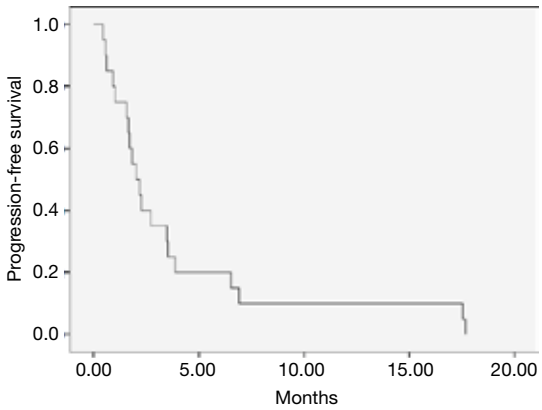

Figure 1 PFS in patients with advanced pancreatic cancer treated with gemcitabine as second-line therapy after progression on FOLFIRINOX. PFS, progression-free survival.

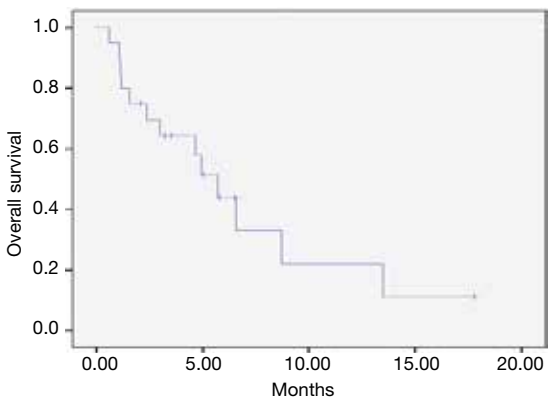

Figure 2 OS in patients with advanced pancreatic cancer treated with gemcitabine as second-line therapy after progression on FOLFIRINOX. OS, overall survival.

and 5.7 months (95% CI, 3.9-7.4), respectively (*Figures 1,2*). No treatment-related deaths were reported.

Discussion

Until recently, gemcitabine-based chemotherapy was the standard approach as first-line therapy in advanced pancreatic cancer. This was based on a phase III trial that enrolled 126 patients and randomly assigned them to gemcitabine (1.000 mg/m^2 IV weekly for 7 weeks followed by one week off, then weekly for 3 weeks every 4 weeks) or to 5-FU (600 mg/m^2 weekly). Gemcitabine showed a clinical benefit of 23.8%, as assessed by improvement in pain (measured by consumption of analgesics and pain intensity), Karnofsky performance status and weight, compared to only 4.8% in the 5-FU/leucovorin group (P=0.0022). Gemcitabine also showed a slight increase in OS (5.65 *vs.* 4.41 months, P=0.0025) (3).

There are currently two more aggressive regimens which could be considered for first line therapy in patients with advanced pancreatic carcinoma and good performance status based on pivotal phase III trials: FOLFIRINOX (4) and nab-paclitaxel/gemcitabine (5). As nab-paclitaxel is yet not approved in Brazil, FOLFIRINOX is our first line regimen for patients with good performance status. However, patients usually progress through development of resistance due to the presence of sub-populations of resistant cells or stromal changes related to inflammation in the cellular microenvironment (6). Therefore, there is a pressing need for more treatment options beyond first-line therapy.

As far as second line treatment for pancreatic cancer is concerned, OFF (oxaliplatin, 5-FU, leucovorin) is the only

regimen evaluated in a randomized trial against placebo in the second-line setting after progression on gemcitabine. The German CONKO trial, which closed prematurely due to low recruitment, randomized 46 patients to receive OFF or BSC, yielding better OS in the chemotherapy group (4.8 *vs.* 2.3 months; HR 0.45; 95% CI, 0.24-0.83; P=0.008). However, the first-line therapy in the CONKO trial consisted of gemcitabine, which was the only standard regimen at that time (7).

On the other hand, the Canadian multicentre trial PANCREOX did not demonstrate improved outcomes for the addition of oxaliplatin to 5-FU in second-line setting after gemcitabine failure. The study enrolled 108 patients who were previously treated with gemcitabine, and randomized them to receive either mFOLFOX6 (5-FU and oxaliplatin) or infusional 5-FU plus leucovorin. The combination of 5-FU and oxaliplatin did not show a significantly increase in PFS (3.1 *vs.* 2.9 months, respectively; HR 1.00; 95% CI, 0.66-1.53; P=0.99), and surprisingly resulted in decreased OS (6.1 *vs.* 9.9 months; HR 1.78; 95% CI, 1.08-2.93; P=0.02) and worse toxicity profile (8).

Recently, a systematic analysis evaluating the role of second-line therapy in advanced pancreatic cancer after progression on gemcitabine was reported. A total of 1,503 patients were included. Among patients treated with second-line chemotherapy (n=1,269), OS was 6 months compared to 2.8 months (P=0.013) in patients who received BSC (n=234). The gemcitabine and platinum-based therapy provided PFS and OS of 4 and 6 months compared with 1.6 and 5.3 months for other regimens, (P=0.059 and 0.10, respectively). The combination of 5-FU and platinum agents obtained a PFS of 2.9 months and an OS of 5.7 months (P=0.60 and 0.22, respectively) (9).

Given the proven benefits of gemcitabine as first-line therapy associated with the absence of a standard second-line regimen for patients who are refractory to FOLFIRINOX, gemcitabine has been consistently used in many services as second-line therapy, despite the lack of clinical trials proving the real benefit of gemcitabine in this setting. We report our experience with gemcitabine in patients who were previously treated with FOLFIRINOX and showed a median PFS of 2 months with a median OS of 5.7 months. Our results compare favorably with the OS data of gemcitabine in the first-line setting, suggesting that patients who progress on FOLFIRINOX may also benefit from second-line treatment.

Whether gemcitabine is the most effective second-line treatment for patients who progress on FOLFIRINOX remains uncertain. In the first-line setting, the combination of gemcitabine and nab-paclitaxel seems superior when compared to single-agent gemcitabine according to the MPACT trial. This study randomly assigned 861 patients with advanced pancreatic cancer to receive gemcitabine alone versus gemcitabine plus nanoparticle albumin-bound paclitaxel as first-line therapy. It showed a significantly increase in OS favoring the combination (5). This data suggests that combined therapy based on gemcitabine plus either a platinum agent or a taxane should be evaluated as second-line therapy in randomized trials.

Our study has important limitations. Its retrospective nature and the small number of patients are the major ones. Moreover, adverse events data could not be evaluated. Despite these limitations, our study is the first, to our knowledge, to report the use of gemcitabine as second-line therapy for patients previously treated with FOLFIRINOX as first line therapy. Besides, the reduced number of patients confirms that only few patients with advanced pancreatic cancer have clinical conditions and performance status to qualify for second-line treatment instead of BSC. Despite these limitations, our study is the first, to our knowledge, to report the use of gemcitabine as second-line therapy for patients previously treated with FOLFIRINOX, the current standard first-line treatment in patients with metastatic pancreatic cancer and good performance status.

Conclusions

Our small retrospective study suggests that gemcitabine is a reasonable treatment option as second-line therapy in patients with advanced pancreatic cancer who progress on FOLFIRINOX. Nonetheless, only a phase III clinical trials comparing gemcitabine versus BSC can evaluate the real benefit of this chemotherapy after progression on FOLFIRINOX.

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Intraperitoneal gemcitabine chemotherapy as an adjuvant treatment for patients with resected pancreatic cancer: phase II and pharmacologic studies

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Background: Currently, the surgical management of pancreas cancer is recognized around the world as inadequate. Despite a potentially curative R0 resection long-term survival is rare. There is a strong rationale for the use of intraperitoneal chemotherapy in the operating room and long term to reduce local-regional progressive disease.

Methods: Gemcitabine monotherapy was administered by an intraperitoneal route in the operating room with hyperthermia. Then, through an intraperitoneal port placed at the time of pancreatectomy a long-term treatment postoperatively was performed. The peritoneal fluid, plasma and urine concentrations of gemcitabine were measured by high pressure liquid chromatography.

Results: The adverse events associated with hyperthermic intraoperative gemcitabine and long-term intraperitoneal gemcitabine through an intraperitoneal port was well tolerated. Pharmacologic studies showed that the exposure of peritoneal surfaces to intraperitoneal gemcitabine is approximately 200-500 times the exposure that occurs within the plasma.

Conclusions: This standardized treatment with intraoperative and long-term gemcitabine chemotherapy was well tolerated. The pharmacologic studies showed marked local-regional chemotherapy concentrations. These results may facilitate further improvements in pancreas cancer treatment and may lead the way to an evolution of more successful treatment strategies of this dread disease. These early phase II and pharmacologic data on a protocol in progress in patients with resected pancreatic cancer show promising results.

Keywords Chemotherapy; mortality; morbidity; randomized trials; pancreatic cancer; chemoradiation; European Organization for Research and Treatment of Cancer (EORTC)

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Introduction

Cancer with the primary site in the pancreas is the fourth leading cause of cancer related deaths in the United States with an estimate of 37,660 deaths in 2011 (1). Surgery represents the only potentially curative treatment option and complete tumor resection is associated with better disease-free and overall patient survival. Advances in surgical technique, anesthesia and perioperative care in the last two decades have led to a marked decrease in perioperative mortality and morbidity especially in large volume centers. Unfortunately, only 10-20% of patients at the time of diagnosis with pancreatic cancer can be offered potentially curative surgery (2). Furthermore, long-term 5-year survival is rare, even after potentially curative R-0 resection. Recently, Cleary reported 18 of 123 (15%) 5-year survival; 4 of these 18 patients died of disease after 5 years (3). In a failure analysis after curative resection, disease recurrence

was documented in the local and regional area (50%), on peritoneal surfaces (40-60%) and within the liver as hepatic metastases (50-60%) (4).

Rationale for intraoperative and long-term intraperitoneal gemcitabine

The mechanisms of failure after an R-0 resection by pancreatico-duodenectomy are unclear. One possible explanation for the large number of local and regional failures is surgically induced tumor dissemination and then implantation within the resection site during surgery as a result of the trauma of resection. Conceptually, this forms the basis for administration of perioperative and long-term intraperitoneal chemotherapy. Also, pancreas cancer cells circulating in the bloodstream may enter the peritoneal space and implant on the surfaces that are created by the pancreatectomy. The major advantage of intraperitoneal chemotherapy is the high drug level that can be achieved locally with low systemic exposure (5). A systematic review of randomized control trials has established the role of adjuvant perioperative intraperitoneal chemotherapy in high risk gastric cancer patients after potentially curative resection (6). Also, long-term intraperitoneal chemotherapy has established efficacy in ovarian cancer (7-9). Success of systemic chemotherapy in controlling local disease has a weaker rationale and has never been confirmed in randomized trials. The pharmacokinetics of gemcitabine makes it an excellent drug for intraperitoneal use. With evidence mounting for use of intraperitoneal chemotherapy after resection in ovarian and gastric cancer, a rationale for the use of intraperitoneal chemotherapy after curative resection in pancreatic cancer should be explored with a formal protocol.

Phase II study of adjuvant intraperitoneal gemcitabine for resectable pancreatic adenocarcinoma: methods and early results

In an Institutional Review Board-approved protocol (MHRI-GU-2009-455) intraperitoneal treatment using gemcitabine monotherapy were conducted. After enrollment and informed consent, a standard pancreatic resection was performed and, if necessary, there was pathologic confirmation of primary pancreatic adenocarcinoma. Patients with adenocarcinoma of the head of the pancreas or tail of the pancreas who have a complete visible resection of disease were eligible.

Following cancer resection gemcitabine at 1,000 mg/m^2 was instilled into the peritoneal cavity in a chemotherapy solution containing 1.5% dextrose peritoneal dialysis solution. The volume of peritoneal dialysis solution is 1.5 L/m^2. There was a single inflow catheter that is placed in the anatomic site from which the pancreatic cancer was removed. Four outflow drains are positioned in the right upper quadrant, left upper quadrant and two within the pelvis. A heater circulator (Belmont, Billerica, MA), was utilized to maintain the chemotherapy solution at 43 °C at the inflow and 41 °C within the whole abdomen. The treatment was continued for 1 hour and there was an open technique used with a vapor barrier that allows continuous manipulation of the abdominal and pelvic contents by the surgeon and uniform distribution of the heated chemotherapy solution (*Figure 1*).

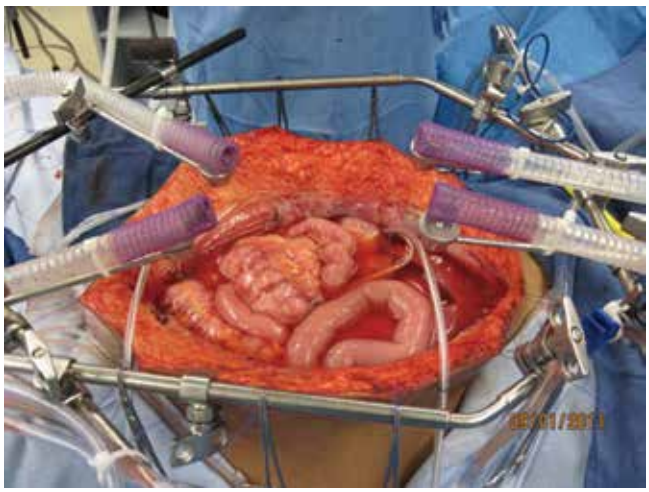

Figure 1 Hyperthermic intraperitoneal chemotherapy for treatment of abdominal and pelvic surfaces following pancreatico-duodenectomy. To administer hyperthermic intraperitoneal chemotherapy there is one inflow catheter and four drainage catheters. The chemotherapy solution is maintained at approximately 43 °C at the inflow catheter and 41 °C throughout the whole abdomen. Four smoke evacuators are placed around the periphery of the open abdomen in order to create a "vapor barrier" above the chemotherapy solution. The surgeon's double-gloved hand is used to maintain a uniform distribution of the heat and chemotherapy solution.

Prior to closing the abdominal incision an intraperitoneal port (Port-A-Cath, Smiths Medical MD, Inc., St. Paul, MN) was positioned. The port was accessed with a non-coring right angle needle (Port-A-Cath Gripper Plus, Deltec, Inc., St. Paul, MN) to temporarily maintain proper position for use in 4 to 6 weeks (10). When the patient was fully recovered from

surgery and the sutures removed from the skin incision, the adjuvant intraperitoneal gemcitabine was begun. There were six cycles, each of which was 4 weeks in length. Gemcitabine at 1,000 mg/m^2 was given by intraperitoneal administration on days 1, 8, and 15 of the 4 week cycle.

Results to date show that the hyperthermic intraperitoneal gemcitabine and the long-term intraperitoneal gemcitabine were well tolerated. A single grade III adverse event occurred in the postoperative period. A fluid collection at the pancreatico-jejunal resection required drainage under CT guidance. No grade III toxicities were observed. To date, eight patients have been treated with hyperthermic gemcitabine as part of the pancreatico-duodenal resection and the accrual process is ongoing.

Pharmacologic studies

As part of this phase II single institution study, a pharmacokinetic analysis of hyperthermic intraperitoneal gemcitabine was performed. There was a standard dose of 1,000 mg/m^2 of gemcitabine in a standard volume of 1.5% dextrose peritoneal dialysis solution (1.5 L/m^2). Peritoneal fluid, plasma, and urine samples were obtained at 15-minute intervals throughout the 60 minutes of hyperthermic intraperitoneal chemotherapy. The results as seen in a single patient are presented in *Figure 2*. Similar data has been obtained in 4 additional patients. The area under the curve ratio of concentration times time of intraperitoneal to intravenous gemcitabine was 210. To date, no data regarding gemcitabine within pancreatic tissues is available.

Six months of normothermic intraperitoneal gemcitabine using an intraperitoneal port was given. This dose and schedule is the same as the current recommendation for use of intravenous gemcitabine. The route of administration in the current study is intraperitoneal rather than intravenous.

The adverse events associated with pancreatico-duodenectomy combined with hyperthermic intraperitoneal gemcitabine were limited. In these eight patients only a single grade III intervention was necessary in order to complete the postoperative course. This patient had a minor leak from the anterior aspect of the pancreatico-jejunal anastomosis. CT was performed and showed a fluid collection which was drained under CT guidance. The return to normal oral nutrition and the time to hospital discharge were not prolonged. There have been no episodes of intestinal obstruction or other symptoms that would suggest peritoneal sclerosis from the hyperthermic gemcitabine or from the long-term intraperitoneal gemcitabine. The median hospital stay for treated patients was 13 days and this was not thought to be different from other patients treated at our institution.

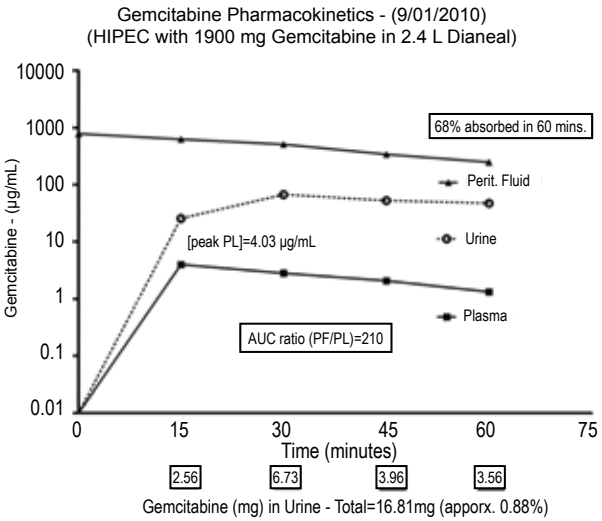

Figure 2 Pharmacology of intraoperative intraperitoneal gemcitabine in a patient with resected pancreas cancer. The drug was used at 1,000 mg/m^2 in 3 liters of 1.5% dextrose peritoneal dialysis solution administered intraperitoneally. The area under the curve ratio of concentration × time intraperitoneal to intravenous was 210. Sixty-eight percent of the drug was cleared from the peritoneal cavity in 60 minutes. Data were taken from the study of a single patient but are similar to those in four other patients. The patient has completed the long-term intraperitoneal gemcitabine without incident.

Discussion: summary of randomized control trials of adjuvant therapy for pancreatic cancer

Realizing that the chances are small of surgical resection alone being curative for pancreas cancer, there have been many studies analyzing the benefits of adjuvant therapy. In 1985 the Gastrointestinal Study Group (GITSG) conducted a 2-arm study trial randomizing patients into 5-fluorouracil (5-FU) based chemoradiation versus observation (11). The mean survival in the chemoradiation arm was 20 months compared to 11 months in the observation arm. The 5-year survival was 18% and 8% respectively. The trial was able to recruit 43 patients in 11 years. It was closed because of slow accrual and significant benefit favoring adjuvant chemoradiation.

The European Organization for Research and Treatment of Cancer (EORTC) trial was an adequately powered

study designed to validate the result of the smaller GITSG trial (12). Adjuvant therapy was similar except that the GITSG study used maintenance chemotherapy while the EORTC trial did not. In the EORTC trial, 218 patients with pancreatic and ampullary cancer were recruited. Randomization was to the observation group or radiotherapy with split-course radiotherapy (40 Gy) and concurrent 5-FU as a continuous infusion. After a median follow-up of 11.7 years, there was no difference in overall survival between the 2 arms. The limitations of this study were the lack of maintenance chemotherapy and a questionable statistical design that limited its ability to detect a small benefit for adjuvant chemoradiation.

The European Study Group for Pancreatic Cancer (ESPAC) conducted a trial between 1994 and 2000 (ESPAC-1) (13). In the 2×2 factorial design, 145 patients were randomized to the chemoradiotherapy arm, and 144 were randomly assigned to no chemoradiotherapy. Radiation was administered as a split course (total 50 Gy), concurrent with 5-FU. There was no difference in the median survival (15.5 months in the chemoradiotherapy arm and 16.1 months in the no chemoradiation arm). In the final results of the ESPAC-1 trial, the median survival was 15.9 months in the chemoradiotherapy arm and 17.9 months in the group not assigned to receive chemoradiotherapy (P=0.05) (14). The estimated 5-year survival was 10% in the chemoradiotherapy arm compared with 20% in those who did not receive chemoradiotherapy (P=0.05). The cause for improved survival in the control group in this trial was not immediately evident.

With both EORTC and the ESPAC-1 studies showing no survival benefit, the evidence to support continued use of adjuvant chemoradiotherapy in pancreatic cancer has been markedly reduced. This lead to increased interest in clinical trials using chemotherapy alone.

The ESPAC-1 trial also studied the possible benefit of a bolus of 5-FU administered intravenously. A total of 289 patients were randomized using the 2×2 factorial design and followed for 47 months (14). The survival with chemotherapy was 20.1 months and without chemotherapy were 15.5. The survival benefit was evident not only with R0 but also with R1 resection.

In contrast to contradictory data from combined chemotherapy and radiotherapy, clinical research with gemcitabine has shown it to be a major advance in the treatment of pancreatic cancer. Gemcitabine is a difluorinated analog of the naturally occurring nucleoside deoxycytidine and has shown significant clinical activity in a variety of solid tumors including pancreatic cancer. A most recent and significant study regarding the use of adjuvant gemcitabine is the CONKO-001 (Charité Onkologie) study (15). This multicenter randomized control trial conducted between July 1998 and December 2004 was designed to test the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of pancreatic cancer improves disease-free survival by 6 months or more. A total of 368 patients with gross complete (R0 or R1) resection of pancreatic cancer and no prior radiation or chemotherapy were enrolled into 2 groups. One group of patients was randomized to receive adjuvant chemotherapy with 6 cycles of gemcitabine on days 1, 8, and 15 every 4 weeks (n=179), and the second group was observed (n=175). Median disease-free survival was 13.4 months in the gemcitabine group and 6.9 months in the control group. Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. These authors concluded that treatment with gemcitabine for 6 months after complete resection of pancreas cancer statistically significantly increases median and disease-free survival. A recent abstract reporting follow-up in 2008 confirms these benefits (16).

The effect of gemcitabine on disease-free survival was significant in patients with R0 and also R1 resection. In the follow-up analysis gemcitabine did improve the overall survival (gemcitabine 22.8 months *vs.* control 20.2 months). The most impressive statistic was the delayed development of recurrent disease after complete resection of pancreatic cancer compared with observation alone. This clinical trial strongly supports use of intravenous gemcitabine as adjuvant chemotherapy in resectable carcinoma of the pancreas.

Given the conflicting data concerning the use of chemoradiotherapy in resected pancreatic cancer, the optimal treatment of patients in this setting remains controversial. In Europe, chemotherapy with gemcitabine alone is generally accepted as standard of care; whereas in the United States, chemoradiation therapy is still commonly recommended.

Recently, a multi-agent chemotherapy regimen used to treat patients with unresectable disease has shown improved survival when compared to single agent gemcitabine. In 342 randomized patients the FOLFIRINOX regimen resulted in a median overall survival of 11.1 months as compared to 6.8 months in the gemcitabine group. Clearly, this multi-

agent chemotherapy regimen becomes a candidate for adjuvant treatment of resected pancreas cancer (17).

Intraperitoneal gemcitabine pharmacokinetics

Gemcitabine is a prodrug which has little or no cytotoxic effect. The drug is metabolized within tissue to the active agent, gemcitabine triphosphate. The efficacy of gemcitabine has been correlated with concentrations of gemcitabine triphosphate accumulated in peripheral blood mononuclear cell (PBMC), which in turn is related to plasma concentration. The rate of intracellular accumulation of gemcitabine triphosphate was highest when plasma gemcitabine was about 20 micromol/L (18). Beyond this there is enzymatic saturation and further increase in plasma concentration does not produce any increase in intracellular gemcitabine triphosphate concentration.

There are two types of infusion regimens followed for gemcitabine. First is the fixed dose rate regimen: In this regimen generally 1,000 or 1,500 mg/m^2 is infused during 100 or 150 minutes. The dose rate of 10 mg/m^2/min achieves the target plasma concentration of 20 micromol/L.

In contrast the standard dose therapy of gemcitabine administered by intravenous infusion is 1,000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Much of the controversy about the use of gemcitabine in further clinical trials has concerned the possible superiority of fixed dose rate over the standard dose schedule. It is a known fact that the fixed dose rate infusion achieves better concentrations of gemcitabine triphosphate in PBMCs but the clinical benefit of this is uncertain (18).

A criticism of the use of intraperitoneal gemcitabine in carcinoma of the ovary was that better plasma concentrations could be achieved by fixed dose rate intravenous infusion of gemcitabine than by intraperitoneal administration. In the study by Sabbatini *et al.* plasma concentrations of intraperitoneal gemcitabine administered were between 0.92-8.2 micromol which was considerably below the threshold for maximum effect (20 micromol) (19). However, this criticism ignores the high likelihood that intraperitoneal chemotherapy acts by direct uptake of the drug into cancer cells or peritoneal implants. Furthermore, as Gandhi *et al.* have pointed out, almost all pharmacokinetic studies on gemcitabine have a caveat that the cellular pharmacokinetic data are obtained from a surrogate tissue (circulating peripheral blood mononuclear cells) rather than from the target solid tumor tissue (18). The gemcitabine drug levels within solid tumor tissue are not known. Also, levels of gemcitabine-activating and -inactivating enzymes within cancerous tissue such as cytidine deaminase, deoxycytidine kinase and nucleotidases are not well defined. It is merely an assumption that fixed dose rate infusion in comparison to intraperitoneal administration would result in greater area under the curve (AUC) and/or peak levels of gemcitabine triphosphate in tumor cells located at the peritoneal surface of the abdomen and pelvis. Gandhi *et al.* has suggested pharmacologic studies in which tumor tissue is directly available for measurement of gemcitabine triphosphate concentration.

Clinical and laboratory studies do show a theoretical advantage of intraperitoneal versus intravenous gemcitabine (20). Pestieau and colleagues studied the pharmacokinetics of intraperitoneal gemcitabine in a rat model. The area under the curve ratio of intraperitoneal to systemic drug exposure in the rat model was between 12.5 and 26.8 depending on the dose of intraperitoneal gemcitabine. All tissue samples from the peritoneal cavity showed an increased drug concentration when administered with intraperitoneal hyperthermia as compared to a normothermic state.

Sugarbaker and colleagues reviewed the data on intraperitoneal gemcitabine in humans by taking plasma and peritoneal fluid samples from patients in the operating room (21). These data showed that gemcitabine used with heated intraoperative intraperitoneal administration at 1,000 mg/m^2 in 3 liters had marked local-regional drug exposure. The area under the curve ratio of concentration times time for intraperitoneal to intravenous drug was 200. In these pharmacologic studies of patients who had resected pancreas cancer treated with intraperitoneal hyperthermic gemcitabine, considerable benefit was suggested.

The adequate plasma concentration of 5.26 mcg/mL has been recommended (19). In our patient presented in *Figure 2*, the peak plasma concentration was 4.03 mcg/mL, very close to the target achieved by a fixed dose rate infusion. Of course, the translation of the pharmacologic advantage into an improvement in local-regional disease control requires further clinical studies.

In a study involving nine patients with advanced pancreatic malignancy reported by Gamblin *et al.*, intraperitoneal chemotherapy was administered using indwelling peritoneal catheters (22). Intraperitoneal gemcitabine was well tolerated and no significant toxicities

were noted. There was rapid decrease in peritoneal gemcitabine concentration due to almost total absorption of the intraperitoneally-administered gemcitabine. Steady plasma concentrations were reached early implying absorption of virtually all intraperitoneally-administered gemcitabine. These findings combined with the fact that gemcitabine has low local toxicity argue well for its use in intraperitoneal chemotherapy.

Intraperitoneal gemcitabine in ovarian carcinoma

A phase 2 study using intraperitoneal cisplatin and intraperitoneal gemcitabine in carcinoma of the ovary was conducted by Sabbatini *et al.* (19). The patients selected were those with persistent disease documented by a second-look assessment. The patients were given intraperitoneal cisplatin (75 mg/m^2) on day 1 and intraperitoneal gemcitabine at 500 mg/m^2 on days 1, 8 and 15 on a 28-day schedule for four courses. The median time to treatment failure and overall survival of 15.9 and 43.5 months, respectively, were consistent with historical data in second-look-positive patients receiving a variety of intraperitoneal platinum-based regimens for consolidation. There was no apparent benefit with intraperitoneal gemcitabine and the authors attributed this to the dense peritoneal fibrosis that they encountered during second-look surgery. The authors of this study (as discussed earlier) have stated that the concentrations in peripheral blood mononuclear cells resulting from intraperitoneal gemcitabine were determined to be much below the maximum therapeutic values in plasma. Data regarding an increased local-regional drug concentration and improved local-regional control of cancer as a result of intraperitoneal administration was not provided.

In the study by Sabbatini *et al.*, patients were treated using intraperitoneal cisplatin at 75 mg/m^2 on day 1 with a dose escalation of gemcitabine at 500, 750, 1,000, or 1,250 mg/m^2 intraperitoneally on days 1, 8, and 15 of a 28-day schedule for four courses (19). The phase I dose-limiting toxicity was grade III thrombocytopenia at day 15 on dose level 1. The chemotherapy protocol was modified to cisplatin (75 mg/m^2) on day 1 and gemcitabine at 500 mg/m^2 on days 1 and 8 of a 21-day schedule for four courses.

Of the 30 patients that were enrolled for the study, 9 were removed from the study; one each for hypersensitivity, cellulitis, and intraperitoneal port malfunction, two for progression of disease, and four for renal toxicity. Other toxicities included grade 3 nausea (7%) and transient grade 3 neuropathy (3%). Grade 1 or 2 neuropathy was frequently seen (80%). Five patients (17%) returned to the operating room at a median of 6 months (range, 1-20 months) after intraperitoneal therapy for evaluation of abdominal pain; two patients had recurrence and all had areas of fibrous tissue with encasement of the bowel. The peritoneal sclerosis was, most likely, related to repeated doses of intraperitoneal cisplatin. The authors suggest that the lack of benefit from intraperitoneal gemcitabine in ovarian cancer patients may be from poor drug distribution and extensive peritoneal fibrosis documented in this group of patients.

Clinical trials of gemcitabine alone or in combination with other drugs in patients with unresectable pancreas cancer

The current available evidence for treatment for unresectable pancreatic cancer suggests that gemcitabine monotherapy chemotherapy should be considered a valid treatment option. In the important study reported by Burris and colleagues, 126 chemotherapy-naïve patients with unresectable pancreatic cancer were randomized to receive either intravenous gemcitabine or 5-fluorouracil. The primary endpoint was a composite of pain measurements, weight, and performance status (23). Patients treated with gemcitabine derived significantly more clinical benefit than those receiving 5-fluorouracil (23.8% *vs.* 4.8%, respectively; P=0.0022). In addition there was a statistically significant improvement in overall survival (median: 5.65 *vs.* 4.41 months, respectively) with a 1-year survival rate of 18% in the gemcitabine cohort compared with 2% in patients receiving 5-fluorouracil (P<0.002).

Berlin and colleagues published an ECOG phase 3 trial including 327 patients with advanced carcinoma of the pancreas (24). They showed that 5-fluorouracil, administered in conjunction with gemcitabine, did not improve the median survival of patients with advanced pancreatic carcinoma compared with single-agent gemcitabine. The authors concluded that further studies with other combinations of gemcitabine and 5-fluorouracil are not compelling and clinical trial resources should address other combinations and novel agents. Several other chemotherapy agents have been tried in combination with gemcitabine.

The combination of gemcitabine with cisplatin and oxaliplatin has been more encouraging. In a German multicenter study, Heinemann *et al.* enrolled 195 patients to receive either gemcitabine alone or in combination with cisplatin (25). These results supported the efficacy and

safety of an every-2-weeks treatment with gemcitabine plus cisplatin. Median overall survival and progression-free survival were more favorable in the combination arm as compared with gemcitabine alone, although the difference did not attain statistical significance. The French Multidisciplinary Clinical Research Group (GERCOR)/ Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) intergroup study compared gemcitabine plus oxaliplatin to gemcitabine alone (26). The pooled analysis of the GERCOR/GISCAD intergroup study and the German multicenter study indicates that the combination of gemcitabine with a platinum analog such as oxaliplatin or cisplatin significantly improves progression-free survival and overall survival as compared to single-agent gemcitabine in advanced pancreatic cancer especially in patients with good performance status (27).

Scheithauer *et al*. reported on gemcitabine in combination with irinotecan (28). A somewhat superior clinical benefit response rate was seen with the drug combination. However, no advantage over single-agent gemcitabine was noted in terms of objective efficacy parameters. Irinotecan with gemcitabine has not shown any benefit as compared to gemcitabine alone (29).

The combination of gemcitabine and mitomycin C was studied by Tuinmann *et al*. in a phase II trial involving 55 patients with advanced pancreatic cancer (30). These patients were given gemcitabine 800 mg/m^2 intravenously on days 1, 8 and 15, and mitomycin C 8 mg/m^2 intravenously on day 1 every 4 weeks in an outpatient setting. A median of 3 cycles was administered. The most frequent toxicity was thrombocytopenia grade III/IV seen in 54% of patients. The objective response rate was 29%. Eighteen patients had stable disease resulting in an overall tumor growth control of 62%. Time to progression was 4.7 months and median overall survival was 7.25 months. The authors concluded that the combination was well tolerated. Survival was similar to monotherapy with gemcitabine.

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Advances of stereotactic body radiotherapy in pancreatic cancer

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Abstract: Pancreatic cancer (PCA) is one of the most aggressive tumors with few effective treatment modalities. It is the 4th and 7th leading cause of cancer death in the United States and China, respectively. At the time of diagnosis, only 20% of cases present with a resectable tumor, and about 40% with a locally advanced tumor that is considered unresectable. Even resected patients still have a poor prognosis, with an incidence of local recurrence ranging from 20% to 60%. It is also reported that up to 30% of PCA patients die from locally obstructive disease with few or no distant metastases. These findings have highlighted the importance of local radiation therapy in the treatment of PCA. As the role of conventional chemoradiotherapy remains controversial, the dawn of the pancreas stereotactic body radiation therapy (SBRT) era represents a potential paradigm shift in the management of PCA. SBRT delivers a higher biological effective dose to the tumor with sharp dose escalation in a shorter treatment time course. Pancreas SBRT is a novel therapeutic option to achieve local tumor control with minimal toxicity. Herein, we review the advancement of SBRT for PCA patients with different stages of pancreatic adenocarcinoma.

Keywords: Stereotactic body radiation therapy (SBRT); pancreatic cancer (PCA)

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Introduction

Pancreatic cancer (PCA) is the fourth leading cause of cancer-related deaths for both genders in the United States, and it is estimated that 48,960 new PCA cases will be diagnosed and 40,560 will die from the disease in the USA in 2015 (1). In China, PCA is the seventh leading cause of cancer death. According to the National Central Cancer Registry (NCCR) of China, PCA accounted for 3% of all cancer deaths in 2010, with the total number of deaths at 57,735 (2). Overall, despite the advances in surgery, radiotherapy, chemotherapy, immune and targeted therapy, the prognosis of PCA remains to be poor, with a 5-year overall survival (OS) rate of 7% for all stages combined (1).

Lack of symptoms at its onset allows PCA to progress to a more advanced stage at the time of diagnosis, with only 20% of cases presenting with a resectable tumor, and about 40% with locally advanced, unresectable disease (3). Surgical resection appears to be the only modality providing a chance of cure (4); however, even resected patients have a poor prognosis, with a 5-year survival of approximately 20% (4,5). The incidence of local recurrence has been reported as 20% to 60% (6-8), and autopsy data reveals even higher rates (9). For those with locally advanced, unresectable disease, the main therapeutic option is a combination of chemotherapy and radiotherapy, with an aim to control the local disease and prevent pain and obstruction, all of which negatively impact the patient's quality of life. In a report from Johns Hopkins Hospital by Iacobuzio-Donahue *et al*., up to 30% of PCA patients died from locally obstructive disease with few or no distant metastases (9). Moreover, advances in systemic chemotherapy and targeted therapy have improved patient outcomes. As patients live longer, the role of local therapy such as radiotherapy becomes even more important. These findings have highlighted the importance of local radiation therapy in the management of PCA.

The role of conventional radiation therapy in the management of PCA

Chemoradiation (CRT) has played a key role in the treatment paradigm for patients with unresectable PCA. Previous clinical trials investigating treatment options for patients with locally advanced pancreatic cancer (LAPC) have demonstrated conflicting results regarding the role of conventional CRT. When compared to chemotherapy alone, an increase in OS with CRT was confirmed in three trials conducted before the 1980s: the Gastrointestinal Tumor Study Group (GITSG) 9283, the Eastern Cooperative Oncology Group (ECOG) 4201, and the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trials. However, a substantial increase in toxicity was also seen in the CRT arms of the first two studies (10,11). In contrast, patients undergoing CRT had decreased OS rates in the Fédération Francophone de Cancérologie Digestive and Société Francophone de Radiothérapie Oncologique

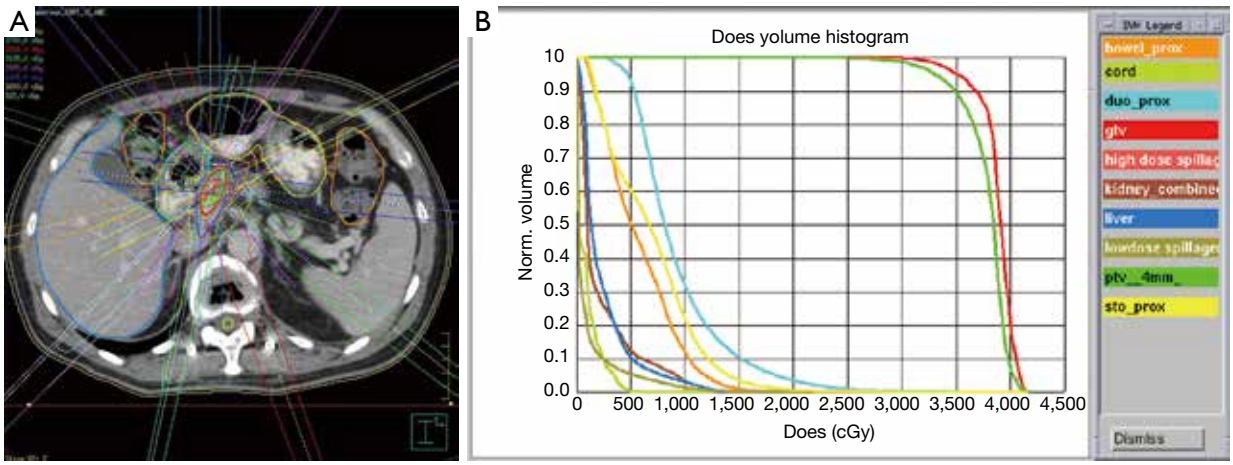

Figure 1 (A) depicts the treatment plan of a patient receiving 33 Gy in 5 fractions to treat a tumor in the head of the pancreas. Note the use of multiple high-dose beams and strict contouring of surrounding organs at risk (OARs). (B) displays the corresponding dose volume histogram (DVH). This demonstrates that dose to the planning target volume (PTV, dark green) and gross tumor volume (GTV, red) is maximized while minimizing dose to the OARs such as the duodenum (light blue), stomach (yellow), bowel (orange), liver (dark blue), kidneys (brown), and spinal cord (light green).

(FFCD-SFRO) study (12).

With the aim to settle the controversy regarding the role of standard CRT for LAPC patients, the phase III GERCOR LAP 07 study sought to evaluate the role of CRT following induction chemotherapy (13). After induction chemotherapy with gemcitabine or gemcitabine/erlotinib, LAPC patients were stratified to two additional months of chemotherapy alone or CRT (54 Gy and capecitabine). The investigators reported no significant improvement in OS with the addition of CRT compared to gemcitabine-based chemotherapy alone (13). The study has showed that LAPC patients receiving chemotherapy alone had a slightly higher median OS of 16.5 months compared to patients receiving CRT (15.3 months) (13). However, there was a significant improvement in first local progression in patients who received CRT. It is important to note that the final data analysis of this study has not yet been published.

Nevertheless, CRT currently remains an important component of treatment in patients with unresectable LAPC. Due to inadequate local control (LC) (~50-60%) observed with standard CRT regimens involving three-dimensional conformal radiation therapy (3D-CRT), emphasis has been shifted towards improved radiation dose escalation of the primary tumor with intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT). Ben-Josef *et al.* reported an impressive median OS of 14.8 months when treating patients with full-dose gemcitabine and IMRT to 50-60 Gy (14). In this study, they incorporated small expansions of the primary tumor and motion management in order to minimize treatment-related toxicity. Similarly, optimizing technologic advancements in radiation dose delivery, image guidance, and motion management, SBRT enables the precise application of multiple high-dose radiation beams to treat the tumor plus a small margin over 1-5 days (*Figure 1*).

Evolution of SBRT in PCA

The Stanford group reported on the first study to demonstrate the feasibility of a single-fraction SBRT (25 Gy) regimen for LAPC (15). Excellent LC rates were achieved; however, increased rates of late gastrointestinal toxicity were also found in subsequent studies from the same group and Hoyer *et al.* (16,17). The reasons for higher toxicity rates in these early SBRT studies might have been attributed to the lack of fractionation, inadequate motion management techniques, absence of image guidance using fiducial markers, and lack of specific dose constraints for organs at risk (OARs).

Following these initial reports, SBRT delivered in 3-5 fractions has been investigated thereafter (18-20). Several retrospective studies have revealed similar LC rates and a lower incidence of high-grade toxicity, as compared to those of single-fraction SBRT. This has led to increasing interest

Table 1 A summary of clinical studies of stereotactic body radiation therapy in pancreatic cancer

Study (year)	Patients (n)	SBRT dose & fraction	1-year LC	Median OS (m)	Toxicity	Chemotherapy
Koong *et al*. (15) 2004	15 LA	15-25 Gy ×1	100%	11	33% Grades 1 & 2 0% ≥ Grade 3	None
Koong *et al*. (16) 2005	16 LA	25 Gy ×1 (boost)	94%	8.3	69% Grades 1 & 2 12.5% ≥ Grade 3	5-FU with EBRT prior to SBRT
Schellenberg *et al*. (21) 2008	16 LA	25 Gy ×1	100%	11.4	19% Acute 47% Late	1 cycle induction GEM + post-SBRT GEM
Hoyer *et al*. (17) 2005	22 LA	15 Gy ×3	57%	5.4	79% Grade 2 4.5% Grade 4	
Mahadevan *et al*. (18) 2010	36 LA	8-12 Gy ×3	78%	14.3	33% Grades 1 & 2 8% Grade 3	Post-SBRT GEM
Mahadevan *et al*. (22) 2011	39 LA	8-12 Gy ×3	85%	20	41% Grades 1 & 2 0% Acute Grade 3 9% Late Grade 3	2 cycle induction GEM
Polistina *et al*. (20) 2010	23 LA	10 Gy ×3	50%	10.6	20% Grade 1 0% Grade 2	6 week induction GEM
Moningi *et al*. (23) 2015	74 LA 14 BR	5-6.6 Gy ×5	61% LPFS	18.4	3.4 % ≥ Acute Grade 3 5.7% ≥ Late Grade 2	Pre-SBRT Chemo in 77 cases
Gerka *et al*. (24) 2013	10 LA	5 Gy ×5	40%	12.2	0% Grade 3	1 cycle pre-SBRT GEM +5 cycle post-SBRT GEM
Herman *et al*. (25) 2015	49 LA	6.6 Gy ×5	83% LPFS	13.9	2% ≥ Acute Grade 2 11% ≥ Late Grade 2	GEM followed by SBRT

BR, borderline resectable; 5-FU, 5-flourouracil; GEM, gemcitibine; LA, locally advanced; LC, local control; LPFS, local progression free survival; OS, overall survival; SBRT, stereotactic body radiotherapy.

in fractionated SBRT.

The application of SBRT provides other advantages. Because SBRT can be completed within a week, the delay to surgery and/or a full-dose chemotherapy course is minimized. Furthermore, a shorter therapeutic course is more convenient for patients. Moreover, the biologically effective dose (BED) delivered with SBRT appears to be higher than conventional fractionation schedules, which may result in improved long-term maintenance of local control.

SBRT in LAPC

Table 1 provides an overview of studies that have explored the role of SBRT in the management of LAPC. The initial clinical report on SBRT in the treatment of LAPC was from the Stanford group using CyberKnife. Patients with LAPC were treated to doses of 25 Gy in a single fraction without chemotherapy. Koong *et al*. reported that the 1-year LC rate was 100%, and the median OS was 11 months. Although none of patients suffered from grade 3 toxicity, 33% of patients experienced grade 1-2 toxicity (15). Koong *et al*. subsequently conducted a phase II study incorporating a SBRT boost of 25 Gy to the pancreatic tumor after a 5-week course of 5-fluorouracil concurrent with external beam radiation therapy. The 1-year LC rate was 94%, 69% of patients experienced grade 1-2 toxicity, 12.5% of patients suffered from grade 3 toxicity, and the median OS was 8.3 months (16). When combining SBRT with standard CRT, toxicities were higher. Most grade 1 toxicities involved mild nausea, whereas more patients encountered grade 2 and 3 toxicities. Two patients developed duodenal ulcers 4-6 months after therapy. To further explore the effect and toxicity of chemotherapy combined with SBRT, Schellenberg *et al*. conducted a phase II study incorporating one cycle of induction gemcitabine followed by single-

fraction SBRT to 25 Gy and maintenance gemcitabine. The 1-year LC rate was 100%, 19% of patients experienced acute toxicity, 47% of patients suffered from late toxicity, and the median OS was 11.4 months (21). These studies demonstrated excellent LC rates but also showed increased late gastrointestinal toxicity. Lack of fractionation likely contributed to higher toxicity rates. Investigators subsequently shifted to delivering SBRT in 3-5 fractions.

Hypo-fractionated SBRT regimens were adopted as a means to further decrease toxicity while maintaining effective LC. First investigated in a phase II study by Hoyer *et al*., a regimen of SBRT to a dose of 45 Gy in three fractions was delivered to 22 LAPC patients. The LC rate was 57%, 79% of patients suffered from grade 2 toxicity, 4.5% of patients suffered from grade 4 toxicity, and the median OS was 5.4 months (17). Of note, the poor outcomes are likely to have resulted from the lack of accurate positioning and lack of dose constraints to OARs. Mahadevan *et al*. performed a similar study involving 36 LAPC patients who received three fractions of SBRT to 24 to 36 Gy followed by gemcitabine. At a median follow-up of 24 months (range, 12-33 months), the LC rate was 78% with median OS of 14.3 months. The authors also reported low rates of toxicities, with only 25% of patients suffering from grade 2 toxicity and 8% of patients suffering from grade 3 toxicity. Late toxicity occurred in two patients in the form of gastrointestinal bleeding (18). The same group subsequently employed an identical SBRT fractionation scheme following three cycles of induction gemcitabine. The LC rate at 1-year was 85% in 39 LAPC patients with a higher median OS of 20 months, and the rate of late grade 3 toxicities such as bowel obstruction and gastrointestinal bleeding was reported to be 9% (22). An Italian study also evaluated a 3-fraction regimen of 10 Gy SBRT following 6 weeks of pre-SBRT gemcitabine in 23 patients with LAPC (20). The overall LC rate was 82.6% (14 partial response, 2 complete response, 3 stable disease). Median OS was 10.6 months, which is lower than other similar reports mentioned above. A much lower rate of toxicity was also reported, with no grade 2 or greater acute toxicity in this group of patients (20). However, the definition of LC can vary tremendously between each study, thereby increasing the difficulty of comparison among these reports.

Recently, in a retrospective series at Johns Hopkins Hospital, 74 LAPC patients received SBRT to 25-33 Gy in 5 fractions following gemcitabine or FOLFIRINOX-based chemotherapy. The median OS from the date of diagnosis was 18.4 months and 15 (20%) patients underwent successful surgical resection following SBRT (23). Gurka *et al*. from the Georgetown group evaluated 10 LAPC patients treated with a multi-fraction SBRT regimen. Patients received one cycle of gemcitabine before SBRT. During week 4 of cycle 1, patients received 25 Gy in 5 fractions, followed by gemcitabine chemotherapy to a maximum of another five cycles (24). The 1-year LC rate was 40% with a median OS of 12.2 months, and no patients suffered from grade 3 acute toxicity (24).

A multi-institutional prospective phase II study involving Johns Hopkins Hospital, Memorial Sloan Kettering Cancer Center, and Stanford University was recently completed (25). In that study, pancreatic fiducial markers were placed, motion management techniques engaged, and strict dose constraints required. Moreover, all therapeutic plans were centrally reviewed before treatment. A total of 49 LAPC patients received SBRT to a dose of 33 Gy in five fractions followed by gemcitabine. The 1-year freedom from local progression (FFLP) rate was 78%, and the median OS was 13.9 months (25). Only 2% of patients experienced grade 2 or more acute toxicity, and 11% of patients suffered from grade 2 or more late toxicity (25).

The use of fractionated SBRT regimens in patients with LAPC has resulted in promising LC rates that are higher than conventional external beam radiation therapy regimens, with acceptable rates of acute and late gastrointestinal toxicity.

SBRT in BRPC

The literature concerning the application of SBRT in the BRPC is limited. Chuong *et al*. at Moffitt Cancer Center recently reported on 30 BRPC patients who received neoadjuvant SBRT and concurrent gemcitabine/taxotere/xeloda (GTX) chemotherapy. Twenty-one (70%) patients underwent resection after this regimen. The margin-negative (R0) resection rate was 95% and the node-negative resection rate was 76%. One patient had a near pathologic complete response and two had a partial response. Median OS was 20 months and 1-year progression-free survival (PFS) was 61%. No high-grade (>2) acute toxicity or late grade toxicity was reported (26). Therefore, SBRT in combination with GTX in the neoadjuvant setting was well tolerated with a high conversion rate from borderline resectable to resectable candidates and an increased rate of margin-negative resection (26).

Chuong *et al*. subsequently performed another

retrospective study of 57 BRPC patients who received induction chemotherapy and SBRT. Median doses of 35 Gy were delivered to the region of vessel involvement and 25 Gy to the remainder of the tumor (19). Thirty-two patients (56.1%) underwent surgery, with 96.9% (31/32) undergoing an R0 resection. Three (9.3%) patients achieved a pathologic complete response and 2 (6.3%) had a near pathologic complete response. Median OS was 16.4 months. No grade 3 or greater acute toxicity was reported whereas 5.3% of patients experienced grade 3 or greater late toxicity (19). Another group from Pittsburgh reported on pathologic response following SBRT for both LAPC (n=5) and BRPC (n=7) patients. Eleven of the 12 (92%) patients received gemcitabine-based or FOLFIRINOX-based chemotherapy before receiving either 24 Gy SBRT in one fraction (n=5) or 36 Gy SBRT in 3 fractions (n=7) (27). Three of the 12 (25%) patients had a pathologic complete response while another two cases (16.7%) demonstrated a near pathologic complete response (<10% viable tumor cells) following tumor resection. Of all resected patients, 92% of the cohort achieved a R0 resection. Rates of OS at 1-, 2-, and 3-year were 92%, 64%, and 51%, respectively (27).

Although the current evidence about SBRT in BRPC is scarce, it appears that BRPC patients may benefit from neoadjuvant SBRT with impressive pathologic response and R0 resection rates. Future research should focus on seeking optimal dose and fractionation regimens in the BRPC setting.

Advances of SBRT as adjuvant therapy in PCA

The postoperative local recurrence rates in patients with resectable PCA are high, with a range of 20% to 60% (6-8). Therefore, adjuvant therapy is needed with the aim to decrease the risk of local recurrence. The incorporation of SBRT and chemotherapy, which has shown significant potential in the therapy of LAPC, is currently being investigated in the adjuvant setting. Rwigema *et al*. reported on 12 patients following a margin-positive resection. The FFLP rate at 1 year was 70.7% and 1-year OS was 81.8%. A median OS of 20.6 months was achieved (28). Rwigema *et al*. subsequently conducted a study that 24 resected patients who had close or positive margins received adjuvant SBRT. FFLP at 1 year was 66% and 1-year OS was 80.4%, with a median OS of 26.7 months. No patients suffered from acute grade 3 or greater toxicity (29). Results of this study highlight that adjuvant SBRT in patients with close or positive margins benefited from the treatment. Additional investigation is needed due to the small sample size of the above studies. Future prospective multi-institutional clinical trial is warranted to fully assess the role of SBRT as adjuvant therapy.

Re-irradiation with SBRT after previous conventional CRT

Wild *et al*. performed a retrospective study from Stanford and Johns Hopkins Hospital on re-irradiation with SBRT for isolated local recurrence or progression of PCA after previous conventionally fractionated CRT. Eighteen locally recurrent or progressive diseases were treated with SBRT to a dose of 20-27 Gy (median, 25 Gy) in 5 fractions (30). Rates of FFLP at 6 and 12 months after SBRT were 78% (14/18) and 62% (5/8), respectively, with a median OS of 8.8 months from SBRT. Effective symptom palliation was achieved in 57% of patients. Five patients (28%) experienced grade 2 acute toxicity; none experienced grade 3 or greater acute toxicity. One patient (6%) experienced grade 3 late toxicity in the form of small bowel obstruction (30). Lominska *et al*. reported their experience of SBRT for salvage or boost treatment after conventional doses of external beam radiation therapy (31). Twenty-eight patients were evaluated, 11 of which were treated with a SBRT boost while the remaining 17 patients underwent salvage SBRT. A dose of 20 to 30 Gy was delivered in 3 to 5 fractions. The rate of FFLP was 86% (12/14), and median OS was 5.9 months (1-27 months) from the date of SBRT treatment. Eleven patients (39%) had 9 months or greater OS. OS at one year was 18%. Patients tolerated the treatment well; only 1 patient had acute grade 2 nausea and vomiting, and two late grade 3 gastrointestinal complications were reported (31).

Although limited treatment options exist for isolated local recurrent PCA after CRT, re-irradiation with SBRT appears to be a safe and reasonable option in well selected cases.

Summary and future directions

While surgical resection appears to be the modality providing an optimal chance of cure, only about 20% of PCA patients present with resectable disease, and 40% present with unresectable, locally advanced disease (3). Even in patients with resectable PCA, the local recurrence rates are high with a range of 20-60% (6-8), and the

recurrent lesions are often unresectable. Traditionally, a combination of chemotherapy and radiotherapy are the optimal therapeutic options, with an aim to control the local disease and prevent pain and obstruction which affect the patient's quality of life. As the role of conventional CRT remains controversial, the dawn of the pancreas SBRT era represents a potential paradigm shift in management of PCA. The advantages of SBRT include the delivery of a higher biological effective dose, the benefit of dose escalation, and a shorter treatment time course. Pancreas SBRT is a therapeutic option to achieve local tumor control; however, whether this translates into improvement in survival remains uncertain. Pancreas SBRT was initially investigated for LAPC and BRPC populations, and has shown promising outcomes in local control for PCA patients as compared to conventional CRT. The acute toxicities have been reported to be mild, with most of them being grade 1 and 2 gastrointestinal side effects, while rates of grade 3 or greater toxicity are less common. The incidence of late complications is also acceptable. Now, SBRT has been expanded to the neoadjuvant setting for resectable disease, adjuvant setting, and recurrent/palliative setting. Exciting data is now accruing such that neoadjuvant SBRT may facilitate margin-negative resection and improve the likelihood of surgical resection among PCA patients who were initially presumed to have unresectable tumors (27,32).

As distant metastases continues to be the most common sites of failure for PCA, there is also a clear need for more effective systemic therapy in these aggressive tumor. The FOLFRINOX regimen has been reported to have superior outcome as compared to gemcitabine for patients with metastatic disease (33-35), thus, investigation of a combination FOLFRINOX or a modified FOLFRINOX followed by SBRT is warranted. Another agent that shows potential is gemcitabine combined with nab-paclitaxel, and exploration of its use in the setting of SBRT in non-metastatic PCA is necessary (36,37).

Patients may also benefit from individualized therapy by screening out suitable cases for SBRT. It was reported that the genetic status can be used to predict the failure pattern among PCA patients. Those with intact tumor suppressor gene DPC4 had a higher proportion of locally advanced carcinomas with no documented metastatic disease (9). It will be helpful if a local therapy such as SBRT could be reserved for the subset of patients with higher risk of locally destructive disease.

Although there are still many unanswered questions such as dose prescription, fractionation optimization, tumor motion control, dosimetric constraints, and optimal sequence of chemotherapy, it is still hopeful that pancreas SBRT will prove to be an effective emerging technique in the multi-modality treatment of PCA.

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Footnote

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The role of radiotherapy in management of pancreatic cancer

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Abstract: Pancreatic cancer is one of the leading causes of cancer death. The treatment options in pancreatic cancer remain limited. This review provides an overview of the role of radiotherapy (RT) alone or in combination with systemic treatment at different settings of treatment strategy. Neoadjuvant chemoradiotherapy (CRT) may downstage the borderline resectable disease and make resection possible, which could translate to a survival benefit. Although the benefit of adjuvant CRT remains controversial due to inconsistent outcome of randomized trials, in North America it is still a common recommendation of the treatment. For locally advanced pancreatic cancer, the treatment option could either be chemotherapy or chemoradiotherapy. By using advanced radiotherapy modalities, the toxicity of RT could be reduced and RT dose escalation becomes possible to improve locoregional control.

Keywords: Pancreatic cancer; chemoradiotherapy; radiotherapy

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Introduction

Pancreatic cancer is the 10th most commonly diagnosed cancer and the 4th leading cause of cancer death in the U.S. An estimated 43,140 new cases were diagnosed and 36,800 deaths occurred in the U.S. in 2010. The survival rate for this deadly disease has not improved substantially in nearly the last 40 years even with aggressive treatment. For all stages combined, the 1- and 5-year relative survival rates are 25% and 6%, respectively. For patients diagnosed with local disease, the 5-year survival is only 22% (1). Improving outcomes for patients diagnosed with pancreatic cancer continues to be a formidable challenge.

Surgical resection (pancreaticoduodenectomy) currently provides the best opportunity for long-term survival. However, only 10-20% of patients have resectable disease at the time of diagnosis. The prognosis of patients after complete resection is still poor, with a 3-year disease specific survival rate of only 27% and a median survival of only 15-19 months (2-4). Locally advanced pancreatic cancer (LAPC), in which the tumor encases the celiac axis or superior mesenteric artery with or without nodal disease but without distant metastases, is by definition unresectable and represents about 25% of the cases at diagnosis. For these patients with LAPC, treatment usually consists of chemotherapy (CT) alone or chemotherapy combined with radiation (CRT), with a resultant median survival only 10-12 months (5-7). Moreover, patients with limited vascular involvement by tumor are considered to have borderline resectable disease and are often treated with nonsurgical therapy such as CT alone or CRT.

Patterns of failure data in pancreatic cancer treated with surgical resection alone show that locoregional recurrence is a large component of failure in 50% to 75% of cases (8,9). In addition, hepatic and distant metastases rate is approximately up to 85% to 90% coincident with evidence of locoregional failure. Even in the series that patients received adjuvant treatment after surgery, the locoregional recurrence rate is still as high as 30% to 60% (10,11). Hence, these patterns of failure indicate that current local and systemic treatments are inadequate and there is significant room for improvement.

Traditionally, radiation therapy as local treatment has been utilized as neoadjuvant, adjuvant or definitive treatment with or without systemic therapy. Anywhere from approximately 20% to 80 % of the patients received

Table 1 Selected studies of neoadjuvant CRT in pancreatic cancer

Trial	No. of patients	Resection rate (%)	Survival (%)	Median Survival in month
Duke University (27)				
CRT	111	55	36 (5 yr. resected)	23
MD Anderson Cancer Center (28, 29)				
Trial 1 CRT (Gem)	86	73	22.7 (5 yr. all) 36 (5 yr. resected)	27 (all)
Trial 2 CT-CRT (Gem)	90	66		17.4 (all) 31.0 (resected) 10.5 (unresected)
Mount Sinai Hospital (30)				
Resectable group	91	100	14 (3 yr.)	14
Unresectable group	68	29.4	21 (3 yr.)*	23.6*
Systematic review and meta-analysis (31)	4,392			
Unresetable group		39.1	50.1 (2 yr. resected)	20.5 (resected)
Resectable group		73.6	47.4 (2 yr.)	23.3

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; Gem, gemcitabine; *, P<0.05.

radiation therapy during the course of their treatment (12). In several other disease sites "models" with high risk of both locoregional and systemic failure, the additional local radiotherapy to systemic chemotherapy has demonstrated improvement of local control and overall survival. Representative examples include gastric cancer and limited stage small cell lung cancer, among others, in which the additional of local radiotherapy reduced the risk of local-regional failure which eventually lead to a decrease in systemic relapses and an improvement in overall survival (13-18). Because of the patterns of recurrence in pancreatic cancer include both locoregional failure in the abdomen and systemic metastasis including the liver; it is logical to consider both local radiotherapy and systemic chemotherapy in the treatment of this cancer. The addition of adjuvant chemoradiation has been reported to decrease local recurrence rates to 20%-40% (19,20) with some studies even reporting local recurrence rates as low as 10% (21-24). To prospectively evaluate the role of radiotherapy on pancreatic cancer treatment, several randomized trials have been conducted with conflicting results. Hence, the routine utilization of radiation for pancreatic cancer remains controversial.

This review will discuss the role of rationale for using radiation therapy (RT) in the management of pancreatic cancer, review the relevant literature, and discuss current ongoing research and future directions.

Neoadjuvant radiotherapy

A neoadjuvant treatment strategy in pancreatic cancer may offer several theoretical advantages: (I) Pancreatic cancer is more likely a systemic disease with high incidence of distal and local regional failure (10,11). By starting systemic treatment early we may be able to reduce the incidence of distal metastasis and improve survival. (II) Neoadjuvant radiotherapy with or without systemic therapy may potentially downstage the disease and increase likelihood of a complete resection (R0 resection). (III) Radiotherapy can be better tolerated because the normal anatomy of the abdominal region by surgery, such as bowel displacement, which could lead to higher gastrointestinal toxicity, has not been distorted. (IV) Neoadjuvant radiotherapy can avoid treating hypoxic tumor tissue caused by surgical disruption of blood supply to tumor cells. In addition, cytokine stimulation after surgery can also potentially adversely affects the efficacy of adjuvant treatment, which can be avoided by neoadjuvant RT (25). (V) Neoadjuvant treatment may also identify those patients with aggressive disease who are likely to develop early metastatic disease, and therefore avoid unnecessary definitive surgical therapy. Given these various rationales for neoadjuvant treatment, several institutions have used this strategy in an effort to improve the survival outcome of patients with pancreatic cancer (*Table 1*). However, there

have been no large randomized controlled trials on the use of neoadjuvant therapy in resectable pancreatic cancer.

The Duke University study investigated neoadjuvant CRT in 96 resectable patients. Patients received dailyfractionated radiotherapy to a total dose of 50.4 Gy concurrent with 5-FU-based chemotherapy. Patients were then re-staged after completion of CRT. Patients were then surgically explored if there was no evidence of metastatic disease. Subsequently, 70% of patients underwent surgery and 55% had a resection. A R0 resection was achieved in 75% of patients and operative mortality was 3.8%. Overall survival (OS) for resected patients was 28% at 5 years, and a median survival was 23months (26,27).

MD Anderson Cancer Center reported their neoadjuvant treatment results using two different treatment strategies. In their first trial, patients received neoadjuvant gemcitabine and radiotherapy followed by surgery. Radiotherapy was given concurrently with 7 doses of weekly gemcitabine to a total dose of 30 Gy in 10 fractions. Of the 86 patients treated from 2004 to 2006, 64 (73%) underwent resection with an 89% R0 resection rate. The perioperative complication was 9%. The median survival and 5-years OS for all 86 patients were 22.7months and 27%, respectively. Patients, who underwent a resection, did better with a 5 year OS of 36% (28). The second trial was built up on this initial treatment regimen using neoadjuvant combination of chemotherapy prior to of CRT in an attempt to reduce distant metastasis and improve OS (29). Ninety patients were enrolled into this trial. Two cycles of cisplatin and gemcitabine were given before concurrent CRT. Gemcitabine was used for concurrent CRT. Sixty-two patients were deemed radiologically resectable and underwent exploratory surgery. A resection was completed in 52 (66%) patients. Positive margins were found in 1 patient (R1 resection rate of 4%) and nodal disease found in 58% of patients undergoing successful resection. Median follow-up was 29.3 months. The median survival was 17.4 months for all patients and 31 months for those undergoing resection. 27 patients who did not undergo surgical resection had a median survival of 10.5 months. The investigators concluded that the addition of induction cisplatin and gemcitabine chemotherapy prior to neoadjuvant CRT did not improve OS.

In a prospective clinical trial comparing neoadjuvant therapy to up-front surgery conducted at Mount Sinai Hospital in New York City (30), laparotomy and/or CT followed by EUS, angiography or laparoscopy was used to determine potential respectability prior to therapeutic intervention. Sixty-eight patients with locally invasive non-resectable tumors were treated with split-coursechemoradiotherapy (5-FU, streptozotocin and cisplatin) and subsequent surgery if rendered amenable to resection. Thirty of them underwent surgery with downstaging observed in 20 patients. Ninety-one patients with resectable tumors underwent immediate pancreaticoduodenectomy. Sixty-three of them received adjuvant radiotherapy or chemotherapy. The median survival and 3-year OS of all patients receiving preoperative treatment were 23.6 months and 21% compared to 14.0 months and 14% for patients who had initial tumor resection (P=0.006), respectively.

Recently, a systematic review and meta-analysis of neoadjuvant therapy in 4,394 patients showed that those patients with initial unresectable tumor but who underwent resection after neoadjuvant treatment had comparable survival (median overall survival 20.5 months) to patients with initially resectable tumors (median overall survival 23.3 months) (31). This met-analysis included 111 trials with total of 4,394 patients. Neoadjuvant chemotherapy was given in 96.4% of the studies with the main agents consisting of gemcitabine, 5-FU (and oral analogues), mitomycin C, and platinum compounds. Neoadjuvant radiotherapy was used in 93.7% of the studies with doses ranging from 24 to 63 Gy. Approximately one third of the initial unresectable tumors were resected after neoadjuvant therapy. For patients with resectable tumors, resection and survival rates after neoadjuvant therapy are similar to the ones observed in "up-front" resected tumors that are treated by adjuvant therapy.

Thus, in spite of decades of investigation of neoadjuvant therapy in pancreatic cancer, there is currently no evidence to support its routine use in clinical practice. However, the available data suggest that patients with locally advanced and/or unresectable tumors should be included in neoadjuvant clinical trials and subsequently be evaluated for resection (31).

Adjuvant radiotherapy

The high incidence of locoregional and systemic failure after resection in pancreatic cancer indicates the need for effective adjuvant treatment (8). The role of adjuvant radiotherapy is controversial due to the conflicting results from the randomized controlled trials (*Table 2*).

The Gastro-intestinal Tumor Study Group (GITSG) conducted first randomized trial in 1980's to evaluate the role of adjuvant CRT in resected pancreatic cancer.

Table 2 Selected studies of randomized and non randomized adjuvant trials in pancreatic cancer

Trial	No. of Patient	Locoregional Failure rate (%)	Sur vival rate (%)	Median sur vival in months
Randomized Trials				
GITSG (32)				
No CRT	22	47	15 (5 yr.)	10.9
CRT	21	33	42 (5 yr.)	20.0*
EORTC (34)				
No CRT	57	36	10 (5 yr. pancrease)	12.6 (pancreas)
	103		22 (5 yr. all)	19.0 (all)
CRT	63	36	20 (5 yr. pancreas)	17.1 (pancreas)
	104		25 (5 yr. all)	24.5 (all)
ESPAC1-2x 2 (36)				
No CRT	69	62	11 (5 yr.)	16.9
CRT	73		7 (5 yr.)	13.9
CRT + CT	75		29 (5 yr.)	19.9
CT	72		13 (5 yr.)	21.6*
RTOG 97-04 (49)				
CRT	230	28	22 (3 yr.)	16.9
CRT - Gem	221	23	31 (3 yr.)	20.5
Non randomized trials				
Mayo Clinic (48)				
No CRT	180		17 (5 yr.)	19.2
CRT	274		28 (5 yr.)	25.2*
John Hopk ins Hospital (47)				
No CRT	345		14.4	15
CRT	271		21.2	20*

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; Gem, gemcitabine; RT, radiation therapy; *, P<0.05.

Fortynine patients after R0 resection were randomized to CRT versus observation (32). Radiotherapy was delivered to 40 Gy in 20 fractions with a planned 2-week break after 20 Gy. Bolus fluorouracil (5-FU) was given concurrently and two more cycles after radiotherapy. The treatment arm yielded significantly longer median OS (20 *vs.* 11 months) and 2-year OS (42% *vs.* 15%) than the observation arm. Due to this significant improvement in survival, thirty additional patients were treated by the GITSG in a nonrandomized fashion using an identical CRT regimen. The outcome was similar to the treatment arm in the randomized trial (33). Thus, the adjuvant CRT became a standard treatment option for patients with resected pancreatic cancer in North America.

In contrast, the adjuvant chemotherapy is considered the standard care for patients with resected pancreatic cancer in Europe because the subsequent randomized trials did not confirm the benefit of adjuvant CRT upon survival (34,36,41). In the European Organization of Research and Treatment of Cancer (EORTC) study, 218 patients with pancreatic or periampullary cancer were randomized to CRT versus observation after resection (34). The RT was delivered in the same fashion as in the GITSG trial. Infusion 5-FU was substituted for bolus 5-FU and no maintenance chemotherapy was administered. The median survival in the subset of patients with pancreatic cancer was 17.1 months in the CRT arm versus 12.6 months in the observation arm, a difference that did not reach statistical significance (P=0.099). An update of this trial with longer median follow up of 11.7 years further confirmed the absence of a statistical significant advantage for adjuvant CRT (35). The ESPAC-1 (European Study Group for Pancreatic Cancer) was a

randomized trial in a 2 × 2 factorial design. After surgical resection, 289 patients were assigned to observation, CT alone, CRT, or CRT followed by CT (36). In addition, investigators had the option of enrolling patients in 2 similar concurrent trials (one testing CRT *vs.* observation and one testing CT alone *vs.* observation), and the data across the 3 trials were pooled for analysis. CRT regimen was similar to those of the GITSG and EORTC trials although the total radiation dose could be 40 or 60 Gy at the discretion of the treating physician. The results showed a beneficial effect of adjuvant CT upon OS, but a deleterious effect of CRT on survival. A more recent analysis included only patients from the 2 × 2 factorial design trial and again showed a benefit for adjuvant chemotherapy (37).

The results of three historical trials evaluating concurrent chemo-radiotherapy (CRT) are confounded by poor design of the trials, sub-optimal compliance of the intended therapy and analysis. The GITSG study was criticized for slow accrual, small sample size, and suboptimal radiotherapy with a low dose delivered in a splitcourse fashion. The EORTC trial also employed suboptimal radiotherapy similar to the GITSG study. The omission of maintenance 5-FU, small sample size, high proportion of patients forgoing the assigned therapy, and the inclusion of patients with positive surgical margins without stratification were all considered as study design flaws (38). In addition, it has been argued that statistical significance of this possible benefit is achieved with a one-sided log-rank test, which could have been justified at the time this trial was designed (P=0.049) (39). The ESPAC-1 trial has been strongly critiqued for allowing uncontrolled and previous therapy in a substantial number of patients, introducing a selection bias in the enrollment process and using suboptimal radiotherapy (40). There was also a high rate of noncompliance to the treatment regiments, which questions the validity of any analysis and therefore its conclusions (42).

As mentioned above, all trials employed an outdated radiotherapy regimen using low doses and a split-course delivery; and there was absence of central radiation quality control. All of these factors could have easily adversely impacted the outcomes against the CRT arms. As evidence for this adverse impact, a recent secondary analysis of the Radiation Therapy Oncology Group (RTOG) 97-04 clinical trial showed that failure to adhere to prospectively designated criteria for radiotherapy delivery was associated with inferior survival (43).

The above available randomized trials have generated conflicting results, and so the role of adjuvant CRT remains controversial. In light of this dilemma, several recent studies analyzed survival outcomes in patients who did or did not receive postoperative RT using the Surveillance, Epidemiology, and End Results (SEER) database (44-46). Although each of these studies suffers from possible pitfalls inherent in any retrospective analysis, these analyses have the advantage of long follow up and large patient numbers, which permit subgroup analyses not previously possible with the randomized trials (46). Hazard and colleagues (44) examined the effect of RT in resected pancreatic cancer patients. On multivariate Cox regression analysis, a survival benefit was noted in patients with T3, N1 disease. No survival benefit, however, was seen for tumors limited to the pancreas. A subsequent study by Artinyan and colleagues (45) examined the role of adjuvant RT in a smaller patient population with only node-negative disease. The survival benefit associated with adjuvant RT was observed with hazard ration (HR) of 0.87 (95% CI, 0.75-1.00). The latest SEER study by Moody and colleagues (46) included 3,252 patients who underwent resection of nonmetastatic disease; the adjuvant RT was associated with increase survival (HR, 0.87; 95% CI, 0.80-0.96). On subgroup analysis, only stage IIB (T1-3N1) patients had a statistically significant benefit associated with RT (HR, 0.70; 95% CI, 0.62-0.79). The age of the patient and stage of disease were identified as independent factors associated with RT use, which means the younger patients with more advanced disease were more likely to receive RT.

Fur thermore, two large nonrandomized studies also suggested a survival benefit with adjuvant CRT in pancreatic cancer (*Table 2*). A prospective study from Johns Hopkins Hospital analyzed 616 pancreatic cancer patients, who underwent surgery. Adjuvant CRT was associated with improved median, 2- and 5-year survivals compared with no CRT (47). Similarly, the Mayo Clinic reported their 3-decade experience of adjuvant therapy in 466 patients, who underwent R0 resection. Adjuvant CRT significantly improved median, 2- and 5-year survival compared with surgery alone. Patients who received CRT had more adverse prognostic factors than that not receiving adjuvant therapy (48). The radiotherapy dose was 50.4 Gy in both studies.

Unlike previous discussed trials, the Radiation Therapy Oncology Group (RTOG) 97-04 (49) evaluated the efficacy of gemcitabine in the adjuvant setting compared to 5-Fluorouracil (5-FU). 451 patients were randomized to pre- and post-CRT 5-FU versus pre- and post-CRT gemcitabine after resection of pancreatic cancer. Univariate

analysis showed no difference in OS. Pancreatic head tumor patients (n=388) had a median survival and 5-year OS of 20.5 months and 22% with gemcitabine versus 17.1 months and 18% with 5-FU, respectively. On multivariate analysis, patients on the gemcitabine arm with pancreatic head tumors experienced a trend toward improved OS (P=0.08). The local recurrence was 28% and the distant relapse rate was 73%. Despite local recurrence being approximately half of that reported in previous adjuvant trials, distant disease relapse still occurred in ≥70% of patients. To address the issue of high rate of distant metastasis and further define the role of radiotherapy in adjuvant setting, the current EORTC/U.S. Intergroup RTOG 0848 phase III adjuvant trial evaluates the impact of targeted therapy Erlotinib and CRT on OS after completion of a full course of gemcitabine. The impact of adjuvant CRT *vs.* CT on outcome of pancreatic cancer is another end point of this study.

Definitive radiotherapy in locally advanced pancreatic cancer

Thirty percent of patients present as locally advanced pancreatic cancer (LAPC) at time of diagnosis (1). The definition of LAPC is unresectable disease in the absence of distant metastases. But in practice, borderline respectable tumor should be regarded as LAPC because of the high likelihood of achieving an incomplete (R1 or R2) resection. Patients with LAPC are potentially curable if a R0 resection (R0) can be performed after downstaging of the tumor, therefore it should be treated with the intention of delivering curative therapy (31). Quite often, LAPC is treated with chemotherapy, which improves quality of life and survival when compared with best supportive care (50). The additional local treatment with RT may slow the progression of local disease and offer palliation and /or prevention of of symptoms, such as pain, biliary obstruction, bleeding, or bowel obstruction. When chemotherapy is combined with RT, long-term survival has been reported (51). However, the role of radiotherapy in LAPC still remains undefined.

The advantage of CRT over best supportive care was studied in a small prospectively randomized trial (52). 16 patients received CRT and 15 had supportive care. The RT dose was 50.4 Gy (ranged from 25.2 to 60 Gy) and CT was continues infusion 5-FU at 200 mg/m2/d. The median survival was 13.2 months for CRT group *vs.* 6.4 months for support care. The study demonstrated significant improvement of OS and quality of life in the patients received CRT.

Early GITSG randomized trial compared combined CRT (using RT doses of 40 Gy and 60 Gy with 5-FU) followed by additional CT *vs.* 60 Gy RT alone (53). Combined CRT was significantly superior to radiotherapy alone, with mean OS times of 10.4 *vs.* 6.3 months. Higher dose (60 Gy) of radiotherapy did not improve OS compared to 40 Gy, although this may have been also a function of the old delivery technique (2-D) of RT. This study established general consensus that radiotherapy should be given concurrently with chemotherapy in patients with LAPC. Several subsequent randomized trials have compared chemotherapy alone to CRT in LAPC, including 2 ECOG trials (1989, 2008), 1 GITSG trial (1988), and 1 trial by the Fondation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique (FFCD/SFRO) (*Table 3*) (54,5,55,56). Two studies (ECOG 1985 and FFCD/SFRO) showed no survival benefit to CRT. It should be noted that radiotherapy delivery in ECOG 1985 trial was sub-optimal with split-course RT technique; and FFCD/SFRO trial used unusually high dose radiotherapy and non-standard chemotherapy regimen (5-FU and cisplatin) in this setting with increasing toxicity. The GITSG (1988) study and the ECOG 4021 demonstrated survival benefit to CRT. The split-course of radiotherapy and more toxic chemotherapy regimen (streptozotocin, mitomycin, and 5-FU) used in GITSG (1980) could have adversely affected the study outcome. The ECOG4201 is only study using modern radiotherapy techniques (3-D conformal radiotherapy) and more effective chemotherapy gemcitabine (5). Thirty-eight patients were treated with gemcitabine alone and 36 with gemcitabine-based CRT. The dose of radiation was 50.4 Gy. The results showed a small but significant 2-month improvement in median survival with the addition of RT (11.0 *vs.* 9.2 months, P<0.05). The median time to progression was also improved with RT. Although the trial accrued only 74 out of 316 patients as study planned, the results suggest that there may be a role for RT in patients with locally advanced disease, in conjunction with gemcitabine chemotherapy.

Advances in radiotherapy

In majority of the trials published before the early 1990s, conventional RT with larger fields of radiation encompassing the pancreas or pancreatic bed and regional nodes with margin were used. The use of this large volume of radiation fields contributed to high incidence of GI toxicity, especially when concurrent chemotherapy was

Table 3 Selected studies of randomized trails of definitive CRT in pancreatic cancer

Trial	No. of patient	Survival rate (%)	Median Survival in month
GITSG (1981) (53)			
40-Gy CRT (5-FU)	83	40 (1 yr.)	10
60-Gy CRT (5-FU)	86	40 (1 yr.)	10
60-Gy RT	25	10 (1 yr.)	6*
ECOG (1985) (54)			
40-Gy CRT (5-FU)	34	28 (1 yr.)	8.3
CT (5-FU)	37	28 (1 yr.)	8.2
GITSG (1988) (55)			
40-Gy CRT (5-FU - SMF)	24	41 (1 yr.)	10
CT (SMF)	24	19 (1 yr.)	8*
FFCD/SFRO (2008) (56)			
60-Gy CRT (5-FU +CDDP – Gem)	59	32 (1 yr.)	8.6
CT (Gem)	60	53 (1 yr.)	13*
ECOG 4201 (2008) (5)			
50.4 Gy CRT (Gem)	34	45	11
CT (Gem)	35	30	9.2*

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; RT, radiation therapy; 5-FU, 5-fluorouracil; Gem, gemcitabine; CDDP, cisplatin; SMF, streptozocin, mitomycin, 5-FU. *. P<0.05.

employed. Three-dimensional conformal radiotherapy (3-DRT), which uses acquired CT images to allow delineation of target volumes and precise localization of normal structures, provides optimum coverage of the target and maximal sparing of surrounding normal critical organs and tissues. Intensity modulation radiation therapy (IMRT) is a more recent advance in the delivery of RT. It generates more conformal coverage of RT on target and maximizes the sparing normal tissue than 3-DRT. University of Maryland treated 46 patients with adjuvant CRT using IMRT (57). The RT field included elective nodal areas. All patients received CRT based on 5-FU in a schema similar to RTOG 97-04. Rates of acute gastrointestinal (GI) toxicity from this study were compared with those from RTOG 97-04, where all patients were treated with 3-DRT (*Figure 1A and B*). The overall incidence of Grade 3–4 acute GI toxicity was significant lower in patients receiving IMRT-based CRT compared with patients who had 3-DRT. With IMRT, it is possible to deliver doses of 45 to 50 Gy to the typically larger RT fields while escalating the dose to the tumor bed to 54 to 60 Gy (58). Such dose escalation may be necessary for patients with high risk of local recurrence. The higher dose of radiation integrated with newer chemotherapeutic and targeted agents, may be needed to improve both local control as well as overall outcome in this subset of patients.

Several other methods for precise targeting and dose escalation have been studied, including stereotactic body radiation therapy (SBRT). SBRT delivers 1 to 5 ablative doses of radiation to small area only including gross disease with tight margin, as opposed to conventional fractionation of 25 to 28 lower-dose fractions to a large field over normal tissue to cover microscopic extension of disease and regional lymph nodes. The studies using SBRT have demonstrated high rate of feasibility with high rate of local control, but with increase toxicity (*Figure 1C*) (59-62). In a phase II study, SBRT was give to total dose of 30 Gy in 3 fractions to unresectable pancreatic carcinoma [62]. The local control rate was 57%; however, small-bowel toxicity was high (18%), consisting of severe GI mucositis/ ulceration, alone with a 4.5% perforation rate. In a trial conducted at Stanford University, single dose of 25 Gy SBRT was given to a small radiation field. An 84% local control rate at 12 months was reported with 4% grade 2 late toxicity and 9% grade 3 or 4 late GI toxicity (60). Mahadevan *et al.* reported their experience on SBRT using 3 fractions to total dose of 24 -36 Gy (61). After SBRT, patients received gemcitabine

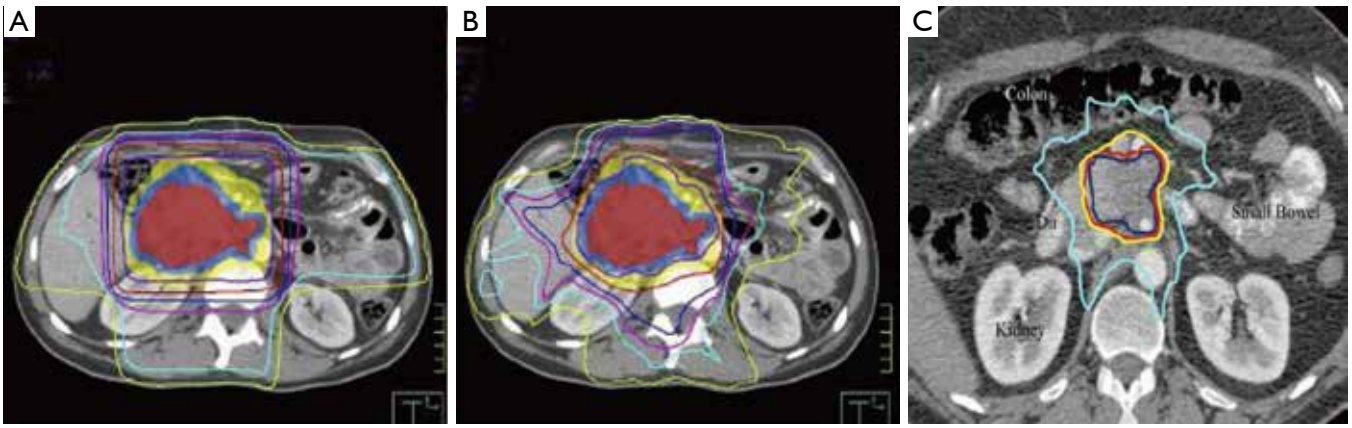

Figure 1 Illustration of isodose plans from 3-D (A), IMRT (B) and SBRT (C).

for 6 months or until tolerance or disease progression. On 36 patients with median follow up 24 months, the local control rate was 78% and the median survival was 14.3 months. Seventy-eight percent of patients developed distant metastasis. There were 25% grade II and 14% grade III GI toxicity. The other application of SBRT in LAPC is to boost primary tumor site after conventional radiotherapy with or without chemotherapy. The Stanford University group (62) enrolled 19 patients onto a prospective study to evaluate this boost concept. 25 Gy single fraction SBRT was delivered to primary tumor site after 45 Gy of conventional radiotherapy delivered in 5 weeks. The local control rate was 94% with 12.5% incidence of late duodenal ulcers. Although the local control rate have been impressive, given the higher rates of GI toxicities and that improved local control has not translated into a survival benefit in these trials, caution should be exercised in using this type of approach.

RT field size is a current topic of interest and research, especially given the increasing interest in dose escalation and more intensity of systemic treatment. Historically, radiation fields have been large, encompassing the pancreas or pancreatic bed with a 2- to 3-cm margin and including lymph node regions, which may be harboring microscopic disease. Growing evidence from other tumor models such as non-small cells lung cancer suggests that small-involved field radiation may be reasonable without compromising local regional control and overall survival (63,64). In a phase I trial of full-dose concurrent gemcitabine and smallinvolved field radiotherapy for LAPC, there was only 1 of 23 patients developed regional nodal recurrence. This trial showed that smaller RT field size might be reasonable (63). In another study using involved field radiation concurrently with full dose of capecitabine 500-600 mg/m^2 twice daily, the local and locoregional progression were 14% and10%, respectively. 14% patients presented with local and systemic disease. There was only one patient who had grade III GI toxicity (64). Although these data are encouraging, the further investigation is still necessary to confirm the use of involved small field of radiation.

Conclusion

The treatment of pancreatic cancer remains challenging. The dismal outcome after various therapeutic strategies highlights the need for continued study of optimizing current treatment and incorporating novel agents into existing regimens. The use of chemotherapy and particularly radiotherapy are controversial because of difficulties interpreting the available randomized data. In neoadjuvant setting, there is no evidence to support routine use of neoadjuvant CRT for resectable disease. However, some patients with borderline resectable pancreatic cancer may benefit from neoadjuvant CRT if the resection can be performed. The assessment of resectability after neoadjuvant CRT is critical to determining the need for surgery, which can have a significant impact on patient survival. With advanced diagnostic images such as CT scan, MRI, PET scan EUS, even minimal invasive procedure of laparoscopy, it is possible to select out such patients, who can be benefit from R0 resection. Newer techniques of delivering RT such as IMRT and SBRT offer the opportunity to improve the efficacy of neoadjuvant treatment due to its better tolerance with chemotherapy and the potential for RT dose escalation.

In the adjuvant setting, CRT is still considered as a standard treatment option in North America. But if an R0 resection can be achieved, only chemotherapy can be recommended. Currently, a reasonable therapeutic strategy in the adjuvant and the definitive settings includes an initial 2 to 4 months of gemcitabine-based chemotherapy, followed by restaging and delivery of 5-FU–based CRT, or gemcitabine-based CRT using 3-DRT or IMRT to involved fields. Further investigations are needed to define more clearly the optimal timing of radiotherapy, dose, field size, and technique. In addition, the employment of more potent systemic agents, including those with radiosensitizing properties may further enhance the efficacy of RT (65). Several phase I/II trials are exploring the efficacy of targeted agents and alternative chemotherapeutic agents (66). ACOSOG Z05031, a phase II trial using cisplatin, 5-FU and α-interferon, has shown promising 2-year OS rate of 55% of and a median survival of 27.1 months (67). Currently, on going RTOG 0848 phase III adjuvant trial is evaluating impact of Erlotinib with CRT on survival in pancreatic cancer.

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Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions

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Abstract: Limited treatment options exist for isolated local recurrence of pancreatic ductal adenocarcinoma (PDA) following surgical resection accompanied by neoadjuvant or adjuvant chemoradiation therapy (CRT). While select patients are eligible for re-resection, recurrent lesions are often unresectable. Stereotactic body radiation therapy (SBRT) represents a possible minimally invasive treatment option for these patients, although published data in this setting are currently lacking. This study examines the safety, efficacy, and palliative capacity of re-irradiation with SBRT for isolated local PDA recurrence.

All patients undergoing SBRT at two academic centers from 2008-2012 were retrospectively reviewed to identify those who received re-irradiation with SBRT for isolated local recurrence or progression of PDA after previous conventionally fractionated CRT. Information regarding demographics, clinicopathologic characteristics, therapies received, survival, symptom palliation, and toxicity was obtained from patient charts. Kaplan-Meier statistics were used to analyze survival and the log-rank test was used to compare survival among patient subgroups.

Eighteen patients were identified. Fifteen had previously undergone resection with neoadjuvant or adjuvant CRT, while 3 received definitive CRT for locally advanced disease. Median CRT dose was 50.4 Gy [interquartile range (IQR), 45.0-50.4 Gy] in 28 fractions. All patients subsequently received gemcitabine-based maintenance chemotherapy, but developed isolated local disease recurrence or progression without evidence of distant metastasis. Locally recurrent or progressive disease was treated with SBRT to a median dose of 25.0 Gy (range, 20.0-27.0 Gy) in 5 fractions. Median survival from SBRT was 8.8 months (95% CI, 1.2-16.4 months). Despite having similar clinicopathologic disease characteristics, patients who experienced local progression greater than *vs.* less than 9 months after surgery/definitive CRT demonstrated superior median survival (11.3 *vs.* 3.4 months; P=0.019) and progression-free survival (10.6 *vs.* 3.2 months; P=0.030) after SBRT. Rates of freedom from local progression at 6 and 12 months after SBRT were 78% (14 of 18 patients) and 62% (5 of 8 patients), respectively. Effective symptom palliation was achieved in 4 of 7 patients (57%) who reported symptoms of abdominal or back pain prior to SBRT. Five patients (28%) experienced grade 2 acute toxicity; none experienced grade ≥3 acute toxicity. One patient (6%) experienced grade 3 late toxicity in the form of small bowel obstruction.

In conclusion, re-irradiation with hypofractionated SBRT in this salvage scenario appears to be a safe and reasonable option for palliation of isolated local PDA recurrence or progression following previous

conventional CRT. Patients with a progression-free interval of greater than 9 months prior to isolated local recurrence or progression may be most suitable for re-irradiation with SBRT, as they appear to have a better prognosis with survival that is long enough for local control to be of potential benefit.

Keywords: Stereotactic body radiation therapy (SBRT); pancreatic cancer; local recurrence; re-irradiation

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Introduction

Recurrent pancreatic cancer after definitive treatment with multimodality therapy universally portends a dismal prognosis, with 5-year survival rates of 5.6% or less (1,2). Unfortunately, this scenario is not uncommon. Among the minority of patients (10-15%) able to undergo potentially curative surgical resection, more than 80% subsequently recur (3,4).

The pattern of recurrence in pancreatic cancer is well-known (4-10). Following resection, approximately 70% develop distant metastases within 2 years, often accompanied by synchronous local recurrence (11,12), while up to 30% exhibit isolated local recurrence (10,13). Autopsy studies have demonstrated that 30% of deaths are due to locally progressive disease, while the remainder result from distant metastases (14). Symptomatic manifestations of local recurrence include pain, bowel obstruction, portal hypertension, biliary obstruction, and malnutrition (15). Although survival is determined chiefly by systemic progression, local progression is an important factor contributing to quality of life (16) and has been associated with decreased time to metastasis (16).

Current therapeutic approaches for patients who develop isolated local recurrence following conventionally-fractionated radiotherapy include palliative chemotherapy and best supportive care, with a very select few undergoing surgical re-resection. Each of these options has significant drawbacks, including: invasiveness and morbidity with re-resection (2,17); systemic toxicity and modest local control with palliative chemotherapy (18); and lack of efficacy with supportive care alone. A possible alternative in this salvage scenario is re-irradiation with stereotactic body radiation therapy (SBRT). SBRT is minimally invasive, can be administered over 5 days or fewer, and may offer a high probability of local control (19-23). Herein, we present a retrospective study of re-irradiation using SBRT at two institutions.

Methods

Patient selection

With IRB approval, records of all pancreatic cancer patients treated with SBRT at two academic centers from 2008-2012 were retrospectively reviewed to identify patients with isolated local recurrence (if previously resected) or isolated local progression (if locally advanced disease) after previous conventional radiotherapy and who subsequently received salvage SBRT. Patients were required to meet the following inclusion criteria: age ≥18, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, histologically confirmed pancreatic adenocarcinoma, local disease recurrence/progression determined by a radiologist on pancreas-protocol CT scan following conventionally-fractionated radiotherapy (≤300 cGy/fraction), and salvage SBRT. Patients with radiographic evidence of distant metastasis prior to SBRT were excluded. Patients received heterogeneous systemic therapies before and/or following re-irradiation with SBRT, but no other forms of local therapy. No exclusions were made based on systemic therapies received.

SBRT planning

Patients underwent simulation supine in an immobilization device. An arterial-phase pancreas-protocol CT scan (1.25-mm slices from T4/T5-L5/S1) with IV and oral contrast was obtained during expiration breath-hold for tumor delineation. A free-breathing CT scan with 4-D respiratory correlation was also obtained to characterize target motion during quiet respiration. If target motion was >5 mm, respiratory gating using the Varian Respiratory Management System™ (Stanford), Cyberknife™ respiratory tracking (Stanford), or the Elekta Active Breathing Coordinator System™ (Hopkins) was utilized during treatment delivery. When available (12 of 18 patients),

FDG-PET/CT scans were fused with simulation scans.

SBRT treatment plans were developed using Eclipse™ (Varian, Palo Alto, CA), Multi-Plan™ (Accuray, Sunnyvale, CA), or Pinnacle™ (Philips, Amsterdam, Netherlands). The gross tumor volume (GTV) was contoured by a radiation oncologist using the simulation scan. An internal target volume (ITV) was then defined after review of diagnostic imaging, respiratory-correlated 4D-CT, pancreas-protocol CT, and FDG-PET/CT scans. Final planning target volume (PTV) was obtained by an additional 1-3 mm uniform margin expansion of the ITV. The dose was prescribed to the isodose line that completely surrounded the PTV and 6-12 co-planar fields were used to generate the plan for non-Cyberknife™ treatments. Dose constraints for organs at risk were employed as follows: duodenum—V_{15Gy}<9 cc, V_{20Gy}<3 cc, V_{33Gy}<1 cc; liver—$D_{50\%}$<12 Gy; stomach—$D_{50\%}$<12 Gy, V_{33Gy}<1 cc; spinal cord—V_{8Gy}<1 cc. Institutional standards for patient-specific dosimetric quality assurance were applied.

SBRT delivery

For non-Cyberknife™-based treatment (N=11), initial patient position was based on cone-beam CT with alignment to spine. Volumetric kV-imaging was then used to align biliary stent and/or fiducials to the digitally-reconstructed radiograph. All fiducials were placed specifically for SBRT image guidance using an endoscopic approach (N=11 patients); complications of fiducial placement were observed in only one patient who experienced laryngospasm and had to return for repeat endoscopy the following day. Common bile duct stents were placed endoscopically for relief of symptomatic biliary obstruction and not for purposes of SBRT image guidance, but if a stent was present, then fiducial placement was deemed unnecessary (N=4 patients). If a stent or fiducials were not present, patients were aligned to spine only (N=3). In patients who had previously undergone intra-tumoral fiducial placement, orthogonal kV/MV or kV/kV projection imaging was used to verify fiducial location before first treatment beam delivery and, if indicated, a secondary shift was performed. Active monitoring of treatment delivery accuracy was accomplished using kV and MV projection imaging.

For CyberKnife™-based treatment (N=7; fiducials required), initial orthogonal kV/MV or kV/kV projection images were obtained to confirm fiducial location. The Synchrony™ respiratory tracking system (Accuray) was then used to correct for tumor-associated motion using a series of optical diodes placed on the patient's chest wall and correlated to the internal fiducials by a computer to generate a model continuously updated during treatment to correct for subtle changes in tumor location.

Clinical outcomes

Clinical data were gathered by retrospective chart review using electronic patient records. Date of progression was defined as the date of first follow-up cross-sectional imaging study showing evidence of distant metastases or local progression as determined by an attending radiologist. Survival was measured from the date of the first fraction of SBRT until date of death or censored at the date of last follow-up if no date of death was available. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistics

Patient demographic, clinicopathologic, and treatment characteristics were summarized using descriptive statistics. Patient characteristics were compared among different patient subgroups using the Mann-Whitney *U* test for comparison of medians and the Pearson chi-square test for comparison of proportions. Survival data were analyzed using Kaplan-Meier statistics and compared between subgroups using the log-rank test. A two-sided alpha level of ≤0.05 was considered significant in all cases. Statistical analyses were performed with SPSS (IBM, Armonk, NY).

Results

Patients

Eighteen patients were identified. Complete demographic, baseline, and treatment characteristics are summarized in *Table 1*. Fifteen patients received neoadjuvant or adjuvant CRT in association with surgical resection, while 3 received definitive CRT for locally advanced disease. Median CRT dose was 50.4 Gy (IQR, 45.0-50.4 Gy) in 28 fractions with median daily fraction size of 1.8 Gy (IQR, 1.8-1.8 Gy). Seventeen of 18 patients (94%) received chemotherapy concurrently with radiotherapy. All patients subsequently received gemcitabine-based maintenance chemotherapy, but eventually developed isolated local disease recurrence/progression without evidence of distant metastasis. Median time to local recurrence/progression following surgery or

Table 1 Demographic, baseline disease, and treatment characteristics

Characteristic	Quantitative measure
Demographics	
Median age [range]	64 [42-72]
Sex	
No. female [%]	8 [44]
No. male [%]	10 [56]
Baseline disease	
Tumor location within pancreas	
No. head [%]	11 [61]
No. body [%]	3 [17]
No. tail [%]	4 [22]
Initial disease stage	
No. resectable who underwent curative surgery [%]	15 [83]
No. with positive margins [%]	6 [40]
No. with positive lymph nodes [%]	11 [73]
No. locally advanced who underwent definitive CRT [%]	3 [17]
First course of radiotherapy (conventional fractionation)	
No. treated neoadjuvantly [%]	4 [22]
No. treated adjuvantly [%]	11 [61]
No. treated definitively [%]	3 [17]
Median dose in Gy [IQR]	50.4 [45.0-50.4]
Median fraction size in Gy [IQR]	1.8 [1.8-1.8]
No. who received concurrent chemotherapy [%]	17 [94%]
No. 5-fluorouracil-based [%]	10 [55]
No. gemcitabine-based [%]	7 [39]
Second course of radiotherapy (re-irradiation with SBRT)	
ECOG performance status prior to SBRT	
No. ECOG 0-1 [%]	17 [94]
No. ECOG 2 [%]	1 [6]
No. who received 5 Gy ×5 (total dose of 25 Gy) [%]	16 [89]
No. who received other regimen [%]	2 [11][a]
No. of patients requiring treatment break or dose reduction [%]	0 [0]
Systemic therapy	
No. who received gemcitabine-based maintenance chemotherapy prior to SBRT [%]	18 [100]
No. who received immunotherapy prior to SBRT [%]	2 [11][b]
No. who received chemotherapy following SBRT [%]	5 [28][c]
Mean no. of cycles received [SD]	2.8 [2.4]

CRT, chemoradiation therapy; SBRT, stereotactic body radiation therapy; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; [a]1 received 4 Gy ×5; 1 received 5.5 Gy ×5; [b]both patients received a pancreatic tumor cell vaccine with ipilimumab; of these 2 patients, one survived for 18.7 months following SBRT and the other currently remains alive 25 months following SBRT; [c]4 received gemcitabine-based regimens, 1 received a 5-FU-based regimen.

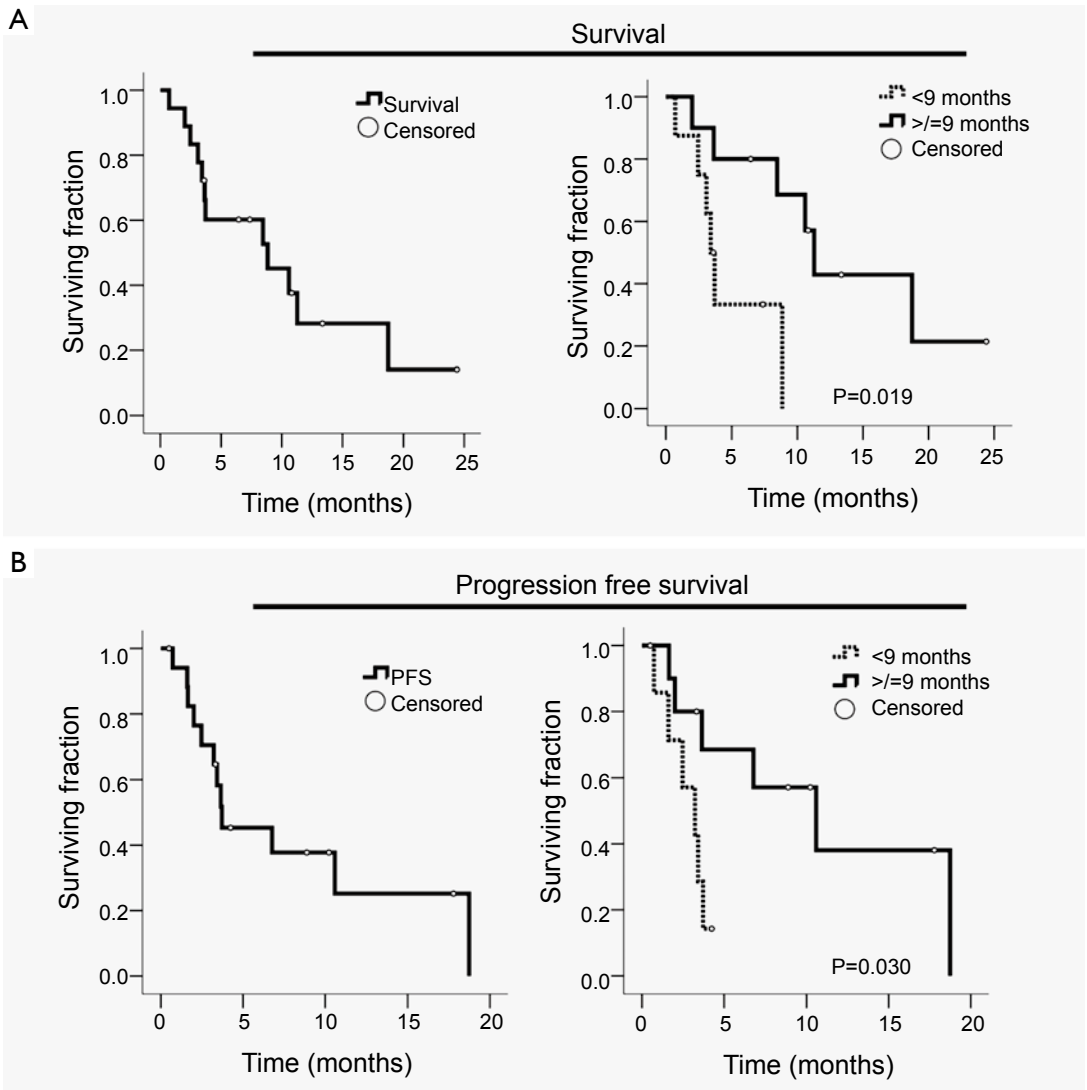

Figure 1 Kaplan-Meier plots. A. Survival measured from the date of SBRT initiation for all patients (left panel) and stratified by time to local recurrence/progression after surgery or definitive chemoradiation of <9 or ≥9 months (right panel); B. Progression-free survival (PFS) measured from the date of SBRT initiation for all patients (left panel) and stratified by time to local recurrence/progression after surgery or definitive chemoradiation of <9 or ≥9 months (right panel). Open circles indicate censored patients.

definitive CRT was 13.1 months (IQR, 7.8-17.5 months). Mean diameter of locally recurrent/progressive disease at SBRT was 2.7 cm (SD, 0.9 cm). All patients underwent re-irradiation of the pancreatic bed with SBRT administered over 5 consecutive daily fractions. Sixteen of 18 patients (89%) received a total dose of 25 Gy (5 Gy ×5), while 1 patient received 20 Gy (4 Gy ×5) and 1 patient received 27 Gy (5.5 Gy ×5). Five patients (28%) received additional chemotherapy following SBRT.

Efficacy

Median follow-up was 34.3 months (range, 6.4-61.6 months) and median interval from local recurrence/progression to SBRT was 2.4 months (IQR, 1.8-5.1 months). Median survival measured from the time of radiographically documented local recurrence/progression was 12.0 months (95% CI, 9.9-14.0 months). Median survival measured from SBRT was 8.8 months (95% CI, 1.2-16.4 months) (*Figure 1A*).

Table 2 Comparison of demographic and clinicopathologic characteristics between patients who developed isolated local recurrence/progression less than versus greater than 9 months following surgery or definitive chemoradiation therapy (CRT)

	All patients (n=18)	<9 months (n=8)	>9 months (n=10)	P
Characteristic				
Age: median years [range]	64 [42-72]	60 [45-72]	67 [42-71]	0.51
Gender: No. male [%]	10 [56]	4 [50]	6 [60]	0.67
ECOG: No. 0-1 [%]	17 [94]	7 [88]	10 [100]	0.25
Tumor diameter: median cm [range]	3 [2.0-4.5]	3 [2.5-4.5]	3 [2.0-4.0]	0.48
Grade: No. moderately differentiated [%]	13 [72]	5 [63]	8 [80]	0.41
Resection margin: No. positive [%]	6 [33]	3 [38]	3 [30]	0.74
No. with lymph node involvement [%]	11 [61]	5 [63]	4 [60]	0.91
No. with perineural invasion [%]	10 [56]	5 [63]	5 [50]	0.60
No. with lymphovascular invasion [%]	10 [56]	4 [50]	6 [60]	0.67
Outcome				
Median survival (months)	8.8	3.4	11.3	0.02
Median progression-free survival (months)	3.7	3.2	10.6	0.03

ECOG, Eastern Cooperative Oncology Group.

Based on previously published surgical data regarding re-resection for isolated local recurrence (2), patients were dichotomized based on whether local recurrence/progression occurred fewer or greater than 9 months following surgery or definitive CRT. The resulting two groups were similar in regard to age, gender, ECOG performance status, median tumor diameter, and histologic grade as well as rates of margin positivity, lymph node involvement, perineural invasion, and lymphovascular invasion (all P>0.05; *Table 2*). Patients who recurred/progressed locally within 9 months of surgery or definitive CRT (*n*=8) survived for a median of only 3.4 months (95% CI, 2.7-4.2 months) after SBRT versus 11.3 months (95% CI, 9.6-12.9 months) for patients who recurred/progressed after more than 9 months (*n*=10; P=0.019) (*Figure 1A*).

Median progression-free survival (PFS) following SBRT was 3.7 months (95% CI, 0.6-6.9 months) (*Figure 1B*). Patients who had recurred/progressed more than 9 months following surgery or definitive CRT had a longer median PFS (10.6 months, 95% CI, 3.1-18.0 months) compared with patients who had recurred/progressed within 9 months (3.2 months, 95% CI, 1.3-5.2 months; P=0.030) (*Figure 1B*). Rates of freedom from local progression at 6 and 12 months were 78% (14 of 18 patients) and 62% (5 of 8 patients), respectively. Of the 12 patients who died during the follow-up period, 8 (67%) remained free from local progression during the interval from SBRT until death. In general, for the patients who did not exhibit local progression, SBRT achieved tumor stabilization, but did not cause a radiographically-evident reduction in tumor size. Seven of the 18 patients (39%) had reported symptoms of abdominal/back pain prior to SBRT; effective symptom palliation was achieved in 4 of these 7 patients (57%) according to follow-up history and physical examination performed within 4-8 weeks of SBRT.

Toxicity

All patients completed SBRT without treatment breaks or dose reductions. Five patients (28%) experienced acute grade 2 toxicity manifesting as fatigue, abdominal pain, anorexia, nausea, and diarrhea. No acute grade ≥3 toxicity was observed. One patient (6%) experienced late toxicity in the form of small bowel obstruction (grade 3). No other late toxicity has been observed at a median follow-up of 8.2 months from SBRT (10.6 months for patients currently alive).

Discussion

Limited treatment options exist for patients with isolated local recurrence/progression of pancreatic cancer after aggressive multimodality therapy including prior irradiation.

Select patients are eligible for re-resection, yet locally recurrent disease is often unresectable as a consequence of vascular involvement, post-radiation fibrosis, or poor performance status. In the largest surgical series examining re-resection with curative intent, resection of disease was achieved in only 16 of 30 patients (53%) who underwent re-laparotomy, and, of these, just 6 (38%) had negative margins, while 3 (19%) were R1 and 7 (44%) were R2 (2). Median survival following re-resection was 11.4 months, while in-hospital morbidity and mortality were 20% and 7%, respectively. Laparotomy additionally interrupted systemic therapy for several weeks. In contrast, SBRT in the setting of locally advanced pancreatic cancer has been shown to have a mild toxicity profile, to achieve high rates of local control, and to require 5 days or fewer for delivery with swift resumption of systemic therapy afterwards (19-21,24) while remaining more cost-effective than conventional radiotherapy or chemotherapy alone (25,26).

Authors of the current study have previously made several prospective reports on SBRT as definitive therapy for locally advanced pancreatic adenocarcinoma (19-21,24). These studies delivered 25 Gy in one fraction [biologically equivalent dose (BED) early/late: 87.5/233.3 Gy], which resulted in acute grade 2 and 3 toxicity ranging from 15-21% and 0-11%, respectively. Extended follow-up from these studies demonstrated late grade ≥3 toxicity to occur at a rate of 9%, typically manifesting as duodenal stricture or perforation (22). These rates were closely reproduced at other institutions, which collectively showed acute and late grade ≥3 toxicity rates of 0-8% and 0-9%, respectively (26-29). Our results (0% acute, 6% late grade ≥3 toxicity) closely correspond to these previously published figures, despite the fact that all patients had undergone conventionally fractionated CRT prior to SBRT. One potential implication of our data, therefore, is that re-irradiation with 5-fraction SBRT (median BED early/late: 37.5/66.7 Gy) may be no more toxic than SBRT administered to radiation-naïve patients, though admittedly the less aggressive dosing regimen employed in the current study renders direct comparison of toxicity rates between studies difficult. One prospective (20) and two retrospective studies (26,30) have examined a similar scenario involving administration of a planned SBRT boost shortly following conventional CRT and offer comparable results with acute and late grade ≥3 toxicity ranging from 0-13% and 0-7%, respectively. It is important to note, however, that the limited median survival of patients with pancreatic cancer may hinder accurate assessment of the true rate of late toxicity following SBRT.

The trials examining SBRT discussed above (19-21) demonstrated excellent local control rates (81-100%), but minimal impact on median survival, which was similar to that observed in our study (8.8 months) at 7.6-11.8 months. This is likely explained by the propensity of pancreatic cancer to microscopically disseminate early (31), rendering local salvage therapy ineffective for prolonging survival due to subsequent emergence of occult distant metastases. Notably, however, two patients in our series who received a pancreatic tumor cell vaccine with ipilimumab prior to local recurrence/progression demonstrated extended survival after SBRT. While we cannot confirm the role of SBRT in prolonging survival in these cases, it is possible that these patients manifested an improved immune response to their tumors following SBRT, similar to the abscopal effect recently reported for patients with melanoma (32,33).

In order to prevent administration of futile local therapy, one strategy is to give chemotherapy for 2-6 months and reassess for metastases before administering re-irradiation with SBRT (30). While this selection approach is preferable, some patients with acute local symptoms may require a more rapid decision regarding local therapy. Our data indicate that SBRT is more effective in prolonging survival for patients who develop isolated local recurrence/progression ≥9 months after surgical resection or definitive CRT. Therefore, in patients for whom a 2-6 month course of chemotherapy is not feasible due to acute symptoms or inability to tolerate further systemic therapy, the decision to give salvage SBRT without induction chemotherapy could be based on the interval between surgery or definitive CRT and local recurrence/progression. Those recurring/progressing after a prolonged time interval (≥9 months) would be more likely to benefit from SBRT, while those recurring/progressing within 9 months would be better served by palliative measures directed at symptom relief (e.g., nerve block, stenting, surgical bypass) with or without salvage chemotherapy.

In conclusion, re-irradiation with hypofractionated SBRT appears to be a safe and reasonable option for palliation of isolated local recurrence or progression of pancreatic adenocarcinoma following previous conventional CRT. Conclusions regarding efficacy are strongly limited by the small number of patients, retrospective study design, and patient heterogeneity. However, our study suggests that a group of patients who locally recur or progress greater than 9 months from surgery or definitive CRT may have a better prognosis regarding long-term survival and may therefore benefit most from re-irradiation with

SBRT given their higher likelihood of living long enough to experience morbidity from eventual local progression. Given the limited data currently available regarding the use of SBRT for salvage treatment of isolated local recurrence or progression of pancreatic adenocarcinoma following previous radiotherapy, these findings may inform clinical decision making and future trial design for this unique patient population.

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Evaluation of normal tissue exposure in patients receiving radiotherapy for pancreatic cancer based on RTOG 0848

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Background: Pancreatic cancer is a highly aggressive malignancy. Chemoradiotherapy (CRT) is utilized in many cases to improve locoregional control; however, toxicities associated with radiation can be significant given the location of the pancreas. RTOG 0848 seeks to evaluate chemoradiation using either intensity-modulated radiation therapy (IMRT) or 3D conformal photon radiotherapy (3DCRT) modalities as an adjuvant treatment. The purpose of this study is to quantify the dosimetric changes seen when using IMRT or 3D CRT photon modalities, as well as proton radiotherapy, in patients receiving CRT for cancer of the pancreas treated per RTOG 0848 guidelines.

Materials: Ten patients with pancreatic head adenocarcinoma treated between 2010 and 2013 were evaluated in this study. All patients were simulated with contrast-enhanced CT imaging. Separate treatment plans using IMRT and 3DCRT as well as proton radiotherapy were created for each patient. All planning volumes were created per RTOG 0848 protocol. Dose-volume histograms (DVH) were calculated and analyzed in order to compare plans between the three modalities. The organs at risk (OAR) evaluated in this study are the kidneys, liver, small bowel, and spinal cord.

Results: There was no difference between the IMRT and 3DCRT plans in dose delivered to the kidneys, liver, or bowel. The proton radiotherapy plans were found to deliver lower mean total kidney doses, mean liver doses, and liver $D_{1/3}$ compared to the IMRT plans. The proton plans also gave less mean liver dose, liver $D_{1/3}$, bowel V_{15}, and bowel V_{50} in comparison to the 3DCRT.

Conclusions: For patients receiving radiotherapy per ongoing RTOG 0848 for pancreatic cancer, there was no significant difference in normal tissue sparing between IMRT and 3DCRT treatment planning. Therefore, the choice between the two modalities should not be a confounding factor in this study. The proton plans also demonstrated improved OAR sparing compared to both IMRT and 3DCRT treatment plans.

Keywords: Pancreatic cancer; RTOG 0848; intensity-modulated radiation therapy (IMRT); proton radiotherapy

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Introduction

Pancreatic cancer accounts for over 30,000 deaths annually in the United States (1). Surgical resection offers the best chance of long term survival. Both local and systemic recurrences are common after a pancreaticoduodenectomy. Adjuvant chemoradiotherapy (CRT) is utilized in many cases to improve locoregional control. But, toxicities associated with radiation may be significant given the location of the pancreas. The ongoing RTOG 0848 protocol seeks to further prospectively investigate the role of CRT using either IMRT or 3D conformal photon radiotherapy (3DCRT) in pancreatic cancer.

Conventional radiation therapy (3DCRT therapy) utilizes X-ray beams which enter and exit the body creating both entrance and exit dose. As a result, non-

Table 1 Patient characteristics

Patient	Histology	Tumor location	TNM stage	Stage grouping	Treatment (Gy/fx)	PTV volume (cm^3)
1	Adenocarcinoma	Head of pancreas	T4 N1 M0	III	50.4/28	639.25
2	Adenocarcinoma	Head of pancreas	T3 N0 M0	IIA	50.4/28	695.62
3	Adenocarcinoma	Head of pancreas	T1 N0 M0	IA	50.4/28	834.17
4	Adenocarcinoma	Head of pancreas	T2 N0 M0	IB	50.4/28	720.85
5	Adenocarcinoma	Head of pancreas	T3 N0 M0	IIA	50.4/28	639.63
6	Adenocarcinoma	Head of pancreas	T4 N0 M0	III	50.4/28	529.97
7	Adenocarcinoma	Head of pancreas	T3 N0 M0	IIA	50.4/28	1,460.02
8	Adenocarcinoma	Head of pancreas	T4 N0 M0	III	50.4/28	885.65
9	Adenocarcinoma	Head of pancreas	T4 N0 M0	III	50.4/28	636.83
10	Adenocarcinoma	Head of pancreas	T4 N0 M0	III	50.4/28	812.61

PTV, planning target volume.

targeted organs and surrounding the pancreatic target are also exposed to radiation. Improvements in radiation delivery techniques have found methods to improve beam conformity around treatment targets. Intensity-modulated radiation therapy (IMRT) is one such method that utilizes multiple beam angles at varying intensities to escalate dose at the target while sparing surrounding normal tissue from high dose regions. One report has suggested IMRT can reduce high grade gastrointestinal (GI) toxicity in the setting of pancreatic cancer (2). Proton radiotherapy is another form of radiation treatment which utilizes charged particle beams. Proton beams deposit most of its energy at a discreet depth within tissue called the "Bragg Peak." The Bragg Peak is predictable and can be created to match the exact depth and thickness of the tumor target. The entirety of the beam's energy is deposited so there is no subsequent exit dose. Some previous dosimetric studies have shown a potential role for proton radiotherapy in the post-operative setting (3). The purpose of this study was to quantify the dosimetric changes seen in using protons or photons with consistent planning parameters in patients receiving CRT for pancreatic cancer.

Patients and methods

Patient selection

We retrospectively evaluated ten patient cases from our institution with pancreatic head adenocarcinoma. See *Table 1* for a summary of patient characteristics. All patients were treated between 2010 and 2013.

Simulation and treatment planning

Patients were simulated in the supine position using intravenous and oral contrast-enhanced CT imaging (GE Lightspeed VCT scanner, Little Chalfont, UK) with 2.5 mm slice thickness. All patients were scanned from above the diaphragm to 3 to 4 cm below the iliac crest. All treatment plans were created with Odyssey 4.8 planning system (Optivus Proton Therapy, Inc., San Bernardino, USA). All planning volume expansions were created per RTOG 0848 treatment guidelines. The gross tumor volume (GTV) was defined as the pre-operative tumor bed, for the purposes of this study, the gross tumor lesions. The clinical target volume (CTV) was defined as the GTV plus a 1 cm manual expansion in all directions. Also included in the CTV were the celiac axis, superior mesenteric artery (SMA), the portal vein (PV) plus a 1 cm expansion in all directions, and an asymmetric aortic expansion. The pancreaticojejunostomy (PJ) or pancreaticogastrostomy (PG) was included in the CTV, if readily visible. Setup uncertainty from respiratory motion and diaphragm movement was accounted for with close attention to target expansions. The planning target volume (PTV) was generated by expanding the CTV by 1.5 and 1.2 cm for the 3DCRT and IMRT plans, respectively. All 3DCRT plans are given a 1 cm margin beyond the PTV to the block edge to account for beam penumbra. The lateral penumbra and distal margin of proton plans generated were between 1-1.5 by the treatment planning system based on the beam energy selected.

A dose of 50.4 Gy given in 28 fractions was delivered to the PTV. All plans were optimized to allow 95% isodose

coverage of at least 90% of the PTV. The proton plan beam arrangements consisted of 2 to 4 beams at oblique angles. The median proton beam energy was 250 MeV with some minor deviations depending on the depth of the target. The depth of the proximal and distal edge helped determine the beam energy selected. Our institution uses a passive scattering beam system which requires a patient portal-specific collimating aperture to shape the dose to the target field laterally. A range compensator was used to conform the dose to the distal aspect of the target volume. A spread-out Bragg peak to cover the target in the beam direction is achieved with a modulator wheel. All IMRT plans consisted of 6 to 9 coplanar, non-parallel opposed 6 MV photon beams delivered with a multi-leaf collimator using a step-and-shoot technique. Each 3DCRT plans each consisted of a 4-field box (AP, PA, RL, LL) using 15-24 MV photon beams delivered with either a multi-leaf collimator or custom-cut block.

Normal tissue dose-volume constraints per RTOG 0848 were strictly adhered to. For total kidney $D_{50\%}$ <18 Gy and mean dose <18 Gy. If there is only one kidney present then the $D_{15\%}$ ≤18 Gy. Mean liver dose was ≤25 Gy. The maximum dose to stomach and bowel was kept ≤54 Gy and $D_{15\%}$ <45 Gy. The max dose to a point 0.03 cm^3 on the spinal cord was kept ≤45 Gy.

Plan evaluation and analysis

In order to compare the plans with the different modalities and beam arrangements, dose-volume histograms (DVH) were calculated and analyzed. The organs at risk (OAR) being evaluated in this study are the kidneys, liver, small bowel, and spinal cord. Analysis was performed for the volume of kidney receiving 15 Gy (V_{15}), 20 Gy (V_{20}), and mean kidney doses were collected for the left, right and bilateral kidneys. The small bowel V_{15} and V_{50}, the dose delivered to 1/3 of the liver ($D_{1/3}$), mean liver dose, and the maximum spinal cord dose were also analyzed. Each plan was created to ensure that 90% of the PTV received at least 95% of the prescription dose and at least 99% of the CTV received 95% of the prescribed dose.

Conformity indices were also obtained and analyzed for plans between the three treatment modalities. The homogeneity index (HI) was defined as the difference between the maximum and minimum dose to the target volume ($D_{1\%}$ and $D_{99\%}$, respectively) divided by the prescription dose (4,5). Uniformity index (UI) was also used; it was defined as the ratio of $D_{5\%}$ to $D_{95\%}$ (6,7). Both HI and UI were utilized to assess overall plan uniformity per previously established methodology (8). The conformity index was defined, per RTOG guidelines, as the volume of the 95% isodose curve divided by the PTV volume. To determine statistical significance, ANOVA and two-tailed paired *t*-tests were performed with P values <0.05 considered to be statistically significant.

Results

A total of ten patient scans were utilized for this study. Three treatment plans were created on each scan: proton, IMRT, 3DCRT. *Table 2* presents dose-volume parameters obtained from these plans. Dose distributions for liver, kidney, and small bowel from two of our study patients are presented in *Figure 1*. The CTV was encompassed by the 95% isodose line in all cases. At least 95% of the PTV was encompassed by the 95% isodose line. Separate plans were generated and optimized for all ten study patients (*Figure 2*). All treatment plans were created in accordance with RTOG 0848 treatment planning parameters. The GTV and CTV were held constant in each patient for each of the three plans.

Proton vs. IMRT

First, we compared dose-volume parameters of the IMRT plans with those of proton plans. The proton plans resulted in a lower mean right (7.59 *vs.* 15.77 Gy, P=0.033), mean left (8.24 *vs.* 17.03 Gy, P=0.004), and mean total kidney dose (8.10 *vs.* 16.43 Gy, P=0.003). The mean liver dose was reduced (5.97 *vs.* 11.81 Gy, P=0.009) as well as the liver $D_{1/3}$ (4.38 *vs.* 13.4 Gy, P=0.017). The maximum dose to the spinal cord was also reduced (12.09 *vs.* 35.16 Gy, P=0.001). IMRT provided better homogeneity (0.43 *vs.* 0.16), uniformity (1.11 *vs.* 1.36), and conformity (1.19 *vs.* 0.74) relative to the proton plans. This was unsurprising given the inverse nature of the IMRT treatment planning.

Protons vs. 3DCRT

The next comparison looked at dose-volume parameters between proton and 3DCRT plans. The proton plans resulted in decreased right, left and total kidney V_{20} and mean doses. There was a lower kidney V_{15} seen in the proton plans. The liver $D_{1/3}$, mean liver dose, maximum spinal cord dose, bowel V_{15} and V_{50} were all decreased in the proton plans (*Table 2*). The 3DCRT plans demonstrated

Table 2 DVH parameters (± SD) averaged over ten patients with P values for comparison

Parameters	Proton	IMRT	3DCRT	P value		
				Proton *vs.* IMRT	Proton *vs.* 3DCRT	IMRT *vs.* 3DCRT
Right kidney						
V_{20} (%)	13.34±17.91	28.56±24.35	40.14±25.34	0.131	0.014	0.311
Mean (Gy)	7.59±7.97	15.77±7.85	18.45±11.35	0.033	0.023	0.547
Left kidney						
V_{20} (%)	16.66±23.57	37.73±23.01	39.83±22.74	0.058	0.038	0.840
Mean (Gy)	8.24±5.05	17.03±6.67	17.38±8.67	0.004	0.012	0.920
Total kidney						
V_{15} (%)	22.22±15.85	45.15±23.57	43.95±19.83	0.020	0.014	0.903
V_{20} (%)	15.57±12.76	33.22±22.10	40.40±20.30	0.042	0.004	0.458
Mean (Gy)	8.10±4.26	16.43±6.54	18.05±8.71	0.003	0.004	0.643
Liver						
$D_{1/3}$ (Gy)	4.38±5.29	13.40±9.41	14.60±12.89	0.017	0.039	0.815
MLD	5.97±2.59	11.81±5.73	11.22±5.44	0.009	0.017	0.814
Spinal cord						
D_{max} (Gy)	12.09±7.80	35.16±3.28	33.04±9.56	0.001	0.001	0.515
Bowel						
V_{15} (%)	54.39±24.27	76.19±17.27	80.71±20.49	0.033	0.017	0.600
V_{50} (%)	4.79±4.20	21.22±18.25	32.43±23.49	0.020	0.005	0.249

DVH, dose-volume histograms; 3DCRT, 3D conformal photon radiotherapy; IMRT, intensity-modulated radiation therapy.

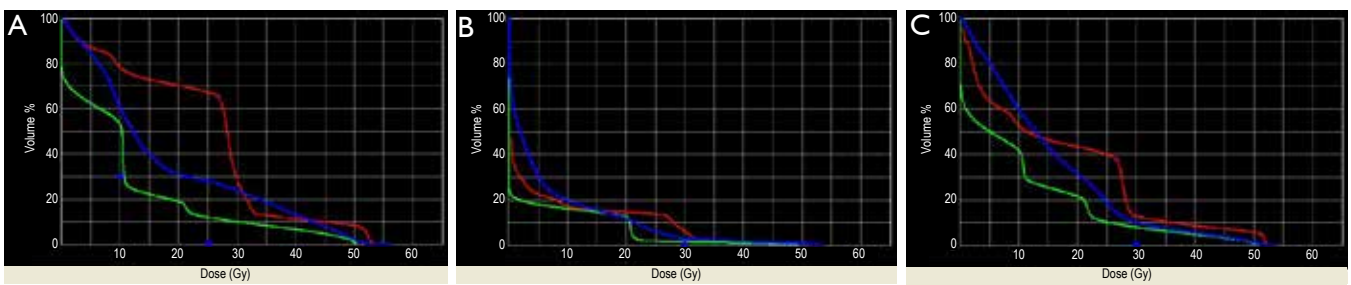

Figure 1 Cumulative DVH graph of one patient. (A) Bowel; (B) liver; (C) bilateral kidney. Red, 3DCRT; blue, IMRT; green, proton. DVH, dose-volume histograms; 3DCRT, 3D conformal photon radiotherapy; IMRT, intensity-modulated radiation therapy.

better homogeneity (0.43 *vs.* 0.16) and better uniformity (1.36 *vs.* 1.18). The conformity was better in the proton plans (0.74 *vs.* 1.47).

IMRT vs. 3DCRT

Finally, we compared dose-volume parameters between IMRT plans with 3DCRT plans. There was no significant difference seen in the OAR between these plans. The IMRT plans resulted in better uniformity (1.11 *vs.* 1.18) and conformity (1.19 *vs.* 1.47) but there was no difference in homogeneity (0.16 *vs.* 0.16).

Discussion

The results of our study demonstrate a significant tissue-sparing benefit of proton plans over the IMRT and 3DCRT plans. Target coverage was adequate in each of these treatment planning modalities but the amount of normal tissue irradiated differed among them. Clinically acceptable

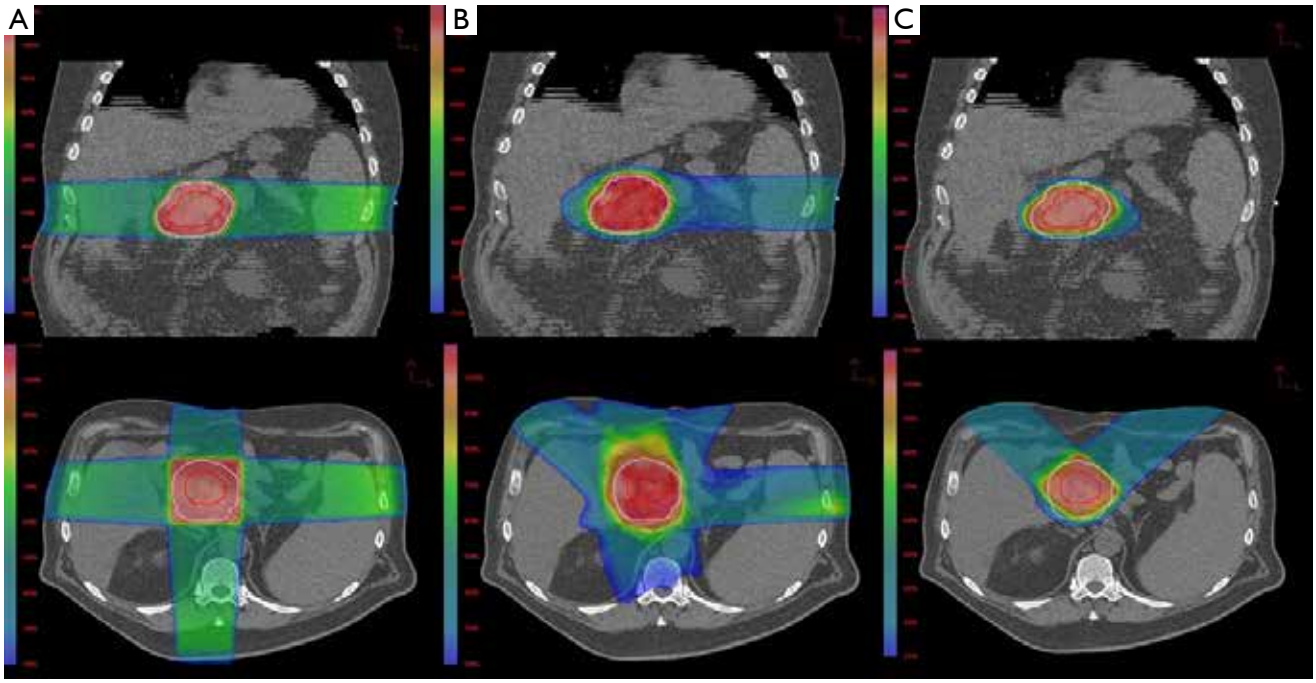

Figure 2 Transverse and coronal images of the (A) 3DCRT; (B) IMRT; and (C) proton plans. 3DCRT, 3D conformal photon radiotherapy; IMRT, intensity-modulated radiation therapy.

plans were generated for all ten patients with each of the three treatment modalities. Target coverage was achieved in each plan despite a significant patient-to-patient variation in target volume size and shape. PTV volumes ranged from 530 to 1,460 cc (median 708 cc), suggesting that each of these three modalities could provide clinically acceptable treatment plans at least in terms of target coverage. All target volumes were drawn per RTOG 0848 radiation guidelines with several patients having locally advanced disease (see *Table 1*). This may explain some of the larger target volumes treated.

Pancreatic tumors arise most frequently in the head of the pancreas, which is typically located to the right of midline. It is not uncommon for one kidney to receive more radiation dose than the other. This is also reflected in our data, which show the right kidney receiving a higher mean dose than the left kidney. The intrinsic properties of proton beams should reduce both total and unilateral kidney dose. Protons have an inherent dosimetric advantage over photons due to their absence of exit dose. This results in a reduction in the volume of kidney receiving low doses of radiation when compared with IMRT and 3DCRT plans (*Figure 1C*). There is a wide separation of the curves in the low dose region of the DVH, indicating a large difference in the volume of tissue being irradiated by low doses of radiation. The difference begins to dissipate at volumes receiving closer to the prescribed dose. Some studies have reported that 3DCRT plans may cause small increases in kidney volumes exposed to higher doses of radiation (9). On the other hand, it is unsurprising that there was a lack of difference in mean total kidney dose between the IMRT and 3DCRT plans. It would be difficult to avoid the nearest kidney with photon beams given its proximity to the pancreatic target.

Proton beams have a Bragg peak that allow for a lower entrance dose. The Bragg peak, in addition to the characteristic absence of exit dose, results in a lower integral dose delivered to the liver. Our results demonstrate a significantly lower MLD in the proton plans, which is consistent with a lower integral liver dose. Even the liver partial volume doses were significantly lower. *Figure 1B* shows distinct separation of the curves in the low-dose region of the DVH. In comparison to the kidney DVH, there is a less striking separation of the curves in the liver DVH.

Radiation toxicity to the bowel is another significant matter that has been evaluated in numerous pancreatic irradiation studies. Previous study findings include a significant dose-response relationship for every increment

of 5 Gy above ≥15 Gy, as well as a significant volume effect with V_{15} volumes greater than 150 cm^3 (10-12). The dose-volume and fraction-size dependence of bowel toxicity is challenging to interpret given the wide range of toxicities reported in the literature. Modern series reviewed by QUANTEC generally confirm the established dose tolerances commonly used in the clinical setting (13), and institutions commonly impose a V_{50} <5% to limit late toxicities such as obstruction and perforation.

In our study, the volume of irradiated bowel was lower in the proton plans at both low (V_{15}) and high (V_{50}) dose regions. Proton beam characteristics, along with the flexibility to select a number of beam arrangements, resulted in a lower integral bowel dose. Looking at *Figure 1A* it is evident that there is a large volume of bowel receiving a low dose in all three plans. The greatest difference in volume irradiated occurred at the lower dose region of the DVH. However, given that the proton plans also have a significantly lower V_{50} volume than the 3DCRT (4.79% *vs.* 32.43%, P=0.005) plans, one clinical implication may be that proton therapy offers a means of improving the therapeutic ratio. The bowel is a large organ and is difficult to avoid when treating the post-operative pancreatic target.

The IMRT and 3DCRT plans generate relatively large low-dose regions in comparison to proton plans. In our study, there was no significant difference between the volumes of low-dose regions treated by the IMRT and 3DCRT plans. This was indicated by the lack of a significant difference between the MLD, V_{15} bowel and V_{15} kidney parameters. In contrast, the proton plans resulted in significantly smaller low-dose regions in comparison to IMRT. Again, the lack of exit dose seen in proton plans contributes to a much smaller integral dose. The optimal radiotherapy technique for pancreatic cancer, however, is still unique for each patient.

Several studies have been performed comparing these treatment modalities focusing on plan optimization and target coverage (3,14). Nichols *et al.* compared IMRT and proton radiotherapy plans on eight patients with resected pancreatic head cancers (3). They found that the proton plans met all normal tissue constraints and were isoeffective with the corresponding IMRT plans in terms of PTV coverage. However, the proton plans offered significantly reduced exposure to the bowel, stomach, and right kidney. Bouchard *et al.* compared IMRT and proton radiotherapy as a means of dose escalation for pancreatic cancer. They concluded that the optimal modality for dose escalation still depended on the pancreatic tumor position in relation to OAR anatomy (14). Hypofractionated proton treatment regimens have also been investigated, both as part of concurrent or neoadjuvant treatment. Preliminary findings from these studies show dosimetrically feasible results with tolerable toxicities and acceptable target coverage (9,15). It appears that proton radiotherapy may warrant further investigation as a means of improving the therapeutic ratio.

The aim of our current study was to compare radiation exposure to normal tissues while using IMRT or 3DCRT to treat pancreatic cancer per RTOG 0848. There was consistent overlap between the PTV and OAR so that no one technique could simultaneously achieve full target coverage while fully respecting OAR constraints. Furthermore, the size and extent of the target volume may preclude the use of certain modalities. Nonetheless, significant conclusions may still be drawn from these generated plans, in which full target coverage was obtained with reasonable uniformity and conformity. Another limitation of the current study was the lack of motion management. However, both motion management and daily IGRT are not required per RTOG 0848. The abdomen is a very mobile part of the body, which creates many challenges with normal breathing motion. Target volume motion during respiration may significantly affect beam selection during the planning process.

In conclusion, there was no difference between the IMRT and 3DCRT plans in dose delivered to the kidneys, liver, or bowel. The proton plans did, however, consistently deliver lower mean total kidney doses, mean liver doses, and liver $D_{1/3}$ compared to the IMRT plans. The proton plans also gave less mean liver dose, liver $D_{1/3}$, bowel V_{15}, and bowel V_{50} in comparison to the 3DCRT plans.

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Neoadjuvant therapy for localized pancreatic cancer: guiding principles

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Abstract: The management of localized pancreatic cancer (PC) remains controversial. Historically, patients with localized disease have been treated with surgery followed by adjuvant therapy (surgery-first approach) under the assumption that surgical resection is necessary, even if not sufficient for cure. However, a surgery-first approach is associated with a median overall survival of only 22-24 months, suggesting that a large proportion of patients with localized PC have clinically occult metastatic disease. As a result, adjuvant therapy has been recommended for all patients with localized PC, but in actuality, it is often not received due to the high rates of perioperative complications associated with pancreatic resections. Recognizing that surgery may be necessary but usually not sufficient for cure, there has been growing interest in neoadjuvant treatment sequencing, which benefits patients with both localized and metastatic PC by ensuring the delivery of oncologic therapies which are commensurate with the stage of disease. For patients who have clinically occult metastatic disease, neoadjuvant therapy allows for the early delivery of systemic therapy and avoids the morbidity and mortality of a surgical resection which would provide no oncologic benefit. For patients with truly localized disease, neoadjuvant therapy ensures the delivery of all components of the multimodality treatment. This review details the rationale for a neoadjuvant approach to localized PC and provides specific recommendations for both pretreatment staging and treatment sequencing for patients with resectable and borderline resectable (BLR) disease.

Keywords: Pancreatic cancer (PC); neoadjuvant therapy

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Introduction

Pancreatic cancer (PC) is a rising public health threat and is anticipated to account for over 48,000 cancer-related deaths by 2020—a death rate which will only be surpassed by lung cancer (1). In an era when the oncologic treatments of many solid organ cancers have made significant advances, it is sobering that the survival of patients with PC remains largely unchanged (2). Over the past 30 years, even among patients with localized PC who were managed with immediate surgery (surgery-first), the median survival rate is, at best, only 24 months (3). The majority of patients developed systemic recurrence even after margin negative (R0) resections, suggesting that PC is a systemic disease, even in the absence of radiographic evidence of distant metastases (4-6). Despite current practice guidelines, which recommend a surgery-first approach for localized PC, the application of a local therapy, such as surgery, for the treatment of a systemic disease is in contradiction with accepted oncologic principles of stage-specific treatment (7). An alternative approach is to administer early systemic therapy prior to surgery (neoadjuvant therapy) for the management of systemic disease that is suspected but not radiographically confirmed. Patients who have aggressive tumor biology and develop disease progression during neoadjuvant therapy can be spared an operative

Table 1 Prospective randomized trials of adjuvant therapy for PC

Study, year	Pt No.	Was it standardized?			Chemotherapy	Outcome
		Pathology review	Pre-Rx Imaging	XRT QA/QC		
GITSG (11), 1985	43	No	No	No	Bolus 5-FU	Improved median survival for those who received adjuvant therapy (20 *vs.* 11 mo). Two-yr OS 42% *vs.* 15%
EORTC (12), 1999	114	Yes	No	No	5-FU infusion	No statistically significant difference in survival (17.1 *vs.* 12.5 mo)
ESPAC1 (13), 2004	541	No	No	No	Bolus 5-FU	Improved median survival for chemotherapy alone (19.4 mo). No benefit for XRT
RTOG 9704 (14), 2006	442	Yes	Yes	Yes	Gemcitabine *vs.* 5-FU infusion	Nonsignificant trend favoring gemcitabine before and after chemoXRT
CONKO-001 (15), 2007	354	No	No	N/A	Gemcitabine	Improved median disease free survival (13.4 *vs.* 6.9 mo)
ESPAC3 (16), 2010	1,088	No	No	N/A	Bolus 5-FU *vs.* gemcitabine	No difference in DFS or OS between 5-FU and gemcitabine

PC, pancreatic cancer.

intervention with limited oncologic benefit. In this review, we will highlight the current status of PC staging, delineate recommendations for stage-specific treatment sequencing, and highlight important time points in clinical decision-making during therapy.

Limitations of current staging of PC

The foundation of modern oncology is the utilization of stage-specific therapies in order to maximize survival and quality of life for all treated patients. The success of achieving this goal is dependent on the ability to accurately discriminate between different disease stages. The staging of PC was once defined by operative exploration and the surgeon's intraoperative assessment of resectability. However, the current staging of PC is now based on the pre-operative, objective radiologic classification of critical tumor-vessel relationships and the presence/absence of extrapancreatic disease (8). Although contrast enhanced computed tomography (CT) provides highly accurate assessments of such tumor-vessel relationships, the detection of metastatic disease is imperfect and approximately 10-20% of PC patients are discovered to have unanticipated metastases at the time of laparoscopy or laparotomy (9,10). Furthermore, over 76% of patients who undergo surgical resection will develop metastatic disease as the first evidence of disease recurrence (5,6). Therefore, the majority of patients with presumed localized PC have clinically occult metastatic disease at the time of diagnosis, and current imaging modalities cannot discriminate between patients who have microscopic metastatic disease and patients who may truly have localized disease.

Given the high likelihood of disease recurrence after resection, multiple randomized clinical trials have assessed the benefit of adjuvant chemotherapy or chemoradiation in an effort to improve survival in patients with localized PC. *Table 1* summarizes the key adjuvant studies which provide a reference to which neoadjuvant therapy must be compared. Although the trials cannot be directly compared to one another due to differences in treatment design, staging requirements, and patient characteristics, it is important to note that the median overall survival for all trials was consistently between 20-24 months (11-13,15). In addition, all trials reported a significant proportion (a minimum of 30-45%) of patients who failed to receive all intended adjuvant treatment and highlight the difficulty in administering adjuvant therapy after pancreatectomy (17). Inherent in the design of adjuvant trials is a selection bias which excludes patients who experience significant surgical morbidity or mortality from surgery. These patients do not an experience an adequate recovery to be considered for trial enrollment. When these additional patients are taken into consideration, approximately 50% of patients who undergo pancreatectomy for PC will not receive adjuvant therapy (18). Given the high risk of patients with localized PC who develop systemic disease recurrence, a reliance

Table 2 Potential advantages of neoadjuvant therapy

Benefits of neoadjuvant therapy
The ability to deliver systemic therapy to all patients
Identification of patients with aggressive tumor biology (manifested as disease progression) at the time of post-treatment, preoperative restaging who thereby avoid the toxicity of surgery
Increased efficacy of radiation therapy; free radical production in a well oxygenated environment
Decreased radiation induced toxicity to adjacent normal tissue as the radiated field is resected at the time of pancreatectomy
Decreased rate of positive resection margins; SMA margin in particular
Decreased rate of pancreatic fistula formation
Potential for the downstaging of borderline resectable tumors to facilitate surgical resection
Disadvantages of neoadjuvant therapy
Potential for complications from pre-treatment endoscopic procedures
Biliary stent related morbidity; stent occlusion during neoadjuvant therapy
Disease progression obviating resectability; loss of a "window" of resectability which may occur (rarely) in the borderline resectable patient
Physicians have to work together during the preoperative phase; discrete handoff from surgeon to medical oncologist to radiation oncologist is not possible in the neoadjuvant setting (as occurs with adjuvant therapy)

on adjuvant therapy to treat micrometastatic disease is troublesome when it can only be successfully administered to half of the at-risk population.

Rationale for neoadjvuant treatment sequencing

To address the limitations of adjuvant therapy, a growing interest has emerged in alternative treatment sequencing. Neoadjuvant therapy for PC has several theoretical advantages over adjuvant therapy (summarized in *Table 2*). In contrast to an adjuvant approach, neoadjuvant therapy ensures the delivery of all components of multimodality treatment to all patients who undergo a potentially curative pancreatectomy. Importantly, since neoadjuvant therapy offers an "induction" phase lasting approximately 2-3 months, individuals with unfavorable tumor biology who develop early metastatic disease are identified prior to surgery. Importantly, in the subset of patients (up to 20-30%) who are found to have disease progression after induction therapy (before surgery), the morbidity of an operation is avoided. When chemoradiation is utilized in neoadjuvant therapy, the delivery of chemoradiation in a well-oxygenated environment improves the efficacy of radiation and decreases the toxicity to adjacent normal tissue (19,20). The addition of radiation has important pathologic implications with several series reporting decreased rates of positive margins (R1 or R2) and node positive disease (21-23).

When neoadjuvant therapy was first introduced as an alternative to a surgery-first approach, several concerns were raised by the surgical community pertaining to safety and feasibility. Foremost was the concern that the patients with localized PC may develop local disease progression which would prevent potentially curative surgical resection; the "window of opportunity" for surgery could be lost. Over the last decade as the experience with neoadjuvant therapy has developed, concerns regarding local disease progression have not been realized. In the largest combined experience with neoadjuvant therapy for patients with resectable PC (a broad definition of resectable used in these studies), less than 1% of eligible patients were found to have isolated local disease progression at the time of re-staging after neoadjuvant therapy (before planned surgery) (24,25). Disease progression during or after neoadjuvant therapy, if it occurs, is usually seen at distant sites such as the liver, peritoneum, and lung. In addition, theoretical concerns over the toxicity of neoadjuvant therapy and the impact of treatment-related side effects on operative morbidity and mortality were also not observed (24-26). In fact, the incidence of pancreatic fistula, the most frequent serious complication associated with pancreatectomy, has been demonstrated to be reduced after neoadjuvant therapy as the treated pancreas becomes more firm with a decrease in enzyme production (21-23). With regard to overall complications, a recent analysis of the NSQIP database demonstrated no differences in 30-day mortality and postoperative morbidity rates among patients

Table 3 Definition of resectability used by the multidisciplinary PC working group at the Medical College of Wisconsin

Resectable
Tumor-artery relationship: no radiographic evidence of arterial abutment (celiac, SMA, or hepatic artery)
Tumor-vein relationship: tumor-induced narrowing ≤50% of SMV, PV, or SMV-PV
Borderline resectable
Artery: tumor abutment (≤180°) of SMA or celiac artery. Tumor abutment or short segment encasement (>180°) of the hepatic artery
Vein: tumor induced narrowing of >50% of SMV, PV, or SMV-PV confluence. Short segment occlusion of SMV, PV, SMV-PV with suitable PV (above) and SMV (below) to allow for safe vascular reconstruction
Extrapancreatic disease: CT scan findings suspicious, but not diagnostic of, metastatic disease (for example, small indeterminate liver lesions which are too small to characterize)
Locally advanced
Artery: tumor encasement (>180°) of SMA or celiac artery
Vein: occlusion of SMV, PV, or SMV-PV without suitable vessels above and below the tumor to allow for reconstruction (no distal or proximal target for vascular reconstruction)
Extrapancreatic disease: no evidence of peritoneal, hepatic, extra-abdominal metastases
Metastatic
Evidence of peritoneal or distant metastases

PC, pancreatic cancer.

treated with neoadjuvant therapy as compared to patients who received surgery-first (27).

Importantly, the multidisciplinary care is the cornerstone of successful administration of neoadjuvant therapy. The scope of the multidisciplinary team is vast and includes medical, surgical, and radiation oncologists, diagnostic radiologists, advanced endoscopists, genetic counselors, dietitians, and endocrine specialists. Before embarking on a neoadjuvant approach, all patients should have the benefit of having their case reviewed in a multidisciplinary conference where the optimal treatment plan can be established and the course of treatment outlined prior to the initiation of any therapy. We have found that when all members of the treatment team are engaged and aligned with basic treatment principles (detailed below), the patients' care and treatment experience are optimized.

Principle #1: radiographic determination of clinical stage of disease

The first and most critical step in the management of PC is the determination of the clinical stage of disease and establishment of a histologic diagnosis. All disease-specific and stage-specific treatment planning is predicated on this step. With PC, it is critically important to use standardized, objective radiologic criteria for clinical staging. Modern imaging techniques have revolutionized the clinical staging of PC. Before the development of multidetector CT, up to 30% of patients with presumed resectable PC were found, at the time of operation, to have either metastatic disease or local tumor-associated vascular invasion which precluded resection (28). Currently, precise and objective anatomic radiographic criteria are used to determine the extent of the tumor-vascular relationship and to categorize clinical staging (*Table 3*). PC can be broadly divided into patients with inoperable disease (metastatic or locally advanced) and operable disease [borderline resectable (BLR) or resectable]. The majority of patients will present with metastatic disease, as evidenced by ascites/peritoneal implants, liver, or lung metastases. In the absence of metastatic disease, the clinical stage is determined by the relationship of the primary tumor to adjacent vasculature. As a general rule, any tumor abutment (≤180 degree tumor-vessel interface) or encasement (>180 degree) of the celiac axis, common hepatic artery, or SMA should be considered a contraindication to immediate surgery. A patient is deemed to have locally advanced, unresectable disease when: (I) the tumor encases the SMA or celiac axis, as defined by >180 degrees of the circumference of the vessel; or (II) there is occlusion of the SMPV confluence without the possibility

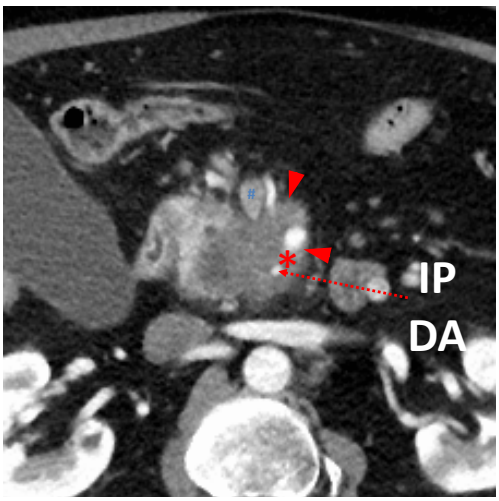

Figure 1 Locally advanced PC. SMA is labelled with * and arrows define the hypodense tumor which encases (>180 degrees) of the SMA. PC, pancreatic cancer.

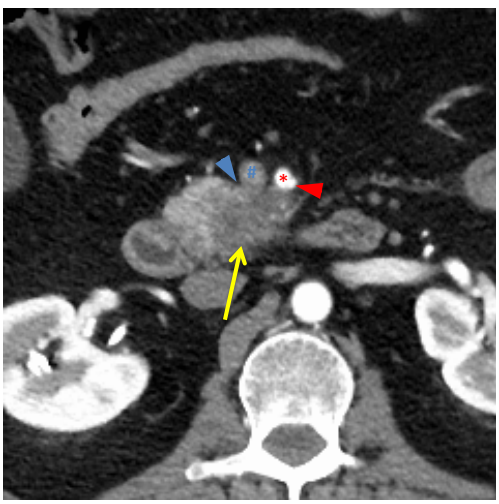

Figure 2 BLR PC. SMV is labelled with # and SMA is labelled with *. Note the hypodense tumor which abuts both the SMV and SMA. BLR, borderline resectable; PC, pancreatic cancer.

for venous reconstruction (*Figure 1*). Patients who have tumor abutment, without encasement, of the SMA or celiac axis, or short segment encasement of the hepatic artery are considered to have BLR PC (*Figure 2*) (29). In addition, patients with tumors that cause >50% narrowing or short segment occlusion of the SMV/PV that may be amenable to reconstruction are also considered to be BLR. There is emerging consensus that even more subtle tumor-

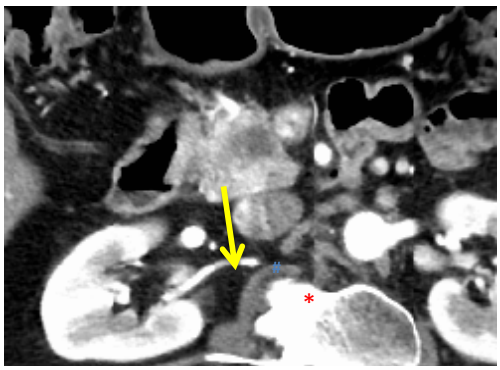

Figure 3 Resectable PC. SMV is labelled with # and SMA is labelled with *. A hypodense tumor is present in the pancreatic head with preservation of the fat plane between the pancreas and the SMV. No tumor abutment of the SMA. PC, pancreatic cancer.

vein abutment may be best considered BLR, especially with respect to the use of neoadjuvant therapy rather than surgery-first (30). Finally, patients who have radiographic lesions which are indeterminate for metastases (usually too small to accurately characterize), even in the absence of SMA abutment or venous narrowing, are also considered by some institutions to have BLR PC (31). Radiographic findings of a resectable PC are (I) the absence of tumor-arterial abutment or encasement; and (II) <50% narrowing of the SMV/PV (*Figure 3*).

Our preferred algorithm for the initial diagnostic work-up and management of suspected PC is summarized in *Figure 4*. The single most important imaging tool for the detection and staging of PC is a CT scan. Current multi-detector protocols utilize dual-phase technique, with the acquisition of arterial phase images at 30 seconds after IV injection of contrast and portal venous images approximately 1 minute after injection. A rapid injection of intravenous contrast allows for the maximal enhancement of the pancreas and mesenteric vasculature (10). At least two phases of contrast-enhanced helical scanning are required. The first (arterial) phase is performed from the diaphragm through the horizontal portion of the duodenum in order to define the relationship of the tumor to the adjacent arteries and to determine the presence or absence of aberrant arterial anatomy. The arterial phase images are used for visualization of the primary tumor and optimal assessment of the tumor-artery relationships. Arterial phase images allow low-density adenocarcinomas to be distinguished from pancreatic neuroendocrine tumors, which are classically hypervascular in the arterial phase. The second (venous)

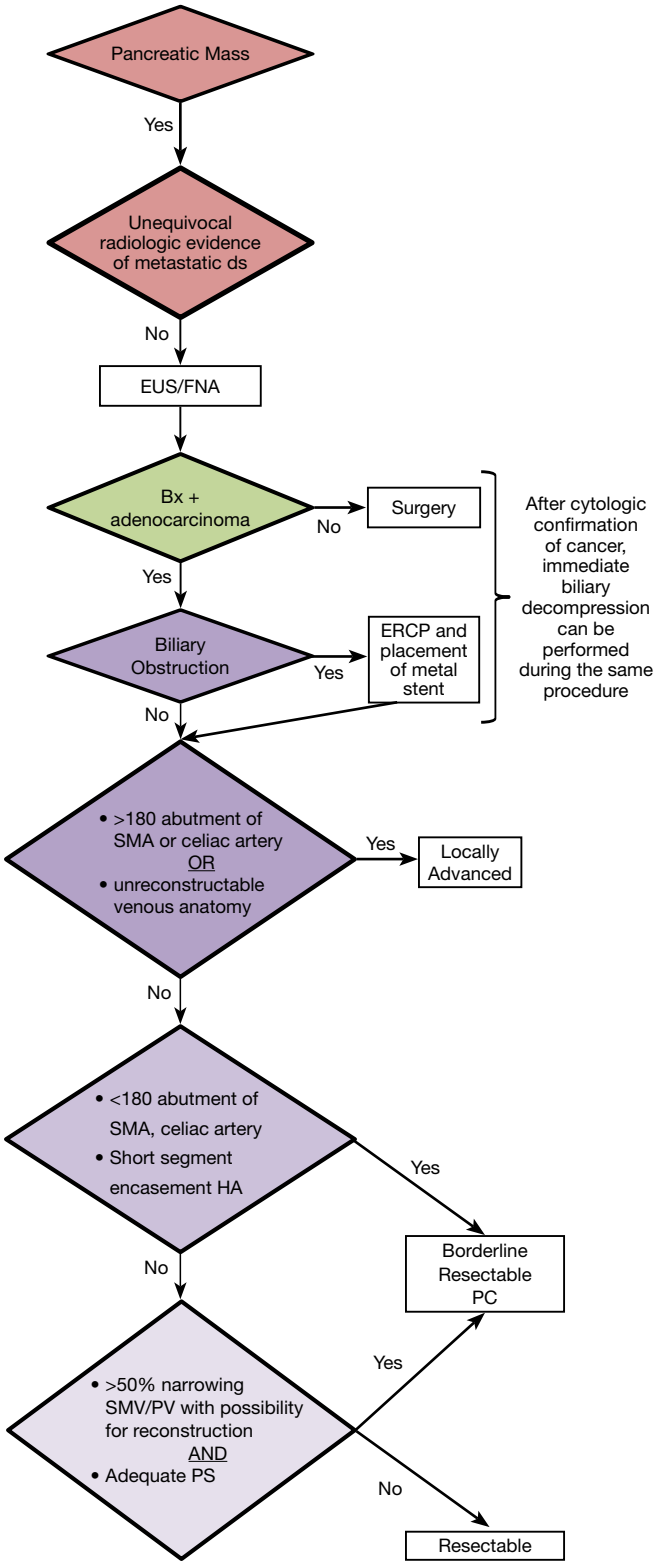

Figure 4 Algorithm for determining clinical disease stage in PC. PC, pancreatic cancer.

phase is performed to define the relationship of the tumor to the surrounding venous structures (SMV, portal vein, and splenic vein) and to uncover metastases to locoregional lymph nodes and distant organs (particularly to the liver). Multidetector contrast enhanced CT provides the most comprehensive evaluation for clinical staging; we reserve additional imaging studies such as magnetic resonance imaging or positron emission testing for indeterminate lesions which are suspicious for metastatic disease.

One non-anatomic consideration which has profound implications for survival, and therefore staging, is the patient's performance status. Especially among PC patients, striking differences in survival can be observed based on performance status alone (32-34). In a study which examined over 3,000 advanced PC patients who were treated with variety of new investigational drugs, the median survival of patients with a Karnofsky performance status (KPS) <70% was 2.4 months as compared with 5.5 months in patients with a KPS ≥70% (34). The median time to disease progression was greater in patients with a KPS score ≥70%. These findings were corroborated in the CALGB 80303 study, where PC patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 experienced a median survival of 4.8-7.9 months as compared to 2.9 months in patients with an ECOG performance status of 2 (32). Because decreased performance status correlates with an increased risk of disease progression and death, performance status has been proposed as an additional criterion for BLR clinical status, even in the presence of an anatomically resectable PC (31).

Principle #2: coordination of endoscopic procedures and establishment of durable biliary drainage

Confirmation of malignancy is required in all patients prior to treatment with systemic therapy or radiotherapy. For patients with localized disease which may be amenable to surgical resection, we prefer EUS-guided FNA biopsy. The sensitivity of EUS-FNA is in range of 85% to 90% with potential false negative results of up to 15% based on tumor size and the experience of the endoscopist. False negative results can be minimized by having a cytopathologist present at the time of EUS to ensure that a cytologic diagnosis is made before the termination of the procedure. When FNA material is examined by an experienced cytopathologist, false-negative biopsies are rare, but can occur, especially when the tumors are small. Therefore, negative results from

EUS-guided FNA should not be considered as proof that a malignancy does not exist, and repeat EUS-guided FNA may improve the yield of positive results in those patients with suspected malignancy. If the patient is jaundiced and EUS fails to identify a mass, an ERCP with biliary brushing may be performed followed by placement of a plastic stent (we prefer an easily removable stent when a tissue diagnosis of malignancy is not readily obtained). Importantly, high-quality CT imaging should be performed before any endoscopic intervention (EUS or ERCP) is attempted because of the risk of biopsy-induced pancreatitis, which may distort the pancreatic and peripancreatic anatomy and result in overstaging of the disease.

Although not essential for staging purposes, patients who present with jaundice will require an ERCP for biliary decompression prior to the initiation of neoadjuvant therapy. Biliary drainage and resolution of hyperbilirubinemia is required to maintain adequate liver function which is necessary for the use of several chemotherapeutic agents (25). In most cases, if on-site cytopathologic confirmation of cancer can be performed at the time of EUS, immediate ERCP can be performed with placement of a metal stent to provide more durable biliary decompression. With regards to the latter concern, large single institution experiences have demonstrated that self-expanding metal stents do not compromise future surgical resections (35). In addition, metal stents have demonstrated superior durability during neoadjuvant therapy with only a 7% rate of stent occlusion as compared to polyethylene (plastic) stents where stent occlusion has been reported in up to 45% of patients (36).

Principle #3: defining clinically important treatment responses

After accurate determination of the clinical stage, the assignment of type(s) of neoadjuvant therapy and the duration of therapy is developed with the intent to both treat radiographically occult micrometastatic disease (present in the majority of patients) and to maximize local control. Importantly, the assessment of treatment response is critically important and should be performed following the completion of any treatment modality. In patients with localized PC, defining treatment response to therapy can be particularly challenging as, by definition, measurable extrapancreatic disease does not exist. At the Medical College of Wisconsin, treatment response is assessed using three critically important criteria: (I) the presence or absence of clinical benefit (for example, the resolution of pain); (II) CT findings to suggest stable or responding disease *vs.* disease progression (change in cross-sectional diameter of the tumor); and (III) the decrease or increase in serum level of carbohydrate antigen 19-9 (CA19-9). Clinical benefit and CA19-9 response are used as surrogate markers of response under the assumption that extrapancreatic micrometatatic disease has likely responded to therapy if the condition of the patient improves and the level of CA19-9 declines. Although modern chemotherapy regimens such as FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) and gemcitabine/nab-paclitaxel have been associated with 30-40% response rates among patients with more advanced disease, the majority of patients with localized PC are likely to have minimal to modest changes in tumor size (9,37-39). Moreover, although tumors may demonstrate a decrease in overall size, the relationship of the tumor to adjacent vessels generally does not change. A change in clinical stage, reflecting a change in local tumor-vessel anatomy, in response to neoadjuvant therapy has been reported to occur in less than 1% of cases (37). Therefore, the utilization of restaging imaging should primarily be performed to: (I) identify disease progression, whether it be local or distant, which would alter clinical management and; (II) facilitate operative planning. Importantly, careful attention to radiographic findings allows for a detailed preoperative plan, especially when vascular reconstruction is anticipated. It is especially important that vascular resections occur as planned events rather than an emergent response to vascular injury, as unexpected vascular injuries can ultimately compromise the completeness of the resection resulting in a positive margin (40,41).

CA19-9 has been demonstrated to be a useful prognostic marker in patients with PC. Among patients with localized PC, a decrease in CA19-9 in response to neoadjuvant therapy has previously been reported to correlate with overall survival. A greater than 50% reduction in CA19-9 levels in response to neoadjuvant therapy has been associated with an improved overall survival (42,43). Importantly, among patients who undergo neoadjuvant therapy and pancreatic resection, the normalization of CA19-9 in response to therapy has been a highly favorable prognostic factor and has been associated with a median survival of 46 months. Equally important is the recognition that an increase in CA19-9 level after therapy correlates with disease progression. Although the majority of patients will experience a decline in CA19-9 in response to neoadjuvant therapy, approximately 20% of patients will have an increase in CA19-9, and among these patients,

metastatic disease was detected in 50% of cases (44). Therefore, clinicians should have a low threshold for expanding the diagnostic workup (MRI of liver or PET) prior to surgery in patients who have a rising CA19-9 after neoadjuvant therapy.

Principle #4: development of a stage-specific treatment plan

Resectable PC

Outside of a clinical trial, neoadjuvant treatment of resectable PC may consist of chemotherapy alone or chemoradiation. If chemoradiation is used, gemcitabine combined with external-beam radiation therapy is favored (*Figure 5A*). This regimen is a slight modification of the neoadjuvant treatment schema reported by Evans and colleagues and includes a standard fractionation course of radiation therapy (1.8 Gy/day, M-F, 28 fractions) to a total dose of 50.4 Gy, with concurrent weekly gemcitabine given on day 1 (day −2 to +1) at a dose of 400 mg/m^2 at fixed dose rate over 40 minutes (25). This program resulted in a median survival of almost 3 years in those patients who completed all therapy to include surgery (24). Restaging with pancreatic protocol CT imaging is completed 4 weeks after the last radiation treatment and in the absence of disease progression, patients are then brought to surgery. The recent reports of both FOLFIRINOX and gemcitabine/nab-paclitaxel, which demonstrated efficacy in patients with advanced disease (38,39), have generated enthusiasm for their use in patients with localized disease, especially those with BLR disease (26,45,46). Acknowledging that the use of chemoradiation remains controversial, neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel delivered over approximately 2 months also represents a logical treatment alternative for patients with resectable disease.

BLR PC

Patients with BLR PC are fundamentally different from those with resectable disease in that they are: (I) at higher risk for harboring radiographically occult distant metastatic disease; (II) at the highest possible risk for a positive margin of resection due to tumor-artery abutment; (III) require a more complex operation usually involving vascular resection and reconstruction, and therefore; (IV) there is a greater possibility that, despite the best efforts of the physician team, a surgical procedure may yield no oncologic benefit for the patient. For these reasons, investigators have applied a more robust level of selection consisting of a longer period of induction therapy, often including chemotherapy followed by chemoradiation prior to considering surgery. The chemoradiation portion of induction therapy has been thought to be particularly important for those patients with arterial abutment in the hope of sterilizing at least the periphery of the tumor and thereby preventing a positive margin of resection.

Our preferred off-protocol neoadjuvant treatment schema for patients with BLR PC consists of an initial two months of systemic therapy followed by chemoradiation (*Figure 5B*). The choice of systemic agents for initial treatment has evolved from gemcitabine-based therapies to consideration of FOLFIRINOX, GTX, gemcitabine/nab-paclitaxel, or other combination therapies (26,39,47-50). After the delivery of systemic therapy, patients are restaged with particular attention to treatment response indicators (clinical, radiographic, biochemical). Importantly, in the absence of a robust response to chemotherapy alone (and assuming no evidence of distant disease), it is our practice to proceed directly to chemoradiation (as discussed above) to minimize the risk of local disease progression after chemotherapy. Treatment sequencing in patients with BLR PC aims to both treat presumed (radiographically occult) systemic disease without the delay imposed by a surgery-first treatment approach—while also avoiding local disease progression which may sacrifice a window of opportunity for surgical resection of the primary tumor. Patients who have stable disease following two months of chemotherapy [no change on CT imaging and a modest decline (or no decline) in CA19-9] should transition to chemoradiation rather than second line systemic therapy which may increase the risk for local disease progression. As therapies evolve and therapeutic options increase, this recommendation may change. Importantly, we may be entering a new era in the management of localized PC, where small but clinically significant advances in systemic therapies improve control of distant metastases and patient survivals to the extent that more patients survive long enough to experience challenging symptoms of local-regional disease recurrence/progression for which we have little contemporary experience. The importance of local disease control, especially in patients with potentially operable disease, cannot be overstated—as clinically significant local-regional disease recurrence may be preventable with an optimal operation and the consistent delivery of multimodality therapy to include chemoradiation

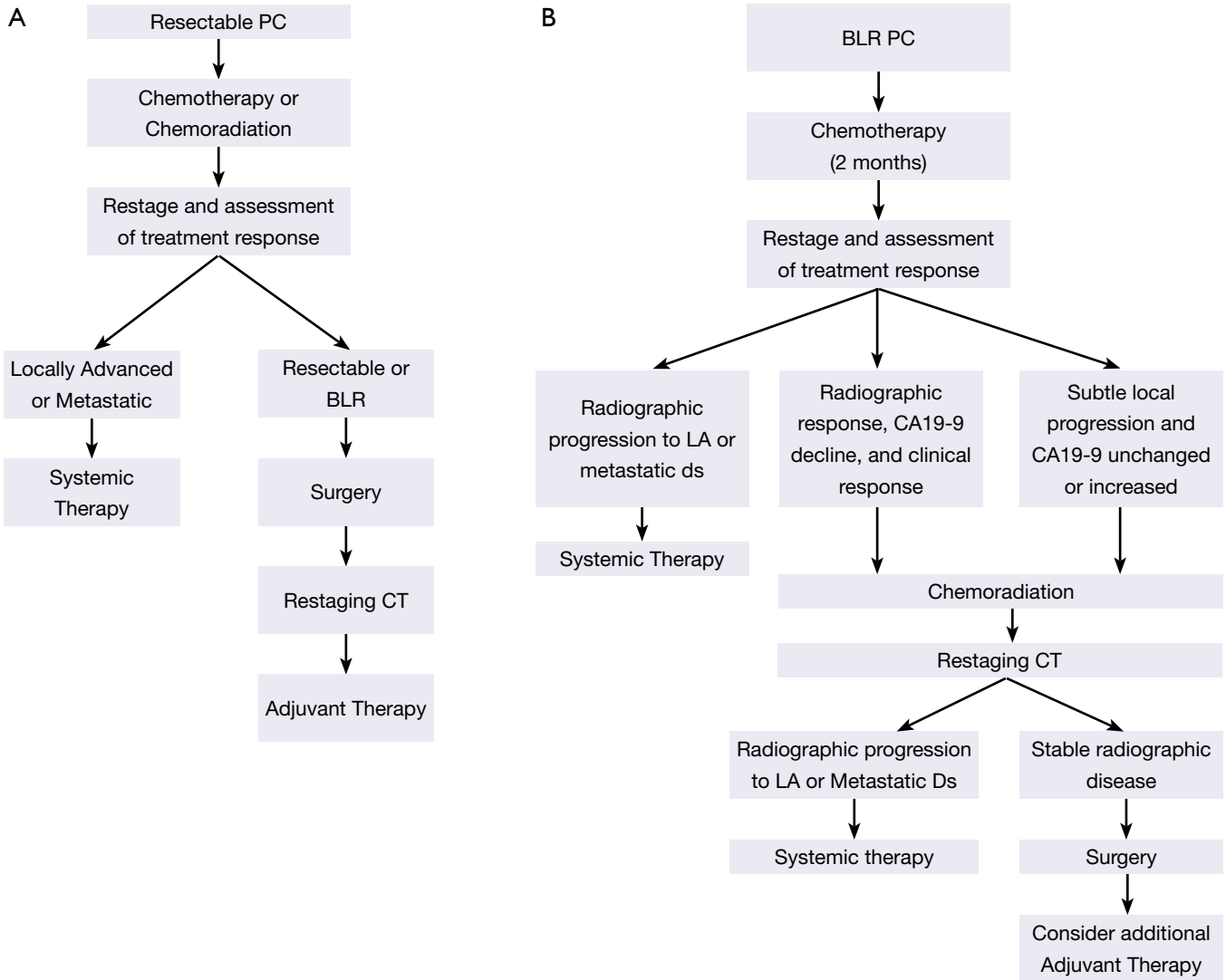

Figure 5 Treatment sequencing in (A) resectable and (B) BLR PC. CA19-9, carbohydrate antigen 19-9; BLR, borderline resectable; PC, pancreatic cancer.

either before or after surgery.

Principle #5: avoid high risk operations in high risk patients

Following the completion of neoadjuvant therapy, at the time of restaging prior to surgery, it is important that a careful assessment of the patient's performance status and medical comorbidities be re-evaluated. Several studies have demonstrated that patients with poor performance status or uncontrolled comorbidities are likely to experience postoperative morbidity and mortality (51-53). The physiologic stress associated with preoperative therapy has the potential to identify/expose patients with poor physiologic reserve who may not tolerate a large operation. If a given patient cannot tolerate induction therapy, they are unlikely to tolerate five to seven hours of surgery and recover to their pre-diagnosis level of independence with self-care. Identification of such patients at the time of diagnosis without the "stress test" of induction therapy may be difficult—a surgery-first treatment approach may incur a higher morbidity and mortality in the absence of the selection advantage afforded neoadjuvant treatment sequencing. During and after induction therapy, physicians can more accurately assess the physiologic tolerance of an individual patient to undergo major surgery. Perhaps even

more importantly, after neoadjuvant therapy, the patient and their family have an improved understanding of the disease, are much better informed (than within one to two weeks following diagnosis) and evolve a much more educated opinion regarding their physicians' recommendation for or against an operation.

In our recent experience, among older patients who completed neoadjuvant therapy but did not undergo surgery (due to either disease progression seen on restaging or a decline in performance status due to the combination of treatment toxicity and underlying comorbidities), the median overall survival was the same regardless of why surgery was not performed. A decline in performance status due to evolving medical comorbidities or the failure to recover from treatment-related toxicity was just as powerful a predictor of poor outcome as was the development of metastatic disease. This confirms previous reports of the powerful impact of performance status on response to anticancer therapy and overall survival in patients with solid tumors (54).

Conclusions

In contrast to many other solid organ tumors, treatment sequencing for patients with localized PC remains highly controversial. The limited (and clinically insignificant) gains in survival for patients with localized PC over the past three decades have been due, in part, to the current inability of physician teams to accurately stage patients. This has resulted in the overuse of surgery in patients with locally advanced and metastatic disease. In contrast to a surgery-first strategy, neoadjuvant treatment sequencing will guide the selection of patients for surgery and help to identify those patients with progressive disease for whom an operation has little oncologic benefit. Considering that surgery has a modest impact on the natural history of PC in most patients, a neoadjuvant approach to treatment sequencing is gaining support from clinicians of all specialties and will form the backbone for most future studies of multimodality therapy in localized PC.

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Novel adjuvant therapies for pancreatic adenocarcinoma

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Abstract: Contemporary adjuvant therapy for pancreatic cancer patients following surgical resection includes chemotherapy and chemoradiotherapy. However, the median survival remains approximately 20 months despite multi-modality treatment using gemcitabine or fluoropyrimidine systemic chemotherapy. Adjuvant randomized trials are currently underway to evaluate cytotoxic combinations found to be active in advanced disease including FOLFIRINOX, gemcitabine/nab-paclitaxel and gemcitabine/capecitabine. Immunotherapy using genetically engineered cell-based vaccines had shown promise in resected pancreatic cancer patients during early phase trials, and algenpantucel-L vaccine is currently being evaluated in adjuvant setting in a randomized trial. This review focuses on novel adjuvant therapies currently in clinical evaluation.

Keywords: Pancreatic cancer; adjuvant therapy; vaccines; immunotherapy

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Introduction

Pancreatic cancer is a very difficult-to-treat disease that the mortality rate almost mirrors the incidence worldwide (1). The majority of the patients are incurable at initial presentation with metastatic or surgically non-resectable disease (2). Only a small proportion of patients (10% to 20%) were deemed resectable at presentation but almost 80% recur within 2 years of surgical resection. The 5-year survival rate for resected patients remains approximately 20% despite adjuvant/post-operative therapy. Furthermore, a molecular analysis showed that the cancer is molecularly highly heterogeneous and each tumor harbors multiple genetic abnormalities (3). Here, we will review the current standards in adjuvant therapy briefly and novel approaches that are currently under clinical evaluation (*Table 1*). Neoadjuvant, or pre-operative, treatment has increasingly being adopted to improve surgical and survival outcome in 'borderline resectable' pancreatic cancer. However, the benefit and optimal approach to administering neoadjuvant therapy in this patient population has yet to be evaluated in randomized studies and this topic is beyond the scope of this article.

Adjuvant therapy in pancreatic cancer

The survival benefit of adjuvant treatment following surgical resection in pancreatic cancer patients had been demonstrated in randomized trials. The Gastrointestinal Tumor Study Group (GITSG) showed that fluorouracil (5FU) treatment was superior to observation only after curative resection for pancreatic cancer in improving the median overall survival (OS) (20 *vs.* 11 months) (4). Later, the EORTC gastrointestinal tract cancer cooperative group showed that adjuvant chemoradiation was superior to surgery alone in prolonging survival (24.5 *vs.* 19 months; P=0.208) (5).

The CONKO-001 trial was the first adjuvant trial to compare systemic gemcitabine treatment with observation after pancreaticoduodenectomy, and showed the superiority of gemcitabine treatment in improving median disease free survival (DFS) (13.4 *vs.* 6.9 months; P=0.001) and median OS (22.1 *vs.* 20.2 months; P=0.06) (6). The DFS improvement persisted and the OS benefit became significant in long term follow-up [hazard ratio (HR) 0.76 (95% CI, 0.61-0.95); P=0.01] (7). The role of chemotherapy and radiation was examined in the European Study Group

Table 1 Novel adjuvant therapies currently in clinical evaluation for resected pancreatic cancer

Clinical trials	Regimens
Cytotoxics	
RTOG-0848 (NCT01013649)	Gemcitabine +/– erlotinib +/– chemoradiation (note: erlotinib arms closed early)
ESPAC-4 (UKCRN ID 4307)	Gemcitabine +/– capecitabine
APACT (NCT01964430)	Gemcitabine +/– nab-paclitaxel
NEPAFOX (NCT02172976)	FOLFIRINOX *vs.* gemcitabine (note: includes primary resectable and borderline resectable)
Vaccines/immunotherapy	
GVAX (phase II, single-arm) (NCT01595321)	GVAX + SBRT + FOLFIRINOX
Algenpantucel-L (NCT01072981)	SOC (gemcitabine +/– 5FU-chemoradiation) +/– algenpantucel-L

All clinical trials are randomized studies unless specified. SBRT, stereotactic body radiation therapy; SOC, standard of care; APACT, Adjuvant Pancreatic Cancer Trial; ESPAC, European Study Group for Pancreatic Cancer.

for Pancreatic Cancer-1 (ESPAC-1) trial, using a '2 by 2' factorial design evaluating observation, chemoradiotherapy alone, chemotherapy alone and chemotherapy plus chemoradiotherapy following curative resection of pancreatic cancer (8). There were a number of criticisms to the study including the lack of statistical power in the design to compare the four arms, and the non-standardized method of delivering radiation among the study sites. The results from the ESPAC-1 trial showed that patients who received chemotherapy achieved better median OS and 5-year OS than those who did not (20.1 *vs.* 15.5 months; 21% *vs.* 8%, respectively). The group who received chemoradiotherapy as part of their treatment course did not achieve survival benefit compared to those who did not receive chemoradiotherapy. The Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer conducted a randomized trial that demonstrated the superiority of gemcitabine following surgery versus surgery alone in prolonging DFS (11.4 *vs.* 5.0 months; HR 0.60, P=0.01) though the OS did not differ significantly (22.3 *vs.* 18.4 months) (9). The result from the on-going RTOG-0848 trial (see below) should hopefully provide further guidance on the role of chemoradiotherapy in the adjuvant setting.

Gemcitabine and fluoropyrimidines (e.g., 5FU, capecitabine) have been the standard agents to be used in the adjuvant treatment of pancreatic cancer (10). The superiority and tolerance of these agents were evaluated in several trials. The ESPAC-3 trial showed no significant difference in survival between 5FU/folinic acid (by bolus infusion) and gemcitabine (median OS 23 *vs.* 23.6 months; HR 0.94, P=0.39) though gemcitabine had a more favorable toxicity profile (11). Interestingly, the JASPAC-01 trial showed that adjuvant S-1 (oral formulation of 5FU) was superior to gemcitabine in prolonging 2-year OS (70% *vs.* 53%) and relapse free survival (49% *vs.* 29%) (12). The continuous infusion mode of 5FU has long been established to be superior to the bolus infusion, and oral formulations of fluoropyrimidines (such as capecitabine, S-1) achieved pharmacokinetic profile and efficacy comparable to the continuous infusion of 5FU. Therefore, the difference in outcomes between ESPAC-3 and JASPAC-01 may be more from the pharmacokinetic characteristics related to the mode of administration than the intrinsic activity of 5FU.

The RTOG-9407 trial compared systemic 5FU versus systemic gemcitabine with interspersing 5FU-based chemoradiation. The 5FU was administered as continuous infusion for 7 days on a 4-week-on/2-week-off schedule. This study demonstrated better, but non-significant, survival outcome for gemcitabine (median OS: 20.5 *vs.* 17.1 months; 5-year OS: 22% *vs.* 18%) (13). More intensive cytotoxic regimens such as those incorporating cisplatin and epirubicin with gemcitabine and 5FU (PEFG) failed to achieve better survival and the combination therapy were more toxic than the standard agents alone (14,15).

Novel adjuvant treatments in clinical evaluation

Historically, the development of adjuvant therapy in pancreas cancer focused on evaluating drug treatments found efficacious in advanced or metastatic setting. The availability of treatment modalities with 'less' toxicities (e.g., vaccines) or that target novel biological processes (e.g., stem cells) offers compelling rationales to initiate their clinical development in adjuvant setting instead of advanced/

metastatic patient population. However, the risk of this approach can be significant given more resource is required for adjuvant trials than those for metastatic disease.

Gemcitabine-based regimens

When combined with gemcitabine, erlotinib, a small molecule inhibitor of epidermal growth factor, achieved a marginal 2 weeks improvement in median OS in unresectable, locally advanced or metastatic pancreatic cancer patients compared to gemcitabine alone (16). The efficacy of erlotinib as adjuvant therapy in resected pancreatic cancer was evaluated in the RTOG-0848 trial (17). The RTOG-0848 trial is a randomized study that aimed to evaluate whether erlotinib and/or radiation will improve survival in resected pancreatic cancer patients. Eligible patients are randomized (Randomization #1) to either gemcitabine alone ×5 cycles (Arm 1) or gemcitabine plus erlotinib ×5 cycles (Arm 2). Upon completion, those who did not recur will be randomized (Randomization #2) to receive one additional cycle of chemotherapy assigned from Randomization #1 (Arm 3) or one cycle of chemotherapy followed by concurrent radiation with a fluorupyrimidine (Arm 4). The analysis will be stratified according to nodal status, CA19-9 level and surgical margins (R1, R0). The study was amended following the results of LAP-07 showing no survival benefit of erlotinib plus gemcitabine compared to gemcitabine alone (HR 1.19, 95% CI, 0.97-1.45; P=0.093) in locally advanced pancreatic cancer patients (18). Furthermore, the erlotinib plus gemcitabine group experienced more grade 3 and 4 adverse events than gemcitabine alone. The RTOG-0848 trial was amended to close enrollment to the erlotinib plus gemcitabine arm (Arm 2) in early-2014. The study is currently on-going to determine whether the use of concurrent fluoropyrimidine and radiotherapy will improve survival in resected pancreatic cancer patients.

Fluoropyrimidines is another anti-cancer drug class that had shown signals of efficacy in pancreatic cancer in adjuvant (as discussed above), locally advanced and metastatic settings. Capecitabine is an oral fluoropyrimidine that exerts similar pharmacokinetic and pharmacologic profile as continuous intravenous infusion of 5FU—lower peak 5FU concentration and extended exposure (19). In a phase III trial of advanced pancreatic cancer patients, capecitabine plus gemcitabine treatment achieved improvement in progression-free survival (HR 0.78; P=0.034) though the OS benefit was not statistically significant (HR 0.86; P=0.08). The meta-analysis of two additional studies evaluating the same combination (total 935 patients) showed a significant OS benefit (HR 0.86; P=0.02). The ESPAC-4 trial is a phase III multicenter randomized trial that plans to enroll 656 resected pancreatic adenocarcinoma patients to receive capecitabine plus gemcitabine or gemcitabine alone for 24 weeks (20). Enrolled patients will start treatment within 12 weeks of undergoing curative-intent surgery. The primary objective is to evaluate whether the combination arm will improve survival compared to gemcitabine alone arm, and the secondary objectives include the impact of toxicity on quality of life.

Nab-paclitaxel, or albumin bound paclitaxel, is pharmacologically superior to the Cremophor formulation with significantly less infusion hypersensitivity reactions and neutropenia (21). In the phase III MPACT trial, the addition of nab-paclitaxel to gemcitabine significantly improved median OS of metastatic pancreatic cancer patients from 6.7 to 8.5 months (HR 0.72; P<0.001) (22). The response rate was three folds higher in the nab-paclitaxel plus gemcitabine arm than gemcitabine alone. The role of nab-paclitaxel in adjuvant setting is now being evaluated in the phase III Adjuvant Pancreatic Cancer Trial (APACT) that plans to randomize approximately 800 patients following surgical resection to receive nab-paclitaxel plus gemcitabine or gemcitabine alone for six cycles (23). The analysis will be stratified according to resection status (R0, R1), nodal status and region. Patients who received prior neoadjuvant and radiation treatment are excluded, and the primary endpoint of the study is DFS. The clinical trial also includes quality-of-life evaluation.

FOLFIRINOX

The success of an intensive cytotoxic combination consisting of 5FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) was a major milestone in the field. The PRODIGE 4/ACCORD 11 trial is a randomized phase II/III trial that enrolled 342 patients with metastatic pancreatic cancer to receive FOLFIRINOX or gemcitabine alone (24). The combination regimen significantly improved the median OS from 6.8 to 11.1 months (HR 0.57; P<0.001). Toxicities from FOLFIRINOX treatment were significant and included febrile neutropenia, fatigues, diarrhea and peripheral neuropathy. Plan is underway to evaluate FOLFIRINOX in resectable pancreatic cancer patients. The NEPAFOX is a randomized multi-center phase II/III study that plans to enroll patients with primary resectable

or borderline resectable pancreatic ductal adenocarcinoma (ClinicalTrials.gov# NCT02172976). Eligible patients will be randomized to receive surgery followed by six cycles of gemcitabine adjuvant treatment (24 weeks) or six cycles FOLFIRINOX neoadjuvant treatment (12 weeks), surgery followed by six cycles FOLFIRINOX adjuvant treatment (12 weeks). The primary endpoint is OS assessed up to 24 months, and secondary endpoints include progression-free survival, perioperative morbidity and mortality and R0 resection rate. The feasibility and tolerability of FOLFIRINOX in this localized resectable patient population will also be evaluated.

Immunotherapy and vaccines

Immunotherapy has long been a focus of anti-cancer therapy development. Immune checkpoint modulators, e.g., anti-CTLA4, anti-PD1/PD-L1, has been successful in improving survival in cancer types such as melanoma, renal cell carcinoma and lung but their role in pancreatic cancer remains unclear. Evidence suggest that the microenvironment of pancreatic adenocarcinoma is characteristically immunosuppressive, and the successful immunotherapy in the disease is likely to be more complicated (25). Vaccine therapy focus on sensitizing the host's immune cells to antigens that are preferentially expressed in the pancreas cancer cells and not by non-cancerous 'normal' cells (26). Currently, there are two cancer vaccines in late-stage clinical evaluation that are modified to enhance the uptake of cancer antigens by the antigen-presenting cells (APCs).

GVAX is an allogenic vaccine developed from irradiated human pancreatic cancer cell lines (Panc10.05, Panc6.03) that have been transfected with human *GM-CSF* gene to secrete high level of GM-CSF at the injection site (27). The increased GM-CSF level attracts and enhances the activity of APCs that then migrate to lymphoid tissues to activate CD4+ and CD8+ cells. The vaccine was evaluated in a phase II clinical trial of 60 pancreatic cancer patients following curative-intent surgical resection (28). Enrolled patients received the first intradermal vaccine 8 to 10 weeks after surgical resection, and subsequently received adjuvant 5FU chemotherapy and chemoradiation per the RTOG-9704 standard arm. Upon the completion of adjuvant treatment, up to three additional vaccine treatments were given at 1 month interval and a final (5^{th} dose) boost was administered 6 months after the 4^{th} vaccine dose. The median and 1-year DFS were 17.3 months and 67.4% respectively, and the median and 1-year OS were 24.8 months and 85% respectively; compared to median OS 17.1 months in the RTOG-9704 standard arm (13). Given the encouraging result, the vaccine is being evaluated in combination with FOLFIRINOX and radiation as adjuvant therapy in resected pancreatic cancer patients (ClinicalTrials.gov# NCT01595321).

Algenpantucel-L vaccine consists of irradiated human pancreatic cancer cell lines (HAPa-1 and HAPa-2) genetically modified to express α-Gal through retroviral insertion of murine *GGTA1* gene (29). The α-Gal glycoprotein is evolutionarily absent on human cells; instead, human has high level of anti-Gal antibody in the circulating immunoglobulins (30). The binding of anti-Gal antibody to α-Gal epitope thus induces hyperacute graft rejection cascade in human bodies by activating complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity that destroy the α-Gal-expressing cells. The intradermal injection of algenpantucel-L therefore harness such hyperacute rejection process to enhance the tumor-related antigen uptake by the APCs that then migrate to regional lymph nodes to activate the CD4+ and CD8+ cells. The vaccine was evaluated in adjuvant setting in a phase II multi-institutional study enrolling pancreatic cancer patients following R0 or R1 surgical resection (29). Enrolled patients received adjuvant treatment using gemcitabine and 5FU-based chemoradiotherapy per the RTOG-9704 trial, and received either 100 or 300 million cells per dose. The vaccination starts within 6 weeks after surgery without chemotherapy on days 1 and 8 (Cycle 1). Cycle 2 starts 1 week after the second vaccination when patients received gemcitabine 1,000 mg/m^2 weekly ×3 followed by 1 week off, concurrently with vaccination on days 1 and 15. Vaccinations then occur on days 1, 15, 29 and 43 during subsequent 5FU-based chemoradiation. Thereafter, patients receive gemcitabine and algenpantucel-L vaccine as per Cycle 1 for another three cycles. The median and 1-year DFS were 21 months and 62% respectively; 1-year OS was 86%. Given the encouraging result, algenpantucel-L vaccine is being evaluated in two phase III trials: as adjuvant therapy in resected patients (ClinicalTrials.gov# NCT01072981), and borderline resectable and locally advanced patients (ClinicalTrials.gov# NCT01836432).

Conclusions

Surgical resection remains the only curative therapy for pancreatic cancer and the median survival remains

approximately 20 months despite contemporary adjuvant treatments with chemotherapy and chemoradiotherapy. Recent advances in metastatic setting using highly active chemotherapy combination regimens such as FOLFIRNOX and gemcitabine/nab-paclitaxel has led to the launch of several phase III adjuvant trials for resected pancreatic cancer patients. The impact of these combination cytotoxic regimens on the quality-of-life in this 'disease-free' patient population will be as important as the efficacy. Cancer vaccines evaluated so far have favorable toxicity profile and early trials suggest promising potential as adjunct to standard adjuvant treatment in resected pancreatic cancer patients. The success of this modality in phase III trial is potentially groundbreaking. In summary, a number of novel treatments consisting of cytotoxics and vaccine/immunotherapy are currently been evaluated in pancreatic cancer patients as adjuvant therapy following curative resection. Given the molecular and genetic heterogeneity of the disease, it is equally important for the integration of prognostic and predictive biomarker studies in these large randomized trials.

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Adjuvant chemoradiation for pancreatic cancer: what does the evidence tell us?

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Abstract: The role of adjuvant chemoradiation (CRT) for pancreas cancer remains unclear. A handful of randomized trials conducted decades of ago ignited a debate that continues today about whether CRT improves survival after surgery. The many flaws in these trials are well described in the literature, which include the use of antiquated radiation delivery techniques and suboptimal doses. Recent prospective randomized data is lacking, and we eagerly await the results the ongoing Radiation Therapy Oncology Group (RTOG) 0848 trial that is evaluating the utility of high quality adjuvant CRT in resected pancreas cancer patients. Until the results of RTOG 0848 are available we should look to other studies from the modern era to guide adjuvant treatment recommendations. Here we review the current state of the art for adjuvant pancreas CRT with respect to patient selection, radiation techniques, radiation dose, and integration with novel systemic agents.

Keywords: Pancreas cancer; adjuvant chemoradiation (CRT); radiation therapy (RT)

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Background

Minimal progress has been made to significantly improve treatment outcomes for pancreas cancer patients despite constant efforts to better understand this devastating disease. According to the American Cancer Society, the 5-year overall survival (OS) rate has only marginally increased from 2% between 1975-1977 to 6% between 2003-2009 (1). The roadblocks to major progress are predominantly related to limitations in early cancer diagnosis when tumors are more likely to be resectable as well as poor detection of occult locoregional and distant metastasis.

While the goal for pancreas cancer patients is ultimately to achieve a margin negative (R0) resection, this is not possible for the majority of newly diagnosed patients typically either due to distant metastatic spread or extensive locoregional involvement of critical vascular structures. The minority of newly diagnosed patients who successfully undergo a R0 resection are at an extremely high risk for both locoregional and distant disease recurrence (2-8). Therefore, adjuvant therapy is the standard of care for resected pancreas cancer. While the benefit of adjuvant chemotherapy is undisputed, the addition of radiation therapy (RT) remains hugely controversial (6,9,10). In this article we will review the published literature with respect to adjuvant RT and optimal patient selection, treatment techniques, and incorporation of systemic agents.

Historical randomized trials

The initial studies that evaluated the addition of postoperative chemoradiation (CRT) for pancreas cancer are extensively discussed and debated in the published literature. Fueling this debate is the combination of limited prospective randomized data comparing the use of adjuvant CRT to no adjuvant CRT, conclusions made by older trials that used outdated RT techniques, and numerous flaws in the design and execution of these historical trials. That being said, we should critically interpret these trials when making treatment recommendations to our patients and

when designing future trials that further examine how best to implement adjuvant CRT.

The Gastrointestinal Tumor Study Group (GITSG) 9173 trial was the first to evaluate whether surgery followed by adjuvant CRT would improve outcomes over surgery alone for resected pancreas patients (11). This trial of 43 patients limited enrollment to only those with negative surgical margins. The authors reported a significant OS benefit favoring the CRT arm despite the trial closing early due to poor accrual. In contrast to how we would treat these patients today, RT was delivered to 40 Gy in 20 fractions with a planned 2-week break after 20 Gy. 5-fluorouracil (5-FU) was given concurrently and after RT for 2 years or until evidence of disease progression. After an additional 30 patients were treated on a non-randomized arm using the same CRT regimen and had similar survival as those from the randomized CRT arm, CRT was considered to be a new standard of care for resected pancreas cancer management (12).

Several European studies were subsequently conducted that challenged whether CRT actually improved survival. The European Organization for Research and Treatment of Cancer (EORTC) randomized patients to surgery alone versus surgery followed by CRT, as was done in the GITSG trial (13). The EORTC trial did not demonstrate a significant survival benefit favoring CRT, although a trend towards improved survival emerged for the subset of patients with pancreatic head tumors (13,14). While many interpret this as a negative trial, others have countered that a number of flaws in trial execution and design likely prevented any CRT benefit from being detected. First, whereas the GITSG only included pancreas cancers nearly 50% of the patients enrolled on the EORTC trial had periampullary tumors, which have a more favorable prognosis. Second, 20% of patients did not receive adjuvant therapy despite being randomized to receive CRT and 44% did not receive chemotherapy per protocol. Third, the EORTC enrolled patients with positive surgical margins without stratifying by margin status while the GITSG excluded patients with positive margins. Fourth, while patients on the GITSG trial received maintenance chemotherapy, this was not given in the EORTC trial. Lastly, some have argued that if the EORTC data were evaluated using a one-sided instead of a two-sided log rank test, then this would have provided statistical significance (P=0.049) to the survival improvement seen with adjuvant CRT (15). Still, Europeans cite this as a negative trial and typically recommend adjuvant chemotherapy alone.

The European Study for Pancreatic Cancer (ESPAC)-1 trial concluded that not only was there no survival benefit obtained by using adjuvant CRT, but also that CRT actually caused a detriment in survival (16). This is the largest prospective study to evaluate adjuvant therapy for pancreas cancer patients, randomizing 254 patients from 61 European institutions after surgery either to chemotherapy alone versus observation or CRT versus observation. An additional 285 patients were included in a 2×2 factorial randomization between observation, chemotherapy alone, CRT alone, and CRT followed by maintenance chemotherapy. In a 2004 report of the patients treated within the 2×2 factorial design, CRT negatively affected 5-year OS versus no CRT (10% *vs.* 20%; P=0.05) while chemotherapy improved 5-year OS compared to no chemotherapy (21% *vs.* 8%; P=0.009). This trial has been widely criticized due to the ability of the treating physician to choose the randomization, the use of "background" therapy, lack of central review, and longer time to treatment in the CRT arm (17,18). Several more recent studies have specifically refuted the claim that CRT is detrimental to survival (19,20). Kinsella *et al.* examined whether unfavorable results in the CRT arm from the ESPAC-1 trial could be related to inadequate radiation delivery (20). They matched pT3N1 patients from the ESPAC-1 trial who were treated per their institutional regimen of 63 Gy and concurrent chemotherapy and concluded that the observed survival outcomes from the ESPAC-1 trial were dramatically inferior to those that would be "expected" using modern and high quality CRT. In fact, the observed results were outside the 95% confidence intervals for "expected" survival. While speculative, these data emphasize that CRT was not fairly assessed in the ESPAC-1 trial.

The next phase III study to include adjuvant CRT was Radiation Therapy Oncology Group (RTOG) 9704, which randomized patients to 5-FU CRT sandwiched between either gemcitabine or 5-FU (21). After an initial report with a median follow up of 4 years showing a significant improvement in survival, with additional follow up (median =7 years), only a trend towards improved survival was detected for pancreatic head tumors treated with gemcitabine (median survival 20.5 *vs.* 17.1 months; P=0.08) (22). This was felt to be potentially related to the interruption of gemcitabine via the "sandwiched" 5-FU CRT and hence became a consideration in the design of the successor trial.

RTOG 0848, the successor study to RTOG 9704, is a phase III trial that is attempting to answer two questions,

the first being whether there is a survival benefit for adding erlotinib to gemcitabine compared to gemcitabine alone among head of pancreas patients who have undergone either an R0 or R1 resection. The second question is whether the addition of CRT in patients who have no evidence of disease progression following a full course of gemcitabine is superior to full course of gemcitabine alone. The results of RTOG 0848 will be critical to shedding light on the role of CRT, and until they are available we have no choice but to look to published literature from the modern era to guide our clinical practice.

Recent studies using modern RT doses and delivery techniques do not universally agree that adjuvant CRT should be used over chemotherapy alone. For instance, results from a randomized phase II trial published in 2010 did not show a difference in survival among resected patients who received CRT in addition to gemcitabine versus gemcitabine alone, although the authors acknowledge that the trial was not designed to detect such a difference (23). Another recently published single institution study of 146 patients actually reported higher median survival in patients who received chemotherapy alone compared to CRT (21.5 versus 16.8 months), although this difference was not statistically significant (P=0.76). On the other hand, recent studies that perhaps most strongly advocate for the use of CRT are from the Mayo Clinic and Johns Hopkins University (19,24-26). A large collaborative study between these two high volume pancreas institutions included 1,386 resected patients (19). When compared to surgery alone, adjuvant CRT improved survival in propensity score analysis by 33% (P<0.001). Matched-pair analyses demonstrated prolonged median survival with CRT (21.9 *vs.* 14.3 months; P<0.001). The survival benefit favoring CRT over surgery alone was also reported individually by each institution (24-26). Interestingly, the median survival of 21.2 months reported in patients who received CRT at Johns Hopkins was remarkably similar to what was reported in the CRT arm of the GITSG trial (20 months) despite the Johns Hopkins patients having more high-risk features such as positive lymph nodes (80% *vs.* 30%) and positive surgical margins (45% *vs.* 0%). While a direct comparison cannot be made between these two studies, modern high quality RT likely improves outcomes compared to the poorly delivered RT used in the previously mentioned historical trials. This observation was demonstrated in RTOG 9704, the first phase III trial which required central quality assurance review of RT fields used (27).

Personalized therapy

Despite adjuvant CRT not being universally adopted, it is generally agreed that a subset of resected patients with a high risk for locoregional disease recurrence may particularly benefit from the addition of RT to chemotherapy (28). For example, RT did not seem to benefit patients in the aforementioned Mayo Clinic experience who did not have any specified negative risk factors while those with at least one negative risk factor did have significantly improved survival (24). Other studies support this strategy in patients with negative features such as older age, large tumor size, advanced tumor stage, high histologic grade, elevated CA 19-9 level, positive lymph nodes, and positive surgical margins (4,24,26,29-34). The literature supports pathologic lymph node status, surgical margin status, and CA 19-9 level as being among the most important.

Lymph node involvement is consistently described as one of the most significant negative prognostic factors for long-term survival after surgery for pancreas cancer (21,30-33,35-37). Merchant and colleagues published a review of 747 pancreas patients from across seven academic medical institutions who had either surgery alone (n=374) or surgery followed by CRT (n=299) (35). While median OS was longer in patients receiving CRT (20 *vs.* 14.5 months, P=0.001), subset analysis showed that only the node positive patients benefitted (HR 0.477; 95% CI, 0.357-0.638, P<0.0001). The survival benefit of CRT has repeatedly been demonstrated among node positive patients using the Surveillance, Epidemiology, and End Results (SEER) database, although Mellon *et al.* were the first to demonstrate that RT conferred a survival benefit despite including information on chemotherapy in their analysis (31,38-41). The importance of lymph node metastasis was also shown in the analysis of RTOG 9704 (21). The data from RTOG 9704 were further analyzed by Showalter *et al.* to better understand the importance of certain lymph node parameters beyond only classifying patients as either having or not having lymph node metastasis (32). Their conclusions were in agreement with work previously published by others that showed a significant association between worse OS and higher number of positive nodes (NPN) (33,42,43), fewer total nodes examined (TNE) (31,43-45), and higher lymph node ratio (LNR) (45-48). While there is substantial evidence that lymph node involvement portends worse outcomes, we should be aware that node positive disease does not necessarily preclude long-term survival as shown

in a study by Schnelldorfer *et al*. in which 32% of the 62 patients alive at 5 years and 29% of the 21 patients alive at 10 years had pathologically positive nodes (37).

Surgical margin status has also been described as being a highly significant negative prognostic factor. Patients who undergo resection with negative surgical margins (R0) have prolonged survival over those who have either microscopically positive (R1) or grossly positive (R2) margins (20,26,33-35,49-51). However, some investigators question the significance of postoperative margin status (52-54). A Pancreatic Cancer Meta-analysis Group (PCMG) study suggested that resection margin status was not a significant factor for survival, although R1 patients had a 28% reduction in the risk of death after CRT (52). Perhaps the benefit of R0 resection is not uniform, as suggested by Tummala *et al*., who showed a dramatic improvement in survival for R0 versus R1 resection, but only for patients with tumors no larger than 25 mm who also had no more than one positive lymph node (55).

The importance of postoperative CA 19-9 levels was most prominently demonstrated by RTOG 9704 in which a secondary endpoint was survival based on a postoperative CA 19-9 cutoff of 180 U/mL. The 5-year survival of patients with CA 19-9 ≥180 U/mL was 0% compared to 25% and 18% in patients with CA 19-9 <180 U/mL treated with either gemcitabine or 5-FU, respectively. In addition, the authors analyzed the RTOG 9704 data using a threshold of 90 U/mL, inspired by the CONKO-001 trial that only included patients with values <90 U/mL. As was seen using the higher cutoff, patients with CA 19-9 <90 U/mL also had significantly higher 5-year OS (23% *vs.* 2%; P<0.0001). Finally, the most important independent predictor of survival in multivariate analyses from RTOG 9704 was postresection CA 19-9 using the cutoffs of 90 U/mL [HR 3.02; P<0.0001 (95% CI, 2.16-4.23)] and 180 U/mL [HR 3.18; P<0.0001 (95% CI, 2.09-4.84)]. Preoperative CA 19-9 level is also thought to be a useful prognostic factor as supported by multiple single institution retrospective reports (56-59), the largest of which was published by the Mayo Clinic (56). Of 226 patients, approximately half received adjuvant CRT alone (n=122) with the remainder receiving CRT followed by additional chemotherapy (n=23), chemotherapy alone (n=6), or observation (n=69). Adjuvant CRT was delivered to a median 50.4 Gy and nearly all received concurrent infusional 5-FU. Multivariate analysis showed preoperative CA 19-9 levels based on cutoffs of 180 and 90 U/mL to each significantly predict survival. Survival was significantly higher among the 101 patients with preoperative CA 19-9 ≥180 U/mL who received adjuvant CRT compared to those who did not (median survival 16.8 *vs.* 11.4 months; 5-year OS 24% *vs.* 5%; P<0.001). Lastly, the utility of preoperative CA 19-9 level may also include the ability to predict for tumor stage, nodal involvement, tumor grade, and surgical margin status. Prospective studies are needed to clarify the importance of preoperative CA 19-9, preoperative versus postoperative CA 19-9, and the ideal CA 19-9 cutoff.

There is increasing awareness that certain biomarkers may correlate with survival (60-62). Arguably the most promising of these is the tumor suppression gene DPC4 (SMAD4), which encodes the Smad4 protein involved in the transforming growth factor (TGF)-β signaling pathway. Smad4 status appears to be associated with patterns of failure; intact Smad4 patients seem to predominantly recur locally while those with loss of Smad4 are more likely to have distant progression (63-65). Herman *et al*. recently evaluated Smad4 status in 29 resected pancreas patients and discovered that recurrence-free survival was prolonged in patients with intact Smad4 (17.4 *vs.* 11.5 months; P=0.003), although there was no OS difference based on Smad4 status (64).

At this time, it is not clear how to precisely incorporate certain prognostic factors within our clinical practice. However, adjuvant CRT should be strongly considered in patients with multiple high-risk features such as positive lymph nodes and positive margins. If Smad4 status proves to reliably predict patterns of recurrence, then patients with intact Smad4 may particularly benefit from adjuvant CRT.

Evolution of radiation therapy (RT) techniques

We should be mindful that interpretation of study results should be within the context of the treatment era and the specific treatment delivered. The previously mentioned historical CRT trials used what is now undoubtedly considered to be antiquated RT including 2-dimensional planning and split-course radiation to a low dose.

In the decades that have followed these initial trials, technological advancements have included 3-dimensional conformal RT (3DCRT) and more recently intensity modulated radiation therapy (IMRT). IMRT is increasingly being used for pancreas cancer as well as other upper abdominal malignancies based on its superior ability to deliver sharp dose gradients at the periphery of the target volume, thereby significantly limiting unintended high dose to nearby normal tissues (*Figure 1*) (66-69). Even further normal tissue sparing may also be achieved using IMRT with noncoplanar beam angles (70), helical tomotherapy

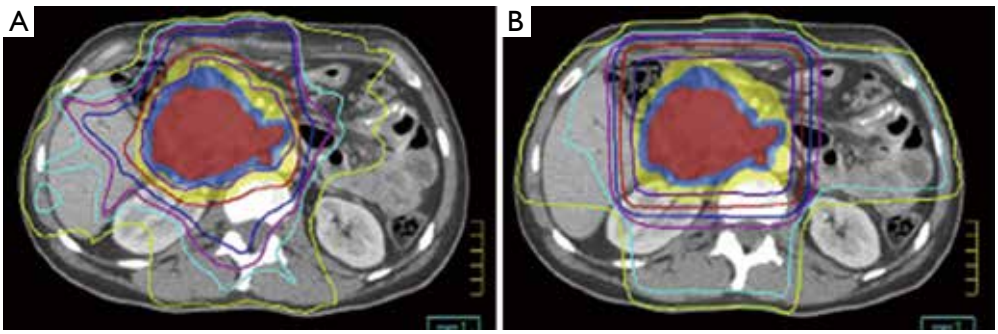

Figure 1 Isodose distributions from treatment plans using intensity modulated radiation therapy (A) and 3D conformal radiation therapy (B). Note the superior dose conformality, especially in the high dose regions, around the target volume using intensity modulated radiation therapy.

(69,71), and dose painting (72). Yovino *et al*. published the first comprehensive report of adjuvant IMRT in 71 pancreas cancer patients (34). They reported a low rate of locoregional failure (19%), alleviating concerns that the high conformality of IMRT did not lead to a compromise in treatment accuracy compared to less conformal techniques such as 3DCRT. In addition, treatment was very well tolerated with a much lower incidence of severe acute and late GI toxicity than would be expected using 3DCRT (34). Because of these favorable outcomes, both 3DCRT and IMRT may be used in RTOG 0848.

Although IMRT plans delivered using photons are incredibly conformal, the physical properties of protons allow for even greater sparing of normal tissues and delivery of lower integral dose. While dose in a photon beam decreases exponentially with increasing tissue depth, dose in a proton beam remains relatively constant until it reaches an area of maximal energy deposition, also known the Bragg peak. Thus, the main advantage of proton beam therapy (PBT) is that there is almost no dose delivered beyond the Bragg peak. While clinical PBT data is lacking for resected pancreas patients, there is data to suggest that PBT offers a dosimetric advantage over highly conformal photon therapy. Investigators at the University of Florida and University of Maryland generated PBT plans using simulation CT scans of eight resected patients who received IMRT. Each PBT plan was generated without knowledge of the corresponding IMRT plan dose distributions. The study authors demonstrated that the PBT and IMRT plans resulted in equivalent target coverage, although PBT was able to better limit dose to normal organs. PBT reduced median small bowel V20 from 47% to 15%, median gastric V20 from 20% to 2%, and median right kidney V18 from 51% to 27%. The University of Florida is now conducting a phase II trial (NCT01553019) of adjuvant CRT using PBT and concurrent chemotherapy.

Finally, there is increasing evidence that stereotactic body radiation therapy (SBRT) may benefit some patients with pancreas cancer although data in the postoperative setting is limited. SBRT is a technique that allows for large ablative doses to be precisely delivered to small focal targets in up to five fractions. Such large doses are thought to have a unique biologic effect and result in an enhanced local effect over standard fraction doses (73). While the pancreas SBRT literature focuses primarily on locally advanced disease (74,75), there is increasing enthusiasm to evaluate its use in borderline resectable (76) and even resectable patients (77). Rwigema *et al*. published a retrospective review of 24 resected pancreas patients who received SBRT, most commonly in a single fraction, for close or positive margins. No grade 3 or higher toxicities were noted while freedom from local progression was 95% at 6 months and 66% at 1 year. The utility of SBRT in the adjuvant setting remains to be seen.

Radiation dose and delivery schedule

Split-course RT, which was used in the GITSG, EORTC, and ESPAC-1 trials, prolongs overall treatment time and results in inferior local control due to accelerated repopulation (30,78). The use of a split-course approach to a lower dose than what is used today (40 Gy) was necessitated by the lack of highly conformal RT delivery resulting in significant dose to large amounts of normal organs. However, modern delivery techniques such as 3DCRT have allowed for doses of at least 50 Gy to be evaluated in prospective trials

such as RTOG 9704 (21,79-81). Although we have the ability to safely deliver doses above 50 Gy, does it mean we should routinely do so? Few studies have measured the impact of RT dose on clinical outcomes for pancreas cancer (82,83). While dose escalation may benefit patients with gross disease (84), it remains unclear whether this holds true for patients with microscopic disease in the postoperative setting. Hall and colleagues recently examined the relationship between RT dose and survival in a cohort of 1,385 non-metastatic resected pancreas cancer patients (82). Most had positive lymph nodes (61.7%) and negative margins (71.3%). Median survival was longest in patients who received 50 to <55 Gy (n=498; 23 months) compared to those who received ≥55 Gy (n=89; 16 months), 40-50 Gy (n=634; 20 months), or <40 Gy (n=164; 15 months). Multivariate analysis revealed that in comparison to the reference range of 50 to <55 Gy, worse OS was predicted by <40 Gy [HR 1.30; (95% CI, 1.03-1.66); P=0.031], 40 to <50 Gy [HR 1.17; (95% CI, 1.00-1.37); P=0.05], and ≥55 Gy [HR 1.44; (95% CI, 1.08-1.93); P=0.013]. There was no significant difference between each group with respect to age, surgical margin status, nodal involvement, tumor size, or tumor stage.

Therefore, modern studies using highly conformal RT delivery and doses of approximately 50 Gy may better reflect the benefit of adjuvant CRT compared to older studies that used split-course RT to 40 Gy (24-26). Furthermore, these older studies did not require central quality assurance of RT plans, which we have learned is critical and can significantly affect OS (27).

What is the appropriate clinical target volume (CTV)?

The predilection of pancreas cancer to involve locoregional lymph nodes has long been recognized, with rates reported from clinical and pathological series of up to 80% (2-8). Imaging studies including CT, PET/CT, and MRI are not able to readily detect subclinical disease (6,85). Therefore, given the high likelihood of subclinical nodal involvement, many radiation oncologists agree that elective nodal irradiation (ENI) should be a standard component of treatment field design for both resectable and borderline resectable pancreas cancer. However, there is not a consensus regarding the use of ENI. Many have argued for omitting ENI altogether (86), particularly in the setting of locally advanced pancreas cancer, especially given the increasing use of SBRT (74,76). Others have favored extensive surgical lymph node interrogation of even the para-aortic nodes (87) despite data suggesting that this may not result in a survival benefit (88).

For the majority of radiation oncologists who utilize ENI, the required extent of lymph node coverage has been somewhat uncertain although this recently has become better characterized (89-92). Brunner *et al*. were the first to publish evidence-based guidelines for target volume delineation in resected head of pancreas patients. These were based on a histopathologic analysis of 178 patients who also had a formal regional systematic lymph node dissection (89). They described a systematic stepwise method by which radiation target volumes should be constructed based on factors including the frequency of nodal spread, respiratory motion, and expected treatment-related toxicity related to treatment volume. In accordance with previously published data, the peripancreatic and pancreaticoduodenal nodes were most commonly involved (93). The authors highlighted the importance of also including the celiac axis, para-aortic, superior mesenteric artery, and hepatoduodenal ligament regions based on their frequency of subclinical involvement. While coverage of these regions would significantly increase the treatment volume, the authors' opinion was that the likelihood of tumor recurrence was outweighed by a potential increase in normal tissue injury. These data has served as the foundation for CTVs that are currently used today.

Sun *et al*. performed an extensive review of the published literature to comprehensively evaluate lymph node positivity rates and patterns of nodal spread in both resected head and body/tail pancreatic cancer patients (91). They included 18 studies representing 5,954 patients that provided a detailed lymph node analysis, including the paper by Brunner and colleagues. They concluded that the pattern and frequency of subclinical nodal involvement was consistent across all of the included studies. Caravatta *et al*. developed guidelines for CTV delineation based on these data published by Sun and colleagues (92). Lymph node regions with at least 3% risk of involvement were considered to be at a clinically significant risk of recurrence, and therefore were included in the CTV. The authors justified this 3% threshold as being appropriate because if the more commonly threshold of 10-15% was used, several classically included nodal groups such as the celiac axis and hepatoduodenal ligament would be excluded. They admit that their proposed target volumes for head of pancreas cancers were actually "quite comparable" to those as described by Brunner and colleagues.

The RTOG has published target volume delineation

guidelines in an attempt to standardize target volume delineation for patients treated on RTOG 0848, given the importance of delivering high quality RT (27,94). These guidelines are in large part based on the previously reviewed data that described patterns of spread. The authors admit that the appropriate CTV definition after a pancreaticoduodenectomy remains uncertain, and that the results of RTOG 0848 will hopefully clarify this.

Finally, some have challenged whether smaller target volumes may effectively allow for dose escalation and decreased treatment toxicity without compromising local control (90,95). To guide target volume construction, investigators from Johns Hopkins University first mapped local recurrences with respect to easily identifiable and reproducible vascular structures including the celiac axis, SMA, and renal veins (90). They suggested a stepwise CTV planning process based on their discovery that 90% of local recurrences were located within a 1-3 cm volumetric expansion from the combined celiac axis and SMA contours. Three simulated treatment plans were generated using these guidelines, and each was noticeably smaller than one generated based on recommendations per the RTOG (94).

Adding novel therapies to adjuvant chemoradiation (CRT)

Because of the limited progress made in treatment for resected pancreas cancer patients using traditional chemotherapy and CRT, novel therapeutic agents are needed.

Biologic agents that target specific molecular pathways potentially provide a novel approach in the fight against pancreas cancer (96). Investigators have developed agents against certain genes that are commonly mutated or overexpressed in pancreas cancer cells including vascular endothelial growth factor (VEGF) (97), human epidermal growth factor receptor type 2 (HER2) (98), and epidermal growth factor receptor (EGFR)/KRAS (99). While these targeted agents have shown anti-tumor activity *in vitro*, their clinical efficacy when added to chemotherapy has been disappointing (83,100-102). The most promising is erlotinib, a tyrosine kinase inhibitor (TKI) against ErbB1-phosphorylation (103). While it's unclear whether the addition of erlotinib to adjuvant chemotherapy and CRT is useful (104), marginal improvements in survival have been reported by the addition of erlotinib to gemcitabine over gemcitabine alone in locally advanced and metastatic pancreas cancer patients (103). RTOG 0848 will attempt to evaluate whether erlotinib improves survival in resected pancreas patients.

Another novel adjuvant treatment approach has been to harness the body's own immune response using vaccine therapy. Several types of vaccines have been evaluated including peptide, recombinant microorganism, and whole-cell vaccines (105). Promising results of a phase II study were published in which irradiated allogeneic granulocyte-macrophage colony stimulating factor (GM-CSF) secreting tumor vaccine was given postoperatively along with CRT (106). Hardacre *et al.* have described their experience using a vaccine that stimulates a hyperacute rejection-type response against two commonly expressed human pancreatic adenocarcinoma cell lines (107). In a phase II study, 70 resected pancreas patients received algenpantucel-L immunotherapy in addition to chemotherapy and CRT as per the gemcitabine arm of RTOG 9704. One-year disease free survival was 62% and OS was 86%, which paved the way for an ongoing phase III trial (NCT01072981).

Conclusions

The role of adjuvant CRT for resected pancreas cancer patients remains controversial, largely due to the conflicting results of several trials conducted decades ago that were plagued by a myriad of flaws. Studies from the modern era consistently demonstrate that adjuvant therapy, particularly including high quality RT, is beneficial especially among patients who have a particularly high risk of locoregional recurrence. In that regard, the results of RTOG 0848 are eagerly awaited. Radiation delivery techniques continue to evolve, as does our understanding of what is an appropriate adjuvant target volume, and both of these will further enhance the therapeutic ratio of RT. Lastly, novel treatments such as vaccine therapy hopefully will help us make desperately needed headway in the struggle against pancreas cancer.

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Adjuvant radiation therapy for pancreatic cancer: a review of the old and the new

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Abstract: Surgery represents the only potential curative treatment option for patients diagnosed with pancreatic adenocarcinoma. Despite aggressive surgical management for patients deemed to be resectable, rates of local recurrence and/or distant metastases remain high, resulting in poor long-term outcomes. In an effort to reduce recurrence rates and improve survival for patients having undergone resection, adjuvant therapies (ATs) including chemotherapy and chemoradiation therapy (CRT) have been explored. While adjuvant chemotherapy has been shown to consistently improve outcomes, the data regarding adjuvant radiation therapy (RT) is mixed. Although the ability of radiation to improve local control has been demonstrated, it has not always led to improved survival outcomes for patients. Early trials are flawed in their utilization of sub-optimal radiation techniques, limiting their generalizability. Recent and ongoing trials incorporate more optimized RT approaches and seek to clarify its role in treatment strategies. At the same time novel radiation techniques such as intensity modulated RT (IMRT) and stereotactic body RT (SBRT) are under active investigation. It is hoped that these efforts will lead to improved disease-related outcomes while reducing toxicity rates.

Keywords: Pancreatic cancer (PC); radiation therapy (RT); chemoradiation therapy (CRT); adjuvant therapy (AT)

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Introduction

Despite improvements in surgical management, chemotherapy, and chemoradiation therapy (CRT) approaches, pancreatic cancer (PC) continues to be a formidable disease for oncologists. Localized PC is categorized on a spectrum spanning from resectable to locally advanced based primarily on the presence or absence of vascular involvement. The determination of resectability involves prospective assessment employing imaging studies, predominantly CT scan, but also MRI and endoscopic ultrasound. Resectable disease is defined by the absence of distant metastases and lack of involvement of the adjacent vasculature [i.e., celiac axis, hepatic artery, superior mesenteric artery (SMA), superior mesenteric vein (SMV) or portal vein (PV)] (1). Though a subjective category with variability between surgeons and institutions, borderline resectable disease allows for venous involvement (PV or SMV) that is deemed resectable and where reconstruction is feasible, as well as lesions with limited SMA abutment (<180°) (2,3).

Surgery represents the only potentially curative treatment for patients with PC. Approximately 20% of patients will present with resectable disease. Despite the ability to remove all gross disease, outcomes for this group of patients are limited by high rates of local (50-90%) as well as distant (peritoneal: 20-35%; liver 20-90%) recurrence (4-7). Local recurrence is a significant driver of morbidity (i.e., pain, ulceration, bleeding, obstruction, cholangitis). Furthermore, uncontrolled local disease is often associated with distant failure as well as subsequent mortality (8). Adjuvant therapies (ATs) including CRT have been extensively investigated with hopes of reducing rates of recurrence and improving long-term outcomes. This review will first discuss the large randomized trials of adjuvant chemotherapy and CRT and then focus on the

Table 1 Trials of adjuvant therapy for resected pancreatic cancer

Trial	Arms	No. patients	Local recurrence	Median survival (months)	P value for survival
GITSG (9)	RT/5-FU	21	NR	20	
	Obs	22	NR	11	0.03
EORTC (10)	RT/5-FU	104	15% local only	25	
	Obs	103	15% local only	19	0.208
ESPAC-1 (11)	5-FU/LV	142	For all patients:	20	
	No chemo	147	62% (35% local only)	16	0.011
	RT/5-FU/LV	145		14	
	No RT	144		17	0.05
CONKO-001 (12,13)	Gem	186	34%	23	
	Obs	182	41%	20	0.01
RTOG (14)	RT/5-FU + 5-FU	230	28% local only	17	
	RT/5-FU + Gem	221	23% local only	20	0.09
ESPAC-3 (15)	5-FU	551	NR	23	
	Gem	537	NR	24	0.39

GITSG, Gastrointestinal Study Group; EORTC, European Organisation for the Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; RTOG, Radiation Therapy Oncology Group; RT, radiation therapy; 5-FU, 5-fluorouracil; LV, leucovorin; Obs, observation; Gem, gemcitabine; NR, not reported.

contemporary role of adjuvant RT. Particular attention will be paid to the emerging role of novel radiation techniques.

Adjuvant therapy (AT) for resected pancreatic cancer (PC)

In an attempt to improve outcomes for this group of patients, a number of studies have been conducted exploring the efficacy of ATs (*Table 1*). Many of the early studies investigating AT for resected PC are limited in their interpretation and generalizability by flaws in study design and analyses. For example, many failed to include pre-operative imaging into the initial determination of resectability (9,10,12,14,16). Most did not include central pathology review (9,12,14,16) or post-operative imaging for re-staging prior to initiation of ATs (9,10,16). Nonetheless, these trials inform current treatment strategies and have guided ongoing and future investigations.

Historical trials of adjuvant therapy (AT)

The GITSG 9173 study established the role for adjuvant CRT. This trial enrolled 43 of an intended 100 patients with PC having undergone pancreaticoduodenectomy (PD) and randomized to no further therapy or adjuvant, split course CRT with 5-fluorouracil (5-FU) (9). Treatment in the CRT arm consisted of a course of radiation to 40 Gy with a planned 2-week treatment break after the initial 20 Gy. Bolus 5-FU was administered weekly during RT and for up to two years thereafter. Though the trial was closed early due to poor accrual, an OS benefit was found with a median survival of 20 *vs.* 11 months and 2-year survival rates of 42% *vs.* 15% (P=0.03). The GITSG trial established adjuvant CRT as an acceptable adjuvant treatment for resected PC.

An attempt to replicate these results was conducted by the European Organisation for Research and Treatment of Cancer (EORTC). The trial enrolled 218 patients and randomized similarly between observation and split course CRT with 5-FU (10). Similar to the GITSG study, RT was delivered in a split course to 40 Gy. The 5-FU was delivered as a continuous infusion. Unlike in the GITSG study, there was no significant survival benefit with AT. With long-term follow-up, 5-year survival rates were 25% (CRT) *vs.* 22% (surgery alone) (17). A notable difference of the EORTC study was inclusion of 104 peri-ampullary tumors. A subset analysis was performed including only pancreatic head tumors, demonstrating a trend towards improved 2-year overall survival with AT with a median 17 (CRT) *vs.* 13 months (surgery alone) (17).

The European Study Group for Pancreatic Cancer-1

(ESPAC-1) study was a 2×2 study designed to investigate both adjuvant chemotherapy and adjuvant CRT compared to observation following resection. Patients were randomized to observation, chemotherapy alone, CRT, or CRT followed by maintenance chemotherapy (16). Clinicians were encouraged to enroll in the 2×2 randomization but given the option to select their patients' randomization. Chemoradiation was delivered in a split course fashion, consistent with the GITSG and EORTC trials. Chemotherapy consisted of bolus 5-FU and folinic acid administered days 1-5 and repeated every 28 days for 6 cycles. Of the 541 patients enrolled, 285 were randomized in the 2×2 design. Long-term results were reported with a median 47 months follow-up and when restricted to patients in the 2×2 randomization, CRT was found to result in a survival detriment (median survival 14 *vs.* 17 months) whereas a survival benefit was found for adjuvant chemotherapy (median survival 20 *vs.* 16 months) (11). In this study, recurrence rates were high regardless of treatment arm. Similar to the aforementioned trials, median survival was poor and the ESPAC-1 trial stands alone in showing a survival detriment with CRT.

These early investigations of adjuvant CRT are limited in their interpretation and generalizability by flaws in trial design and conduct. These trials utilized split course, low dose RT schedules with no RT quality assurance and bolus 5-FU. A dose of 40 Gy is likely inadequate to establish disease control while split course radiation prolongs overall treatment time, reducing potential biological effectiveness. Post-operative complications precluding adjuvant treatment occurred in nearly 20-30% of patients. In reality, the GITSG study tested two interventions against the control by incorporating both adjuvant CRT and additional adjuvant chemotherapy. Furthermore, the study was hindered by poor enrollment and significant protocol violations. The EORTC trial included a heterogeneous population of peri-ampullary and pancreatic tumors, potentially diluting the benefit of CRT among PC patients. Results of the ESPAC-1 study have been questioned, among many reasons, due to its 2×2 design and concerns for selection bias. The results of these early trials, though flawed, guided treatment for patients with resected PC and informed the future trials.

Modern trials of adjuvant therapy (AT)

Given the lack of benefit of CRT seen in the EORTC and ESPAC-1 studies, further investigation in Europe has attempted to optimize adjuvant chemotherapy strategies. The German Charité Onkolgie (CONKO-001) trial (12) investigated the efficacy of adjuvant gemcitabine whereas the ESPAC-3 trial compared adjuvant 5-FU *vs.* gemcitabine (18). In the United States, the Radiation Therapy Oncology Group (RTOG) conducted a randomized trial comparing adjuvant 5-FU-based CRT with either additional 5-FU or gemcitabine (14).

The German CONKO-001 trial enrolled 354 patients post-PD with R0 (83%) or R1 resection and randomized to observation or gemcitabine (12). Gemcitabine was administered in three weekly infusions for a total of six cycles. With a median follow-up among survivors of 4.5 years, gemcitabine resulted in a near doubling of disease-free survival (DFS), with median intervals of 13 *vs.* 7 months for observation. Grade 3-4 toxicities were primarily hematologic. With longer follow-up adjuvant gemcitabine resulted in reduced risk of death (HR 0.76, P=0.01) (13).

The ESPAC-3 trial similarly enrolled 1088 patients having undergone PD with R0 (65%) or R1 resection and randomized to observation, adjuvant fluorouracil (bolus ×6 cycles) or gemcitabine (×6 cycles) (15). Following the publication of ESPAC-1, the observation arm was closed and the trial became a comparison of 5-FU and gemcitabine. With a median follow-up of 34 months, there was no difference in survival seen between adjuvant gemcitabine or 5-FU with median survivals of 24 and 23 months, respectively. Rates of grade 3-4 toxicities were higher with 5-FU (primarily diarrhea, stomatitis) compared to gemcitabine (hematologic).

After improved results of gemcitabine in patients with metastatic disease (19), the RTOG conducted a randomized trial (97-04) investigating whether gemcitabine compared with continuous infusion 5-FU, administered before and after standard 5-FU based CRT (50.4 Gy), could improve outcomes in the adjuvant setting (14). The study enrolled patients having undergone PD with R0 or R1 resections. Chemotherapy was administered for three weeks prior and 12 weeks following chemoradiation and all RT plans underwent prospective quality assurance. With a median follow-up of 4.7 years among surviving patients, the addition of gemcitabine led to a trend in improved survival (mean 17 *vs.* 20 months, P=0.09), although at the expense of higher grade 4 hematologic toxicity. Results among the 86% of patients with pancreatic head tumors suggested a benefit for gemcitabine (14), though with longer follow-up there was no statistically significant difference (20). Patients with a post-operative CA 19-9 level ≤90 experienced a significantly longer median survival compared to >90,

at 23 *vs.* 10.4 months respectively (21). This finding was confirmed on multivariate analysis (HR 3.34, P<0.0001). One hypothesis is that this group of patients with higher CA-19-9 levels may harbor micrometastatic disease, which may have implications for selection of appropriate adjuvant treatments. A secondary analysis assessed outcomes for patient treated with per-protocol RT (n=216) as compared to those with protocol violations (n=200) (22). It was found that patients treatment with per-radiotherapy protocol had significantly improved overall survival. Moreover, on multivariate analysis, per-protocol treatment was more closely linked with survival than was the randomized treatment assignment.

What are the summative conclusions of the randomized trials of AT reported to date? Based on the results of the CONKO-1 and the ESPAC trials, adjuvant chemotherapy has been shown to consistently improve outcomes. Gemcitabine appears superior to 5-FU in terms of toxicity. The results of these trials are less clear on the role of adjuvant CRT. The GITSG, EORTC, and ESPAC-1 trials resulted in differing conclusions, though this may be at least partially explained by the many deficiencies of these studies as previously discussed. The more recent RTOG study is the only trial to incorporate "modern" RT and quality assurance of RT plans, yet the trial was not designed to test the efficacy of CRT.

Available data does suggest lower rates of local recurrence with the incorporation of optimal CRT. In RTOG 97-04, the local recurrence rate was only 26% despite substantial proportions of patients with T3/T4 disease (75%), involved lymph nodes (66%) and positive margins (34%). The EORTC and ESPAC-1 trials, with suboptimal CRT techniques and omission of RT in some ESPAC-1 patients, resulted in substantially higher local recurrence rates (36-62%) despite including predominantly patients with T1/T2 disease (EORTC), negative margins (EORTC and ESPAC-1) and low CA 19-9 levels (CONKO-001). Similarly, local recurrence rates in the (CONKO-001) (34-41%) and ESPAC-3 (63%) trials compare unfavorably to the RTOG and other trials incorporating adjuvant CRT. The ability of adjuvant CRT to reduce local recurrence rates was demonstrated by a smaller randomized phase II study conducted in patients undergoing R0 resection (23). In this study 90 patients were randomized between four cycles of gemcitabine or two cycles of gemcitabine followed by CRT with concurrent gemcitabine. While there was no difference in DFS or OS, there was a reduction in local recurrence as first progression with chemoradiation (11% *vs.* 24%). As more efficacious systemic therapies are developed, the ability to safely achieve local control may become increasingly important.

The ongoing RTOG 08-48 is a phase III trial randomizing patients post-PD to five cycles of gemcitabine or gemcitabine and the tyrosine kinase inhibitor, erlotinib. The rationale of erlotinib was based on efficacy data in the locally advanced or metastatic setting, though this arm has now been closed (24,25). Patients are then re-imaged to evaluate for progression, and if no progression, are randomized to one additional cycle of chemotherapy or one additional cycle of chemotherapy (six cycles total) followed by 5-FU-based CRT. The study utilizes modern radiation techniques to a dose of 50.4 Gy and incorporates centralized, prospective quality assurance of RT plans. In Europe, the ESPAC-4 trial seeks to investigate the efficacy of adding capecitabine to standard gemcitabine in the adjuvant setting. The results of these trials will potentially provide valuable information regarding the optimal adjuvant treatment strategy as well as further assess the role of CRT.

Given the conflicting results of randomized trials, several groups have published their institutional results of treatment with adjuvant CRT. A prospective series from Johns Hopkins reports outcomes of 616 patients undergoing PD for pancreas cancer, of which 271 received adjuvant 5-FU based CRT (26). Pathologic tumor characteristics between those who did and did not receive CRT were similar in regards to involved nodes (82% *vs.* 79%, NS) and positive margins (48% *vs.* 42%, NS). With a median follow-up of 18 months, patients receiving AT showed statistically and meaningfully improved median survival time (21 *vs.* 14 months) as well as 5-year overall survival (20% *vs.* 15%). This benefit persisted after adjusting for covariates and an analysis of treatment effect showed the benefit to exist for both positive and negative margins. A second series from the Mayo Clinic reported on 466 patients with T1-3N0-1 PC undergoing curative, margin negative resection, 274 of who received adjuvant CRT (27). Despite more patients with T3 tumors, involved nodes, and high-grade disease, survival was superior for patients receiving CRT (median 25 *vs.* 19 months; 2-year OS 50% *vs.* 39%). Analyses of the effect of CRT by tumor characteristics confirmed a survival benefit for patients with involved lymph nodes and high-grade tumors, but not for patient with uninvolved nodes. A follow-up matched pair analysis, combining data from both institutions (496 patients), confirmed a survival benefit for adjuvant chemoradiation with a relative risk of 0.59 (0.48-0.72) (28).

Novel radiation therapy (RT) techniques

In the decades since the inception of the GITSG study, significant advances in radiation technology have allowed for more conformal delivery of dose to target volumes. Intensity modulated RT (IMRT) and stereotactic body RT (SBRT) are two such techniques. Unlike 3-dimensional conformal RT, IMRT incorporates a planning technique, called inverse planning, whereby both target volumes and organs at risk are delineated by the radiation oncologist. A treatment plan is then generated through an optimization process that uses volumetric and dosimetric constraints (i.e., radiation prescription) for both target volumes and organs at risk, as inputs. IMRT breaks up a typical radiation treatment field into smaller "beamlets". It is implemented either as dynamic IMRT (collimating leaves move in and out of the radiation beam path during treatment) or as "step and shoot" IMRT (leaves change field shape while the machine is off). The cumulative effect is that the prescription dose conforms around delineated target volumes, significantly reducing doses to adjacent normal tissues.

Stereotactic body RT [also known as stereotactic ablative radiotherapy (SABR) and high-dose image guided radiotherapy (HIGRT)] can employ many of the same strategies and couples a high degree of anatomic targeting accuracy and reproducibility with high doses of ionizing radiation. This maximizes the cell-killing effect on the target while minimizing injury to adjacent normal tissues. Both SBRT and IMRT incorporate rigorous image guidance, accounting for day-to-day variations in location of the target volumes and adjacent normal tissues. The proposed benefits of a shortened course of RT are two-fold. First, radiobiological principles suggest that large fractional doses of radiation increase the biologically effective dose. Second, by shortening the overall treatment time, patients can more quickly proceed to systemic therapies.

A fundamental principle of these conformal radiation techniques is accurate delineation of target volumes. This requires an intimate knowledge of normal anatomy and patterns of lymphatic drainage. Appropriate delineation of target volumes must also thoroughly consider preoperative tumor features (determined by preoperative imaging) as well as account for surgical and pathologic features. In an effort to standardize this process, the RTOG has developed contouring guidelines which have been incorporated into the protocol of RTOG 0848 (29). The recommended contours are based on a combination of preoperative tumor location, surgical anastomoses, and nodal regions based on vasculature. A combined effort from Johns Hopkins and the University of Maryland investigators draws from their patterns of failure analysis of 202 patients with resected disease to generate target volumes (30). It was found that a target volume that would encompass 80% of recurrences could be generated by expanding a combined contour of the proximal CA and SMA by 2.0 cm right lateral, 1.0 cm left lateral, 1.0 cm anterior, 1.0 cm posterior, 1.0 cm superior, and 2.0 cm inferior. A volume encompassing 90% of recurrences could be generated by expanding an additional 1.0 cm right lateral, 1.0 cm left lateral, and 0.5 cm anterior. An example of IMRT is shown in *Figure 1*.

Clinical experiences utilizing IMRT

In the context of PC, IMRT has been employed in the locally advanced (31-35) and adjuvant settings (32,35,36) (*Table 2*). Given the small patient numbers in these series, they should be considered primarily as feasibility studies and for their toxicity assessments.

The University of Chicago published initial experience of IMRT with concurrent 5-FU in a mixed population of patients with resected disease (n=8), unresectable disease (n=13), and unresected recurrence (n=3) (32). In their study, radiation volumes included the tumor bed (45-50.4 Gy) or gross disease (50.4-59.4 Gy) and regional lymphatics (41.4-50.4 Gy). In six patients, dosimetric analysis of the IMRT and a 3-dimensional conformal plan was performed. They found statistical reductions in dose to the kidneys, small bowel, and liver. Treatment was relatively well tolerated and with a median follow-up of 14 months, a total of six acute and one late grade 3 or 4 non-hematologic toxicities occurred. With the caveat of small patient numbers, none of the eight patients who were resected experienced a local recurrence with a median follow-up of 17 months.

Investigators at the University of Michigan conducted a phase I/II prospective study of dose escalated (up to 60 Gy) IMRT with concurrent gemcitabine (34). In their series of 50 patients, radiation was delivered to gross disease only with customized margins allowing for target respiratory motion. Concurrent gemcitabine was delivered at full dose (1,000 mg/m^2) to maximize local and distant control. Of note, prior studies had found full dose gemcitabine with concurrent RT to be unacceptably toxic (37). The current study hypothesized that the use of IMRT would improve the safety of this approach by reducing the dose to normal tissues. A total of 11 dose limiting toxicities occurred (52.5-57.5 Gy) including anorexia, nausea, vomiting or dehydration

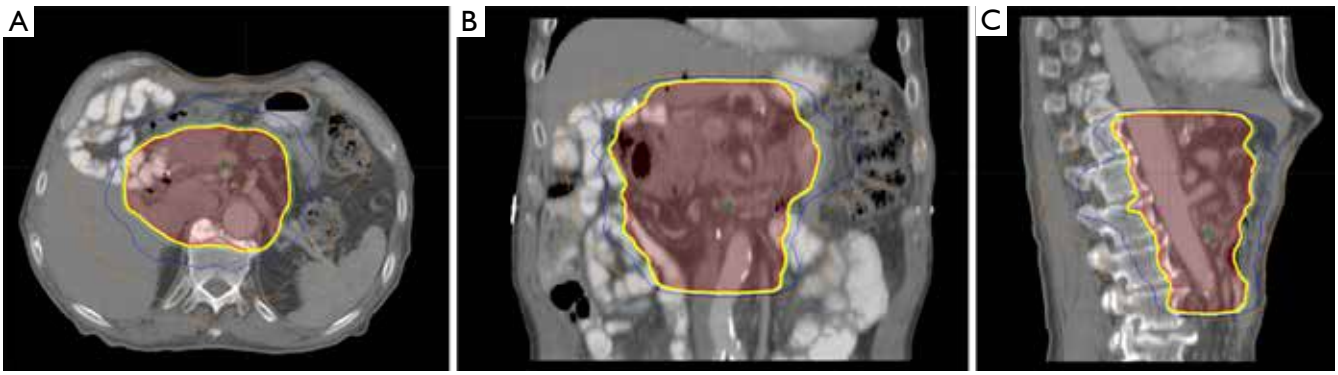

Figure 1 Representative images of an IMRT plan in a patient with PC being treated with adjuvant RT. The shaded red volume represents the target and the bold yellow line depicts the prescription isodose line. Images are (A) axial; (B) coronal; and (C) saggital. IMRT, intensity modulated radiation therapy; PC, pancreatic cancer.

Table 2 Select series of IMRT in pancreatic cancer

Author	Setting	No. patients	Chemotherapy	Targets and dose (total dose/# fractions)	Acute 3+ toxicity (%)	Late 3+ toxicity (%)	Notes
Passoni *et al.* (31)	LAPC	25	Cap	Gross disease: 44.25 Gy/ 15; involved vessels: 48-58/15	4	13	Simultaneous integrated boost, prospective phase I
Combs *et al.* (33)	LAPC	57	Gem	Gross disease: 54 Gy/ 25; elective nodes: 54 Gy/ 25	–	–	Simultaneous integrated boost: 31 underwent surgery, 11/31 with IORT (10-15 Gy)
Ben Josef *et al.* (34)	LAPC	50	Gem	Gross disease: 50-60 Gy/ 25	24	–	Prospective study
Yovino *et al.* (36)	Resected	71	Cap/Gem	Gross disease: 50.4-59.4 Gy/28-33; elective nodes: 45 Gy/ 25	8	7	Crude local control: 80%
Abelson *et al.* (35)	LAPC/ resected	47	5-FU	Gross disease: 54 Gy/ 30; elective nodes: 50.4/28	9	9	1 year local control: 92%

IMRT, intensity modulated radiation therapy; No., number; LAPC, locally advanced pancreatic cancer; Cap, capecitabine; Gem, gemcitabine; IORT, intraoperative radiation therapy; 5-FU, 5-fluorouracil.

(n=7), duodenal bleed (n=3), and duodenal perforation (n=1). Two deaths were considered to be potentially due to therapy (peritonitis and duodenal perforation). The authors concluded that 55 Gy was a safe dose. Importantly, it was found that freedom from local progression (a secondary endpoint) was improved with dose escalation.

A combined series of 71 patients from the Johns Hopkins Medical Institutions and the University of Maryland is the largest to assess outcomes for IMRT employed in the setting of resected disease (36). Targets included elective coverage of the regional nodes (45 Gy) with a boost target encompassing the tumor bed (50.4-59.4 Gy). With a median follow-up of 2 years, 14 (20%) of patients experienced a local recurrence. Importantly, 9/14 local recurrences were without a distant component. Treatment was well tolerated with 8% grade 3 acute toxicity (no grade 4) and 7% late toxicity (small bowel obstruction or fistula).

Early clinical experience of SBRT and ongoing clinical trials

There is a paucity of available data detailing the efficacy and

safety of adjuvant SBRT for PC. One of the few published reports comes from the University of Pittsburgh. In this series, 24 patients were treated with post-operative radiation with single fraction SBRT (20-24 Gy). With a median of 12.5 months of follow-up, grade 1-2 toxicity was 12.5%. No grade 3 or higher toxicities were reported and 19/24 patients were able to proceed to systemic gemcitabine-based chemotherapy. Freedom from local progression was 66%. Among 16 patients with positive resection margins, 10 (62.5%) were free of local progression (38).

There are at least two ongoing prospective studies of adjuvant SBRT. Building upon their early experience, the University of Pittsburgh is enrolling patients with resected disease and close or positive margins (NCT01357525). Radiation doses of 36 Gy in 12 Gy fractions are planned. The primary endpoint is local progression-free survival with a secondary analysis of quality of life. Investigators at Johns Hopkins are expanding on their experience using SBRT in a randomized phase II trial that investigates the safety and efficacy of an immune-modulating vaccine in conjunction with FOLFIRINOX (oxaliplatin, irinotecan, 5-FU, leucovorin). All patients will be treated with SBRT fraction sizes of 6.6 Gy for 5 days followed by FOLFIRINOX. The experimental arm will include the vaccine (NCT01595321). Results of these trials will provide important information regarding the safety of SBRT in the adjuvant setting.

Conclusions

Adjuvant chemotherapy has consistently led to improvements in outcomes for patients with PC following resection and should be incorporated into adjuvant treatment strategies. The role of adjuvant RT remains controversial. Early trials were flawed in their utilization of what is now recognized as sub-optimal RT leading to mixed results. Ongoing trials of adjuvant RT, such as RTOG 08-48, incorporate evidence-based delineation of target volumes and rigorous quality assurance. Results of this study will serve to clarify the role of adjuvant radiotherapy in resected PC patients. The incorporation of modern radiation techniques such as IMRT and SBRT hold the promise of maximizing dose to target volumes while minimizing dose to normal tissues, thus broadening the therapeutic window and improving disease outcomes.

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Self-expanding metal stents (SEMS) provide superior outcomes compared to plastic stents for pancreatic cancer patients undergoing neoadjuvant therapy

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Background: Neoadjuvant therapy is increasingly utilized for pancreatic cancer patients to decrease tumor burden in anticipation of later surgical resection. However, infectious complications such as life threatening cholangitis may occur for those with biliary obstruction. We hypothesized that placement of metal rather than plastic stents in such patients results in lower rates of stent-related complications, leading to improved clinical outcomes.

Methods: Retrospective cohort of pancreatic cancer patients treated by the University of Michigan Multidisciplinary Pancreatic Cancer Destination Program between January 2005 and June 2010. Only patients undergoing neoadjuvant therapy with one or more biliary stents placed for malignant obstruction were studied. Time to stent complication was compared between metal and plastic stents. The complication rate was estimated as the ratio of complications to total stent exposure time and 95% confidence intervals were calculated.

Results: 52 patients met inclusion criteria. A total of 113 stents were placed in 52 patients (70 plastic, 43 metal). The complication rate was almost 7 times higher with plastic stents, 0.20 (95% CI, 0.14-0.30), than with metal stents, 0.03 (95% CI, 0.01-0.06). Moreover, the rate of hospitalization for stent-related complications was 3-fold higher in the plastic stent group than the metal stent group. The first quartile estimate of time to stent complication was almost 5 times longer for metal than for plastic stents (44 *vs.* 200 days) (P<0.0001).

Conclusion: Compelling evidence indicates that self-expanding metal, not plastic stents should be used for malignant biliary obstruction in patients undergoing neoadjuvant therapy for pancreatic cancer.

Keywords: Pancreatic cancer; jaundice; chemotherapy; bile duct stents

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Introduction

With a 5-year survival rate of only 5%, pancreatic cancer is the fourth leading cause of cancer-related death in the United States (1). Neoadjuvant therapy is increasingly utilized for patients with pancreatic cancer with the goal of decreasing tumor burden in anticipation of later surgical resection (2,3). The intent is that, by local control and/or tumor down-staging with therapy, there will be a resultant survival benefit, which recent data has confirmed (4). The majority of patients are treated with a combination of gemcitabine, 5-FU and platinum compounds along with radiation therapy (5). Although the pool of patients who are candidates for neoadjuvant therapy has been estimated to be only 4.5% of the overall number diagnosed with pancreatic cancer (3), this represents an important population for whom there is an opportunity to prolong survival and

increase quality of life. Chemotherapy in patients with obstructing pancreatic cancers requires stenting to relieve the biliary obstruction, as many chemotherapeutic agents require functioning bilirubin transport mechanisms and bile excretion to avoid toxicity (6). Stent occlusion in these high-risk patients can lead to life-threatening complications. Metal stents have larger diameters than plastic stents, and therefore are less susceptible to occlusion. Although it was once thought that metal stents would interfere with surgical margins, such that they were only placed in patients whose cancers were so advanced as to preclude surgical resection, it is now accepted that metal stents can be successfully removed at the time of definitive surgery (7-9).

While there are a number of studies comparing use of plastic versus metal stents in the pancreatic cancer population, there is little data specifically evaluating that subset of patients who undergo neoadjuvant therapy in anticipation of later pancreaticoduodenectomy. This unique population may be different for a number of reasons. First, this population is more susceptible to chemotherapy-induced neutropenia, and thus may be more prone to infection (2). Patients undergoing neoadjuvant chemotherapy may be at increased risk for biliary sludge due to sloughing of cellular material generated as a result of chemotherapy, increased bacterial colonization of the stent due to immune compromise, as well as hemobilia due to chemotherapy-induced thrombocytopenia, all increasing the risk of stent obstruction and subsequent cholangitis. Our study aims to expand current knowledge by undertaking a head-to-head analysis of patients with plastic and metal stents among this neoadjuvant therapy cohort, which has not been evaluated in prior studies. We hypothesized that placement of metal rather than plastic stents in patients undergoing neoadjuvant chemotherapy results in lower rates of stent-related complications, leading to improved stent-related outcomes.

Methods

The study was approved by the Institutional Review Board of the University of Michigan Health System. We undertook a retrospective review of pancreatic cancer patients treated by the University of Michigan Multidisciplinary Pancreatic Cancer Destination Program between January 1, 2005 and June 31, 2010. Using an electronic database, a list of patients who were seen as part of the Destination Program during this time period and later underwent neoadjuvant therapy was generated. The records of each of these patients were individually examined, and only patients who had one or more biliary stents placed for malignant obstruction were included in the study. For example, patients with pancreatic tail cancers, with no need for stenting, were excluded. Procedural and treatment records were reviewed. Data including patient demographics, procedural details and complications were collected. Demographic information collected included age at diagnosis, gender, and race. Procedural details included tumor location, resectability (unresectable, borderline resectable, resectable), TNM stage (if documented), stent type (plastic vs. metal), stent diameter, and time from stent placement to stent occlusion or surgery/attempted surgery. Furthermore, data regarding complications, whether they were stent-related, and whether they required patient hospitalization, were collected. In terms of complications, stent obstruction was defined as biochemical evidence of cholestasis, along with evidence of biliary dilation on imaging, including ERCP. Cholangitis was defined as fever with biochemical evidence of cholestasis. Cholecystitis was defined as characteristic pain, fever or leukocytosis, in combination with supportive evidence on imaging. Pancreatitis was defined as a three-fold elevation in amylase or lipase or evidence of pancreatic inflammation on imaging. We also collected data regarding whether a given patient actually underwent surgical resection or attempted surgical resection after undergoing neoadjuvant therapy. The (n) number of stent exchanges in a single patient was also noted, as was time from initial stent placement to surgery and total survival time from initial stent placement. If a patient was lost to follow-up (receiving local care), the date of the last clinical contact at the referral center was used as the end-date for purposes of calculating stent survival time.

Statistical methods

Continuous data were summarized using means and standard deviations (SD) or ranges. Categorical variables were summarized by counts and percentages. Time to stent complication was compared between metal and plastic stents using Kaplan-Meier estimation and log-rank testing with all stents assumed to be independent. Stent complications were assumed to follow a Poisson process. The complication rate was estimated as the ratio of complications to total stent exposure time and 95% confidence intervals were calculated. A probability (P) value of 0.05 or smaller was considered significant for all hypothesis tests. The above procedures were done in SAS 9.2 (SAS Institute Inc., Cary, NC).

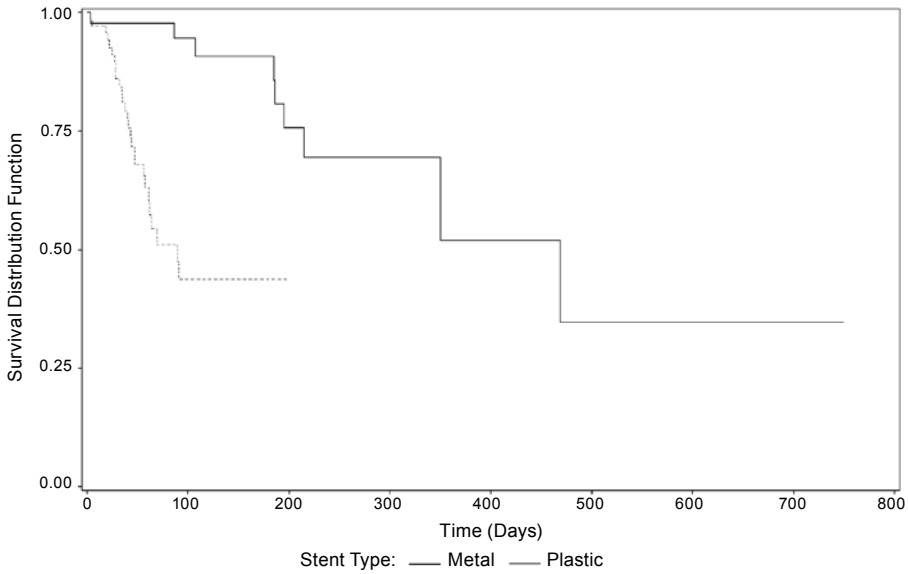

Figure 1 Kaplan-Meier curve for time to stent complication.

Results

52 patients met inclusion criteria, with a mean age of 65 years (SD 9.58). 54% were male, and 85% were borderline resectable (15% resectable) at initial diagnosis. All received gemcitabine-based neoadjuvant regimens. A majority (71%) ultimately underwent surgery, whether an aborted operation (23%) or successful resection (48%). In patients eventually undergoing surgery, the mean time from initial stent placement to surgery was 134.1 days (range, 26-420 days). Only 21% of patients (11 of 52) made it to surgery with their initial stent in place. Of these eleven patients, 7 had a plastic stent and 4 had a metal stent. A total of 113 stents were placed in these 52 patients (70 plastic, 43 metal). Plastic stents were the initial stent placed in 43 patients. There were 9 complications in 276 months with metal stents in place, compared with 27 complications in 129 months with plastic stents in place. The complication rate was almost 7 times higher with plastic stents, 0.21 (95% CI, 0.14-0.30), than with metal stents, 0.03 (95% CI, 0.01-0.06). Of the stent complications, nearly 70% involved stents 10 French or larger. Furthermore 67% of complications occurred in patients who ultimately underwent surgery.

All 9 metal stent complications were due to stent occlusion, 3 with cholangitis and 1 involving migration. For plastic stents, there were 23 cases of stent occlusion, 15 with cholangitis, 7 stent migrations, and 1 episode of cholecystitis. A total of 15 patients were hospitalized for plastic stent complications, while 5 patients were hospitalized for metal stent complications. The first quartile estimate of time to stent complication (*Figure 1*) was almost 5 times longer for metal than for plastic stents (44 *vs.* 200 days) (P<0.0001).

Discussion

The superior patency of metal biliary stents over their plastic counterparts among the spectrum pancreatic cancer cohorts with biliary obstruction has been firmly established in a number of prior studies. A recent retrospective study by Decker *et al*. examined the rate of repeat endoscopic intervention in 29 pancreatic cancer patients who underwent biliary stent placement prior to pancreaticoduodenectomy (10). This study was not limited to the neoadjuvant treatment population, but found that 39% (7 of 18) of patients in the plastic stent group required pre-operative stent intervention, while no patients in the metal stent group (11 patients) required re-intervention. However, there is a paucity of information available regarding the rates of re-intervention in the specific subset of pancreatic cancer patients who are candidates for neoadjuvant therapy in anticipation of later surgical resection.

A recent retrospective study by Boulay *et al*. evaluated 49 patients with resectable or locally advanced pancreatic cancer who had plastic stents placed for malignant biliary obstruction, and then underwent neoadjuvant therapy (11). The majority of patients (55%) underwent repeat endoscopic intervention with stent exchange due to plastic stent

complications including, most commonly, stent occlusion and cholangitis. The study concluded that plastic stents were not advisable in this subset of patients because they do not remain patent for the amount of time necessary for most patients to complete neoadjuvant therapy, which often lasts 2 to 4 months. While their report did include 7 metal stent patients, showing a 14% rate of repeat intervention, it represented too small a sample population to allow statistical comparison (11). The expanded cohort size in our study has facilitated meaningful comparisons, allowing conclusions that may guide clinical decision making. No published randomized controlled trials exist currently to examine this issue.

While, in theory, patients undergoing chemotherapy may be more susceptible to stent complications for reasons set forth earlier, at least some studies refute this conclusion. In one retrospective analysis of 80 patients with plastic stents, the rate of stent occlusion was not found to be significantly different between those exposed to chemotherapy (37%) and those unexposed (39%), and mean duration of patency was not shortened by chemotherapy (12). A later Japanese study of 147 patients, also retrospective, showed that the rate of biliary infectious complications in metal stents was unchanged by administration of chemotherapy (13). However, the treatments may not be directly comparable. The key consideration is that for patients undergoing neoadjuvant therapy, a stent complication may render disease unresectable due to local complications or delay surgery to the point that disease progression renders the patient inoperable.

It is also important to recognize, as demonstrated by our data, that neoadjuvant therapy is not a complete solution to the challenge of treating pancreatic cancer, which has an extremely poor 5-year survival rate. Of the patients in our study, over a quarter either had progression of disease or no improvement in tumor burden after neoadjuvant therapy, such that they were not ultimately operative candidates despite the neoadjuvant therapy. Furthermore, of those patients who underwent surgery, roughly one third were not successfully resected due to progression of disease discovered during surgical exploration. This confirms earlier estimates that neoadjuvant therapy is able to convert approximately 33% of borderline resectable patients to resectable candidates, but may not improve overall outcome (11). We were unable to accurately estimate overall survival outcome in our study, due to the high number of patients who were lost to follow-up (local care), either prior to or following surgical resection.

One argument against routine use of metal stents has been their increased cost as compared to their plastic counterparts. However, our data supports the conclusion that it is actually more economically sound to use metal stents for two reasons. First, since metal stents remain in place substantially longer without complication, they do not need to be exchanged like plastic stents, which must be routinely exchanged roughly every 3 months based on the known median time to occlusion. Our data shows that the mean time from initial stent placement to surgery is roughly 4.5 months, and up to 7.5 months, such that a plastic stent would have to be exchanged at least once prior to surgery. This overall mean duration of stent patency is consistent with that elucidated in prior published studies (14). One meta-analysis concluded that a metal stent would be cost-effective if future re-interventions cost greater than $1,820, representative of a patient expected to have at least a 4 to 6 month survival following initial stent placement (14). Furthermore, our data shows that patients who receive plastic stents have a roughly 3-fold greater rate of hospitalization for stent-related complications than patients receiving metal stents. The extra cost of a metal stent pales in comparison to the economic cost of even a short hospital stay.

Our data expands the literature in this unique and growing patient population by including a formal metal stent comparison group, and demonstrating a statistically significant difference in stent patency and complication rate in the metal stent group. Metal stents not only have a 7-fold lower absolute complication rate, they also remain in place approximately 5 times longer without complication as indicated by our Kaplan-Meier analysis. Recent data have shown that metal stents neither interfere with surgical margins, nor obscure tumor imaging pre-operatively. The importance of successful neoadjuvant therapy has been recently emphasized by evidence of its association with improved outcomes for this lethal malignancy (4).

In terms of our study's practical application for the interventional endoscopist, our group reserves ERCP for palliation of jaundice after a pancreatic protocol CT provides staging information. A tissue diagnosis may be confirmed by EUS-FNA and/or on-site review of ERCP brushings followed by metal stent placement. Many of the patients in our study cohort had stenting performed at initial presentation, often with plastic stents of small caliber and typically prior to referral. Therefore, the choice of plastic versus metal stent at initial presentation depended in large part on the level of suspicion and/or confirmation of malignancy versus benign causes of biliary obstruction.

For cases of confirmed malignant obstruction, our data supports the clear improved efficacy of metal stents due to their longevity without complications both in patients who are destined for surgical resection, as well as those who are ultimately poor candidates for resection due to the extent of their disease. The presence of a metal stent is no longer considered the barrier to surgery it once was.

We acknowledge several important limitations to our study. First, the comparatively small number of patients in our metal stent group limits the power of the study. Second, for purposes of statistical analysis, we chose to look at stents independently, rather than individual patients, in order to account for the fact that an individual patient may have multiple stents placed during their course of treatment. While this made some elements of our analysis easier, it may have obscured other factors. Finally, given the retrospective nature of our study, factors other than stent choice may have impacted the clinical outcomes of each cohort.

In summary, our compelling evidence indicates that self-expanding metal, not plastic stents should be used for malignant biliary obstruction in patients undergoing neoadjuvant therapy for pancreatic cancer, due to lower rates of complication, hospitalizations, and longer stent patency.

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Nanovector-based therapies in advanced pancreatic cancer

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Abstract: Systemic therapy for advanced pancreatic cancer has been largely disappointing owing to the unfavorable pharmacokinetic profile and poor penetration of current chemotherapeutic agents ,as well as the fragile patient population with compromised tolerance to toxic chemotherapies. Nanovectors can provide passive drug delivery through abnormal tumor neo-vasculature microanatomy or active targeting via binding to receptors or macromolecules associated with the tumor. In such a manner, nanovector-based therapy may not only modulate the pharmacokinetics and therapeutic index of chemotherapeutic agents but also provide new treatment options in patients with advanced pancreatic cancer. In this article, we present the rationale and currently available clinical results of nanovector-based therapies to highlight the potential use of this class of agent in patients with advanced pancreatic cancer.

Keywords: Nanovector; pancreatic cancer; liposome; PEP02; nab-paclitaxel; EndoTAG-1; nanoplatin; platinum; CPT-11

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Introduction

Pancreatic cancer is one of the most detrimental malignancies and the fourth most common cause of cancer-related death in the United Stated. There were 43,140 newly diagnosed cases and 36,800 deaths in 2010 (1). Early detection is uncommon with no more than 15-20% of the patients being amenable for curative intent surgery at the time of diagnosis. Gemcitabine either alone or in combination with erlotinib are the only approved treatments for patients with advanced pancreatic cancer, of whom the overall survival time is generally around 6 months (2-5). Recently, Conroy *et al.* showed that a gemcitabine-free triplet chemotherapy, FOLFIR INOX regimen consisting of oxaliplatin, irinotecan and infusional 5-FU/leucovor in, could achieve significantly better tumor response rate, progression-free survival and overall survival than gemcitabine monotherapy in patients with metastatic pancreatic cancer in a randomization phase III trial (6,7). However, the application of either doublet of triplet combination chemotherapy in patients with advanced pancreatic cancer is often hindered by their toxicity and the performance status of the patients.

New treatment strategies are mandatory to improve the therapeutic outcomes of patients with advanced pancreatic cancer. Recently, two major potential new approaches are emerging that may have the chance to change our practice in treating advanced pancreatic cancer. The first one is molecular targeted agent targeting on dysregulated signaling pathway and the second is the use of nanovector drug delivery system to provide 'passive" or "active" targeting drug delivery thus to modulate the pharmacokinetics and therapeutic index of chemotherapeutic agents in pancreatic cancer (8).

This review will focus on the selective nanovector treatments in pancreatic cancer, especially those with available clinical data , including albumin-bound

nanoparticles, liposome-encapsulation nanoparticle, cationic liposomal nanoparticle, polymeric micellar agents, and a non-replicating, retroviral vector delivered gene therapy construct.

Albumin-bound Nanoparticle Paclitaxel (Nab-paclitaxel)

Albumin is a particular vehicle for drug delivery in oncology because it is a natural carrier of hydrophobic molecules with reversible, noncovalent binding characteristics and able to enhance the delivery of drug into the extravascular space through a process of receptor-mediated endothelial transcytosis. Such process is initiated by the binding of albumin to an endothelium surface, 60-kDa glycoprotein (gp60) receptor (albondin), which will then bind with an intracellular protein (caveolin-1) to result in the invagination of the endothelium membrane to form transcytotic vesicles, the caveolae (9). The caveolae will subsequently move across the cytoplasm and release the albumin and its conjugated compound into the extracellular space (the peritumoral microenvironment) where the albumin will bind to SPARC (secreted protein acid and rich in cysteine), an extracellular matrix albumin-binding glycoprotein that is structurally and functionally closely related to gp60, and overexpressed in a variety of cancers, including breast cancer, gastric cancer and pancreatic cancer.

Nab-paclitaxel (Abraxane®) is a cremophor (CrEL)-free, albumin-bound, nanoparticle formulation of paclitaxel. Its CrEL-free formulation permits nab-paclitaxel to be administered within a shorter infusion period of time (30 minutes) and without the requirement of routine premedications for preventing the hypersensitivity reactions in association with the administration of cremophor solventbased paclitaxel (10). In preclinical study, the transport of radiolabeled paclitaxel across the endothelial cell monolayer *in vitro*, and intratumor paclitaxel accumulation after equal doses of paclitaxel *in vivo* were both significantly enhanced by 4.2-folds ($P<0.0001$) and 33% ($P<0.0001$), respectively, for nab-paclitaxel as compared with CrEL-paclitaxel with an increase 4.2 folds. In addition, endothelial transcytosis was completely inhibited by inhibitor of gp60/caveolar transport, methyl ß-cyclodextrin (11). These observations supported that gp60-mediated transcytosis and SPARCaided sequestration may be an important biological pathway to target tumor cells by novel albumin-bound therapeutics.

In a phase I trial, the maximum tolerated dose (MTD) of intravenous injection nab-paclitaxel monotherapy, every 3 weeks in 19 patients with standard therapy-failure solid tumors was 300 mg/m^2. No acute hypersensitivity reactions were observed. The most frequent toxicities were myelo-suppression, sensory neuropathy, nausea/vomiting, arthralgia and alopecia (12). The drug has subsequently approved for the treatment of metastatic breast cancer after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. The commonly used dose/schedule was 260 mg/m^2, 30-min intravenous injection, every 3 weeks.

Because SPARC is f requently overexpressed and associated with poor clinical outcomes in pancreatic cancer, Von Hoff *et al.* conducted a phase I/II study to evaluate the MTD of weekly nab-paclitaxel (100-150 mg/m^2/week) in combination with gemcitabine (1,000 mg/m^2/week), and the therapeutic efficacies of the regimen. Both agents were given on day 1, 8, and 15 every 28 days (13). A total of 67 patients were treated. Despite MTD of nab-paclitaxel was determined as 125 mg/m^2/week, dose reduction was required in 30% (6/20), 18% (8/44) and 33% (1/3) of patients receiving 100 mg/m^2, 125 mg/m^2 and 150 mg/m^2, respectively. The most common grade 3-4 toxicity at the MTD dose were fatigue 23%, neutropenia 59% (grade 4 in 23%), thrombocytopenia 20% (grade 4 in 9%) and sensory neuropathy in 9%. Of the 58 patients whose CT image were revaluated with RECIST criteria by independent reviewer, the best tumor response was partial response in 40% and stable disease in 37%, with an overall disease control rate of 78%. The median progression-free and overall survival of the intent-to-treat (N=67) patients were 6.9 months and 10.3 months, respectively; while the survival parameters for the 44 patients receiving MTD dose were 7.9 months and not yet reached, respectively. Of 54 patients with available CA19.9 level, 42 (77.8%) patients had a more than 50% reduction of CA19.9 level after the treatment (14). The therapeutic efficacy of nab-paclitaxel in combination with vandetanib, a potent inhibitor of VEGF2, RET and EGFR, has also been evaluated in a phase I trial with expansion cohort of patients with pancreatic cancer (15). The MTD of vandetanib in combination with two different schedule of nab-paclitaxel, either 100 mg/m^2 weekly or 260 mg/ m^2 every 3 weeks, was 300 mg daily. Of the 29 enrolled gemcitabine-refractory pancreatic cancer patients, the best tumor was partial response in 6 (20.7%) and stable disease in 10 (34.5%), and the median progression-free survival and overall survival were 5.3 (95% CI: 3.7 to 7.3) months and 8.2 (95% CI: 6.2 to 11.5) months, respectively. No statistical significant correlation

between SNP (rs1059829 and rs3210714) of SPARC and clinical outcomes was observed.

Liposome-based drugs

A liposome is often a spherical vesicle with a bilayer membrane whose size typically ranges from ~40 nanometers to several microns. Because the micro- or nanoparticles can form spontaneously and are generally easier to prepare compared to viral-mediated systems, this nontoxic phospholipid-based drug carrier has become a favorable drug delivery system for various purposes since the 1970s. However, so-called conventional liposomes are easily bound with insoluble circulating plasma protein, i.e. opsonins and lipoproteins, and the complex will be subsequently eliminated from the circulation by reticuloendothelial cells system. Stealth liposome technology, with incorporationof high molecular weight polymers (i.e., polyethylene-glycol (PEG)) to the liposome surface, can effectively protect the liposome from circulating protein binding and subsequently phagocytosis by RER system, and thus improving its plasma clearance, prolonging the circulation time, and enhancing drug delivery efficacy.

Besides its characteristic slow-release pharmacokinetic property, liposome encapsulated drugs can potentially provide improved tumor localization via the "enhanced permeability and retention" (EPR) effect. Such agents can therefore, (i) lower drug elimination to increase systemic circulation time, (ii) lower maximum plasma concentration (C_{max}) to reduce drug side effects, (iii) enhance tumor tissue uptake and exposure to the anti-cancer drug; these principles can in turn yield an improved therapeutic index for cancer therapy.

Several liposomal formulated cancer drugs have been evaluated in various cancers, but only a limited number have been applied to pancreatic cancer.

Liposomal doxorubicin

The first liposomal anti-cancer drug approved by the Food and Drug Administration (FDA) was pegylated liposomal doxorubicin (Caelyx®/Doxil®) in 1995 for Karposi's sarcoma (16-18). It has been subsequently approved for the treatment of multiple myeloma and recurrent epithelial ovarian cancer as well. It also has been evaluated for the treatment of pancreatic cancer in animal xenograft model and in clinical trials. In a preclinical study, Vagge *et al.* showed that pegylated liposomal doxorubicin was significantly more effective in inhibiting the growth of human pancreatic cancer xenograft in nude mice as compared to free form doxorubicin (19). Using confocal laser scanning microscopy and microf luorimetry to quantitate the uptake of intravenously injected doxorubicin in tumor tissue, the authors found that the content of doxorubicin in tumor site of animal receiving liposomal formulated drug was 6 folds or higher compared to free doxorubicin. Based on the results, Halford *et al.* conducted a phase II trial to evaluate the therapeutic efficacy of Caelyx® in 22 chemo-naïve patients with unresectable pancreatic carcinoma. The dose was escalated from 30 mg/m^2 (in the first two patients) to 50 mg/m^2 intravenous injection every 3 weeks (20). Of the 20 patients received the treatment, the most common grade 3 toxicity were stomatitis (20%) and nausea (10%), the best tumor response was stable diseases in 6 (30%), and the median overall survival was 3.2 months with one year survival rate of 10%. These finding excluded the use of Caelyx® monotherapy in the treatment of advanced pancreatic cancer.

The combination of Caelyx® with infusional 5-FU/ leucovorin and mitomycin-C has been evaluated in a phase I trial in patients with upper gastrointestinal cancer. In that study, escalating dose of Caelyx® (15 – 35 mg/m^2) day 1 and 29 in combination with weekly 24-hour infusion of 5-FU and leucovorin (2,000 and 500 mg/m^2, respectively) for 6 weeks, and mitomycin-C 7 mg/m^2 day 8 and 36, every 8 weeks as one cycle. The most common grade 3-4 toxicities were nausea/vomiting (29%), diarrhea (18%) and leucopenia (12%). Of the 14 accruals with pre-treated pancreatic cancer, the best tumor response was partial response in one and minor response in 2, and the overall survival after the study treatment was 6.5 months (21).

Liposomal platinum

Platinum is one of the most active and wildly used anticancer agents in the world, including in combination with gemcitabine to treat non-small cell lung cancer and pancreatic cancer. Although each single trial had failed to demonstrate the superiority of gemcitabine/ platinum combination over gemcitabine single agent in the prolongation of the survival in patients with advanced pancreatic cancer, however, the sur v iva l benef it of gemcitabine/platinum doublets was demonstrated in a pooled, meta-analysis survival with a hazard ratio of 0.81, P=0.031 (22).

It is also well known that the use of cisplatin is frequently limited by its nephrotoxicity, peripheral sensory neuropathy,

ototoxicity and the aggravation of hematological toxicity while in combination with other cytotoxic agents. Therefore, several liposomal formulations of cisplatin have been developed aiming to reduce its toxicity profile and hopefully to enhance it activity. Based on previous experience of gemcitabine/cisplatin combination and the result of metaanalysis, several liposomal formulated cisplatin have been evaluated in patients with pancreatic cancer.

L ipoplatin is one of the pegylated liposome cisplatin, whose nanoparticulate liposomes are reversemi scelles , composed of dipa lmitoyl phosphat idyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine (mPEG2000-DSPE). Lipoplatin exhibits the fundamental pharmacologic characteristics of pegylated liposomal agents, for example, protecting from the engulfment of reticuloendotheralial system to prolong circulating time, and extravasating from the fenestrate between endothelial cells of tumor vasculature to preferentially localize in per-tumor interstitial tissue and uptake by tumor cells. The anionic, fusogenic nature of the DPPG lipids enables lipoplatin to cross cell membranes more easily than native cisplatin. In addition, with intraperitoneal injection of a "sheath" liposomes wrapped reporter β-galactosidase gene, which had same structure like lipoplatin, into human tumor bearing nude mice, Boulikas *et al.* were able to demonstrate the preferential expression of the reporter gene in the tumor and the tumor neo-vasculature. The findings indicate the potential antiangiogenic activity of the lipoplatin (23).

In phase I trial of lipoplatin monotherapy, the drug was diluted in 5% glucose water and administered as 8 hour intravenous infusion every 14 days. The dose was escalated from 25 mg/m^2 to 125 mg/m^2. Even at the targeted dose of 125 mg/m^2, only grade 1-2 gastrointestinal and hematological toxicities were observed, but neither nephrotoxicity nor neuropathy. Higher doses, 200, 250 and 300 mg/m^2, were also tested in one each patient, respectively. The half-life of lipoplatin was estimated ranging from 60-117 hours. Of the 27 accruals (19 with pretreated, advanced pancreatic cancer) in this phase I trial, the objective tumor response rate and disease control rate were 11.1% and 63.0%, respectively. Based on the exciting results, the drug has been further tested in combination with gemcitabine in non-small cell lung cancer and pancreatic cancer patient cohorts (24).

In a phase I/II study, Stathopoulos GP *et al.* evaluated the maximum tolerated dose of lipoplatin in combination with gemcitabine in patients with previously treated advanced pancreatic cancer (25). Lipoplatin was given as an 8-hour infusion followed by 60 minutes infusion of 1,000 mg/m^2 of gemcitabine at day 1 and 15 every 28 days. The dose of lipoplatin was stepwise escalated from 25 mg/m^2 to 125 mg/m^2. Of the 24 enrolled patients, two of four patients at 125 mg/m^2 experienced grade 3-4 neutropenia. Therefore, the MTD of lipoplatin in this combination was determined to be 100 mg/m^2. In this dose escalating study, there were two (8.3%) partial responders and 14 (58.3%) disease stabilizers, and the median overall survival was 4 month. Further randomized phase II/III trial against gemcitabine monotherapy is under evaluation.

Liposome-entrapped cis-bisneodecanoato-*trans*-R,R- 1,2-diaminocyclohexane (DACH) platinum(II) (L-NDDP, Aroplatin™) is a lipophilic cisplatin analog that has been formulated in relatively large-size multi-lamellar liposomes measuring from 1 to 3 μm in diameter. L-NDDP has been demonstrated to be non–cross-resistant with cisplatin in cisplatin-resistant Lovo DDP 3.0 (human colon cancer cells) and L1210/PPD (human leukemia cells) both *in vitro* and *in vivo* models. In a phase I study, L-NDDP was given intravenously once every 4 weeks, ranging from 7.5 mg/m^2 to 390 mg/m^2 (26). The infusion rate was set at 4 mg NDDP per minute for all cases. In this particular study, intra-patient dose escalation was allowed. Grade 1-2 nausea/vomiting, diarrhea and fever were frequently observed in patients receiving 100 mg/m^2 or higher dose of L-NDDP. Six out of the 10 patients who had 390 mg/m^2 experienced grade 4 hematological toxicities manifesting as thrombocytopenia, granulocytopenia or both. The MTD of intravenous L-NDDP every 4 weeks was determined as 300 mg/m^2. In 2004, Aronex Pharmaceuticals had registered a phase I/II study of L-NDDP and gemcitabine combination in patients with advanced pancreatic cancer resistant to standard therapy in a public clinical trial registration website, the clinicaltrials.gov, with an indentifier of NCT00081549. Unfortunately, the latest trial information was updated in June 2005, and no further publication on this trial can be found.

Liposomal Irinotecan (Nanoliposomal CPT-11, PEP02, MM-398)

Irinotecan hydrochloride (CPT-11) is a water-soluble semi-synthetic derivative of camptothecin targeting topoisomerase I, and has been an approved agent for the treatment of metastatic colorectal cancer worldwide,

and also for gastric cancer (Japan and Korea), non-small cell lung cancer, small cell lung cancer, cervical cancer, and non- Hodgkin's lymphoma in Japan. In pancreatic cancer, earlier trial showed that combination of gemcitabine and CPT-11 did not provide any survival benefit over gemcitabine monotherapy in patients with advanced pancreatic cancer, and thus CPT-11 has not been considered to be a clinically useful drug in this disease. However, in the recent PRODIGE 4/ACCORD 11 trial, Conroy *et al.* demonstrated that a gemcitabine-free, CPT-11-containing regimen, FOLFIRINOX (CPT-11, oxaliplatin plus intermittent infusion of 5-FU/leucovorin), provided significantly better objective tumor response rate, progression-free survival and overall survival versus gemcitabine monotherapy in patients with metastatic pancreatic cancer. Notable and not unexpectedly, this triplet regimen is associated with significant hematologic toxicity including higher rates of grade-3/4 febrile neutropenia. The results of the PRODIGE/ ACCORD 11 trial have revived interest in CPT-11-based therapy in advanced pancreatic cancer (6,7).

Although the original CPT-11 drug is now of interest in pancreatic cancer management, potentially superior versions incorporating drug delivery technologies offer a next generation approach. CPT-11 exhibits well-known pharmacologic liabilities and signif icant associated toxicities, which in turn make it an obvious candidate for drug delivery strategies The camptothecins exist in a pHdependent equilibrium between an inactive carboxylate form (predominant at neutral-to-basic pH) and an active lactone form (predominant under acidic conditions); hence, intravenous injection of free CPT-11 results in rapid inactivation as well as clearance. Furthermore, CPT-11 is largely a prodrug which is converted into the much more potent metabolite SN-38. Hepatic activation and hepatobiliary excretion of SN-38 result in substantial risk of GI injury, especially in individuals having impaired SN-38 glucuronidation. These metabolic conversions contribute to notable heterogeneities in both efficacy and toxicity, and ultimately to a rather narrow therapeutic index. The concept of nanoparticle delivery of CPT-11 is thus very attractive based on potential advantages including: overcoming solubility limitations of the camptothecins; protecting drug in the active lactone configuration; chaperoning drug away from sites of toxicity such as the GI tract; prolonging circulation time and increasing tumor accumulation via the enhanced permeability and retention (EPR) effect; and providing sustained release and prolonged tumor exposure.

To realize the potential advantages of nanoparticle delivery, a novel liposome-based construct termed "nanoliposomal CPT-11 (nLs-CPT-11)" was developed, which encapsulates CPT-11 with unprecedented efficiency and stability (27). PK studies showed long circulation times for the carrier and undetectable drug release in plasma. Furthermore, nanoliposomal CPT-11 provides protection of drug in its active lactone form within the liposome aqueous interior, preventing its hydrolysis as well as premature conversion to the potent and toxigenic metabolite, SN-38. This contrasts markedly with free CPT-11, which is rapidly cleared from circulation, is subject to immediate hydrolysis of the lactone ring, and is also conver ted to SN-38 contributing to its dose-limiting GI toxicity.

In a series of preclinical studies, nanoliposomal CPT-11 demonstrated significantly superior efficacy when compared to free CPT-11 at the same or higher dose, including frequent cures in some models. The superiority of nanoliposomal CPT-11 over free CPT-11 has been observed in different tumor models including colorectal, gastric, breast, cervical, glioma, pancreatic and lung cancer models. In addition to superior efficacy, nanoliposomal CPT-11 has shown a more favorable pharmacologic profile and reduced toxicity in multiple preclinical models.

In order to evaluate this novel agent as a potential therapy for pancreatic cancer, a bioluminescence-based orthotopic xenograft model of pancreas cancer was developed (28). COLO357, a human pancreatic cell line, was passaged multiple times *in vivo* to generate the subline L3.6pl. This cell line was then modified by lentiviral transduction (L3.6pl-T) to express firefly luciferase. L3.6pl-T cells were implanted during open surgery directly into the pancreas of a nude mouse to form an orthotopic tumor xenograft. Therapeutic studies in this model compared nanoliposomal CPT-11 versus free drug at the equivalent dose, along with vehicle control (*Figure 1*). All treatments were administered intravenously by tail vein beginning at 7 days post-tumor implantation and continued weekly for a total of 3 planned treatments. At 20 mg/kg, free CPT-11 showed some tumor growth inhibition, but all mice required euthanization after 2 doses due to massive tumor progression. In contrast, nanoliposomal CPT-11 at the equivalent 20 mg/kg dose showed potent antitumor activity, including complete tumor inhibition during the entire post-treatment period. Systemic toxicity was not observed with any treatment. These studies indicated that nanoparticle- mediated delivery via nanoliposomal CPT-

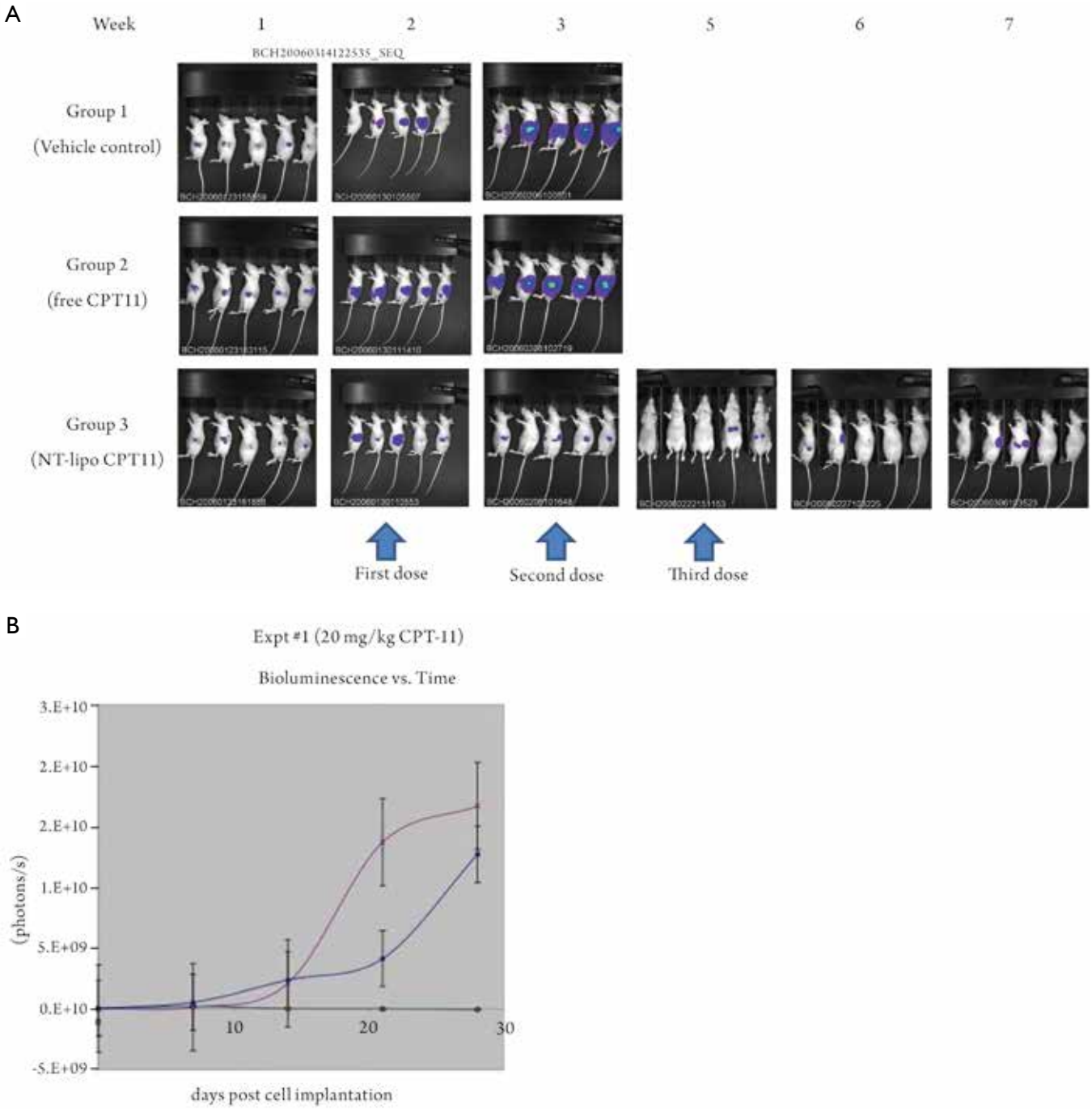

Figure 1 Nude mice were orthotopically implanted with COLO357/L3.6pI-T xenografts into the pancreas. Following ip administration of luciferin, animals were immediately imaged using a Xenogen IVIS 100 bioluminescence system, and subsequently imaged at weekly intervals. The signal was quantified by defining regions of interest (ROIs) and measuring photons/sec/str. Quantitative BLI values at post implantation day 7 were used to assign mice to treatment groups of five mice per group. Treatments included nanoliposomal CPT- 11 at 20 mg/kg, free CPT-11 at 20 mg/kg or vehicle control. All treatments were administered i.v. by tail vein injection beginning at 7 days post- tumor implantation and continued weekly for a total of 3 planned treatments. (A) Bioluminescence images of nude mice on weeks 1-7. (B) BLI values over time. Free CPT-11 treatment (diamonds) produced partial inhibition of tumor growth at initial time points, followed by rapid growth approaching that of the vehicle control group (+). Nanoliposomal CPT-11 treatment (circles) produced complete inhibition of tumor growth at all time points.

11 greatly enhances antitumor efficacy in the COLO357/L3.6pI-T orthotopic pancreatic xenograft model.

In the first-in-human phase I trial, patients with standard therapy-failure solid tumor were enrolled to determine the maximum tolerated dose, safety profile and pharmacokinetics of nanoliposomal CPT-11 (formerly PEP02, PharmaEngine, Inc., Taiwan, and now under the designation of MM-398, Merrimack Pharmaceuticals, Inc, USA). The drug was delivered intravenously for 90 minutes, once every 3 weeks, with starting dose of 60 mg/m^2. The maximum tolerated dose was 120 mg/m^2. Two patients achieved partial response including cervical cancer in one and pancreatic cancer in one (29). The observation was further extended in a phase I trial for nanoliposomal CPT-11in combination with weekly 24-hour infusion of high-dose 5-FU/LV (HDFL). In the two phase I trials, 7 pancreatic cancer patients who failed gemcitabine/HDFL +/- platinum had received PEP02 with or without HDFL. The best response was partial response in one, stable disease in 4 and progressive disease in 2, which indicated a potential activity of PEP02 in treating gemcitabinerefractory advanced pancreatic cancer. Based on these clinical observations and preclinical results, clinical testing of nanoliposomal CPT-11 was pursued in patients with gemcitabine-based chemotherapy failure advanced pancreatic cancer in an international phase II trial with the target of the primary end-point of 3-month overall survival rate ($OS_{3\text{-month}}$) = 65%. The results have been presented at the 2011 ASCO meeting (30). Of the 40 treated patients, more than three fourths had failed to first-line gemcitabine-based doublet or triplet chemotherapy. Mean cycle of treatment was 5.4 (range, 1-26) cycles. The most common G3/4 toxicities were: neutropenia (30%), leucopenia (22.5%), anemia (15%), diarrhea (7.5%), and fatigue (7.5%). Dose modification due to adverse events was required in 10 (25%) patients. The best tumor response rate was partial response in 7.5% and stable disease in 40% (overall disease control rate of 47.5%). The overall survival was 5.2 months with a 3-month and 6-month survival rate of 75% and 42.5%, respectively. The results highlight the feasibility and activity of nanoliposomal CPT-11 in previously heavily treated patients with gemcitabine-refractory advanced pancreatic cancer, which deserves further exploration.

Cationic Liposome Encapsulated Paclitaxel (EndoTAG™–1)

Tumor angiogenesis, the formation of neovasculature from pre-existed peri-tumor vessels, is a crucial process in supporting the development and growth of tumor mass, and the dissemination of tumor metastases. Tumor angiogenesis is mainly triggered by growth factors that are secreted by tumor cells per se and/or by miscellaneous types of cell within the microenvironment, for example, tumor associated macrophages or fibroblasts. Tumor vessels are often dilated and torturous, and characterized by large inter-endothelial cell gap (up to 100-600 nm versus < 6 nm in normal vessels), aberrant pericytes and basement membrane coverage, overexpression of specific surface receptor or antigen, and the presence of negative charged macro-molecules for example, anionic phospholipids and glycoprotein. Based on these characters, several strategies have been used to develop neo-vascular targeting liposomal drugs, which include conjugating with specific antibody again surface antigen or receptor and modified, non-functional receptor binding ligand, or incorporating positive (cationic) charged molecules in the surface of liposome. Of them, cationic liposome is a unique and interesting approach (31). In a preclinical study, Kalra and Campbell showed 5-FU and doxorubicin-loaded cationic liposome could preferentially bind with human endothelial (HMEC-1 and HUVEC) rather than pancreatic cancer cells. (HPAF-II and Capan-1)(32). Subsequently, Eichhorn *et al.* showed that both cationic lipid complexed paclitaxel (EndoTAG™-1) and camptothecin (EndoTAG™-2) could preferentially bind at endothelial cells of neo-vasculature in solid tumor preclinical model (33-35). The selectively targeting of both agents on tumor microvasculature was confirmed by quantitative fluorescence microscopy. Further study suggested the anti-vascular effect of cationic liposome encapsulated paclitaxel (EndoTAG™-1) is schedule-dependent with metronomic schedule better than the maximum tolerated dose schedule. In addition, the combination of EndoTAG™-1 and gemcitabine could significantly inhibit the incidence of metastatsis in L3.6pl orthotopic pancreatic cancer mice model.

Based on these data, EndoTAG™-1, a cationic liposome (prepared from 1,2 dioleoyl-3-trimethyl-ammoniumpropane (DOTAP) and 1,2 dioleoyl-sn-glycero-3- phosphocholine (DOPC)) encapsulated paclitaxel, has been used in combination with gemcitabine to treat chemonaïve pancreatic cancer patients. The latest follow-up data of the four-arm randomized, phase II trial comparing weekly gemcitabine 1,000 mg/m^2 alone versus gemcitabine plus twice weekly EndoTAG™-1 at three different doses, 11, 22 and 44 mg/m^2) was presented in the 2009 ASCO Annual Meeting (36). Of the 200 chemo-

naïve advanced pancreatic cancer patients who participated the study, 80% had metastatic diseases and 20% had locally advanced diseases. Disease-control rates in the gemcitabine monotherapy arm and the three gemcitabine plus EndoTAG-1 arms was 43% and ranging from 53% to 69%, respectively. The median progression-free survival time in corresponding group of patients were 2.7 months versus 4.1 to 4.6 months, respectively. The median overall survival time of patients receiving gemcitabine plus either high-dose (44 mg/m^2) or intermediate-dose of EndoTAG-1 were 9.4 months and 8.7 months, respectively, as compared with the 7.2 months in the gemcitabine monotherapy arm. The adjusted hazard ratio for overall survival for either arm was 0.72 (95% CI, 0.46 to 1.13) and 0.67 (95% CI, 0.43 to 1.07), respectively. The data is exciting but large-scale study to validate the data is mandatory.

Polymeric Micelles

Polymeric micelles-based anticancer drug, consisting of the incorporation of chemotherapeutic agent into polymeric micelles in size of 20-100 nm, was originally developed by Professor Kataoka(37). The polymeric micelle has two major components, a polyethylene glycol (PEG) constituted hydrophilic outer shell and a cytotoxic chemotherapeutic agent incorporated hydrophobic inner core. The main action mechanism of the polymeric micelles is similar to lipomosal agents and through the passive targeting based on the enhanced permeability of tumor neo-vasculature and the impeding clearance of macromolecules from lymphatic-deficient tumor interstitial tissue. Several cytotoxic chemotherapy-incorporating polymeric micellar nanoparticles have been in clinical trials, including paclitaxel-incorporating PEG-polyaspartate (NK105), cisplatin-incorporating PEG-polyglutamate/cisplatin complex (NC-6004) and SN-38-incorporating PEG-ploy glutamate/SN-38 (NK012). Of them, NC-6004 is currently evaluated in a phase Ib/II trial for patients with advanced pancreatic cancer, and will be discussed (38-41).

Cisplatin-incorporating Polymeric Micelles, NC-6004

In animal study, NC-6004 showed characteristic delayed total body clearance and higher area-under curve as compared with free cisplatin with a ratio of 1/19 and 65 folds, respectively (42). In addition, both histopathological and biochemical studies suggested NC-6004 significantly reduced cisplatin-associated nephrotoxicity. In phase I trial for patients with refractory advanced solid tumor, escalating dose of NC-6004 was administered intravenously every 3 weeks. Despite the implantation of pre-medication and post-therapy hydration, nephrotoxicity and allergic reaction were observed in patients receiving 120 mg/m^2 and further dose escalation was withheld. The MTD and the recommended dose were determined as 120 mg/m^2 and 90 mg/m^2, respectively. Pharmacokinetic study showed the maximum plasma concentration and area under curve of ultra-filterable platinum after 120 mg/m^2 of NC-6004 were 1/34 and 8.5 folds of those with free cisplatin (43). Seven out of 17 accruals achieved stable diseases, including two of two pancreatic cancer patients who had NC-6004 at dose level of 90 mg/m^2. Perhaps owing to earlier metaanalysis showed he combination of gemcitabine and platinum could significantly improved the overall survival of advanced pancreatic cancer patients as compared to gemcitabine monotherapy, NC-6004 is currently proceeded into a phase Ib/II trial to evaluate the maximum tolerated dose of NC-6004 in combination with gemcitabine and the therapeutic efficacy of the combination in patients with chemo-naïve advanced pancreatic cancer, clinicaltrials.gov identifier NCT00910741.

Rexin-G

Rexin-G is a highly engineered, nonreplicating retroviral vector displaying a von Willebrand factor–derived collagenbinding motif at its amphotropic envelope, and expressing a dominant negative cyclin G1 gene (44-46). This Willebrand factor-derived collagen-binding motif on the retrovector' s surface enables the nanoparticle drug to seek and be selectively delivered to primary and secondary tumor sites where angiogenesis and collagen matrix exposure characteristically occur. The encoded dominant negative cyclin G1 gene will thus to disrupt tumor cell cyclin G1 activity to lead to the destruction and/or growth inhibition of tumor.

There were two dose escalating phase I trials evaluating different dose/schedule of Rex in-G in patients with gemcitabine-failed advanced pancreatic cancer. The first trial evaluating 3 dose levels of Rexin-G administered intravenously, level I, 7.5 × 10^9 colony forming units (CFU) per day, days 1-7 and 15-21 every 28 days; level II, 1.1 × 10^{10} CFU per day, days 1-7 and 15-21 every 28 days; and level III, 3 × 10^{10} CFU per day, 5 days per week × 4 weeks/ cycle with 6 weeks rest between two cycles. A total of 12

Table 1 Nanovectors in pancreatic cancer treatment

Name	Compound	Nanocarrier	Size	Status
Abraxane™	Paclitaxel	Nanoparticle-albumin	130 nm	Phase I/II
Caelyx™	Doxorubicin	Liposome	100 nm	Phase I/II
Lipoplatin™	Cisplatin	Liposome	110nm	Phase I/II
Aroplatin™	Platunum	Liposome	1-3 μm	Phase I/II
MM-398	Irinotecan	Liposome	110±30 nm	Phase II
Endotag-1™	Paclitaxel	Liposome	180-200 nm	Phase II
Nanoplatin™	Cisplatin	Polymer Micelle	30 nm	Phase I/II
Rexin-G™	Cyclin G1 gene	Viral vector	110 nm	Phase I/II

patients were enrolled, only one patient with doselimiting toxicity manifesting as grade 3 transaminitis was observed at dose level II. However, the best tumor response was stable disease in one (8.3%) and the median time to tumor progression and overall survival of intent-to-treat population were 32 days and 3.5 months, respectively (47). In the second trial, the dose of Rexin-G was increased to 1×10^{11} CFU per day, twice or thrice per week for 4 weeks as one cycle (dose levels 0 and I), and 2×10^{11} CFU per day, thrice per week for 4 weeks as one cycle (dose levels II). A total of 13 patients were enrolled, 6 in dose level 0-I and 7 in dose level II. There was no DLT observed. On intent-to –treat analysis, the tumor control rate was 50% (3/6) and 85.7% (6/7 with one partial responder) of patients at dose level 0-I and II, respectively. The median overall survival in corresponding group of patients was 2.6 months and 9.3 months, respectively (48). Based on the results, the US FDA has granted Rexin-G fast-track designation as second-line treatment for pancreatic cancer in June 2009. Currently, a phase II/III pivotal two-arm randomized study aiming to validate the survival benefit of Rexin-G monotherapy versus physician's choice in gemcitabine-refractory pancreatic cancer is under discussion.

Conclusion

Systemic therapy for advanced pancreatic cancer has been largely disappointed owing to the unfavorable pharmacokinetic profile and poor penetration of current chemotherapeutic agents and the fragile patient population hard to tolerate toxic combinat ion chemotherapy. Nanovector can provide passive or active targeting drug delivery to reduce the system exposure and enhance local drug retention in tumor tissue. In this review, we provide pre-clinical and clinical evidence to support the potential use of nanovector-based therapy in patients with advanced pancreatic cancer. Unfortunately, most of trials reported here are relatively small and without control group. Prospective, large-scale randomization trials are warranted to confirm their efficacy in this difficult tumor. In addition, the combination of the relatively low toxic nanoparticle drug with conventional cytotoxic agent and/or recently emergent molecular targeted agent should also be investigated to improve the clinical outcomes of patients with advanced pancreatic cancer.

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Immunotherapy for pancreatic ductal adenocarcinoma: an overview of clinical trials

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Authors' introduction: Dr. Alessandro Paniccia is a surgical resident at the University of Colorado in Denver (USA) and a research fellow in tumor immunology in the Department of Surgery.

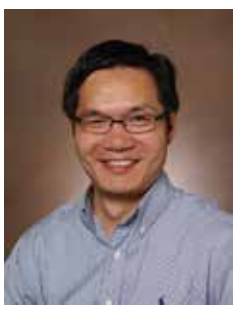
Originally a native of Rome (IT), Dr. Paniccia earned his medical degree, graduating magna cum laude, from the University of Rome "Sapienza" [2008]. He then completed 2 years of general surgery residency at The Johns Hopkins Hospital (USA) before being recruited to the University of Colorado to continue his surgical training under the guidance of Dr. Richard Schulick. While at the University of Colorado, Dr. Paniccia enrolled in a 2-year post-doctoral research fellowship in tumor immunology. During this time, his work focused on the identification and characterization of new T-cell immunologic checkpoints.

During his residency he was awarded the Ernest E. Moore Award in Basic Science Research from the University of Colorado for outstanding presentation of basic science research at the Annual Department of Surgery Research Symposium. In addition, Dr. Paniccia received training in clinical research design and statistical analysis through the Global Clinical Scholar Research-Training program (GCSRT) at Harvard Medical School.

His primary academic interests are in pancreatic cancer translational research and in particular neoadjuvant treatment for borderline resectable pancreatic adenocarcinoma and cancer immunotherapy.

Dr. Yuwen Zhu obtained his PhD in immunology from the Mayo Clinic, Rochester, Minnesota, USA, and was trained as a postdoctoral fellow and worked as a research faculty member in Dr. Lieping Chen's laboratory at Johns Hopkins University and Yale University. He is now an assistant professor in the Department of Surgery at the University of Colorado Anschutz Medical Campus, Colorado, USA. His research focuses on the discovery of novel immunomodulatory pathways and their potential applications in cancer immunotherapy.

Dr. Alessandro Paniccia



Yuwen Zhu

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death and current therapeutic strategies are often unsatisfactory. Identification and development of more efficacious therapies is urgently needed. Immunotherapy offered encouraging results in preclinical models during the last decades, and several clinical trials have explored its therapeutic application in PDAC. The aim of this review is to summarize the results of clinical trials conducted to evaluate the future perspective of immunotherapy in the treatment of PDAC.

Keywords: Immunotherapy; pancreatic neoplasm; cancer vaccines; clinical trial

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Evolution of tumor immunology

The role of the immune system in the development of neoplastic diseases has been the subject of investigation and controversy for several decades. In 1891, William Coley offered one of the first examples of the efficacy of the immune system in treating cancerous lesions. His strategy consisted of intratumoral injections of live or inactivated Streptococcus pyogenes and Serratia marcenses, known as "Coley's toxin". The injected bacteria were capable of initiating a local inflammatory response resulting in activation of antibacterial phagocytes and potential killing of nearby tumor cells by virtue of profound inflammatory response (1). Data derived from Coley's work were collected for over 40 years and the results of his studies were published in 1953 (2,3). As a result of his pioneering work, Coley is often credited as the father of cancer immunotherapy.

The current view of immune surveillance suggests that cancerous cells are maintained in check by the immune system, which recognizes and eliminates abnormal cells (4-7). The process of immune-surveillance depends on a series of events that are necessary to mount an effective antitumor response (1). Cancer cells express specific epitopes (i.e., neo-antigens) on their cell surface as a result of cancerous transformation (8,9). These epitopes are also known as tumor-associated antigens (TAAs) and are usually captured, processed and presented by dendritic cells (DCs) (10,11). DCs, which are often recognized as the most potent antigen-presenting cells in the human body, require activation and/or maturation signals to differentiate and eventually migrate to regional lymph nodes (12,13). Once in the lymph nodes, mature DCs present TAAs to naive T cells that then undergo expansion and differentiation to become activated T cells. activated T cells eventually leave the lymph nodes and infiltrate into the tumor site where they execute their cytotoxic activity to kill tumor cells (1).

Tumor cells, however, can evade immune control through several complex mechanisms, utilizing immunosuppressive and tolerogenic strategies including immunoediting (14,15). Immunoediting is composed primarily of three sequential stages known as elimination, equilibrium, and escape (7,14,16). During the first phase of "elimination", cancerous cells are identified and appropriately destroyed by the immune system. During the second phase of "equilibrium," the immune system prevents further tumor outgrowth but it fails to eliminate cancerous cells completely. The third phase, "escape," is a direct consequence of the previous two phases, and can be seen as the product of selective pressure of the immune system on cancer cells. In this final phase, cancer cells, which evolve from the original cancerous cell, are now capable of evading the immune surveillance and continue to proliferate.

The pancreatic cancer microenvironment

Pancreatic ductal adenocarcinoma (PDAC) presents several challenges that set it apart from those more immunogenic tumors, such as melanoma and renal cell cancer (17,18). A dysregulation of the immune system is one of the facilitating factors for PDAC development, thus legitimizing the role of the immune network in PDAC (19-22).

One of the principal characteristics of PDAC is the abundance of stromal desmoplasia that constitutes the tumor microenvironment in which the components of the immune network are distributed (23,24). This extensive stromal desmoplasia, also known as fibrosis, has been shown to promote tumor development and most importantly to prevent the penetration and uptake of chemotherapeutic

agents (25,26). One of the major players in PDAC desmoplasia is the pancreatic stellate cell (PSC). Stimulated by transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF), the PSCs initiate a process of synthesis and deposition of extracellular matrix (ECMs) proteins that eventually leads to the extensive desmoplastic reaction seen in PDAC (27,28). Preclinical models have shown that targeting the signaling cascade leading to ECMs protein synthesis could enhance drug penetration in the pancreatic neoplastic tissue (29). However, PDAC clinical trials have yet to show a significant benefit from this approach. In addition, activation of inhibitory T-cell checkpoints (i.e., CTLA-4, PD-1) may have a contributing role as does the particularly hostile tumor microenvironment characterized by abundant stroma that prevents the effector T-cell from functioning in various manners (30).

Several cytokines appear to be dysregulated and contribute to cancer progression in PDAC. In particular, higher levels of circulating interleukin-6 (IL-6) are identified in patients with PDAC and appear to promote cancer progression through enhancement of protumorigenic Stat3 signaling (20,31). Furthermore, members of the IL-1 family [e.g., IL-α, IL-β and IL-1 receptor antagonist (IL-1ra)] seem to play a role in PDAC development (32-34). Immunosuppressive cytokine IL-10 is up regulated in PDAC, which leads to a reduction in effector cell function in the PDAC microenvironment and indicates a worse prognosis (35,36).

Tumor-infiltrating lymphocytes (TILs) have a paramount role in tumor specific cellular adaptive immunity. The main components of this population are CD8+ cytotoxic T cells, CD4+ helper T cells (e.g., Th1, Th2, and Th17), and regulatory T-cells (T_{regs}) (18). CD8+ T-lymphocytes are the dominant subset of T-lymphocytes in the PDAC microenvironment and their presence is associated with prolonged survival (37-39). CD8+ cytotoxic T-cells recognize TAA peptides associated with major histocompatibility complex class I on tumor cells, resulting in cancer cell destruction. In addition to their direct cytotoxic effect on tumor cells, CD8+ T cells are capable of mobilizing and triggering macrophage tumoricidal activity (18,40,41). The presence of Th1 and Th2 lymphocytes in the tumor microenvironment appears to have opposite prognostic significance in the setting of PDAC progression (42,43). In fact, the presence of Th1 is associated with favorable prognosis while a predominant infiltration of Th2 and its related cytokines (IL-4, IL-5 or IL-13) often correlates with disease progression (18). Of interest is the role of IL-5 and IL-13, these cytokines likely stimulate the desmoplastic reaction increasing ECM deposition and collagen synthesis (44). Furthermore, IL-13 appears to downregulate proinflammatory cytokines (IL-1, IL-6, TNF-α) and chemokines, and effectively inhibits antibody-dependent cellular toxicity (45,46). Nevertheless, IL-13 acts as an autocrine growth factor for PDAC (47,48). Regulatory T-cells (T_{regs}), which are positive for CD4+, CD25+, and Foxp3, are enriched in the tumor microenvironment (49,50). T_{regs} effectively suppress the adaptive immune response and their presence in the tumor microenvironment leads to a decreased presence of CD8+ T-cells and often correlates with poor prognosis (50,51). Other cell types, like myeloid-derived suppressive cells (MDSCs) and neutrophils, also participate in the immune reaction during the development and progression of PDAC resulting in dynamic interactions between the tumor cells, and the immune system.

Strategies of cancer immunotherapy

Different strategies for cancer immunotherapy have been proposed and investigated. These therapeutic strategies can be grouped into active or passive, based on the involvement of the host immune system. Active immunotherapy aims to stimulate the host immune response to recognize TAAs and eventually destroy tumor cells. This often requires administration of cytokines, immunomodulatory agents, or therapeutic vaccines that eventually lead to the expansion of tumor-specific T cells. Passive immunotherapy requires the exogenous administration of activated lymphocytes (e.g., tumor-specific immune effector cells) or antibodies that mediate an immune response (52).

Overview of clinical trials in PDAC immunotherapy

Results from recent clinical trials conducted between 2005 and 2015 are summarized in *Table 1*. In addition, trials conducted between 2010 and 2015 are discussed in the following sections.

Adoptive therapy

In one of the most recent phase II trials, Chung *et al*. evaluated the use of adoptive immunotherapy in patients with advanced pancreatic cancer who experienced disease progression during gemcitabine-based chemotherapy (73). In this study, the authors utilized *ex vivo* expanded, cytokine-induced killer (CIK) cells (i.e., heterogenous cell population

Table 1 Pancreatic cancer immunotherapy: an overview of selected clinical trials

Type of immune therapy	Phase	Population	Outcome	n	Year	References
Vaccine						
GV1001 (TeloVac) (telomerase vaccination) Chemotherapy Chemotherapy with sequential GV1001 Chemotherapy with concurrent GV1001	III	Locally-advanced and/or metastatic PDAC	MST: 7.9 mos with chemotherapy alone, 6.9 mos (sequential chemotherapy) *vs*. 8.4 mos (concurrent with chemotherapy)	1,062	2014	(30)
WT1 peptide-based cancer vaccine Combined with gemcitabine	I	Locally-advanced and/or metastatic or recurrent PDAC	MPFS: 4.2 mos MST: 8.1 mos OS: 71% and 29% (6 mos and 1 yr)	32	2014	(53)
KIF20A-derived peptide with gemcitabine (kinesin superfamily motor proteins)	I	Locally-advanced and/or metastatic PDAC	MST: 173 days OS: 11.1% (1 yr)	9	2014	(54)
Personalized peptide vaccination (PPV)	II	Advanced PDAC that failed 1st-line chemotherapy	MST: 7.9 mos OS: 26.8% (1 yr)	41	2013	(55)
HLA-A24-restricted peptide vaccine from KIF20A	I/II	Locally-advanced and/or metastatic PDAC	MPFS: 56 days MST: 142 days	31	2013	(56)
Algenpantucel-L + chemotherapy/ chemoradiotherapy	II	Resected PDAC	DFS: 62% (1 yr) OS: 86% (1 yr)	72	2013	(57)
muRAS-transfected EBV-transformed lymphoblastoid cell lines	I	Relapsed or metastatic, muRas-positive cancer	MPFS: 3.1 mos	7	2012	(58)
MUC1-peptide pulsed dendritic cells	I	Recurrent or metastatic PDAC, MUC1-positive cancer	Diseases progression observed in all patients within 3 mos	7	2012	(59)
GM-CSF secreting vaccine	II	Resected pancreatic cancer	Median DFS: 17.3 mos MST: 24.8 mos	60	2011	(60)
VEGF-receptor 2+ gemcitabine	I	Locally-advanced and/or metastatic PDAC	MPFS: 3.9 mos MST: 7.7 mos	18	2010	(61)
Personalized peptide vaccination (PPV) + gemcitabine	II	Locally-advanced and/or metastatic PDAC	MST: 9 mos OS: 38% (1 yr)	21	2010	(62)
OK432-pulsed DCs + CD3-LAKs + GEM	I	Locally-advanced PDAC	MST: 478 days	5	2009	(63)
Preoperative immunotherapy IL-2	III	Resected PDAC	The arm pre-treated with IL-2 had a longer MPFS and OS compared with surgery only ($P<0.01$ and $P<0.05$)	30	2008	(64)
GM-CSF cancer cell line (CG8020/CG2505) Arm 1: vaccine alone Arm 2: vaccine + cyclophosphamide	III	Advanced PDAC	Arm 1: MST =2.3 mos Arm 2: MST =4.3 mos	50	2008	(65)
Poxvirus-based vaccine targeting CEA and MUC-1	I	Locally-advanced and/or metastatic PDAC	MST: 6.3 mos Patients who generated specific immune response to CEA and/or MUC-1 showed a survival advantage (15.1 *vs*. 3.9 mos; P=0.002)	10	2007	(66)

Table 1 (*continued*)

Table 1 (*continued*)

Type of immune therapy	Phase	Population	Outcome	n	Year	References
Vaccine						
Heat shock protein (HSPPC-96)	I	Resected PDAC	MST: 2.2 yr	10	2007	(67)
Personalized peptide vaccination (PPV) + gemcitabine	I	Locally-advanced and/or metastatic or recurrent PDAC	MPFS: 17 weeks MST: 7.6 mos	13	2007	(68)
Telomerase peptide GV1001 (dose escalating trial)	I/II	Non-resectable PDAC	Low dose group: MST =4.O mos Intermediate dose group: MST =8.6 mos* High dose group: MST =5.1 mos	48	2006	(69)
Personalized peptide vaccination	I	Locally-advanced and/or metastatic or recurrent PDAC	OS: 80% (6 mos) OS: 20% (12 mos)	11	2005	(70)
MUC1 + SB-AS2 (patients were allowed to receive adjuvant therapy after completing three vaccinations)	I	Resected or locally advanced PDAC	MST: 12 mos	16	2005	(71)
Immunotherapy check-point						
Single agent ipilimumab (anti-CTLA-4)	II	Locally advanced or meastatic PDAC	Significant delayed regression of metastatic pancreatic cancer in 1 out of 27 patients	27	2010	(72)
Passive immunotherapy						
Cytokine-induced killer (CIK) cells	II	Advance pancreatic cancer with disease progression during gemcitabine-based therapy	MPFS =11.0 weeks MST =26.6 weeks	20	2014	(73)
Combination strategies						
Ipilimumab (anti-CTL-4) + GM-CSF cell-based vaccine (GVAX)	Ib	Advanced PDAC, previously treated	Arm 1: Ipilimumab alone MST: 3.6 mos OS: 7% (1 yr) Arm 2: Ipilimumab + GVAX MST: 5.7 mos OS: 27% (1 yr)	30	2013	(74)
Survivin 2B-derived peptide vaccination + α -INF	I	Advanced PDAC	No survival information	6	2013	(75)
Cytokine-induced killer (CIK) cells + α -Gal-dendritic cells (DCs)	I	Locally-advanced PDAC	MST: 24.7 months	14	2013	(76)
MUC1-DC + MUC1-CTL	II	Locally advanced or recurrent PDAC	Mean OS: 9.8 mos OS: 20% (1 yr) OS: 10% (2 yr) OS: 5% (3 yr)	20	2008	(3)

*, significantly increased survival in the intermediate group compared to low dose (P=0.006) and high dose (P=0.05). OS, overall survival; MST, median overall survival time; DFS, disease free survival; MPFS, median progression free survival; mos, months; yr, year; PDAC, pancreatic adenocarcinoma; WT-1, Wilms tumor 1; VEGF-R, vascular endothelial growth factor; IL-2, interleukin- 2; α -Gal, alpha-galactosyl epitope; α -INF, alpha-interferon; LAK, lymphokine-activated killer; GEM, gemcitabine; MUC1, human-mucin1; CTL, cytotoxic T-lymphocyte; CEA, carcinoembryonic antigen; GVAX, irradiated cancer cell lines (PANC 6.03 and PANC 10.05) that were engineered to express GM-CSF (whole cell vaccine); EBV, Epstein-Barr virus.

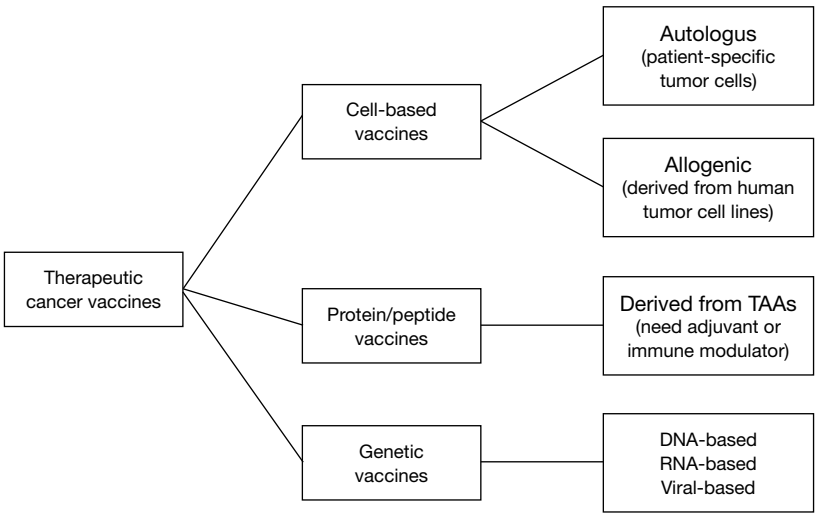

Figure 1 Therapeutic cancer vaccine categories. TAA, tumor associated antigen.

containing >20% of CD3+ CD56+ cells) previously shown to have cytolytic activity in a major histocompatibility complex (MHC)-unrestricted manner (77). Patients enrolled in this study received CIK as the sole cancer therapy. The authors reported a median estimated progression free survival (PFS) of 11.0 weeks and a median estimated overall survival (OS) of 26.6 weeks, which were similar to prior studies using conventional cytotoxic chemotherapy (73,78-80).

Cancer vaccines

Cancer vaccines aim to stimulate the immune system to produce tumor-specific T cells and B cells (81). The primary mechanism of action of therapeutic cancer vaccines is their capacity to increase the presentation of TAAs to the immune system. Generally vaccines can be classified in three major approaches: cell-based vaccines, protein/peptide vaccines, and genetic vaccines. Each strategy has been well-investigated, and each seems to have its own advantages and disadvantages (*Figure 1*).

Table 2 summarizes the most common cellular targets utilized in recent clinical trials of PDAC cancer vaccines, including: telomerase, Wilms tumor gene, KIF20A, alpha-galactosyl (α-Gal), survivin, mutated Ras protein, human mucin MUC1 protein, and vascular endothelial growth factor receptor 2 (VEGFR2).

The TeloVac study is one of the largest randomized, phase III clinical trials to evaluate the efficacy of cancer vaccine in PDAC (30). This trial was conducted in 51 hospitals in the United Kingdom and enrolled 1,062 subjects. It aimed to assess the efficacy and safety of sequential or simultaneous telomerase vaccination (GV1001) in combination with chemotherapy in patients with locally advanced or metastatic pancreatic cancer. Results showed that adding GV1001 vaccine either simultaneously or sequentially to a standard treatment regimen of gemcitabine and capecitabine did not improve OS. The authors suggest that the lack of response seen in this trial may be due to the characteristic rapid progression of pancreatic cancer to metastatic disease, which could prevent an active immune response from developing.

Active peptide-based immunotherapy utilizing Wilms tumor (WT1) protein has been investigated in combination with gemcitabine for patients with advanced pancreatic cancer (53). In this phase I clinical trial, vaccination with WT1 in combination with gemcitabine was found to be safe. Furthermore, although the trial was not designed to evaluate survival benefit, it appears that the patients in whom a WT1 specific immunity was induced had better clinical outcomes translating to a 12-month or longer survival time and an improved quality of life (QOL).

Suzuki *et al*. conducted the first phase I trial aimed to investigate the use of a vaccine composed of an epitope peptide KIF20A in combination with gemcitabine in patients with advanced pancreatic cancer (unresectable and/or metastatic) who had already received prior conventional chemotherapy and/or radiotherapy (54). The authors reported no adverse events directly attributable to the vaccine and demonstrated enhancement of INF-γ-producing cells in 8 out of the 9 patients enrolled (54).

Table 2 Common cellular targets utilized in recent clinical trials for PDAC cancer vaccine

Cellular targets	Rationale	References
Telomerase	Enzyme that is reactivated during oncogenic transformation Prevents the naturally occurring shortening of the telomeric ends of DNA during replication, which would lead to cell senescence and eventually cell death	(82-84)
Wilms tumor gene (WT1)	Identified on the cell surface of several cancerous cells including pancreatic cancer cells Highly immunogenic, eliciting both humoral and cellular responses	(53,85-91)
KIF20A (RAB6KIFL)	Member of the kinesin superfamily of motor proteins, that has a paramount role in the intracellular trafficking of molecules and organelles during the growth of pancreatic cancer	(54)
Alpha-galactosyl (α -Gal) epitope	Human cells do not present the α-Gal epitope and on the contrary the anti-Gal antibody is abundant in human serum (about 1% of circulating human antibody) Genetically modified tumor cells that express α-Gal in addition to TAAs, in an attempt to induce a complement and antibody-dependent cell-mediated hyperacute rejection that would favor the processing and presentation of TAAs	(76,92-95)
Survivin (also known as baculoviral inhibitor of apoptosis repeat-containing 5; BIRC5)	Member of the inhibitor apoptosis protein (IAP) that is highly expressed in neoplastic tissues but absent in non-neoplastic human cells	(75,96-98)
Mutated Ras protein	Derives from the Ki-*Ras* p21 oncogene and is expressed in cancer derived from different histologies and in approximately 90% of PDAC cases A point mutation at codon 12 results in specific substitution of a normal glycine (Gly) amino acidswith an aspartic acid (Asp), valine (Val), cysteine (Cys), or arginine (Arg) which can easily be targeted by a formulation of four different vaccines	(58,99)
Human mucin MUC1 protein	This protein is specifically expressed on the surface of pancreatic cancer cells and can be used as a specific tumor associated antigen (TAA)	(48,59,71,100)
Vascular endothelial growth factor receptor 2 (VEGFR2)	VEGFR2 is highly expressed on endothelial cells of tissues undergoing a process of tumor-induced neovascularization but it is absent in normal blood vessels VEGFR2 has been identified on PDAC cancer cells Vaccination leads to the generation of CTL able to interfere with the processes associated with PDAC neovascularization. In addition, specific-CTLs have the potential to target PDAC cancer cells directly	(61,101-103)
Mesothelin	Overexpressed in most PDAC Participate in cell adhesion and has a potential role in metastatic progression	(104)
Personalized peptide vaccination (PPV)	Relatively new strategy of peptide-based vaccination The peptide utilized is chosen from a number of different pooled peptides and selected based on the patient's HLA-class IA types and levels of peptide-specific IgG responses prior to vaccination	(55,62,68)

The enthusiasm that followed two trials conducted by Yanagimoto *et al*., aimed at the evaluation of personalized peptide vaccination (PPV) in combination with gemcitabine (62,68), prompted Yutani *et al*. to test this vaccination strategy in a phase II trial in patients with chemotherapy–resistant advanced pancreatic cancer (55). Patients enrolled in this trial had a median survival time (MST) of 7.9 months with a 1-year survival rate of 26.8%. However the authors noted that patients who were treated solely with PPV (n=8) had a MST of 3.1 months compared to patients who received PPV vaccination combined with chemotherapy (9.6 months; P=0.0013). Therefore, Yutani *et al*. concluded that PPV offers no advantages as a single therapy in patients with advanced PDAC, although its use combined with chemotherapy could positively influence OS.

Algenpantucel-L (NewLink Genetics Corporation,

Ames, IA, USA) is an allogenic cancer vaccine composed of two human PDAC cell lines (HAPa-1 and HAPa-2) (57). These cells express the α[1,3]-galactosyl epitopes (α-Gal) as a result of genetic engineering processes. Injection of algenpantucel-L generates a hyperacute rejection that ultimately stimulates the patient's immune system to target the existing PDAC lesions (57,105). In the phase II trial conducted by Hardacre *et al*., algenpantucel-L was administered in combination with standard chemotherapy and chemoradiotherapy (gemcitabine + 5-fluorouracile-based chemoradiotherapy) as adjuvant treatment following surgical resection of a primary PDAC lesion. Results from this trial were encouraging; with a reported 12-month disease free-survival of 62% and 12-month OS of 86% with a median follow-up of 21 months. The authors remarked that the percentage of patients surviving at 12-month was higher than survival predicted by the widely accepted prognostic nomogram described by Brennan *et al*. (86% *vs*. 55-63%) (57). Another positive note was that patients treated with algenpantucel-L experienced minimal side effects, mainly consisting of injection site pain and induration. Although several interesting findings emerged from this study, its results should be interpreted carefully as no definitive conclusion was achieved on the advantage provided by the addition of algenpantucel-L to standard chemotherapy regimens.

Asahara *et al*. conducted a non-randomized, open-label, phase I/II clinical trial utilizing the KIF20A-66 epitope restricted to the HLA-A2402 (the most common HLA-A allele in the Japanese population enrolled in the study). The KIF20A-66 is a member of the kinase superfamily protein (see above) that is highly expressed in pancreatic cancer cells. Patients with advanced PDAC who failed gemcitabine-based therapy comprised the cohort selected for this trial. Median survival time was compared to a historic cohort and patients treated with cancer vaccine therapy showed an overall median survival time of 142 days compared to 83 days (P=0.0468) of the historic cohort. Interestingly, the authors reported the case of one patient who experienced complete response with resolution of liver metastatic lesion. This patient was noted to have a strong cytotoxic T-cell (CTL) response to KIF20A-66 epitope that remained detectable even 2 years from the last dose of vaccine administration (56).

Kubuschol *et al*. investigated the use of an autologous lymphoblastoid cell line (LCL)-based vaccine. LCLs are "professional" antigen presenting cells (APCs) characterized by a very high immunostimulatory capacity that are easily obtained from EBV-positive patients. These cells are a particularly attractive source of APCs because they are characterized by a rapid growth *in vitro* providing an easily accessible cell pool (58). In this trial LCLs where engineered to express a mutated Ras-protein on the cell surface (muRas-LCL). Patients enrolled in the study, received weekly subcutaneous injections with muRac-LCL vaccine. Tumor specific T-cell response (muRas-specific) was observed in six of the seven patients enrolled in the trial (85%). However, despite an initial clinical response observed in 57% of cases, after 4 months from initial vaccination, all patients showed disease progression. One of the most important findings of this study was that the use of tumor antigen-transfected LCL proved to be an efficient alternative to DCs to serve in the role of APCs for future vaccine trials (58).

Rong *et al*. investigated the immunological response induced by the administration of MUC1-peptide-pulsed DCs-based vaccine in a cohort of advanced PDAC patients (59). Patients were selected based on tumor expression of MUC1. Patients' autologous DCs were collected, pulsed with MUC1-peptide and injected intradermally for three to four administrations. Although the vaccination regimen was safe, evidence of a significant immune response was observed in only two of the seven patients enrolled.

Lutz *et al*. conducted a phase II clinical trial enrolling 60 patients with resected pancreatic adenocarcinoma (60). In their trial, the authors utilized an allogenic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine (GM-CSF), based on cancer cell lines PANC 10.05 and PANC 6.03, injected directly into lymph node regions. The initial vaccine dose was followed by 5-FU based chemoradiotherapy and additional vaccine doses were given after chemotherapy completion in patients that remained disease free. Patients that completed all 4 doses of the vaccine therapy received a final vaccine booster 6 months after the administration of the fourth dose. The first observation from the study was that the regimen of vaccination with GM-CSF-secreting tumor cells following adjuvant chemoradiotherapy was well tolerated. In fact, no local or dose-limiting toxicities were observed. Additionally, when the study cohort was compared to a historical cohort treated at the same institution, the authors found no significant difference in the median OS (HR: 0.96, 95% CI, 0.68-1.35, P=0.8).

Miyazawa *et al*. investigated the use of a peptide vaccine for human vascular endothelial growth factor receptor 2 (VEGFR-2) in combination with gemcitabine adjuvant therapy (61). In this phase I clinical trial, 21 patients with

advanced pancreatic cancer were enrolled and 18 patients were able to complete the vaccination schedule and were evaluated in their final analysis. Although the treatment was well tolerated, and specific CTL response against the vaccinated peptide was observed in the majority of the treated patients (61%), no correlation of CTL response and overall clinical outcome was appreciated. Following the results of this study a new double-blind, placebo-controlled trial was designed to investigate the role of an oral VEGFR-2 vaccine in patients with stage IV and locally advanced pancreatic cancer. The study is currently ongoing (NCT01486329) (106).

The use of GVAX, a whole-cell vaccine composed of two irradiated cancer cell lines (PANC 6.03 and PANC 10.05) engineered to express GM-CSF has been investigated in multiple phase I and II studies. Early studies showed that vaccination with GVAX leads to induction of CD8+ T-cell responses against multiple mesothelin-specific epitopes that has been shown to correlate with improved survival (60,65,107).

Although designed to evaluate a mixed cohort with advanced solid tumor, the study conducted by Le and colleagues offered interesting results on the use of Listeria-based vaccines (108). *Live-Attenuated Listeria vaccines* are used based on the ability of *Listeria monocytogenes (Lm)* to stimulate both innate and adaptive immunity. After administration, Lm is phagocytized in the liver and generates a local inflammatory response leading to the activation and recruitment of natural killer (NK) and T cells. Le and colleagues, investigated the use of live-attenuated *Lm*-based vaccines in two cohort of patients with liver metastasis originated from PDAC (108). In the first phase of their study, the safety and efficacy of the use of *Lm*-based vaccine (ANZ-100) was tested and found to be acceptable. Following these initial findings, Lm was modified to express human mesothelin (CRS-207), a tumor associated antigen (TAA) known to be expressed by PDAC. The ultimate goal was to induce an immune response that would produce tumor antigen-specific T cells directed toward PDAC expressing human mesothelin protein. Three of the seven patients treated with (CRS-207) survived more than 15 months and showed specific T-cell response to the vaccine component listeriolysin O (LLO), although all three patients had received prior immunotherapy with GM-CSF-based whole-cell vaccine (GVAX) which confounds the overall results. Unfortunately, LLO-response was not evaluated in the remaining patients who survived less than 15 months.

Taken together these results suggest that cancer vaccines are in general well tolerated and able to generate an immune response directed toward specific cancer targets. However, with the exception of some isolated but remarkable clinical responses, the impact of cancer vaccines on OS in PDAC appears to be minimal for the majority of patients. Several explanations for this lack of efficacy have been proposed. It is worth noting that advanced stages of PDAC are characterized by rapid disease progression that might not allow enough time for the immune system to mount an effective response that often requires weeks to months to develop.

Immune checkpoint blockade

T cell response can be controlled by a few cosignaling receptors with inhibitory functions, now known as immune checkpoints, which include CTLA-4, PD-1 and BTLA. Agents blocking these molecules are able to unleash endogenous anti-tumor T cell responses, so as to limit tumor growth (109). Royal *et al*. investigated the role of single agent Ipilimumab, an anti-CTLA-4 antibody, in a cohort of locally advanced or metastatic pancreatic adenocarcinoma (72). Ipilimumab has been previously effective in the treatment of melanoma, renal cell carcinoma, and prostate cancer (110-112). CTLA-4 is transiently expressed on the T-cell surface following activation and leads to a decrease in T-cell response following its binding to B7-1 or B7-2 on APCs or target tissue (113). In this phase 2 trial, the authors observed a significant delayed regression of metastatic pancreatic cancer in one out of the twenty-seven patients enrolled in the study. The findings of this phase 2 trial were particularly interesting as they underlined the mechanism of action of Ipilimumab represented by immunomodulation rather than direct tumoricidal activity. In fact, the patient who showed a response to Ipilimumab treatment had initially experienced marked progression of the disease. The authors concluded that Ipilimumab alone might not be a valuable treatment for advanced pancreatic cancer, however they laid the basis for future trials of combination therapy with immune checkpoint blockade combined with vaccine or chemotherapy (72).

Combination immunotherapy trials

Cancer vaccine and immune checkpoint blockade

Although the study conducted by Royal *et al*. (phase II trial) showed minimal efficacy of anti-CTLA-4 (Ipilimumab) therapy on advanced pancreatic cancer, one patient enrolled in this initial trial showed a significant delayed response suggesting a possible role for immune checkpoint blockade

in PDAC (72). Several preclinical studies suggest a possible synergistic role of cancer vaccine therapy that stimulates the immune system and the use of immune checkpoint blockade to allow for the unopposed effector function of cytotoxic T-cells (114,115). On this premise, Le *et al*. conducted a phase Ib, open-label, randomized study to the determine the safety profile of ipilimumab alone or in combination with GVAX in patients with previously treated PDAC (74). This study showed that the use of Ipulimumab in PDAC patients, with or without GM-CSF-based cell therapy, has an acceptable side effect profile. Induction of immune response was observed as a result of the treatment regimen and correlated with clinical activity, although prolonged treatment appears to be required to obtain a clinical response in the setting of advanced PDAC disease (74). One of the most interesting aspects of this study was the difference in 12-month OS of 27% *vs*. 7% and the median OS of 5.7 *vs*. 3.6 months (HR =0.51; P=0.072) respectively for combination therapy *vs*. monotherapy. Although the trial was not designed to show significant survival differences, the results obtained point to a superiority of the combination therapy over monotherapy (74).

Active immune therapy combined with passive immune therapy

Qiu *et al*. investigated the use of a combination of DC-based and CIK-based therapy (76). In this study, DCs were initially pulsed with patients' primary pancreatic carcinoma cells previously transfected *in vitro* to express α-Gal epitope and opsonized with anti-Gal IgG. This approach enhances the antigenicity of TAAs and facilitates phagocytosis by DCs (76). Subsequently, DCs were co-cultured with CIKs derived from bone marrow stem cells, ultimately generating tumor specific immune responders cells *ex vivo* (76). The generated CIKs and the mature DCs were then injected in 14 patients with inoperable stage III/IV pancreatic adenocarcinoma. The authors reported a significant increase in patients' cellular immunity, especially in the percentage of cytotoxic T cells (CD3+CD8+), activated and memory T cells (CD3+CD45RO+), and activated T and NK cells (CD3+CD56+). Furthermore, no serious side effects were experienced during treatment and the reported median OS was 24.7 months (108.1±35.1 weeks), higher than the usual survival reported in the literature for unresectable stage III/IV PDAC.

Kameshima *et al*. investigated the use of a vaccination protocol of survivin-2B80-88 plus incomplete Freud's adjuvant (IFA) and α-interferon (INFα) based on favorable results previously obtained in the treatment of colon cancer (75,116,117). The authors reported that more than 50% of the treated patients showed positive clinical and immunological response.

Immunotherapy combined with chemotherapy

Algenpantucel-L is currently being investigated in an open label, phase III, randomized trial in combination with FOLFIRINOX (oxaliplatin, 5-FU, irinotecan, and leucovorin) in patients with borderline resectable or locally advanced pancreatic cancer (NCT01836432). The estimated primary completion date is September 2015. This is currently the first study that is using a FOLFIRINOX based chemotherapy.

Conclusions and prospective

Traditional treatments for PDAC are limited and ineffective, and novel therapeutic strategies are greatly needed. Despite recent advancements in systemic chemotherapeutic regimens, the median survival time of advanced pancreatic cancer patients remains 4-11 months (118-121). The identification and development of more efficacious therapies is of paramount importance. Immunotherapy offers encouraging results in preclinical models but often fails to show clear benefits in clinical trials for PDAC. Immunotherapy, as a single treatment strategy, might not be sufficient to effectively treat PDAC. For example, evidence suggests that active immunotherapy should be used in combination with traditional chemotherapy and/or radiotherapy or even in combination with other forms of immune therapy (e.g., immune checkpoint blockade or passive immune therapy) (122). This strategy could take advantage of the various effects traditional chemotherapeutic agents and/or radiotherapy exert on the immune system (123,124). Acting through direct killing of cancerous cells, chemotherapeutic agents indirectly lead to the release of pro-inflammatory molecules and TAAs (85). In addition, chemotherapy can suppress the inhibitory mechanism in the tumor microenvironment. In fact, reduction of the number of T_{regs} cells and myeloid derived suppressor cells (MDSC) and their related cytokines (IL-17 and IL-15) are one of the recognized positive effects of chemotherapy on tumor microenvironment. This change in the composition of cells in the tumor microenvironment could facilitate the development of a more efficacious effector immune response against cancer cells (52,122,125). However, the potential synergistic effects of chemotherapy

have to be balanced with its potential immunosuppressive effects. Future studies should focus on identifying appropriate dosing and timing of synergistic chemotherapy administration in order to mitigate its immunosuppressive effects and maximize the effect of immunotherapeutic cancer treatments. Several aspects remain to be clarified in PDAC cancer immunotherapy, including optimal cellular targets, delivery vectors for cancer vaccines, combination with existing treatment strategies, and patient selection. Future clinical trials should be designed to address these unresolved aspects of PDAC immunotherapy.

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Footnote

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Diagnosis and management of cystic lesions of the pancreas

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Abstract: Pancreatic cystic lesions (PCLs) are being increasingly identified in recent years. They show a wide spectrum of imaging and clinical features. The diagnosis and discrimination of these lesions are very important because of the risk for concurrent or later development of malignancy. PCLs are usually first diagnosed and characterized by conventional imaging modalities such as trans-abdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). However, their ability to differentiate the benign and malignant lesions remains limited. Endoscopic US may be more helpful for the diagnosis and differentiation of PCLs because of its high resolution and better imaging characteristics than cross-sectional imaging modalities. It also allows for fine-needle aspiration (FNA) of cystic lesions for biochemical, cytological and DNA analysis that might be further helpful for diagnosis and differentiation. The management options of PCLs are to observe, endoscopic treatment or surgical resection. However, the decision for management is sometimes hampered by limitations in current diagnostic and tissue sampling techniques. As further diagnostic and non-invasive management options become available, clinical decision-making will become much easier for these lesions.

Keywords: Pancreas; cystic lesions; pseudocyst; mucinous cyst; intraductal papillary mucinous neoplasms (IPMNs); endoscopic ultrasonography (endoscopic US)

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Introduction

Pancreatic cystic lesions (PCLs) are a broad group of pancreatic tumors that have varying demographical, morphological, histological and clinical characteristics. There has been a large increase in the number of patients with PCLs in recent years. The rising prevalence might be caused by significant improvement of imaging technologies, increased awareness of their existence and the growth of the aging population. Besides, PCLs are being discovered increasingly in patients who are otherwise asymptomatic (1). Image-based studies report prevalence of PCLs ranging from 1.2% to 19% (1-3). Among 24,039 computed tomography (CT) or magnetic resonance imaging (MRI) scans, 290 patients (1.2%) had pancreatic cysts, and a majority of the patients had no history of pancreatitis (4). In an autopsy series of 300 patients, 186 cystic lesions were found in 73 of 300 autopsy cases (24.3%) (5). The prevalence of cysts increases with age (2).

PCLs may be classified simply into two main classes such as non-neoplastic and neoplastic cysts (*Box 1*). Neoplastic cysts are more commonly defined as pancreatic cystic neoplasms (PCNs). It is important to distinguish non-neoplastic cysts from neoplastic or non-mucinous from mucinous cysts because the latter are considered being premalignant lesions. In general, non-neoplastic cysts account up to 80% of all PCLs. However, the rate of PCNs increases significantly with age (1,4). Diagnostic methods, management algorithms and treatment options of PCLs have been developed significantly in recent years. In this chapter, the major types of PCLs are reviewed based on the recent advances in diagnosis and management.

Non-neoplastic cysts

Pseudocysts

Pancreatic pseudocysts are inflammatory fluid collections

Box 1 Classification of pancreatic cystic lesions (PCLs)

- Non-neoplastic cysts
  - Pseudocyst
  - Simple or congenital cyst
  - Retention cyst
- Neoplastic cysts [pancreatic cystic neoplasms (PCNs)]
  - Mucinous cystic lesions
    - Intraductal papillary mucinous neoplasm (IPMN)
    - Mucinous cystic neoplasm (MCN)
  - Non-Mucinous cystic neoplastic lesions
    - Serous cystic neoplasm (SCN)
    - Solid-pseudopapillary neoplasm (SPN)
    - Cystic neuroendocrine neoplasm
    - Acinar-cell cystic neoplasm
  - Other neoplastic lesions
    - Ductal adenocarcinoma with cystic degeneration

associated with pancreatitis and account approximately 80% of PCLs. They predominantly develop in adult men as a complication of alcoholic, biliary, or traumatic acute pancreatitis (6). The term "pseudocyst" refers to the fact that this cystic lesion has no epithelial lining and therefore is not a true cyst. Fluid collections adjacent to the pancreas are the most common complication of acute and chronic pancreatitis. In the setting of acute pancreatitis, a focal fluid collection located in or near the pancreas occurs without a wall of granulation and or fibrous tissue (7). The development of a well-defined wall composed of granulation or fibrous tissue distinguishes a pseudocyst from an acute fluid collection. The formation of a pseudocyst usually requires four or more weeks from the onset of acute pancreatitis. Without an antecedent episode of acute pancreatitis, pseudocyst may arise insidiously in patients with chronic pancreatitis (8). A pseudocyst is usually rich in pancreatic enzymes and is usually sterile. Pseudocysts are mostly single but can be multiple in 10% of cases. They are commonly round or oval, but some may be multilocular and irregular in shape (*Figure 1*). The size of pseudocysts varies from 2 to 20 cm (6-8).

Small pancreatic pseudocysts are usually intimately associated with the pancreas and are surrounded by a thin wall. Large pseudocysts may occupy spaces adjacent to the stomach and pancreas or remote areas, including the chest. The histologic features of pseudocyst walls are similar in all types of pseudocysts, consisting of fibrosis and inflammatory tissue. Most pancreatic pseudocysts originate from large or small leaks from the ductal system and persist because of the constant filling by pancreatic secretions (7).

The symptoms associated with chronic pancreatic pseudocysts are usually mild. The common symptoms are recurrent abdominal pain, early satiety, nausea and vomiting. In general, the size and the duration of the clinical course of the pseudocyst are the most important predictors of symptoms (9). With large pseudocysts, there may be a palpable fullness or a mass that is sensed by the patient or an examining physician. As a result of gastric compression, weight loss is observed in 20% of patients, and is a result of poor intake as well as maldigestion. Jaundice as manifest by icterus, dark urine, and pruritus, and acolic stools may be noted in 10% of patients. The onset of jaundice is usually slow, as a result of bile duct compression by the pseudocyst or the inflamed pancreas itself. Fever is unusual in chronic, uncomplicated pseudocysts and its presence should raise the suspicion of an occult infection of a pseudocyst (10).

Diagnosis

Pancreatic pseudocysts are commonly diagnosed based on clinically apparent clues or patient history, but in some instances this diagnosis can be difficult to conclude because the acute episode of pancreatitis may not be apparent or the patient may have mild chronic pancreatitis. Trans-abdominal ultrasonography (US) is usually the method of choice for the initial investigation of the pseudocysts. They usually appear as an echoic structure associated with distal acoustic enhancement. The sensitivity of US is inferior to CT which has a sensitivity of 90% to 100% for detection of pancreatic pseudocysts. A round, fluid filled structures surrounded by a thick, dense wall adjacent to pancreas on an abdominal CT in a patient with a history of pancreatitis is nearly diagnostic for pancreatic pseudocysts (6). The adjacent pancreas typically may reveal evidence of acute or chronic pancreatitis. Large pseudocysts may appear in the mediastinum or pelvis or involve the mesentery. Although pseudocysts are most commonly unilocular, fibrotic strands within the cavity may cause multiple septations, commonly encountered in patients with post pancreatitis, complex fluid collections. The pseudocyst cavity may also contain debris, blood, or infections that appear as high-attenuation areas within the fluid-filled cavity. It may be difficult to distinguish between pseudocysts and pancreatic mucinous cysts without the use of cyst fluid analysis in some cases. CT scans can also provide more detailed information regarding the surrounding

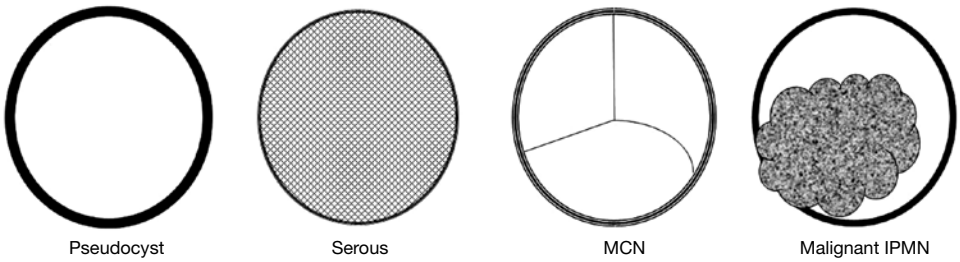

Figure 1 A schematization of morphologic details in common cysts of pancreas. MCN, mucinous cystic neoplasm; IPMN, intraductal papillary mucinous neoplasm.

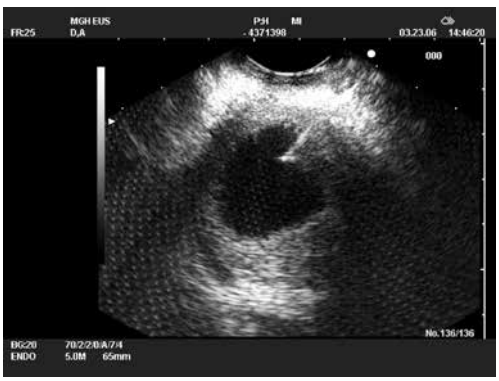

Figure 2 EUS-FNA of a pseudocyst with alcoholic chronic pancreatitis. Cyst fluid amylase was very high and cyst cytology was negative for malignant cells, and no definitive epithelial cells were identified. FNA, fine-needle aspiration.

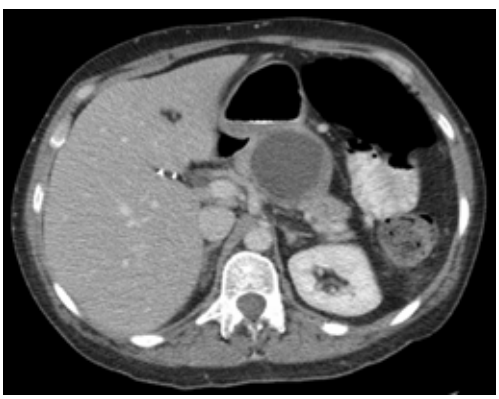

Figure 3 A unilocular, 7 cm in diameter pancreatic pseudocyst with debris.

anatomy and can demonstrate additional pathology. MRI and magnetic resonance cholangiopancreatography (MRCP) are also sensitive diagnostic methods but they usually do not add extra information on CT (11). Endoscopic retrograde cholangiopancreatography (ERCP) is not used for diagnosis of pseudocysts but it can be helpful for treatment in some cases.

EUS is usually used to further evaluate pancreatic cysts detected by other imaging modalities and most useful to distinguish pseudocysts from other PCLs (12). Pseudocysts appear as anechoic, fluid-filled structures adjacent to the upper GI tract and pancreas in EUS (*Figure 2*). Early fluid collections associated with acute pancreatitis will not be surrounded with a wall, whereas pseudocysts are often surrounded by a thick, hyperechoic rim. Calcifications in a cyst wall are highly suggestive of a mucinous cystadenoma, rather than a pseudocyst. Debris in the dependent portion of the cavity is common and may represent blood, infection, or necrotic material. Color Doppler of the wall will often reveal multiple, prominent vessels, including paragastric varices. EUS guided fine-needle aspiration (FNA) with cyst fluid analysis will differentiate between pseudocysts and neoplastic cysts in more than 90% of patients (*Figure 3*) (10). A high concentration of amylase in aspirated fluid is predictive of a connection with the main pancreatic duct and helps confirm the diagnosis of a pseudocyst duct and helps confirm the diagnosis of a pseudocyst. Pseudocysts should have relatively low levels of CEA and this might be helpful for differentiation from intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasm (MCN) (13). The aspirated fluid is examined cytologically for degenerative debris, inflammatory cells and histiocytes. If there is cytologic evidence of epithelial cells with the cyst fluid, this should raise the suspicion of a cystic neoplasm rather than a pseudocyst (13). The presence of granulocytes in the aspirated fluid is suggestive of an acute infection.

Treatment

Simple, peripancreatic fluid collections that arise during acute pancreatitis usually resolve spontaneously. Without a constant source of fluid from an epithelium, pseudocysts have also the potential for spontaneous resolution. Small pseudocysts, less than 4 cm in diameter, often resolve and

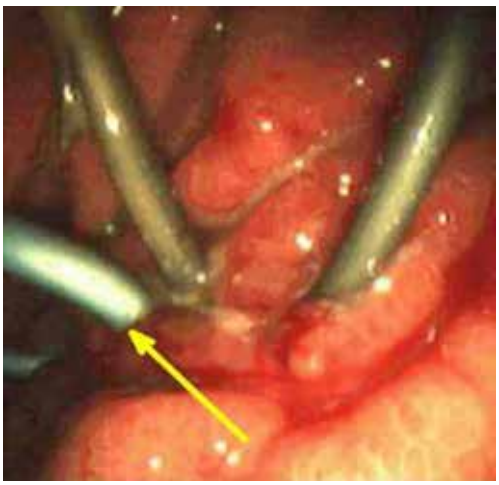

Figure 4 Endoscopic cystgastrostomy.

are rarely associated with complications, but in general, larger cysts are more likely to become symptomatic or cause complications. Spontaneous resolution of pseudocysts takes place through drainage into the GI tract or the pancreatic duct. In longterm observational studies, fewer than 10% of patients will suffer a complication. The main indications for drainage of pseudocysts are persistence or complications (infection, bleeding, gastric outlet or biliary obstruction). Forty percent of pseudocysts less than 6 cm will require drainage (14).

Drainage of pancreatic pseudocysts may be accomplished with a variety of procedures (15). A drainage catheter may be placed percutaneously into the fluid cavity under the CT/US guidance, and fluid is drained into an external collection system. The short-term success rate of this relatively simple technique is very high but it has a high risk of infections and creates significant patient discomfort (6). Surgical drainage of pseudocysts is performed by providing a large anastomosis between the pseudocyst cavity and the stomach or small bowel. Overall success rate of surgical drainage is very high but it is an invasive technique with high complication rates. It should be reserved for those patients that cannot tolerate or failed other drainage methods (16).

Drainage of pancreatic pseudocysts using endoscopic techniques is the current preferred method (17). Drainage is accomplished with either a transpapillary approach with ERCP or direct, endoscopic drainage across the stomach or duodenal wall. A transpapillary approach with drainage is used when the pseudocyst communicates with the main pancreatic duct, usually in the head of the pancreas. The transpapillary approach has also proven successful in the drainage of infected pseudocysts or pseudocysts associated with strictures or leaks of the main pancreatic duct (18). A transgastric or duodenal approach is used when the pseudocyst is directly adjacent to the gastroduodenal wall. EUS is used to determine the size, location, and thickness of the pseudocyst wall. A cyst wall thickness of more than 1 cm or the presence of large intervening vessels or varices as evident by the EUS examination are relative contraindications for endoscopic drainage. With the presence of a visible bulge in the wall of the stomach or the duodenum, endoscopic drainage is successful by the placement of transmural catheters or stents. EUS guidance is required if a bulge is not evident during the endoscopic evaluation prior to drainage. EUS-guided drainage is possible with the therapeutic linear echoendoscopes. This approach has proven highly successful and can be used for infected pseudocysts. Endoscopic drainage of necrotic pancreatic tissue through an endoscopic cystgastrostomy or duodenostomy is possible using balloon dilation and creating a fistulous tract (*Figure 4*). Overall, the complication rate of elective endoscopic drainage is about 13%, with success rates of more than 90% and recurrence rates of less than 10% (10).

The major pancreatic cystic neoplasms (PCNs)

PCNs are classified at *Box 1*. The four major types of PCNs are IPMN, MCN, serous cystic neoplasm (SCN) and solid-pseudopapillary neoplasm (SPN). The proportion of PCNs varies with population. In the Western Hemisphere, SCNs account for 32% to 39%, MCNs for 10% to 45%, IPMNs for 21% to 33%, and SPNs for less than 10% of all PCNs. A nationwide survey from Korea reports the proportions of PCNs which are composed of IPMNs (41.0%), MCNs (25.2%), SPNs (18.3%), SCNs (15.2%), and others (0.3%) (1,19). Distinguishing among the four most common types of cysts is important, since the diagnosis and management varies with each type of cyst (*Table 1*).

Intraductal papillary mucinous neoplasms (IPMNs)

IPMNs are mucinous cystic lesions of the pancreas that are characterized by neoplastic, mucin-secreting, papillary cells projecting from the pancreatic ductal surface (20). They arise from the epithelial lining of the main pancreatic duct or its side branches. Intraductal proliferation of mucin-producing columnar cells is the main histologic

Table 1 Characteristics of common pancreatic cysts

Parameters	Pseudocyst	IPMN (MD and BD)	MCN	SCN
Demographic	Alcohol abuse, the history of pancreatitis, middle-aged men	Middle aged and older individuals	Middle-aged women	Usually in older women
Location	Common in tail, solitary small to very large size	Common in pancreatic head, may be incidental and multifocal	Body and tail, incidental, single lesion	Entire pancreas, many small cysts or oligo/macrocystic
CT/MRI	Usually unilocular cyst, paranchimal inflammatory changes	MD: diffuse or focal involvement of MPD; BD: cyst or cluster of cysts, may be multifocal, ductal communication	Large cysts with thick septae, peripheral calcification, wall thickening	Microcystic multiple small cyst, central fibrous scar with calcification, sometimes oligocytic
EUS findings	Thick-walled, anechoic, unilocular cystic lesion, chronic pancreatitis	MD: dilation of MPD, hyperechoic nodules arising ductal wall; BD: small-cluster of grape-like dilations of BD, mural nodule	Macrocystic lesion with few septations. Sometimes focal, peripheral, calcification, no ductal dilation. Atypical papillary projections may seen	Multiple, small, anechoic cystic areas and 'honeycamp' appearance, sometimes central fibrosis or calcification
Cytology	Degenerative debris, inflammatory cells, histiocytes, no epithelial cells	Colloid-like mucin, mucin stains positive, mucinous epithelial cells with varying degrees of atypia, sparsely cellular	Mucinous epithelial cells with varying degrees of atypia, colloid-like mucin, mucin stains positive	Usually acellular and non-diagnostic, small cluster of cells with bland cuboidal morphology, glycogen stain positive, mucin negative
Cyst fluid analyses	Thin, clear or brown to green, non-mucinous, sometimes hemorrhagic, CEA concentration very low, amylase and lipase concentrations usually high	Thick, viscous mucus, CEA concentration usually high, amylase concentration may be high c (60%), KRAS mutation (+) (80%)	Thick, viscous mucus, CEA concentration usually high, KRAS mutation (+) (14%), GNAS mutation (–)	Clear and thin, may be hemorrhagic, CEA and amylase concentrations very low
Confocal endomicroscopy	No description yet	Epithelial villous structures; no vascular networking	Epithelial villous structures; no vascular networking	Thickened cyst wall; unilocular vascular networking; fibrous bands

MD, main duct; BD, branch duct; MPD, main pancreatic duct; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; CT, computed tomography; MRI, magnetic resonance imaging; CEA, carcinoembryonic antigen.

characteristics of IPMNs and intraluminal growth cause dilatation of the involved duct and its proximal segment. They are usually found in the head of the pancreas as a solitary cystic lesion, but in 20% to 30% of the cases they may be multifocal. In 5% to 10% of cases they may involve the pancreas diffusely (20,21). IPMNs have become a major clinical focus as a result of their increased identification in recent years. This may be due to a true increase in the incidence by aging of the population, improvement in the understanding of IPMN, and/or increased use of cross-sectional imaging in clinical practice. In fact, the true incidence of IPMN is unknown; however, they are reported to be the one of the most common among the PCNs which accounts 20% to 50% of all PCNs (1,20,21).

IPMNs may range from premalignant lesions with low-grade dysplasia to invasive malignancy and they have a

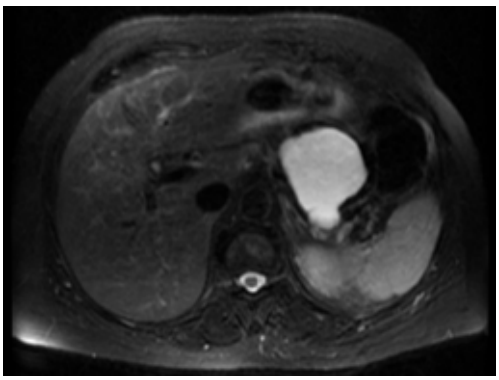

Figure 5 MRI finding of a branch-duct IPMN (BD-IPMN) at the tail of the pancreas. Note the fine septations. MRI, magnetic resonance imaging; IPMN, intraductal papillary mucinous neoplasm; BD-IPMN, branch-duct IPMN.

clear tendency to become invasive carcinoma (22,23). The World Health Organization (WHO) classified IPMNs into three subgroups according to degree of dysplasia: (I) IPMN with low- or intermediate-grade dysplasia; (II) IPMN with high-grade dysplasia (carcinoma *in situ*); and (III) IPMN with an associated invasive carcinoma. According to the involvement of pancreatic ductal system, IPMNs are classified as either main-duct IPMN (MD-IPMN) or branch-duct IPMN (BD-IPMN). If both main and branch ducts are involved together, then defined as combined-type IPMN. The clinicopathologic behavior of combined-type IPMN is similar to that of MD-IPMN. The neoplastic epithelium may show diverse architecture and cytology. Four subtypes of IPMNs have been characterized: gastric, intestinal, pancreatobiliary, and oncocytic. Most of BD-IPMNs are composed of gastric-type epithelium. However, intestinal type is more common in MD-IPMN. In a recent report, the four subtypes of IPMNs were associated with significant differences in survival (24). Patients with gastric-type IPMN had the best prognosis, whereas those with intestinal and pancreatobiliary type had a bad prognosis.

Diagnosis

IPMNs are most commonly asymptomatic and discovered incidentally on routine imaging. Some patients may present with recurrent non-specific or pancreatitis-like symptoms such as abdominal discomfort, abdominal pain, malaise, nausea and vomiting (20). Weight loss, diabetes mellitus, and jaundice may be detected especially in patients with an associated invasive carcinoma. IPMNs are usually detected in the elderly, mostly diagnosed after the fifth decade of life with a slight male dominance. Routine blood tests, such as complete blood count, liver function test, amylase, and lipase, are usually within normal limits or show nonspecific changes in patients with IPMNs. Serum CA19-9 and carcinoembryonic antigen (CEA) are generally not of diagnostic value (1).

Imaging plays a crucial role for detecting IPMNs (25). The aim of imaging for IPMN are: (I) to detect IPMN and exclude other cystic lesions of the pancreas; (II) to differentiate the MD-IPMN and BD-IPMN; (III) to determine the risk of malignancy and to evaluate the resectability. Different imaging modalities are used to reach these goals.

ERCP was the standard diagnostic tool for IPMN in the past (25). In MD-IPMN, the hallmark finding is a diffusely dilated main pancreatic duct with filling defects correlating to mucinous filling or papillary tumors. For BD-IPMN, the affected branch ducts are cystically dilated and communicate with the main pancreatic duct. In some occasions, the cystic side branch ducts do not fill with contrast due to mucus plugging. In some cases, duodenoscopy during ERCP reveals a patulous duodenal papilla and mucin extrusion through the orifice. The use of ERCP for the diagnosis of IPMN is limited by its invasiveness and risk of complications. In some cases, visualization of the entire pancreatic duct system is not possible because of copious amount of mucin.

In clinical practice, PCLs including IPMN are usually first diagnosed by conventional imaging modalities such as transabdominal US, CT and MRI (26,27). These tests are usually performed for unrelated conditions. The anatomic location, size, number, locularity, septation, calcification, pancreatic duct dilation and appearance of cysts on the conventional imaging might be helpful to differentiate the type of the cysts (*Figure 5*). MRCP can show communication between the duct and cyst more clearly and might be better than CT for the diagnosis of IPMN. However, with advances in multidetector CT, imaging details of CT including visualization of ductal communication have improved similar to those of MRI/MRCP (1,25). Both CT and MRI can also detect metastasis in case of invasive carcinoma associated with IPMN.

EUS may be more helpful for the diagnosis and differentiation of IPMNs because of its high resolution and better imaging characteristics than cross-sectional imaging modalities (28). It is particularly useful when the diagnosis is uncertain at cross-sectional imaging methods, for cysts with worrisome features in CT/MRI and for verification of malignancy before surgery in high risk patients with

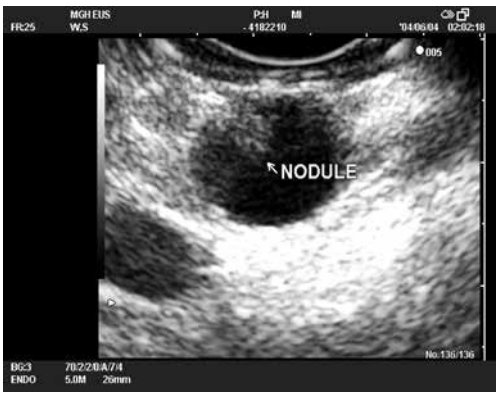

Figure 6 EUS finding of a branch-duct IPMN (BD-IPMN) with a mural nodule (arrow). IPMN, intraductal papillary mucinous neoplasm; BD-IPMN, branch-duct IPMN.

comorbidities or older age. EUS findings of IPMN include segmental or diffuse, moderate to marked dilatation of the main pancreatic duct, often associated with intraductal nodules in MD-IPMN. Obstruction of the main pancreatic duct with mucus can result in parenchymal changes. The pancreas may appear to be enlarged and may show signs of pancreatitis, or pancreatic parenchymal atrophy. Because of these changes, it is sometimes difficult to differentiate IPMN from chronic pancreatitis. BD-IPMN consists of multiple 5 to 20 mm cysts that have the appearance of a "cluster of grapes." The main duct is mildly dilated or not dilated in BD-IPMN. The internal septation, debris, cyst wall thickening, papillary projections and mural nodule of cysts can be visualized effectively (*Figure 6*). Vascular invasion and lymph node metastases can also be detected successfully (1,12,20,28).

EUS criteria associated with malignancy in IPMN patients include marked dilatation of the main pancreatic duct (>10 mm) in MD-IPMN and large tumors (>40 mm) with irregular septa in BD-IPMN; mural nodule greater than 10 mm in height was associated with malignancy in both MD-IPMN and BD-IPMN (29). Large unilocular cystic component, focal hypoechoic mass, thick septations and thickening of cyst wall are also features of malignant or potentially malignant lesions. Based on these criteria, the accuracy of EUS to discriminate between benign and malignant IPMN varies from 40% to 90% in different studies (30). EUS has been found more accurate than transabdominal US, ERCP and cross-sectional imaging methods for the diagnosis of malignancy in patients with IPMN. The limitations of EUS include operator dependence and the inability to differentiate between malignancy and areas of focal inflammation that infiltrate pancreatic parenchyma and mimic malignancy.

EUS also allows for FNA of cystic lesions for biochemical, cytological and DNA analysis that might be further helpful for diagnosis and differentiation (31,32). Macroscopically, highly viscous fluid is the first clue that the cyst is likely IPMN or MCN. High concentration of CEA reflects the presence of a mucinous epithelium and it is elevated in both IPMNs and MCNs. Thus, it is mainly beneficial to distinguish mucinous cysts from non-mucinous. It does not differentiate IPMNs from MCNs or benign IPMNs from malignant IPMNs. A cut-off CEA level of 192 ng/mL has the sensitivity of 73%, specificity of 84%, and accuracy of 79% for differentiating mucinous from non-mucinous PCLs (33). Among all the cyst fluid diagnostic parameters, CEA concentration alone is the most accurate test for the diagnosis of cystic mucinous neoplasms. Due to connectivity to the pancreatic ductal system, amylase level may be elevated in IPMNs. However, the utility to differentiate IPMNs from other PCLs is not clear.

A recent study identified glucose and kynurenine to be differentially expressed between non-mucinous and mucinous pancreatic cysts (34). Metabolomic abundances for both were significantly lower in mucinous cysts compared with non-mucinous cysts. The clinical utility of these biomarkers will be addressed in future studies. Cytological examination alone is often non-diagnostic due to the low cellularity of the aspirated fluid. Cytology is the most accurate test for the detection of malignancy in patients with mucinous cysts and a "positive" or "malignant" diagnosis is generally 100% specific (35). In addition, the presence of high grade epithelial atypia in the cyst fluid analysis has a high accuracy of 80% to predict malignancy (36).

DNA analysis of pancreatic cyst fluid demonstrated that KRAS mutation is highly specific (96%) for mucinous cysts but the sensitivity is only 45%. KRAS is an early oncogenic mutation in the adenoma-carcinoma sequence but cannot distinguish a benign from malignant mucinous cyst. A recent study demonstrated that the GNAS mutation detected in cyst fluid can separate IPMN from MCN but, similar to KRAS mutations, do not predict malignancy (37). The absence of a GNAS mutation also does not correlate with a diagnosis of MCN because not all IPMNs will demonstrate a GNAS mutation. A *GNAS* mutation was present in 66% of IPMNs and either *KRAS* or *GNAS* mutations were identified in 96% of IPMNs.

Confocal laser endomicroscopy (CLE) is a novel imaging

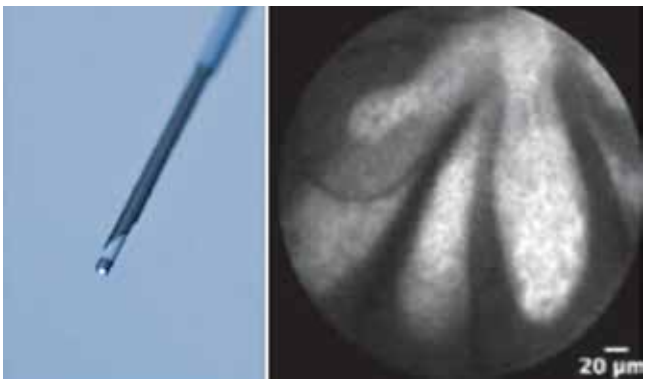

Figure 7 nCLE probe and papillary structures in an intraductal papillary mucinous neoplasms (IPMN) case.

Table 2 "High-risk stigmata" and "worrisome features" of IPMN on cross-sectional imaging

High-risk stigmata
Obstructive jaundice in a patient with cystic lesion of the head of the pancreas
Enhancing solid component within cyst
Main pancreatic duct size of 5-9 mm
Main pancreatic duct >10 mm in size
Worrisome features
Cyst >3 cm
Thickened/enhancing cyst walls
Non-enhancing mural nodule
Lymphadenopathy
Worrisome features

IPMN, intraductal papillary mucinous neoplasm.

technology that uses low-power laser to obtain in vivo histology of the gastrointestinal mucosa. Recently, a CLE miniprobe has been developed to use during EUS-FNA to visualize cyst wall and epithelium directly through a 19-gauge FNA needle (*Figure* 7). Technical feasibility of this probe was shown and the preliminary studies of PCLs revealed that the presence of epithelial villous structures was associated with IPMNs, with 59% sensitivity and 100% specificity (38).

Management

The mean frequency of malignancy in MD-IPMN is 61.6% and the mean frequency of invasive IPMN is 43.1%. Considering these high incidences of malignant/invasive lesions and the low 5-year survival rates (31-54%), international consensus guidelines recommend resection for all surgically fit patients with MD-IPMN (29). If the margin is positive for high-grade dysplasia, additional resection should be attempted to obtain at least moderate-grade dysplasia at the surgical margin. The same guideline recommended evaluation but no immediate resection for patients with a MPD diameter of 5-9 mm as a "worrisome feature".

The mean frequency of malignancy in resected BD-IPMN is 25.5% and the mean frequency of invasive cancer is 17.7%. BD-IPMN mostly occurs in elderly patients, and the annual malignancy rate is only 2-3%. These factors support conservative management with follow-up in patients who do not have any symptoms or risk factors predicting malignancy such as mural nodule, rapidly increasing cyst size and high grade atypia in cytology. There is insufficient data to support immediate resection for all BD-IPMNs >3 cm without "high-risk stigmata" and "worrisome features" (29) (*Table 2*).

According to international guidelines, there is still an important group of patients who surgical treatment is controversial. Particularly younger patients (<65 years) with BD-IPMN need long-term follow-up which increase the cumulative risk of malignancy and cost of management. The resection is also not clear for BD-IPMNs >3 cm without "high-risk stigmata" and "worrisome features". In addition, there are patients who refuse surgery or high-risk surgical candidates. As a result, these kinds of patients warrant a more conservative management for IPMNs and EUS-guided cyst ablation therapies has been introduced as an alternative treatment (39). Injection of a cytotoxic agent into a PCL will result in ablation of the cyst epithelium. The first cytotoxic agent used was ethanol and it was found to provide greater rates of complete ablation as compared with saline lavage. Ethanol lavage has been coupled with paclitaxel injection in a large series with a variety of PCLs (39,40). The combination of ethanol and paclitaxel injection resulted in elimination of the cysts, as determined by CT scanning, in 29/47 (62%) of patients, in a median follow-up period of 21.7 months. These studies were not specifically for IPMNs alone, the participating subjects were heterogeneous and contained IPMNs and other PCLs. Radiofrequency ablation (RFA) of PCNs has been recently described in a pilot study of six patients (41). The post procedure imaging at 3-6 months showed complete resolution of the cysts in two patients, whilst in three patients there was 48.4% reduction in size. These initial results suggest that the procedure is technically easy and

safe. However, more studies are needed to show especially the effectiveness of the method.

After resection, the overall recurrence rate of IPMN varies from 7% to 30% and regular follow-up and monitoring of disease for recurrence is needed. A regimen consisting of yearly CT or MRI/MRCP for non-invasive, and every 6 months for invasive IPMNs have been mostly suggested during follow-up (29).

The aims of long term follow-up for unresected IPMNs are to detect a possible malignant transformation from originally benign lesion, and a concomitant ductal adenocarcinoma of the pancreas (42). The international guidelines have suggested follow-up of patients with BD-IPMNs <2 cm and without any "worrisome features" by cross-sectional imaging modalities (<1 cm in 2-3 years, 1-2 cm in yearly then lengthen interval if no change). For BD-IPMNs >2 cm and without any "worrisome features", EUS follow-up for 3-6 months, then lengthen the interval if there is no change and alternating MRI have been recommended.

Mucinous cystic neoplasms (MCNs)

MCNs are defined as cyst-forming epithelial neoplasms that are usually without communication with the pancreatic duct and composed of columnar, mucin-producing ductal epithelium with an underlying ovarian-type stroma (1,43). Nearly all MCNs are surrounded by a thick layer of spindle cells containing receptors for progesterone and estrogen. The dense ovarian-like tissue simulates an ovarian hamartoma and, at times, a sarcoma. The possible derivation of the stromal component of MCNs from ovarian tissue is supported by morphology and the tendency to undergo luteinization. It has been hypothesized that ectopic ovarian stroma incorporated during embryogenesis in the pancreas may release hormones and growth factors, causing nearby epithelium to proliferate and form cystic tumors. The mucinous transitional epithelium is the source of nearly all malignancies arising from MCNs. Similar to IPMNs, MCNs are classified according to the grade of dysplasia: (I) MCN with low or intermediate-grade dysplasia; (II) MCN with high-grade dysplasia; and (III) MCN with an associated invasive carcinoma (44,45).

Macroscopically, MCNs present as single spherical masses. The lesions may be unilocular or multilocular. The cysts contain thick mucin or a mixture of mucin and hemorrhagic-necrotic material. There is no communication between the tumor and the pancreatic duct, unless there is fistula formation. The frequency of the lesion communicating with the pancreatic duct system may be high. In a Japanese multi-institutional report, 18.1% (25 of 138 patients) of MCNs demonstrated communication with the pancreatic duct (46).

MCNs almost exclusively occur in women, with a peak incidence in the fifth decade. The body and the tail of the pancreas are predominantly affected. Up to one-third of MCNs are reported to harbor an invasive carcinoma. Risk factors for the presence of malignancy include large tumor size, associated mass or mural nodules, and advanced age. Around 30% of the patients may be without symptoms or signs (47). Symptomatic patients may complain of abdominal pain, palpable mass, weight loss, anorexia, fatigue, or jaundice. Some patients may present with pancreatitis. The results of routine laboratory testing are usually nonspecific. Patients with bile duct obstruction display a cholestatic liver function abnormality (48).

On CT, MCNs appear as large cysts with thin septae; the septae are best shown after the administration of intravenous contrast. Calcifications may be seen, which are lamellated and located on the periphery of the lesion, in contrast to the central, stellate calcifications of the SCN. On MRI, the cysts have high signal intensity (bright) on T2-weighted images. On T1-weighted images with intravenous gadolinium administration, the wall and the septae are more conspicuously demonstrated. The presence of peripheral calcification, wall thickening, and thick septations can be suggestive of a malignant MCN. In a study of 52 patients with MCNs, the presence of these three findings predicted a 95% risk of malignancy (49).

EUS findings of MCN are thin-walled, septated fluid-filled cavities with diameter greater than 1 to 2 cm (3). Duct communication is rarely seen. Increased size, cyst-wall irregularity and thickening, intracystic solid regions, or an adjacent solid mass are findings suggestive of malignancy. Cyst CEA levels are high as a result of secretion by the mucinous epithelium. As mentioned, it is difficult to distinguish MCN from IPMN on the basis of cyst fluid cytology. Since MCNs rarely communicate with the pancreatic duct, ERCP is not routinely performed in the evaluation of MCNs.

Current consensus guideline advocates that all MCNs should be resected, unless there are contraindications for operation (29). For MCNs of <4 cm without mural nodules, laparoscopic resection as well as parenchyma-sparing resections and distal pancreatectomy with spleen preservation is recommended. Surgical resection is curative

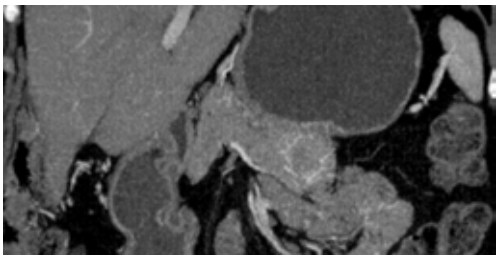

Figure 8 CT findings of SCN. (A) Axial image. Note the septa coming from the central scar; (B) sagittal image. Note the focal high-intensity lesion within a cyst representing hemorrhage (arrow). CT, computed tomography; SCN, serous cystic neoplasm.

in nearly all patients with noninvasive MCN. Non-invasive MCNs require no surveillance after resection. For MCNs with an associated invasive carcinoma, prognosis depends on the extent of the invasive component, tumor stage, and resectability. The 2-year survival rate and 5-year survival rate of patients with resected MCN with an associated invasive carcinoma are about 67% and 50%, respectively (1). EUS-guided cyst ablation therapies may be considered for patients who are not a good candidate for surgery or refused the surgery.

Serous cystic neoplasms (SCNs)

SCNs are cystic neoplasms arise from centroacinar cells and composed of cuboidal, glycogen-rich epithelial cells. The lesions are filled with serous fluid. According to the degree of dysplasia, they are classified as either serous cystadenoma or serous cystadenocarcinoma. SCNs occur more frequently in women. Patients are usually diagnosed with SCN in their late 50s or early 60s. They occur more frequently in the body or the tail of the pancreas. Despite their benign nature, these lesions tend to grow slowly and may achieve large diameters (50).

Nearly 90% of von Hippel-Lindau (VHL) syndrome patients are reported to develop SCNs and 70% of serous cystadenomas has a mutation in the *VHL* gene (51). K-ras mutations are rarely seen in SCNs. SCNs are rarely malignant; only about 25 malignant cases have been reported to this date (1). SCNs are usually single, round lesions, with diameters that can be greater than 20 cm. On cross section, the cysts are composed of numerous microcysts filled with serous fluid (*Figure 1*). SCNs do not communicate with the pancreatic duct. A dense fibronodular scar is often located in the center of the lesion. A single layer of cuboidal epithelial cells lines the cysts. The central scar is composed of acellular hyalinized tissue and a few clusters of tiny cysts. The lesions are rich in vascular epithelial growth factor receptors, and a complex vascular structure supports the lesion. Four variants of serous cystadenoma are known. The serous epithelial components of these variants are identical to those of serous cystadenoma. They are macrocystic serous cystadenoma, solid serous adenoma, VHL-associated SCN, and mixed serous neuroendocrine neoplasm. Macrocystic serous cystadenomas include previous serous oligocystic and ill-demarcated serous adenoma. Solid serous adenomas are well-circumscribed neoplasms that have a solid gross appearance; they share the cytologic and immunohistologic features of classic SCN. VHL-associated SCN describes multiple serous cystadenomas and macrocystic variants that occur in VHL syndrome patients. In patients with VHL, SCNs typically involve the pancreas diffusely or in a patchy fashion (52). The mixed serous neuroendocrine neoplasm is the rare entity of serous cystadenomas associated with pancreatic neuroendocrine neoplasms. This is highly suggestive of VHL syndrome.

Most patients are without symptoms or signs on diagnosis. Symptomatic patients may present with abdominal pain, palpable mass, anorexia, jaundice, fatigue/malaise, or weight loss (45).

On CT and MRI, SCNs may have the classic microcystic appearance or the less common oligocystic appearance (*Figure 8*). Microcystic-type lesions comprise multiple small cysts. A central fibrous scar with calcification, which occurs up to 30% in SCNs, is considered pathognomonic. The dense tissue is arranged in a stellate form. In some cases, the small cysts and dense fibrous component may make the lesions appear solid on CT. The oligocystic pattern is often difficult to differentiate from MCN on CT/MRI because of the morphologic similarities (53).

Oligocystic SCNs should be suspected when a unilocular cystic lesion with lobulated contour without wall enhancement is located in the pancreatic head (45). On T1-weighted fat-suppressed MRI, the fluid component shows lower signal intensity compared to the fibrous matrix. On T2-weighted images, the fluid becomes bright. On EUS, the typical SCN has multiple small, anechoic cystic areas and thin septations. Because of the vascular nature of the SCN, aspirants from EUS-FNA may be bloody or contain hemosiderin-laden macrophages. Aspirated cyst fluid is low in CEA concentration. The yield of cytology with EUS-FNA is poor (54). A superficial vascular network sign, corresponding to a dense and subepithelial capillary

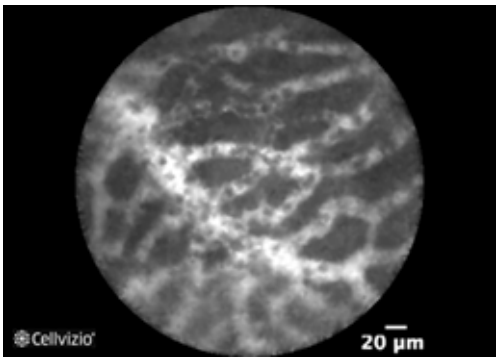

Figure 9 Demonstration of vascular network on cyst wall by confocal laser endomicroscopy (CLE) in a patient with serous cystadenoma.

vascularization, has been visualized in SCNs by nCLE of with 63% sensitivity and 100% specificity in a recent study of 18 cases (*Figure 9*).

The prognosis for patients with SCN is excellent. Even in the rare cases of serous cystadenocarcinoma, there are reports of a long-term survival after resection. Currently, proposed indications for surgical resection are presence of symptoms, size of greater than 4 cm, and uncertainty about the nature of the cystic neoplasm. Although increased size does not predict malignancy, large SCNs are reported to grow at a faster rate and are more likely to cause symptoms (50,52).

Solid-pseudopapillary neoplasms (SPNs)

SPNs are low-grade malignant neoplasms composed of monomorphic epithelial cells that form solid and pseudopapillary structures. Microscopically, they are a combination of solid pseudopapillary component and hemorrhagic-necrotic pseudocystic components. The solid portion is formed with poorly cohesive monomorphic cells and myxoid stromal bands containing thin-walled blood vessels. When the poorly cohesive neoplastic cells fall out, the remaining neoplastic cells and the stroma form the pseudopapillae. Mucin is absent, and glycogen is not conspicuous. Macroscopically, SPNs are large, round, single masses (average size, 8-10 cm). They are well demarcated and often fluctuant. The cut section discloses lobulated solid areas and zones with a mixture of hemorrhage, necrosis, and cystic degeneration. SPNs frequently undergo hemorrhagic cystic degeneration (55).

SPNs without histologic criteria of malignant behavior, such as perineural invasion, angioinvasion, or infiltration of the surrounding parenchyma, may metastasize. Therefore, all SPNs are classified as low-grade malignant neoplasms (56). SPNs occur predominantly in young women. The mean age at diagnosis is in the patient's 20s or 30s. Symptomatic patients may present with pain, mass, anorexia, nausea/vomiting, jaundice, or weight loss. SPNs are reported to occur evenly throughout the pancreas.

On CT, SPNs appear as well-circumscribed and encapsulated masses with varying areas of soft tissue and necrotic foci. The capsule is usually thick and enhancing. Peripheral calcification has been reported up to 30% of patients. No septations are visualized. On MRI, the neoplasm is shown as a well-defined lesion with a mix of high and low signal intensity on T1- and T2-weighted images, which reflects the complex nature of the mass. Areas filled with blood products demonstrate high signal intensity on T1-weighted images and low or inhomogeneous signal intensity on T2-weighted images (57).

On EUS, SPNs are usually well-defined, hypoechoic masses. They may be solid, mixed solid and cystic, or cystic. Internal calcifications can be seen in some patients. The reported diagnostic accuracy of EUS-FNA for SPN based on cytology and immunohistochemistry is 65%. Aspirated cyst fluid may display necrotic debris. The cyst fluid CEA is low, reflecting the presence of nonmucinous epithelium (58).

The mainstay of treatment is surgery. After complete surgical resection, 85% to 95% of patients are cured (1). Even in cases with local invasion, recurrences, or metastases, long-term survival have been documented (59). No definite biological or morphologic predictors of outcome have been documented. Suggested indicators of poor outcome include old age and SPNs with an aneuploidy DNA content.

General approach to pancreatic cystic lesion (PCL)

There are many suggested algorithms on the management of PCLs (*Figure 10*) (14,60). Much emphasis is placed on the size and the morphology of the PCLs. Once confronted with a PCL, the first step is to differentiate PCNs from pseudocysts. The diagnosis of pseudocysts is primarily based on a patient history compatible with pancreatitis, with additional information from biochemical and imaging features. However, patients with PCNs may present with pancreatitis; patients with pseudocysts may have no apparent history suggestive of pancreatitis. Once pseudocysts have been excluded, the type of PCN should be determined. The primary focus should be on differentiating between mucinous (IPMN and MCN) and serous (SCN) cysts. Once a mucinous cyst has been diagnosed, patients with MD-IPMN, combined-type IPMN, and MCN should

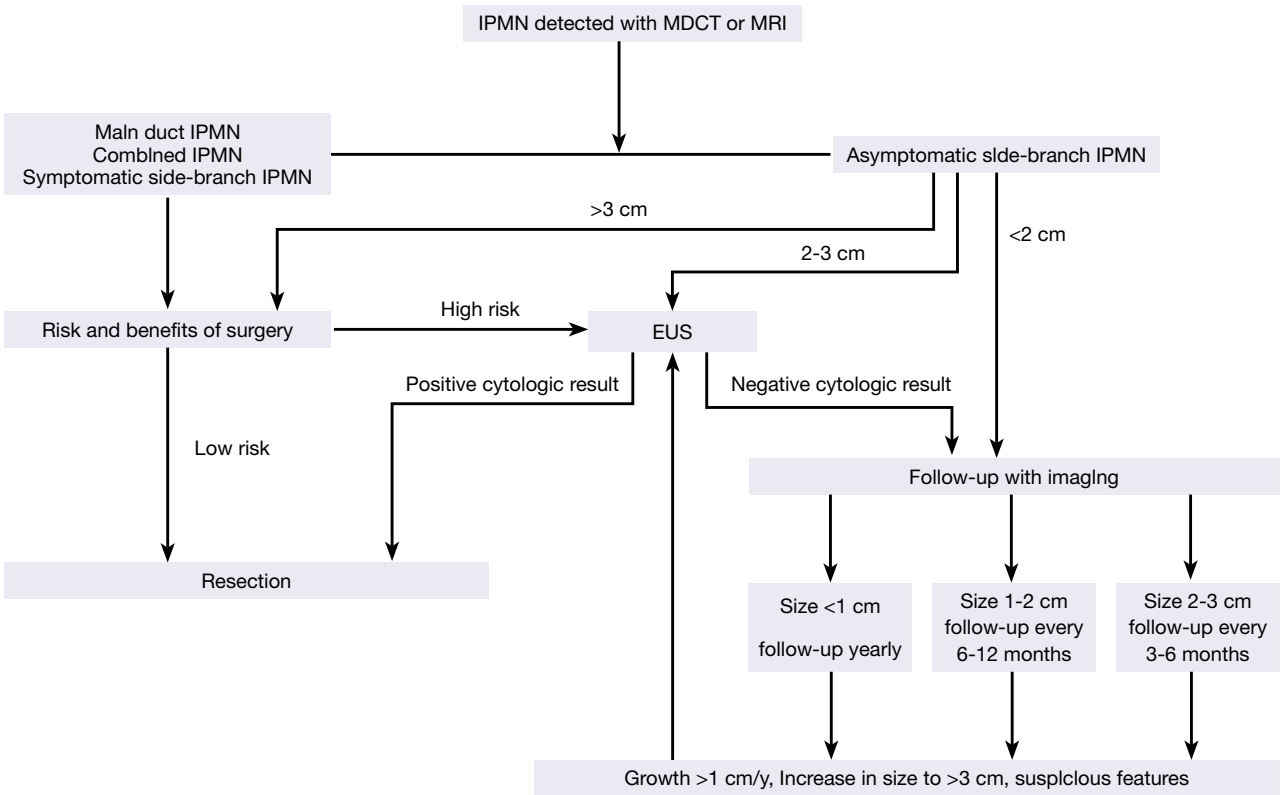

Figure 10 Suggested algorithm for pancreatic cyst management.

undergo a surgical consultation. Patients with BD-IPMN should be managed using the algorithm of the consensus guideline. SCNs should be observed, unless they are symptomatic or large (>4 cm).

There are no strict published guidelines on the indication for EUS-FNA of PCLs. In general, there is no need for EUS-FNA of all cystic lesions with a clear diagnosis by cross-sectional imaging unless the results will impact patient management. IPMN lesions measuring more than 2 cm should be aspirated if the findings of a benign cytology will indicate the need for continued surveillance. If there is diagnostic uncertainty, the cyst fluid should be analyzed for CEA, *KRAS* and GNAS. Each analysis can be performed with less than 0.3 mL of fluid. If the primary question is whether the cyst is malignant or benign, the fluid should be sent for cytology. Cyst fluid for DNA mutations may supplement the results of cytology, particularly when a small volume of cyst fluid is available.

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Current and future systemic treatment options in metastatic pancreatic cancer

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Abstract: Although pancreatic adenocarcinoma is the fourth leading cause of cancer death, only modest improvement has been observed in the past two decades, single agent gemcitabine has been the only standard treatment in patients with advanced disease. Recently newer agents such as nab-paclitaxel, nimotuzumab and regimens such as FOLFIRINOX have been shown to have promising activity being superior to gemcitabine as a single agent. With better understanding of tumour biology coupled with the improvements in targeted and immunotherapies, there is increasing expectation for better response rates and extended survival in pancreatic cancer.

Keywords: Pancreatic cancer treatment; nabpaclitaxel; FOLFINOX; targeted therapy; immunotherapy

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Introduction

Pancreatic adenocarcinoma is the fourth most-frequent cause of tumor related death in western world (1). Median survival is 4 to 6 months and median 5-year survival is less than 5% (2). Great majority of the patients with pancreatic adenocarcinoma presents at advanced stage, either with metastatic or locally advanced disease. Actuarial 5-year survival rate for early stage operable disease with adjuvant treatment is around 20% (3,4). However, 70% of them recurs and need palliative treatment. Standard treatment of metastatic and locally advanced pancreatic cancer patients who cannot be treated with chemoradiation or surgery is chemotherapy. Pancreatic cancer is a well-known relatively chemo-refractory disease. Evidence changed in recent years from single agent gemcitabine treatment to combination regimens. FOLFIRINOX and gemcitabine plus nab-paclitaxel became two standard options for metastatic pancreatic cancer for patients with good performance status (5,6). Targeted agents, immunotherapy and vaccines are the most popular fields of clinical trials in advanced pancreatic cancer and we will reach a bulk of new clinical data in the treatment of metastatic pancreatic cancer in near future.

Cytotoxic therapy

Cytotoxic chemotherapy is the standard treatment option for metastatic and locally advanced pancreatic cancer patients cannot be treated with surgery or radiochemotherapy. Chemotherapy trials had been failed to show benefit for a long time in the past. In 1997 gemcitabine monotherapy became the standard treatment with the landmark study by Burris *et al*. (7). Gemcitabine (n=63) monotherapy was compared with weekly blous 5-fluorouracil (n=63) and modest survival benefit was shown in gemcitabine group (5.6 *vs*. 4.4 months). But clinical benefit was evident regarding performance status and pain control in gemcitabine group. Gemcitabine was used as the standard treatment for many years due to good patient tolerance and improved quality of life in metastatic cancer patients. Several agents including capecitabine, irinotecan, oxaliplatin and cisplatin were tested in combination with gemcitabine but survival benefit could not be shown in any of those phase III studies (8-11). Several targeted agents

were also studied in combination with gemcitabine in phase II or III trials. Studies of vismodegib, masitinib, sorafenib, AMG479 and IPI926 in combination with gemcitabine failed to show survival benefit (12-16). Significant phase III studies of gemcitabine were summarized in *Table 1*. A small survival benefit was shown with platinum derivatives and capecitabine when added to gemcitabine in meta-analyses due to underpowered studies to show small differences (18,19). Additional toxicity came with this marginal survival benefit with gemcitabine and platinum or capecitabine combinations.

Combination therapy for advanced pancreatic cancer was controversial until year 2011. Prodige 4-ACCORD 11 randomized phase III trial compared FOLFIRINOX regimen with gemcitabine in good performance status, 336 untreated, metastatic pancreatic adeno cancer patients (5). Inclusion criteria were strict as permitting patients up to age of 75 years, with ECOG performance status 0 or 1, nearly normal bilirubin, good bone marrow and renal function, and without a history of heart disease. This study met the primary endpoint of OS as 11.1 *vs.* 6.8 months in FOLFIRINOX and gemcitabine arms, respectively (HR=0.57, P=0.0001). ORR (31.6% *vs.* 9.4%, P=0.0001) and PFS (6.4 *vs.* 3.3 months, P=0.001) was also superior in FOLFIRINOX compared to gemcitabine group consistent with OS results. These better survival rates and responses came with the expense of excess toxicity. Febrile neutropenia (5.4% *vs.* 0.6%, P=0.009), thrombocytopenia (9.1 *vs.* 2.4, P=0.008), peripheral neuropathy (9% *vs.* 0%, P=0.001), vomiting (14.5% *vs.* 4.7%, P=0.002), diarrhea (12.7 *vs.* 1.2, P=0.0001), thromboembolic events (6.6% *vs.* 4.1%) and growth factor support (42.5% *vs.* 5%) rates were higher in FOLFIRINOX compared to gemcitabine group. But elevated LFTs were higher in gemcitabine group (20.8% *vs.* 7.3%). FOLFIRINOX combination regimen was approved for the first line treatment of metastatic pancreas adenocarcinoma patients with good performance status regarding results of this trial.

Chemoresistance of pancreatic cancer is partly attributed to stroma rich characteristic of the tumor. Albumin-bound paclitaxel (nab-paclitaxel) was shown to bind to protein SPARC (secreted protein acidic and rich in cysteine) also known as osteonectin, which is overexpressed by fibroblasts in the pancreatic cancer microenvironment (20,21). Thus nab-paclitaxel renders an effective amount of cytotoxicity by depleting tumor stroma. The molecular mechanism of nab-paclitaxel is not fully understood and simply albumin avidity of tumor cells might deliver a high concentration of chemotherapeutic in the tumoral tissue. Nab-paclitaxel came as another combination option with gemcitabine for patients with advanced stage pancreatic cancer. After the impressive response rate (48%) and survival of 12 months from the phase I-II trial, phase III trial was conducted (22). The MPACT trial compared gemcitabine plus nab-paclitaxel with gemcitabine in 861 untreated metastatic pancreatic adeno cancer patients (6). This study also met the primary endpoint of OS and nab-paclitaxel was the first agent showed OS increment with addition to gemcitabine (8.5 *vs.* 6.7 months, HR=0.72, P=0.000015). One year survival rate (35% *vs.* 22%), PFS (5.5 *vs.* 3.7) and ORR (23% *vs.* 7%) were higher in gemcitabine plus nab-paclitaxel compared to gemcitabine group. Toxicity related deaths were similar in groups (4% for each) but grade 3-4 neutropenia (38% *vs.* 20%), fatigue (17% *vs.* 7%), neuropathy (17% *vs.* <1%) were higher in combination group. In the subgroup analyses patients with poorer performance status (KPS 70-80) and more bulky disease (liver metastases, >3 metastatic sites and >59XULN CA19.9 level) much benefited from the gemcitabine plus nab-paclitaxel combination regimen.

Table 1 Gemcitabine based phase III studies for palliative setting in pancreatic cancer

Treatment	N	Response rate (%)	Overall survival (months)	P	Reference
Gemcitabine	63	5.4	5.65	0.0025	(7)
Bolus 5FU	63	0	4.41		
Gemcitabine	284	8.0	5.91	0.038	(17)
Gemcitabine + erlotinib	285	8.6	6.24		
Gemcitabine	266	12.4	6.2	0.02	(18)
Gemcitabine + capecitabine	267	19.1	7.1		
Gemcitabine	430	7	6.7	0.000015	(6)
Gemcitabine + nab-paclitaxel	431	23	8.5		

Treatment selection

Decision of two new standard options for metastatic pancreatic adenocarcinoma might be given according to age (number of patients >70 was lower in Prodige4 ACCORD 11 trial), performance status (MPACT trial consisted a broader spectrum for performance status; KPS 70-100),

patients preference of treatment routes and frequency (46 hours infusional 5-fluorouracil *vs*. weekly nab-paclitaxel treatment) and toxicity profiles (increased hematologic toxicity, febrile neutropenia, diarrhea, fatigue and growth factor support need in FOLFIRINOX regimen and alopecia in nab-paclitaxel combination treatment). Patients who will not tolerate the FOLFIRINOX combination chemotherapy or who do not want a central access might be good candidates for gemcitabine plus nab-paclitaxel study. However gemcitabine monotherapy must be kept in mind as the oldest standard for patients cannot receive FOLFIRINOX or nab-paclitaxel.

Drug sensitivity model for gemcitabine, irinotecan, oxaliplatin, nab-paclitaxel, 5-fluorouracil and oxaliplatin was generated with pharmacogenomic studies in pancreatic cancer cell lines according to genetic expression of molecular pathways i.e., the transforming growth factor B (TGF-B), hedgehog and jak-stat (8,23-26). Sangar *et al*. validated this pharmacogenomic test in a phase II trial in pancreatic adenocarcinoma patients (n=20) and patients sensitive to drug had longer TTP compared to intermediate sensitive and resistant patients (7.3 *vs*. 5.3 *vs*. 3.7 months) according to pharmacogenomic analysis (27). Pharmacogenomic test was shown to be predictive for treatment efficacy regarding TTP. Future studies with this pharmacogenomic tests might help 1st and 2nd line treatment decisions and treatment choice of nab-paclitaxel plus gemcitabine or FOLFIRINOX as the 1st line treatment. A high SPARC expression is associated with improved response to nab-paclitaxel and pre-treatment pharmacogenomic testing of SPARC might be useful for choosing patients for gemcitabine plus nab-paclitaxel treatment (22). There are a number of ongoing trials mostly with gemcitabine chemotherapy backbone on the first line treatment of advanced pancreatic cancer listed in *Table 2* and a third treatment option might come from these trials.

Data on second line treatment of metastatic pancreatic cancer is sparse. The only second line, randomized phase III study in advanced pancreatic cancer tested FOLFOX versus best supportive care after first line treatment with gemcitabine failure. This study demonstrated a median second line survival benefit of 4.82 months compared to 2.30 months with best supportive care (53). That might be a good option in fit patients progressed on gemcitabine treatment. In FOLFIRINOX trial 47% of the patients were treated with second line therapy and most of them received gemcitabine (5). Thus gemcitabine might be an option patients progressed on FOLFIRINOX treatment. Ongoing trials for the second line treatment of advanced pancreatic cancer are summarized in *Table 3*.

Targeted therapy

During last 10 years various targeted agents were tested alone or in combination with gemcitabine for treatment of advanced pancreatic cancer. But all but one failed to improve patients' survival significantly. Erlotinib, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor was the first agent achieved survival benefit when added to gemcitabine (17). However the difference was minimal (6.24 *vs*. 5.91 months, P=0.038) and raised the question of clinical significance. A prolonged survival of 10.5 months was seen in a subgroup of patients who developed grade 2 or severe skin rash. Skin rash was the most important adverse effect. Skin rash was proposed as a predictive marker for erlotinib benefit (60). However it is not clearly defined as a predictive tool. The EGFR monoclonal antibody cetuximab and VEGF antibody bevacizumab were failed in phase III studies of advanced pancreatic cancer (61,62). Another EGFR monoclonal antibody nimotuzumab in combination with gemcitabin had shown better overall survival compared to gemcitabine plus placebo (8.7 *vs*. 6.1 months) with tolerable toxicity in a recent phase II trial in first line treatment of locally advanced or metastatic pancreas cancer patients (63). Other members of small molecule tyrosine kinase inhibitors axitinib, sorafenib and tipifarnib (a farnesyl transferase inhibitor) with combination of gemcitabine were compared with single agent gemcitabine in different phase III trials. But they were also failed to show any benefit in treatment of advanced pancreatic cancer (64-66). Masitinib a c-kit inhibitor of mast cell function, marimastat an agent against secreted matrix proteases were also tested in phase III randomized trials with or without gemcitabine. However no survival benefit was seen with adding these agents to gemcitabine in advanced pancreatic cancer (67,68).

Insulin like growth factor 1 receptor (IGF1R) is highly expressed in pancreatic cancer and takes role in downstream signalling cascades for cancer cell survival and proliferation thorough a KRAS-dependent and independent pathway. It was another target for drug development for several solid tumors and also pancreatic cancer. However IGF1 R inhibitor AMG-479 and monoclonal antibody cixutumumab failed to show a survival benefit (15,69).

K-ras is a major driver in pancreatic cancer and mutated in 90% of the cases. It causes an uncontrolled activity of downstream pathway of raf, MEK and ERK,

Table 2 Ongoing first line trials on advanced pancreatic cancer

Target	Phase	N	Treatment	Reference
Mitotic inh; polo like kinase	II-III	150-650	Gem +/- Rigosertib	(28)
Hypoxia	III	660	Gem +/- TH302	(29)
hENT1	III	175	Gem *vs*. FOLFOX (hENT1 high *vs*. low)	(30)
Hyaluronan	II	132	Gem + Nab-pacl +/- PEGPH20	(31)
Antistromal	II	148	Gem + Nab-pacl +/- M402	(32)
TGF-B	I-II	168	Gem +/- LY2157299	(33)
Hedgehog	II	80	Gem + Nab-pacl + Vismodegib	(34)
	II	106	Gem +/- Vismodegib	(35)
	I-II	25	Gem + Vismodegib	(36)
	I	40	FOLFIRINOX + LDE225	(37)
	II	122	Gem +/- IPI-926	(16)
Notch inh. Stem cells	II	140	Gem + Nab-pacl +/- OMP59R5	(38)
Notch inh.	I	60	Gem + MK0752	(39)
HSP27	II	132	Gem + Nab-pacl +/- 068-428	(40)
Mek	II	174	Gem +/- MSC19363699D	(41)
Akt	II	31	Gem +/- RX-0201	(42)
EGFR, HER2,4	II	117	Gem +/- Afatinib	(43)
Angiogenesis	II	80	Gem +/- TL-118	(44)
Myostatin	II	120	LY249555 + Chemo	(45)
Ras	II	70	Pacl + carbo +/- Reovirus	(46)
PARPI (BRCA +)	II	70	Gem + Cisp +/- Veliparib	(47)
mTOR + tyrosine kinase	II	120	Gem, erlotinib +/- metformin	(48)
mTOR	I-II	21	Gem + Everolimus	(49)
Stem cells	II	82	PEXG +/- Metformin	(50)
HDAC	I-II	50	Radiotherapy + cape +/- vorinostat	(51)
DNA-methylation	I	30	Gem + 5-Azacytidine	(52)

TGF-B, transforming growth factor B.

Table 3 Ongoing trials beyond first line on advanced pancreatic cancer

Target	Phase	N	Treatment	Reference
Liposomal irinotecan	III	405	MM-198 +/- 5-FU/LV	(54)
JAK1,2	III	138	Capecitabine +/- ruxolitinib	(55)
Ifosfamide conjugate	III	480	5FU/LV (bolus) *vs*. glufosfamide	(56)
MEK, AKT	III	133	FOLFOX *vs*. selumetinib + MK2206	(57)
MEK, tyrosine kinase	II	46	Erlotinib + AZD6244	(58)
mTOR, VEGFR, tyrosine kinase	II	12	Sorafenib + everolimus	(59)

leading to tumor cell proliferation and survival. Mitogen activated protein kinase MEK is an important druggable target in pancreatic carcinoma in which activating K-ras mutation is seen frequently. Trametinib (GSK1120212) a MEK inhibitor failed to show survival benefit when added to gemcitabine in advanced pancreatic cancer (70).

Another MEK inhibitor MSC1936369B is being tested in combination with gemcitabine in first line treatment of advanced pancreatic cancer in a phase II trial (41). A phase II study is evaluating another MEK inhibitor AZD6244 in combination with tyrosine kinase inhibitor erlotinib in second line treatment of advanced pancreatic cancer (58).

The PI3K/Akt and mTOR pathway takes role in tumor cell proliferation, survival and metabolism is another therapeutic target in advanced pancreatic cancer. Increased activity of PI3K/Akt and mTOR pathway might take an important role in resistance of drugs effecting ras-raf-MEK and ERK pathway. A phase II study of an Akt antisense oligonucleotide, RX-0201 in combination with gemcitabine is completed and results are awaited (42). A study of PI3K inhibitor BKM120 in combination with mFOLFOX-6 regimen in advanced stage solid tumors including pancreatic cancer is going on (71). The BEZ235 is a combined inhibitor of PI3Kand mTOR. A phase I study of BEZ235 in combination with the MEK inhibitor MEK162 with the strategy of hitting two pathways at the same time is completed in advanced solid tumor patients carrying K-ras, Nras and/or Braf mutations including pancreatic cancer and results are awaited (72). The study of mTOR inhibitor everolimus monotherapy by Wolpin *et al*. had shown a PFS and OS of 1.8 and 4.5 months respectively in gemcitabine refractory pancreatic cancer patients (73). Another phase II study of everolimus in combination with erlotinib in previously treated advanced pancreatic cancer patients was terminated due to futility and significant adverse effects (74). A phase II trial of the other mTOR family member temsirolimus is completed in locally advanced or metastatic pancreas cancer patients and results are pending (75). A phase I and II combination study of everolimus and sorafenib in advanced solid tumor patients including pancreas cancer refractory to gemcitabine was completed and results are also pending (76). A phase I/II study of everolimus in combination with gemcitabine in advanced pancreas cancer patients is completed and results are awaited (49). A list of novel therapeutic targets and drugs is given in *Table 4*.

A commonly used oral antidiabetic drug metformin was shown to activate adenosine monophosphate-activated protein kinase (AMPK).The AMPK inhibits mTOR pathway by phosphorylation and stabilization of the tumor suppressor gene TSC2 (86). One of the mechanisms for TKI-resistance is hyperactivation of mTOR pathway. Blocking the mTOR pathway might be a good strategy for overcoming TKI resistance. A phase II randomized study of metformin in combination with erlotinib and gemcitabine compared to placebo in advanced pancreatic cancer patients is going on (48).

Novel therapeutics

Pancreas cancer has an extensive stromal tissue which is a unique histological feature. This dominant desmoplastic tissue might contribute the weak penetration of the applied drugs and act as a protective barrier from the treatments. It was hypothesized as a chemoresistance mechanism of pancreas carcinoma (87). Sonic hedgehog pathway takes an important role for stimulating stromal reaction. Vismodegib an hedgehog inhibitor is the first drug approved in advanced and metastatic basal cell skin carcinoma (88). Various clinical trials of vismodegib in combination with gemcitabine and gemcitabine plus nab-paclitaxel are ongoing in recurrent or advanced pancreatic cancer patients (34-36). Another hedgehog inhibitor IPI-926 or placebo in combination with gemcitabine is studied in a phase II randomized study in metastatic pancreas cancer patients (16). This study is completed and results are pending. Hedgehog inhibitor LDE225 is tested in combination with FOLFIRINOX in untreated advanced pancreatic cancer patients and the study is ongoing (37).

The Notch pathway is thought to take role in pancreas carcinogenesis and Notch ligand and receptor are shown to be highly expressed in pancreas cancer (89,90). OMP-59R5 is a fully human monoclonal antibody that targets the Notch2 and Notch3 receptors. It downregulates Notch pathway signaling and affects pericytes, tumor stroma and microenvironment and thought to have anti-cancer stem cell effect. The ALPINE trial testing OMP-59R5 with gemcitabine and Nab-paclitaxel in first-line advanced pancreatic cancer patients showed well tolerability and responses (PR=46%, DCR=77%) in early phase I results (91). Gamma secretase is an enzyme causes proteolytic cleavage and release of the intracellular domain of the Notch and activates Notch signalling pathway. A phase II study of gamma-secretase inhibitor RO4929097 monotherapy is going on in pretreated metastatic pancreas cancer patients (92). Another gamma-secretase inhibitor MK0752 and gemcitabine combination are being tested for first line treatment of stage III and IV pancreas cancer patients (39).

Histone de-acetylation (HDAC) and DNA hypermethylation are two major epigenetic changes cause tumor supressor gene silencing and tumor cell proliferation,

Table 4 Summary of novel therapeutic agents

Drug	Class	Target-pathway	Reference
Tipifarnib	FT inhibitor	RAS, RAF, MEK	(66)
Selumetinib	C-met inh		(77)
Erlotinib	TKI	EGFR	(17)
Everolimus, temsirolimus	MTOR inh	MTOR/PI3K/AKT/MEK	(49)
Metformin	AMPK act.		(48)
MK-2206	AKT		(57)
RX-0201	AKT		(42)
XL765	PI3K/MTOR		(78)
BKM120	PI3K		(71)
MSC1936369D	MEK		(41)
Vismodegib	Small molecule Shh inh	Hedgehog	(34-36)
Saridegib (IPI-926)			(16)
LDE-225			(37)
R04929097	Gamma secretase inh	Notch	(79)
MK0752	Gamma secretase inh		(39)
OMP59R5	Notch2/3 Antibody (antiSC)		(38)
Vorinostat	HDAC inh	HDAC	(51)
5-Azacytidine	DNA-methyltransferase inh.	DNA-methyltransferase	(52)
AGS-1C4D4	Antibody to PSCA	PSCA	(80)
LY2157299	TGF-B type-1 receptor inh.	TGF-B	(33)
Dasatinib, Saracatinib	SRC,bcr-abl inh	SRC	(81,82)
Olaparib, veliparib	PARP inh	PARP/BRCA/PALB2, Fanconi pathway	(47,83)
Ipilimumab, nivolumab	Check point inh	Immune/AntiCTLA-4, AntiPD-1	(84,85)

TGF-B, transforming growth factor B.

growth and progression. Vorinostat, HDAC inhibitor is being tested in locally advanced pancreas cancer patients in combination with capecitabine and radiotherapy in a phase I and II study (51). The chemical cytosine analogue 5-azacitidine inhibits DNA methyltransferase and a phase I study in combination with gemcitabine is going on in first line treatment of advanced pancreatic cancer patients (52).

TGF-B is another regulator pathway of stromal reaction and TGF-B takes role in stimulating stromal reaction, invasion, metastasis and promoting angiogenesis in pancreas cancer (93). Trabedersen, an antisense oligodeoxynucleotide which inhibits TGF-B2 expression was shown to have good efficacy and safety profile in the second line treatment of pancreas cancer patients (n: 37; median OS, 13.4 months) (94). A phase II study of gemcitabine in combination with a specific type 1 receptor inhibitor of TGF-beta, LY2157299 or placebo is recruiting patients (33).

Pancreas cancers are rich of tumor stroma and have a high level of hyaluronan. PEGPH20 degrades hyaluronan, reduces interstitial fluid pressure and facilitates drug delivery (95,96). It has shown to improve efficacy when used with cytotoxics. A phase IB trial of gemcitabine plus PEGPH20 had shown promising efficacy and phase II and III trials of gemcitabine + nabpaclitaxel ± PEGPH20 (HALOZYME) and FOLFIRINOX +/- PEGPH20 (SWOG-NCI) are planned (97,98).

The DNA double-strand breaks (DSBs) are mainly repaired by homologous recombination, a process mediated by BRCA1 and BRCA2 proteins which sustains genomic stability and cell survival (99). Alternative poly (ADP-ribose) polymerase (PARP) pathway takes the main role for DNA repair when BRCA dysfunction occurs. PARP is a critical enzyme of cell proliferation and DNA repair mediates repair of DNA single strand breaks (SSB), and rescues

tumor cells from DNA damage. PARP represents a good therapeutic target in BRCA mutated/dysfunctional tumors. Inhibition of PARP-1 activity prevents the recruitment of DNA repair enzymes and leads to failure of SSB repair. DNA single strand breaks accumulate, induce formation of DNA replication fork arrests, and form DSBs (100). In the combined absence of PARP activity and BRCA1 or BRCA2 activity, both repair pathways are disabled; DNA DSBs cannot be repaired properly. DSBs can induce genomic instability and ultimately lead to tumor cell death. PARP inhibitors have shown efficacy in BRCA mutated ovary and breast cancer patients (101-105). A 5% to 7% of pancreatic cancer patients show germline mutations of BRCA 1 or 2. Preclinical data showed susceptibility to alkylating agents and Parp inhibitor in Capan-1 BRCA 2 deficient pancreatic cancer cell line (106). A randomized phase II study of gemcitabine + cisplatin +/- veliparib in BRCA 1-2 and PALP-2 mutated locally advanced or metastatic pancreatic cancer patients is being continued (47). The second part of this trial which is a single arm phase II, is going on in previously treated pancreatic cancer patients. Novel agents on the treatment of advanced pancreatic cancer are summarized in *Table 4*.

Platinum compounds directly bind to DNA and causes double strand breaks. A dysfunction in BRCA1 and its pathway is associated with a specific DNA-repair defect that sensitizes cells to platinum drugs in animal models (107,108). Platinum compounds showed high responses in triple negative breast cancer which share similar features with BRCA deficient patients (109,110).

Immunotherapies

Immunologic treatments are increasingly studied in last few years in various tumors in medical oncology. Unmet medical need in pancreatic cancer directed researchers to investigate new pancreatic cancer treatments and also immunological approaches. After the first positive results of ipilimumab came from phase III study of metastatic malignant melanoma, interest on immunological treatments increased. Immunologic treatments might be classified as passive immunotherapy approaches as the use of antibodies or *in vitro* generated effector cells, and vaccination for stimulating antitumoral response. There are different ways of delivering vaccines. Dendritic cell (DC) vaccines combine tumoral antigen with DCs for presenting them to effector T cells. Viral or bacterial DNA is inserted to human cells to modulate cell-mediated immunity by the DNA vaccines. Peptides are inserted to human cells by T-cell receptor peptide vaccines for increasing cell mediated immunological response. DCs are the most potent antigen presenting cells. They can cause a high antigenic response via stimulating T and B cells. Kimura *et al.* showed DC vaccine plus lymphokine activated killer cell treatment and chemotherapy prolonged overall survival compared to patients received only DC vaccine or chemotherapy (111). Carcinoembryonic antigen (CEA) is an oncofetal antigen that is expressed in epithelial malignancies and pancreatic cancer. It is one of the highly expressed antigens in pancreatic cancer might be used with DCs for vaccine treatment of pancreatic cancer (112). MUC1 is another protein which is highly expressed in pancreatic cancer (113). Phase I and II studies of MUC1 antigen pulsed DC vaccines showed hopeful results in advanced pancreatic cancer (114,115). A phase I study in advanced pancreatic cancer with vaccine containing vaccinia virus expressing CEA and MUC1 and costimulatory molecules showed well tolerability an overall survival advantage in immune responsive patients (116). But a phase III trial of fowlpox viruses expressing CEA and MUC1 and costimulatory molecules failed to improve overall survival when compared to chemotherapy or best supportive care in palliative setting in pancreatic cancer patients (117). Heat shock proteins are a family of chaperone proteins expressed in all species which are induced by stress conditions. They are presented within HLA class I complex on the cell surface. HSPPC-96 is a HSP-based vaccine used in a small study of resected pancreas cancer patients with tolerable toxicity profile and long survival durations in some patients (118).

Algenpantucel-L is an irradiated, live combination of two human allogeneic pancreatic cancer cell lines. These cells express the murine enzyme alpha-1,3-galactosyl transferase (alpha-GT) which directs the synthesis of alpha-galactosyl epitopes on surface proteins and glycolipids of such cell lines. Alpha-Ga1 epitopes are absent in humans but large amount of alpha-Ga1 antibodies exists (119). Alpha-Ga1 antibodies and alpha Ga1 epitopes in algenpantucel–L activates complement mediated lysis and antibody dependent cell mediated toxicity against algenpantucel-L cells (120). Phase II adjuvant study of algenpantucel in combination with radiation plus 5-fluorouracil and gemcitabine treatments in resected pancreatic cancer patients reached a one year DFS of 62% and OS of 86% meeting primary and secondary endpoints (121). This promising result in the adjuvant setting was one of the important factors directing researchers' focus on vaccine trials in pancreatic cancer.

Granulocyte monocyte colony stimulating factor (GM-CSF) is a potent cytokine able to mobilize monocytes, eosinophils and lymphocytes to the tumor sites. Early studies have shown the efficacy of GM-CSF vaccine in resected pancreatic cancer patients and trials in metastatic pancreas cancer with GM-SCF are ongoing (122).

K-ras mutations are found in up to 90% of pancreatic cancers (123). K-ras mutation is specific for tumor cells and is not present in normal cells. These mutations can be targets for a specific T cell mediated toxicity. A phase I/II trial of synthetic mutant ras peptides with GM-CSF showed a prolonged survival in immune responders compared to nonresponders (5 *vs*. 2 months) in advanced pancreatic cancer patients (124). Median survival was also longer for also immune responders among resected pancreatic cancer patients (Median OS: 20% *vs*. 0%, for 10 years).

Telomerase is a ribonucleotide enzyme that is expressed in almost all of the cancer but not in normal cells (125). Telomerase maintains telomers which exist at the end of the chromosomes and elicits stability. It is generally activated in cancer cells and was shown to be expressed in pancreatic cancer (126). A telomerase peptide vaccine GV1001 with GM-CSF was shown to prolong survival in unresectable pancreatic cancer patients in a phase I-II study (127). However, phase III study of GV1001 with gemcitabine sequential combination versus gemcitabine was closed due to lack of survival advantage in unresectable pancreas cancer patients (128,129). Another phase III study of capecitabine plus gemcitabine with or without GM-CSF plus GV1001 in locally advanced or metastatic pancreatic cancer patients was completed and results are awaited (130). Ongoing phase II vaccine trials are summarized in *Table 5*.

Pancreatic cancer is one of the immunologically quiescent tumors. Effector T cell infiltration is not a natural response for pancreatic cancer. But immune system can be provoked. Gemcitabine plus CD40 agonist activating T cells has been shown to reduce tumor burden in advanced pancreatic cancer patients in a phase I study (150). Zheng *et al*. studied a vaccine with or without intravenous low dose or oral metronomic cyclophosphamide in pancreatic cancer patients in a three arm neoadjuvant and adjuvant study (151). Cyclophophamide was used to deplete regulatory T cells. Intratumoral and peritumoral lymphoid aggregates were found in surgical specimens of the vaccinated patients (152). Lymphoid aggregates in pancreatic adenocarcinomas consisted organized T and B cell zones and germinal center like structures. PD-L1 expressing and PD-1 positive cells were upregulated in lymphoid aggregates but not in pancreatic adenocarcinomas without T cell infiltration. Vaccines can induce tumor infiltrating lymphocytes in non-immunogenic tumors. These tumor infiltrating lymphocytes can secrete IFN-gamma and other cytokines that up-regulate PD-1 and PD-L1 pathway. But vaccine induced T cells might be downregulated by the suppressive mechanisms within the tumor. Thus vaccines must be given with agents modulate these suppressive mechanisms and activate T cell response. Anti-PD-1 antibody was shown to enhance infiltration of vaccine induced tumor specific infiltrating lymphocytes active against mesothelin epitope in a preclinical pancreatic cancer model (153).

Modulating regulatory pathways might be another strategy to enhance vaccine's efficacy in pancreatic cancer. Ipilimumab an anti-CTLA4 antibody (Four, 3 weekly, 10 mg/kg induction doses and maintenance q 12 weeks if stable disease or better response is seen at week 22) was given alone or with vaccine to metastatic pancreatic cancer patients in a phase 1B study (154). Thirty metastatic pancreatic patients received two or more lines of chemotherapy were included to this study. Overall survival was longer in ipilimumab + GVAX than ipilimumab alone treated patients (5.5 *vs*. 3.3 months). Twelve month OS and response rate was also higher in the combination arm (27% *vs*. 7% and 45% *vs*. 0%, respectively). Survival was found to be correlated with CD8+, mesothelin specific T cell quantity. Phase II study of this protocol is under development due to this promising result. Targeting more than one checkpoint pathway at the same time might be another option for getting increased efficacy. Anti-PD-1 agent nivolumab and anti-CTLA-4 agent ipilimumab was given concomitantly to malignant melanoma patients and a higher response with the cost of increased toxicity was seen compared to response rate in single agent ipilimumab studies (40% *vs*. 32% for responses and 14% *vs*. 51% for grade 3-5 toxicity) (155,156). Regarding the low amount of T cells in pancreatic cancer microenvironment, combining these immune checkpoint pathway modulators might not be a beneficient strategy due to increased toxicity. Listeria monocytogenes, peptide, DNA, and DC based vaccines are the new vaccines might induce T cells better. Vaccines and immune checkpoint inhibitors as anti-CTLA-4 plus GVAX and anti-PD-1 plus GVAX prime/Listeria boost are the emerging combination strategies. Targeting methylation might unchain the anti-inflammatory signals with hypomethylating strategy and combination with immune checkpoint inhibitors might increase the efficacy. Engineered T cells targeting pancreatic cancer antigens is

Table 5 Ongoing phase II and III vaccine trials in advanced pancreatic cancer

Target		Phase	N	Line	Treatment	Reference
Telomerase	Advanced	III	1110	1st	Capecitabine + Gemcitabine +/- GMCSF + GV1001	(130)
CEA, MUC1	Advanced	III	250	2nd (after gem failure)	PANVAC-F *vs*. BSC *vs*. CT	(131)
Alpha-Ga1	Borderline resectable/ Locally advanced unresectable	III	280	1st/2nd and adjuvant	FOLFIRINOX + Algenpantucel-L→PD; Gem + Nab-Pacl. + Algenpantucel-L →No distant mets;5-FU / Cape + RT + Algenpantucel-L	(132)
GMCSF transduced whole tumor cell	Metastatic	II	92	Maintenance	FOLFIRINOX (If non-progressive)→Ipilimumab + GVAX	(133)
GMCSF transduced whole tumor cell	Metastatic	II	90	1st/2nd	GVAX + cyclophosphamide or GVAX + cylophosphamide + CRS-207 (attenuated Listeria monocytogenes)	(134)
GMCSF transduced whole tumor cell	Metastatic	II	240	2nd line or beyond	GVAX + cyclophosphamide + CRS-207 or CRS207 or Gem/Cape/5-FU/Iri/Erlo	(135)
CEA	Advanced/ metastatic	I/II	28	2nd or beyond	AVX701	(136)
Whole tumor cell	Advanced	II	40	1st or beyond	IFNα or IFN$_\gamma$ treated tumor cell vaccine+ GMCSF + cylophosphamide	(137)
Whole tumor cell	Advanced	II	14	1st line or beyond	IFNα treated tumor cell vaccine+ GMCSF + cylophosphamide	(138)
CEA	Advanced/ metastatic	II	24	1st or beyond	ALVAC-CEA + IL-2 + GMCSF	(139)
RAS	Stage II/III/IV	II	NA	1st or beyond	DETOX-PC + IL-2 + GMCSF	(140)
CEA peptide -1-6D	II/III/IV	II	7	Maintenance	Standart tx (if non progressive)→Cap1-6-D + GMCSF + incomplete Freund's adjuvant	(141)
Whole cell	II/III/IV	II	NA	1st line or beyond	Allogeneic tumor cell vaccine (incubated with IFNα) + GMCSF + cyclophosphamide	(138)
Plasmid DNA pancreatic tumor cell	III/IV	II	60	1st line or maintenance	Vaccine + cyclophosphamide + GMCSF	(142)
MUC1	Adjuvant/ Unresetbale	II	25	1	Vaccine (MUC-1 antigen + SB AS-2 adjuvant)	(143)
CEA /Modified CEA	Adjuvant/locally advanced	II	15	Adjuvant/1	Vaccine (CEApeptide/Modified CEA –CAP1-6D)	(144)
VEGFR1 and VEGFR2 epitope	Locally advanced/ metastatic	I/II	17	1st	Vaccine (VEGFR1-1084, VEGFR2-169) + Gem	(145)
Cancer stem cell	Metastatic	I/II	40	1st line or beyond	Cancer stem cell vaccine	(146)
Survivin (HLA-A1, A2, B35)	Metastatic	I/II	70	1st line or beyond	Survivin HLA-A1, A2, B35 epitope vaccine	(147)
DC	Unresectable	I/II	30	1st line or beyond	İntratumoral DC vaccine	(148)
Plasmid DNA (DTA-H19)	Locally advanced	II	70	1st line	Intratumoral BC-819 (Plasmid DNA accine against DTA-H19)	(149)

another emerging era of treatment in advanced pancreatic cancer.

Combining two vaccines might be another strategy to enhance efficacy. GVAX is a DC vaccine which is exposed to whole pancreatic cancer cell irradiated and incubated with GMCF. CRS 207 is a Listeria based vaccine in which a tumor specific antigen mesothelin is incorporated to the Listeria's chromosome and of which two virulence genes (actA, inlB) were deleted. Listeria is an intracellular microorganism and it secretes and expresses tumor antigens inside the antigen presenting cells. Induction of robust innate and antigen specific adoptive immunity occurs by this way. GVAX alone or in combination with CRS207 was given to advanced pancreatic cancer patients (2 to 1 randomization; n=90) who have failed or refused previous chemotherapy (85). Median OS was higher in combination compared to GVAX alone arm (6.1 *vs*. 3.9 months, P=0.0172, HR=0.59). Overall survival benefit was more clear among patients treated as 3rd line (5.7 *vs*. 3.9 months, P=0.0003, HR=0.29). Immunotherapy might be synergistic with different combinations of treatment i.e. chemotherapy and targeted agents.

A randomized phase II study of gemcitabine with or without AGS-1C4D4, a fully human monoclonal antibody to prostate stem cell antigen (PSCA) showed better 6-month survival rates in combination (n=133; 60.9%) versus gemcitabine arm (n=63; 44.4%) in metastatic pancreatic cancer (157). Median survival was and response rate were also higher in the combination group (7.6 *vs*. 7.6 months and 21.6% *vs*. 13.1%, respectively). The 6-month SR was higher in PSCA-positive subgroup (79.5% *vs*. 57.1%).

Immunotherapy might be a promising treatment option for pancreatic cancer. Immunologic treatments have no potential side effects like conventional chemotherapeutics have unique toxicity profile like autoimmune phenomena. There is no phase III data of immunological treatment showing benefit in metastatic pancreas cancer. Absence of pancreatic cancer cell specific antigen and immunological quiescent microenvironment of pancreas cancer are difficulties for investigations on immunologic treatment approaches. Combinations of active and passive immunologic treatments, targeted agents and conventional chemotherapies might be important strategies for increasing efficacy.

In conclusion, FOLFIRINOX and gemcitabine + Nab-paclitaxel are new standard combinations in frontline setting. However they can be integrated to all disease settings in clinical practice. Gemcitabine + nab-paclitaxel combination seems to be more tolerable and might be given to patients with a broader spectrum of performance status. Trials are ongoing with addition of various targeted agents with these two standard chemotherapy backbones. Data for second and third line treatment are emerging. Treatment agents targeting stroma, immune pathways and inflammation are under development.

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Treatment of locally advanced unresectable pancreatic cancer: a 10-year experience

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Purpose: We retrospectively analyzed the results of patients with locally advanced unresectable pancreatic cancer (LAPC) treated with either chemoradiation (CRT) or chemotherapy alone over the past decade.

Methods and materials: Between December 1998 and October 2009, 116 patients with LAPC were treated at our institution. Eighty-four patients received concurrent chemoradiation [RT (+) group], primarily 5-flourouracil based (70%). Thirty-two patients received chemotherapy alone [RT (-) group], the majority gemcitabine based (78%). Progression-free survival (PFS) and overall survival (OS) were calculated from date of diagnosis to date of first recurrence and to date of death or last follow-up, respectively. Univariate statistical analysis was used to determine significant prognostic factors for overall survival.

Results: Median patient age was 67 years. Sixty patients were female (52%). Median follow-up was 11 months (range, 1.6-59.4 months). The RT (+) group received a median radiation dose of 50.4 Gy, was more likely to present with ECOG 0-1 performance status, and experienced less grade 3-4 toxicity. PFS was 10.9 versus 9.1 months (P=0.748) and median survival was 12.5 versus 9.1 months (P=0.998) for the RT (+) and RT (-) groups respectively (P=0.748). On univariate analysis, patients who experienced grade 3-4 toxicity had worse overall survival than those who did not (P=0.02).

Conclusions: Optimal management for LAPC continues to evolve. Patients who developed treatment-related grade 3-4 toxicity have a poorer prognosis. Survival rates were not statistically significant between chemotherapy and chemoradiotherapy groups.

Keywords: Pancreatic cancer; unresectable; chemoradiation; survival; locally advanced

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Introduction

Pancreatic cancer remains a highly lethal malignancy despite advances in treatment. In 2009 there were 42,470 new cases of pancreatic cancer and 35,240 deaths from the disease (1). At initial diagnosis, 50% of patients present with metastatic disease, 30% present with a locally advanced tumor, and only 20% are resectable. Surgical resection remains the only potentially curative therapy. The large number of recurrences and/or distant failures following resection suggest that microscopic metastases continue to be an obstacle to better outcomes. Patterns of spread include direct extension, lymphatic spread to regional lymph nodes, and hematogenous spread to distant sites. For all stages, the 1- and 5-year survival rates are 25% and 6%, respectively. Even for patients diagnosed with localized disease, the 5-year survival rate is only 22% (2).

Treatment of locally advanced unresectable pancreatic cancer (LAPC) has evolved to consist of chemotherapy alone or in combination with radiation, in hopes of

achieving better survival. Although the reported benefits of chemoradiation (CRT) are controversial, it remains a management option for patients with LAPC. The survival advantage to a chemoradiation approach has not been consistently demonstrated (3) and there are few randomized phase III studies evaluating the role of combined modality therapy in recent years (4-10). There is thus a need to further examine the role of chemoradiation in LAPC.

In this study, we retrospectively analyzed the results of patients with LAPC treated with either CRT or chemotherapy alone over the past decade.

Materials and methods

Patients

Between December 1998 and October 2009, 253 patients with pancreatic adenocarcinoma were identified. Of these, 159 underwent treatment with CRT or chemotherapy alone. Patients with metastatic disease at presentation and those that underwent surgery for definitive resection were excluded from analysis, as were patients with islet-cell tumors and mucinous cystadenocarcinoma. The remaining 116 patients formed the study population for this Institutional Review Board-approved retrospective analysis. Baseline patient and tumor characteristics were reviewed, including age, gender, race, weight loss >10%, Eastern Cooperative Oncology Group performance status, tumor diameter (mm), tumor location, T stage, nodal status, histologic grade, and non-obstructive pre-treatment CA 19-9 levels when available. Stage was determined according to the American Joint Committee on Cancer staging system, 6th edition (11). Patient data were obtained through the tumor registry and review of medical records.

Treatment

Referral for chemoradiation was done at the discretion of the attending surgeon and/or medical oncologist after multidisciplinary discussion. Chemoradiation was offered primarily to patients with T3 or higher disease and/or with nodal involvement. These patients were deemed unresectable based on radiographic imaging, surgical consultation, and multidisciplinary consensus.

Patients who received radiation underwent CT simulation for treatment planning and received three-dimensional conformal external-beam radiation to the abdomen. Radiotherapy was delivered on linear accelerators using 6-23 MV photons. CT-based treatment planning was done using the Theraplan Plus treatment planning system (MDS Nordion, Ottawa, Ontario, Canada) and the Eclipse Treatment Planning System (Varian Medical Services, Palo Alto, CA, USA). Targets and organs at risk were contoured. Treatment field arrangements were designed to encompass targets with margin while sparing organs at risk. Planning dose constraints used were consistent with those postulated by Emami *et al*. (12). Toxicity from treatment was graded per Radiation Therapy Oncology group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) common toxicity criteria (13) by a single person after review of medical records.

Endpoints

Patterns of failure were defined by first relapse event, determined based on radiographic imaging, and categorized as locoregional versus distant. Progression-free survival (PFS) was calculated from date of diagnosis to date of first recurrence, date of death, or date of last follow-up. Date of first recurrence was determined based on radiologic follow-up imaging. Overall survival (OS) was calculated from date of diagnosis to date of death or last follow up.

Statistical analysis

Univariate statistical analysis was used to determine significant prognostic factors for OS and PFS. Statistical analyses for comparing groups in regards to categorical variables were performed using Fisher's exact test. Similar comparisons for continuous variables were done using the Wilcoxon non-parametric test with exact p-values. The Kaplan-Meier method was used to obtain PFS and OS estimates. Survival was compared between groups using the log-rank test. Estimates of risk were obtained using the proportional hazard model. Values for continuous variables are given as median (range). Values for categorical data are specified as frequency. Statistical analysis was performed using SAS statistical analysis software version 9.2 (SAS Institute Inc, Cary, NC, USA). A nominal significance level of 0.05 was used.

Results

Of the 116 patients, 60 (52%) were female with a median age of 67 years (range, 43-89). Eight-four patients (72%) received chemoradiation [RT (+) group] and 32 (28%) patients received chemotherapy alone [RT (-) group].

Table 1 Patient and treatment characteristics

Characteristic	RT (+) [n=84]	RT (-) [n=32]	P-value
Age			
Median	67	68	0.156
(yrs)	[43-89]	[51-88]	
Gender			
Male	41	15	1.000
Female	43	17	
Race			
White	77	26	0.184
Non-White	7	6	
Weight Loss >10%*			
Yes	50	21	0.478
No	26	7	
ECOG			
0-1	81	26	0.013
2	3	6	
Tumor diameter (mm)†			
Median	40	40	0.548
Range	[13.00-85.00]	[10.00-76.00]	
Tumor location‡			
Head	52	17	0.755
Body/Tail	15	5	
Overlapping	14	8	
Others	3	1	
T-stage			
T4	60	28	0.090
T3	24	4	
Node status			
Negative	51	19	1.000
Positive	33	13	
Histologic grade◊			
I-II	46	19	0.610
III-IV	15	8	
Pre-treatment CA 19-9#			
Median	290.65	391.40	0.233
Range	[1.2-61070.0]	[5.0-19142.0]	
Grade 3-4 toxicity			
Yes	16	14	0.0078
No	68	17	

Patient and treatment characteristics of both groups are summarized in *Table 1*. RT (+) and RT (-) groups were similar with respect to age, gender, percent weight loss, tumor size, T-stage, nodal status, histologic grade, pre-treatment CA 19-9, and use of gemcitabine based chemotherapy (all P=ns). The median radiation dose was 50.4 Gy (range, 32.4-60) in the RT (+) group. Patients in the RT (+) group were more likely to have an ECOG of 1-2 (96% *vs.* 81%, P=0.01) and experience less Grade 3-4 toxicity than the RT (-) group (19.1% *vs.* 45.1%, P=0.01).

Of the 84 patients in the RT (+) group, 24 received induction chemotherapy followed by CRT and then

Table 2 Patterns of failure according to treatment modality

Parameter	RT (+) (n=84)	RT (-) (n=32)
Total no. of treatment failures	50	11
Local only	4	1
Distant only	37	10
Locoregional +distant	9	0

Table 3 Univariate analysis for progression-free survival and overall survival

Variable	1-yr PFS (%)	P (CI)	1-yr OS (%)	P (CI)
Age				
<65	48.5	0.1464	54.6	0.0675
>65	38.90	(0.49,1.12)	45.0	(0.45,1.03)
Tumor size>30 mm				
Yes	38.50	0.4863	43.4	0.3747
No	43.70	(0.74, 1.91)	51.3	(0.77,2.00)
T stage				
T4	43.6	0.4227	49.2	0.6289
T3	38.3	(0.52,1.32)	45.4	(0.56,1.42)
Nodal Status				
Positive	44.1	0.9285	57.0	0.5941
Negative	41.1	(0.66,1.46)	42.4	(0.75,1.66)
Grade III/IV				
Yes	26.7	0.0053	36.7	0.0231
No	47.6	(0.57,1.53)	52.1	(1.07,2.54)
Pre-treatment CA 19-9>1,000				
Yes	52.9	0.7725	51.4	0.9590
No	47.0	(0.51,1.64)	57.8	(0.55,1.77)
Chemotherapy regimen				
Gem	40.6	0.1549	48.4	0.2932
Non-gem	52.4	(0.87,2.43)	52.4	(0.79,2.22)
RT (+)				
Yes	44.2	0.7482	52.6	0.9976
No	37.5	(0.60,1.44)	37.5	(0.64,1.55)

additional chemotherapy; 41 received CRT followed by chemotherapy and 19 received CRT alone. Concurrent chemoradiation was primarily (70%) 5-fluourouracil based. The remaining 32 patients comprising the RT (-) group received chemotherapy alone with the majority (78%) receiving gemcitabine-based chemotherapy.

With a median follow-up of 11 months (range, 1.6-59.4 months), local recurrences and/or distant metastasis were observed in 53% of patients. The majority (92%) had distant metastatic disease. The most frequent site of distant metastasis was the liver (47%). Detailed patterns of failure by treatment modality are shown in *Table 2*.

Univariate analysis showed that grade 3-4 toxicity was an adverse prognostic factor affecting PFS and OS. Other patient and treatment factors including age, tumor size, T stage, nodal status, histologic grade, pre-treatment CA 19-9, chemotherapy regimen, and the use of RT were also analyzed and are summarized in *Table 3*.

When evaluated by treatment modality, PFS was 10.9 months for the RT (+) group versus 9.1 months for

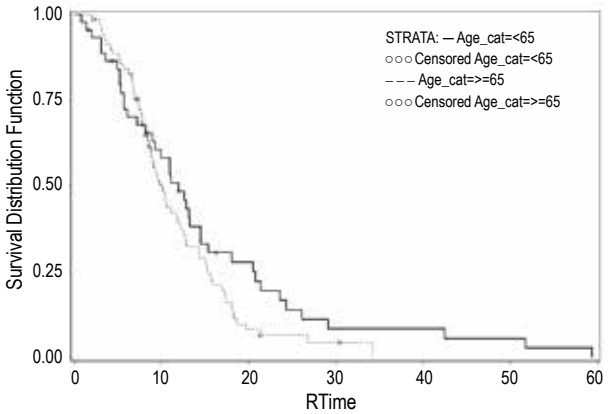

Figure 1 Progression free survival (months).

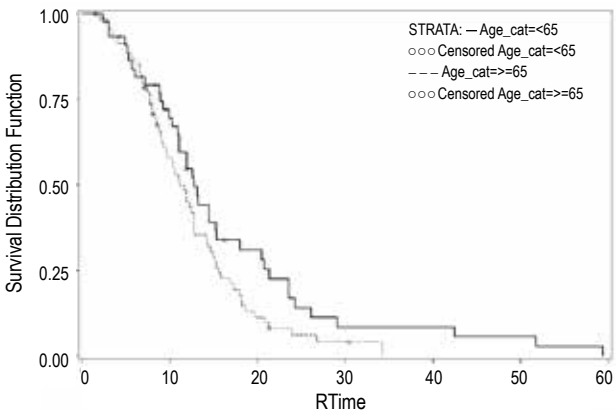

Figure 2 Overall survival (months).

the RT (-) group (*Figure 1*). One-year OS was 52.6% alive at one year in the RT (+) group versus 37.5% in the RT (-) group (P=0.15). Median OS was 12.5 versus 9.1 months for the RT (+) group and RT (-) groups, respectively (*Figure 2*).

In patients with good or excellent performance status (ECOG 0-1), subset analysis showed that PFS was 10.5 months compared to 7.6 months for the RT (+) and RT (-) groups, respectively (P=0.7574). The median OS was 12.2 months versus 7.6 months for the RT (+) groups and RT (-) groups, respectively (P=0.54) in the ECOG 0-1 subset.

Discussion

The role of combined therapy for LAPC continues to evolve. The goals of radiotherapy in LAPC include improvement in local control and palliation of pain and/or obstructive symptoms. Trials of chemoradiation versus chemotherapy alone in LAPC have reported mixed findings regarding survival and are summarized in *Table 4* (4-6,9,10). In a trial conducted by the Gastrointestinal Tumor Study Group (5), the effect of concurrent chemoradiotherapy versus chemotherapy alone in LAPC was evaluated and a benefit in survival from combined modality therapy was noted. The chemoradiation arm consisted of radiation combined with 5-fluorouracil to a total dose of 54 Gy in 1.8 Gy fractions followed by maintenance streptozocin, mitomycin and 5-fluorouracil (SMF). The chemotherapy-only arm was SMF combination chemotherapy for two years or until progression. In this trial, the one-year OS was 41% in the chemoradiation arm compared to 19% in the chemotherapy-alone arm (P<0.02).

Modern chemotherapy and radiation techniques have been tested in two recent phase III trials evaluating the efficacy of chemoradiation. In the trial by the Eastern Cooperative Oncology Group (E4201), patients with LAPC were randomly assigned to chemoradiation (50.4 Gy in 28 fractions) with concurrent gemcitabine (600 mg/m^2 weekly ×6) followed by 5 cycles of gemcitabine alone (1,000 mg/m^2 weekly ×3 every 4 wks) versus gemcitabine alone (1,000 mg/m^2 weekly ×3 every 4 wks) for 7 cycles. This trial showed that chemoradiation was associated with a slightly improved survival (11 versus 9.2 months, P=0.044) (4).

In a second recent study by Chauffert *et al.* reported in 2008 (10), chemoradiation was delivered to a total dose of 60 Gy concurrently with cisplatin (20 mg/m^2/day, days 1-5 during weeks 1 and 5) and 5-fluorouracil (300 mg/m^2/day, days 1-5 for 6 weeks). The chemotherapy-alone arm consisted of gemcitabine (1,000 mg/m^2 weekly for 7 weeks). Maintenance gemcitabine (1,000 mg/m^2 weekly, 3/4 weeks) was given in both arms until disease progression or toxicity. Overall survival in this trial was shorter in the chemoradiotherapy arm (13.0 *vs.* 8.6 months, P=0.044) and these patients experienced a higher rate of grade 3-4 toxicity compared with the chemotherapy arm (66% *vs.* 40% respectively; P=0.0008). A potential explanation for increased toxicity is the combination of aggressive chemotherapy delivered with concurrent radiation (60 Gy concurrent with cisplatin followed by high-dose weekly maintenance gemcitabine). Due to inferior survival in the chemoradiation arm, this study was stopped prior to planned enrollment. However, it adds to the growing body of opinion that the benefit of chemoradiation for LAPC is likely confined to a carefully selected group of patients.

We observed prolonged median survival, from 9 to 12 months, in the RT (+) group. Although not statistically significant, our limited sample size precluded our ability

Table 4 Randomized trials comparing chemoradiation versus chemotherapy

Study	N	Arms	Median survival	One year survival
Hazel *et al.* 1981	30	Arm A (n=15): CT: 5FU 500 mg/m^2/wk bolus + methylCCNU PO 100 mg/m^2/6 wk until progression Arm B (n=15): CRT: RT 46 Gy (5x2Gy/wk) + FU 520 mg/m^2/wk bolus+maintenance CT as arm A until progression	Arm A: 7.8 months Arm B: 7.3 months	
Klaassen *et al*. 1985	91	Arm A (n=44): CT FU 600 mg/m^2/wk bolus until progression Arm B (n=47): CRT: RT 40 Gy, 5×2 Gy/wk + FU 600 mg/m^2 on days 1-3+ maintenance FU 600 mg/m^2/wk until progression	Arm A: 8.2 months Arm B: 8.3 months	28% *vs*. 30%
GITSG *et al*. 1988	43	Arm A (n=21): CT: FU 600 mg/m^2 bolus on days 1,8,29,36 + streptozocin 1 g/m^2/8 wk + MMC 10 mg/m^2/8wk until progression Arm B (n=22): CRT: RT 54 Gy, 5×1.8 Gy/wk + FU 350 mg/m^2 bolus on days 1-3 and 36-38 + maintenance CT as arm A until progression.	Arm A: 8.0 months Arm B: 10.5 months	19% *vs*. 41% (P<0.02)
ECOG 4201 2009	74	Arm A: CT: gemcitabine 1,000 mg/m^2/wk on days 1,8,15;7 cycles Arm B CRT: RT 50.4 Gy, 5×1.8 Gy/wk + gemcitabine 600 mg/m^2/wk-maintenance gemcitabine 1,000 mg/m^2/wk on days 1,8,15; 5 cycles	Arm A: 9.2 months Arm B: 11 months (P=0.044)	
FFCD/SFRO 2008	119	Arm A (n=60): CT: gemcitabine 1,000 mg/m^2/wk +maintenance gemcitabine 1,000 mg/m^2/wk until progression Arm B (n=59): CRT: RT 60 Gy, 5×2 Gy/wk + FU 300 mg/m^2/wk CI 5 d/wk + cisplatin 20 mg/m^2/d on days 1-5 and 29-33 + maintenance gemcitabine 1,000 mg/m^2/wk until progression	Arm A: 13.0 months Arm B: 8.6 months (P=0.03)	

to detect such a difference. Retrospective power analysis revealed that it would require more than 500 patients to detect the difference between the 9 and 12 month median survival observed in the RT (-) and RT (+) groups respectively with 80% power. Excluding the study of Chauffert *et al*., phase II and III multi-institutional data have reported similar survival results for patients with LAPC treated with chemotherapy (range, 9.1-9.0 months) (4,14,15) and chemoradiation (range, 11.0-11.9 months) (4,16,17).

Comparison of patient characteristics between each treatment modality group [RT (+) and RT (-) groups] using the Fisher's exact test revealed that some of the potential prognostic factors were not evenly distributed between the groups. Patients in the RT (-) group were more likely to have co-morbidities and poor performance status than those in the RT (+) group. Therefore, these patients were less likely to be selected for chemoradiation. We observed that the patients in the RT (+) experienced fewer grade 3/4 toxicities from treatment than did historical controls. Univariate analysis of patient characteristics showed that a reduced frequency of grade 3/4 toxicity predicted for improved PFS and one-year OS.

Our data suggest that chemoradiation can be delivered

safely and that acceptable toxicity is achievable with strict quality assurance, multidisciplinary management, and appropriate patient selection. It also highlights the need for a consistent approach to modern radiotherapy in an anatomic region with unique planning considerations, to avoid overdosing the neighboring radiosensitive organs reported by our group previously (18-21). CT simulation and three-dimensional conformal treatment planning was used in our study. Radiotherapy up to 54 Gy was delivered over a period of 5-7 weeks using standard fractionation. No planned treatment break or altered fractionation schemes were used. Potential detrimental effects of treatment interruptions and lack of effective systemic effect during a protracted radiation course on tumor control has led to the investigation of altered fractionation schemes, including shorter courses of high-dose radiotherapy using image guidance, as well as more conformal techniques (22-27). This is an area under active investigation and needs to be tested in a randomized setting (23,24,28,29).

Although local control rates have been improved by innovations in radiation therapy, systemic failure remains a major obstacle in improving survival. In our patterns of failure analysis, we found that the majority of treatment failures in both groups occurred at distant sites. The proportion of patients with a component of distant metastasis in the RT (+) group was 92% (46 of 50) and it was 91% (10 of 11) in the RT (-) group. The need for more effective chemotherapy is suggested by the high rate of distant metastasis in the RT (+) and RT (-) groups as shown in *Table 2*.

Over the last 10 years, gemcitabine alone and in combination has evolved as a standard of chemotherapy in LAPC (30,31). In more recent phase I/II studies, concurrent gemcitabine with radiation has shown promise in the treatment of locally advanced unresectable disease with manageable toxicity (32-40). In some of these trials, radiation targets included elective coverage of draining lymphatics, resulting in large treatment volumes that may have contributed to the increased toxicity that was described. Conformal radiation fields combined with newer systemic agents may help to reduce toxicity of treatment. More recently, biologic agents such as erlotinib have been tested in combination with gemcitabine, with varying success (7,14,41). There is a need for clinical trials using newer systemic agents and molecular targets to evaluate their efficacy in reducing the incidence of distant metastases.

Our study is limited by its retrospective nature, small sample size, and lack of data regarding quality of life. Many of the cited studies in this patient population have not incorporated assessments of quality of life, improvement in performance status, and palliation of symptoms (4-6,9,10). These endpoints are important to consider in patients with limited survival and marginal performance status who are at increased risk for toxicity from chemoradiation. In 2002, a study in Japan looked at combined-modality therapy versus best supportive care and found that locally advanced patients who underwent treatment derived benefit in quality of life as measured by a maintained performance status (42).

An attractive strategy to facilitate patient selection for CRT is through a trial of upfront systemic therapy followed by re-assessment. Radiotherapy may offer a survival benefit in patients with disease that proves to be localized after a period of time. Many patients will progress during induction chemotherapy and may be spared the added toxicity of combined-modality therapy.

In a study by The Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) LAP07, 181 patients were reviewed who were treated with 5-fluorouracil (5-FU) or gemcitabine-based chemotherapy for four months. Those without evidence of disease progression were given additional chemotherapy or chemoradiation. Overall survival was improved in patients who went on to receive chemoradiation (43). In our study, 24 patients received induction chemotherapy followed by CRT and then additional chemotherapy. The median survival of these patients was 14.5 months (95% CI, 11.1-18.4) compared to 11.9 months (95% CI, 9.8-12.8) for the patients who did not receive induction chemotherapy prior to chemoradiation.

In addition to appropriate patient selection, a more effective surrogate marker is needed to identify those patients most likely to benefit from additional therapy. CA19-9 is the most commonly used tumor marker in patients with pancreatic cancer. Occult metastatic disease may be suggested by rising tumor markers such as CA 19-9 during the induction period. Perioperative CA 19-9 levels have been shown to be prognostic in patients with resectable disease (44); CA 19-9 is a useful marker to incorporate into decisions regarding adjuvant therapy. Similarly, recent studies have shown that the peri-chemoradiation serum CA 19-9 level is an independent predictor of recurrence and survival after chemoradiation in LAPC (45,46).

Conclusion

Optimal management for locally advanced, unresectable

pancreatic cancer continues to evolve. Chemoradiation is a management option in appropriately selected patients. Chemotherapy alone is also an option, especially for patients with marginal performance status.

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A comparison of three treatment strategies for locally advanced and borderline resectable pancreatic cancer

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Background: The optimal treatment strategy for locally advanced and borderline resectable pancreatic cancer is not known. We compared overall survival (OS), local control (LC), metastasis free survival (MFS), and percent of patients who were able to undergo successful surgical resection for three treatment strategies.

Methods: We retrospectively reviewed 115 sequentially treated cases of locally advanced (T4) or borderline resectable (T3 but unresectable) pancreatic cancer. Patients were treated with either chemotherapy alone (C), concurrent chemoradiation therapy (CRT), or chemotherapy followed by chemoradiation therapy (CCRT). We compared survival between groups using Kaplan-Meier analysis and Cox-proportional hazards models.

Results: Median follow-up was 18.7 months. Fifty-six (49%) patients had locally advanced disease. Of the patients who received chemotherapy up-front, 82/92 (89%) received gemcitabine-based chemotherapy. Of the patients receiving C alone, 11/65 (17%) were diagnosed with distant metastases or died before 3 months. The rate of successful surgical resection was 6/50 (12%) in patients treated with radiation therapy (CRT or CCRT). Median survival times for patients undergoing C, CRT, and CCRT were 13.9, 12.5, and 21.5 months respectively. Patients treated with CCRT experienced statistically significant improved OS and MFS compared to C alone (P=0.003 and P=0.012 respectively). There was no difference in LC between treatment groups. On multivariable analysis younger age (P=0.009), borderline resectable disease (P=0.035), successful surgery (P=0.002), and receiving chemotherapy followed by chemoradiation therapy (P=0.035) were all associated with improved OS.

Conclusions: Treatment with CCRT is associated with improved median OS and MFS compared with C alone. This strategy may select for patients who are less likely to develop early metastases and therefore have a better prognosis.

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Introduction

Pancreatic cancer is the fifth most common cause of cancer related death in the United States (1). It is a deadly disease that is found to be distantly metastatic by radiographic imaging in up to two-thirds of new diagnoses. When distant metastases are not found, surgical resection is the only potentially curative therapy, yet 80% of newly diagnosed patients are not eligible for surgery because of metastatic or locally advanced disease at presentation (2,3). Even when patients with clinically localized pancreatic cancer undergo surgical resection there is still a high rate of treatment failure due to local tumor regrowth, incomplete resection, or metastatic disease.

Non-metastatic but locally unresectable pancreatic cancer can be divided into two categories: (I) borderline resectable and (II) locally advanced disease. Borderline resectable pancreatic cancer can involve the superior mesenteric vein (SMV) or portal vein (PV), the gastroduodenal or hepatic arteries, or less than half the circumference of the superior mesenteric artery (SMA). Locally advanced pancreatic

cancer includes disease that encases more that 50% of the superior mesenteric artery (SMA) or celiac artery (CA), or invades or encases the aorta or involves lymph nodes that are outside of the resection field (4).

While surgery remains the only potentially curative option for localized pancreatic cancer, the optimal initial treatment strategy when surgery is not possible is unknown. Three treatment strategies commonly employed in the current era include chemotherapy alone (C), concurrent chemoradiation therapy (CRT), or induction chemotherapy followed by chemoradiation therapy (CCRT). Trials examining the inclusion of radiation have mostly examined up-front CRT and have had mixed results. Emerging data suggests that CCRT is a valuable strategy for patients with borderline resectable or locally advanced disease because it allows more time for more aggressive or micrometastatic disease to declare itself before the addition of local therapy (5,6). The primary aim of this study was to compare overall survival (OS), metastasis free survival (MFS), local control (LC), and percent of patients who were able to undergo margin-negative resection for these three treatment strategies. We also conducted univariable and multivariable analyses to determine factors associated with better survival.

Methods

We retrospectively reviewed 115 sequentially treated cases of borderline resectable (T3 but unresectable) or locally advanced (T4) pancreatic adenocarcinoma who were treated at our institution between the years 2000 and 2010. Pathologic diagnosis was obtained for every patient. Workup included a computed tomography (CT) scan of the chest, abdomen, and pelvis with oral and IV contrast, endoscopic ultrasound, complete blood count, basic metabolic panel, and CA 19-9. Patients had a performance status of less than three according to the Eastern Cooperative Oncology Group (ECOG) scale. Patients were evaluated by a multi-disciplinary team which consisted of a medical oncologist, radiation oncologist, and a surgeon and all patients were felt to have locally unresectable, non-metastatic disease at the time of diagnosis.

Patients were treated with either chemotherapy alone (C), up-front chemoradiation therapy (CRT), or chemotherapy followed by chemoradiation therapy (CCRT). Patients who were treated with radiation therapy received between 45 and 54 Gy in 1.8 to 2 Gy fractions using 3D conformal radiation therapy, usually with a 3-field or 4-field technique. Following initial therapy, most patients who remained ineligible for surgery were treated with maintenance chemotherapy until disease progression or toxicity.

Of the patients who received up-front chemotherapy, 16/92 (17.4%) received gemcitabine alone, and 67/92 (72.8%) received gemcitabine combined with another(other) drug(s) including oxaliplatin (32/92, 34.8%), cisplatin (13/92, 14.1%), erlotinib (7/92, 7.6%), oxaliplatin and cetuximab (5/92, 5.4%), AVN-944 (3/92, 3.3%), docetaxel (2/92, 2.2%), S-1 (2/92, 2.2%), oxaliplatin and erlotinib (1/92, 1.1%), oxaliplatin and bevacizumab (1/92, 1.1%), and capecitabine (1/92, 1.1%). Nine patients did not receive gemcitabine including 4/92 (4.3%) patients who received irinotecan and docetaxel, 3/92 (3.3%) patients who received Genexol-PM, and 2/92 (2.2%) patients who received FOLFIRINOX. During concurrent chemoradiation therapy, patients received either 5-fluoruracil (5-FU) (21%), capecitabine (72%), or gemcitabine (7%). In patients who received CCRT the median time from the start of chemotherapy to the start of radiation therapy was 4.6 months with a range of 1.0 to 26.1 months.

Local failure was defined as findings of local disease progression on CT or MRI consisting of at least a 20% increase in the sum of the longest diameter of the lesion taking as reference the smallest longest diameter recorded since the treatment started (7). One- and two-year metastasis free survival (MFS) was calculated as defined by the proportion of patients alive without distant metastasis at those time points. One- and two-year local control (LC) was calculated as defined by the proportion of patients with no local progression with all other events including death being censored.

We calculated OS, MFS, and LC using Kaplan-Meier analysis and used the two-tailed log-rank test to compare survival between the three treatment groups. Time zero was defined as the day of the start of therapy. We repeated the log-rank analysis for the comparison of C and CCRT excluding patients who died or progressed before three, six, and nine months in order to test whether potential advantages in the CCRT group were due to selection of patients with less aggressive disease. We also calculated OS, MFS, and LC for the subsets of patients with (I) borderline resectable disease and (II) locally advanced disease using Kaplan-Meier analysis and used two-tailed log-rank analysis to compare outcomes for these two groups. Univariable and multivariable survival analyses were performed using Cox-proportional hazards models. The input variables for multivariable analysis were those found to be statistically significant on univariable analysis. ANOVA was used to

Table 1 Patient and tumor characteristics

	Total	C	CRT	CCRT	P-value
N	115	65	23	27	
Male	62 (54%)	36 (55%)	12 (52%)	14 (52%)	0.937
Female	53 (46%)	29 (45%)	11 (48%)	13 (48%)	
Mean age	64	66	62	62	0.068
Mean CA 19-9	1,348	1,790	753	545	0.308
Mean tumor size	3.9 cm	3.6 cm	3.9 cm	4.4 cm	0.169
Borderline resectable (T3 with vessel involvement)	58 (51%)	33 (51%)	10 (43%)	15 (56%)	0.694
Locally advanced (T4)	57 (49%)	32 (49%)	13 (57%)	12 (44%)	
Margin-negative resection	10 (9%)	4/65 (6%)	2/23 (9%)	4/27 (15%)	0.406
T3 Disease initially	8/58 (14%)	4/33 (12%)	2/10 (20%)	2/15 (13%)	0.817
T4 Disease initially	2/57 (4%)	0/32 (0%)	0/13 (0%)	2/12 (17%)	0.021

P-Values correspond to Chi-square tests of each variable. C, Chemotherapy; CRT, Chemoradiation therapy; CCRT, Chemotherapy followed by chemoradiation therapy.

Table 2 Outcomes by treatment type

	C	CRT	CCRT
Median OS in months	13.9 (11.4-15.9)	12.5 (8.3-19.0)	21.5 (16.1-29.7)
1-year OS	0.60 (0.47 to 0.71)	0.56 (0.33 to 0.73)	0.78 (0.57 to 0.89)
2-year OS	0.15 (0.08 to 0.25)	0.23 (0.09 to 0.42)	0.44 (0.25 to 0.61)
Median MFS in months	10.2 (6.5-12.7)	5.7 (3.1-9.8)	16.1 (10.0-25.0)
1-year MFS	0.42 (0.30-0.53)	0.30 (0.14-0.49)	0.52 (0.32-0.69)
2-year MFS	0.10 (0.04-0.18)	0.17 (0.05-0.35)	0.36 (0.19-0.54)
1-year LC	0.63 (0.50 to 0.74)	0.84 (0.58 to 0.94)	0.80 (0.58 to 0.91)
2-year LC	0.48 (0.32 to 0.62)	0.54 (0.23 to 0.77)	0.74 (0.50 to 0.88)

All time values are given in months. Ninety-five percent confidence intervals are in parentheses. C, Chemotherapy; CRT, Chemoradiation therapy; CCRT, Chemotherapy followed by chemoradiation therapy.

compare means in age and pretreatment CA 19-9 among the treatment groups. Chi-square was used to test for differences in categorical parameters among the treatment groups. Chi-square was also used to test for differences in patterns of failure. Statistical analyses were conducted using Stata 12.0. This study was approved by an institutional review board.

Results

Median follow-up was 18.7 months. Twelve of 115 patients were still alive at the time of last follow-up. There were no statistically significant differences in the baseline characteristics of the treatment groups (*Table 1*). Fifty-seven patients (49%) had locally advanced disease and 58 patients (51%) had borderline resectable disease and there was no difference in the distribution of treatment strategies between these two groups. There was a trend toward older age and higher CA 19-9 in patients receiving chemotherapy alone. However, there was considerable variation in the CA 19-9. The mean age was 64 years. Surgical resection was ultimately attained in 8/58 (14%) patients with borderline resectable disease and 2/57 (4%) patients with locally advanced disease. Likewise, surgical resection was attained in 6/50 (12%) patients treated with radiation therapy (CRT or CCRT) and 4/65 (6%) of patients treated with chemotherapy alone (C). There was no statistically significant difference in the rate of margin-negative resection by treatment type (P=0.406). Patients with borderline resectable disease were more likely to undergo

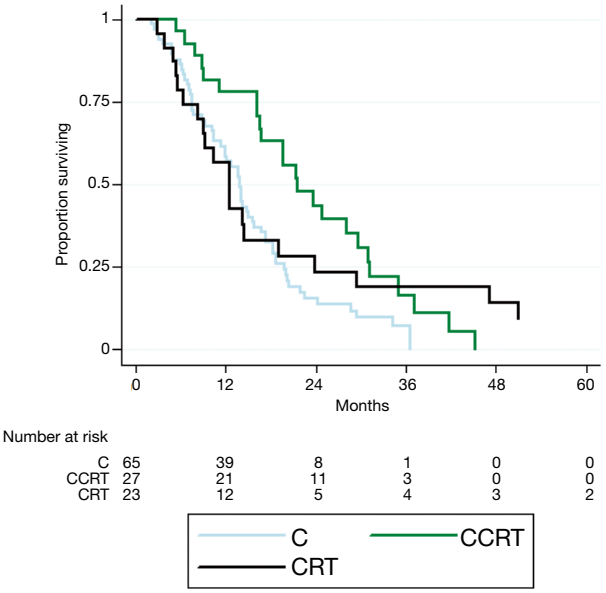

Figure 1 Overall survival by treatment group. Kaplan-meier curves for overall survival are shown for the three treatment groups. C, Chemotherapy; CRT, chemoradiation therapy; CCRT, chemotherapy followed by chemoradiation therapy.

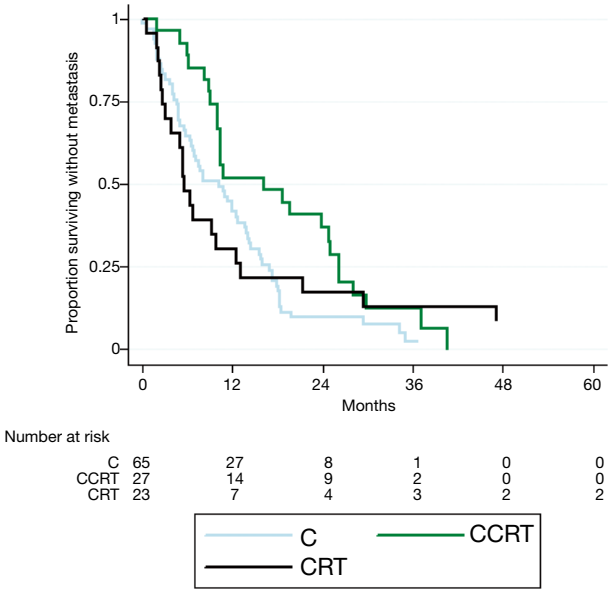

Figure 2 Metastasis free survival by treatment group. Kaplan-meier curves for metastasis free survival are shown for the three treatment groups. C, Chemotherapy; CRT, chemoradiation therapy; CCRT, chemotherapy followed by chemoradiation therapy.

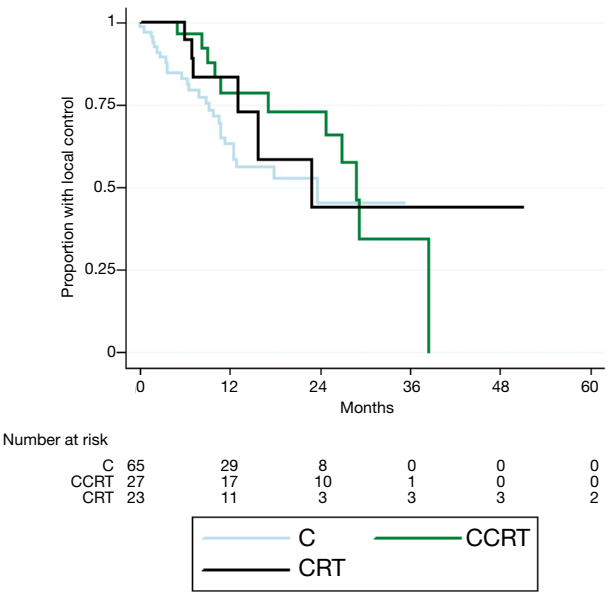

Figure 3 Local control by treatment group. Kaplan-meier curves for local control are shown for the three treatment groups. Patients are censored at the time of death. C, Chemotherapy; CRT, chemoradiation therapy; CCRT, chemotherapy followed by chemoradiation therapy.

margin-negative resection than patients with locally advanced disease, although this finding was not statistically significant (P=0.094). Of the patients receiving C alone, 11/65 (17%) were diagnosed with distant metastases or died before 3 months.

Values for median OS and MFS, and 1- and 2-year OS, MFS, and LC are found in *Table 2*. Patients treated with CCRT experienced improved median OS compared to C alone (21.5 *vs.* 13.9 months, P=0.003) (*Figure 1*). Patients treated with CCRT also experienced improved median MFS compared to C alone (16.1 *vs.* 10.2 months, P=0.012) (*Figure 2*). There was no statistically significant difference in OS between CRT and C (P=0.441) or CCRT and CRT (P=0.544). Likewise, there was no statistically significant difference in MFS between CRT and C (P=0.971), or CCRT and CRT (P=0.231). There was no statistically significant difference in LC between any of the treatment groups (CCRT *vs.* C, P=0.193; CRT *vs.* C, P=0.330; CCRT *vs.* C, P=0.870) (*Figure 3*). The improvement in OS in patients receiving CCRT compared to chemotherapy alone was more pronounced in patients with locally advanced disease (P=0.010) than in patients with borderline resectable

Table 3 Cox proportional hazard models for overall survival

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.03	1.01-1.05	<0.01	1.03	1.01-1.05	<0.01
T4 (*vs.* T3)	1.53	1.03-2.25	0.03	1.55	1.03-2.32	0.04
N1 (*vs.* N0)	1.07	0.65-1.52	0.53	-	-	-
Margin-negative resection	0.27	0.13-0.55	<0.01	0.30	0.14-0.63	<0.01
Treatment type (*vs.* C)						
CRT	0.68	0.39-1.18	0.17	0.94	0.54-1.67	0.85
CCRT	0.55	0.34-0.89	0.02	0.58	0.35-0.95	0.03
CA 19-9	1.00	0.99-1.00	0.25	-	-	-

HR, Hazard Ratio; CI, Confidence Interval; C, Chemotherapy; CRT, Chemoradiation therapy; CCRT, Chemotherapy followed by chemoradiation therapy.

Table 4 Sites of failure by treatment group

	Local [%]	Distant [%]	Both [%]	Neither [%]
Sites of initial failure				
C	13 [20]	23 [35]	9 [14]	20 [30]
CRT	4 [17]	12 [52]	0 [0]	7 [30]
CCRT	7 [26]	13 [48]	2 [7]	5 [19]
Sites of any failure				
C	26 [40]	36 [55]	17 [26]	
CRT	6 [26]	13 [57]	3 [13]	
CCRT	11 [41]	18 [67]	7 [26]	

C, Chemotherapy; CRT, Chemoradiation therapy; CCRT, Chemotherapy followed by chemoradiation therapy.

disease (P=0.089). Likewise, the improvement in MFS in patients receiving CCRT compared to chemotherapy alone was more pronounced in patients with locally advanced disease (P=0.020) than in patients with borderline resectable disease (P=0.218). Median OS for the eight patients with borderline resectable disease achieving margin-free resection was 47.1 months (95% CI, 9.0 months - undefined). Median OS for the two patients with locally advanced disease achieving margin-free resection was 29.7 months.

The statistically significant improvement in OS of CCRT compared to chemotherapy alone persisted when limiting the analysis to patients who were still alive with no progression at three months (P=0.015), six months (P=0.015), and nine months (P=0.011). The improvement in MFS of CCRT compared to chemotherapy alone was still statistically significant when limited the analysis to patients who were still alive with no progression at three months (P=0.042), but not at six months (P=0.198), or nine months (P=0.242).

In patients with borderline resectable disease median OS was 16.7 months (95% CI, 12.7-20.4 months) and median MFS was 10.5 months (95% CI, 8.1-14.5 months). In patients with locally advanced disease median OS was 13.7 (95% CI, 10.5-16.1 months) and median MFS was 9.2 months (95% CI, 5.0-13.2 months). OS and MFS were improved in patients with borderline resectable disease compared to locally advance disease by log-rank analysis (P=0.032 and P=0.039 respectively). There was no difference in LC between patients with borderline resectable and locally advanced disease (P=0.318).

On univariable survival analysis, younger patients had improved overall survival (P=0.001) (*Table 3*). Patients with locally advanced disease had worse overall survival than patients with borderline resectable disease (HR 1.53, P=0.033). Patients who received chemotherapy followed by chemoradiation therapy and patients who were able to undergo margin-negative resection had better survival (P=0.015, and P<0.001 respectively). Nodal status at

diagnosis did not affect overall survival. There was also no difference in survival based on the CA 19-9 level prior to treatment. On multivariable analysis younger age (P=0.009), borderline resectable disease (P=0.035), margin-negative resection (P=0.002), and receiving chemotherapy followed by chemoradiation therapy (P=0.035) were all associated with improved OS.

More patients experienced distant metastasis than local progression for the overall group, and for all three treatment groups (*Table 4*). There was no difference in the overall percent of patients experiencing local progression among the three treatment groups (P=0.46). Isolated local progression without distant metastasis at any time before death occurred in 9 patients (14%) in the C group, 3 patients (13%) of the CRT group, and 4 patients (15%) in the CCRT group (P=0.73). Distant metastasis without local progression at any time before death occurred in 19 patients (33%) in the C group, 10 patients (43%) of the CRT group, and 11 patients (41%) in the CCRT group (P=0.38). Most distant recurrences occurred in the liver, lung, or peritoneum.

Discussion

We report our experience treating a large series of patients with borderline resectable and locally advanced pancreatic cancer using three treatment strategies including chemotherapy alone, concurrent chemoradiation therapy, or induction chemotherapy followed by chemoradiation therapy. Patients treated with induction chemotherapy followed by chemoradiation therapy had an improved OS and MFS compared to patients treated with chemotherapy alone. The use of induction chemotherapy followed by chemoradiation therapy was associated with improved survival compared to chemotherapy alone on multivariable survival analysis as well.

The optimal strategy for upfront treatment of borderline resectable and locally advanced pancreatic cancer has not been elucidated by prospective clinical trials. Both early (8,9), and more modern (10,11) randomized trials of C *vs.* CRT have produced conflicting results. CCRT has been compared to CRT in a retrospective review of 323 patients that showed improved OS (8.5 *vs.* 11.9 months) and progression free survival (4.2 *vs.* 6.4 months) in the CCRT group (6).

No prospective randomized trials directly comparing CCRT to chemo alone have been reported. The Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) retrospectively analyzed patients treated on prospective phase II and III GERCOR studies (5) to compare the survival of patients treated with C *vs.* CCRT. This analysis included patients with both borderline resectable or locally advanced disease according to the NCCN definition (4). Patients treated with CCRT had improved progression free survival (10.8 *vs.* 7.4 months, P=0.005), and improved overall survival (15.0 *vs.* 11.7 months, P=0.0009). Our data are consistent with the GERCOR's prospectively gathered data in showing a survival benefit of CCRT over chemotherapy alone. The GERCOR LAP 07 phase III trial (12) is a randomized prospective phase III trial that will examine the role of CCRT after chemotherapy alone and the benefit of adding erlotinib for locally advanced pancreatic cancer.

Induction chemotherapy prior to chemoradiation therapy allows for the selection of patients for local radiation therapy who are less likely to have more aggressive or micrometastatic disease and therefore have a better prognosis. The success of this strategy in pancreatic cancer may result from better systemic control or possible eradication of micrometastatic disease from newer gemcitabine based therapy compared to older fluoropyrimidine-based therapy (13,14). FOLFIRINOX has recently been shown to confer a survival advantage compared to gemcitabine in the setting of metastatic pancreatic cancer and is receiving attention as a way to further improve induction chemotherapy in locally unresectable disease (15).

Other mechanisms of screening for patients who are more likely to benefit from localized therapy are being investigated. The expression of Smad4(Dpc4), a tumor suppressor gene activated in more than half of pancreatic cancers, has been shown to be associated with local rather than distant tumor progression (16,17). Testing for Smad4(Dpc4) status at initial diagnosis may help individualize treatment regimens to either focus on local control with radiation for Smad4(Dpc4) activated tumors versus systemic control with chemotherapy and/or targeted agents for non-Smad4(Dpc4) activated tumors. A phase II clinical trial, RTOG 1201, will attempt to assess the validity of Smad4(Dpc4) as a method of determining the optimal treatment for patients with locally unresectable pancreatic cancer.

Our analysis suggests that the OS and MFS benefits of CCRT *vs.* C are not entirely due to metastatic disease or death that occurs in the first few months before radiation is started. In this series, patients who survived without metastatic disease for three, six, or nine months on chemotherapy alone still benefitted from the addition of chemoradiation therapy. However, other unrecorded factors such as performance

status and cancer or non-cancer related comorbidities may have pushed healthier patients into the CCRT group and accounted for the better survival in this group.

Surgery remains the only treatment of localized pancreatic cancer that offers the possibility of a cure. In our analysis, undergoing margin-negative resection was associated with improved OS on both univariable and multivariable analysis. Twelve percent of patients who received radiation therapy (CRT or CCRT) were able to undergo margin-negative resection. In the subset of patients with locally advanced (T4) disease, only 2/53 patients (4%) achieved margin-negative resection. Both of these patients were treated with CCRT. This very small percentage of the patients is slightly higher, yet perhaps trivially so, than that shown in a prospective study attempting to convert LAPC to resectable disease where only 1/87 patients (1%) achieved a margin-negative resection (18). Until better therapies are developed, this small group of patients is the only group that we can hope to offer durable survival.

The rate of distant metastases before three months in patients receiving chemotherapy alone is low in our study (17%) compared to previously reported results (29-35%) (19). While patients were restaged before starting chemoradiation therapy in the CCRT group, there was no uniform policy requiring restaging at three months. Such a policy might have resulted in a higher percentage of disease progression at that time. The median time to the start of chemoradiation therapy in the CCRT group was 4.6 months.

The strengths of this study are that it examines a recent series of patients treated by a multidisciplinary gastrointestinal oncology group using modern therapeutics and supportive measures to directly compare three treatment strategies. The patients underwent uniform staging techniques, and had thorough follow-up. While much of the published data about the treatment of locally unresectable pancreatic cancer compares two strategies (C *vs.* CRT or CRT *vs.* CCRT), our study benefits from the comparison of all three strategies in the same setting. While our study is retrospective and hypothesis-generating, the inclusion of three treatment strategies provides important perspective given the inconsistent and confusing results of past studies.

Among the weaknesses of this study are that it was conducted retrospectively. Though available staging and patient characteristics were controlled for in our analysis, there is a possibility of selection bias in that patients with a poor functional status or greater comorbidities might not have been offered radiation therapy as often. While there were no statistical differences in baseline characteristics, there was a trend toward higher initial CA 19-9, and older age in the group that received chemotherapy alone. The benefits of CCRT shown here should be validated in a randomized clinical trial.

Conclusions

In conclusion, our retrospective results strongly suggest that, until a randomized controlled clinical trial is reported, patients who have been treated with chemotherapy alone with no progression may benefit from the addition of chemoradiation therapy if they can tolerate it. Providers should plan to add chemoradiation therapy after a trial period of chemotherapy alone for any patient who doesn't progress and can tolerate combined therapy. Treatment with CCRT is associated with improved median OS and MFS compared to chemotherapy alone. This is a strategy that selects for patients who are less likely to develop early metastases and therefore have a better prognosis. A prospective randomized study is needed to confirm these findings. Our analysis suggests that other factors that portend improved survival include younger age, borderline resectable disease, and margin-negative resection.

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Locally advanced versus metastatic pancreatic cancer: two different diseases with two different treatment approaches?

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Abstract: The results of the SCALOP trial were reviewed and interpreted at the light of previous trials and of the more recent LAP-07 trial. In this latter trial the role of radiotherapy after an induction chmeotherapy has been questioned. Based on these findings data from the SCALOP trial loose most of their value. In fact, while it showed that capecitabine may be combined with radiotherapy more safely than gemcitabine and it could be a standard regimen as a consolidation regimen after an induction chemotherapy, the LAP-07 trial showed that radiotherapy in combination with chemotherapy does not add any valuable effect to chemotherapy alone.

Keywords: Pancreatic cancer; locally advanced disease; chemoradiotehrapy

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Locally advanced unresectable disease represents around one third of the cases of pancreatic cancer at diagnosis. Although locally advanced pancreatic cancer has a poor prognosis, it is clearly better than that of metastatic disease, with a median survival of 9 months compared with the 3-month survival of the metastatic disease. However, in a few months the majority of patients with locally advanced disease develop metastastes (1). This natural history of disease is probably one of the reasons for the controversies about the optimal management of these patients (2). In fact, after two decades of clinical research, a debated issue is still the contribution of a local regional treatment such as radiotherapy in a disease, apparently localized, but in reality already metastatized. While in US most of the patients receive chemoradiotherapy upfront, in Europe radiotherapy is generally reserved to patients not progressing after 2 or 3 months of chemotherapy. This latter approach is based on the previous considerations but mainly on a retrospective analysis by GERCOR and a systematic overview (2,3). It was shown in fact that patients receiving radiotherapy after an induction chemotherapy seems to have a better survival in comparison with patients receiving only chemotherapy (15 *vs.* 11.7 months) (2,3). These clinical results are supported also by biological findings. Recently, it was demonstrated that EMT and dissemination are early events in pancreatic cancer and precede even tumor formation (4). Obviously, these new biological insights question the role and efficacy of a local treatment such as radiotherapy, in a disease only apparently localized. This has been shown, clinically, in the Chauffert's study where patients with locally advanced disease were randomised to receive gemcitabine or radiotherapy plus 5fluorouracil followed by gemcitabine (5). In the chemoradiotherapy arm survival was significantly worse: 8.6 versus 13 months. It seems to confirm that a local treatment is not a good therapeutic approach for locally advanced pancreatic cancer. Furthermore, radiotherapy or chemoradiotherapy may produce higher rates of toxicity affecting the patients quality of life and even contributing to a worst prognosis since treatment may be delayed or discontinued. On the contrary, reserving radiotherapy as a consolidation treatment in only patients not progressing after 2-3 months of treatment may spare an useless upfront locoregional treatment in several patients showing an early systemic progression of disease. This leads to a significant reduction of severe side effects and costs for patients and health system.

Another debated issue has been which drug is preferable to combine to radiotherapy. Fluorouracil is commonly associated with radiotherapy in several different cancer types. Gemcitabine is a potent radiosensitizer but it is often associated with an increased toxicity.

Three small randomised trials and a meta-analysis suggested a survival advantage of gemcitabine in comparison with fluorouracil when combined to radiotherapy in locally advanced pancreatic cancer (6-9).

The paper by Mukherjee *et al.*, published in the *Lancet Oncology*, reports the results of an interesting trial exploring the role of gemcitabine or capecitabine, combined with radiotherapy, as consolidation treatment in patients with locally advanced unresectable pancreatic cancer not progressing after an induction chemotherapy. Although there were no differences in activity and efficacy, the authors suggested that a capecitabine-based regimen might be preferable in terms of toxicity in the context of a consolidation chemoradiotherapy after an induction chemotherapy (10).

This may be an useful information for the clinical practice since most of the pancreatic cancer patients receive radiotherapy after chemotherapy and it was not completely clear in spite of the previous trials which drug should be better combined with radiotherapy. Gemcitabine is not a "friendly" drug when combined with radiotherapy and, although gemcitabine is popular in metastatic pancreatic cancer more than for its favourable toxicity profile than for its efficacy, it is not reccomandable to combine it with radiotherapy since toxicity may represent a clinical relevant problem.

Can we learn something else from this study? It seems to support the strategy of giving firstly chemotherapy and only in the case of a not progressing disease to deliver radiotherapy. In fact, a minority of patients were candidated to receive radiotherapy: only 74 patients out of the 216 patients assessed for eligibility were randomized in this study. Most of the patients were considered not eligible because of progressive disease or an early deterioration of the clinical conditions.

A critical point in this trial is the regimen chosen as induction chemotherapy. A combination of gemcitabine and capecitabine does not represent a standard therapy in advanced pancreatic cancer worldwide. In fact, the combination of gemcitabine and capecitabine is not clearly superior to gemcitabine alone while other regimens such as FOLFIRINOX or nab-paclitaxel/gemcitabine are more effective in the control of the micrometastatic disease (11,12). In reality, we do not know if a better induction chemotherapy may improve the overall results, by decreasing the rate of metastatic dissemination, and therefore to give some value to radiotherapy in the control of the local disease. Several trials with these new regimens are exploring this hypothesis and we have to wait these results before planning future clinical studies (13,14).

Another problem limiting the potential clinical value of this trial is the results of the LAP-07 trial, presented at the last ASCO meeting (15). In the French trial, 269 patients not progressing after 4 cycles of gemcitabine were randomised to receive gemcitabine alone or capecitabine plus radiotherapy. Surprisingly, there were no differences in survival (16.4 *vs.* 15.2 months). These unexpected results question the role of radiotherapy and suggest that chemotherapy alone could be the standard approach even for locally advanced pancreatic cancer patients. Once again caution should be recommended since the induction chemotherapy regimen does not represent the potentially best chemotherapy in pancreatic cancer.

The SCALOP trial is also of some merit because it allows to interpretate and to put in the right context the LAP-07 trial results. In fact, one of the possible doubts in the interpretations of the negative results of the LAP-07 trial could be the non optimal combination of chemoradiotherapy. Data from the SCALOP trial showed that it could not be the reason since a capecitabine-based regimen is the preferable regimen in this setting.

If we look at the results of the SCALOP trial on the basis of the LAP-07 trial we can learn another important lesson. SCALOP trial was designed on the basis of the results of retrospective data. It is a well designed and conducted trial but it has no clinical value since the assumption of the trial, a consolidation chemoradiotherapy is better than chemotherapy alone, was not demonstrated by the LAP-07 trial. In fact, now we know that capecitabine may be the preffered drug to be combined with radiotherapy but, unfortunately, we know also that the role of radiotherapy in the management of locally advanced pancreatic cancer is marginal. Therefore, the SCALOP trial is completely devoid of any clinical utility and, even, most patients receive a toxic and ineffective regimen raising ethical concerns.

Retrospective analyses can give us relevant informations but they should be prospectivelly confirmed before to be regarded as standard in the clinical practice or as a reference arm in clinical trials. The risk is that several trials, designed on the basis of retrospective findings, can give controversial results by treating several patients with a non optimal

regimen or strategy. Even from an ethical point of view these approaches are not reccomandable.

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HIFU for palliative treatment of pancreatic cancer

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Abstract: High intensity focused ultrasound (HIFU) is a novel non-invasive modality for ablation of various solid tumors including uterine fibroids, prostate cancer, hepatic, renal, breast and pancreatic tumors. HIFU therapy utilizes mechanical energy in the form of a powerful ultrasound wave that is focused inside the body to induce thermal and/or mechanical effects in tissue. Multiple preclinical and non-randomized clinical trials have been performed to evaluate the safety and efficacy of HIFU for palliative treatment of pancreatic tumors. Substantial tumor-related pain reduction was achieved in most cases after HIFU treatment, and no significant side-effects were observed. This review provides a description of different physical mechanisms underlying HIFU therapy, summarizes the clinical experience obtained to date in HIFU treatment of pancreatic tumors, and discusses the challenges, limitations and new approaches in this modality.

Keywords: Therapeutic ultrasound; focused ultrasound; HIFU; pancreas cancer; review

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Introduction

Within the last year more than 42,000 people in the United States were newly diagnosed with pancreatic cancer, which makes it the fourth leading cause of cancer mortality (1). A majority of patients diagnosed with pancreatic cancer are considered inoperable at the time of the diagnosis due to locally advanced disease or the presence of metastasis, and the efficacy of systemic chemotherapy is limited (2). The prognosis for these patients is one of the worst among all cancers: according to EUROCARE study, based on over 30,000 cases, overall survival at 1,3 and 5 years was 16%, 5% and 4%, respectively (3). Pain is often reported by patients with advanced disease, and palliative treatment methods are commonly employed and include opioid therapy and celiac plexus neurolysis (4). However, opioids may produce a range of side-effects from dysphoria to respiratory depression, and celiac plexus neurolysis provides limited benefit in pain relief, in addition to being an invasive procedure (5,6).

High intensity focused ultrasound (HIFU) therapy is a non-invasive ablation method, in which ultrasound energy from an extracorporeal source is focused within the body to induce thermal denaturation of tissue at the focus without affecting surrounding organs (*Figure 1*). HIFU ablation has been applied to treatment of a wide variety of both benign and malignant tumors including uterine fibroids, prostate cancer, liver tumors and other solid tumors that are accessible to ultrasound energy (7-10). Preliminary studies have shown that HIFU may also be a useful modality for palliation of cancer-related pain in patients with advanced pancreatic cancer (11-14). The objective of this article is to provide an overview of the physical principles of HIFU therapy and to review the current status of clinical application of HIFU for pancreatic cancers.

Physical mechanisms underlying HIFU therapy

Ultrasound is a form of mechanical energy in which waves propagate through a liquid or solid medium (e.g., tissue) with alternate areas of compression and rarefaction. The main parameters that are used to describe an ultrasound wave are its frequency, or the number of pressure oscillations per second, and pressure amplitude, as illustrated in *Figure 2C*. Another important characteristic

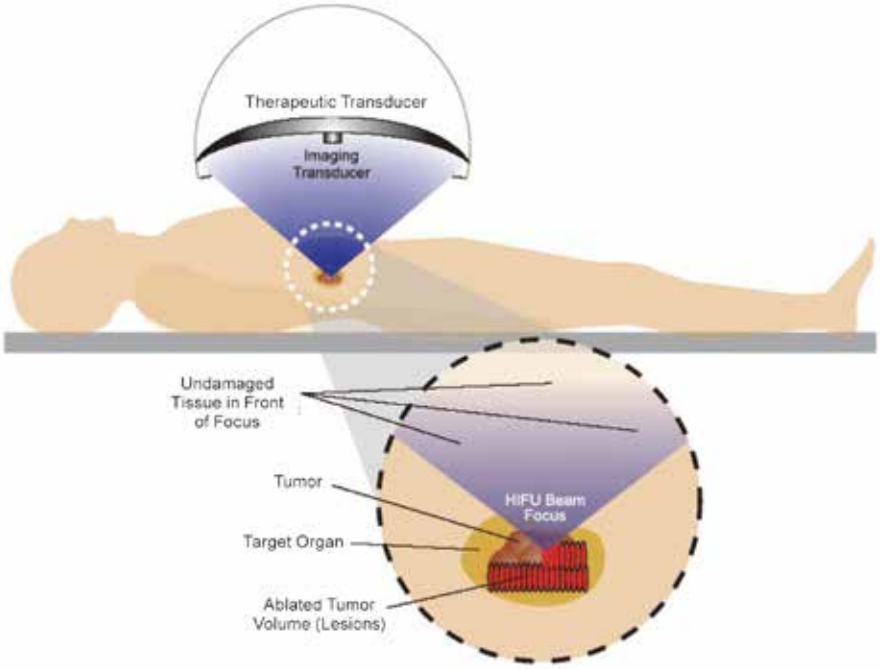

Figure 1 Illustration of extracorporeal high intensit y focused ultrasound treatment of a pancreatic tumor using a transducer that is located above the patient that is in the supine position. Reproduced with permission from Dubinsky *et al.* (10).

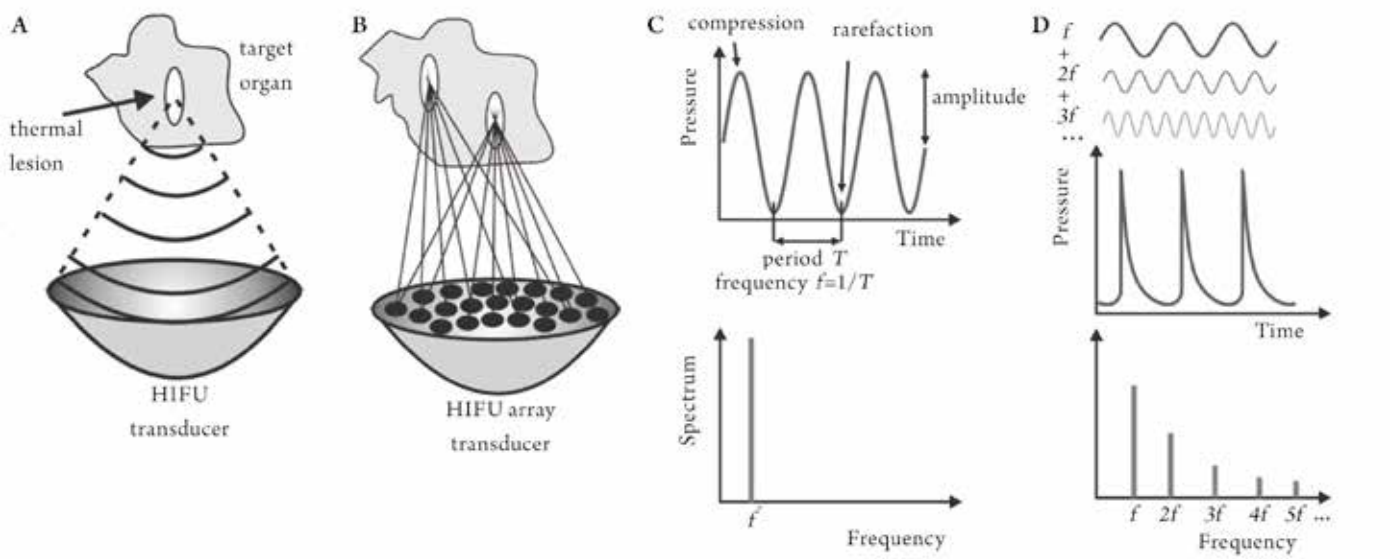

Figure 2 (A) A single-element HIFU transducer has a spherically cur ved surface to focus ultrasound energ y into a small focal region in which ablation takes place, leaving the surrounding tissue unaffected. (B) In a phased-array HIFU transducer the position of the focus can be steered electronically by shifting the phases of the ultrasound waves radiated by each element without moving the transducer. (C) A n example of a linear (sine) ultrasound wave; its frequency spectrum contains a single frequenc y f. (D) A nonlinear ultrasound wave is formed by the energ y transfer from the linear wave w ith the f undamental frequency f into the waves with higher frequencies (also known as harmonics): $2f$, $3f$, etc., and superimposition of these waves. 1herefore, the frequency spectrum contains the fundamental frequency f as well as higher harmonics: $2f$, $3f$, etc.

of an ultrasound wave is its intensity, or the amount of ultrasound energy per unit surface, which is proportional to the square of the wave amplitude.

Both HIFU devices and diagnostic ultrasound imagers utilize ultrasound waves with frequencies t ypically ranging from 0.2-10 megahertz (MHz), but the difference is in the amplitude and in how the ultrasound waves are transmitted. Diagnostic ultrasound probes transmit plane or divergent waves that get reflected or scattered by tissue inhomogeneities and are then detected by the same probe. In HIFU the radiating surface is usually spherically curved, so that the ultrasound wave is focused at the center of curvature in a similar fashion to the way a magnifying lens can focus a broad light beam into a small focal spot (*Figure 2A*). This can result in amplification of the pressure amplitude by a factor of 100 at the focus. Another method of focusing is using ultrasound arrays, as illustrated in *Figure 2B*: each element of the array radiates a wave with a pre-determined phase, so that waves from all elements interfere constructively only at a desired focal point. The size and shape of the focal region of most clinically available transducers is similar to a grain of rice: 2-3 mm in diameter and 8-10 mm in length.

As mentioned above, diagnostic ultrasound and HIFU waves differ in amplitude. Typical diagnostic ultrasound transducers operate at the pressures of 0.001-0.003 MPa which corresponds to time-averaged intensity of 0.1-100 mW/cm^2. HIFU transducers produce much larger pressure amplitudes at the focus of the transducer: up to 60 MPa peak compressional pressures and up to 15 MPa peak rarefactional pressures, which corresponds to intensities of up to 20000 W/cm^2. For comparison, one atmosphere is equal to 0.1 MPa. Ultrasound of such intensities is capable of producing both thermal and mechanical effects on tissue, which will be discussed below.

Tissue heating

The fundamental physical mechanism of HIFU, ultrasound absorption and conversion into heat, was first described in 1972 (15). Absorption of ultrasound, the mechanical form of energy, in tissue is not as intuitive as absorption of electromagnetic radiation (e.g., light or RF radiation) and can be simplistically explained as follows. Tissue can be represented as viscous f luid contained by membranes. When a pressure wave propagates through the tissue, it produces relative displacement of tissue layers and causes directional motion or microstreaming of the fluid. Viscous friction of different layers of fluid then leads to heating (16).

Both diagnostic ultrasound and HIFU heat tissue, however, since the heating rate is proportional to the ultrasound intensity, the thermal effect produced by diagnostic ultrasound is negligible. In HIFU the majority of heat deposition occurs at the focal area, where the intensity is the highest. The focal temperature can be rapidly increased causing cell death at the focal region. A threshold for thermal necrosis, the denaturing of tissue protein, is calculated according to the thermal dose (*TD*) formulation:

$$TD(t) = \int_0^t R^{43-T(t')} dt' \quad [1]$$

where t is treatment time, and R = 0.25 if T(t) < 43 ℃ and 0.5 otherwise (17). The thermal dose required to create a thermal lesion is equivalent to the thermal dose of a 240-min exposure at 43 ℃, hence the common representation of thermal dose in "equivalent minutes". This definition originated from the hyperthermia protocol, when the tissue was heated to a temperature of 43-45 ℃ during a long exposure of several hours. However, it has been shown that this model gives good estimations of the thermal lesion dose for the higher temperatures caused by HIFU. For example, thermal lesion forms in 10 s at 53 ℃ and 0.1 s at 60 ℃. In HIFU treatments, the temperature commonly exceeds 70 ℃ in about 1-4 s. Thus, tissue necrosis occurs almost immediately. *Figure 3A* shows an example of a lesion with coagulation necrosis after a single treatment with a 1 MHz HIFU device in *ex vivo* bovine liver.

It is worth mentioning here that ultrasound absorption in tissue increases nearly linearly with ultrasound frequency; hence, more heating occurs at higher frequencies. However, the focus becomes smaller with higher frequency (18), and penetration depth is also limited by the higher absorption. Therefore, HIFU frequency should be chosen appropriately for smaller and shallower targets or larger targets located deeper within the body.

In most applications that utilize the thermal effect of HIFU the goal is to induce cell necrosis in tissue from thermal injury. However, several studies have reported that HIFU can also induce cell apoptosis through hyperthermia, i.e. sub-lethal thermal injury (19). In apoptotic cells, the nucleus of the cell self-destructs, with rapid degradation of DNA by endonucleases. This effect may be desirable in some cases, but may also present a limitation for HIFU ablation accuracy. Since cell death due to apoptosis occurs

at lower thermal dose than thermal necrosis, the tissue adjacent to the HIFU target might be at risk from this effect (20).

Acoustic cavitation

Acoustic cavitation can be defined as any observable activity involving a gas bubble(s) stimulated into motion by an exposure to an acoustic field. The motion occurs in response to the alternating compression and rarefaction of the surrounding liquid as the acoustic wave propagates through it. Although live tissue does not initially contain gas bubbles, tiny gas bodies dispersed in cells may serve as cavitation nuclei that grow into bubbles when subjected to sufficiently large rarefactional pressure that "tears" the tissue apart at the site of a nucleus. Thus, cavitation activity in tissue may occur if the amplitude of the rarefactional pressure exceeds a certain threshold, which in turn depends on ultrasound frequency with lower frequencies having lower rarefactional pressure thresholds. Cavitation threshold has been measured in different tissues in a number of studies, but there is still no agreement (21-23,28). For example, cavitation threshold in blood is estimated to be 6.5 MPa (23) at 1.2 MHz.

Once formed, the bubble can interact with the incident ultrasound wave in two ways: stably or inertially. When the bubble is exposed to a low-amplitude ultrasound field, the oscillation of its size follows the pressure changes in the sound wave and the bubble remains spherical. Bubbles that have a resonant size with respect to the acoustic wavelength will be driven into oscillation much more efficiently than others; for ultrasound frequencies commonly used in HIFU the resonant bubble diameter range is 1-5 microns (24). Inertial cavitation is a more violent phenomenon, in which the bubble grows during the rarefaction phase and then rapidly collapses which leads to its destruction. The collapse is often accompanied by the loss of bubble sphericity and formation of high velocity liquid jets. If the bubble collapse occurs next to a cell, the jets may be powerful enough to cause disruption of the cell membrane (25,26).

In blood vessels, violently collapsing bubbles can damage the lining of the vessel wall or even disrupt the vessel altogether. One may assume that the disruption occurs due to bubble growth and corresponding distension of the vessel wall. However, it was shown that most damage occurs as the bubble rapidly collapses and the vessel wall is bent inward or invaginated, causing high amplitude shear stress (27).

Stable cavitation may lead to a phenomenon called "microstreaming" (rapid movement of fluid near the bubble due to its oscillating motion). Microstreaming can produce high shear forces close to the bubble that can disrupt cell membranes and may play a role in ultrasound-enhanced drug or gene delivery when damage to the cell membrane is transient (28).

Cavitation activity is the major mechanism that is utilized when mechanical damage to tissue is a goal. At its extreme, when very high rarefactional pressures (> 20 MPa) are used, a cloud of cavitating bubbles can cause complete tissue lysis at the focus (29). In such treatments the thermal effect is usually to be avoided, therefore, short bursts of very high amplitude ultrasound of low frequency (usually below 2 MHz) are used. The time-averaged intensity remains low, and the thermal dose delivered to the tissue is not sufficient to cause thermal damage. Cavitation can also promote heating if longer HIFU pulses or continuous ultrasound is used (30-32). The energy of the incident ultrasound wave is transferred very efficiently into stable oscillation of resonant-size bubbles. This oscillatory motion causes microstreaming around the bubbles and that, in turn, leads to additional tissue heating through viscous friction, which can lead to coagulative necrosis.

Nonlinear ultrasound propagation effects

Nonlinear effects of ultrasound propagation are observed at high acoustic intensities and manifest themselves as distortion of the pressure waveform: a sinusoidal wave initially generated by an ultrasound transducer becomes sawtooth-shaped as it propagates through water or tissue (*Figure 2D*). This distortion represents the conversion of energy contained in the fundamental frequency to higher harmonics that are more rapidly absorbed in tissue since ultrasound absorption coefficient increases with frequency. As a result, tissue is heated much faster than it would if nonlinear effects did not occur. Therefore, it is critical to account for nonlinear effects when estimating a thermal dose that a certain HIFU exposure would deliver. For most clinically relevant HIFU transducers, nonlinear effects start to be noticeable if the intensity exceeds 4,000 W/cm^2, and at 9,000 W/cm^2 it dominates over linear propagation (33).

Probably, the most important consequence of nonlinear propagation effects is that the boiling temperature of water, 100 ℃, can be achieved as rapidly as several milliseconds, which leads to the formation of a millimeter-sized boiling bubble at the focus of the transducer (34). This changes the course of treatment dramatically: the incident ultrasound

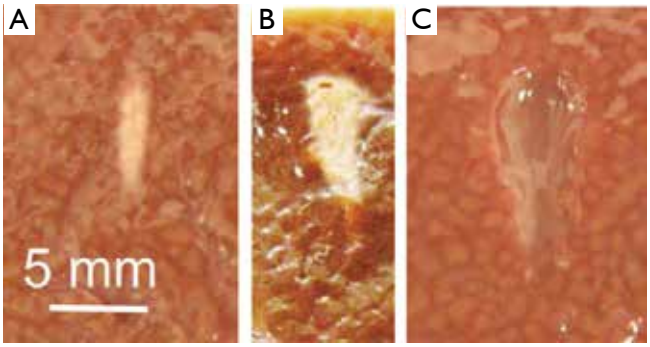

Figure 3 Examples of HIFU lesions produced in ex vivo bovine liver tissue with different sonication reigimes. (A) Absorption of linear ultrasound waves results in predictable cigar-shaped thermal lesion. (B) Irregularly-shaped thermal lesion with evaporated core results from boiling which is induced in tissue by rapid absorption of continuous nonlinear HIFU waves. (C) A lesion containing liquefied tissue may be produced by very short, high-amplitude nonlinear HIFU pulses.

wave is now reflected from the bubble and heat deposition pattern is distorted in unpredictable manner. The lesion shape becomes irregular, generally resembling a tadpole, as illustrated in *Figure 3B*. Moreover, the motion of the boiling bubble may cause tissue lysis that can be seen as a vaporized cavity in the middle of the thermal lesion. Sometimes this effect may be desirable and can be enhanced by using HIFU pulses powerful enough to induce boiling in several milliseconds, and with duration only slightly exceeding the time to reach boiling temperature (35). In that case the temperature rise is too rapid for protein denaturation to occur, but the interaction of the large boiling bubble with ultrasound field leads to complete tissue lysis, as illustrated in *Figure 3C* (36).

Radiation force and streaming

Radiation force is exerted on an object when a wave is either absorbed or reflected from that object. Complete reflection produces twice the force that complete absorption does. In both cases the force acts in direction of ultrasound propagation and is constant if the amplitude of a wave is steady. If the ref lecting or absorbing medium is tissue or other solid material, the force presses against the medium, producing a pressure termed "radiation pressure." For most clinically relevant devices and exposures this effect is not very pronounced: radiation pressure does not exceed a few pascals (14). However, if the medium is liquid (i.e., blood) and can move under pressure, then such pressure can induce streaming with speeds of up to 6 m/s (37). This effect has important implications in sonotrombolysis, in which a clotdissolving agent is driven by streaming towards and inside the clot blocking a vessel (38).

Image guidance and monitoring of HIFU therapy

There are currently two imaging methods employed in commercially available HIFU devices: magnetic resonance imaging (MRI) and diagnostic ultrasound. The role of these methods in treatment is three-fold: visualization of the target, monitoring tissue changes during treatment and assesment of the treatment outcome. In terms of tumor visualization, both MRI and sonography can provide satisfactory images; MRI is sometimes superior in obese patients (39), but is more expensive and labor-intensive.

Unfortunately, to date none of the monitoring methods can provide the image of the thermal lesion directly and in real time as it forms in tissue. The biggest advantage of MRI is that, unlike ultrasound-based methods, it can provide tissue temperature maps overlying the MR image of the target almost in real time. The distribution of sufficient thermal dose is then calculated and assumed to correspond to thermally ablated tissue. The temporal resolution of MR thermometry is 1-4 seconds per image, and the spatial resolution is determined by the size of the image voxel which is typically about 2mm × 2mm × 6mm (40). Therefore, MR-guided HIFU is only suitable for treatments in which the heating occurs slowly, on the order of tens of seconds for a single lesion. Motion artifact due to breathing and heartbeat is also a concern in clinical setting. The only US FDA-approved HIFU device available for clinical therapy utilizes MR thermometry during treatment of uterine fibroids (39,41).

Ultrasound imaging used in current clinical devices does not have the capability of performing thermometry, but it provides real-time imaging using the same energy modality as HIFU. This is a significant benefit, because adequate ultrasound imaging of the target suggests that there is no obstruction (e.g., bowel gas or bone) to ultrasound energy reaching the target, and the risk of causing thermal injury to unintended tissue is minimized. One method that is sometimes used for confirmation of general targeting accuracy is the appearance of a hyperechoic region on the ultrasound image during treatment. This region has been shown to correspond to the formation of a large boiling bubble at the focus when

Figure 4 FEP-BY high intensity focused ult rasound dev ice for tumor therapy. Components include a treatment table with upper and lower high intensit y focused ult rasound t ransducers (A), B -mode ultrasound imaging system (B), and computer control system (C). In addition, there is an electrical power system and water treatment system (not pictured). Reproduced with permission (Yuande Biomedical Engineering Corp. Ltd., Beijing, China).

tissue temperature reaches 100 ℃, and underestimates the actual size of the thermal lesion since thermal lesions develop at temperatures below 100 ℃ (42).

Imaging methods to assess HIFU treatment are similar to those used to assess the response to other methods of ablation such as radiofrequency ablation and include contrast enhanced CT and MRI (43). In addition, the use of microbubble contrast-enhanced sonography is also being examined as a method to evaluate the treatment effect of HIFU (44). These methods all examine the change in vascularity of the treated volume.

HIFU of pancreatic tumors

Devices

Currently, HIFU treatment of pancreatic cancer is widely available in China, with limited availability in South Korea and Europe. There are two US-guided HIFU devices that are commercially available outside of China for treatment of pancreatic tumors, both manufactured in China: The FEP-BY™ HIFU tumor therapy device (Yuande Biomedical Engineering Limited Corporation, Beijing, China, *Figure 4*) and HAIFU (Chongqing Haifu Technology Co.,) (45). Both devices operate at similar ultrasound frequencies – 0.8 and 1 MHz respectively; both are capable of putting out total acoustic power of about 300 W (corresponding intensity up to 20,000W/cm^2). B-mode ultrasound is also used in both machines for targeting and image guidance. In addition, a patient with pancreatic tumor was recently treated in Italy using the MR-guided ExAblate™ system (InSightec, Israel) for palliation of pain.

Animal studies

All the preclinical *in vivo* studies of HIFU ablation of the pancreas utilized the swine model because of its size and anatomy relevance to humans (46-48). The animals were not bearing tumors in the pancreas, therefore, it was not possible to evaluate survival benefits of HIFU therapy; however, the main goal of these studies was to systematically evaluate the safety and efficacy of HIFU ablation of the pancreas. In the earliest study the pancreata of 12 common swine were successfully treated *in vivo* using the FEP-BY02 device, without any significant adverse effects such as skin burns or evidence for pancreatitis during the 7-day post-treatment observation period (46). A subsequent study by another group ut i l izing the HAIFU dev ice used both l ight microscopy and electron microscopy to confirm that

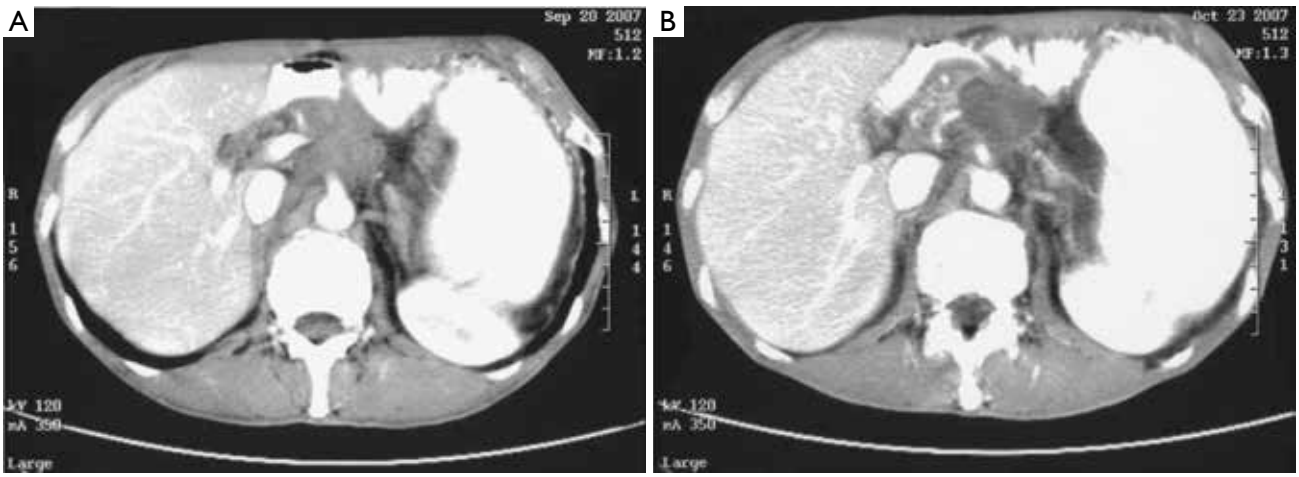

Figure 5 Contrast enhanced-CT scan of a 52-year-old male demonstrating a tumor in the body of the pancreas (A) prior to high intensity focused ultrasound therapy; (B) with evidence of ablation and necrosis following high intensity focused ultrasound therapy. Reproduced with permission from Xiong *et al.* 2009 (13).

complete necrosis is confined to the target regions with clear boundaries and no damage to adjacent tissues (47). Pancreatitis was an important safety concern because the mechanical effects of HIFU can cause cell lysis and release of pancreatic enzymes. Although the cavitation or boiling bubble activity during HIFU was confirmed by electron microscopic examination (intercellular space widening and numerous vacuoles of different sizes in the cytoplasm), pancreatitis was not observed thus confirming the safety of treatment protocol. Another preclinical study showed that a combined treatment of HIFU ablation followed by radiation therapy may be a promising method. The injury to the targeted pancreas was increased compared to either modality alone, without additional injury outside of the targeted region (48).

Clinical studies

As mentioned above, most patients diagnosed with pancreatic cancer are considered inoperable and systemic chemotherapy has only modest effect. Development of effective local therapies and strategies for pain relief are both important aspect of managing these patients. HIFU has been first used for the palliative treatment of pancreatic cancer in an open-label study in China in 251 patients with advanced pancreatic cancer (TNM stages II–IV) (49). HIFU therapy resulted in significant pain relief in 84% of the patients. In some cases significant reduction of tumor volume was achieved without any significant adverse effects or pancreatitis, which appears to have prolonged survival. Multiple nonrandomized studies that followed, mostly from China, provided additional evidence to show that HIFU does provide palliation of tumor-related pain and does not cause adverse effects (12-14, 50-56). The mechanism of pain relief in these patients is still unclear, but is hypothesized to result from thermal damage to the nerve fibers in the tumor. In two studies HIFU was used in combination with systemic chemotherapy (gemcitabine), and similar findings were reported in terms of pain relief and safety, even suggesting a survival benefit (14,51). *Figure 5* shows representative CT images of a pancreatic tumor before and after HIFU therapy.

In a small study from Europe (55) 6 patients with pancreatic tumors in difficult locations were treated with HIFU, the difficult location being defined as a tumor adjacent to major blood vessels, gallbladder and bile ducts, bowel, or stomach. This study was performed under general anesthesia, after 3-day of bowel preparation to avoid the presence of bowel gas in the acoustic pathway. Symptoms were clearly palliated within 24 hours after treatment in all patients, and the amylase level showed no statistically significant elevation over baseline 3 days after treatment. According to PET/CT and MDCT scans, the entire tumor volume was successfully ablated in all cases. A major

Table 1 Clinical studies of HIFU for palliative therapy of pancreatic cancer [Adapted from Jang HJ *et al.* (11)]

Author	Year	No. of patients	Treatment	Pain relief	Adverse effects
Xiong *et al.*	2001	21	HIFU	15/17 (88%)	None
Wang *et al.*	2002	13	HIFU	8/10 (80%)	Mild pancreatitis (2)
Xie *et al.*	2003	41	HIFU alone *vs.*	66.7%	None
			HIFU+gemcitabine	76.6%	
Xu *et al.*	2003	37	HIFU	24/30 (80%)	None
Yuan *et al.*	2003	40	HIFU	32/40 (80%)	None
Wu *et al.*	2005	8	HIFU	8/8 (100%)	None
Xiong *et al.*	2009	89	HIFU	54/67 (80.6%)	2nd degree skin burns (3) Subcutaneous sclerosis (6) Pancreatic pseudocyst (1)
Zhao *et al.*	2010	39	HIFU+gemcitabine	22/28 (78.6%)	None
Orsi *et al.*	2010	6	HIFU	6/6 (100%)	Portal vein trombosis (1)
Wang *et al.*	2011	40	HIFU	35/40 (87.5%)	None

complication – portal vein thrombosis – was observed in one patient, who was hospitalized for 7 days.

The results of the studies are summarized in *Table 1*, and, as seen, pain relief was achieved consistently in all studies. However, no randomized, controlled trials have been performed to date to confirm these findings or to determine if HIFU can improve overall survival by inducing local tumor response.

Challenges and future directions

The major factors that complicate HIFU ablation of pancreatic tumors are the presence of bowel gas, respiratory motion and the absence of ultrasound-based temperature monitoring methods. Bowel gas may obstruct the acoustic window for transmission of HIFU energy, which may lead to not only incomplete ablation of the target, but also thermal damage to the bowel or colon due to rapid heat deposition at the gas-tissue interface. Therefore, it is critical to evacuate the gas in the stomach and colon, which can be achieved by having the patient fast the night before treatment. Applying slight abdominal pressure to the target area also helps to displace gas and clear the acoustic window.

Respiratory motion of the tumor during the treatment leads to redistribution of acoustic energy over the area larger than the focal region and may result in incomplete treatment of the target and damage to adjacent tissues. Respiratory motion tracking techniques that would allow for rapid focal adjustment in sync with the target position are currently in development (57). An approach that would avoid both the problem of bowel gas and respiratory motion altogether is the use of a miniature HIFU transducer integrated with an endoscopic ultrasound probe. This approach would be particularly beneficial in obese patients. Such miniature endoscopic systems are not yet available commercially, but are currently in development.

Another problem that is inherent to any HIFU system with ultrasound guidance is the absence of direct operator control over the thermal dose that the target tissue received. In order to estimate thermal dose, one needs to know the output acoustic energy of the device, the absorption coefficient of the target tissue and the attenuation by the intervening tissue (primarily abdominal wall and viscera). Therefore, careful calibration of HIFU fields and studies on in-vivo measurement of acoustic attenuation and absorption in different tissues are of great importance (46).

Summary

HIFU ablation has been shown a promising method for palliative treatment of pancreatic tumors. A number of preliminary studies suggest that this technique is safe and can be used alone or in combination with systemic chemotherapy or radiation therapy. Further clinical trials are currently being planned and will help to define the future role of HIFU in the treatment of patients with pancreas cancer.

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Use of irreversible electroporation in unresectable pancreatic cancer

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Abstract: Irreversible electroporation is a non-thermal injury ablative modality that has been in clinical use since 2008 in the treatment of locally advanced soft tissue tumors. It has been reported to be utilized intraoperatively, laparoscopically or percutaneously. The method of action of IRE relies on a high voltage (maximum 3,000 volts) small microsecond pulse lengths (70 to 90 microseconds) to induce cell membrane porosity which leads to slow/protracted cell death over time. One of the largest unmet needs in oncology that IRE has been utilized is in locally advanced (stage III) pancreatic cancer. Recent studies have demonstrated the safety and palliation with encouraging improvement in overall survival. Its inherent limitation still remains tissue heterogeneity and the unique settings based on tumor histology and prior induction therapy. There remains a high technical demand of the end-user and the more extensive knowledge transfer which makes the learning curve longer in order to achieve appropriate and safe utilization.

Keywords: Locally advanced pancreatic cancer; irreversible electroporation; palliation

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Introduction

Irreversible electroporation is one of the newer novel non-thermal ablative modalities that has been successfully performed intraoperatively (1,2), laparoscopically (3) or percutaneously (4,5). What makes this new palliative option novel is its method of action which does not rely on a thermal-based coagulative necrosis but on a high voltage (maximum 3,000 volts) small microsecond pulse lengths (70 to 90 microseconds). This unique method of action has allowed for IRE to be successfully utilized in locally advanced pancreatic cancer with effective safety and palliation with potentially encouraging improvement in overall survival.

Currently multi-modality therapy including chemotherapy, surgery and/or radiation therapy remains the optimal treatment option for patients with pancreatic adenocarcinoma especially stage II disease. Given the higher incidence of more advanced staged disease (stage III and stage IV), only a small percentage of patients who are diagnosed with pancreatic adenocarcinoma are eligible for definitive surgical resection. Because of this high incidence optimal palliative strategies in order to improve quality-of-life time have become of utmost importance especially in patients with stage III pancreatic adenocarcinoma. The current options for palliation for appropriately and precisely staged locally advanced pancreatic cancer include systemic chemotherapy [Gemcitabine-based or FOLFIRINOX (6)], radiation therapy [IMRT, cyberknife (7) and proton therapy (8)] and surgical therapy [celiac axis alcohol ablation thoracoscopic thoracic splanchnicectomy (9), biliary bypass and gastric bypass]. All of these current modalities have been utilized with various effectiveness and with fairly well-established risks/benefits being known. Currently, optimal quality-of-life parameters have been limited in some of these studies with only the most recent studies demonstrating the stabilization of quality-of-life while undergoing systemic and/or local therapy (10).

Table 1 Histologic effects of thermal ablation modalities (radio-frequency, microwave ablation, and cryo-ablation) and irreversible electroporation

Effect	Thermal ablation	Irreversible electroporation
Act of damage	Entire cell	Only cell membrane
Protein denaturation	Typical	Not present
Blood flow	Effects efficacy ablation	No effect
Connective tissue	Damaged	Spared
Region of damage	Gradual change	Better defined
IHC effects	Present	Not present

IHC, immuno-histochemistry.

Method of action of IRE

Irreversible electroporation in the clinical setting has recently been established to induce permanent cell death through cell membrane perforation which induces electrolyte instability and causes a protracted cell death by apoptosis (11). This immune mediated cell death allows for cellular clearance of this debris and creates a minimal tissue distortion of the surrounding vital structures as have been published in previous clinical follow-up manuscripts. The ability to induce nanopores through effective irreversible electroporation has been demonstrated by electron microscopy in perfused porcine liver (12). Similarly, an optimal dose-response curve has also been validated and established for both the safe use of irreversible electroporation in order to prevent thermal damage as well as the effective use of irreversible electroporation in order to avoid just as importantly reversible electroporation which is synonymous with an ineffective therapy and thus persistence of viable malignancy (13). The tissue effects of irreversible electroporation have also been well established through the ability to irreversibly electroporate the cell membrane alone and to not damage the cartilaginous structures such that vital structures, specifically in locally advanced pancreatic cancer being the superior mesenteric vein (SMV), portal vein complex, the superior mesenteric artery (SMA) and/or celiac order and the bile duct are not thrombosed nor strictured when irreversible electroporation is appropriately performed (2,3,14).

Pre-clinical work and publications

Initial pre-clinical data has been published supporting both the safe and effective use of irreversible electroporation within the pancreas as well as within the hilum of the liver. Bower *et al*. recently published a chronic animal study demonstrating no adverse events of IRE around the portal venous or SMA complex in a large porcine animal model study. Complete ablations as well as volume ablations were also optimized with this therapy (13). Similar results were confirmed by Charpentier *et al*. who performed an acute animal model (2 hours survival) and also demonstrated no vascular thrombosis as well as effectiveness of complete ablation (15). Similar studies within the hilum of the liver have also further confirmed the safe and effective use in these non-tumor bearing *in vivo* porcine models.

Differences of IRE when compared to other thermal injury ablation therapies

Key to the understanding of the method of action of irreversible electroporation is the understanding of the significance difference when compared to thermal ablative modalities. It has been well established that the method of action on the action of damage, protein denaturation, blood flow, connective tissue, region of damage and the immediacy of the immunohistochemical effects are all significantly different in irreversible electroporation when you compare that to a thermal-based modality (*Table 1*). It is this difference especially in the ability to pathologically confirm the effects of IRE that has been both its key to method of action but also its significant limitation because of the lack of truly established "treat and resect" type studies. The earliest pathologic confirmation of irreversible electroporation cannot be seen until at least 2 to 4 hours after irreversible electroporation with either electron microscopy or specific immunohistochemical effects as long as the irreversible electroporation tissue has remained perfused for that 2 to 4 hours in order to establish those types of pathologic changes. Additional challenges with IRE has also been around its significant size limitation such that the current optimal size of a locally advanced

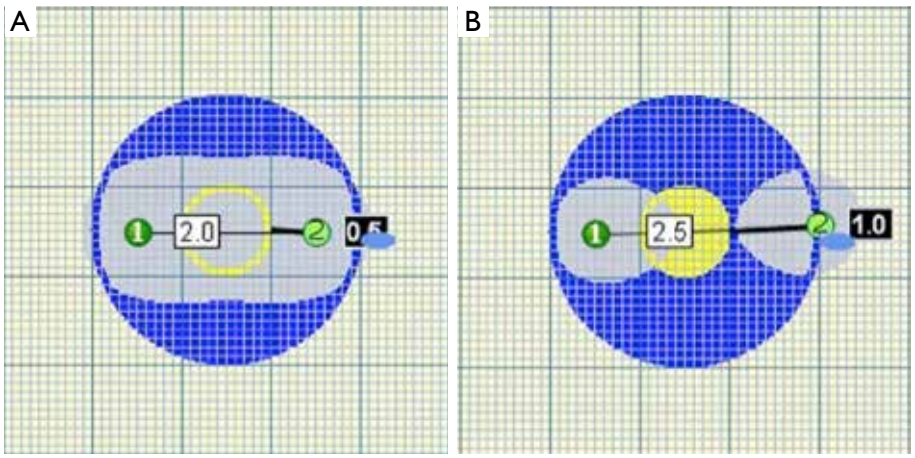

Figure 1 The demonstration of the precision of needle placement spacing that must be obtained between all IRE probe pairs in order to obtain a complete IRE (A). A difference of 5 mm or more between IRE probes will lead to ineffective therapy, i.e., reversible electroporation and subsequent electroporation recurrence (B).

pancreatic adenocarcinoma should be 3.0 cm or less for the potential new user and 4.0 cm or less for more established IRE end user. The reasons for these are the optimal spacing (1.7 to 2.2) that must be achieved with all probe pairs in order to safely and effectively deliver optimal electrical current between two probes. Inherent to those optimal tumor sizes is also the requirement of appropriate probe pairs being placed with optimal intra-operative image confirmation since variance of greater than 4.0 mm can lead to an ineffective irreversible electroporation (*Figure 1*). Those probe pairs when placed requires appropriate energy delivery that at times can take upwards to 60 minutes to deliver because of the multiple probe pairs that are required to deliver the energy as well as the optimal probe exposure being no more than 1.0 to 1.5 cm in size which commonly requires at least 2 to 3 pull backs in order to optimal electroporate along the cranial-to-caudal plane. It is this inherent emphasis on the end-user to understand all factors of intra-electroporation energy delivery that is of utmost importance in order to achieve both safety as well as efficacy of the device.

Current clinical use

The current clinical use of IRE has predominantly been within locally advanced stage III pancreatic adenocarcinoma of either the pancreatic head or body/neck. There have been much smaller percentages of use in margin accentuation for borderline resectable pancreatic tumors, in the treatment of locally recurrent pancreatic adenocarcinoma, as well as within metastatic disease to the pancreas most commonly metastatic renal and melanoma. Key in appropriate patients for the use of IRE is in locally advanced (stage III) only without any evidence of metastatic disease. We commonly utilize at least 4 months of induction chemotherapy in the appropriately and precisely staged stage III pancreatic adenocarcinoma so as to ensure that we are not missing sub radiologically occult microscopic metastatic disease that obviously would not benefit from a local therapy. Appropriately staged locally advanced stage III pancreatic adenocarcinoma at the initial diagnosis must include a high-quality tri-phasic CT scan with thin pancreatic protocol or dynamic MRI in addition to diagnostic laparoscopy and peritoneal washings in order to truly assess and optimally stage and differentiate a stage III pancreatic adenocarcinoma from a potentially sub-radiologically occult stage IV patient. Following that induction chemotherapy repeat staging is then performed to ensure stage III disease is still present and then definitive local therapy and/or additional palliative surgical procedures that being biliary bypass if needed or gastric bypass are needed are performed simultaneously. It is of utmost importance that the appropriate clinician performs irreversible electroporation in locally advanced pancreatic adenocarcinoma. That clinician must have extensive experience in thermal ablative modalities with RFA, microwave and cryoablation as well as being technical facile with the use of high-quality intraoperative procedural imaging most commonly being ultrasound when performed

open and/or laparoscopically.

This fairly rigorous staging, induction therapy requirements and high-quality end user understanding and intraoperative imaging has allowed the initial publish experience with the use of IRE in locally advanced pancreatic cancer to be performed safely as well as with encouraging results. Briefly, our initial experience with 27 patients we were able to confirm that IRE of locally advanced pancreatic cancer was both safe and feasible but there were essential keys to safely that being appropriate patient selection, the requirement of high-quality imaging as well as an upper level of understanding in the use of the IRE technology (2). From this initial safety evaluation further comparison of IRE against a group of patients with stage III pancreatic adenocarcinoma who underwent standard-of-care chemotherapy and chemoradiation therapy alone was also performed with initial encouraging results in regards to overall efficacy (1). This report demonstrated an initial hypothesis generating improvement in both local progression-free survival (14 *vs.* 6 months, P=0.01), improved distant PFS (15 *vs.* 9 months, P=0.02), as well as improved overall survival (20 *vs.* 13 months, P=0.03). There have obviously been inherent limitations to the current published results in the use of IRE of pancreatic cancer, the largest being the lack of true understanding as well as true standard-of-care management of patients with locally advanced pancreatic adenocarcinoma. There still remains a wide variability in the use of both induction chemotherapy as well as the timing of utilization of induction radiation therapy in the management of this unique subset of disease. The current largest hurdle that must be overcome in all of the oncology community is a more thorough understanding and acceptance that stage III pancreatic adenocarcinoma is a distinctly different biologic disease than synchronous stage IV metastatic pancreatic adenocarcinoma. Inherent to that acceptance and belief is also the use of high-quality diagnostic imaging and laparoscopy at initial diagnosis. Additional inherent limitations have been to further optimize the quality-of-life improvements that IRE has obtained with an initial signal demonstrating an improvement in overall narcotic use as we have previously published.

Further optimization with the use of IRE in locally advanced pancreatic adenocarcinoma will also come from standardization of technique in regards to optimal probe placement which we believe must be performed in a transmesocolic caudal-to-cranial needle insertion with continuous intraoperative ultrasound imaging being utilized from needle insertion to needle endpoint in order to avoid any type of underlying needle damage to vital structures. Optimal probe exposure being 1.0 to 1.5 cm at maximum as well as understanding of clinical irreversible electroporation endpoints with initial signal demonstrating that an overall change in resistance is going to be more optimally reproducible than any type of intra-ablation ultrasound imaging assessment because of the significant amount of edema that occurs with and after IRE delivery.

In conclusion IRE of locally advanced pancreatic adenocarcinoma is not a standard-of-care practice this time because of a number of keys to acceptance. First and foremost must be an overall optimization in staging and diagnosis of locally advanced pancreatic adenocarcinoma and the paradigm shift to stop grouping this patient with known stage IV metastatic disease. Additional keys will also be standardization of needle device placement as well as optimization of intra-electroporation efficacy endpoints, which are currently being optimized. After those keys have been established then a true validation either single-arm or randomized phase II study will have to be performed in order to truly validate the utilization of IRE in locally advanced pancreatic adenocarcinoma as an optimal treatment in patients who have undergone appropriate induction chemotherapy after they have been appropriately staged.

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Pain management of pancreatic head adenocarcinomas that are unresectable: celiac plexus neurolysis and splanchnicectomy

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Background: Pancreatic adenocarcinoma is often incurable at the time of diagnosis. For patients with unresectable or recurrent disease, palliation of pain is a key component of care. Medical management with narcotics has numerous side effects and may be ineffective. Interventions for pain control include celiac plexus neurolysis (CPN) and splanchnicectomy. The purpose of this review is to outline pertinent anatomy, techniques, side effects, complications, and efficacy of interventions for palliation of pain from pancreatic cancer.

Methods: We reviewed current literature, as well as our own patients, to assess the role and outcomes of CPN and splanchnicectomy. Short descriptions of procedural techniques and functional illustrations are provided.

Results: Both CPN and splanchnicectomy have excellent outcomes with regard to pain control. Quality of life and survival, however, have not been conclusively demonstrated to improve with either technique. Data regarding head-to-head comparisons of the two interventions is lacking.

Conclusions: Patients with incurable pancreatic carcinoma should be offered either CPN or splanchnicectomy when medical management with narcotics has failed.

Keywords: Splanchnic nerves; celiac plexus; ganglia sympathetic; pancreatic cancer; palliative care

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Introduction

Adenocarcinoma of the pancreas is the fifth leading cause of cancer death in the world (1). Because patients often present with locally advanced or metastatic disease, curative resection is rarely an option. As a result, intervention for these unfortunate patients is often limited to palliation. The primary goal of palliation is ensuring that patients do not suffer painful effects of cancer progression, like obstruction of the common bile duct and/or duodenum and abdominal pain from malignant infiltration into the celiac plexus.

Up to 90% of patients with pancreatic cancer experience pain (1). Narcotics may be given initially, but significant side effects, such as a reduction in quality of life, have been reported. Because of this, attention has been given to two palliative interventions: celiac neurolysis and splanchnic neurectomy. Both celiac plexus neurolysis (CPN) and splanchnicectomy have been examined and described in the literature for a number of years. The purpose of this paper is to outline pertinent anatomy, techniques, side effects, complications, and the efficacy of CPN and splanchnicectomy for palliation of pain from pancreatic cancer.

Anatomy

Pain from pancreatic cancer is believed to stem from malignant neural invasion and the stimulation of visceral afferent neural fibers which travel from the celiac plexus through the splanchnics (2). A majority of patients report pain in the epigastrium and over half of these same patients complain of associated back pain. Only a minority of patients, however, report back pain without epigastric discomfort (3).

Neurolytic treatment is directed at the celiac plexus, while a neurectomy is performed on the splanchnic nerves, either unilaterally or bilaterally. The celiac plexus is made up of the right and left ganglia, surrounding the aorta at the level of the celiac artery. It consists of visceral afferent, as well as sympathetic, and parasympathetic efferent fibers (4), and is located in the peri-aortic fat pads at the level of the diaphragmatic hiatus and celiac artery. There are commonly two to five celiac ganglia lying between T12 and L2 (5). Sympathetic nerve fibers run from the spinal cord to the sympathetic chain and then synapse in the celiac ganglia. In turn, pain from the foregut and midgut travels retrograde via parasympathetic visceral afferent nerve impulses from the celiac plexus through the splanchnic nerves to the central nervous system.

The splanchnic nerves are easily recognized as neural branches from the sympathetic trunk running anterior and inferiorly toward the diaphragmatic hiatus overlying the thoracic vertebral column. There are three classically described splanchnic nerves: the Greater, Lesser, and Least. Branches at levels T5-T9 most commonly form the greater splanchnic nerves, while the lesser splanchnics are formed from ganglia associated with T8-T12 and the least splanchnic nerves are formed by T10-L1. After being relayed from the splanchnics, stimuli reach the thalamus and cortex of the brain; this information is perceived as pain (6).

Celiac plexus neurolysis (CPN)

Originally described in 1914, modern CPN may be performed percutaneously, at the time of laparotomy, or under the direction of endoscopic ultrasound (EUS) (7). Alcohol is typically injected into the plexus but it may also be injected into the ganglia proper. Although steroid injections have been described for CPN, they are more commonly used for pain associated with chronic pancreatitis than for pain with pancreatic cancer.

Technique

Historically, percutaneous and surgical neurolysis was considered the mainstay treatment. Percutaneous CPN is generally approached posteriorly with imaging guidance, while surgical neurolysis, which was originally performed during staging laparotomy, has been replaced by laparoscopy (4,8). Over time, however, both treatments seem to have yielded to the EUS approach. EUS CPN offers several advantages over radiologic and surgical techniques, including enhanced needle precision, the ability to inject the neurolytic agent into a larger area, and the ability to perform CPN at the time of tumor biopsy and staging (9). Regardless of which technique is chosen, alcohol is injected bilaterally into the peri-aortic fat pad at the level of celiac artery and diaphragmatic hiatus.

EUS-guided CPN is currently the most common technique used today. Consistent with other endoscopic procedures, traditional preoperative questioning and positioning is performed. Next, adequate hydration is ensured and anticoagulants are held as indicated. Pulse oximetry and non-invasive blood pressure monitoring are obtained while the patient is sedated and recovering. Antibiotics are administered for those on proton pump inhibitors due to the risk of post-operative abscess from bacterial overgrowth of the upper GI tract. EUS may be performed using linear-array endosonographic imaging by way of a GF-UC30P (Olympus Corporation, Center Valley, PA, USA), GF UC140P-AL5, or GF UC 160 PAT8 (Pentax Precision Instruments, Orangeburg, NY, USA).

Visualization of the celiac plexus is best seen from the posterior lesser curve of the stomach. The aorta is seen longitudinally, and the first arterial branch below the diaphragm is identified (*Figure 1*). With experience, the celiac plexus and ganglia can be readily identified. Traditionally, a 22-guage needle is advanced through the scope after being purged of air in anticipation of injection. There are larger specialty needles for CPN, including needles with multiple side-holes, to allow for a larger injection field (EUSN-20-CPN: Cook Endoscopy, Winston-Salem, NC, USA). The needle is advanced near the lateral anterior aorta, flushed, and aspirated. For CPN in pancreatic cancer patients, 10 mL (0.25%) of bupivacaine is injected, followed by 10 mL of dehydrated (98%) alcohol. The needle is then flushed and directed to the contralateral side of the aorta where the injection sequence is repeated. Impediments to visualization include lymphadenopathy or direct tumor encasement of the plexus and/or ganglia. In these cases, unilateral injection may be the only possibility, which could result in an associated decrease in efficacy (10). This procedure typically takes well under an hour. Afterwards, the patient is monitored and then discharged home in the absence of unstable vital signs as appropriate.

Literature

Multiple studies have compared CPN to medical pain management. In 1995, Eisenberg *et al.* reported pain relief

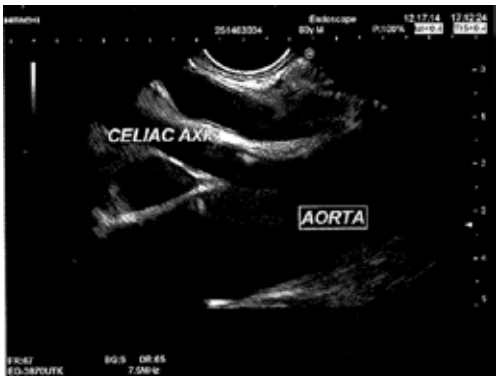

Figure 1 Endosonographic view of aorta and celiac artery origin (Image furnished by Dr. D Palma).

in 90% of their patients at 3 months from CPN, with a majority of those having significant relief until death (11). Lillemoe *et al.* and Wong *et al.* both reported pain control beyond 6 months to be common (8,12). In 2004, JAMA published a randomized control trial (RCT) that compared patients who underwent percutaneous CPN using a posterior approach with patients given systemic analgesic medications (12). Their results showed a significant difference in pain scores between the two groups, with the CPN patients reporting less severe pain (14% *vs.* 40%; P=0.005). This same study, however, did not show CPN to improve patient quality of life or survival. In 2007, Yan *et al.* performed a meta-analysis of five randomized trials comparing CPN to medical management (13). A significant difference was found between groups in visual analog scores and opioid usage, the results favored CPN. A second meta-analysis of nine RCT's performed by Puli *et al.* in 2009, showed an 80% decrease in pain with CPN compared to non-interventional management (14). In a RCT by Wyse *et al.* [2011], patients were randomized to CPN had significantly less pain than those who did not have intra-operative neurolysis (15).

Predictive factors for failure of CPN include direct tumor invasion of the plexus and unilateral injection (10). To date, there have been no head-to-head comparisons between CPN techniques. As a result, endoscopic, percutaneous, and surgical approaches to CPN are considered equally effective.

Complications

Complications of CPN are rare, occurring in approximately 1.5-2% of patients. Possible complications, however, do include transient, usually asymptomatic hypotension, retroperitoneal abscess, and severe self-limited post-procedural pain. Transient complications include post-procedural diarrhea and hypotension due to sympathetic blockade. Permanent, unremitting diarrhea has been reported in very rare cases (16). There is also a risk of cephalic spread of the neurolytic agent, which may result in involvement of the cardiac nerves and plexus (17). Spinal complications have also been reported, particularly with posterior approaches; fortunately, these are rare, occurring in less than 1% of patients. Lower extremity weakness, paresthesias, paraplegia have all been reported. This is likely due to the alcohol injection causing spasm or thrombosis of the Artery of Adamkiewicz, which supplies the inferior spinal cord (18,19). At least one fatality has been reported from associated complications (20).

Thoracoscopic splanchnicectomy

The first description of palliative chemical splanchnicectomy dates back to 1969. The first description of bilateral splanchnicectomy for pain secondary to pancreatic cancer was described by Sadar *et al.* in 1974 (21,22). Splanchnicectomy was initially performed under direct vision at the time of thoracotomy and combined with sympathectomy (22). The use of the thoracoscope to aid in the performance of splanchnicectomy for palliation of pain associated with pancreatic cancer was later described in 1993 in the *British Journal of Surgery* (23). Since then, several short case series have been published as techniques continue to be refined. Today, thoracoscopic splanchnicectomy may be performed either unilaterally or bilaterally.

Prior to consideration for splanchnicectomy, we ensure patients have failed medical management. Failure of medical managements is a subjective opinion, but if a patient's pain is able to be controlled by fewer than three daily doses of moderate strength narcotics, and they are able to maintain a productive life, surgical management may be avoided or at least delayed. We define pain control as a patient rating his or her pain as ≤3/10 on a visual analog score, and a productive life as being able to leave one's home and/or accomplish activities of daily living in line with the expectations of the patient. If these criteria are not met, consideration for bilateral thoracoscopic splanchnicectomy (BTS) is given.

When interviewing the patient, special attention should be given to his or her pulmonary reserve as well as to previous thoracic disease and/or interventions. Clues to possible thoracic adhesions should be explored. These

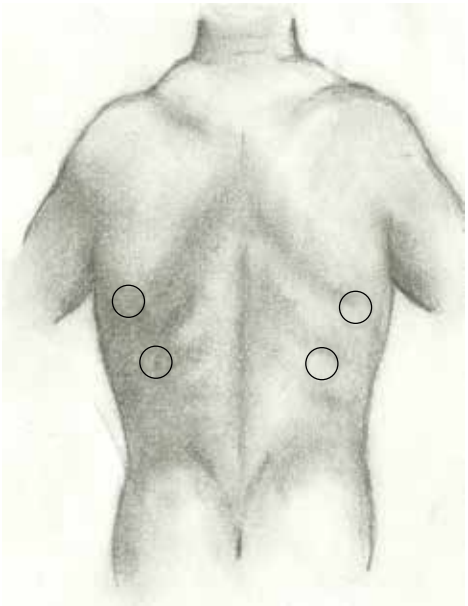

Figure 2 Author's illustration of the posterior thorax: trochar placement sites are denoted by circles placed at the inferior apex of the scapula and two intercostal spaces inferior and 2 cm medially.

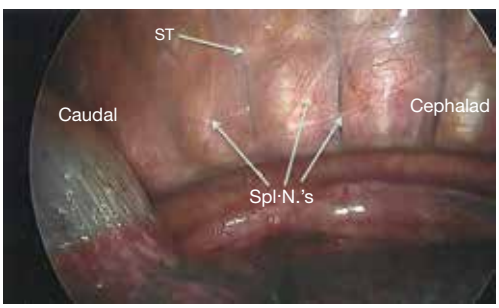

Figure 3 A thoracoscopic view of the right hemithorax is shown. Sympathetic trunk (ST) and splanchnic nerves (Spl N.'s) are labeled.

include previous severe pulmonary infections with associated empyema or parapneumonic effusions, the need for previous thoracostomy drainage or thoracentesis, thoracic trauma with associated hemothorax, previous pneumothorax, and previous thoracoscopy or thoracotomy. If any of these situations apply, the patient should be informed that it may be challenging to visualize the splanchnic nerves on the affected side without extensive dissection and/or thoracotomy. In a palliative operation, these patients should be largely avoided because of increased morbidity. Counseling should also be provided on the limited but distinct possibility of continued pain despite a technically successful operation. Following appropriate preoperative discussions, the patient is consented for the procedure.

Technique

At our institution, we perform BTS. Although this has not been compared head-to-head with unilateral splanchnicectomy, we are of the opinion that pain control is better with a bilateral neurectomy. This procedure can be easily executed with a single-lumen endotracheal tube; there is no need for continuous arterial blood pressure monitoring or central venous access. We prefer a posterior approach as described by Cuschieri *et al.* (24). The patient is placed in the prone position with the arms abducted and flexed at the elbow. To perform a BTS, we use two 5 mm trochars. We start initially on the left side, as it has been our experience that the left pleura is often thicker with more retro pleural fat, which can make visualization of the nerves on the left side often harder than the right. Despite that, the nerves are typically easy to find if one is familiar with their normal position, a skill that is acquired after only a few operations. The first trochar is placed at the inferior apex of the scapula while the anesthetist suspends respirations. Once placed, carbon dioxide (CO_2) insufflation is instilled at a pressure of 12 mmHg. A 5 mm, 30-degree angled scope is used to assess for successful trochar placement. Once the surgeon is satisfied, respirations can be resumed. In all, this initial step generally takes less than 1 minute. Next, the second trochar is placed two intercostal spaces inferior to the first and about 2 cm medially (*Figure 2*). It may also be placed two intercostal spaces superior to the first in the event there is elevation of the hemi-diaphragm. A third trochar may be used if needed, but this is rarely the case. The surgeon will then turn his or her attention to the posterior thorax to identify the sympathetic trunk. The arch of the aorta is used as a landmark, above which the splanchnics do not lie. The costophrenic angle is seen as well, below which the splanchnics are never found. The splanchnic nerves are seen running in an inferior and medial position from the sympathetic trunk (*Figure 3*). Once the splanchnics are identified, a small opening is made in the pleura on either side of the nerve with a right angle cautery. To avoid the risk of bleeding, the nerve is divided on the corpora of the vertebral body between the intercostal vessels. We recommend lifting the nerve with the right angle cautery so that division is obvious once the nerve recedes into the pleura (*Figure 4*). There are typically two to five nerves easily found on each side. After searching for

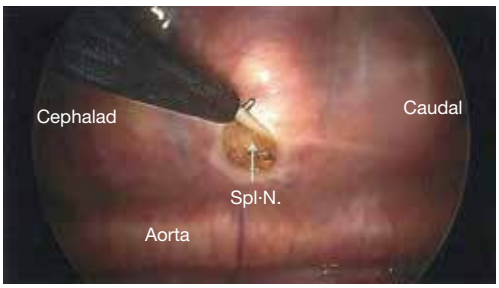

Figure 4 Thoracoscopic view of left-sided splanchnic nerve (Spl N.) lifted from pleura prior to division with hook cautery is demonstrated.

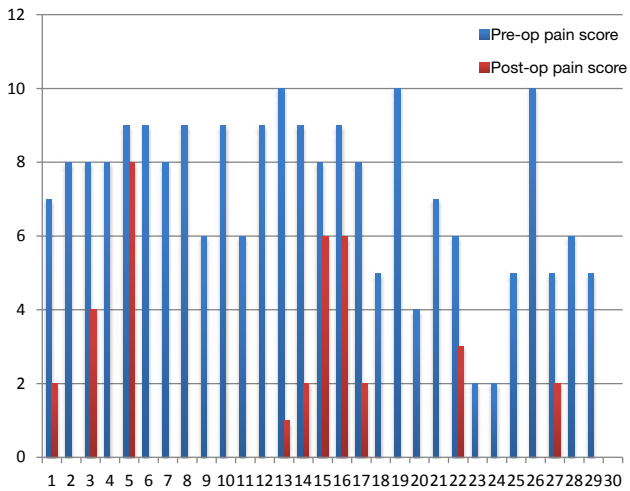

Figure 5 Histogram of pre-operative and post-operative visual analog pain scores of patients who underwent bilateral thoracoscopic splanchnicectomy at Greenville Health system.

and dividing all of the nerves, the insufflation is released, a rubber catheter is placed into the hemithorax, and large tidal volumes are given by the anesthetist. The exterior end of the rubber catheter is placed under water at the level of the skin, creating a water seal. Once the lungs are fully re-inflated, the trochars and catheter are removed, the skin incisions closed, and the procedure is repeated on the right side.

At this point, the patient is awakened and a chest X-ray is performed in the recovery room to assess for retained CO_2. If the patient is stable, even in the presence of pneumothorax, observation is safe and an X-ray should be repeated on post-operative day 1. In the event the patient is unstable during or after emergence from anesthesia, urgent X-ray in the operating room (if possible, quickly) and auscultation of the chest are used to assess for tension pneumothorax. A chest thoracostomy tube is then placed on the affected side. We admit our patients for overnight observation in a non-telemetry room; however, outpatient procedures have been reported without complication. Operative time is usually less than 1 hour and the total hospital length of stay rarely exceeds 1 post-operative day.

Literature

Outcomes of splanchnicectomy for palliation of pain associated with pancreas cancer are encouraging. Results of this procedure for chronic pancreatitis are more readily available in the literature but remain sparse for the treatment of malignant pancreatic disease. Pietrabissa *et al.* reported on 20 patients who experienced significant improvement in visual analog scores for at least 3 months post-operatively (25). In a study by Lică *et al.*, similar outcomes on another 15 patients were demonstrated (26). At the 2010 Asian Pacific Hepato-Pancreato-Biliary meeting. Vitale *et al.* presented data on 36 patients who underwent BTS for pancreatic cancer. In that study, mean survival was 229 days and average pain scores dropped from 8.3 to 2.0 on a 0-10 scale. The quality of life survey on these same patients, however, only demonstrated a limited improvement. At our institution we internally reviewed the first 29 patients who underwent BTS. We too found a significant decrease in patient pain scores post-operatively (4.1 to 1.1; P value =0.004) (*Figure 5*).

Complications

Complications of splanchnicectomy are rare, occurring in less than 2% of patients. Similar to other thoracoscopic procedures, specific complications include pneumothorax, chylothorax, hemothorax, need for thoracotomy, persistent pain, transient hypotension, and diarrhea (3). Pneumothorax was the most commonly reported complication, as two out of the 92 patients reviewed required an unplanned thoracostomy tube.

Conclusions

Pancreatic cancer is a pervasive disease that is often incurable. As a result, pain control is a key component of palliation of this disease. Given the side effects of high-dose narcotics, interventional approaches focused on neurolysis and/or neurectomy are attractive options. This can be

done using a variety of approaches, each of which has been shown to be efficacious with minimal morbidity. Currently published data is heterogeneous, and head-to-head comparisons of each is lacking. Regardless, each approach appears to be safe, effective, and technically easy to perform. There is little reason any patient with this disease should suffer from abdominal pain without an attempt at either celiac plexus block or splanchnicectomy.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Quality-of-life (QoL) as a predictive biomarker in patients with advanced pancreatic cancer (APC) receiving chemotherapy: results from a prospective multicenter phase 2 trial

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Purpose: Pancreatic cancer is rapidly fatal with median survival of only 6 months (mo). Quality-of-life (QoL) was analyzed prospectively in a phase 2 study of gemcitabine (G), capecitabine (C) and bevacizumab (B) in APC patients.

Methods: A total of 50 patients with APC received B 15 mg/kg, C 1,300 mg/m^2 daily for 2 weeks and G 1,000 mg/m^2 weekly 2 times; cycles were repeated every 21 days. Endpoints: progression free survival (PFS), overall survival (OS) and assessment of QoL prior to each cycle using the European organization for research and treatment of cancer (EORTC) PAN-26 QoL questionnaire. An exact 95% confidence interval (CI) (Clopper-Pearson method) was used to assess rate of improved QoL (defined as >5 % decrease in two consecutive scores compared with baseline).

Results: Patient characteristics- Stage IIB/III/IV: 3/5/42; Sex: 28 M/22 F; Median age: 64 years. QoL in patients- improved: 56%, no improvement: 24%; unevaluable: 20%. Median PFS: 5.8 mo, OS: 9.8 mo. QoL improvement rate: 28/40=0.7 (95% CI: 0.53-0.83) in evaluable patients. Using QoL improvement rate, no significant difference was seen in patients with OS ≥6 mo compared to OS <6 mo. However QoL scores at 3 and 6 weeks from start of treatment correlated strongly with ≥6 mo survival (P value 0.0092 and 0.0081, respectively).

Conclusions: Baseline score and change in QoL scores of patients on G, C and B were not predictive of survival ≥6 mo. Post treatment scores at 3 and 6 weeks from start of therapy however, were predictive of survival ≥6 mo suggesting the potential predictive value of this tool for use in future studies.

Keywords: Quality of life (QoL); pancreatic cancer; biomarkers; neoplasm, European organization for research and treatment of cancer (EORTC); palliative care; supportive oncology; outcomes; pancreas

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Introduction

Pancreatic cancer is the fourth leading cause of cancer death in men and women in the United States (1). This cancer is characterized by aggressiveness and high mortality rates that nearly parallel its incidence. This is a challenging disease in many ways. Due to the anatomical location of the pancreas, initial signs of cancer are easily missed by both the patient and the doctor. To date there is no screening method for early detection. As a result, at diagnosis, 30% of patients with pancreatic cancer are unresectable stage 3 locally advanced (2). While there have been some advances in the treatment options of pancreatic cancer, there has only been a dismal increase from 2% to 6% in 5-year pancreatic cancer survival rates from 1975-2008 (1).

When success of treatment options and their impact on traditional outcomes such as progression free survival (PFS)

or overall survival (OS) is so limited, the focus of treatment should shift towards better quality-of-life (QoL).

Our study has found that demonstration of an improved QoL, using a well validated tool, of patients while on treatment can predict which patients will have prolonged survival at a stage earlier than most other prognostic/predictive biomarkers currently used in APC. This is a step beyond simply incorporating QoL as an endpoint in cancer trials.

Methods

A total of 50 patients with advanced pancreatic cancer were enrolled in a phase II study of bevacizumab 15 mg/kg, capecitabine 1,300 mg/m^2 daily for 2 weeks and gemcitabine 1,000 mg/m^2 weekly 2 times; cycles were repeated every 21 days.

All patients provided written informed consent before study enrollment. Adult patients with previously untreated metastatic or locally advanced unresectable pancreatic cancer, Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, normal blood counts (leucocytes >3,000 per μL, neutrophils >1,500 per μL, platelets >100,000 per μL) and chemistries (bilirubin <2 mg per 100 mL, AST/ALT <5 times upper limits of normal, creatinine <1.5 mg per 100 mL) were included. Prior adjuvant therapy was permitted if completed >6 months before enrollment. Exclusion criteria included proteinuria, pregnancy, lactation, bleeding diathesis, uncontrolled hypertension or cardiovascular disease, brain metastases or recent surgery.

Pretreatment evaluations included complete history and physical exam, complete blood count, chemistry including liver function tests, prothrombin time, pregnancy test for women and 12-lead electrocardiography. Urine protein/creatinine ratio was measured at baseline and every 6 weeks. History and physical exam were performed every 3 weeks. Complete blood count, serum CA 19-9 level and serum chemistries (including liver function tests) were measured on day 1 of each treatment cycle. Computed tomography scans to assess tumor size and response were obtained every 6 weeks.

Gemcitabine was administered in a dose of 1,000 mg/m^2 intravenously over 30 min on days 1 and 8; capecitabine 650 mg/m^2 twice daily was administered on days 1-14 and bevacizumab 15 mg/kg was administered after gemcitabine on day 1 of a 21-day cycle. Treatment was continued until disease progression, death or toxicity. A maximum of 1 year of bevacizumab therapy was permitted. However, patients could receive gemcitabine and capecitabine beyond 1 year if indicated. Institutional review board approval was obtained for this study.

The PFS was defined as the length of time during and after treatment in which the patient remained alive with cancer without disease progression. OS was defined as the time from treatment initiation until demise. Responses were estimated using the response evaluation criteria in solid tumors (RECIST) (3). QoL was assessed using the EORTC PAN-26 QoL questionnaire which was administered at baseline and then after every treatment cycle.

An exact 95% confidence interval (CI) using the Clopper-Pearson method was given for the rate of improved quality of life. The definition of improved quality of life was as follows: a greater than 5% decrease in two consecutive scores compared with the baseline score. Two sample *t*-test was used to compare the two survival groups for baseline, 3-week and 6-week quality of life scores. Fisher's exact test was used to compare the two survival groups for categorical variables. The estimated overall and PFS distributions were obtained using the Kaplan-Meier method. Ninety-five percent CI for the median overall and PFS were calculated using Greenwood's formula. Statistical assessment of observed differences in the survival distributions between improved and un-improved quality of life groups was done using the log-rank test. A 0.05 nominal significance level was used in all testing. All statistical analyses were done using SAS (version 9.4).

Results

A total of 50 patients from three institutions were enrolled in this study between 7 September 2004 and 3 March 2007. The median follow-up duration was 8-9 months. Median age of the patients was 64 years (range, 38-83 years), 28 males and 22 females, 3/50 (6%) had locally advanced cancer while the remaining 47 (94%) had metastatic disease at the time of enrollment.

A total of 348 cycles were administered. Median number of cycles delivered was 6 (range, 1-18). Reasons for treatment discontinuation in all 50 patients were as follows: one patient completed the 1 year of bevacizumab (2%), 24 patients had disease progression (48%), 18 patients experienced toxicity of the drugs (36%) and 4 patients died while on treatment (8%). Of the last 3 patients (6%), 1 had symptomatic deterioration, 1 had open wounds and 1 was at the discretion of the investigator.

All 50 patients were included in an intention-to-treat survival and response analysis. The radiological responses

Table 1 Survival and toxicities in patients in cycle 1 and cycle 2

Cycle	Survival	Level	Grade 3/4/5 toxicity		Overall, n (%)	P value
			No, n (%)	Yes, n (%)		
1	OS 6 mo	<6 mo	12 (32.4)	2 (20.0)	14 (29.8)	0.6997
		≥6 mo	25 (67.6)	8 (80.0)	33 (70.2)	
2	OS 6 mo	<6 mo	10 (30.3)	2 (16.7)	12 (26.7)	0.4660
		≥6 mo	23 (69.7)	10 (83.3)	33 (73.3)	

OS, overall survival; mo, months.

were independently confirmed by the Response Review Committee. There was a response rate (RR) of 11/50 (22%) in this trial. RR was obtained by adding patients with complete response (CR) and partial response (PR). 30 patients (60%) had stable disease (SD), 5 patients (10%) had progressive disease (PD) and the remaining 4 patients (8%) had clinical disease progression. The median PFS was 5.8 months (95% CI: 4.2-7.8 months) and the median OS was 9.8 months (95% CI: 7.6-11.9 months). 1-year survival was 35.5% (95% CI: 21.7-49.5%) and 1-year PFS was 19% (95% CI: 9.4-31.6%).

Patients who suffered Grade 3/4/5 toxicities during the first two cycles of treatment, defined as neutropenia, thrombocytopenia, thromboembolic events, hypertension and hemorrhage, were divided into two groups according to 6-month survival as shown in *Table 1*. There was no significant difference between the frequency of grade 3/4/5 toxicities suffered by patients in the two survival groups after cycle 1 and cycle 2 of treatment, with P value of 0.6997 and 0.4660 respectively.

QoL was assessed using the EORTC PAN-26 QoL questionnaire which was administered at baseline and then after every treatment cycle. The lower the score, the better the quality of life. QoL was considered improved if there was a >5 % decrease in two consecutive scores compared with baseline, unimproved if none or ≤5% decrease and not-evaluable if less than three questionnaires were filled. A total of 28 patients showed improvement (56%), 12 patients showed no improvement or unimproved (24%) and 10 patients were not evaluable (20%).

Therefore among the 40 patients whose QoL could be assessed, the improvement rate was 0.7% (95% CI: 0.53-0.83) with P value (one sample proportion test comparing with 0.5 or 50% improvement rate) of 0.017. Among 'improved' individuals mean duration (until the score less than 5% decrease after showing the first improvement) was 3.0 survey times (median 2.0, SD 1.53) and mean number of showing the score greater than 5% decrease throughout the study was 5.7 survey times (median 5.0, SD 3.6). Average time between surveys was 22.45 days (Median 21.93). Thus, 3.2 survey times can be translated to 71.84 days.

Median PFS for patients with unimproved QoL was 6.6 months (95% CI: 2.2-8.3) and for patients with improved QoL it was 7.1 months (95% CI: 4.5-9.8) with log rank test P value of 0.641 (*Figure 1A*).

Median OS for patients with unimproved QoL was 7.9 months (95% CI: 3.1-17.4) and for patients with improved QoL it was 11.3 months (95% CI: 9.1-14.5) with log rank test P value of 0.5501 (*Figure 1B*).

QoL plot was formulated as shown in *Figure 2*, representing data from the 46 patients who had an evaluable response to treatment. Of note, the QoL score of 96 is worst and 0 is best.

QoL analysis: (total 40 evaluable patients)

Using rate of QoL improvement, no significant difference was seen in patients with OS ≥6 months compared to OS <6 months (P=0.1680), as shown in *Table 2*.

Score comparison by visits: (note: The lower score, the better QoL)

QoL scores at initial visit were not related to survival, however QoL scores at visit 2 and visit 3 correlated strongly with ≥6 month survival and achieved statistical significance (Visit 2: P=0.0092; Visit 3: P=0.0081), as shown in *Table 3* and *Figure 3A-C*.

Discussion

This study found that gemcitabine, capecitabine and bevacizumab in patients with APC was associated with

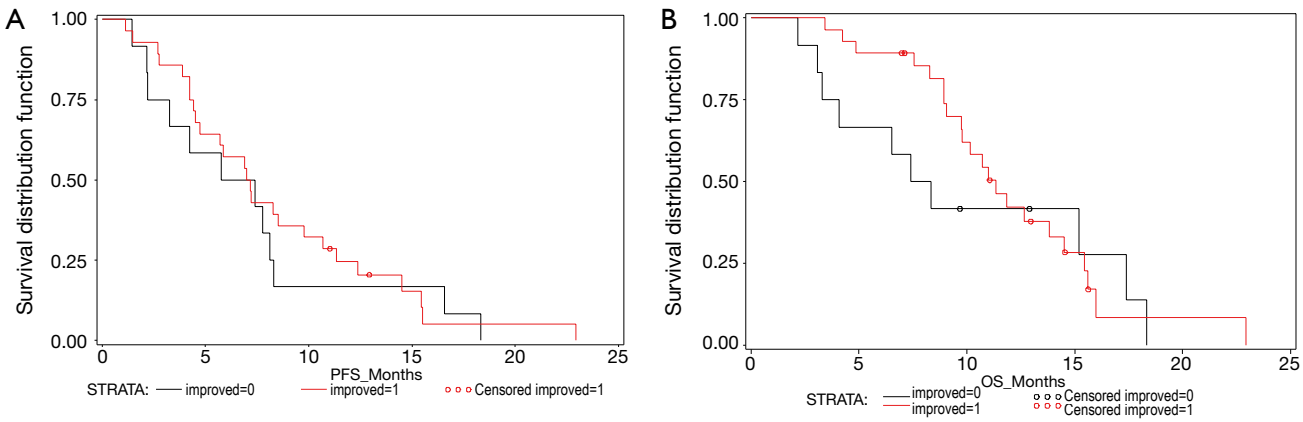

Figure 1 (A) Progression free survival (PFS) curve. Unimproved (black), improved (red); (B) Overall survival (OS) curve. Unimproved (black), improved (red).

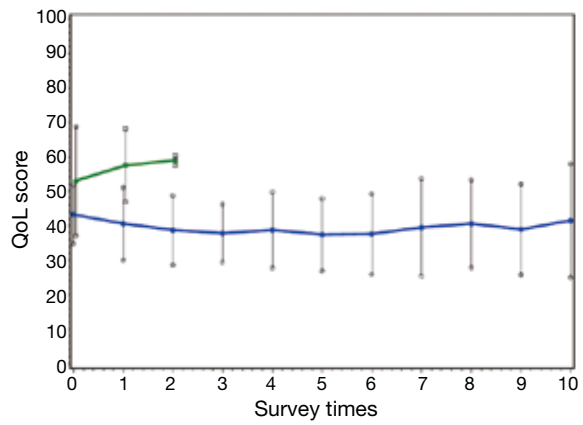

Figure 2 Quality-of-life (QoL) plot. At baseline (time 0): progressive disease (PD) (green) represents 5 pts, and complete response (CR) + partial response (PR) + stable disease (SD) (blue) represents 41 pts, total of 46 pts data. Vertical lines for each point indicate standard deviation. For Green, the last point (at 2) has only 2 pts. For Blue, the last point (at 10) has about 10 pts data. Average days between surveys are 22.5 days.

Table 2 QoL analysis

Survival	Level	QoL		Overall	P value
		Improved	Unimproved		
OS 6 mo	<6 mo	3	4	7	0.1680
	≥6 mo	25	8	33	
Total		28	12	40	

QoL, quality-of-life; OS, overall survival; mo, months.

median PFS of 5.8 months, median OS of 9.8 months and improved QoL. Baseline score and change in QoL scores were not predictive of survival ≥6 months. However post treatment QoL scores at 3 and 6 weeks from start of therapy were predictive of survival ≥6 months suggesting the potential predictive value of this tool.

The results support our original hypothesis that better QoL can be associated with improved survival in patients with APC, more specifically once the patients have started receiving treatment. This provides the backbone for introducing QoL as a predictive biomarker in pancreatic cancer. Predictive markers are the most clinically informative, since they directly influence patient outcomes by optimizing therapy (4).

Traditionally the choice to undergo cytotoxic therapy in pancreatic cancer is based on analysis of various prognostic and predictive markers such as patient's age, performance status, baseline albumin levels, WBC, BUN, bilirubin, AST, LDH, CRP and CA 19-9 (5-7). However, when there are many treatment options available, all with associated risks and toxicities, and the benefits to the patient remain unclear, as with APC, there is a need for alternate markers to further stratify these patients and help drive the decision of who would be a better candidate for chemotherapy. As an example, patients with ECOG PS of 0 and 1 have increased chances of favorable outcomes on chemotherapy as compared to patients with ECOG PS of ≥2. By the addition of QoL in our trial we were able to additionally classify prognosis even amongst patients with ECOG PS 0-1.

While increasingly sophisticated methods are being

Table 3 QoL scores at subsequent clinic visits, correlated with ≥6 mo survival

Visit	95% two-sided CL	QoL scores		P value
		≥6 mo survival	<6 mo survival	
1 (initial day of treatment)	Lower			0.0880
	Mean	39.314	39.705	
	Std Dev	6.0914	9.8603	
	Mean estimate			
	Mean	42.000	53.857	
	Std Dev	7.5746	15.302	
	Upper			
	Mean	44.686	68.009	
	Std Dev	10.019	33.695	
	Std Err	1.3186	5.7835	
	Total	33	7	
2 (3 weeks into treatment)	Lower			0.0092
	Mean	35.635	45.359	
	Std Dev	8.6039	6.6266	
	Mean estimate			
	Mean	39.759	56.500	
	Std Dev	10.842	10.616	
	Upper			
	Mean	43.883	67.641	
	Std Dev	14.663	26.037	
	Std Err	2.0133	4.334	
	Total	29	6	
3 (6 weeks into treatment)	Lower			0.0081
	Mean	33.124	40.988	
	Std Dev	6.6836	5.8808	
	Mean estimate			
	Mean	36.481	49.429	
	Std Dev	8.487	9.1261	
	Upper			
	Mean	39.839	57.869	
	Std Dev	11.631	20.096	
	Std Err	1.633	3.4493	
	Total	27	7	

QoL, quality-of-life; mo, months; CL, confidence limits.

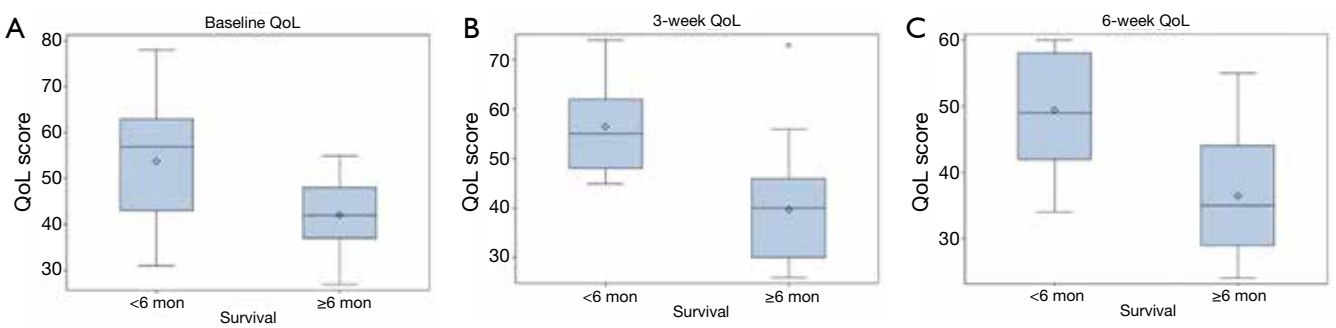

Figure 3 A Quality-of-life (QoL) scores at visit 1 (initial day of treatment); (B) QoL scores at visit 2 (3 weeks into treatment); (C) QoL scores at visit 3 (6 weeks into treatment).

employed for such further stratifications, such as assessment of genetic mutations that may predict response to certain chemotherapies in APC, namely mutations in *BRCA1*, *BRCA2* (8) and the *PALB2* gene (9), QoL scoring remains a simple yet greatly underestimated tool for guiding therapy in patients with APC, and perhaps for all kinds of cancers. This is not entirely unexpected as QoL still struggles to find its place as a designated endpoint in cancer trials, let alone being taken a step further, as in our study, to guide patient management. In 2006, Panzini *et al*. analyzed 405 randomized, controlled clinical trials (RCCTs) according to the level of importance of QoL as a measure of outcome (primary, important and secondary) and found the disappointing conclusion that more attention to QoL in all components of RCCTs (design, choice of instruments, data management and processing) was required from both clinicians and statisticians (10).

The strengths of this study lie in the fact that this is a prospective, multicenter trial which utilized a well validated tool for measuring QoL, the European organization for research and treatment of cancer (EORTC) PAN 26 QoL questionnaire (11). Unlike other biomarkers derived from blood or radiological imaging, which may be invasive and costly, measurement of QoL is quick, free of cost and allows patients to contribute significantly to their own care. Furthermore, no other biomarkers can give reliable predictive information at such precise points in time and in such a short interval from the start of treatment, such as 3 and 6 weeks as demonstrated in our trial. Patients have typically already suffered toxicities and increased morbidity over months before traditional markers are able to predict unfavorable outcomes and treatment ceased.

As clinicians typically neglect QoL, they instead use surrogate markers such as toxicities to decide whom to exclude from treatment. As shown in our results, grade 3/4/5 toxicities suffered by patients was in no manner predictive of 6-month survival, highlighting this as a poor replacement of better predictive and prognostic tools available.

Some physicians may argue that QoL remains a highly subjective measure and dependent on individual needs; for example lack of sexual drive scored more leniently by elderly patients compared to the younger. However it is to be noted that the landmark trial conducted by Burris *et al*. in 1996, which led to gemcitabine becoming the reference regimen for APC, used OS and improvement in tumor-related symptoms, including pain, as endpoints. The authors note that at the time of the study had a disease-specific QoL instrument been available, it could have given them a way to measure both disease-related as well as drug-related symptoms (12). More recently in 2011, QoL was again used as a measurable end point in a study comparing the combination chemotherapy consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) to gemcitabine as first-line therapy in patients with metastatic pancreatic cancer (13). These trials prove that measurement of QoL is not only undoubtedly important but is also extremely feasible as they were conducted across multiple institutions.

Also, by placing the emphasis on better QoL physicians are making sure that patients are able to carry out their lives in a manner as comfortable as possible and can then address psychosocial aspects that often get neglected in cancer patients or end-of-life care. When physical symptoms and suffering are controlled, it is easier to address patients' concerns regarding psychological integrity, their families and about finding meaning in their lives. Enhanced understanding of the common psychological concerns of patients with serious illness can improve not only the clinical care of the patient, but also the physician's sense of satisfaction and meaning in caring for the dying (14).

We are in an era where there is emphasis on informed decision making based on all facts bring provided to the patient. Measuring outcomes with validated tools are essential to communicate the measured rather than perceived impact on QoL. Classically physician's interpretation relies on frequency of side effects rather than the psychosocial impact the diagnosis, complications, available support and treatment have.

As for future directions, the predictive value of QoL scores need to be studied further in the context of multiple chemotherapy regimens compared against each other. This way, when scores in the first few weeks remain unimproved, clinicians can give patients the choice to either cease treatment or switch to a different regimen. The effect of the new treatment should then again be continually assessed and measured in terms of improved or unimproved QoL. This can be accomplished if future comparative studies of various chemotherapy regimens for pancreatic cancer are structured to incorporate analysis of QoL at different stages during the trial.

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Change in CA 19-9 levels after chemoradiotherapy predicts survival in patients with locally advanced unresectable pancreatic cancer

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Purpose: RTOG 9704 demonstrated a prognostic role for postoperative CA 19-9 in patients with resectable pancreatic carcinoma following surgery. Our study aimed to investigate whether CA 19-9 provided similar prognostic information in patients with locally advanced unresectable pancreatic cancer (LAPC) treated with chemoradiotherapy (CRT) and to determine whether such endpoints should therefore be reported in future randomized trials.

Methods and materials: Between December 1998 and October 2009, 253 patients with LAPC were treated with 5-fluourouracil-based concurrent CRT at our institution. Median radiation dose was 50.4 Gy. Only patients with a bilirubin of less than 2 mg/dL at the time the CA 19-9 was evaluated were included in the analysis to avoid the confounding effect of hyperbilirubinemia. Of the eligible patients, 54 had pre and post CRT CA 19-9 values available. The median age was 68 years and 52% were female. Categorized versions of the first post-CRT CA 19-9 were tested in 50 point increments beginning at <50 to >1,000 and percent change in pre to post-CRT CA 19-9 using cut points of 10% increments from <0% (increased) to >90%. Survival was measured from the date of first post CRT CA 19-9 level until death or last follow-up. Univariate and multivariate statistical methodologies were used to determine significant prognostic factors for overall survival.

Results: Median CA 19-9 prior to CRT was 363 U/mL and post CRT median was 85.5 U/mL. Following CRT, patients with a decrease of >90% from their baseline CA 19-9 level had a significantly improved median survival than those that did not (16.2 *vs*. 7.5 months, P=0.01). The median survival of patients with a CA 19-9 level lower than the median post CRT value was 10.3 months, compared with 7.1 months for those with a CA 19-9 level greater than the median (P=0.03). Post CRT CA 19-9 less than 50 U/mL and histologic grade I-II also showed prognostic significance (both P=0.03). In multivariate analysis, post CRT CA 19-9 less than the median level of 85.5 U/mL was an independent prognostic factor for overall survival (HR 0.34; 95% CI, 0.13-0.85, P=0.02).

Conclusions: Our results indicate that post treatment CA 19-9 is predictive for overall survival in patient with LAPC following CRT. We recommend that pre and post treatment CA 19-9 levels be obtained in patients receiving CRT and that these values be considered for prognostic nomograms and future clinical trials.

Keywords: CA19-9; pancreatic cancer; chemoradiotherapy (CRT)

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Introduction

Most patients with adenocarcinoma of the pancreas present with metastatic disease or locally advanced unresectable pancreatic cancer (LAPC) that are defined as surgically unresectable at the time of diagnosis. With only about 1% of patients is still alive 5 years from the time of diagnosis, these patients have a very poor prognosis. Current therapeutic approaches for patients with LAPC include these of chemoradiotherapy (CRT) or chemotherapy (1,2). Tumor-associated antigens, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide, cancer antigen (CA) 125, and carbohydrate antigen (CA) 19-9 have been linked to pancreatic adenocarcinoma. CA 19-9 is a sialylated Lewis a blood group antigen most commonly expressed in pancreatic cancer as well as benign hepatobiliary disease.

Several studies have demonstrated a relation between the kinetics of CA 19-9 levels in patients with resectable pancreatic carcinoma undergoing surgery. Low postoperative serum CA 19-9 levels and a decrease in serial levels following surgery have been shown to correlate with survival (3). RTOG 9704 demonstrated a prognostic role for postoperative CA 19-9 levels in patients with resectable pancreatic carcinoma following surgery (4). The National Comprehensive Cancer Network recommends measurement of serum CA 19-9 level following surgery prior to the administration of adjuvant therapy. Although initial CA 19-9 levels have been shown to correlate with survival in patients with LAPC or metastatic disease, there is conflicting evidence regarding the predictive value of peri-treatment CA 19-9 levels in patients with LAPC treated with radiotherapy or chemotherapy (5-8). In patients who receive chemoradiation for LAPC, data is limited regarding the prognostic significance of peri-treatment CA 19-9 (9-11).

Our study aimed to investigate whether CA 19-9 provides prognostic information in patients with LAPC treated with CRT and to determine whether such endpoints should be reported in future randomized trials. This could help to identify patients who may likely benefit from various therapeutic strategies.

Methods

Patients

From December 1998 to October 2009, 253 consecutive patients with pancreatic adenocarcinoma treated at Roswell Park Cancer Institute (RPCI) were identified. All patient data were entered retrospectively by a single investigator after approval from the hospital institutional review board. Of the 253 patients, 159 underwent treatment with CRT or chemotherapy alone. Patients with metastatic disease at presentation and those who underwent surgery for definitive resection were excluded. Patients with islet-cell tumors and mucinous cystadenocarcinoma were also excluded from the analysis.

The variables evaluated included age, gender, race, Eastern Cooperative Oncology Group performance status, weight loss >10%, chemotherapy regimen, grade 3-4 toxicity, tumor diameter, and tumor location, T stage, nodal status, histologic grade, hemoglobin at diagnosis, pre and post CRT CA 19-9 and percent change from pre and post CRT. Stage was determined according to the American Joint Committee on Cancer staging system 6th edition (12). Patient data was obtained through the tumor registry and review of medical records and abstracted by a single investigator.

To avoid false-positive elevation of serum CA19-9 due to hepatobiliary diseases, chronic pancreatitis, obstruction of the common bile duct, all CA l9-9 levels were matched to a concomitant bilirubin to ensure biliary obstruction was not affecting the interpretation of CA 19-9 concentration. Patients with a serum bilirubin more than 2 mg/dL at the time of CA 19-9 measurement were excluded. The median pre-CRT CA 19-9 and post-CRT values were obtained. This was tested in 50 point increments beginning at <50 to ≥1,000. Percent change in pre to post-CRT CA 19-9 levels were calculated as follows: [(pre-CRT CA 19-9)-(Post-CRT CA 19-9)]/(pre-CRT CA 19-9) and were tested using cut points of 10% increments were from <0% (increased) to ≥90%.

Statistical analysis

Survival was measured from the date of first post CRT CA 19-9 level until death or last follow-up to ensure meaningful interpretation for the variable when evaluating a decrease in value. Progression free survival was calculated from date of first post CRT CA 19-9 level until recurrence as evidenced by radiographic imaging. Initial (univariate) log-rank tests were performed to determine the predictive value of categorized versions of the first post-CRT CA 19-9. Univariate and multivariate statistical methodologies were used to determine significant prognostic factors for overall survival.

The Kaplan-Meier method was used to obtain overall survival and recurrence free survival estimates while survival was compared between groups using the log-rank test. P values for multiple comparison were adjusted using the

Table 1 Patient and treatment characteristics

Characteristics		Number (%) n=54
Age	<65	23 (42.6)
	≥65	31 (57.4)
Sex	Male	26 (48.2)
	Female	28 (51.9)
Race	White	50 (92.6)
	Nonwhite	4 (7.4)
ECOG	0-1	51 (94.4)
	2	3 (5.6)
Weight loss >10%	Yes	33 (64.7)
	No	18 (35.3)
Chemo regimen	Gem	46 (85.2)
	Non-Gem	8 (14.8)
T stage	T4	34 (63.0)
	T3	20 (37.0)
Node status	Negative	32 (59.3)
	Positive	22 (40.7)
Grade 3-4 toxicity	Yes	9 (16.7)
	No	45 (83.3)
Tumor >30 mm	Yes	37 (69.8)
	No	16 (30.2)
Tumor location	Head	31 (57.4)
	Body/Tail	10 (18.5)
	Overlap	11 (20.4)
	Other	2 (3.7)

method developed by Lausen and Schumacher (13). Values for continuous variables are given as median (range). Values for categorical data are specified as frequency (percent). Statistical Analysis was performed using SAS Statistical analysis software version 9.2 (SAS Institute Inc, Cary, NC, USA). A nominal significance level of 0.05 was used.

Results

Patient and treatment characteristics

Of 116 patients, 84 underwent CRT and 32 received chemotherapy alone. Of the 84 patients that underwent CRT, 54 patients had available pre and post CRT CA 19-9 levels and a bilirubin of less than 2 mg/dL at the time the CA 19-9 was measured. The characteristics of the patients are shown in *Table 1*.

The median follow up was 7.15 months (range, 3.0-10.6 months). The median pre-CRT Ca 19-9 level was 363.7 and the median post CRT CA 19-9 level was 85.5. Median time from the end of RT to post CRT CA 19-9 was 35.89 days (range, 0.00-168.81 days). CA 19-9 values ranging from 50-1,000 were tested in 50 point increments and % change was tested in 10% increments (*Tables 2,3*).

Patient characteristics including age, sex, race, performance status, weight loss >10% were tested and not statistically significant on univariate analysis. Tumor and treatment factors including chemo regimen, T stage, node status, grade 3-4 toxicity, tumor >30 mm, and tumor location were tested and not statistically significant. On univariate analysis, post CRT CA 19-9 <50, postCRT CA 19-9 <85.5, percent change ≥90%, and histologic grade all showed prognostic significance (*Table 4*).

The median survival of patients with a postCRT CA 19-9 level <85.5 U/mL was 10.3 months compared with 7.1 months in patients with higher levels (P=0.0242) (*Figure 1*). The median survival of patients with a decrease in CA 19-9 of >90% post CRT was 16.3 months compared with 7.5 months in those with a <90% post CRT CA 19-9 change (P=0.0179) (*Figure 2*). The median survival of patients with a post CRT CA 19-9 levels <50 U/mL was 11.1 months compared with 7.1 months in patients with levels ≥50 U/mL (P=0.0287)

On multivariate analysis, post CRT CA 19-9 <85.5 U/mL was an independent prognostic factor for overall survival (HR 0.34, 95% CI, 0.13-0.85, P=0.0216) (*Table 5*).

Discussion

The majority of patients with pancreatic cancer present with unresectable disease and appropriate selection of patients for CRT continues to be a challenge and the treatment of LAPC continues to evolve. Analysis of prognostic factors may be useful in determining which patients would benefit from intensification of therapy and designing future clinical trials.

CA 19-9 is the most common and important tumor marker used in for patients with pancreatic cancer. There have been many studies evaluating CA 19-9 as prognostic for resectable pancreatic cancer. RTOG 9704 demonstrated a prognostic role for postoperative CA 19-9 in patients with resectable pancreatic carcinoma following surgery. With a post-resection CA 19-9 higher than 90 U/mL, patients had a highly significant increased risk of death (HR, 3.34; P<0.0001) compared with those with a value less

Table 2 First post-CRT CA 19-9 level in increments of 50

Variable	Median survival	P-value	No. of patients	Median RFS	P-value	No. of patients
<50	11.0710 (7.1945,14.4875)	0.0661	23	8.5085 (4.4678,14.36)	0.30735	23
≥50	7.0959 (4.4678,8.5742)		31	5.4534 (4.1721,7.8844)		31
<100	8.5742 (7.1945,14.3890)	0.12986	29	7.6873 (4.7963,12.2208)	0.42710	29
≥100	7.0959 (4.1721,8.7714)		25	5.4534 (2.8252,7.8844)		25
<150	8.5742 (7.0959,14.3561)	0.19159	31	7.6873 (5.0920,11.0710)	0.51395	31
≥150	5.5191 (4.1721,8.7714)		23	5.4534 (2.8252,8.7714)		23
<200	8.5414 (7.0959,14.3561)	0.30101	32	7.1945 (5.0920,11.0710)	0.66898	32
≥200	7.4901 (3.6137,9.1327)		22	5.0591 (2.7267,8.7714)		22
<250	8.5414 (7.0302,12.2208)	0.42058	34	7.0959 (4.7963,8.5742)	1.0000	34
≥250	7.4901 (2.8252,9.1327)		20	5.4534 (2.7267,9.1327)		20
<300	8.5414 (7.0302,12.2208)	0.42058	34	7.0959 (4.7963,8.5742)	1.0000	34
≥300	7.4901 (2.8252,9.1327)		20	5.4534 (2.7267,9.1327)		20
<350	8.5742 (7.0959,12.2208)	0.25902	36	7.1945 (5.0920,9.4284)	0.91659	36
≥350	5.4534 (2.8252,8.7714)		18	5.0591(2.7267,8.7714)		18
<400	8.5742 (7.0959,12.2208)	0.25902	36	7.1945 (5.0920,9.4284)	0.91659	36
≥400	5.4534 (2.8252,8.7714)		18	5.0591 (2.7267,8.7714)		18
<450	8.5414 (7.0302,11.4652)	0.89806	38	7.0959 (4.7963,8.5742)	1.0000	38
≥450	7.4901 (2.8252,9.1327)		16	5.4534 (2.0039,9.1327)		16
<500	8.5414 (7.0302,11.4652)	0.89806	38	7.0959 (4.7963,8.5742)	1.0000	38
≥500	7.4901 (2.8252,9.1327)		16	5.4534 (2.0039,9.1327)		16
<550	8.5414 (7.0302,11.4652)	0.89806	38	7.0959 (4.7963,8.5742)	1.0000	38
≥550	7.4901 (2.8252,9.1327)		16	5.4534 (2.0039,9.1327)		16
<600	8.5414 (7.0302,11.4652)	0.89806	38	7.0959 (4.7963,8.5742)	1.0000	38
≥600	7.4901 (2.8252,9.1327)		16	5.4534 (2.0039,9.1327)		16
<650	8.5085 (7.0302,11.0710)	1.0000	39	7.0959 (4.4678,8.5742)	1.0000	39
≥650	7.5230 (2.8252,9.1327)		15	7.4901 (2.0039,9.1327)		15
<700	8.5085 (7.0302,11.0710)	1.0000	39	7.0959 (4.4678,8.5742)	1.0000	39
≥700	7.5230 (2.8252,9.1327)		15	7.4901 (2.0039,9.1327)		15
<750	8.5414 (7.0302,11.0710)	1.0000	40	7.0959 (4.7963,9.1327)	1.0000	40
≥750	7.4901 (2.8252,8.7714)		14	5.4534 (2.0039,8.7714)		14
<800	8.5414 (7.0302,11.0710)	1.0000	40	7.0959 (4.7963,9.1327)	1.0000	40
≥800	7.4901 (2.8252,8.7714)		14	5.4534 (2.0039,8.7714)		14
<850	8.5414 (7.0302,11.0710)	1.0000	40	7.0959 (4.7963,9.1327)	1.0000	40
≥850	7.4901 (2.8252,8.7714)		14	5.4534 (2.0039,8.7714)		14
<900	8.5085 (7.0302,11.0710)	1.0000	41	7.0959 (4.4678,8.5742)	1.0000	41
≥900	7.5230 (4.1721,10.5453)		13	7.4901(2.0039,10.5453)		13
<950	8.5085 (7.0302,11.0710)	1.0000	41	7.0959 (4.4678,8.5742)	1.0000	41
≥950	7.5230 (4.1721,10.5453)		13	7.4901 (2.0039,10.5453)		13
<1,000	8.5085 (5.7162,10.3154)	1.0000	42	7.0302 (4.4678,8.5742)	1.0000	42
≥1,000	7.5230 (4.172,10.5453)		12	7.4901 (1.2484,10.5453)		12

Table 3 Percent change in pre to post CRT CA 19-9 level

Variable	Median survival	P-value	No. of patients	Median RFS	P-value	No. of patients
<0% (increased)	5.0591 (2.726,17.477)	1.0000	12	4.4678 (2.7267,5.0591)	0.28719	12
≥0% (decreased)	7.8844 (7.095,10.315)		42	7.6873 (5.519,9.132)		42
<10%	5.0591 (2.726,17.477)	1.0000	13	4.4678 (2.726,7.194)	0.26456	13
≥10%	8.5085 (7.095,10.315)		41	7.6873 (5.453,9.428)		41
<20%	7.1945 (3.613,14.487)	1.0000	15	4.4678 (2.825,8.771)	1.0000	15
≥20%	7.8844 (7.030,10.315)		39	7.4901 (5.453,9.132)		39
<30%	7.8844 (4.467,14.487)	1.0000	19	5.0591 (3.613,9.428)	1.0000	19
≥30%	7.6873 (5.716,10.315)		35	7.0959 (5.092,8.574)		35
<40%	7.8844 (4.467,9.428)	1.0000	22	5.0920 (3.613,8.771)	0.90931	22
≥40%	7.6873 (7.030,11.071)		32	7.4901 (4.796,11.071)		32
<50%	7.8844 (4.467,10.315)	1.0000	25	5.0920 (3.613,8.508)	0.42786	25
≥50%	7.6873 (7.030,11.465)		29	7.6873 (4.796,11.071)		29
<60%	7.1945 (5.059,9.428)	1.0000	27	5.0920 (3.613,7.884)	0.15978	27
≥60%	8.5414 (7.030,11.465)		27	8.5414 (4.796,11.465)		27
<70%	7.6873 (5.519,9.428)	0.87356	33	7.0959 (4.467,8.508)	0.29637	33
≥70%	8.5742 (4.172,12.220)		21	8.5742 (2.825,12.220)		21
<80%	7.6873 (5.519,9.428)	1.0000	38	5.9790 (4.467,8.508)	0.46802	38
≥80%	8.5742 (2.003,12.220)		16	8.5742 (0.788,12.220)		16
<90%	7.5230 (5.519,8.771)	0.017853	48	5.9790 (4.467,7.687)	0.0066	48
≥90%	16.2615 (8.574,52.825)		6	16.2615 (8.574,52.825)		6

than or equal to that cutoff. This was the most important predictor of death in this cohort of patients. The results of this analysis of postoperative CA 19-9 level are important because they clearly identify a subgroup of patients who have a much higher risk of death after surgery with curative intent.

In patients receiving systemic chemotherapy for metastatic disease as well as LAPC, CA 19-9 levels have also been shown to be of prognostic significance in terms of overall survival. Tsavaris *et al.* demonstrated through multivariate analysis CA 19-9 levels of >30 times the normal limit had a significant independent effect on survival (5). Serum CA 19-9 alterations have been defined in a number of ways. In a study by Takahashi *et al.*, they developed a new classification utilizing pretreatment CA 19-9 and proportional alteration of CA 19-9 2 months after the initiation of treatment (14) Their categories were defined as: I (increased), MD (modestly decreased), and SD (substantially decreased). In a study by Halm *et al.*, a decrease of CA 19-9 during chemotherapy with gemcitabine predicted overall survival time in patients with advanced pancreatic cancer (8). In their study, they found that a decrease in CA 19-9 of >20% had the greatest prognostic impact.

There is limited data identifying CA 19-9 as a prognostic factor in patients with LAPC treated with concurrent CRT as the primary therapy (10-11). In a study by Micke *et al.* patients with LAPC were treated with hyperfractionated accelerated radiotherapy to a total dose of 44.8 Gy combined with 5-fluorouracil and folinic acid. Patients with a pretreatment CA 19-9 less than the median of 420 U/mL had a better median survival versus those with levels greater than the median (12.3 *vs.* 7.1 months, P=0.0056) (10). The median post-treatment CA 19-9 level for all patients was 293 U/mL and also exhibited prognostic significance. The median survival of patients with a CA 19-9 less than the post-treatment median was 13.5 months compared with 7.2 months for those with a CA 19-9 level greater than the median (P=0.003). Patients with no decline in CA 19-9 had a significantly lower tumor response rate and a significantly worse overall survival (6 months compared to 13.9 months, P=0.0002). On multivariate analysis, pretreatment CA

Table 4 Univariate Analysis of prognostic factors associated with survival in patients with locally advanced pancreatic carcinoma

Variable	N	Median survival (months)	1-year survival rate (%)	Relative risk (CI)	P-value
Age (yrs)					0.3803
<65	23	7.5	32.6	0.76 (0.41-1.41)	
≥65	31	8.51	19.6		
Gender					0.1135
Male	26	7.1	18.0	1.63 (0.89-2.99)	
Female	28	9.4	32.4		
Race					0.2633
White	50	7.6	22.0	1.94 (0.59-6.34)	
Non-White	4	12.2	66.7		
ECOG					0.9425
0-1	51	7.8	25.5	0.93 (0.12-6.88)	
2	3	--	0		
Weight loss >10%					0.0566
Yes	33	7.0	14.8	1.94 (0.97-3.86)	
No	18	9.1	28.6		
Chemotherapy regimen					0.3023
Gemcitabine based	46	7.6	22.2	1.57 (0.66-3.76)	
Non-Gemcitabine based	8	8.5	37.5		
Grade 3-4 toxicity					0.0638
Yes	9	10.3	44.4	0.84 (0.39-1.76)	
No	45	7.6	20.01		
Tumor >30 mm					0.3453
Yes	37	7.7	30.1	0.71 (0.35-1.44)	
No	16	7.6	9.23		
Tumor location					0.6763
Head	31	7.2	24.7	Ref;	
Body/tail	10	11.5	38.1	0.67 (0.28-1.59);	
Overlap	11	7.5	18.2	1.21 (0.59-2.50);	
Other	2	--	0	0.84 (0.11-6.32)	
T stage					0.4630
T4	34	7.9	30.7	0.78 (0.48-1.48)	
T3	20	7.6	13.7		
Node status					0.7049
Negative	32	8.5	29.0	0.89 (0.48-1.63)	
Positive	22	7.7	20.2		
Pre-treatment CA 19-9 >1,000					0.1066
Yes	16	7.5	7.5	1.70 (0.88-3.26)	
No	38	8.5	32.8		
PostCRT CA 19-9					0.0287
<50	23	11.1	45.7	0.50 (0.26-0.94)	
>50	31	7.1	8.3		
PostCRT CA 19-9					0.0242
<85.5	27	10.3	43.9	0.50 (0.26-0.92)	
>85.5	27	7.1	8.6		
Percent change					0.0084
<90%	48	7.5	18.0	4.45 (1.33-14.79)	
>90%	6	16.3	80.0		
Histologic grade					0.0288
I-II	31	10.3	40.5	0.37 (0.15-0.90)	
III-IV	9	7.5	0		
Hemoglobin at diagnosis					0.3832
>12	44	7.9	27.7	0.70 (0.31-1.56)	
<12	10	7.6	12.7		

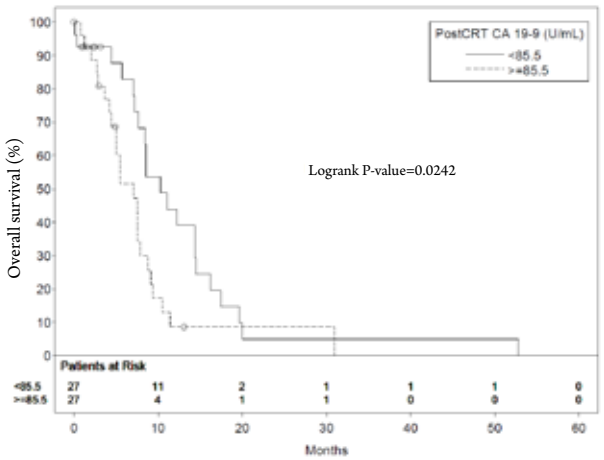

Figure 1 Median survival of patients with postCRT CA 19-9 level <85.5 U/mL compared with those with higher levels.

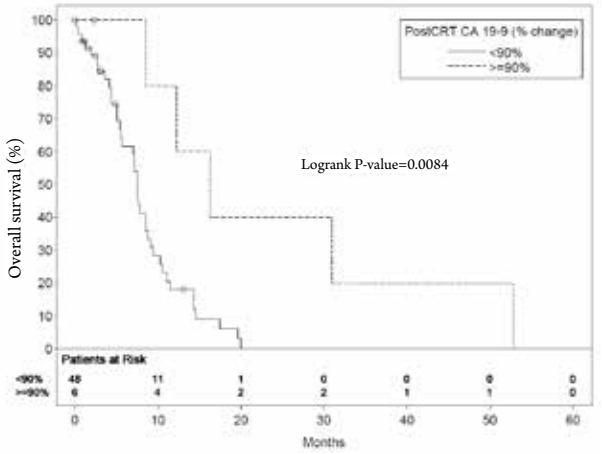

Figure 2 Median survival of patients with postCRT CA 19-9 level <90% increased compared with those with higher levels.

Table 5 Multivariate analysis for overall survival

	Hazard ratio (95% CI)	P-value
Post-CRT CA 19-9 (<50 *vs*. ≥50)	0.41 (0.14-1.22)	0.1081
Post-CRT CA 19-9 (<85.5 *vs*. ≥85.5)	0.34 (0.13-0.85)	0.0216
Percent change (<90% *vs*. ≥90%)	3.56 (0.81-15.66)	0.0935

19-9 values greater than and less than the median value of 420 U/mL, post-treatment CA 19-9 values, and a tumor marker decrease during therapy were significantly independent prognostic factors for overall survival. In another concurrent CRT with conventional fractionation as the primary treatment in sixty-nine patients with LAPC, Koom *et al.* documented that the powerful cutoff points were pretreatment CA 19-9 level of 1,200 U/mL, post-treatment CA 19-9 level of 100 U/mL, and CA 19-9 decline of 40% (11). Their data support the theory that post-treatment CA19-9 levels and CA19-9 decline are significant prognostic factors.

These results are very similar to our findings in the present study. On univariate analysis, we found that post CRT CA 19-9 <50 U/mL, post CRT CA 19-9 <85.5 U/mL, percent change ≥90%, and histologic grade all showed prognostic significance predictor of survival. The median survival of patients with a CA 19-9 less than the post-treatment median was 10.3 months compared with those with a CA 19-9 level greater than the median value of 85.5 U/mL (P=0.0242). Our results were confirmed on multivariate analysis showing that a post treatment CA 19-9 level less than the median value of 85.5 U/mL was an independent prognostic factor for overall survival.

A strength of our study was that the first post-CRT CA 19-9 levels was tested in 50 point increments and percent change in pre and post treatment CA 19-9 was tested in 10% increments. This allowed us to detect subtle incremental changes that would otherwise not have been detected if a different method was used. In addition, all patients with a serum bilirubin more than 2 mg/dL at the time of CA 19-9 measurement were excluded to account for altered biliary excretion, for which bilirubin is a reasonable marker. This has been documented to occur at levels 1.5× the upper limit of normal or at a level of approximately 2.0 mg/dL (15).

The retrospective nature and sample size are limitations of our study. Patients with CA 19-9 levels within normal limits were not tested for the Lewis antigen. Lewis^{a-b-} and are unable to increase their serum CA 19-9 levels and were not excluded from our analysis (16). However, only approximately 5% of the population are Lewis^{a-b-} so this was unlikely to have a significant effect on our patient population In this study, we analyzed CA 19-9 as a prognostic factor and determined its utility in developing treatment strategies and designing future clinical trials. We analyzed whether peri-chemoradiation CA 19-9 values in the setting of normal bilirubin could predict

post treatment survival. Additionally, the optimal time to evaluate CA 19-9 has not been fully investigated in patients receiving definitive CRT, chemotherapy alone, as well as postoperative setting. In our study, median time from the end of concurrent CRT to post CRT CA 19-9 was 36 days (range, 0.00-168.81 days). In RTOG 9704, the median time from surgery to the blood draw for postoperative CA 19-9 determination was 45 days (range, 11 to 57 days) as a secondary end point of its phase III study (4). To correct for the variability in the time between CRT and evaluation of the first post CRT CA19-9 value, we chose to measure survival as a time-varying covariate from the time of post CRT CA19-9 measurement rather than from CRT. Further study is warranted to determine the best time for CA 19-9 measurement to predict survival.

Patients who develop early metastasis are unlikely to benefit from radiation, and identifying this population prior to radiation would be ideal. An attractive strategy to facilitate patient selection for CRT is through a trial of systemic therapy. The time interval between the onset of chemotherapy and CRT provides an observation period of approximately 2 to 3 months. Restaging at the end of this period may identify the emergence of overt metastatic disease. In a study by The Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) LAP07, 181 patients were reviewed who were treated with 5-fluorouracil (5-FU) or gemcitabine based chemotherapy for four months. Those without evidence of disease progression were given additional chemotherapy or chemoradiation. Overall survival was improved in patients who went on to receive chemoradiation (17). An accurate surrogate marker for disease progression such as CA 19-9 could further identifying those patients that would most benefit from intensification of therapy. Substantially rising CA 19-9 levels during the induction period may be a harbinger of occult metastatic disease which would allow more careful selection of patients who would most likely benefit from local therapy. The half-life of serum CA 19-9 levels are approximately 1 day but can vary from less than 1 day to 3 days. The median lead time for CA 19-9 elevation before detection of a clinical relapse was 23 weeks (range, 2-48 weeks) (10). Thus, there is a need to optimize the timing of serum measurement that must be validated in a prospective clinical trial.

We demonstrated the prognostic impact of the post CRT CA 19-9 levels. Patients with a post CRT CA 19-9 level greater than 85.5 U/mL had significantly worse overall survival in multivariate analysis. These patients may not benefit from intensification of therapy and could be considered for alternative management scheme as those with lower levels of CA 19-9 would benefit from a more aggressive therapeutic approach.

Conclusions

We suggest that CA 19-9 levels be obtained pre and post chemoradiotherapy. Our results indicate that post CRT CA 19-9 levels may have predictive value for prognosis of patients with locally advanced unresectable pancreatic cancer receiving concurrent CRT. These findings should be validated in future randomized trials and considered for prognostic nomograms.

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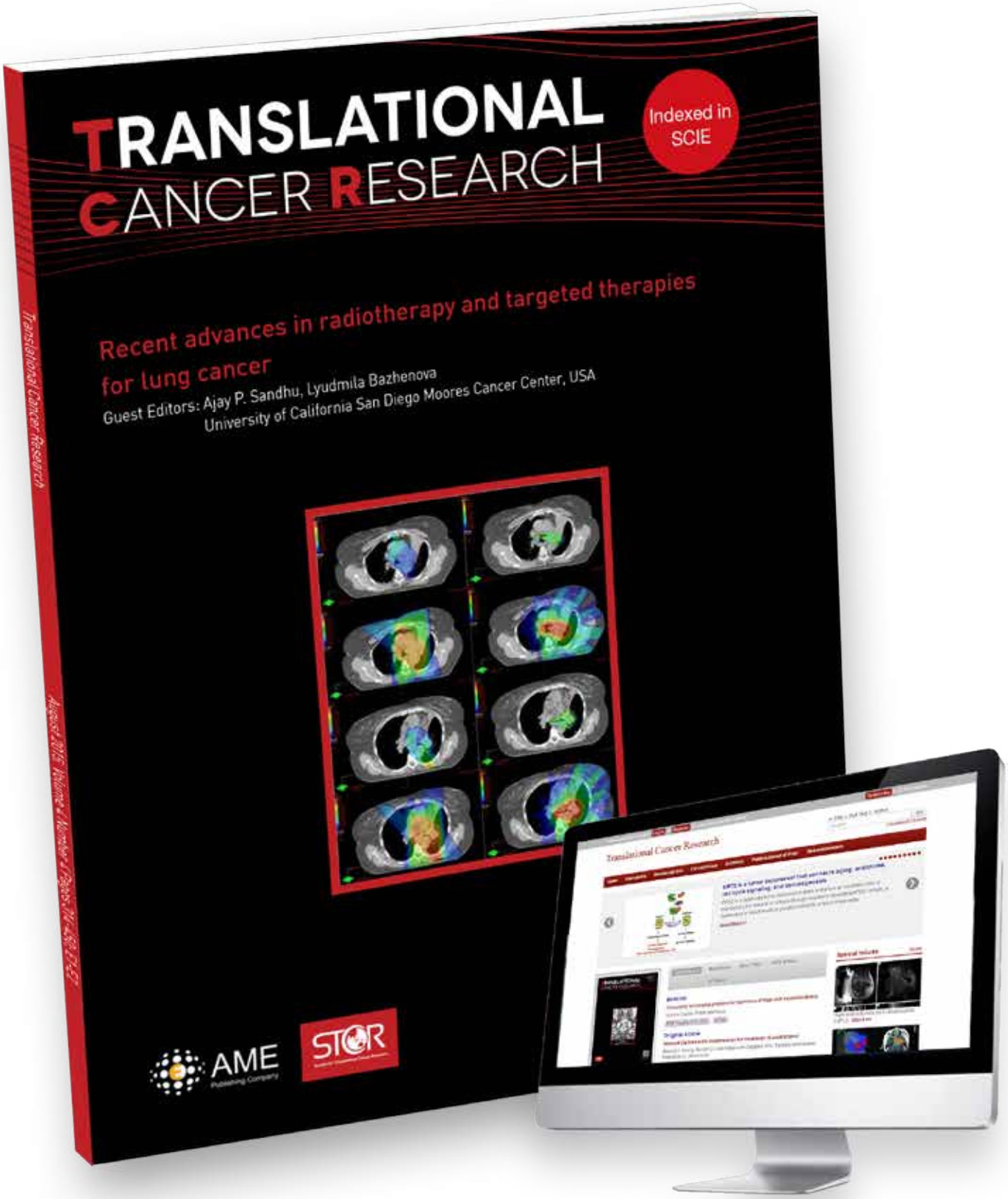
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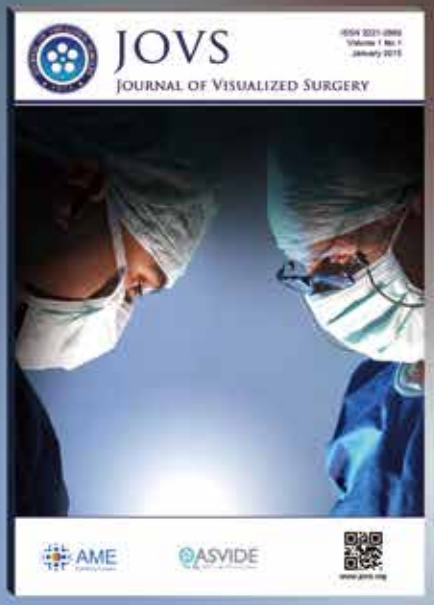

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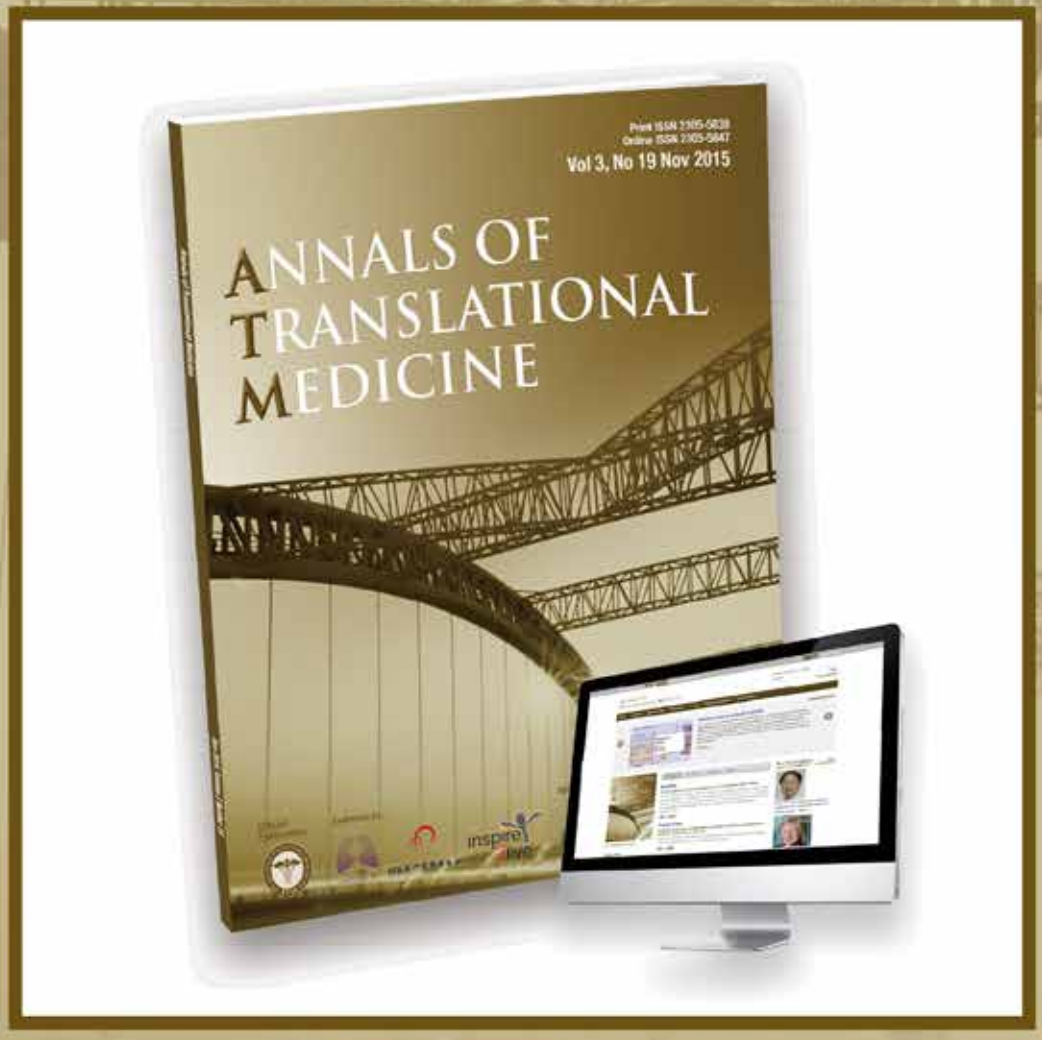

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