AME Surgery Series (6A002)

Progress in Pancreatic Surgery

Honorary Editor:
Ho-Seong Han

Editors:
Jihui Hao
Jin He
Cosimo Sperti

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Progress in Pancreatic Surgery
(FIRST EDITION)

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Foreword

The Annals of Cardiothoracic Surgery, one of AME's peer-reviewed journals, is lucky to have an author from Rochester, USA. He is left-handed. When he began his training in surgery, he encountered huge obstacles. For example, when using scissors or knotting during a surgery, his actions were the opposite of what was described in textbooks. Therefore, he often "took a beating" from his mentors when performing a surgery.

Later, he summarized his experience and published it in a journal in an attempt to find other surgeons that "suffer from the same fate". Surprisingly, after his article was published, many surgeons e-mailed him, asking him how left-handed doctors should undergo surgical training, and so on. Then he met Professor Tristan D. Yan, the editor-in-chief of Annals of Cardiothoracic Surgery, who happens to be a left-handed doctor. Tristan encouraged him to become a heart surgeon because there are steps in cardiac surgery that require the use of the left hand to complete the suture threading technique. Tristan's view was that it was better if surgeons were trained to use both their left and right hands.

A few days ago, on my daughter's first day of kindergarten, I chatted with her teacher for a while; finally, she asked me if there was anything about my daughter that she should take note of . "Please do not correct my daughter's left-handedness," I said, "Just let it be." "Why?" the teacher asked in wonder.

On December 7, 2013, we held the second AME Academic Salon in the Hospital Affiliated to Nantong University. After dinner, Dr. Shen Yaxing from the Department of Thoracic Surgery of Shanghai Zhongshan Hospital invited several attendees to have tea in his room. The elevator was in the middle of the hotel. After we walked out of the elevator, he led us to the left, then to the left, then to the left, then to the left, and finally to the door of his room. Although we were somehow confused and disoriented, some of us did find out that the door was just diagonally across the elevator. We all burst into laughter. Yaxing shared that he took this route the first time he entered his room, and so he decided to bring us on the same route on the second time. Yaxing then said that this was the behavior of a 'typical' surgeon!

During the training to be a surgeon, each step and each action are done under the strict direction and supervision of a senior surgeon. Thus, many surgeons like to affectionately address their mentors as their "masters".

How, then, can you become a master of surgery? In addition to your own intelligence and diligence, the expertise and mentorship offered by a "master" is also very important. Just like in the world of martial arts, there are many different schools that are independent from each other and have their own strength and weakness, and the surgical world is very much the same.

Therefore, it is important for a young surgeon to gain knowledge and skills from different masters by taking in only the essence and discarding the dregs. Therefore, we have planned to publish the AME Surgery series, in an attempt to share with our readers the surgical skills of some prominent surgical teams in China and abroad, as well as their philosophical thinking and some interesting stories. We sincerely hope that our colleagues in the surgical departments find these books insightful and helpful.

Stephen D. Wang
Founder and CEO,
AME Publishing Company

Preface

The Greek philosopher Heraclitus once said, "Everything changes and nothing remains still." This utterance basically echoes the development of the diagnosis and treatment of pancreatic diseases, which we witnessed revolutionary changes throughout history.

Endoscopic ultrasonography has become an essential diagnostic tool for pancreatic lesions and tumors. Pancreatic surgery has been more personalized owing to the coming of age of perioperative care. Laparoscopic surgery is now more accepted due to the insatiable demand from patients and surgeons. Although debates remain hot on the use of minimally invasive surgery, such as the capability of laparoscopic surgery in treating pancreatic cancer, and the effectiveness of laparoscopic pancreaticoduodenectomy, more and more pancreatic surgeries have been performed by means of minimally invasive methods. Besides, robotic surgery has been introduced to overcome the drawbacks of laparoscopic surgery with regard to the degree of freedom. Moreover, there have been a number of ongoing attempts to prevail over postoperative complications and pancreatic fistula. The development of adjuvant and neoadjuvant therapies has also reached new heights in examining the malignancies of pancreatic tumors, which only few armamentaria were available in the past.

Hardly can usual textbooks include timely contents, as the entire process of turning concepts into end products requires significant time. However, this textbook incorporates newly published articles of best quality from journals of AME Publishing Company to ensure a broad coverage of cutting-edge knowledge and state-of-the-art techniques over the field of pancreatic diseases.

In this rapidly evolving world, we believe this textbook will serve as an excellent source of in season knowledge and up-to-date technical information for physicians and surgeons in the field of pancreatic diseases to open up new horizons and ultimately benefit patients whom we treat with sincere passion.

I would like to extend my gratitude to Dr. Jihui Hao, Dr. Jin He and Dr. Cosimo Sperti for their tremendous help to this excellent book.

Acknowledgement

We here would like to extend our thanks to Mr. Brad Li for the editing support.

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Preface

In the era of the precision medicine and minimally invasive surgery, we need a comprehensive book to summarize the current expertise of perioperative management of patients with pancreatic disease.

Pancreatic surgery has historically been associated with high operative morbidity and classically been performed through a large abdominal incision. Minimally invasive techniques are associated with less postoperative pain, lower wound infection rates, decreased physiological stress, and fewer postoperative hernias and bowel obstructions. Recent studies have suggested that the benefits of minimally invasive techniques may be true for pancreatic surgery as well.

The particular book on "*Progress in Pancreatic Surgery*" aims to provide the comprehensive update on pancreatectomy with a focus on minimally invasive surgical techniques to surgeons around the world. We believe this book will be beneficial to the growth of young surgeons.

All chapters were contributed by the experts in the field. They are internationally renowned specialists and bring great insight based on their extensive personal experience. This comprehensive book covers the preoperative EUS, imaging, open and minimally invasive pancreatic surgery, postoperative complications and their management, and the adjuvant therapy for pancreatic cancer and the prognosis after surgical resection. This book brings the most updated perioperative knowledge on the pancreatic surgery from international experts to readers. Besides preoperative workup and postoperative complications management, this book emphasizes the techniques of the open and minimally invasive pancreatic surgery.

The diligent efforts of all authors have provided our readers the most updated knowledge and clinical expertise. We believe that this extraordinary book will reflect a collaborative effort from multiple international contributors as the state-of-the-art on pancreatic surgery. The editors great appreciate their contribution and support. We appreciate that all the contents of this issue will be open access and thus freely available to clinicians and scientists.

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Preface

The first edition of *Progress in Pancreatic Surgery* is a themed collection of related articles from journals of AME (http://amegroups.com/), which aims to deliver the updated progress and technique of pancreatic surgery in the academic arena. Dr. Jihui Hao, deputy president from Tianjin Cancer Hospital and Prof. Jin He from Johns Hopkins Hospital, are the editors of the book. They have assembled an outstanding group of several international contributors, with major experience and professionalism in the field of pancreatic neoplasms. In particular, special attention is given to new surgical techniques in pancreatic surgery, such as laparoscopic and robotic techniques, which have gained an increasing use in this field, and are nowadays routinely performed for different pancreatic conditions in many high-volume centers.

The first part of the book focuses on endoscopic ultrasound (EUS) and imaging studies for pancreatic adenocarcinoma. The role of EUS in pancreatic cancer is extensively reviewed, both in its more traditional use and in its innovative applications, which are rapidly expanding with new diagnostic and therapeutic modalities. The role of different imaging techniques is also analysed, with a detailed section on the accurate assessment of the primary tumor and its relationship to/involvement of neighboring structures (particularly vascular structures), which is fundamental for accurate characterization of disease as resectable, borderline resectable and unresectable, and therefore for the correct management of the patient. The central and main part of the book analyses the different surgical approaches to pancreatic pathologies, focusing on minimally invasive techniques (both laparoscopic and robotic). Finally, there is a section regarding the frequency and management of postoperative complications and the role of adjuvant and neoadjuvant therapy, with reviews of randomized controlled Trials, and recent studies dealing with these topics.

The book presents a wide revision of the major minimally invasive approaches, with attention to both indications and surgical techniques, as well as to postoperative complications and management. Throughout the book, articles are enriched with many links to videos available online, photos and figures, showing the different surgical interventions in detail. In this way, the book appears to be a useful tool of consultation not only for surgeons specialized in this field, but also for general surgery residents who are approaching pancreatic surgery for the first time.

Despite the initially high mortality and morbidity following pancreatic resections, in more recent years the rate of both postoperative complications and mortality has dropped to acceptable levels, thanks to the development of surgical technique and concentration of patients in high-volume centers, as well as to the improvement in perioperative care. In the same way, laparoscopic pancreatic surgery has lagged behind for many years because of its intrinsic difficulties, such as major vascular proximity and retroperitoneal location. However, with improvements in laparoscopic skills and surgical technology, laparoscopic pancreatic resections have been proven to be safe and may provide better outcomes compared to open surgery, with an increasing number of procedures performed in experienced centers. As for laparoscopic approach, also robotic surgery has recently gained a more extensive use in pancreatic surgery. Robotic technology adds several advantages to the traditional laparoscopic approach, such as a three-dimensional operative view, reduction of natural tremors, introduction of EndoWrist® technology, and a more comfortable and ergonomic position for the surgeon to operate.

Laparoscopic distal pancreatectomy has become the standard of care for body and tail pancreatic lesions (cystic lesions, neuroendocrine tumors, chronic pancreatitis, intraductal papillary mucinous neoplasms, and pseudocysts), and recent studies have demonstrated its feasibility and oncological adequacy also for pancreatic adenocarcinoma. On the other hand, the role of laparoscopic pancreaticoduodenectomy remains debated. Even if in recent years the number of this surgical approach has increased in experienced centers, the location and intimate relationship of the pancreas to major blood vessels and the reconstruction complexity of a pancreatoduodenectomy render this procedure demanding. Moreover, several years are necessary to overcome the learning curve and achieve high-quality outcomes. In the same way, the role of robotic surgery needs to be confirmed, mostly for the total cost per operation which is usually higher in the robotic approach.

In conclusion, minimally invasive techniques are gaining an increasingly important role in pancreatic surgery in high volume centers, but future prospective studies and randomized clinical trials will be necessary to better define the cost effectiveness of these approaches.

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Endoscopic ultrasound of pancreatic lesions

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Abstract: Endoscopic ultrasound (EUS) is a well-established tool for the evaluation of pancreatic lesions. Due to the closer proximity of EUS to the pancreas, EUS offers a high sensitivity for detection of small pancreatic mass and is the preferred modality for obtaining tissue for diagnosis of pancreatic mass. Contrast-enhanced EUS and/or elastography provide additional information to the fundamental B—mode ultrasound images, leading to more accurate diagnosis. The aim of this video-article is to show the different steps in performing EUS on pancreatic lesions and to provide some tips and tricks to improve and facilitate the execution of EUS on pancreatic lesions.

Keywords: Endoscopic ultrasound (EUS); endoscopic ultrasonography; fine needle aspiration (FNA); pancreas

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Introduction

Since its first introduction into clinical practice in 1980, endoscopic ultrasound (EUS) has clearly established itself as an important diagnostic tool for a wide range of pancreatic lesions, from solid to cystic lesions (1). One of the earliest successful applications was the detection of small pancreatic neoplasms, where the performance of EUS was shown to be superior than endoscopic retrograde cholangiopancreatography (ERCP), computed tomography (CT) and transabdominal ultrasound (2,3).

Echoendoscopes can be categorized into radial and linear types. Radial echoendoscope produces ultrasound images in a plane that transects the axis of the scope (*Figure 1*). It was the first to be developed and is used for diagnostic imaging. Linear echoendoscope produces ultrasound images in the plane that lies along the axis of the scope (*Figure 2*). It is used to facilitate image guided tissue sampling and intervention.

EUS is now used as a primary (i.e., initial imaging modality) or secondary (i.e., in the assessment of abnormalities detected by other imaging modalities) diagnostic tool. It is essential in the diagnosis of a wide variety of pancreatic lesions, as well as for tumour staging. This article describes how EUS is performed for pancreatic lesions.

Patient selection and workup

In patients presenting with symptoms concerning for pancreatic neoplasms, non-invasive cross-sectional imaging modalities such as CT or magnetic resonance imaging (MRI) are often the initial step in the evaluation. EUS can add important information to guide clinical management in patients with suspected pancreatic lesions, and can be safely performed in patients without conventional contraindications for endoscopy.

Previous studies have shown that EUS has a higher sensitivity for detecting a pancreatic mass lesion and preoperative tumor staging in patients with suspected non-metastatic pancreatic cancer when compared with CT (3,4). If an obvious pancreatic lesion is observed on cross-sectional imaging, EUS can provide important information for tumor staging and/or tissue diagnosis by fine needle aspiration (FNA). If a pancreatic lesion is highly suspected, but cannot

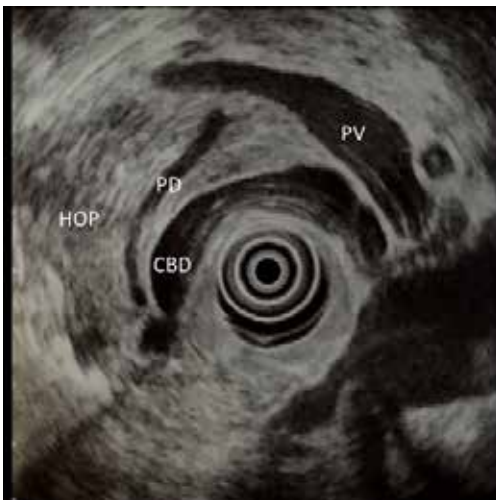

Figure 1 Radial endoscopic ultrasound (EUS) image of pancreatic head. PV, portal vein; CBD, common bile duct; PD, pancreatic duct; HOP, head of pancreas.

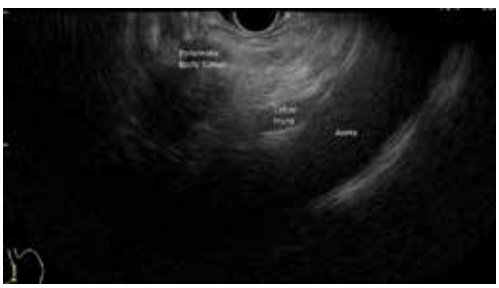

Figure 2 Image of linear endoscopic ultrasound (EUS) showing a pancreatic body tumor and its relationship with aorta and celiac trunk.

be clearly detected on initial cross-sectional imaging, EUS is particularly valuable in detecting small pancreatic lesions. In a systematic review of 66 studies, EUS has been shown to be the most sensitive and specific investigation technique in identifying pancreatic lesions <2 cm when compared to other imaging modalities (5).

Whether tissue acquisition by FNA is necessary depends upon the stage of the pancreatic tumor and the practice of the individual institution. In patients with inoperable pancreatic cancer, tissue diagnosis by FNA is usually preferred before subjecting the patient to chemotherapy. On the contrary, it is still debatable whether FNA should be performed for potentially resectable small pancreatic tumors in surgically fit patients given concern for tumor seeding along the needle tract of FNA and the fact that a negative FNA may not entirely exclude malignancy. However, if there is a concern for a benign alternative diagnosis such as pseudotumor due to autoimmune pancreatitis, then FNA of such potentially resectable lesion should be considered to clarify the diagnosis.

Pre-operative preparation

Prior to performing EUS, a review of patient symptoms and investigation results should be conducted to optimize procedural results and minimize adverse events. Large pancreatic head lesions may result in gastric and duodenal obstructions, increasing the risk of high gastric residual despite fasting, and aspiration risk during EUS. Pancreatic malignancies may also be associated with splenic vein thrombosis, predisposing to gastric varices development, which maybe complicated by gastrointestinal bleeding. More advanced disease could result in ascites, which may influence patient positioning during EUS.

On bloodwork, thrombocytopenia as a result of splenomegaly from splenic vein thrombosis should be noted if interventional procedures such as FNA, EUS guided biliary access are to be performed. Ideally, cross sectional imaging either CT or MRI is performed prior to EUS. Pre procedural imaging review can help the endoscopist anticipate findings at the various stations during EUS, particularly important when interventional procedures are planned.

When FNA is required, lesion location on imaging can help initially decide on size of FNA needle to be used. For celiac plexus/ganglia neurolysis, tumor involvement of the celiac axis on CT or MRI can alert the endoscopist the expected site for neurolysis will be different. For EUS guided biliary interventions, deciding between hepatogastrostomy versus choledochoduodenostomy can be aided by the extent of biliary dilation on imaging.

Equipment preference card

The conventional equipments for EUS include radial and linear echoendoscope, high-end ultrasound platforms, fine needles with different gauges, e.g., 19 G, 22 G and 25 G. For contrast-enhanced EUS, contrast agent, like SonoVue®, will be necessary.

If planned for advanced procedures like pseudocyst drainage or biliary drainage, additional materials, including fluoroscopy, carbon dioxide insufflation, guidewires of different calibers and stents with different shapes and sizes, will be necessary.

Procedure

Conventional EUS (radial and linear)

Procedure will be performed with patient in left lateral position.

Radial EUS (Figure 3)

Radial echoendoscope produces images in cross sectional orientation. Techniques involved are usually easier to capture because images are orientated in a similar way as CT which we should be familiar with. Pancreatic body and tail are best examined from the stomach while pancreatic head and uncinate process are best examined from duodenum. For the pancreas examination, we use station approach. *Table 1* summarized the basic scanning positions, visualized regions and the landmarks.

The first station is from the stomach, at the esophagogastric junction (OGJ). Left lobe of liver readily seen when the probe is placed at OGJ. Rotate the scope clockwise until aorta is seen at the 6 o'clock position. Then advance the scope, follow the aorta until the celiac take off is seen, which will then bifurcate into hepatic artery on the left side of the screen and splenic artery on the right side of the screen. Once the splenic artery is detected, follow it with slightly clockwise turn and pulling out of the scope. This movement allows you to examine the pancreatic body and tail all the way towards the splenic hilum. Main pancreatic duct (PD) can be visualized with back-and-forth movement of the scope. At the splenic hilum, we follow the splenic vein back to the genu of pancreas with counter-clockwise and advance movement. Splenic vein can be traced from splenic hilum back to the splenic vein and portal vein (PV) confluence, which is also called the club-head view.

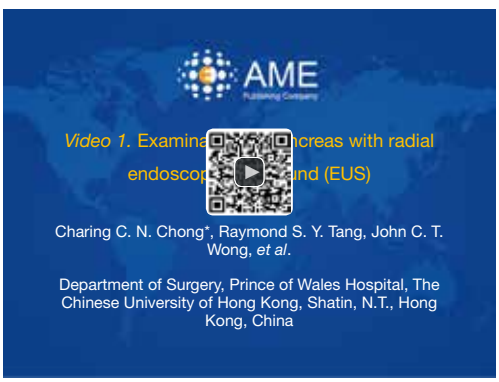

Figure 3 Examination of pancreas with radial endoscopic ultrasound (EUS) (6).
Available online: http://www.asvide.com/articles/1042

The second station is from the duodenal bulb. Insert the scope into the duodenal bulb, aspirate air and inflate the balloon. We can start the examination while slowly withdrawing the scope. Liver will usually come into the view from the upper left-hand corner and gallbladder will be visualized between the scope and the liver. PV will be visualized at the lower left hand portion of the screen and pancreatic head is located between the scope and PV. The bile duct is visualized as a tubular structure between the PV and the scope. This area may include image of PD as tubular structures, without Doppler signals.

The third station is from the descending part of duodenum. Advance the tip of the scope to the apex of the duodenal bulb. Then rotate the "right/left" knob to the right and reduce the scope back to the short scope position as in ERCP. With a slightly right and maximum up torque, we can identify the aorta which is usually located at the left side of the screen. Slowly withdrawn the scope at this juncture will show up the uncinate process and head of the pancreas at 6 o'clock position. Here allows a detail examination of pancreatic head and uncinate.

Linear EUS

Figure 4 demonstrated the linear EUS examination in cases with carcinoma of pancreas. In linear echoendoscope, the ultrasound signals are transmitted out in a linear manner.

Table 1 Stations and landmarks for orientation and scanning in EUS examination of pancreas

Station	Visualized regions	Landmarks
Stomach	Pancreatic body; pancreatic tail	Splenic vessels; left kidney; superior mesenteric vessels; celiac trunk; aorta
Duodenal bulb	Pancreatic head; pancreatic body; bile duct; gallbladder	PV; SMV; splenic vein
Descending part of duodenum	Pancreatic head; pancreatic genu; major papilla; gallbladder	Aorta; inferior vena cava; superior mesenteric vessels; PV

EUS, endoscopic ultrasound; PV, portal vein; SMV, superior mesenteric vein.

Figure 4 Examination of pancreas with linear endoscopic ultrasound (EUS) (7).
Available online: http://www.asvide.com/articles/1043

Figure 5 Video showing endoscopic ultrasound (EUS) fine needle aspiration (FNA) of a pancreatic body tumor (8).
Available online: http://www.asvide.com/articles/1044

For pancreatic examination, we usually use aorta as a starting point which is readily located by positioning the scope at the OGJ. Similar to radial examination, pancreatic examination with linear scope is mainly carried out in three positions: the stomach, duodenal bulb and the second part of duodenum. Once the scope entered OGJ, the left lobe of liver is readily visible. We then rotate the scope clockwise and we can see the hepatic vein, IVC and subsequently the abdominal aorta. From here, we move the scope in and out to locate the celiac take off. Follow the celiac trunk and advance the scope slightly to identify splenic artery. Once splenic artery is identified, rotate the scope clockwise and slightly withdraw to follow it to the splenic hilum. From these positions, we can have a close and detail examination of pancreatic neck, body and tail. After that, we trace the splenic vein back by anti-clockwise rotation and slight scope advancement. Then we will see the splenic vein joining superior mesenteric vein (SMV) to form PV. Further anti-clockwise rotation will see the PD and common bile duct (CBD), as well as the surrounding pancreatic head.

Inserting the scope into duodenal bulb can produce better image on pancreatic head. After entering the duodenal bulb, rotate the scope clockwise to see three luminal structures, i.e., PV, bile duct and common hepatic artery. Trace along the PV to the confluence of SMV allows a detail examination of the pancreatic head. In case of carcinoma of head of pancreas (HOP), we also look for any vascular invasion from this position.

At the second part of duodenum, we use the same maneuver as in ERCP to reduce the scope and rotate clockwise to see aorta and inferior vena cava. Then, follow the aorta; we slowly withdraw the scope to observe the lower part of pancreatic head and uncinate process, which is located between the aorta and the transducer.

EUS-guided FNA

Figure 5 demonstrated the steps in performing EUS-guided FNA on pancreatic body tumour. Linear echoendoscope is used for FNA. After the target lesion is endosonographically visualized, the region would be scanned for intervening vessels. Check the ultrasound image or endoscopic image to make sure that the sheath of the aspiration needle is projecting from the instrument channel. This is to protect the endoscope channel from damage from the FNA needle. If significant resistance is encountered upon insertion of the FNA needle through the channel, adjust the scope angulation until the FNA needle can be inserted smoothly without resistance. Then, check the insertion angle based on the EUS image of the sheath and measure the distance from the site of needle entry to the puncture target so that the needle would not overshoot beyond the puncture target (*Figure 6*). Once the lesion is penetrated, the stylet is pushed in and removed completely. The FNA needle would pass through the largest diameter possible in each lesion. Moreover, aspiration of lesion should be targeted to the periphery of the lesion or at multiple areas since the center of a cancerous mass is usually more necrotic, which may sample non-diagnostic tissue. The needle would be moved to and fro within the lesion to a total of 10–15 times. Some endosonographers use fanning technique, in which the needle is positioned at different areas within the lesion and then moved back and forth multiple times in each area to procure tissue (9). The trajectory of the needle can be altered not only by using the elevator, but

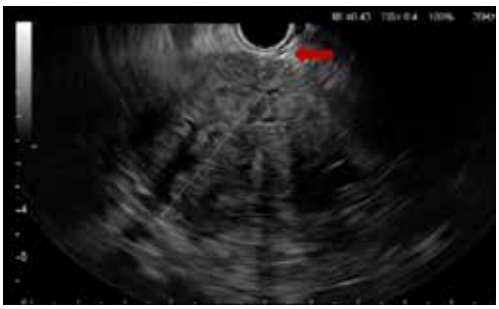

Figure 6 Image of linear endoscopic ultrasound (EUS) showing the sheath of fine needle aspiration (FNA) needle protruding out from the channel, indicated by the red arrow.

also the "up/down" endoscope dial. The use of suction at EUS-guided FNA remains a hot issue of debate. In general, the use of suction at EUS-guided FNA yields specimens that are more bloody but may not have any improvement in diagnostic yield. For this reason, FNA of solid lesions can be initiated without suction. If the aspirate obtained is scant, then suction can be used to procure a better aspirate.

When FNA completed, pull the needle tube back insider the sheath and remove the FNA needle from the scope. The specimen can be pushed by reinserting the stylet into the needle. Then submit the specimen for cytology and cell black preparation for histology.

Role of team members

Diagnostic pancreatobiliary EUS with or without FNA can be performed by gastroenterologists or surgical endoscopists who are familiar with the anatomy of pancreatobiliary systems, their surrounding vasculatures, as well as the current pancreatobiliary cancer staging/treatment guidelines. An endoscopy nurse with experience in echoendoscope and equipment setup, and FNA specimen handing is also key to a smooth and successful procedure. While diagnostic pancreatobiliary EUS can usually be performed with standard conscious sedation with benzodiazepine and/or opioid analgesic administered by the endoscopist or endoscopy nurse, more complex interventional EUS procedures would benefit from sedation by an anesthetist, e.g., monitored anesthetic care (MAC).

EUS guided FNA cytology specimen should be evaluated by a dedicated cytopathologist during or after the EUS procedure. The presence of an on-site cytopathologist has been shown to improve diagnostic sensitivity, and reduce the number of FNA passes needed to obtain a diagnostic specimen (10).

Post-operative management

Post-procedure management mainly focuses on the monitoring for potential complications. Despite an increasing range of indications, complications of EUS have remained low. Complications of EUS include perforation, bleeding and bacteremia. The reported complication rate of pancreatic EUS is 0.03% and the reported complication rate of EUS-guided FNA is 1–2% (11,12).

For diagnostic EUS, procedure can be done on outpatient basis. Patients are usually kept nil by mouth for 1 hour and kept closely monitored in the recovery area. They can be discharged if no adverse event happens.

For interventional EUS, post-procedure management should be individualized depends on the interventions performed. Patient should be closely monitored for the presence of bleeding, perforation, leakage and sepsis especially when advanced interventions like EUS-guided pseudocyst drainage or biliary drainage have been done.

Tips, tricks and pitfalls

Although EUS has been shown to be superior to CT in detecting small pancreatic tumors in general, there are circumstances in which false-negative EUS examinations can result in patients with suspected pancreatic malignancy. In a multi-center study involving nine experienced endosonographers, the presence of chronic pancreatitis, a diffusely infiltrating carcinoma, a prominent ventral/dorsal split, and a recent episode of acute pancreatitis (<4 weeks) were associated with missed pancreatic cancer on the initial EUS examination (13). A follow up EUS should be arranged in 2 to 3 months if clinical suspicion for pancreatic tumor remains high despite an initial unrevealing EUS examination.

Detection of small pancreatic tumors may still be challenging at times despite the use of conventional EUS imaging. Novel diagnostic EUS imaging techniques such as contrast enhanced harmonic EUS (CEH-EUS) and elastography can further improve detection and characterization of small pancreatic lesions (14). In CEH-EUS, an ultrasound contrast agent composed of microbubbles is injected intravenously to highlight the slow-flowing intra-tumoral vessels. Pancreatic cancer is most commonly depicted as a hypo-enhanced lesion on CEH-EUS (14). Elastography allows real-time assessment of the stiffness of a suspected lesion. In general, malignant tumors are noted to be stiff, while normal tissue or a benign lesion is generally noted to be soft on elastography (14). *Figure* 7 illustrates the detection and characterization of a

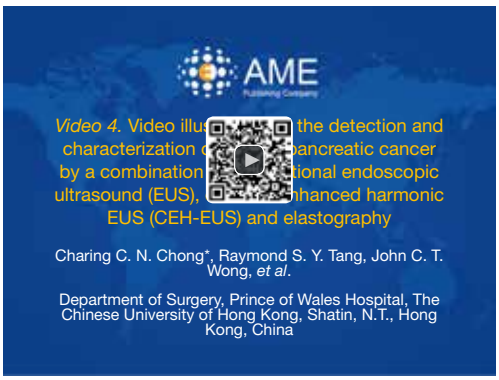

Figure 7 Video illustration on the detection and characterization of a small pancreatic cancer by a combination of conventional endoscopic ultrasound (EUS), contrast enhanced harmonic EUS (CEH-EUS) and elastography (15).
Available online: http://www.asvide.com/articles/1045

small pancreatic cancer that was not clearly seen on initial CT by a combination of conventional EUS, CEH-EUS and elastography.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Endoscopic ultrasound in pancreatic cancer: innovative applications beyond the basics

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Abstract: Endoscopic ultrasound (EUS) has become a mainstay in assisting in the diagnosis and staging of pancreatic cancer. In addition, EUS provides a modality to treat chronic pain through celiac plexus neurolysis. Currently, there is growing data and utilization of EUS in more diverse and innovative applications aimed at providing more sophisticated diagnostic, prognostic and therapeutic options for patients with pancreatic cancer. EUS delivery of chemotherapy, viral and biological vectors and fiducial markers may eventually revolutionize the way clinicians approach the care of a patient with pancreatic cancer.

Keywords: Endoscopic ultrasound (EUS); pancreatic cancer; fine needle injection (FNI); fiducial markers; immunotherapy

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Introduction

Pancreatic ductal adenocarcinoma (PDA) is rarely curable at the time of diagnosis as most patients present with either locally advanced or metastatic disease. It has been estimated that less than 20% of patients with newly diagnosed pancreatic cancer have surgically resectable disease, and approximately 30% of patients present with locally advanced disease (1). Locally advanced disease is defined as unresectable pancreatic cancer without evidence of distant metastatic disease. Of the patients who are eligible for surgical resection, most will relapse and experience a median survival of 23 months (2). Even in patients with margin-negative resection, the risk of both local and systemic recurrence is high, and in the cases without adjuvant therapy, the 5-year survival is 10–13% (3,4).

Endoscopic ultrasound (EUS) represents one of the most innovative gastrointestinal procedures that has been developed in recent years with respect to the diagnosis and treatment of patients with pancreatic cancer. EUS is routinely used to assist in the diagnosis and staging of pancreatic cancer along with providing a modality for pain control during celiac plexus neurolysis. The role of EUS in pancreatic cancer is rapidly expanding with new prognostic and therapeutic modalities becoming more common. This review will aim to summarize these innovative applications of EUS in pancreatic cancer outside its more traditional uses.

Targeted EUS guided delivery of chemotherapy

EUS has the potential to revolutionize the delivery of chemotherapy by improving selectivity of treatment and reducing undesirable side effects in surrounding healthy tissue (5). Currently, one of the main limiting factors of systemic chemotherapy is its side effects. The common chemotherapy agents used for pancreatic cancer include 5-flurouracil and gemcitabine, each of which has significant clinical toxicity. EUS enables access to the pancreas in a minimally invasive manner. EUS allows for a less invasive way to apply localized chemotherapy to the

pancreatic tumor, thus preventing side effects of systemic chemotherapy. It also allows for a more comprehensive real-time image, a shorter puncture pathway, and a lower risk of complications when compared to via computed tomography (CT) or abdominal ultrasound (US)-guided procedures.

EUS-guided fine needle injections (EUS-FNIs) were initially studied in a porcine model where they injected paclitaxel into the pancreas; clinically detectable concentrations of the drug could not be detected beyond a distance of 30–50 mm from the injection site (6). Levy *et al*. studied EUS-FNI of gemcitabine in patients with unresectable cancer and demonstrated that several patients were able to be down staged and undergo subsequent resection (7). EUS-FNI of chemotherapy can be limited by the high density of fibrosis in pancreatic cancer, making it difficult to pierce the needle into the pancreatic tumor, and make it challenging to inject adequate amounts of an injected solution into the mass (7). Although interventional EUS has not been shown to significantly improve the survival rate and prolong the survival time in patients with pancreatic cancer, it can effectively induce tumor cell death. Additional studies are needed to further explore this therapeutic application in the future.

EUS in predicting prognosis and response to chemotherapy

In addition to the potential for directly administering chemotherapy, assessing the prognosis and response to therapy is another developing role for EUS. Currently, many academic institutions and industry trials have adopted the response evaluation criteria in solid tumors (RECIST) criteria to help standardize the assessment of prognosis and response to therapies (8). RECIST criteria are largely based on radiographic cross-sectional imaging. It has been proposed that tumor response to neoadjuvant chemotherapy (defined by the RECIST criteria) would be required prior to surgery for borderline resectable pancreatic tumors. However, in a study by Katz *et al*. only 12% of cases had radiographic changes associated with neoadjuvant chemotherapy that met the RECIST criteria (9). Furthermore, only one patient out of 129 patients had enough of a reduction in tumor size to be reclassified as resectable via radiographic criteria, and yet 60% of those patients underwent surgical resection, suggesting that surgical resection in patients with borderline resectable cancer should not be based only on these radiographic changes. The current literature suggests that patients with borderline resectable pancreatic adenocarcinoma undergoing neoadjuvant therapy should undergo resection unless they develop metastatic disease, local progression that would prohibit resection, or a decline in performance status. In patients with locally advanced disease, such as those with tumors encasing or obliterating celiac or superior mesenteric vessels, it is extremely uncommon to be able to downstage their tumors with current neoadjuvant therapies (10).

Imaging modalities such as contrast-enhanced endoscopic ultrasound (CE-EUS) could also be used to help select patients for chemotherapy that are predicted to have an improved survival with chemotherapy. Pancreatic cancer usually has a hypovascular nature and appears as such on CE-EUS. The hypovascular nature of pancreatic cancer typically results in poor drug delivery, and gemcitabine, one of the current chemotherapies of choice for unresectable pancreatic cancer, is not always effective (11,12). In the study by Sofuni *et al*., the authors indicated that CE-EUS could be utilized to identify patients who have more intratumor blood flow, since these patients have a significantly better response to chemotherapy (13). They suggested that when there is greater intratumor blood flow, more of the chemotherapeutic agent can enter the tumor, which may provide better drug delivery. Recent studies have also shown that patients with large intratumoral vessels also have significantly longer progression-free survival and overall survival, and that a positive vessel sign was an independent factor associated with longer survival (14).

CE-EUS has also been shown to be an effective method by which to demonstrate response to chemotherapy. Early studies in pigs have suggested that CE-EUS could be utilized to visualize pancreatic perfusion after tissue ablation, and how it could aid in post-treatment follow-up (15). Sofuni *et al*. demonstrated that the before and after treatment imaging patterns of CT and CE-EUS did not always correlate, as the rate of concordance before treatment was 92% and only 76% after treatment (13). In this study, CT imaging after treatment with gemcitabine often failed to show significant changes despite the fact that CH-EUS often did reveal an increase of intratumor blood flow (13). Furthermore, increasing intratumor blood flow was found to correlate with decreasing CA19-9 serum levels and better outcomes. Additional studies evaluating CE-EUS as a means to follow the response of pancreatic cancer to chemotherapy could establish it as a safe, highly accurate, and cost-effective alternative to CT and PET imaging (16).

EUS may therefore become indispensable in diagnosing and prognosticating pancreatic adenocarcinoma, monitoring tumor response to chemotherapy, and delivering chemotherapy in patients with pancreatic cancer in the

near future. Large prospective, randomized controlled trials are still needed to prove that CE-EUS monitoring and interventional EUS are effective in pancreatic adenocarcinoma treatment. However, considering the variety of chemotherapeutic options, it is possible that survival for patients with pancreatic cancer could be significantly improved, and the goal of qualifying for surgery with a curative intent may be achieved more frequently.

EUS delivery of viral and biologic vectors

Introduction

In pancreatic cancer, the pathophysiology leading to the development of a pancreatic tumor has been shown to have three precursor lesions that proceed in a multistep progression to become pancreatic adenocarcinoma. These include pancreatic intraepithelial neoplasia, intraductal papillary neoplasia, and mucinous cystic neoplasms (17). Typically, the initial mutation is an activation mutation in the *KRAS* gene, followed by a mutation in one or more tumor suppressor genes (18). Progression to metastatic pancreatic adenocarcinoma has been found to require both activating mutations and the loss of a tumor suppressor gene in murine models. The difficulty in treating pancreatic cancer is thought to be in part due to the anatomic and histologic features of the involved tissue. The dense extracellular matrix in pancreatic cancer distorts the normal architecture of tissue and causes an abnormal configuration of blood and lymphatic vessels, resulting in a hypoxic tumor mass. The resulting tumor often has poor perfusion, and is thought to be one reason why systemic chemotherapy has not been more effective in treating pancreatic cancer (19).

The application of utilizing viruses to deliver oncotherapy, in part due to their tumor selectivity and ability to cause lysis in cancer cells, remains an emerging topic in the treatment of pancreatic cancer. Such viruses are genetically engineered to target genes on malignant cells, while avoiding the binding to, viral replication of, and eventual destruction of normal cells (20). In addition, these viruses have been engineered to replicate throughout tumor cells in order to more effectively attack them (21). Viral vectors have previously been administered intravenously, intraoperatively when tumors have been found to be unresectable, and percutaneously via CT guidance. All of these methods, however, have been found to carry significant side effects and morbidity. As a result, the administration of viral vectors via EUS has gained popularity, and EUS as a method to deliver multiple types of viruses has been studied in both animal models and clinical trials. It has also been suggested that EUS administration can provide a more diffuse viral infectivity of the tumor due to the ability to perform multiple FNIs (22).

Adenovirus

Adenovirus is a double stranded DNA virus that incorporates itself into its host genome for replication and binds to cells with higher affinity than other viruses (23). It also subsequently infects nearby cells after cellular lysis, making it a desirable vector for oncolytic therapy. Two types of adenovirus, Gendicine and Oncorine, are already currently approved for treatment of multiple types of cancer in China (24).

Enabling adenoviruses to be specifically active towards malignant cells involves the deletion of essential viral genes needed for replication in normal cells, rendering the virus only functional in tumor cells not requiring these genes. An example of this is ONYX-015, an adenovirus engineered to lack the *E1B* gene, which in normal cells binds to tumor suppressor *p53* and causes progression of the cell cycle and viral replication. E1B-deleted viruses do not typically replicate in normal cells. Pancreatic tumors, however, lack *p53* in 50–75% of tumor cells, allowing E1B-deleted viruses to replicate and spread to nearby malignant cells. ONYX-015 was shown to be effective, and increased survival when intratumorally injected in murine models (25). Although prior administration of ONYX-015 has been performed via intravenous route and CT-guided injection, administration via EUS poses to be an alternative delivery method. This is in part due to the lack of systemic effects that intravenous administration can carry, as well as the less cumbersome nature and shorter injection pathway of EUS as compared with CT-guided injection, and the ability to perform multiple injections, to diffusely spread virus throughout the entire tumor (22). ONYX-015 was the first replication-competent virus used in a clinical trial, and when administered via EUS in phase I/II clinical trials for patients with pancreatic cancer, it was found to be a well-tolerated therapy (22). Unfortunately, no significant responses (i.e., decrease in tumor size or prolonged survival) were seen when ONYX-015 was used as a single agent, and only 2/21 patients showed mild responses when EUS injection was combined with gemcitabine (22). Similar adenoviruses with other deletions have also proven effective in treating pancreatic cancer, including Oncorine, another adenovirus with a larger deletion of the *E1B* gene, and

adenoviruses with deletion of the *E1A* gene, which binds to retinoblastoma protein (pRb). These viruses remain to be tested via EUS administration, but given the successful administration of ONYX-015, they may show promise as another EUS-delivered therapy. Adenoviruses are also being developed that incorporate multiple gene deletions, further increasing the selectivity towards cancerous cells. Importantly, these viruses have been shown to remain equally efficacious in addition to having increased selectivity with multiple deletions (26,27).

Though the use of adenoviruses has shown significant promise, there are disadvantages to their use as well. One disadvantage is that they are not very infective towards malignant pancreatic tumor cells. This is due in part to the primary type of adenovirus used in oncolytic models, which uses a receptor to bind to cells that is typically expressed very little in pancreatic cancer cells. The attempt to overcome this involves using new adenovirus mutants, which have a different binding site, increasing their infectivity towards pancreatic tumor cells (28). Another technique devised to improve efficacy of adenoviruses involves equipping these viruses with therapeutic genes which prime the immune system to improve destruction of cancerous cells. An example of this involves interleukin 24 (IL-24), which has been shown to improve the immune system's recognition of pancreatic cancer, but has severe side effects, which limits its use in systemic administration. When an adenovirus was engineered to manufacture IL-24 locally within tumor cells *in vitro*, there was a significant decrease in tumor growth and a strong immune response to pancreatic cancer (29). Thus, the administration of adenovirus equipped with IL-24 via EUS may have significant therapeutic effects while avoiding systemic side effects.

Herpes virus

Herpes simplex 1 virus (HSV-1) is a double stranded DNA virus that has shown promise against pancreatic cancer. The HSV genome is larger than most viruses, and as a result can have many therapeutic genes inserted to replace many of the nonessential genes, while not integrating itself into host DNA (30). Most importantly, HSV has a strong T-cell mediated tumor reactivity, and it can indirectly cause an immune response to cancer, causing local killing and destruction of the tumor by the body's own defense cells. Like adenoviruses, HSV viruses use two major strategies for improving selectivity towards cancer cells. These include the deletion of viral genes for replication and the deletion of genes that regulate the protein kinase response pathway. One particularly encouraging HSV oncolytic virus is FusOn-H2, which has a deletion of the *ICP10* gene, which is involved in the Ras-mitogen activated protein kinase pathway. Intratumoral injections showed complete eradications of pancreatic xenografts in mouse models. Intravenous administration showed significant antitumor effects, and intraperitoneal administration showed eradication of 75% of tumors and prevention of metastasis (31).

Although other types of HSV viruses have been used in intraoperative injection of pancreatic tumors (32), HSV has also showed promise when injected into tumors via EUS. An example of this is OncoVex GM-CSF, which has a deletion that makes it selective to tumor cells. In addition, it is hypothesized that the ability of this virus to express human GM-CSF will potentiate the recruitment and activation of dendritic T cells to the location of the tumor, and promote tumor destruction (33,34). The OncoVex GM-CSF virus has been shown to be well-tolerated in clinical trials in other solid tumors, including head and neck, squamous cell, and breast cancer, and is currently being used as an EUS-guided therapy in a phase I trial for pancreatic cancer, the results of which have not yet been published (34).

Other viruses

In addition to the above-mentioned viruses, there remain other viruses that may show benefit in the treatment of pancreatic cancer in the future, particularly by EUS administration. Among these are poxviruses, which have been shown to be equally infective under hypoxic conditions, which as mentioned, is a feature of pancreatic cancer thought to make it so resistant to systemic chemotherapy. A number of poxviruses have been studied both *in vitro* and *in vivo*, and have shown a benefit to oncolysis when combined with gemcitabine (35,36). Similar in nature to poxviruses, parvoviruses have direct oncolysis and immunomodulatory effects. Parvovirus has been shown to reduce tumor growth *in vivo*, and improve animal survival and decrease metastases when given with gemcitabine (37). Measles viruses have also been shown to have oncolytic activity in pancreatic tumor xenografts in mice, and improve survival (38). Another type of measles virus, which was engineered to target prostate stem cell antigen (PSCA), a protein expressed in pancreatic cancer, has been shown to have beneficial effects particularly in gemcitabine resistant

pancreatic adenocarcinoma (39). Reovirus, a virus whose replication is dependent on KRAS, a frequently found mutation in pancreatic cancer, has been shown to decrease tumor mass both locally and in the liver when administered intraperitoneally (40,41). Although there have not been clinical trials using EUS for these viruses, they have shown promise in treating pancreatic cancer, and delivery via EUS should strongly be considered in the future.

Immunotherapy

In addition to viral therapies, other forms of endoscopically-administered immunotherapy have been used in pancreatic cancer with promising results. These include local administration of immunologic agents, in an attempt to boost the local immune response to the malignant cells of pancreatic adenocarcinoma. The first example of this involved administration of cytoimplant, which was an EUS-administered injection of mixed lymphocytic tissue, derived from both healthy donors and the patient's own peripheral blood lymphocytes (42). Of the eight patients with advanced pancreatic cancer in whom cytoimplant was used, only minimal side effects occurred, including low grade fevers, gastrointestinal toxicity, and hyperbilirubinemia. The median survival of the eight patients was 13 months, with two partial responses and one minor response. A second form of administration, involving EUS-guided administration of dendritic cells, was reported by Nonogaki *et al.* in 2007. Of the five patients with unresectable pancreatic cancer, one patient showed a partial response, with two others showing stable disease for over 6 months (43). Multiple other small studies were subsequently performed, which did not demonstrate complications with dendritic cell injection, and showed stable disease in some patients receiving therapy (44,45).

In addition to adenovirus being used as previously discussed to infect and lyse pancreatic cancer cells, it has also been used as a vector to carry human tumor necrosis factor-alpha genes into pancreatic cancer cells. This therapy, named TNFerade, was shown by Hecht *et al.* to have benefit when locally injected into advanced pancreatic cancers using both EUS and percutaneous administration (46). In the phase I/II study performed, patients also received concomitant radiation therapy and chemotherapy. Of the 50 patients who received therapy, one showed a complete response, 3 patients showed a partial response, and 12 patients showed stable disease. Seven patients were able to undergo surgery, with three surviving over 2 years. There was no difference in outcomes from the different method of delivery (EUS versus percutaneous route). Another randomized phase III multi-institutional study, however, showed that injected TNFerade, either by EUS or percutaneous transabdominal injection, when combined with fluorouracil and radiotherapy, was not effective for prolonging survival in patients with locally advanced pancreatic cancer (47). It was found, however, to be a safe treatment alternative. As in the prior study, responses appeared similar by EUS and percutaneous administration.

Another novel treatment of pancreatic cancer involves plasmids, double stranded DNA molecules independent of the host cell's DNA. Intratumoral injection by both EUS and CT guided percutaneous injection of BC-819, a double stranded DNA plasmid, has been studied in a recent phase I/II clinical trial (48). BC-819 carries the diphtheria toxin-A gene, which is activated by an H19 promoter, which is overexpressed in multiple malignancies, including pancreatic cancer. In a phase I/II trial performed by Hanna *et al.*, BC-819 was injected via both EUS and percutaneously. Although this study involved only nine subjects, it was found to be well-tolerated with only asymptomatic elevation of lipase in one patient, three patients were found to have a partial response 3 months after injection, with two patients being able to have their tumors downgraded to surgically resectable. More success was seen with patients with a higher dose of BC-819 (48).

Although much more research needs to be performed on novel therapies of treating pancreatic cancer, the above-mentioned local treatments have shown promise, particularly by EUS, and may be able to improve the currently bleak survival in locally advanced pancreatic cancer.

EUS guided implantation of fiducial markers

Introduction

Stereotactic body radiation therapy (SBRT), also known as image guided radiation therapy (IGRT), is a technique that allows for the delivery of high doses of radiation to a precise target area within the body. The technique involves directing beams of radiation in three separate planes to converge on a specific locus, allowing for concentrated high doses of radiation to be delivered while limiting radiation exposure to surrounding areas. SBRT is modeled after stereotactic radiosurgery (SRS), which was first introduced in 1951 by the Swedish neurosurgeon Lars Leksell (49,50).

Using the fixed anatomical structures of the bony skull as fixed landmarks to guide beams of radiation, SRS was initially developed for the treatment of intracranial tumors. SRS was effective because of its ability to deliver high doses of radiation therapy within the frame of a fixed space. SBRT is the extension of SRS to lesions outside the skull, and is now being applied to the treatment of locally advanced pancreatic adenocarcinoma (50).

One of the main challenges of applying SBRT to pancreatic tumors is the need to account for movement. Unlike intracranial tumors, pancreatic tumors do not exist within a fixed space such as the bony skull, and are estimated to move as much as 2–3 cm during the respiratory cycle (51). Radiographic markers (i.e., fiducials) implanted into pancreatic tumors help to overcome the challenge of a moving target by acting as fixed reference points within the tumor. Tracking fiducials as surrogates of the tumor allows for real time targeting of radiation beams (50). As the use of fiducials in the treatment of pancreatic tumors continues to evolve, one of the key questions that arise is determining what is the safest and most effective method to implant fiducials. This section will review the current literature as it pertains to the placement of fiducials using EUS. It will include sections dedicated to the methods, materials, and outcomes of fiducial markers placed by EUS.

Placement of fiducial markers by EUS versus traditional methods

Traditionally, fiducial markers have been implanted either surgically or percutaneously via CT or US guidance. Percutaneous placement of fiducial markers under CT or US guidance is often feasible when lesions are relatively superficial or have a clear window (52). There are, however, risks associated with percutaneous placement. One notable risk is of vascular damage or puncture. In a retrospective review by Kothary *et al*. of 61 cases of CT guided percutaneous fiducial marker implantation for pancreatic cancer performed between 2003 and 2008, 3.3% were complicated by minor hemorrhage (53). Authors such as Park *et al*. have hypothesized that the placement of fiducial markers using EUS reduces the risk of bleeding secondary to damage or puncture of vascular structures due to the ability to use real time Doppler imaging (54). In his own prospective case series of 57 patients who underwent fiducial marker implantation for locally advanced pancreatic adenocarcinoma, one case was reported to be complicated by "*minor bleeding…with no significant decrease in hemoglobin*," ultimately limiting the number of fiducials able to be placed (54). An additional risk with the percutaneous approach, though uncommon, is tumor seeding of the peritoneum. Tumor seeding has been estimated to occur between 0.005% and 0.009% during percutaneous FNA under CT or US guidance (52). Multiple authors have stated that this risk, similarly, seems to be lower with EUS compared to a percutaneous approach, as the puncture path is considerably shorter (52,54,55). To date, only three cases of tumor seeding as a result of EUS-FNA have been reported (56-58).

Fiducial markers can also be implanted during surgery. This method typically involves tying sutures into the periphery of the tumor, then tying fiducials into the sutures (59). Despite clearly being a more invasive technique compared to EUS, there have been advantages reported with surgical implantation, namely, the ability to achieve ideal fiducial geometry (IFG) when multiple fiducials are implanted. Parameters of IFG have been specified by systems such as the Cyberknife System (Accuray, Sunnyvale, California, USA) to ensure fiducial tracking during IGRT. For example, the Cyberknife System recommends that at least three fiducials are placed with a minimum interfiducial distance of greater than 2 cm and minimum interfiducial angle of 15 degrees, with noncollinear placement in the imaging plane (60). According to a study by Majumder *et al*., IFG for this system was achieved at a higher rate with surgical placement compared to EUS, with rates of 47.4% during surgery and 17.9% by EUS (P<0.005) (59). Interestingly, however, fiducial tracking and subsequent successful delivery of IGRT was achieved in 90% of cases placed by EUS, compared to 82% of cases placed by surgery (95% CI, 67–92%) (59). Based on the results of this study, it would seem that IFG is not a necessity for successful tracking and delivery of IGRT. Furthermore, in contrast to the Cyberknife System, other systems currently exist which only require one fiducial to be placed, making the importance of IFG even less relevant.

Fiducial markers

Fiducial markers come in a variety of lengths and diameters, though in terms of design, fiducials are typically either traditional or coiled. Unlike traditional fiducial markers, coiled fiducials are flexible, which theoretically helps to decrease the rate of fiducial migration once implanted. In a study by Khashab *et al*., a total of 103 fiducials were placed in 39 patients, 77 of which were traditional and 26 coiled. The

results of the study revealed that there was no significant difference in the rate of fiducial migration between the two groups. Additionally, there was no significant difference in the number of fiducials able to be placed, indicating similar degrees of technical difficulty between the two groups. Notably, however, visibility was significantly better for traditional fiducials compared to the coiled fiducials used in the study (61).

Technique of EUS-guided fiducial implantation

Several techniques have been published describing ways to implant fiducial markers by EUS, and currently, no singular technique exists as the standard method. All the techniques described have utilized linear-array EUS, however, variations exist in the gauge of needle used, how fiducials are loaded within the needle, and how the fiducial is ultimately advanced and deployed. Many of the early techniques include the use of a 19-gauge needle, in order to accommodate the commercially available fiducials at the time (62). More recently, however, fiducial markers have been designed that are compatible with 22-gauge needles. Authors such as Ammar *et al*. advocate for the use of 22-gauge as opposed to 19-gauge needles and state that smaller gauge needles allow for greater flexibility, and therefore, easier passage of the needle through the endoscope even in the setting of acute endoscope angulations (63). Additionally, it has been suggested that smaller caliber needles carry less risk of mechanical complications, such as puncturing the channel of the endoscope (64). In a study of 13 patients referred for EUS-guided placement of fiducial markers, Ammar *et al*. found that fiducial markers were successfully implanted in all 13 patients using a 22-gauge needle, 9 by transgastric approach and 4 by transduodenal approach (63).

The two main approaches to loading fiducials into the lumen of a needle are the back-loading technique and the push-stylet technique. In the back-loading technique, as described by Owens *et al*., the stylet is drawn back from the tip of a 19-gauge needle in order to leave adequate space for a fiducial to be loaded directly into the hollow needle tip. Once loaded, bone wax is then pressed onto the needle tip to seal the fiducial inside (65). The needle with the back-loaded fiducial is then passed through the working channel of the endoscope. When ready for deployment, the fiducial is advanced by pushing the stylet to the end of the needle.

In the push-stylet technique, the needle is first inserted into the target lesion. The stylet is then fully retracted, and the fiducial is loaded into the hollow needle through the handle, and advanced forward by reinserting the stylet and pushing the fiducial forward. In the description of the procedure by Ammar *et al*., the stylet is advanced until approximately 10 mm of the stylet remains exposed, so as to avoid pushing the fiducial forward into the lesion, and potentially coiling the fiducial. Instead, the fiducial is deployed by withdrawing the needle the remaining 10 mm, while keeping the stylet in place, leaving the fiducial within the target lesion (63).

Advantages and disadvantages have been described with both techniques. One notable disadvantage reported with the push-stylet technique is the inability to advance the fiducial with the stylet due to resistance or kinking, especially when the tip of the endoscope is angulated (63,65). This complication, however, has primarily been reported to occur when using a 19-gauge needle, and both Ammar *et al*. and Ghassemi *et al*. have reported success using the push-stylet technique with a 22-gauge needle, without meeting resistance due to kinking (63,66). Ammar *et al*. goes on to point out that, compared to the back-loading technique, other potential advantages of the push-stylet technique include less risk of injury related to manually back-loading a fiducial into the tip of a needle, decreased risk of fiducial loss while advancing the needle down the accessory channel of the endoscope and accessing the target lesion, and the ability to implant multiple fiducials without completely removing the needle in systems that require more than one fiducial to be implanted (63,67).

Another disadvantage pertaining more to the push-stylet technique is that once the fiducial has been loaded, air is often introduced into the tumor during deployment as the stylet is advanced, thereby obscuring EUS visualization (65). While the back-loading technique does overcome this disadvantage to a degree, a hydrostatic deployment technique, used in conjunction with back-loading, has been described. In the hydrostatic technique, described by Park *et al*., the stylet is completely removed and the needle channel is then flushed with sterile water. Multiple fiducials can then be back-loaded into the tip of the needle and sealed with bone wax. The needle is then inserted into the tumor under EUS guidance, and 1–2 mL of sterile water is then injected through the needle channel to deploy the fiducials. This technique, according to Park *et al*., decreased the amount of air artifact and also overcame difficulties related to angulations of the endoscope encountered during push-stylet technique (54).

Challenges and complications

Multiple studies have shown EUS to be a safe and effective technique capable of implanting fiducial markers for SBRT in the treatment of pancreatic cancer (52,54,62,65-67). Reasons for failed implantation of fiducials seem to stem primarily from mechanical and technical factors, such as difficulty inserting fiducial markers through an acutely angled endoscope tip, early deployment of fiducials before the use of sterile bone wax, and needle malfunction (54,62). Other reasons for failure involve characteristics of the pancreatic tumor itself, such as a very hard or fibrotic pancreatic head tumor preventing deployment, or inability to position the endoscope in alignment with the tumor due to gastric outlet obstruction or difficult tumor location (62).

Generally, the safety profile of fiducial placement by EUS is similar to that of diagnostic and interventional EUS (62). There have not been many reports of significant early post-procedure complications thus far other than minor bleeding during the procedure, with no significant decrease in hemoglobin, some complaints of post-procedural abdominal pain or nausea, and mild pancreatitis (54,59). Pishvaian *et al*. reported one case of cholangitis in a patient 25 days post-procedure, though stated that it was unclear if infection was related to the procedure (62). In all subsequent patients, Pishvaian *et al*. used prophylactic antibiotics at the time of procedure and for 3 days afterward (62). The practice of prophylactic antibiotics has been adopted and applied by others as well (54,63,67).

Migration of fiducials after deployment by as much as several millimeters has been reported to occur, occasionally resulting in inability to proceed with SBRT (54,59). Migration is thought to occur secondary to resolution of procedurally-related inflammation, or due to movement of fiducial markers within the tumor. Notably, however, there has not been shown to be a significant difference in the rate of fiducial migration when placed by EUS versus surgery. Additionally, as previously discussed, Ammar *et al*. demonstrated a higher rate of successful fiducial tracking and delivery of IGRT with EUS compared to surgery despite fiducial migration (54,59).

Conclusions

The role of EUS in pancreatic cancer is rapidly evolving and its current and potential applications are limitless. As its role continues to expand, it will hopefully maintain an important role in revolutionizing the diagnosis and treatment in patients with pancreatic cancer.

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Footnote

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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

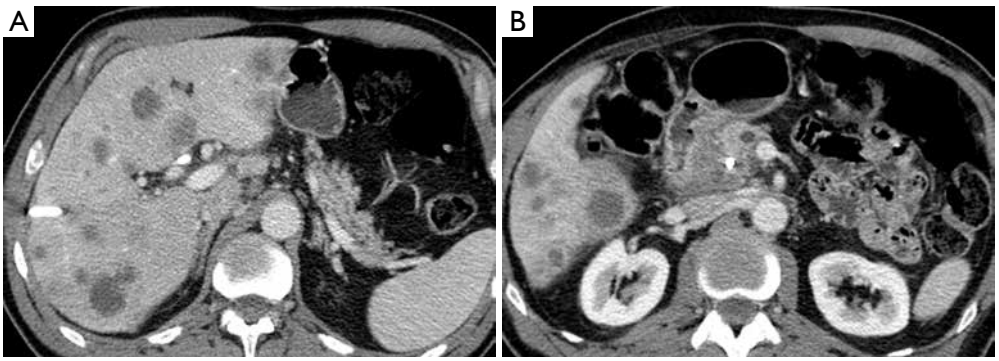

Figure 1 A 58-year-old man with stage IV pancreatic adenocarcinoma at presentation. (A) Portal venous phase 5 mm axial MDCT image through the pancreatic body and tail reveals slight dilation of the main pancreatic duct and numerous liver metastases; (B) at a more caudal level, the hypovascular mass in 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

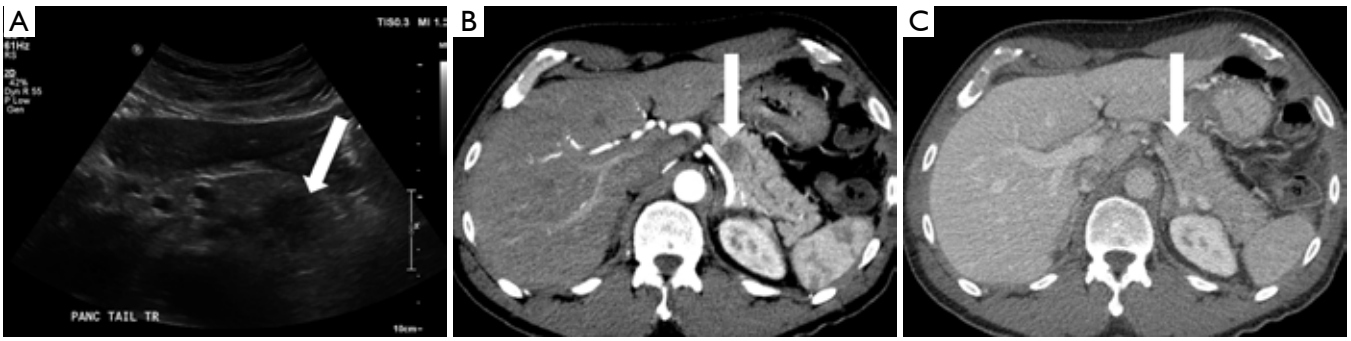

Figure 2 A 50-year-old man who underwent abdominal sonography for abdominal pain. (A) Transabdominal sonographic transverse image through the pancreatic body and tail in the upper abdomen shows a poorly marginated hypoechoic lesion (arrow); same patient, multiphasic MDCT the next week demonstrates that 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

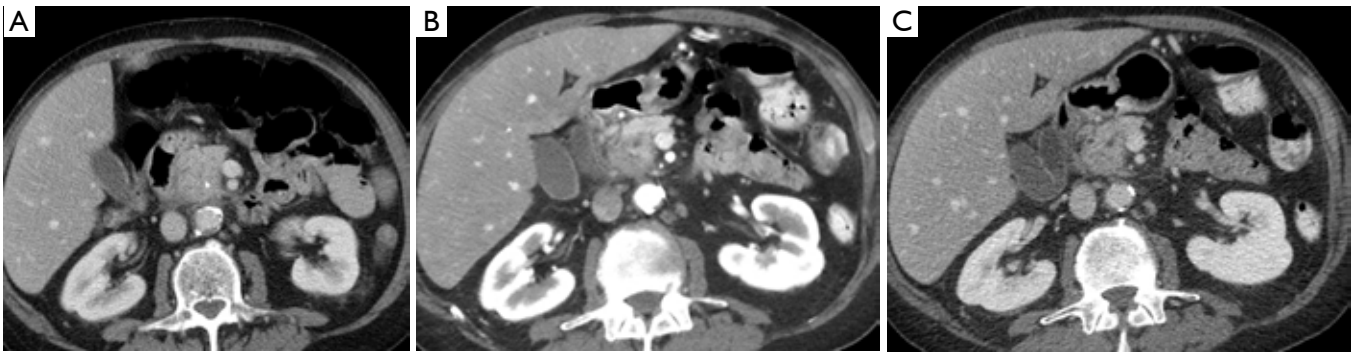

Figure 3 A 60-year-old man who presented to the emergency department with nausea and abdominal pain was found to have possible pancreatic head mass. (A) Portal venous phase 5 mm axial image demonstrates fullness in the pancreatic head, but a mass is not clearly discernable. A multiphasic MDCT examination 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.

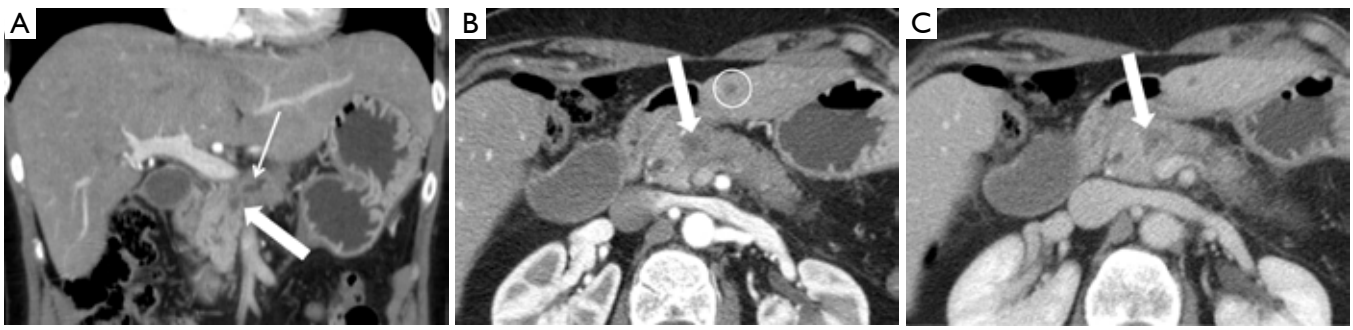

Figure 4 A 63-year-old woman with small pancreatic adenocarcinoma and upstream main pancreatic duct dilation. (A) Coronal reformatted 3 mm MDCT portal venous phase image demonstrates the dilated main pancreatic duct (small arrow) leading in to the 1.0 cm ductal adenocarcinoma (large arrow) in the pancreatic 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

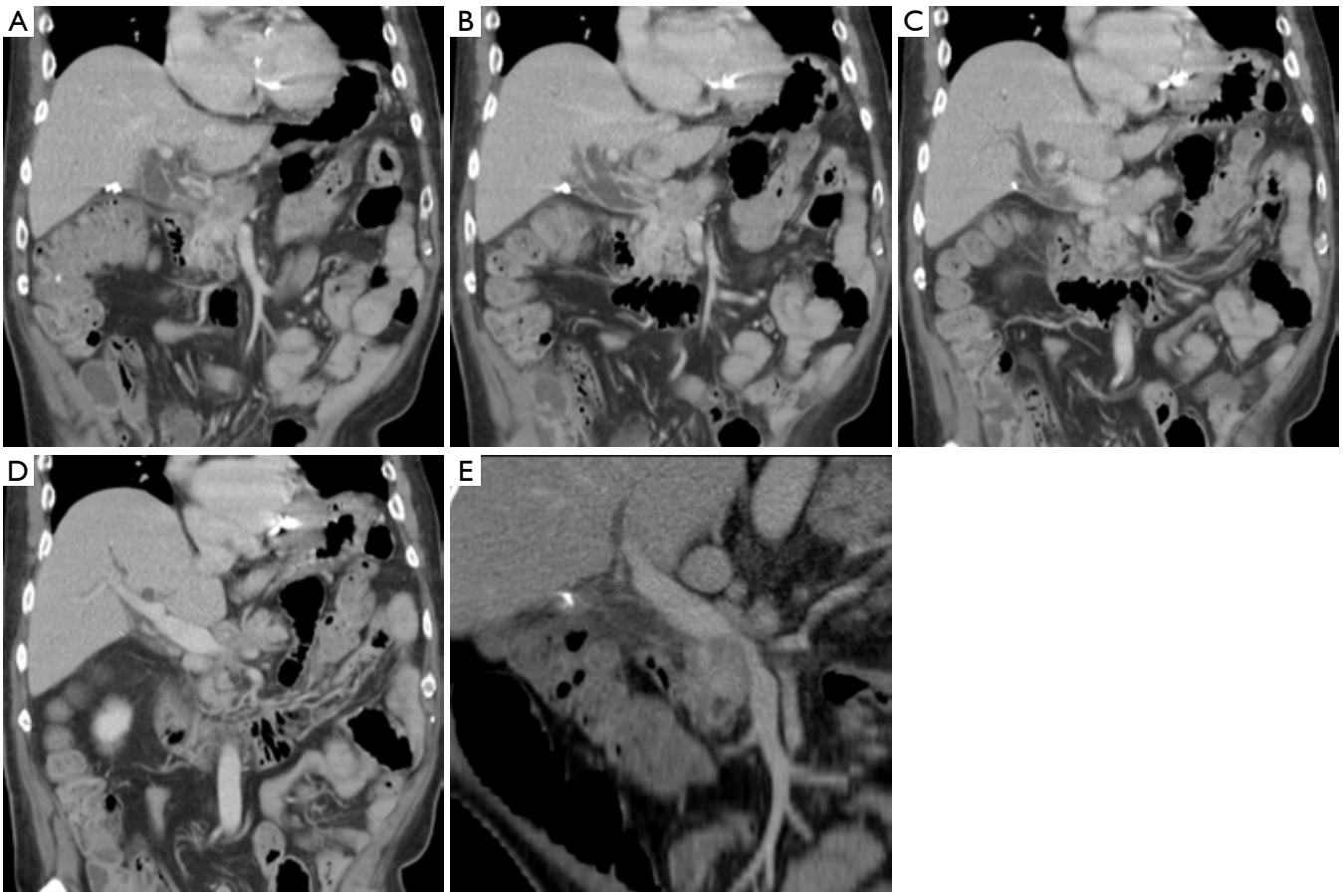

Figure 5 A 69-year-old man with a narrowed superior mesenteric vein. (A-D) Successive coronal reformatted images progressing from anterior to posterior demonstrate narrowing of the portal confluence by the hypovascular pancreatic adenocarcinoma in the superior head region, much better depicted, particularly 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.

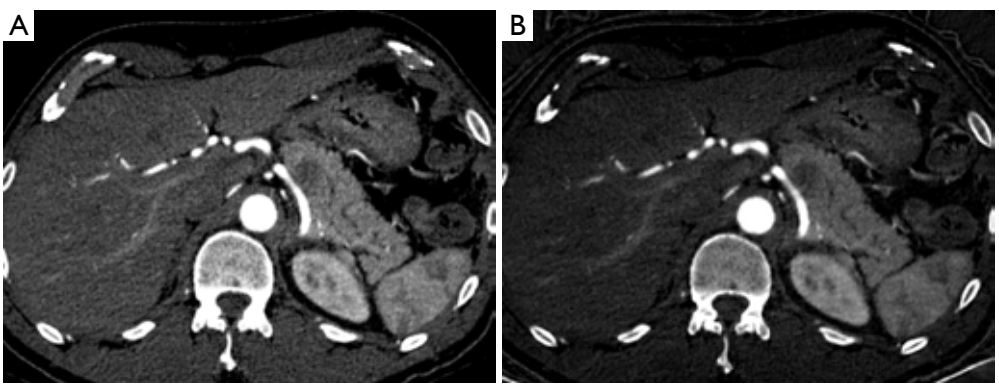

Figure 6 Dual energy MDCT in a 50-year-old man with a small resectable pancreatic ductal adenocarcinoma in the body region (same patient as *Figure 2*). (A) Low viewing energy (52 keV) axial 2.5 mm image and (B) iodine material density 2.5 mm image demonstrate increased conspicuity of the lesion and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

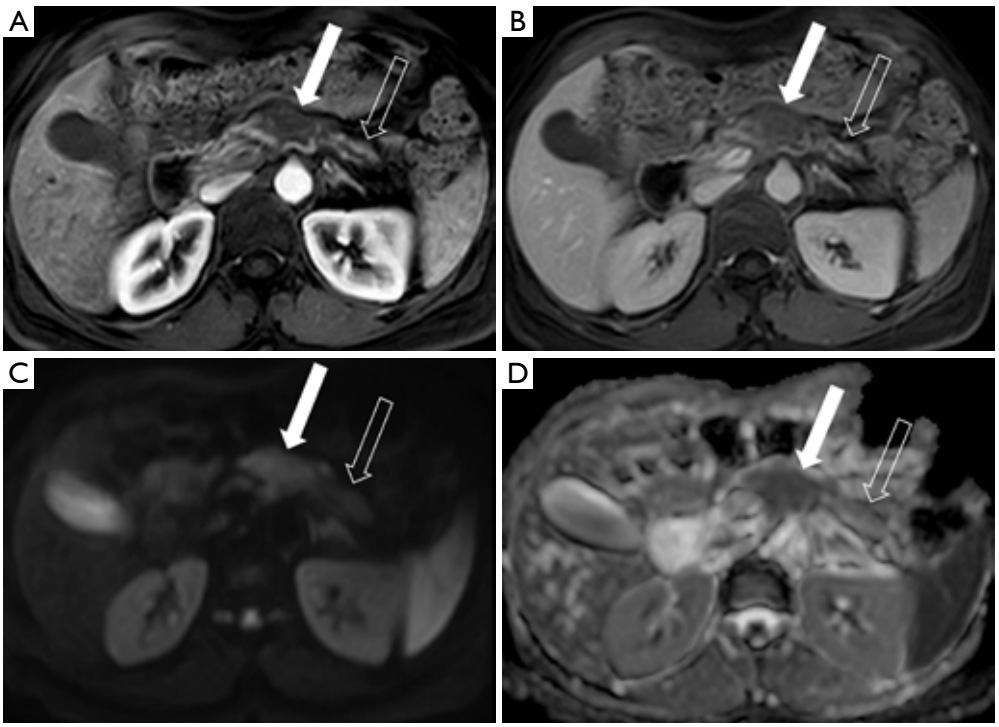

Figure 7 A 49-year-old woman who underwent upper abdominal MRI to evaluate an incidental hepatic lesion detected on abdominal ultrasound obtained for abdominal pain. (A) Pancreatic parenchymal; and (B) portal venous phase 5 mm axial images well depict the 3.0 cm mass (solid arrows) in the pancreatic 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).

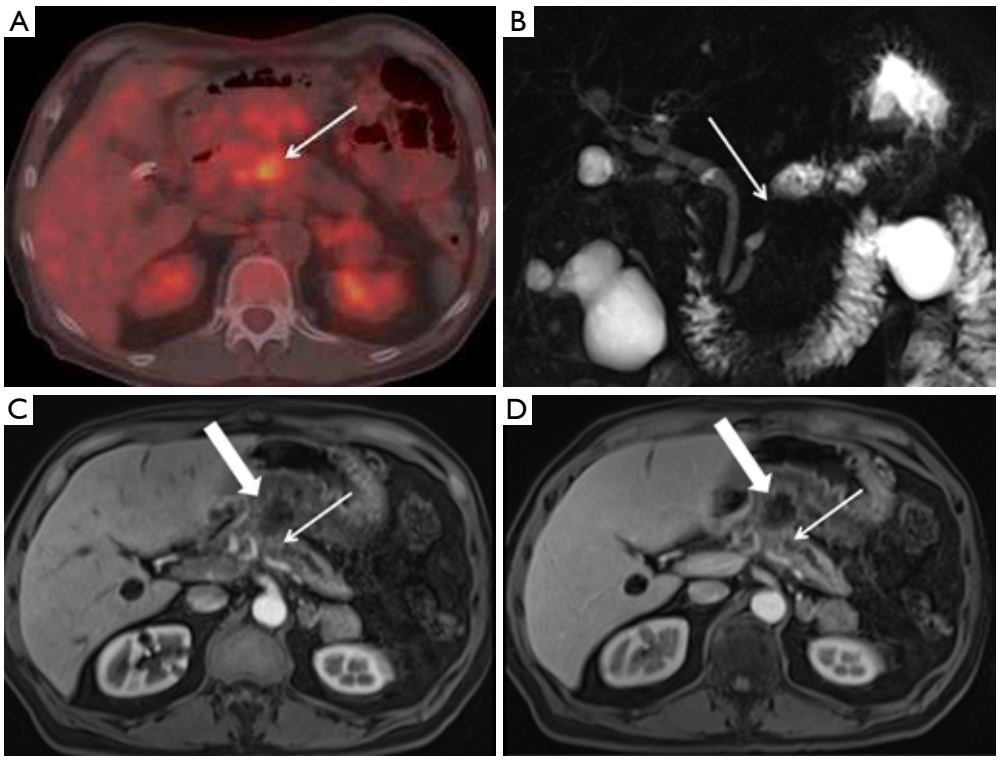

Figure 8 A 75-year-old man with SMV occlusion and locally advanced pancreatic cancer who underwent PET/CT. (A) Axial PET/CT image through the pancreatic body and neck regions reveals an FDG-avid lesion in the midline (arrow). No distant metastatic lesions were detected, but there is abnormal, less FDG 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).

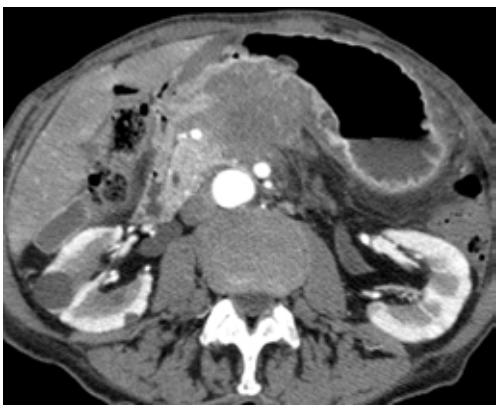

Figure 9 An 85-year-old woman with locally invasive pancreatic adenocarcinoma. Pancreatic parenchymal phase axial image demonstrates the low attenuation hypodense mass in the pancreatic neck/body extending through the posterior antral wall and disrupting the enhancing gastric mucosa.

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,

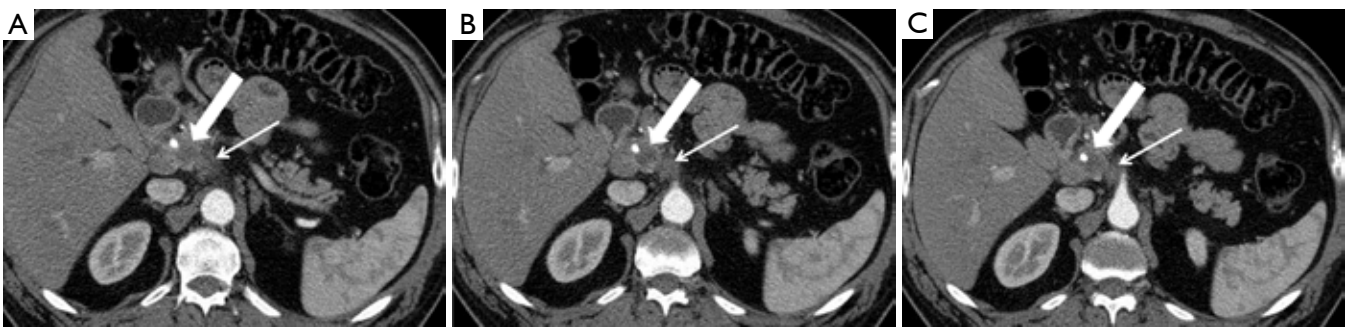

Figure 10 A 61-year-old man with small pancreatic cancer and perineural spread to the celiac ganglion. (A-C) Successively caudal pancreatic parenchymal phase 2.5 mm axial images demonstrate the hypovascular mass in the medial pancreatic head extending posteriorly along the plexus pancreaticus capitalis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

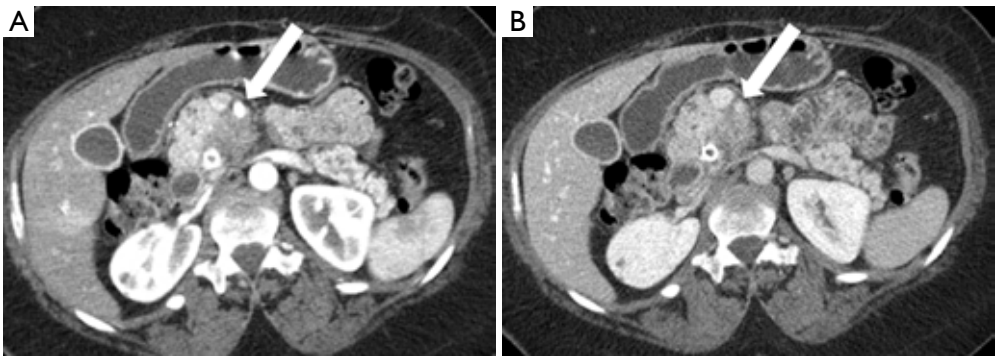

Figure 11 A 55-year-old woman with SMA encasement. (A) Pancreatic parenchymal phase 2.5 mm axial image depicts the relationship of the hypovascular mass in the medial pancreatic head to the SMA (arrow) where there is ≥180° contact indicating encasement; note that this relationship is better seen on this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

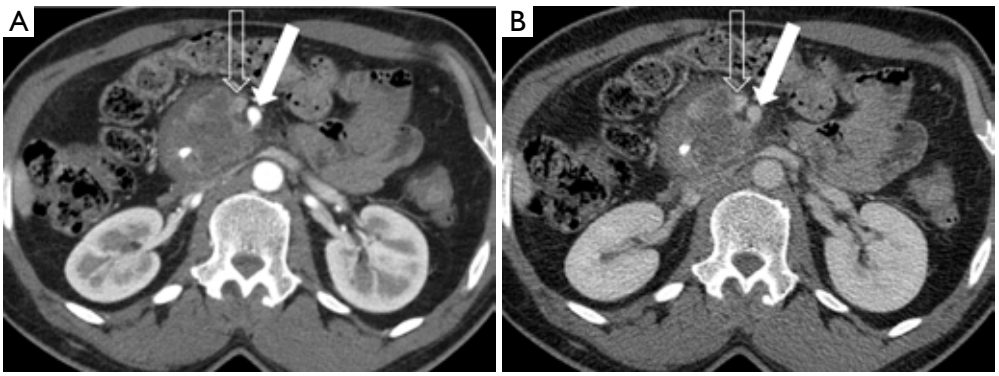

Figure 12 A 52-year-old man with SMA abutment. (A) Pancreatic parenchymal phase 2.5 mm axial image demonstrates contact of the large mass in the pancreatic head with <90° of the SMA (arrow); the SMV (open arrow) is not well evaluated in this phase of contrast, but is better seen on (B) the portal venous 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.

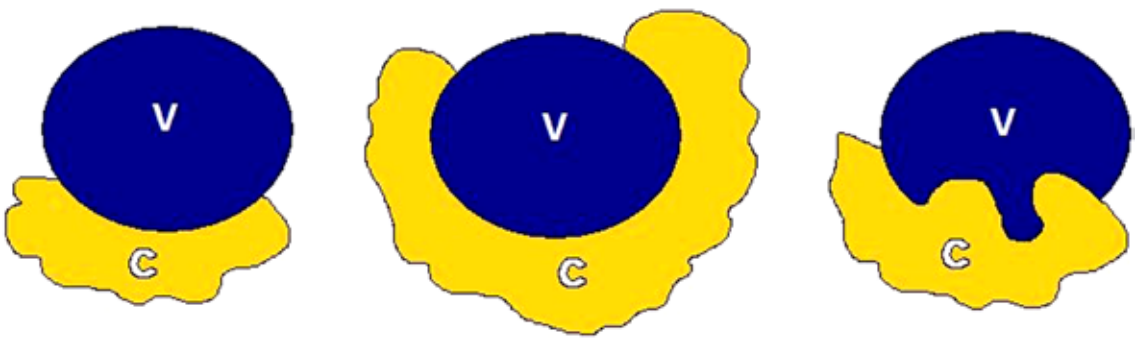

Figure 13 Cartoon depiction of vascular involvement. (A) Abutment of the C with the V; (B) encasement; and (C) involvement/invasion with teardrop deformity. C, cancer; V, vessel.

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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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Pancreaticoduodenectomy for pancreatic cancer: perspective from the United States

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Introduction

Despite being a relatively rare cancer, pancreatic cancer is the third leading cause of cancer death in the United States with over 41,000 patients succumbing to the disease in 2016 alone (1). In fact, pancreatic cancer is projected to be the second most common cause of cancer deaths by 2030 (2).

Approximately 75% of all pancreatic cancers arise in the head of the pancreas. Among patients with resectable disease, a pancreaticoduodenectomy (PD) is required for complete extirpation of the tumor among eligible patients and offers the best chance for long-term survival. The surgical resection of the head of the pancreas was first performed by Walther Kausch in Germany in 1909 but later popularized by Allen Whipple (3,4). Over the past several decades, PD has become a safe operation with recent perioperative mortality rates quoted at less than 1% (5,6). Perhaps equally important as the surgical treatment of pancreatic cancer, a comprehensive evaluation and multi-disciplinary treatment team including medical oncologists, gastroenterologists, pathologists, and radiation oncologists are necessary for the treatment of this deadly disease. As such, this article will focus on the multi-disciplinary approach to the patient with pancreatic cancer requiring PD in the United States.

Preoperative workup

All patients presenting with known or suspected pancreatic cancer are required to undergo high-resolution pancreas-specific imaging. Based on the available data (7) and practice preferences of the surgeons at our institution, multi-detector thin-slice pancreas protocol CT scans are performed. MRI is utilized if patients have a contraindication to CT scan (i.e., dye allergy) or for closer evaluation of small indeterminate liver or pancreatic lesions unable to be characterized following CT scan. Patients are seen in our multi-disciplinary pancreas clinic, which is attended by pancreatic surgeons, radiologists, gastroenterologists, pathologists, and medical oncologists. Each individual case is thoroughly reviewed during our multi-disciplinary conference. A treatment decision is created based on individual patient and disease-related factors. Preoperative endoscopy is often unnecessary except for patients requiring preoperative biliary drainage or to obtain a biopsy for those patients set to receive neoadjuvant chemotherapy. As previous studies have shown that preoperative biliary drainage/stent placement may cause an increase in perioperative complications (8), this modality is used sparingly at our institution and often only when total bilirubin >10 mg/dL or when cholangitis is suspected.

Neoadjuvant chemotherapy

Patients with clearly resectable disease most commonly proceed directly to PD without any neoadjuvant therapy. An ongoing randomized controlled clinical trial at our institution, however, is currently testing a granulocyte-macrophage colony-stimulating factor (GM-CSF) secreting vaccine in combination with cyclophosphamide in the neoadjuvant and adjuvant setting (9). Though several clinical trials evaluating the impact of neoadjuvant chemotherapy among patients with resectable disease remain ongoing (10), the standard of care remains to proceed with PD without neoadjuvant therapy in the absence of a clinical trial protocol.

Patients with locally advanced and borderline resectable disease are commonly referred for neoadjuvant chemotherapy, though the benefit of such an approach remains indeterminate without level 1 evidence. Current guidelines by the National Comprehensive Cancer Network recommend neoadjuvant therapy for borderline resectable disease. Several retrospective studies have evaluated the use of neoadjuvant chemotherapy among patients with locally advanced pancreatic cancer with varying results (11-16). Despite a consensus by the International Study Group of Pancreatic Surgery, variations in the definitions of borderline resectable and locally advanced pancreatic cancer remain (17). As such, resectability rates following neoadjuvant chemotherapy vary widely in the literature.

Among patients with initially unresectable disease, radiographic and pathologic response to neoadjuvant chemotherapy may lead to resectability in a subset of patients. In a systematic review of 57 studies, Gillen et al reported that 33.2% of patients were able to undergo resection after neoadjuvant therapy. However none of the included trials involved the administration of the now commonly utilized FOLFIRINOX chemotherapy regimen (18). More recently, Sadot *et al.* found that nearly one-third of patients with stage 3 locally unresectable diseases that received FOLFIRINOX ultimately underwent resection in a single institution review (19). Furthermore, median overall survival was significantly improved among patients who responded to FOLFIRINOX, potentially indicating favorable tumor biology. In other recently published data, Hackert *et al.* found that the neoadjuvant administration of FOLFIRINOX resulted in a 61% resection rate among patients with locally advanced pancreatic cancer as compared to only 46% among those receiving gemcitabine and radiation (20). In a meta-analysis involving 13 studies and 253 patients, Petrelli *et al.* found a R0 resection rate of 40% with the use of FOLFIRINOX-based neoadjuvant chemotherapy in borderline or unresectable pancreatic cancer (21). Based on these and other available data, it is the preference of our institution to use FOLFIRINOX for neoadjuvant chemotherapy, if tolerable by the patient, reserving a regimen of gemcitabine/protein-bound paclitaxel or others for those with dose-limiting toxicities or non-response to therapy.

Neoadjuvant chemoradiotherapy

Neoadjuvant radiation therapy in conjunction with chemotherapy has shown utility in many gastrointestinal cancers and is also used in the management of locally advanced and borderline resectable pancreatic cancer. The impact of the addition of radiotherapy to standard neoadjuvant chemotherapy regiments has been evaluated in numerous studies with wide-ranging results (14,22,23). In a retrospective analysis by Stessin *et al.* using Surveillance, Epidemiology, and End Results (SEER) data, median survival was significantly improved with neoadjuvant radiotherapy (22). In a multi-institutional study involving our own institution, the use of radiation therapy in conjunction with gemcitabine/oxaliplatin was well tolerated and resulted in an R0 resection in 84% of patients (23). In a meta-analysis involving 11 studies with 4,400 patients, Gillen *et al.* reported that neoadjuvant chemoradiotherapy resulted in a resectability rate of 74%; this rate dropped to 33% among those initially deemed unresectable (18). Interestingly, patients who had their cancer converted to resectable disease after neoadjuvant therapy had a median survival of 21 months, which was equivalent to that of patients who initially presented with resectable disease (18). Taken together, our team routinely offers neoadjuvant radiotherapy in addition to chemotherapy among patients with unresectable locally advanced disease without distant metastasis.

Preoperative preparation

Epidural placement is utilized based patient and provider preferences. All patients receive 5,000 units of subcutaneous heparin approximately one hour prior to incision (24). Aerobic and anaerobic antibiotic prophylaxis is administered within one hour prior to incision and continued for 24 hours postoperatively (25). Hair is trimmed prior to incision using a razor and a chlorhexidine-based solution is used as surgical antiseptic.

Surgical approach and technique

Minimal invasive PD

Operative approach is based on both patient-specific factors (patient body habitus, performance status, patient preference) and surgeon preference and experience. Recent data has shown that the use of minimally invasive techniques for complex pancreatic surgery throughout the United States is increasing (26). Laparoscopic PD has been shown to be a safe and cost-effective operation (27-29). In a review of 108 patients undergoing laparoscopic PD,

Croome *et al.* found total laparoscopic PD resulted in a shorter hospital length of stay and a longer progression-free survival as compared to patients undergoing open PD (30). Even among patients requiring major venous resection, laparoscopic PD was found to be safe and feasible (31).

Robotic PD has gained popularity in recent years. In one of the largest analysis of robotic PD, Zureikat *et al.* found robotic PD to be a safe and feasible operation (32). As with most new technology, there appears to be a learning curve as Boone et al found statistical improvements in several quality metrics following robotic PD with increasing number of cases (33). In a recent multi-institutional comparison of open versus robotic PD, robotic PD was associated with lower blood loss and reductions in major complications (34). At our institution, both laparoscopic PD and robotic PD are offered and an operative approach is decided upon after a thorough discussion with the patient. Regardless of the operative approach, intra-operative resection and reconstruction techniques remain similar.

Open PD

Due to the high-sensitivity of high-resolution imaging, diagnostic laparoscopy is not routinely performed. We utilize a midline incision from the sub-xiphoid process and extending to the level of the umbilicus. Several variations in PD are possible and are discussed below:

- Pylorus-preserving *vs.* classic PD: several randomized trials have shown equivalent outcomes between pylorus-preserving and classic PD and thus we consider both techniques to be equivalent and choose it based on surgeon's preference (35,36);
- Extended lymphadenectomy: as many randomized trials and systemic reviews have shown a lack of benefit and an increase in postoperative complications, extended lymphadenectomy is not routinely performed (37-41);
- Major venous resection: resection of the portal vein/superior mesenteric vein is occasionally necessary to achieve an R0 resection. Major venous resection (SMV/PV) is performed in approximately 5% of all cases at our institution and is getting more common (6). Primary repair *vs.* patch venoplasty is performed depending on the amount of vein resected and the potential flow compromise of the repaired vessel. In instances that require the entire vein to be resected, a primary end-to-end anastomosis is performed after mobilization of the SMV/PV if feasible. If this is not technically possible due to a long-segment involvement, an interposition graft using allograft femoral vein is often used for better size match.

  Riediger *et al.* reported their experience in 53 patients with vein resection and showed that this technique is safe with no increase in postoperative morbidity (42). Many other series have also confirmed the feasibility of vein resection during PD (43-45);
- Pancreaticojejunostomy *vs.* pancreaticogastrostomy: though several trials have shown mixed results between pancreaticojejunostomy and pancreaticogastrostomy reconstruction (46,47), the preference at our institution is to reconstruct the pancreatic remnant using a pancreaticojejunostomy technique. Pancreatic reconstruction is performed using a two-layer duct to mucosa pancreaticojejunostomy at our institution. Postoperative pancreatic fistula (POPF) can be significantly reduced by meticulous anastomosis with optimization of blood supply at the pancreaticojejunostomy (48);
- Gastrojejunostomy: the antecolic location of gastrojejunostomy has been shown to reduce the incidence of delayed gastric emptying in several publications and is the preferred method of enteric reconstruction (49,50). Furthermore, a side-to-side anastomosis is also preferred, as previous studies have shown this to reduce delayed gastric emptying as compared to an end-to-side anastomosis (51);
- Pancreatic drainage: though there remains to be consensus as to the necessity of routine intraperitoneal drainage following PD (52-54), routine intraperitoneal drainage with closed suction drains is commonly used at our institution.

Postoperative care

All patients are admitted to the intensive care unit postoperatively. A nasogastric tube is left in overnight and removed on the morning postoperative day 1. An enhanced recovery after surgery (ERAS) pathway is followed and includes a stepwise increase of diet, early ambulation, and minimization of narcotics. Early drain removal is encouraged after minimal drainage (<50 mL/24 hours) and low drain amylase levels (<3 times of serum amylase) following postoperative day 3. Based on randomized trial results from our institution (55), the use of erythromycin to prevent delayed gastric emptying is used at the discretion of the surgeon. Similarly, octreotide or Pasireotide may

be utilized in patients with high-risk for pancreatic fistula including those with soft glands and small pancreatic ducts (56, 57).

Complications

In our recent series of PD of 1,687 patients with pancreatic ductal adenocarcinoma, the overall complication rate was 41% (6). The most common complications following open PD include delayed gastric emptying (DGE) (16%), wound complications/surgical site infection (11%), and POPF (6%) (6). The incidence of wound complications and DGE after minimal invasive PD is much lower comparing to open PD (58,59). DGE and wound complications are often related to POPF. In the absence of POPF, the management of DGE is mainly supportive. Nasogastric tube is used to decompress the stomach if DGE persists or is severe. Parental nutrition support is rarely needed but utilized if necessary. Based on our institutions randomized controlled trial (55), patients with DGE may benefit from prokinetics such as metoclopramide and erythromycin.

Follow-up

The average length of stay after PD is 7 days. Patients are seen for follow-up appointments following hospital discharge at 2 to 3 weeks and then every 3 months thereafter. The overwhelming majority of patients receive adjuvant chemotherapy +/– radiotherapy based on previous clinical trial results (18,60-62). Several clinical trials are ongoing evaluating different combinations of systemic chemotherapy as well as the safety and efficacy of targeted agents and immunotherapy (63). Postoperative surveillance imaging scans and laboratory studies (including CA 19-9 levels) are performed every 3–6 months to evaluate for disease recurrence.

Conclusions

Pancreatic cancer is an aggressive cancer with increasing incidence in the United States. PD for pancreatic cancer can be performed in a safe manner that offers the best hope for long-term survival. Complications following PD, however, are common. Further experience with minimally invasive techniques, as well as ongoing trial results in various neoadjuvant and adjuvant chemotherapy, immunotherapy, and targeted therapy regiments may result in improved future patient outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Management of pancreatic cancer in China: the Tianjin Medical University Cancer Institute and Hospital experience

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Abstract: Pancreatic cancer is one of the most aggressive malignancies with a dismal prognosis. The incidence and mortality of pancreatic cancer in China has been increasing dramatically during the past several decades. With the development of surgery, chemotherapy drugs and radiotherapy technologies, the prognosis of pancreatic cancer has changed greatly in recent years in China, especially in our cancer center, Tianjin Medical University Cancer Institute and Hospital. First, we will make a precise pre-surgery diagnosis in our center involves computerized tomography (CT) images, circulating tumor cell (CTC) measure and KRAS sequence. Second, according to the pre-surgery diagnosis, we will perform the *en bloc* resection and standard lymphadenectomy for pancreatic cancer patient. Third, multidisciplinary team (MDT) is a feature in our cancer center that choose the best therapy for different stage patients with individualized treatment. Finally, clinical trial is important characteristic in our cancer center because the new drug and target drug can be used to treat pancreatic cancer in time. This article reviews the development of pancreatic cancer diagnosis and therapy, highlights the hallmarks of management in our cancer center and discusses the future necessary efforts to improve the quality of life and prognosis for Chinese patients.

Keywords: Pancreatic cancer; Tianjin Medical University Cancer Institute and Hospital; management

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies which is the fourth leading cancer death in USA, with a 5-year overall survival rate of only 7.7% and a median survival time of less than 6 months (1). The incidence and mortality of pancreatic cancer in China has been increasing dramatically during the past several decades. Among the most common cancers considered in the trend analyses for men, incidence rate of pancreatic cancer increased dramatically from 2000 to 2011. An upward trend in age-standardized mortality rates was observed for pancreatic cancer in men (2).

For localized pancreatic cancer (15–20%) patients, surgical resection is the only potentially curative therapy and the 5-year survival rate is about 20%. For the 80% to 85% patients who have locally advanced or metastatic disease, the median survival rate is about 6 months (3). Assessment the localization, size, local vessels and lymph nodes metastasis of tumor are the key to determine the resectability. And importantly, surgeon's expertise and patient's overall status are the major factors influencing prognosis. With safety improved on pancreatic surgery in the past years, surgeons still focused on the role of more extensive surgery for improving long-term survival. However, whether surgeon should perform extended lymphadenectomy for patients

or not is controversial. The data shows that the extended lymphadenectomy during pancreaticoduodenectomy did not benefit overall survival and may increase morbidity (4). So, in our pancreatic cancer center, standard lymphadenectomy during pancreaticoduodenectomy continues to be the choice for pancreatic cancer patients.

To improve the prognosis, early diagnosis and treatment is crucial for management of pancreatic cancer. Combined with our basic experiments data [circulating tumor cell (CTC), BRAC1 and WT1 sequencing], the rate of early diagnosis for pancreatic cancer improved greatly. According to the condition of patients, neoadjuvant therapy and chemotherapy are applied to improve the survival in our cancer center. Immunotherapy and targeted therapy are potential methods to achieve better and more durable clinical responses.

Currently, multidisciplinary team (MDT) dominates the treatment for pancreatic cancer, although surgery and other therapies have rapidly development. As we perform the highest number of pancreatic cancer surgeries in Tianjin and the 5-year survival rate has reached 7% for operable patients, we will introduce the overall management mode of pancreatic cancer in our cancer center, Tianjin Medical University Cancer Institute and Hospital, and share our experiences of clinical exploration during the last decade in this review.

Diagnosis

Imaging techniques have been used in the finding and diagnosis of pancreatic cancer. We will introduce computerized tomography (CT) scan and Endoscopic ultrasound in pre-surgery diagnosis. CT scan for upper abdomen with arterial and venous phase enhancement is the preferred examine method and can assess local and regional disease extent. Thin slice cuts of CT allow for better visualization of essential vasculature including the celiac trunk, superior mesenteric artery, and portal vein that determine the resectability of the pancreatic cancer. Endoscopic ultrasound is also important for diagnosis and management of pancreatic cancer. It not only can measure the depth and wide of the tumor, but also can guide a fine needle biopsy to obtain tissue diagnosis (5).

CTCs are the cells that fall off from solid tumor lesions and circulate into the peripheral blood, and they can be detected by the CellSearch system and used as promising biomarker to evaluate chemotherapeutic efficacy in prostate cancer, breast cancer and colorectal cancer (6-8). Recent study shows that CTCs have the diagnostic value in PDAC. Total CTC number had 75.8% sensitivity and 68.7% specificity at a cutoff value of 2 CTC cells/3.2 mL. This report is the first to demonstrate that CTC number is useful in PDAC diagnosis. It concluded that both CTC subtype and total CTC number may act as potential biomarkers for PDAC (9). In our pancreatic cancer center, we also detect CTCs in PDAC patients for diagnosis and evaluation the distal metastasis. We use the negative enrichment combined with immunofluorescence and *in situ* chromosomal hybridization (NE-iFISH) to detect CTCs in PDAC patients. The NE-iFISH system can measure aneuploidy in CTCs from PDAC patients and dynamically monitored CTCs during the process of chemotherapy in PDAC patients. We also explored the sensitivity and specificity of the combination of carbohydrate antigen 19-9 (CA19-9) and CTCs determined by the NE-iFISH system in the early diagnosis of pancreatic cancer (10). Our data showed that the NE-iFISH system exhibited a dramatically high detection rate of CTCs in PDAC patients (90%). The diagnostic rate of PDAC reached 97.5% when combining CTCs ≥2 and CA19-9 >37 μmol/L.

BRAC1 and *BRCA2* are two tumor suppressor genes which can repair DNA sequence. Somatic mutations and germline genetic variants on *BRCA1/BRCA2* have been found associated with the tumorigenesis of pancreatic cancer. It reported that three tag missense variants on *BRCA1/BRCA2* in 603 sporadic pancreatic cancer patients in a Chinese population. The data discovered a germline missense variant on *BRAC1* associated with dismal prognosis of PDAC patients with locally advanced stage (11). In our center, we also measure the mutation of *BRCA1/BRCA2* genes by sequencing from peripheral blood of PDAC patients. If the patients with *BRCA1/BRCA2* or other DNA repair mutations, we will choose gemcitabine + cisplatin as chemotherapy according to the NCCN Guideline for Pancreatic Adenocarcinoma, Version 2.2017 (12). These works may contribute to the precision management of this disease.

The Wilms' tumor 1 (*WT1*) gene is act as a tumor suppressor gene expressed in the etiology of Wilms' tumor (13). It has been reported 75% of PDAC cells express *WT1* gene and protein (14). And recent reports have showed that *WT1*-targeted cancer vaccines have an obviously antitumor effect combined with chemotherapy for PDAC patients (15). Therefore, we will sequence the *WT1*

gene to find and confirm the mutation. After analysis the sequence data, we want to set the criteria to help diagnosis and instruct chemotherapy and immunotherapy.

In a word, in our cancer center, to make a precise diagnosis for pancreatic cancer we will make a regular CT scan and combined with CA19-9, CTCs measure, *BRCA1/2* and *WT1* sequence.

Precise surgical mode: en bloc resection and standard lymphadenectomy

Radical resection is the only potentially curative therapy for pancreatic cancer patients. For PDAC patients, it is important to give a precise tumor-node-metastasis (TNM) staging pre-surgical resection according the CT and ultrasound. Therefore, during the surgical operation, we will make an *en bloc* resection for tumor and perform the standard lymphadenectomy. The meta-analysis comparing standard lymphadenectomy with extended lymphadenectomy for pancreatic cancer showed that the extended procedure did not benefit overall survival, and may even cause a trend towards increased morbidity (16). So, in our cancer center, standard pancreaticoduodenectomy is the choice for pancreatic cancer.

In our center, for early stage pancreatic cancers and benign and low-malignancy tumors, laparoscopic operation is the best choice for patients. The meta-analysis showed that laparoscopic pancreatectomy resulted in less loss of blood and time during operation, and lower rates of overall complications and infections compared with open pancreatectomy (17). Another choice is application of robotic surgery, because of the advantages including the rate of R0 resections, greater lymph node yield, shorter hospitalization and faster recovery. Robotic pancreatectomy is not a common procedure in China due to cost.

Current and future therapies for pancreatic cancer

Adjuvant therapy

Recurrent disease can be seen in up to 70% of the resected patients (18). Adjuvant chemotherapy is recommended in all resected cancers including T1N0 disease. In our center, the current standard adjuvant treatment is the gemcitabine (1,000 mg/m^2 on days 1, and 8, of each 21-day cycle) for six cycles. We will examine the CT scan and CA19-9 value to evaluate the abdominal situation of patients every two-cycle.

Borderline resectable cancer and locally advanced pancreatic cancer (LAPC)

There is no uniform treatment for borderline resectable pancreatic in the world. Using the rationale neoadjuvant therapy for borderline resectable pancreatic cancer can achieve a negative surgical margin. It reported that pancreatic cancer patients receiving neoadjuvant FOLFIRINOX have a significant increase in median overall survival compared with patients who were treated with surgery but not neoadjuvant therapy (P=0.008) (19). Other centers use neoadjuvant FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) to treat borderline resectable pancreatic cancer and get an R0 rate of approximately 90% (20,21). Prof. Von Hoff reported that combined with Nab-paclitaxel (albumin-bound paclitaxel particles) and the standard gemcitabine treatment regimen significantly improved overall survival, progression-free survival, and response rate with metastatic pancreatic cancer (22). In our cancer center, firstly, we will conduct the FOLFIRINOX or the combination of gemcitabine and nab-paclitaxel chemotherapy for borderline resectable patients according overall status and cost situation, and then repeat the CT scan to reevaluate the tumor by RECIST criteria.

LAPC is recognized inoperable due to primary tumor encasement the celiac axis or the superior mesenteric artery. In our center, LAPC patients get FOLFIRINOX or gemcitabine and nab-paclitaxel chemotherapy to eradicate micro-metastatic disease and downstage the primary tumor (5).

Advanced and metastasis pancreatic cancer

Gemcitabine has been the standard treatment for unresectable pancreatic cancer patients for a couple of decades. Gemcitabine with a low response rates (only 5–10%) and short survival (less than 6 months) due to drug resistance. Attempts were made to combine with gemcitabine and other chemical-drugs and target-drugs but there was no improve in overall survival of pancreatic cancer patients over the past years.

In 2010, there is a breakthrough in the treatment of metastatic pancreatic cancer when FOLFIRINOX versus gemcitabine chemotherapy get a doubling of median overall survival (11.1 *vs.* 6.8 months, HR 0.57, P<0.0001) and response rate significantly improved (31.6 *vs.* 9.4%, P=0.0001) (19). Results of the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) were showed an obviously improvement in OS with the combination of

gemcitabine plus nab-paclitaxel over gemcitabine alone (8.5 *vs.* 6.7, HR 0.72, P=0.000015) and PFS (5.5 *vs.* 3.7, HR 0.69, P=0.000024) and RR (23% *vs.* 7%) (22). The toxicity profile of nab-paclitaxel was better than FOLFIRINOX chemotherapy.

There is another novel oral fluoropyrimidine derivative, S-1, used for treating gastric, pancreatic, lung, head, neck and breast carcinomas. It consists of three pharmacological agents (at a molar ratio of 1:0.4:1)—tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and Oxonic acid (Oxo) (23). The S-1 has been used to treat pancreatic cancer since the early 2000s in Japan (24). The randomized phase III GEST (Gemcitabine and TS-1 Trial) study for locally advanced or metastatic pancreatic cancer investigated the superiority of gemcitabine plus S-1 (GS) and the non-inferiority of S-1 alone versus gemcitabine alone on OS (25). Recently, GS achieved better health-related quality of life (HRQOL) than gemcitabine alone, resulting a good balance between overall survival and HRQOL benefits (26).

So, in our cancer center, the choice of FOLFIRINOX, gemcitabine and nab-paclitaxel or GS determined by the patient's functional status, general condition, comorbidities and economic condition, etc.

Current and future biomarkers for pancreatic adenocarcinoma

Diagnostic biomarkers

Up to now, there is no ideal biomarker for early diagnosis of PDAC. The following part reviews the present and future diagnostic biomarkers for pancreatic cancer.

CA19-9 and carcinoembryonic antigen (CEA)

CA19-9 is the most used biomarker for PDAC diagnosis and the only biomarker permitted by the FDA (27,28). Nevertheless, the sensitivity and specificity of CA19-9 are only 75.5% and 77.6% for the diagnosis of PDAC (29). In other disease, for example, liver cirrhosis, acute cholangitis, pancreatitis, obstructive jaundice and digestive tumor, CA19-9 is also elevated. Important, CA19-9 does not secret in patients with Lewis-null blood type.

CEA is also limited for early detection and diagnosis PDAC. The sensitivity and specificity of CEA is only 39.5%/81.3% (29). Recently, Liu *et al.* reported that serum of CEA(+)/CA125(+)/CA19-9 ≥1,000 U/mL is associated with poor surgical outcome and can be applied to choose proper patients for pancreatectomy (30).

Genetic and epigenetic markers

KRAS is an oncogene and the mutation rate is more than 90% in pancreatic cancer (31). A recently research show that combination KRAS mutation analysis with the cytological analysis of an EUS-FNA specimen can obviously improve the sensitivity from 80.6% to 88.7%, compared to EUS-FNA alone, with a specificity of 92% (32). According to the surprisingly result, we also examine the KRAS mutation by sequence from peripheral blood of PDAC patients in our center.

There are other genes including *TP53*, *SMAD4*, and *CDKN2A* (cyclin dependent kinase inhibitor 2A) also mutated in PDAC (33). Thus, additional studies are needed to investigate the potential role of *TP53*, *SMAD4*, and *CDKN2A* mutation as a diagnostic biomarker.

MicroRNAs (miRNAs)

miRNAs are a group of small non-coding RNAs consisting of 18–25 nucleotides that regulates post-transcriptional modifications of multiple genes (34). Nowadays, using miRNA as a potential biomarker for pancreatic cancer has increased. miRNAs have been investigated in pancreatic tumor tissue, blood samples, pancreatic juice, stool, and urine (35). Among these, miR-21, miR-155, miR-196a, and miR-210 were shown to be upregulated in pancreatic tissue (36), serum samples (37), fecal specimen (38) and pancreatic juice (39) of PDAC patients. Future studies need to assess the benefit of miRNAs as early detection marker. There are other non-coding RNAs [including long non-coding RNAs (lncRNAs) and small ncRNAs] might play a potential function as a detection marker for PDAC (28).

In our cancer center, we not only detect the value of CA19-9 and CEA for detection and diagnosis, but also measure the level of KRAS and other miRNAs for clinical trial.

Conclusions

In conclusion, Tianjin Medical University Cancer Institute and Hospital performs standard, distinctive management based on clinical guidelines, research studies and the context in China. It can be summarized in following parts. First, pre-surgery diagnosis in our center involves CT images, CTC measure and KRAS sequence to increase accuracy. Second, we will perform the *en bloc* resection and standard lymphadenectomy for pancreatic cancer patient. Third, MDT is a feature in our cancer center that choose the best therapy for different stage patients. Finally, clinical trial is important characteristic in our cancer center because the

new drug and target drug can be used to treat pancreatic cancer in time. In a word, our therapy experience always considers patient survival and quality of life and is consistent with international therapy standards.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Pancreatic surgery: evolution and current tailored approach

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Abstract: Surgical resection of pancreatic cancer offers the only chance for prolonged survival. Pancretic resections are technically challenging, and are accompanied by a substantial risk for postoperative complications, the most significant complication being a pancreatic fistula. Risk factors for development of pancreatic leakage are now well known, and several prophylactic pharmacological measures, as well as technical interventions have been suggested in prevention of pancreatic fistula. With better postoperative care and improved radiological interventions, most frequently complications can be managed conservatively. This review also attempts to address some of the controversies related to optimal management of the pancreatic remnant after pancreaticoduodenectomy.

Keywords: Pancreatic cancer; pancreatic resection; pancreatic fistula; total pancreatectomy; pancreatic anastomosis

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Introduction

Pancreatic cancer is an uncommon type of cancer, the incidence of which has been on the rise worldwide, likely correlated with an increased incidence of obesity. Pancreatic cancer rates are highest in North America and Europe, where the frequency of its occurrence puts it in the eighth place (1,2). Although it is not very common, its significance lies in the fact that it is most often diagnosed in the late stage of the disease, it is almost always fatal, surgical treatment is rather complex and there is no adequate adjuvant treatment. Moreover, it is the only type of cancer in Europe of which increased mortality is anticipated in 2014 (3). Five-year survival rate in Europe and North America is around 6%, which makes it the fourth cause of death according to cancer mortality statistics (1,2). However, within the 10% of patients who have been diagnosed in the early, localised stage, the 5-year survival rate rises to 25% (4,5).

There has been immense progress in surgical treatment of pancreatic cancer patients since Kausch and the first pancreaticoduodenectomy of periampullary tumor (6), Whipple and his modification of pancreaticoduodenectomy in the 1930's (7), Priestley and the first successful total pancreatectomy reported in 1944 (8), and Traverso and Longmire with pylorus-preserving pancreaticoduodenectomy in 1978 (9) (*Table 1*). Despite the initially high mortality and morbidity following surgical treatment (12,13), with the development of surgical technique and concentration of patients in high-volume centres, as well as with improvement in perioperative care, the rate of morbidity and mortality following pancreaticoduodenectomy has dropped to acceptable levels. Morbidity and mortality following total pancreatectomy have also become more acceptable, as well as long term outcome with better blood glucose regulation and exocrine insufficiency management which has been made possible by developing novel insulin formulations and pancreatic enzyme supplements. Improved management of endocrine and exocrine insufficiency following total pancreatectomy and the discovery of novel clinical entities, such as IPMN (intraductal papillary mucinous neoplasm), have revived what was once a rare surgery, with an increased number of procedures and widened indications for surgical treatment.

Despite its complications, curative resection is the single most important factor determining the outcome in patients with pancreatic adenocarcinoma (14). Surgery remains the

Table 1 History and evolution of pancreaticoduodenectomy

1909: Kausch 2-stage procedure, first cholecystectomy, followed 6 weeks later by resection of the head of pancreas, pylorus, first and second half of duodenum, with gastroenterostomy, closure of common bile duct and anastomosis of pancreas and the third part of duodenum (6)
1935: Whipple 2-stage procedure, first posterior gastroenterostomy, ligation and division of the common bile duct with cholecystogastrostomy, followed by resection of the duodenum and pancreatic head, with closure of pancreatic stump (7)
1940: Whipple completed the procedure in a single stage, in 1942, modification of the procedure with pancreaticojejunostomy (10)
1946: Waugh and Clagett first used pancreaticogastrostomy (11)
1978: Taverso and Longmire reported pylorus preserving pancreaticoduodenectomy (9)

Table 2 Risk factors for pancreatic leak

Pancreas related
Soft pancreatic parenchyma
Small size pancreatic duct
Ampullary, duodenal, cystic and bile duct neoplasms
Patient related
Male sex
Age >70 years
Cerebrovascular disease
Duration of jaundice
Procedure related
Type of pancreatic anastomosis
Use of somatostatin
Surgeon's experience
Intraoperative blood loss

principal treatment for pancreatic cancer and offers the only chance for cure (15,16).

Complications of pancreaticoduodenectomy

Pancreaticoduodenectomy is indicated for patients with neoplasma of the head of the pancreas, ampullary, duodenal and distal bile duct neoplasms. It is also performed for chronic pancreatitis and rarely for trauma. Although high mortality rate approaching 25% and morbidity rates up to 60% (12,13) were initially related to pancreaticoduodenectomy, in the last few decades there has been a significant decline in mortality rates which is now 3-5% in highly specialized centres (17-19). On the other hand, there are still numerous possible postoperative complications related to pancreaticoduodenectomy and morbidity rates are as high as 30-60% (20-24). Most common local complications are delayed gastric emptying with prevalence of 8-45% (25-30), pancreatic fistula with reported rates from 2% to 22% (20,23,24,30-34), infectious complications, most commonly intra-abdominal abscesses, with prevalence from 1-17% (30,35) and hemorrhage. Postoperative bleeding occurs in 3-13% of patients (5,17). Hemorrhage within the first 24 hours is result of the inadequate hemostasis at the time of surgery, a slipped ligature, bleeding from an anastomosis or diffuse hemorrhage from the retroperitoneal operation field, most likely caused by underlying coagulopathy, frequently seen in jaundiced patients (36,37). Late hemorrhage, occurring 1-3 weeks after surgery, is often caused by an anastomotic leak with erosion of retroperitoneal vessels (38) with mortality rates from 15%to 58% (39,40). Other causes of late hemorrhage are pseudoaneurysm and bleeding from the pancreaticojejunostomy. Management includes completion pancreatectomy or formation of pancreatic neoanastomosis (36). Other, not so common, complications are cholangitis, colonic and biliary fistulas. Within the systemic complications group, cardiopulmonary and neurological complications prevail (34,36). Over the years the most significant pancreaticoduodenectomy complication was the development of pancreatic leak and fistula (33,41,42) due to its frequency of occurrence and high mortality. However, with the refinement of surgical techniques, improved post-operative intensive care and concentration of patients in high-volume centres decreased mortality, this also resulted in decline of pancreatic fistula incidence. Depending on the definition used, the incidence of pancreatic fistula used to be 10-29% (43). Nowadays, according to the International Study Group Pancreatic Fistula Definition the incidence of pancreatic fistula is from 2% to 10% in the centres of excellence (30,34,41). The seriousness of pancreatic fistula can be seen in its possible consequences, such as septicaemia and hemorrhage, which makes it the leading risk factor for postoperative death, longer hospital stay and increased hospital costs after pancreaticoduodenectomy even today. Risks for developing the fistula can be divided into a few groups (*Table 2*). The first group is pancreas related. One

Table 3 Trials of pancreatic management

Varibles	Authors	Number of patients	Pancreatic fistula (%)
Trials comparing outcomes of the use of somatostatin and analogues	Büchler *et al*. 1992 (53)	125 somatostatin *vs*. 121 control	17.6 *vs*. 38
	Friess *et al*. 1995 (54)	122 *vs*. 125	12 *vs*. 28
	Yeo *et al*. 2000 (55)	104 *vs*. 107	11 *vs*. 9
	Sarr *et al*. 2003 (56)	135 *vs*. 140	24 *vs*. 23
	Suc *et al*. 2004 (57)	122 *vs*. 108	17 *vs*. 19
Trials comparing outcomes of PG and PJ	Yeo *et al*. 1995 (58)	73 PG *vs*. 72 PJ	12 *vs*. 11
	Duffas *et al*. 2005 (59)	81 *vs*. 68	16 *vs*. 20
	Bassi *et al*. 2005 (60)	69 *vs*. 82	13 *vs*. 16
Trials comparing outcomes after duct stenting	Winter *et al*. 2006 (61)	115 with stent *vs*. 119 no stent	11.3 *vs*. 7.6
	Poon *et al*. 2007 (62)	60 *vs*. 60	6.7 *vs*. 20
	Pessaux *et al*. 2011 (63)	77 *vs*. 81	26 *vs*. 42
Trials comparing outcomes after different anastomotic technique	Marcus *et al*. 1995 (64)	68 duct-to-mucosa *vs*. 18 invag	4.4 *vs*. 5.5
	Bassi *et al*. 2003 (65)	144 duct-to-mucosa *vs*. invag	13 *vs*. 15
	Berger *et al*. 2009 (66)	97 duct-to mucosa *vs*. 100 invag	24 *vs*. 12
	Peng *et al*. 2007 (67)	106 binding *vs*. 111 invag	0 *vs*. 7.2

Table 4 Solutions for pancreatic leak

Use of Somatostatin & analogues
Pancreaticogastrostomy
Binding or invaginating pancreaticojejunostomy
Pancreatic duct stenting
Pancreatic duct occlusion
Total pancreatectomy

of the most widely recognized risk factors is texture of the remnant pancreas; the relation between high rates of pancreatic fistula up to 25% (42,44-47) in the presence of soft pancreatic parenchyma has been repeatedly reported. The pancreatic duct size has been implicated as another relevant factor. Pancreatic duct diameter under 3 mm is related to a significantly higher risk of pancreatic fistula development (42,44,46,47). Pancreatic fistula development is also predisposed by pancreatic pathology: ampullary, bile duct, duodenal carcinoma and cystic neoplasms are correlated with an increased risk of pancreatic fistula (48,49). The second group of risk factors are patient related, including male sex, advanced age (older than 70) (48,50), cardiovascular disease probably due to poor blood supply of anastomosis (30), duration of jaundice (51). The last group is procedure related and includes a type of pancreaticodigestive anastomosis, use of somatostatin, surgeon's experience and increased operative blood loss (20,21,23,24,30,43-47,52).

Prevention of complications

A great deal of research has been conducted over the years aimed at decreasing the risk of pancreatic fistula occurrence (*Table 3*). It has focused on the influence that somatostatin, pancreatic duct stenting and pancreatic occlusion have on the reduction of PF rate. In addition, a number of studies have become available which compare pancreaticogastric anastomosis versus pancreaticojejunal anastomosis and different pancreaticojejunal anastomotic technique and their influence on frequency of PF occurrence (*Table 4*).

Somatostatin and analogues

Octreotide is a synthetic long acting analogue of somatostatin, a potent inhibitor of pancreatic endocrine and exocrine secretion, and gastric and enteric secretion as well. Somatostatin and its analogue are administered postoperatively as prophylaxis. The idea behind this is that the decrease of pancreatic secretion would result in the pancreatic fistula prevention. A number of RTC have examined the benefit of somatostatine in pancreatic leakage prevention, but the results were inconsistent (68). In 2005, Connor conducted meta-analyses of ten RTCs which showed benefits of the use of somatostatin and its analog octreotide in reducing the rate of biochemical fistula formation, pancreas-specific complications and total morbidity. The incidence of clinical anastomotic disruption and mortality

rate was not reduced (69). Cochrane Database Systematic Review from 2013 involved 2,348 patients in 21 trials. Conclusion drawn from it was that there was no significant difference in postoperative mortality, reoperation rate or hospital stay between the group of patients who were administered prophylactic somatostatin or its analogue and the group which received either placebo or nothing at all. In the somatostatin analogue group, the incidence of pancreatic fistula was lower, as was the overall number of patients with postoperative complications. On the other hand, when only patients with clinically significant fistulas were considered, there was no relevant difference between the groups. Based on the current available evidence, somatostatin and its analogues are recommended for routine use in people undergoing pancreatic resection (70).

Duct stenting

Internal, transanastomotic stent diverts the pancreatic juice from the anastomosis, and enables easier placement of sutures reducing the risk of iatrogenic duct occlusion. Its drawbacks are possibility of migration of the stent and occlusion which may lead to pancreatic fistula formation. There are not enough studies on internal stenting and their results have been contradictory (71,72). RTC from Winter *et al*. (61), involving 234 patients, demonstrated that internal duct stenting did not reduce the rate or the severity of pancreatic fistulas. The pancreatic fistula rates were 11.3% in patients with internal stent and 7.6% in patients without internal pancreatic stent. External stent has the possibility of a complete diversion of the pancreatic juice away from the pancreaticojejunal anastomosis which prevents the activation of pancreatic enzymes by bile. The RTC by Poon *et al*., involving 120 patients, showed that the external stent group pancreatic fistula rate was significantly lower (6.7%) compared to the group which did not undergo the same procedure (20%) (62). In prospective multicenter randomized trial from Pessaux *et al*., it was shown that external drainage reduces pancreatic fistula rate (26% *vs*. 42%), morbidity and delayed gastric emptying after pancreaticoduodenectomy in high risk patients (soft pancreatic texture and a nondilated pancreatic duct) (63). Cochrane database systematic Review from 2013 involved 656 patients in order to determine the efficacy of pancreatic stents, both external and internal, in preventing pancreatic fistula after pancreaticoduodenectomy. The use of external or internal stents was not associated with a statistically significant change in incidence of pancreatic fistula, re-operation rate, length of hospital stay, overall complications and in-hospital mortality. In the subgroup analysis, it was found that the use of external stents is associated with lower incidence of pancreatic fistula, the incidence of complications and length of hospital stay. The review concludes that the external stenting can be useful, but further RCTs on the use of stents are recommended (73).

Pancreatojejunal anastomosis technique

Ever since Whipple modified pancreaticoduodenectomy in 1942 by performing pancreaticojejunostomy instead of occlusion of pancreatic remnant, this type of anastomosis has been most commonly used for a reconstruction of pancreaticodigestive continuity. There have been further modifications over the years. For example, jejunal loop can be positioned in antecolic, retrocolic or retro-mesenteric fashion, or the isolated Roux loop pancreaticojejunostomy can be performed. The anastomosis can be performed as an end-to-end anastomosis with invagination of the pancreatic stump in the jejunum or as an end-to-side anastomosis with or without duct-to-mucosa suturing (*Figure 1*) (47,65,74,75). In 2002, Poon *et al*. su compared duct-to-mucosa with invagination anastomosis, and found that the duct-to-mucosa anastomosis was safer (49). In 2013, Bai *et al*. conducted a meta-analysis of randomized controlled trials comparing duct-to-mucosa (467 patients) and invagination pancreaticojejunostomy (235 patients). Pancreatic fistula rate, mortality, morbidity, reoperation and hospital stay were similar between techniques (76). Peng described a binding pancreaticojejunostomy technique with a pancreatic fistula rate of 0%. This was further validated in an RTC demonstrating that the binding pancreaticojejunostomy in comparison with end-to-end pancreaticojejunostomy demonstrated significantly decreased postoperative pancreatic fistula rates, morbidity, mortality and shortened the hospital stay (67,77). However, multiple authors reported better results with binding or invaginating pancreaticojejunostomy technique in patients with soft pancreatic parenchyma and small size duct (42,64).

Type of pancreatic anastomosis

In 1946, Waugh and Clagett first introduced pancreaticogastrostomy in clinical practice (11) (*Figure 2*). There are several advantages of this anastomosis—the proximity of the stomach and the pancreas enables tension-free anastomosis, the excellent blood supply to the stomach

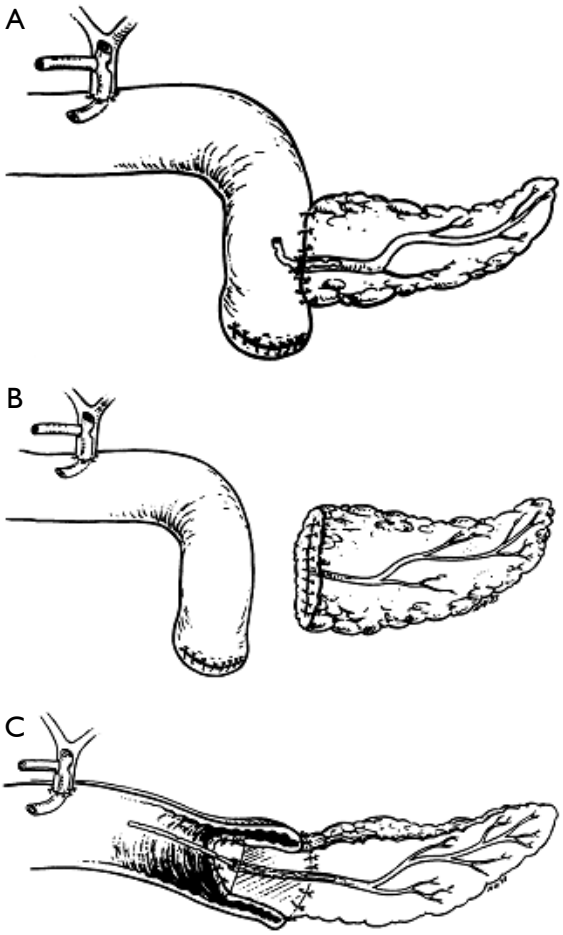

Figure 1 Different ways of doing the anastomosis for a pancreaticoduodenectomy. (A) End-to-side pancreaticojejunostomy; (B) oversewing of the pancreatic remnant; (C) end-to-end pancreaticojejunal invagination

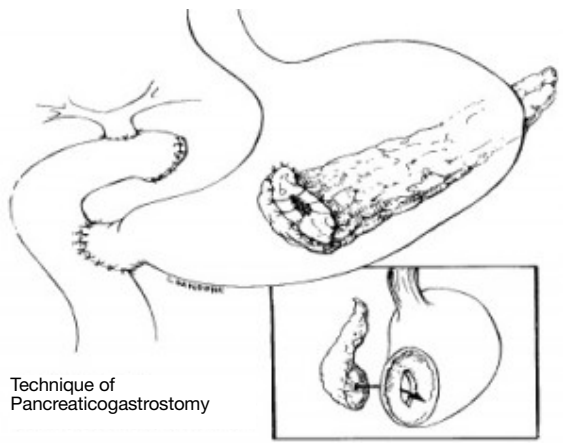

Figure 2 Pancreaticogastrostomy.

enhances the anastomotic healing, the acidity of the stomach content inactivates pancreatic enzymes, and the lack of enterokinase in the stomach prevents the conversion of trypsinogen to trypsin and subsequent activation of the pancreatic enzymes, which reduces the risk of pancreatic leakage due to anastomosis autodigestion (78). Yeo *et al*. were first to conduct prospective randomized trial comparing pancreaticojejunostomy and pancreaticogastrostomy, but this trial failed in finding a significant difference in pancreatic fistula incidence (58). Statistically relevant difference regarding pancreatic fistula rates, postoperative complications or mortality has not been found in two RTCs from Duffas *et al*. (59) and Bassi *et al*. (60) as well. In 2014 Menahem *et al*. published their meta-analysis of seven randomized controlled trials, involving 562 patients with pancreaticogastrostomy and 559 patients with pancreaticojejunostomy after pancreaticoduodenectomy. The pancreatic fistula rate was significantly lower in the PG group (11.2%) then in the PJ group (18.7%). The biliary fistula rate was also significantly lower in the PG group (2% *vs*. 4.8%) (79). Liu *et al*. dealt with the same RTCs, but focused also on morbidity, mortality, hospital stay, reoperation and haemorrhage and intra-abdominal fluid collection. As well as having lower incidence of pancreatic and biliary fistula, the PG group showed a significantly lower incidence of intra-abdominal fluid collection and shorter hospital stay (80).

Duct occlusion

In 1935 Whipple reported on the first series of results after pancreaticoduodenectomy, at which time he did not anatomize pancreas with digestive tract. Since there was a high PF incidence rate, he abandoned the aforementioned concept and implemented pancreaticojejunostomy as a standard part of surgical procedure. Where there was suture ligation of the pancreatic duct, without anastomosis, the rates of pancreatic fistulas was as high as 80% (64,81,82). In a randomized controlled trial, conducted by Tran *et al*., involving 86 patients with duct occlusion and 83 patients with pancreaticojejunostomy, it was revealed that the da ductal occlusion group had a significantly higher pancreatic fistula rate (17% *vs*. 5%), but it failed to show any relevant difference regarding other postoperative complications, mortality and exocrine insufficiency. After 3 and 12 months, there were significantly more patients with diabetes mellitus in the ductal occlusion group (83). Occlusion of the main pancreatic with fibrin glue was also abandoned (83,84) based on results from several RCTs because of high fistula

rates and higher incidence of postoperative diabetes mellitus (83,85).

Treatment

Surgical interventions for complications after pancreatoduodenectomy are nowadays rare, as low as 4% in centers of excellence (33,34) and 85-90% of patients with pancreatic fistula can be treated conservatively by means of fluid management, parenteral nutrition, suspension of oral intake and antibiotics administration. Lower percentage of surgical interventions can also be attributable to more advanced radiologic interventions for intrabdominal fluid collections, fistulas and bleeding. Indications for surgical intervention are clinical deterioration of the patient, disruption of pancreatic anastomosis, signs of spreading peritonitis, abdominal abscess, haemorrhage, and wound dehiscence. Delayed hemorrhage can be managed, if a patient is stable, by angiographic embolization of the bleeding vessel. In the remaining number of cases, emergency surgery is indicated (86,87). The type of surgical procedure depends on the underlying cause, and includes procedures such as peripancreatic drainage, control of hemorrhage, disruption of the pancreatic anastomosis without a new anastomosis or a conversion in another type of pancreatic anastomosis and a completion pancreatectomy (68,78).

Completion pancreatectomy has nowadays become a rare procedure, owing to improvements in conservative treatment and radiologic interventions. Completion pancreatectomy is indicated in patients with pancreatic anastomotic leak accompanied by sepsis or bleeding (88). Owing to the seriousness of the patient's condition, this procedures postoperative mortality is between 38% and 52% (89,90).

Total pancreatectomy

Total pancreatectomy was first performed in 1943 by Rockey (91), but the patient died soon after it. In 1944 Priestley performed the first successful total pancreatectomy (8). During the 1950's this procedure was popularised by Ross (92) and Porter (93) who considered it to be safer than pancreatoduodenectomy with pancreatojejunostomy, because pancreatic anastomosis related morbidity and mortality was avoided. Because of high local recurrence rates and poor long-term survival after Whipple operation, combined with the erroneous belief that pancreatic adenocarcinoma is a multicentric disease, total pancreatectomy was thought to be an oncologically more radical procedure (94,95). Later reports revealed disadvantages of this procedure: long-term survival after total pancreatectomy was similar or lower than after pancreatoduodenectomy (96), morbidity and mortality were as high as 37% (95-97), with obligatory development of brittle diabetes mellitus and exocrine insufficiency. Development of steatohepatitis with progressive liver failure (98) is another potential long-term complication. Without advantages of oncologic radicality and with diabetes mellitus and malabsorption difficult to control, total pancreatectomy was abandoned for treating pancreatic tumors.

Number of total pancreatectomy procedures has been on the rise over the last two decades, for which several reasons can be named. Concentrating patients in high-volume centres and enhancements in surgical techniques have resulted in morbidity and mortality decline, the rates of which are now as low as 35% and 5% respectively (99-101) and are comparable to those following pancreatoduodenectomy. The second reason lies in the development of novel insulin formulations and better pancreatic enzyme preparations. While exocrine insufficiency can be relatively easily managed using pancreatic enzyme supplements, the control of endocrine insufficiency demands intensive insulin programmers, extensive patient education and continuing care (102). Total pancreatectomy is followed by not only insulin insufficiency, but also of glucagon and pancreatic polypeptide insufficiency, which leads to development of diabetes mellitus with tendencies to severe hypoglycemia. However, with intensive insulin programmers utilizing multiple daily insulin injections or pumps, and with glucagon rescue therapy, glycemic control can be achieved with satisfactory levels of HBA1c, similar to those in patients with insulin-dependent diabetes from other causes (99,102-104) and quality of life comparable to those of the patients after PPPD (99,100).

The third reason is the existence of broader spectre of indications which now include in situ neoplasia with malignant potential such as intraductal papillary mucinous neoplasm and multifocal islet cell neoplasm; hereditary pancreatitis and familiar pancreatic cancer syndromes. Other indications include locally advanced or multicentric pancreatic adenocarcinoma, neuroendocrine tumors, metastases in the pancreas, end-stage chronic pancreatitis with disabling pain, trauma, unsafe pancreatic anastomosis and completion pancreatectomy after dehisced pancreato-enteric anastomosis (98,99,102).

Given that the postoperative total pancreatectomy

morbidity and mortality outcomes do not differ significantly from those after pancreatoduodenectomy (17,33,34,98,99), and the quality of life is fairly acceptable, there are no restrictions for performing total pancreatectomy on patients with indication for total pancreatectomy (99,101).

Discussion

After decreasing a 30-day mortality rate after pancreaticoduodenectomy to about 5%, surgeons have now focused their efforts on reducing morbidity, which is still as high as 30-60% (17,105-107). This mainly concerns reduction in incidence of pancreatic fistula, which is regarded the main cause of other frequent complications such as delayed gastric emptying, septic complications and intraabdominal haemorrhage.

Ever since Whipple's first pancreaticojejunostomy after pancreatoduodenectomy, surgeons have paid special attention to anastomosis between pancreatic remnant and digestive tract. In highly specialized centres pancreatic fistula incidence is from 0 to 18% (108), with death rate of 5%. Among the reports classifying pancreatic fistulas as A, B or C, following ISGPF grading system, incidence of grade C pancreatic fistulas was 2-5% (109-111). Grade C pancreatic fistulas were associated with sepsis from intrabdominal collections and bleeding, with high reoperation rate, prolonged length of hospital stay and with mortality rates from 35-40%. Soft pancreatic parenchyma is the most widely recognized risk factor for pancreatic fistula (112,113), along with three other relevant factors: duct size smaller than 3 mm, excessive intraoperative blood loss and specific pathology: ampullary, duodenal, cystic or islet cell neoplasms (111). The question is what to do when one or more risk factors for development of pancreatic fistula are present. There are multiple factors that will influence a decision which procedure to perform. First, to preserve a sufficient endocrine pancreatic function, approximately 50% of alpha and beta cells must be preserved (114). Alpha and beta cells are located predominately in the tail of the pancreas (115), so, theoretically, classical pancreaticoduodenectomy procedure should not cause endocrine insufficiency. When a pancreatic duct is occluded, without pancreatic anastomosis, pancreatic exocrine insufficiency will surely develop. Besides exocrine insufficiency, there is a significantly higher incidence of diabetes mellitus in patients with chemical occlusion of pancreatic duct in comparison with patients with a pancreaticojejunostomy (83). On the other hand, exocrine insufficiency will also develop in 9-20% of patients after Whipple procedure (116,117). The underlying cause are probably stenosis of pancreatic anastomosis and postoperative inflammation of the pancreas and fibrosis of pancreatic parenchyma (118,119). Other factors include patient's preexisting diabetes mellitus or exocrine insufficiency, patient's overall health and performance status and patient's compliancy. A surgeon has several possibilities. First option is to perform a pancreatoduodenectomy with pancreatogastrojejunostomy, because of the lower incidence of pancreatic fistula with this type of anastomosis (79,80) or pancreatoduodenectomy with invagination pancreaticojejunostomy, recommended by a number of authors in case of soft pancreatic parenchyma and small pancreatic duct (67,113). Second option is also pancreatoduodenectomy, but with occlusion of the pancreatic remnant, either by ligation of the main pancreatic duct or by occlusion of the main pancreatic duct by Neoprene, Ethibloc or fibrin glue injection. This procedure is related to a higher incidence of pancreatic fistula, but with more benign clinical course, because pancreatic enzymes are not activated. The last option is total pancreatectomy for initial treatment of patients with multiple risk factors. With this procedure potential risks of a pancreatic fistula are eliminated, but with establishment of a total pancreatic state. Because of glycemic instability, predisposition for severe, life-threating hypoglycemia, and need for close glucose monitoring and intense insulin programme, patient's compliance after total pancreatectomy is essential.

When a surgeon encounters such a significant problem, the decision about proper surgical management can be difficult to make. Besides purely technical challenges, patients overall health status, existing comorbidities, pancreas pathology and expected survival are crucial in the decision-making process.

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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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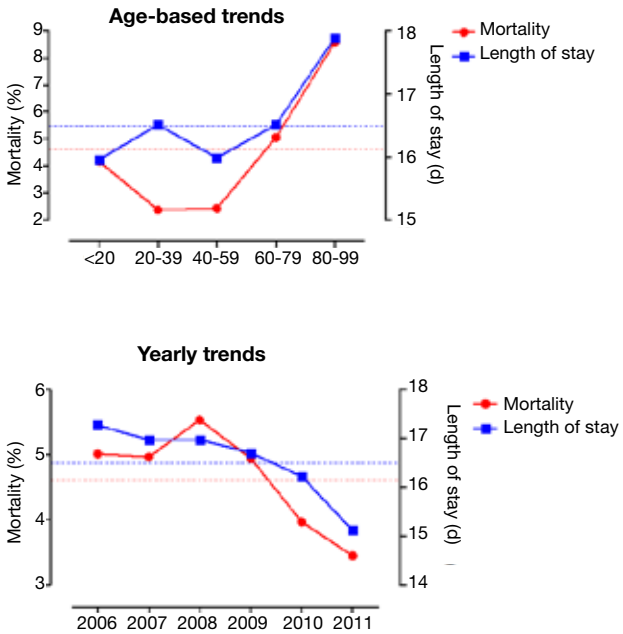
Introduction

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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Footnote

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Minimally invasive central pancreatectomy and pancreatogastrostomy: current surgical technique and outcomes

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Abstract: Recent improvements in imaging techniques and more frequent use of cross-sectional imaging have led to an increase in the identification of benign and low-grade lesions of the pancreas. Patients with resectable cancers are commonly treated by either a Whipple procedure or distal pancreatectomy (DP) based on the location of the tumor. Central pancreatectomy (CP) is a less commonly performed operation that has recently been utilized for resection of these now more frequently diagnosed low-grade and benign lesions located in the mid pancreas. Lesions that may have a relatively more indolent nature include branch-type intraductal papillary mucinous neoplasm (IPMNs), mucinous cystic neoplasms, neuroendocrine tumors, and solid pseudopapillary tumors. The goal of a CP is complete extirpation of the lesion, while preserving pancreatic parenchyma to reduce the risks of developing diabetes and exocrine insufficiency (EI). Although open CP has been shown to be safe and efficacious, the outcomes of a minimally invasive approach are still relatively underreported and therefore unknown. In this paper, we describe our surgical approach to performing a CP with an accompanying video demonstration of the key portions of the operation.

Keywords: Central pancreatectomy (CP); minimally invasive; robotic surgery; pancreatogastrostomy

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Introduction

With improvements in surgical techniques and perioperative care, the mortality associated with pancreatic resection (PR) has decreased dramatically; however the morbidity associated with this procedure remains high. Centrally located lesions pose a particular challenge due to the variety of options available for surgical resection. Patients may undergo pancreaticoduodenectomy (PD), distal pancreatectomy (DP) or central pancreatectomy (CP) depending on the size, location and malignancy potential of the lesion (1). CP (also known as middle pancreatectomy or median pancreatectomy) was first ascribed to Ehrhardt in 1908 (2,3). Guillemin and Bessot performed the first CP with pancreato-enteric reconstruction in 1957 for chronic pancreatitis, and subsequently Dagradi and Serio described the operation for resection of a benign lesion (insulinoma) in 1982 (1,4-6). The primary aim of performing a CP is the preservation of both endocrine and exocrine function of the pancreas while still maintaining oncologic efficacy (7). Specifically, for centrally located low-grade lesions, a DP or PD obligates a substantial volume of the pancreas removed, placing patients at higher risk of post-operative diabetes and exocrine dysfunction (7-9). In comparison to DP, CP also allows for preservation of spleen (7). Advantages of CP over PD include reduced mortality and preservation of the duodenum and bile duct, with only a single anastomosis needed for reconstruction as opposed to

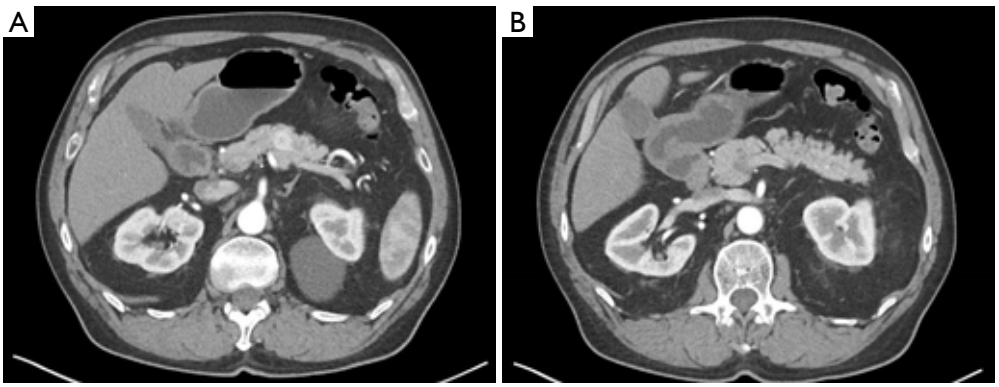

Figure 1 Pancreatic neuroendocrine tumor. (A) Cross sectional imaging demonstrates the characteristic appearance of a neuroendocrine tumor (arrow) located in the central pancreas. Given the location of the tumor, enucleation would not be an appropriate option; (B) the patient could potentially undergo a distal pancreatectomy (DP), however, there would be a significant volume of normal pancreas resected (box). Therefore, a central pancreatectomy (CP) would be a reasonable option for this patient.

multiple anastomoses required for restoring continuity of the hepatic duct, pancreatic duct and intestinal tract (1,10). The concerns surrounding CP include high incidence of post-operative pancreatic fistula (POPF) and potentially inadequate oncologic resection in cases of malignancy (9). However, studies have shown that although the rates of POPF after CP are relatively high (20–50%), oftentimes these patients possess soft glands and small ducts, which are both well-established risk factors for POPF (9). Also, in most cases the POPF is clinically insignificant [International Study Group on Pancreatic Fistula (ISGPF) grade A] (9). Therefore, CP is a reasonable approach for centrally located, benign or low-grade pancreatic lesions that allows preservation of pancreas parenchyma and adjacent organs.

With increasing utilization of laparoscopic and robotic pancreatectomy, patients can now undergo either an open or minimally invasive surgery (MIS) procedure. Laparoscopic and robotic PD has gained interest due to comparable morbidity, mortality and oncologic outcomes versus open PD when performed in select patients (11-15). For DP, MIS approach has now become the standard of care due to its favorable outcomes in comparison to open DP (11,16). In a recent meta-analysis comparing 1,814 patients undergoing open versus laparoscopic DP, the laparoscopic approach resulted in less blood loss, shorter hospital length of stay (LOS), fewer surgical site infections and lower morbidity (17). Similarly, a MIS approach for CP has become increasingly common with the goal of decreasing the impact of morbidity related to the decreased size of incisions, shorter hospital stays, and shorter time until return to work. While both laparoscopic and robotic CP are being performed, laparoscopy may be somewhat limited given the restricted workspace and the inability to articulate instruments in a manner requisite for these complex procedures (18-21). These limitations are potentially alleviated by the use of robotic surgery. Herein, we report our technique of performing an MIS CP, with accompanying video demonstration of the key portions of the operation. Indications for CP and a brief summary of outcomes following CP are also discussed.

Indications for CP

Pancreatic lesions of the central pancreas can be extirpated via numerous operative approaches depending on their size, location and pathology. Extended PD or near-total DP are performed for pancreatic ductal adenocarcinoma (PDAC) or main-duct-type intraductal papillary mucinous neoplasm (IPMN) with potential invasive component, in order to achieve adequate resection of the tumor and also the surrounding lymph nodes, which is not always achievable with CP (7,8). However, for low-grade malignant tumors or benign lesions, use of PD or DP would consequently remove much of the normal pancreatic parenchyma which is likely of no therapeutic benefit (*Figure 1*). Enucleation can also be considered; however, this should not be the procedure of choice for malignant tumors or benign lesions greater than 2 cm, or location adjacent to the main pancreatic duct (19). Therefore, CP may be an appropriate alternative for a subset of patients possessing low-grade malignant tumors or benign lesions restricted to the central pancreas (19). The most common indications for

Table 1 Indications for CP

Tumor type
Cystic lesions
Branch-type IPMN*
Cystic neuroendocrine tumor
Serous cystadenoma
Lymphoepithelial cyst
Mucinous cystic neoplasm
Solid lesions
Solid pseudopapillary tumor
Nonfunctional neuroendocrine tumor
Functional neuroendocrine tumor
Select metastases

*, main duct intraductal papillary mucinous neoplasm (IPMN) is often cited as a contraindication. CP, central pancreatectomy.

CP include neuroendocrine tumors followed by cysts that display indeterminate characteristics such as branch-duct-type IPMNs, and solid pseudopapillary neoplasms (*Table 1*) (1,7,8,19). Contraindications to this procedure include PDAC, main-duct-type IPMN, neoplastic involvement of adjacent organs, and large lesions where it is impossible to preserve the left pancreatic stump (2).

Surgical technique and technical aspects of MIS CP

All patients should be evaluated for a pancreatic lesion using a pancreas protocol CT or MRI and serum CA19-9 levels when deemed necessary. If a patient is found to have a lesion amenable to resection via an MIS CP, a preoperative assessment by an anesthesiologist is performed and medical clearance should occur similar to an open approach.

After surgical consent has been obtained, the patient is placed in a supine position with right arm extended to 90° and the left arm is tucked. Intravenous access, monitoring lines, and a Foley catheter are placed. A nasogastric tube is inserted for stomach decompression. The abdomen is prepped and draped in the standard manner. Safe entry to the abdomen is obtained via the Hassan technique (supraumbilical) or a Veress needle. The abdomen is then insufflated to 15 mmHg and a camera port is placed in the periumbilical position (12 mm). A 5 mm port for the liver retractor is placed in the right anterior axillary line. Subsequent ports include two right-sided abdominal robotic ports (8 mm) and a left-sided abdominal port (8 mm). The exact location of the robotic ports depends on whether a Si or Xi robot (da Vinci® Surgical System) will be used. The assistant port is placed in the left lower quadrant and should be 12 mm in order to accommodate a laparoscopic stapler. The robot is then docked over the patient's head or towards their left in case of the SI or XI robot (da Vinci® Surgical System) respectively.

Although the indications for MIS CP are generally low-grade neoplasms or benign tumors, inspection of the abdominal cavity and surface of the liver is performed to identify any pathologic implants. Subsequently, the lesser sac is entered with the vessel-sealing device and the gastrocolic omentum is dissected free from the stomach while preserving the gastroepiploic vessels. This dissection is carried from the pylorus up along the greater curvature of the stomach to allow elevation of the stomach and adequate exposure of the anterior surface of the pancreas. At this stage, if the lesion cannot be readily visualized, ultrasound can be used to delineate the extent of the tumor and its relationship to the surrounding structures. The inferior border of the pancreas is mobilized and SMV is identified coursing posterior to the pancreatic neck. The superior border of the pancreas is also mobilized, and the common hepatic artery, gastroduodenal artery and portal vein are identified. Once both the inferior and superior borders of the pancreas have been mobilized, tunneling is performed behind the neck of the pancreas to dissect the pancreas free from the superior mesenteric vein/portal vein. Dissection is then performed in a medial-to-lateral manner to free the undersurface of the pancreas from the splenic vein. The splenic artery may follow a tortuous course behind the pancreas or through the pancreas, highlighting the necessity for a meticulous dissection to avoid injury to this vessel or the underlying splenic vein. While dissecting the central pancreas free from the splenic artery, caution must be taken to identify the overlying coronary vein (left gastric vein), which in our experience serves as a critical anatomic landmark of the celiac trunk. This vein can be ligated if necessary. The dissection of the central pancreas from the splenic vein and artery is continued until the distal extent of the tumor has been reached. Liberal use of intraoperative ultrasound can confirm the location of the tumor and a duplex can also confirm arterial/venous anatomy. The plane of transection of the pancreas to the left of the tumor is identified and marked to represent the distal margin of the specimen during pathological examination, and the transverse pancreatic arteries are suture ligated. The pancreatic neck to the right of the tumor is routinely divided with a GIA stapler. The parenchyma located to the

Figure 2 Robotic central pancreatectomy operative video (22). This video demonstrates a robotic central pancreatectomy (CP) performed for a neuroendocrine tumor. After port placement and exploration of the abdominal cavity, the lesser sac is entered by dividing the gastrocolic omentum. This exposes the anterior surface of the pancreas. The caudal aspect of the pancreas is then dissected by dividing the inferior attachments, which exposes the superior mesenteric vein. The pancreas is then divided with an energy device at the neck of the pancreas, overlying the superior mesenteric/portal vein. Once the neck of pancreas is divided, the inferior edge and superior edge of the pancreas is mobilized until beyond the extent of tumor. The distal extent of pancreas transection is marked here, and transected with an energy device. The specimen is removed from the abdominal cavity. Subsequently, the right side of the pancreas is oversewn while the left side of the pancreas is drained through a pancreatogastrostomy. The pancreatogastrostomy is completed with a two-layer closure, approximating the transected surface of the pancreas with the posterior aspect of the stomach.
Available online: http://www.asvide.com/articles/1097

left of the tumor is then transected with cautery scissors or a thermal device in order to allow for identification of the pancreatic duct, which will later be sewn to the intestinal mucosa. The specimen is placed in a 15 mm Endo Catch™ (Covidien, New Haven, CT) bag and removed through the accessory left lower quadrant port. The specimen is then sent to confirm pathological diagnosis and ensure adequate margins. At this point, if the pathology is confirmed as a benign tumor or a low-grade neoplasm, we proceed with the reconstruction. However, if the pathology is found to be malignancy or high-grade neoplasm, we believe a PD or DP should be performed.

Reconstruction following CP can be performed by either a pancreatogastrostomy or a Roux-en-y pancreaticojejunostomy. Pancreatogastrostomy is favored at our institution due to the formation of a single anastomosis (in comparison to roux-en-y pancreaticojejunostomy) and maintenance of physiologic drainage (7). The transected surface of the pancreatic head is oversewn using a running V-Loc™ (Medtronic, Minneapolis, MN, USA) suture to ensure hemostasis. Attention is then paid to the reconstruction of the pancreatogastrostomy. The stomach is allowed to lie flat in the retroperitoneum and an optimal location in close proximity to the transected pancreas is marked with a marking pen. At this stage the pancreatic tail should be mobilized further to ensure enough mobility out of the retroperitoneum for a tension free anastomosis. Corner sutures are placed to anchor the pancreas to the stomach on the cranial and caudal aspect of the pancreas. The anterior surface of the pancreas is sutured to the posterior surface of the stomach to create the 'back row' of the pancreatogastrostomy, using a running V-Loc™ suture. A small gastrotomy is created and duct-to-mucosa anastomosis is performed with simple interrupted 5–0 absorbable monofilament sutures over a 5-Fr pediatric feeding tube as a stent in the pancreatic duct. The posterior surface of the pancreas is then sutured to the stomach using a running V-Loc™ suture, completing the outer layer of the anastomosis. All layers of the pancreatogastrostomy are performed using running V-Loc™ sutures except the duct-to-mucosa layer, which we perform in an interrupted manner with 5–0 absorbable monofilament sutures. In the event that the non-dilated pancreatic duct is too small to visualize, we perform an invagination by making a larger gastrotomy and suturing the entire face of the gland into the stomach itself (similar manner to description above), utilizing two layers.

There are multiple members of the team that are critical for success of this operation. This includes anesthesiologists and anesthetists that monitor the airway and stability of the patient, the surgeon who is at the console following port-placement, and the surgical trainee or assistant who is at the bedside, and is responsible for assisting with port-placement, docking of the robot, instrument exchanges and providing help during the operation through the assistant port. Additionally, a scrub nurse is important for providing the appropriate instruments and suture as well as a circulator nurse who maneuvers the robot patient cart to the bedside and is able to acquire any instruments or suture that is not on the operative field. This multi-disciplinary approach ensures a cohesive and safe operation (*Figure 2*).

Table 2 Summary table of published series regarding open CP and outcomes

Authors	Year	N	Morbidity (%)	Mortality (%)	Return to OR (%)	POPF (%)	DM (%)	EI (%)	Recon PG/PJ	OR time, min (mean)	Mean LOS (days)
Ikeda *et al.* (24)	1995	24	3 (13.0)	0 (0.0)	0 (0.0)	3 (13.0)	0 (0.0)	2 (8.0)	—/14	NR	NR
Sauvanet *et al.* (1)	2002	53	22 (41.0)	1 (2.0)	3 (5.7)	16 (30.0)	1 (2.0)	4 (8.0)	26/25	NR	NR
Balzano *et al.* (25)	2003	32	20 (62.0)	0 (0.0)	1 (3.1)	16 (50.0)	3 (10.0)	2 (6.2)	—/22	207	13.5
Goldstein *et al.* (33)	2004	12	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (17.0)	0 (0.0)	12/—	226	6.5
Efron *et al.* (29)	2004	14	7 (50.0)	0 (0.0)	0 (0.0)	5 (36.0)	0 (0.0)	1 (7.0)	14/—	229	11.1
Iacono *et al.* (30)	2005	20	7 (35.0)	0 (0.0)	0 (0.0)	5 (25.0)	0 (0.0)	0 (0.0)	—/20	NR	NR
Brown *et al.* (28)	2006	10	6 (60.0)	0 (0.0)	0 (0.0)	4 (40.0)	0 (0.0)	0 (0.0)	4/6	255	9
Crippa *et al.* (9)	2007	100	58 (58.0)	0 (0.0)	0 (0.0)	44 (44.0)	4 (4.0)	5 (5.0)	5/95	248	13
Allendorf *et al.* (10)	2007	26	8 (31.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	0 (0.0)	26/—	226	6.9
Adham *et al.* (27)	2008	50	23 (46.0)	0 (0.0)	6 (12.0)	4 (8.0)	0 (0.0)	11 (22.0)	44/6	201	19.3
Sudo *et al.* (7)	2010	19	10 (53.0)	0 (0.0)	0 (0.0)	9 (47.0)	0 (0.0)	1 (6.0)	19/—	215	NR
Shikano *et al.* (26)	2010	26	10 (38.0)	0 (0.0)	3 (11.5)	8 (31.0)	0 (0.0)	1 (4.0)	26/—	295	NR
DiNorcia *et al.* (8)	2010	77	30 (39.0)	0 (0.0)	2 (2.6)	15 (20.0)	7 (9.1)	5 (6.5)	74/3	254	6
LaFemina *et al.* (32)	2010	23	16 (70.0)	0 (0.0)	2 (8.7)	6 (26.0)	0 (0.0)	0 (0.0)	23/—	191	5
Goudard *et al.* (31)	2014	100	72 (72.0)	3 (3.0)	6 (6.0)	63 (63.0)	2 (2.0)	6 (6.0)	98/—	245	25
Total	—	586	50.3	0.7	3.9	34.1	3.2	6.5	—	—	—

CP, central pancreatectomy; POPF, post-operative pancreatic fistula; OR, operating room; DM, diabetes mellitus; EI, exocrine insufficiency; LOS, length of stay.

Outcomes of MIS CP

With a recent increase in the use of cross-sectional imaging, there has been a concomitant increase in the identification of low-grade and benign pancreatic lesions which are amenable to a CP (23). Therefore, an increasing number of patients are now undergoing CPs and have been reported. In select higher volume series on open CP, mean morbidity was found to be 50.3% and mortality 0.7% (1,7-10,24-33) (*Table 2*). The mean re-operative rate was 3.9%. Rates of POPF (34.1%) are comparable to those reported for PD and DP (8,34), while postoperative diabetes mellitus (DM) (3.2%), and exocrine insufficiency (EI) (6.5%) are a relatively infrequent complication. In comparison to open series, the quantity of patients reported in MIS series of CP is even more limited (20,21,35,36). The largest series on laparoscopic CP was performed by Rotellar and colleagues, which included nine patients (20). In this group of patients, morbidity was 44% including one reoperation (11%) and two patients who developed POPF (22%); there were no mortalities and no patients experienced endocrine or EI. The largest series of robotic CP was reported by Abood and colleagues, and also included outcomes for 9 patients with low-grade neoplasms (19). In this series, there was one conversion to an open procedure and 78% of patients experienced a POPF, with clinically significant pancreatic fistula occurring in 22%. This coincides with the rates published for open CP (median =21.2%), where most often only clinically significant fistulas were noted (1,7,9,10,25-27,37). There were no cases of EI or endocrine dysfunction, and Clavien grade III or higher complications occurred in one patient (11%) with no reoperations or mortality. Similar outcomes were seen in additional reports of robotic CP, indicating it is a viable approach to select central pancreas lesions in specialized centers (18,19,23,38,39) (*Table 3*).

Conclusions

Robotic CP is safe and efficacious for lesions located in the central pancreas. This approach is likely to gain acceptance for select patients that have benign or low-grade neoplasms in the central pancreas given preservation of pancreatic volume and avoidance of adjacent organ resection. Furthermore, robotic CP can achieve similar outcomes with comparable rates of mortality and morbidity as the open approach.

Table 3 Summary of published series regarding MIS CP

Authors	Year	N	Morbidity (%)	Mortality (%)	Return to OR (%)	POPF (%)	DM (%)	EI (%)	Recon PG/PJ	OR time, min (mean)	Mean LOS (days)
Laparoscopic CP											
Ayav *et al.* (36)	2005	1	NR	NR	NR	NR	NR	NR	NR	NR	NR
Orsenigo *et al.* (35)	2006	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—/1	330	10
Sa Cunha *et al.* (21)	2007	6	2 (33.0)	0 (0.0)	0 (0.0)	2 (33.0)	0 (0.0)	0 (0.0)	6/—	225	18
Rotellar *et al.* (20)	2008	9	4 (44.0)	0 (0.0)	1 (11.0)	2 (22.0)	0 (0.0)	0 (0.0)	—/9	435	4
Total	—	17	35.3	0.0	5.9	23.5	0.0	0.0	—	—	—
Robotic CP											
Giulianotti *et al.* (39)	2010	3	1 (33.0)	0 (0.0)	0 (0.0)	1 (33.0)	0 (0.0)	0 (0.0)	3/—	320	15
Kang *et al.* (22)	2011	5	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	5/—	480	12
Abood *et al.* (19)	2013	9	8 (89.0)	0 (0.0)	0 (0.0)	7 (78.0)	0 (0.0)	0 (0.0)	7/2	425	10
Zureikat *et al.* (18)	2013	13	13 (100.0)	0 (0.0)	1 (8.0)	12 (92.0)	NR	NR	NR	394	8
Total	—	30	76.7	0.0	3.3	70.0	0.0	0.0	—	—	—

OR, operating room; POPF, post-operative pancreatic fistula; DM, diabetes mellitus; EI, exocrine insufficiency; LOS, length of stay; NR, not recorded; CP, central pancreatectomy; MIS, minimally invasive surgery.

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Footnote

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Impact of a nationwide training program in minimally invasive distal pancreatectomy (LAELAPS)

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Comment on: de Rooij T, van Hilst J, Boerma D, *et al.* Impact of a Nationwide Training Program in Minimally Invasive Distal Pancreatectomy (LAELAPS). Ann Surg 2016;264:754-62.

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de Rooij and colleagues from the Dutch Pancreatic Cancer Group (DPCG) report on their experience disseminating a nationwide training program for minimally invasive distal pancreatectomy (MIDP) called LAELAPS (1). This effort included 32 surgeons at 17 medical centers in the Netherlands. The perioperative results prior to and following LAELAPS are compared, and conversion rate (38% *vs.* 8%, P<0.001), blood loss (350 *vs.* 200 cc, P=0.03) and length of hospital (9 *vs.* 7 days, mean, P<0.001) were all improved significantly presumably as a result of the training and experience. The assessment was made according to STROBE guidelines (2). Robotic and laparoscopic procedures were included, as performed using the same techniques, and patient selection was according to the criteria of Yonsei (3).

I congratulate the DPCG for their systematic approach and clear reporting of results with what appear to be direct cause and effect improvements. Innovation in surgery is both crucial and complex. Acceptance of innovation is a process, which takes time. Innovators and early adopters are often ridiculed and condemned as heretics and showmen by non-adaptors. Moving the process forward requires dedication and careful introspection to ensure that said innovation is not inferior to the original way of doing things, and that it may add additional value. Innovation may also raise concern, as innovators and early adopters may have abilities and access beyond what the general population can achieve, such as unusual skill and/or use of limited available technology. As we move along the innovation curve and more surgeons perform the newer technique, risks rises that inadequate training will lead to poor outcomes, increased patient risk, and loss of progress.

Laparoscopic colectomy is a commonly performed operation. In 2004, the results of the COST trial were presented and the concerns of surgeons who perform colon surgery were assuaged (COST), as the trial demonstrated non-inferiority of the laparoscopic approach to right, left, and sigmoid colectomy as compared with their open counterparts for the surgical removal of colon cancer (4). Industry supported training courses to increase technology sales and minimally invasive colectomy is a standard approach for appropriate patients with colon cancer.

Distal pancreatectomy is a less-commonly performed procedure than is partial colectomy, and the pancreas is a deep-seated retroperitoneal organ adjacent to foreboding vasculature. Merging experience in pancreatic resection with advanced laparoscopic technique for a relatively uncommonly performed procedure made systematic dissemination of MIDP slower than for colectomy. Coordinated efforts like LAELAPS are necessary to achieve this endpoint.

What we do not gain from this study is a true appreciation for the actual contribution of the training program. It could be that the "tipping point" was reached and more surgeons in the Netherlands gained comfort with MIDP, and that some of the post-LAELAPS improvement

are circumstance. This is probably unlikely as the number of cases performed doubled in the 22 months after training as compared with the previous 9 years. The DPCG is unique in that it is a nationwide organization which demonstrates unusual collaborative spirit, as has been demonstrated in the Netherlands through various collaborative randomized studies. Problem with comparing longitudinally is that the surgeons already have increased experience, which can affect the significance. The B/C fistula rate of 30% seems higher than reported in other studies, but did not change following LAELAPS (5,6). I would not have included robotic procedures in this report, as robotic experience is even more reliant on a team approach and some important differences exist between robotic and laparoscopic distal pancreatectomy (7).

Overall, this study represents an important step in patient safety and collaboration. Current practice in the United States is to learn technique as a trainee during fellowship, or as faculty from course, mentorship, and/or trial and error. Systematic training programs for surgical innovation are crucial to achieve these results. LAELAPS and the collaborative effort from the Netherlands is a great example of this.

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Footnote

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Laparoscopic distal pancreatectomy

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Abstract: After technological advances and increased experiences, more complicated surgeries including distal pancreatectomy can be easily performed with acceptable oncologic results, and decreased mortality and morbidity. Laparoscopic distal pancreatectomy (LDP) has been shown to have several advantages including less blood loss, less hospital stay, less pain. Several studies comparing open distal pancreatectomy (ODP) and LDP resulted that both techniques have similar results according to pancreas fistulas, oncological results, costs and operation indications. Morbidity is very low in high volume centers, for this reason at least ten cases should be performed for the learning curve. Several authors remarked important technical points in LDP in order to perform safe and acceptable LDP in several studies. Here in this review, we aimed to overview the results of previous studies about LDP and discuss the technical points of LDP.

Keywords: Pancreas; distal pancreatectomy; laparoscopic; pancreatic resection

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Introduction

Despite the developments in minimally invasive surgery for intraabdominal pathologies, laparoscopic pancreatic surgery has lagged behind because of its limitations, such as major vascular proximity, retroperitoneal location, and adjacent organs (1). However, with improvements in laparoscopic skills and surgical technology, laparoscopic distal pancreatectomy (LDP) has been proven to be safe and have better outcomes (2). In the present study, we compared LDP with the traditional method of open distal pancreatectomy (ODP).

Early series of LDP consisted of benign lesions, such as premalignant lesions, benign pancreatic strictures, and neuroendocrine pancreatic lesions (3). In these early series, LDP reduced postoperative morbidity and hospital stay and increased quality of life in young patients. Then, the number of LDP procedures performed for malignant disease increased (2,4). It has been shown in several studies that tumors can be resected with adequate lymph nodes using LDP, with similar pancreatic fistula rates (4). On the other hand, technically demanding spleen-preserving distal pancreatectomies have been performed (5). In this article, we describe current concepts of LDP.

Indications

Symptomatic benign lesions, premalignant lesions, and cancer located in the body or tail of the pancreas are candidates for distal pancreatectomy. Until recently, the number of distal pancreatectomy procedures performed was limited because of the low incidence of pancreatic lesions and the high proportion of lesions unresectable at first presentation. Today, however, new diagnostic tests are available that are capable of providing an early diagnosis of pancreatic lesions with high quality, and the number of indications for distal pancreatectomy has increased. Since the first series of LDP cases published in 1996, the benefits and safety of LDP have been proven (4,6). During preoperative assessment, medical

comorbidities, tumor size, organ involvement, and major vascular involvement are evaluated.

Recent studies show that there is no absolute indication about how the type of surgery (open or laparoscopic) is decided. Consideration of individual patients' features to decide on the type of operation has been reported in several studies (7-11). There were no differences between LDP and ODP cases in terms of patient age, gender, American Society of Anesthesiologists score, body mass index (BMI), or presence of diabetes mellitus (7-11). Cho *et al.* showed that no preoperative evaluable variables were associated with a higher likelihood of significant fistula after LDP *vs.* ODP (12). Greater BMI, larger specimen size, and increased blood loss were much more important risk predictors for postoperative complications after ODP as compared with LDP (12).

In selected studies, the ratios of ODP and LDP were 14.2% and 8.8% for endocrine tumors, 16.8% and 9.7% for mucinous cystic neoplasias, 9.7% and 6.7% for chronic pancreatitis, 7% and 8% for pseudocysts, 8.5% and 6.2% for intraductal papillary mucinous neoplasms, 7.8% and 17.5% for ductal adenocarcinomas, 7.3% and 16.5% for pancreatic tumors, and 16.1% and 17% for cystic lesions, respectively. These results show that LDP and ODP have been performed in similar ratios for cystic lesions, chronic pancreatitis, intraductal papillary mucinous neoplasms, and pseudocysts. Ductal adenocarcinomas and pancreatic tumors, however, have been treated more often with ODP. Mucinous cystic neoplasias have been treated much more often with LDP (13). Because of the concern about achieving good oncological outcomes, LDP has been thought to be contraindicated in patients with malignant disease. Trocar site metastasis, promotion of neoplastic growth by pneumoperitoneum, and wound recurrence have not been proven to be risks of LDP (14,15). However, no evidence has been presented in the literature that the use of the laparoscopic technique increases the risk of neoplastic dissemination, and none of the patients in recent studies developed any trocar site or peritoneal metastasis (4,16-19). The results described above show that there is no exact preoperative indication for ODP or LDP.

Distal adenocarcinomas of the body and tail of the pancreas comprise only 20–25% of all diagnosed pancreatic adenocarcinomas, and surgical resection remains the only potentially curative therapy (20). In pancreatic cancer, negative surgical margins and adequate lymph node harvesting are crucial. These factors lead to long survival. To achieve these oncological outcomes, radical antegrade modular pancreatosplenectomy (RAMPS) seems superior to conventional distal pancreatectomy (21). It has been hypothesized that improved oncological resection could be achieved with RAMPS, with a higher likelihood of obtaining negative tangential margins (89%) and increased rates of R0 resection (81%) (22). Use of the RAMPS approach can increase R0 rates. The RAMPS technique has been adopted for laparoscopic surgery and is an option for the laparoscopic resection of distal pancreatic adenocarcinomas (19,23). Advanced laparoscopic operations, such as RAMPS can be easily performed. Also, additional organ resections are not contraindications to LDP. Colectomy, gastrectomy, cholecystectomy, and repair of colovesical fistulas have been laparoscopically performed with LDP (19,24).

Surgical techniques

Since Gagner first described the LDP method, this operative technique has been modified at different centers. LDP is usually performed with the patient supine or on the left side (25,26). The advantages of the supine position are ease of setup, clearer airway access for anesthesia, and ability to access the pancreatic head and neck. Four or five trocars are placed in a semicircular fashion around an umbilical camera. Alternatively, trocar sites are placed under direct visualization, depending on the patient's body habitus and the location of the lesion. A left lateral decubitus position facilitates exposure of the left upper abdominal quadrant (1). A lateral position allows gravity retraction of the stomach and spleen, more direct visualization of the body and tail of the pancreas, and superior ergonomics and comfort for the surgeon (27).

In our practice, the patient is placed supine. The hand-guided approach has been defined by several authors (28,29). The advantages of the hand-guided approach include preserving the surgeon's ability to perform direct palpation of the tumor and anatomy, ease of removal of larger malignant specimens through the hand port, use of manual dissection, increased surrounding inflammation, improved ability to operate on obese patients, and opportunity to apply direct pressure in case of bleeding. It is not necessary for the surgeon's hand to feel the borders of the lesion. Most authors advocate the use of intraoperative laparoscopic ultrasound to localize the lesion and define the extent of the resection (30). If the lesion is obvious, dissection is initiated by mobilizing the lower pancreatic margin 2 cm proximal to the lesion. However, for malignant lesions, a formal left pancreatectomy is performed at the level of next to the junction of the superior mesenteric vein (SMV) and the

portal vein.

There is controversy about splenectomy in LDP. Some authors believe splenectomy should be performed routinely because splenic artery preservation is hazardous for oncological radicality in distal pancreatectomy (31). In order to ensure extensive resection of lymph nodes located along the splenic artery and splenic hilum, splenectomy with splenic artery resection is advised (32). Distal pancreatectomy with splenic vessel preservation may lead to remnant pancreatic tissue on the splenic vessel, and therefore it is not advised in patients with malignant disease. However, in chronic pancreatitis or benign diseases, the number of cases with spleen preservation is high (33,34). Spleen preservation was shown to be associated with reductions of postoperative infection and length of hospital stay. In benign disease, attempts to preserve the spleen are important. In cases of chronic pancreatitis, however, pancreatic calcification, marked edema and fibrosis may occur in splenic vessels, and splenic vessel preservation in those cases may not be possible.

The Warshaw technique has been used with LDP to resect and preserve the spleen (35). It is unclear whether the Kimura or the Warshaw technique is superior. However, spleen-related complications are seen much more often after use of the Warshaw technique than with the Kimura technique, such as postoperative splenectomy (2% *vs.* 0%, respectively), splenic infarction (20.8% *vs.* 2%, respectively), and chronic abdominal pain (38% *vs.* 0%, respectively) (36,37). Symptomatic splenic infarctions have been reported to be significantly less common after vessel-preserving splenectomies. Interestingly, none of these infarcts evolved to an abscess, and they were all conservatively treated (37). In the study of Baldwin *et al.*, only four patients treated with splenic vessel ligation developed symptomatic splenic infarcts, and three patients underwent splenectomy (38). Patients were routinely monitored postoperatively with computed tomography (CT) in only a limited number of previous studies. For this reason, the number of splenic infarcts might be underestimated. Also, the patients in the Baldwin *et al.* study were elderly. It is possible that short gastric vessels do not supply enough collateral circulation to support the splenic mass (38). Moreover, supplying enough blood to the spleen might be difficult in patients with large spleens. Thus, it is of paramount importance to evaluate the spleen's dimensions during surgery when deciding on the type of operation to perform.

During spleen-preserving procedures, the spleen should be checked for extensive splenic ischemia, which may be seen in 10% of patients. Splenic infarction is seen mostly in the early period. It is reasonable to prefer a distal pancreatectomy with splenectomy to splenic vessel ligation when vessel preservation fails intraoperatively. Perigastric varices and related gastric mucosal bleeding are risks after distal pancreatectomy. In the study of Hwang *et al.*, four patients treated with distal pancreatectomy with splenic vessel ligation had perigastric varices, and only three patients developed submucosal varices (39). Butturini *et al.* reported perigastric varices in 60% of patients treated with splenic vessel ligation and 22% of patients treated with splenic vessel preservation (40); however, bleeding was not seen.

Thus, perigastric varices are not a risk after splenic vessel ligation. The Kimura technique is more demanding, as the splenic vessels are preserved. LDP with splenic vessel preservation is much more time-consuming. However, authors of several systemic reviews have shown that spleen-preserving LDP is much more preferred (7,12). The enhanced surgical view during laparoscopic surgery, with better visualization of splenic vessels, has contributed to these findings. Only 14 patients were converted from vessel preservation to vessel ligation in one study (37). The presence of small breakage of tributary vessels from splenic vessels could potentially obscure the surgical field and result in intraoperative bleeding, splenectomy, or conversion. In spleen-preserving LDP, the pancreas is separated from the splenic vessels. However, this maneuver might be bloody, and it is difficult to manipulate the pancreas.

Velanovich has described the lasso technique, in which a Penrose drain around the neck of the pancreas is used to manipulate the dissection (41). LDP with splenic vessel ligation is 27 min shorter than LDP with splenic vessel preservation. Eom *et al.* reported significantly prolonged operative time in spleen preservation compared with splenectomy (194 *vs.* 251 min; P=0.02) (42). The mean operative time for LDP ranges from 156 to 383 min, whereas the mean operative time for ODP ranges from 145 to 330 min. The endpoint showed a nonsignificant extension of 9.21 min of the operative time (13). Blood loss during splenic preservation is reported to be much more than that in LDP with splenectomy (225 *vs.* 495 mL) (23). However, intraoperative blood loss was reported to be less in LDP than in ODP (13). Spleen preservation is much more time-consuming, technically more demanding, and leads to much more bleeding in LDP than in ODP. The conversion rate for LDP with splenectomy ranges from 0% to 43% and LDP with splenic preservation ranges from 72% to 100% (1). With increasing experience and specialized centers, the

Figure 1 Port placement.

Figure 2 Presentation of laparoscopic distal pancreatectomy (LDP) (43). Available online: http://www.asvide.com/articles/1100

Figure 3 Opening lasser sac.

conversion rates are expected to decrease. The most common reasons for conversion are obesity, dense omental fat, intraoperative bleeding, malignant disease requiring lymph node dissection, inability to detect the tumor, bulky tumors, and peritoneal adhesions due to previous surgery (30).

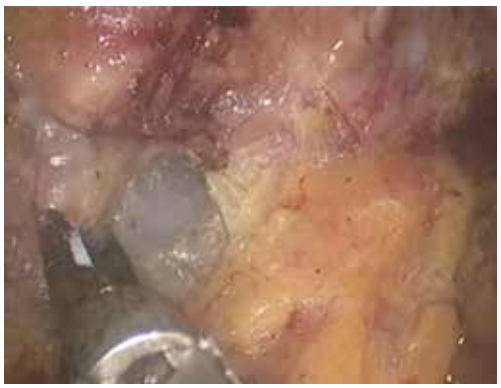

Figure 4 Identification of superior mesenteric vein (SMV).

The patient should be positioned with legs apart or in the left lateral or supine position. The surgeon stands between the patients' legs. An assistant stands on the left side of the patient for camera and a scrub nurse stands on the opposite side. A 10-mm trocar is inserted at the umbilicus for use of the 30° telescope. A second trocar is inserted in the xiphoid area for retraction of the stomach. A third trocar is inserted in the left subcostal area on the midaxillary line and in the left subcostal area to the midclavicular line (*Figure 1*).

The patient is placed in a reverse Trendelenburg position to facilitate displacement of the transverse colon and small bowel from the operative field. Video presentation of one of LDPs is given (*Figure 2*). The patient has a mass with irregular borders in the tail of the pancreas. The lesser sac is opened using an energy device through the avascular plane while preserving the gastroepiploic vessels (*Figure 3*). Short gastric vessels are dissected to the superior part of the stomach as far as possible. The stomach is grasped and elevated with a nontraumatic grasper introduced through the xiphoid port to enable investigation to the entire neck, body, and tail of the pancreas.

At this step, we routinely use intraoperative laparoscopic ultrasonography to identify the precise location of the tumor and its relation to the splenic vessels and to demarcate its extent. We routinely explore SMV at the inferior border of the pancreas for resectability before starting the dissection. This maneuver requires finding SMV and developing a space between the pancreatic neck and vein. SMV is then readily identified at the inferior margin of the pancreatic neck with a blunt dissector (*Figure 4*). If there is no invasion, a tunnel is developed easily between the pancreatic neck and splenic vein. Next, the pancreas is hanged with nylon tape for manipulation. After determining resectability, deciding on the dissection begins at SMV and is carried

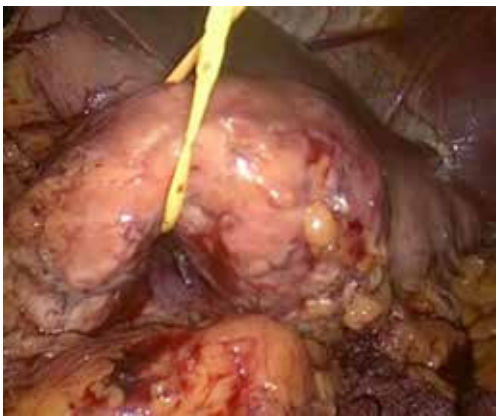

Figure 5 Hanging pancreas.

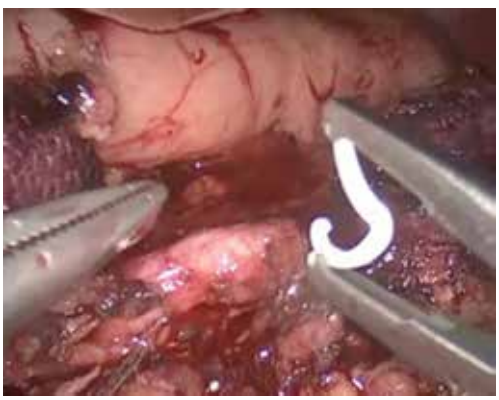

Figure 6 Division of the splenic artery.

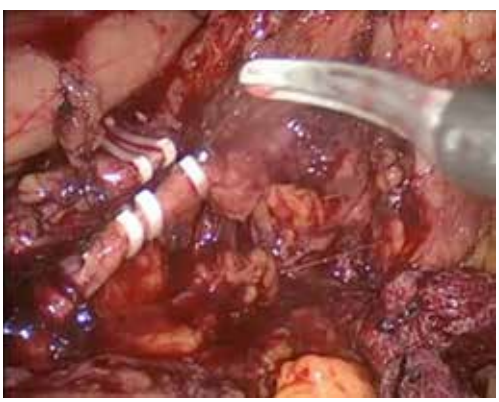

Figure 7 Division of the splenic vein.

laterally along the inferior border of the pancreas, allowing elevation of the posterior margin of the pancreas out of the retroperitoneum (*Figure 5*).

The splenic flexure of the colon must be mobilized so that the colon does not require continuous retraction to expose the pancreas. At this step, the venous mesentericoportal axis is visualized, and typically, the inferior mesenteric vein can be divided between Weck clips. Then, to start initial mobilization of the spleen, care must be taken regarding progression into the splenic hilum; instead, the dissection should be directed to the inferior pole of the spleen. Complete mobilization requires division of the lateral colon attachments. The splenic artery is controlled on the superior border of the pancreas. Retracting the pancreas inferiorly and laterally reveals the splenic artery and celiac truncus. Circumferential dissection is achieved with a blunt dissector, and initially the splenic artery is divided, usually with a vascular load Endo GIA (Covidien Surgical Boulder, CO, USA) or, on occasion, between Weck clips (*Figure 6*). At our center, we do not use energy devices for dividing the splenic artery at this step. The artery transection precedes transection of the vein to avoid splenic congestion and bleeding from the transected short gastric vessels.

Because of its fragility and close relation to the pancreas, splenic vein dissection is difficult. The splenic vein is dissected circumferentially, with care taken to identify insertion into both the inferior mesenteric vein and the coronary veins. Then the splenic vein is dissected and divided with the vascular Endo GIA, or, on occasion, between Weck clips, after transection of the pancreas (*Figure 7*).

The splenic vein has multiple braches that drain the body of the posterior pancreas. Therefore, the pancreas neck must be transected before continuing the dissection. To transect the pancreatic neck, the portal vein must be exposed at the superior margin of the pancreas by identifying the hepatic artery. After clearing a space superiorly and inferiorly, an endoscopic linear stapler can be inserted. Selection of the correct stapler cartridge depends on gland thickness. The goal is to avoid fracturing the gland with a staple length that is too short. If necessary, two staplers can be used for transecting the pancreas. After the splenic vessels are divided, the posterior retroperitoneal space can be dissected easily with the pancreas retracted anteriorly (*Figure 8*). The spleen is mobilized by continuing the posterior dissection laterally, although the most lateral diaphragmatic attachment may require rotating the spleen medially. This dissection is accomplished with energy devices.

The spleen and pancreas are usually detached at the splenic hilum with ultrasonic shears so that the pancreas can be delivered as an intact specimen and the spleen as a morcellated specimen. The specimen is placed in an Endo Catch bag and extracted through a Pfannenstiel incision.

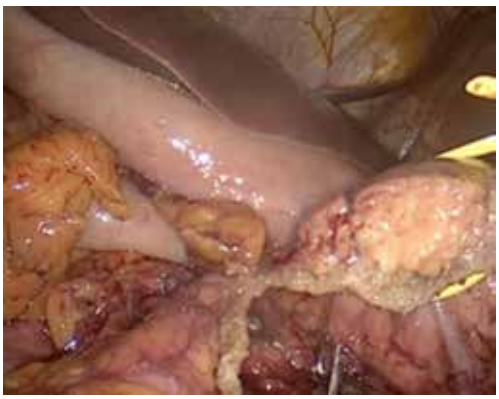

Figure 8 Division of the pancreas.

Pancreatic fistulas

The most common and clinically relevant complication after distal pancreatectomy is the pancreatic fistula, which may lead to further complications, such as intraabdominal abscess, sepsis, wound infection, delayed gastric emptying, ileus, and lethal bleeding. Treatment of pancreatic fistulas after distal pancreatectomy has not changed for more than 15 years, despite progress in other areas of pancreatic surgery. Several surgical techniques and instruments have been studied with the goal of decreasing pancreatic fistulas. These include hand-sewn sutures, different kinds of staplers, combinations of staplers and sutures, pancreaticojejunal anastomosis, transection by harmonic scalpel, and fibrin glues (44). The experience and results in ODP were the same as those in LDP. Unfortunately, LDP did not decrease the rate of pancreatic fistulas. In a meta-analysis, postoperative pancreatic fistulas were found to occur in 21.7% of the patients, with no difference between LDP and ODP.

Hand-sewn closures and stapler closures are both used in LDP. As shown in the DISPACT trial, stapler closure is not superior to hand-sewn closure (45). In LDP, stapler closure is the most commonly performed technique. Use of a stapler with 2.5 staple cartridges is associated with fewer pancreatic fistulas than the 4.5 staple cartridges (46). Also, gradual closing of the staple over the course of approximately 2–3 min could reduce the fistula rate (47). In the study by Johnston *et al.*, reinforcement of the staple line with mesh was shown to reduce the fistula rate from 25% to 10% (48). Fibrin glue, sealant patches, and seromuscular patches have been used during LDP (25,49,50). However, these modalities were not confirmed in the randomized study of Oláh *et al.* (51).

As mentioned, LDP can be performed according to oncological principles and with comparably safe procedures. Shorter hospitalization, less intraoperative blood loss, and decreased pain are advantages of LDP over ODP. On the other hand, cost and the learning period are important factors related to LDP. LDP is a complex abdominal operation and requires experience in laparoscopy. With increasing experience with LDP, operative time is shortening, postoperative pancreatic fistula rate is declining, and operative blood loss is decreasing. Braga *et al.* found substantial reduction of the conversion rate, operative time, and operative blood loss after experience with the first ten procedures (52). The results of last 20 cases of Braga *et al.* were similar to the results of high-volume centers (52). The operative time in the learning period was 254 min, but it decreased to 183 min after the learning period. However, hospitalization time did not show any difference after the learning period. The learning period is usually shorter in high-volume centers than in low-volume hospitals.

Several studies have been performed to compare the costs of LDP and ODP. Korean, Italian, and British studies have shown that LDP is more expensive than ODP (42,53,54). However, decreased length of hospital stay after LDP led to equivalent total hospital costs in the British and Italian studies (42,53,54). In a North American study, overall hospital costs related to LDP were less than those for ODP (55). These studies showed that LDP is a financially reasonable approach to resection. In experienced centers, shorter operative time and decreased complications led to less cost.

Conclusions

LDP can be safely performed and may produce similar oncological results compared with ODP. Length of hospitalization and intraoperative blood loss in LDP are less when performed at experienced centers. Pancreatic fistula rates are similar with open cases in high-volume centers. Costs of LDP are reasonable in experienced centers. Although LDP surgery is complex, it can be performed safely when standard steps are carefully followed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Laparoscopic total pancreatectomy with islet autotransplantation for chronic pancreatitis

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Background: Pain from chronic pancreatitis can be debilitating and have far-reaching personal and societal consequences. These consequences can include patient debilitation, worsening of comorbid conditions, narcotic dependence, and implications for health care policy. A variety of surgical procedures have shown limited efficacy for relieving pain in this cohort of patients, and a highly select subset may benefit from a total pancreatectomy (TP). While a brittle form of diabetes can result from TP alone, when combined with islet cell autotransplantation this procedural complication can be minimized. Further, utilizing a minimally invasive approach may be associated with decreased periprocedural pain and length of hospital stay.

Methods: We describe our experience at a single high-volume center in the United States. We present our preferred preoperative evaluation, our updated operative techniques, and the standard perioperative care required following this complex laparoscopic procedure.

Results: Between 2013 and 2015, there were 20 patients who underwent laparoscopic total pancreatectomy with islet autotransplantation (LTPIAT). Perioperative mortality was 0%.

Conclusions: At a high volume pancreatic center with experienced laparoscopic pancreatic surgeons, LTPIAT is feasible and safe for the management of chronic pancreatitis refractory to prior medical and surgical therapies.

Keywords: Laparoscopic pancreatectomy with islet autotransplantation; laparoscopic pancreatectomy; minimally invasive pancreatectomy; chronic pancreatitis; diabetes after pancreatectomy

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Introduction

Chronic pancreatitis is a debilitating disease characterized by progressive and irreversible destruction of the gland parenchyma. The clinical management of these patients is particularly challenging. The repetitive inflammatory insult to the gland often results in intractable, refractory abdominal pain that produces a poor quality of life despite maximal medical management (1). End-stage pancreatitis is often characterized by heterotopic calcification of the pancreatic ducts that are thought to cause functional obstruction of the exocrine portion of the gland. Procedural approaches to decompress this functional obstruction have been used for decades. Options trialed have included endoscopic decompression, functional operative diversion (i.e., pancreaticojejunostomy), or operative gland extirpation (i.e., pancreatectomy). A recent randomized trial suggests that operative approaches are more effective at relieving pain and more durable without need for repeat intervention than endoscopic approaches (2).

There are multiple surgical approaches to this disease. Functional diversion, often completed through the creation of a longitudinal pancreaticojejunostomy, may alleviate some

Table 1 Patient demographics and operative outcomes of LTPIAT (n=20)

Characteristics	Data
Patient demographics	
Male (n)	8
Age, mean ± SD [range] (years)	39±13 [21–58]
Prior abdominal operations (n)	17
Post-operative outcomes	
Operative time, mean ± SD (min)	430±98
Length of stay, mean ± SD [range] (days)	11±5 [5–27]
Mortality (n)	0
Insulin requirement (U/day) [%]	
1–10	12 [60]
11–20	2 [10]
>20	6 [30]

LTPIAT, laparoscopic total pancreatectomy with islet autotransplantation.

of the exocrine insufficiency seen in chronic pancreatitis. While there are also several endocrine advantages, potential downsides to this approach include leaving much of the native gland in place and failing to adequately address chronic pain issues. This downside also applies to partial pancreatectomy in all of its forms, either with resection of the pancreatic head (with or without duodenal preservation) or resection of the body/tail, risking incomplete pain relief or disease recurrence. Total pancreatectomy (TP) removes the whole gland, eliminating the underlying cause of the pain in the chronic pancreatitis patient. TP was historically avoided as the resulting combination of exocrine dysfunction with brittle endocrine dysfunction was particularly difficult to manage. However with recent improvements in postoperative medical management TP is a technique used with increasing frequency. Exocrine function is increasingly able to be managed with the assistance of oral enzymatic supplements. In many specialized centers, the resulting endocrinopathy after TP is being mitigated by a technique to preserve beta-cell mass, intraoperative isolation and autotransplation of pancreatic islets. The use of concomitant islet autotransplantation (IAT) has been demonstrated to reduce or eliminate the need for exogenous insulin administration after a TP in many modern series (3).

The first total pancreatectomy with islet autotransplantation (TPIAT) was performed in 1977 at the University of Minnesota (4). Our experience at Johns Hopkins Hospital was first described in 1981 with a series of eight patients with chronic pancreatitis who underwent pancreatectomy and IAT (5). Since that time, advancements in technique have steadily improved the outcomes for this option and our program was re-started in 2010. Laparoscopy, particularly in the setting of benign disease, is being increasingly utilized for pancreatic surgery. Limited pancreatectomy (pancreaticoduodenectomy or distal pancreatectomy), for example, when performed by experienced surgeons has been demonstrated to be safe, produce similar outcomes at equal or lesser cost, and lead to decreased length of hospital stay when compared to open pancreatectomy (6-10). The generalization of these findings to TP appears appropriate (as one of the most technically challenging hurdles in pancreaticoduodenectomy, the pancreaticojejunal anastomosis, is eliminated in TP) and is now being utilized in select centers. Beginning in 2013, we began to offer a laparoscopic approach to all appropriate candidates referred to our institution for TPIAT. We present our preferred preoperative evaluation, our updated operative techniques, and the standard perioperative care required following this complex laparoscopic procedure. Finally we briefly discuss our recent outcomes and areas for future consideration with regards to laparoscopic total pancreatectomy with islet autotransplantation (LTPIAT).

Patient and methods

Patient selection and workup

Individuals being considered for LTPIAT at our institution have typically had a long antecedent disease course. All referred candidates were diagnosed with chronic pancreatitis refractory to other therapies with 85% having undergone prior surgical procedures. *Table 1* reviews our population data and postoperative outcomes.

Complete preoperative workup includes clinical history, physical examination, and evaluation of baseline glucose tolerance. We will often receive a plethora of imaging studies to evaluate upon initial presentation, including magnetic resonance imaging (MRI), computed tomography (CT) and endoscopic retrograde cholangiography (ERCP). If the patient has not received a high-quality pancreatic-protocol CT scan we obtain one in the immediate preoperative period. Our exclusion criteria unique to a LTPIAT include patients who are unable to safely undergo laparoscopy or those who already manifest insulin dependent diabetes.

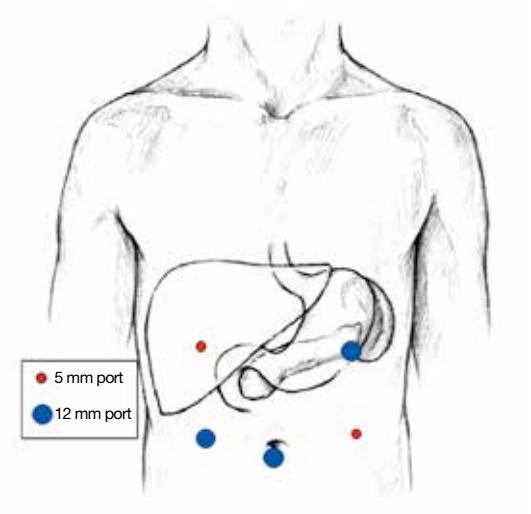

Figure 1 Initial laparoscopic port placement for total pancreatectomy with islet autotransplantation (TPIAT).

Equipment preferences

Use of a 10-mm, 45-degree laparoscope is preferred for optimized visualization. All sutures used during the duration of the procedure are swedged on to the needle to avoid inadvertent loss within the peritoneal cavity. Of note, for all advanced laparoscopic pancreas procedures, a #10 blade scalpel and Mayo scissors are always available if rapid conversion to open is necessary. Additional device availability is based on surgeon preference including: 30-degree laparoscope, laparoscopic bipolar energy device such as ligaSure, laparoscopic monopolar cautery such as hook dissector, laparoscopic linear stapler, laparoscopic needle driver or endostitch device.

Pre-operative preparation

Standard perioperative prophylaxis is administered in the preoperative area, including a prophylactic dose of heparin, injected subcutaneously, within 1 hour prior to procedure start and prophylactic antibiotics 30 minutes prior to incision. Preoperative organization and identification of team roles is a key factor in ensuring a smooth and safe procedure. Prior to the day of surgery the availability of the islet cell isolation team is coordinated appropriately. The patient is positioned supine with arms out. Large-bore peripheral intravenous access and a radial arterial line are placed with additional central venous catheter insertion left to the discretion of the operating surgeon and anesthesiology team. The patient is secured to the table at the thighs and chest, ensuring safety as the operating table may need to be tilted during the procedure to aid in laparoscopic visualization. Preoperative imaging is immediately accessible throughout the operation. Prior to incision, a routine checklist is completed conforming to all institutional and WHO standards.

Role of team members

The primary surgeon and assistant stand on opposite sides of the table and control the four working instruments, rotating sides based on optimal visualization. A second surgical assistant holds and controls the camera. The laboratory pathology team is stationed in the operating room with a sterile hood for preparation, isolation and purification of islet cells for re-implantation. Endocrinology and pain management consultation teams are used liberally postoperatively to assist with management of blood glucose levels and pain respectively.

Procedure

Our preferred method for obtaining entry into the abdomen is via a Hassan approach just inferior to the umbilicus. Here a 12 mm port is placed and pneumoperitoneum is established to a maximal abdominal pressure of 15 cm of water. The abdomen is then inspected with a laparoscope and adhesions from prior interventions or manifestation of severe pancreatitis are noted. These are taken down sharply and additional laparoscopic ports are placed sequentially as permitted by exposure. In sum, we will typically use five ports. On the right abdomen, one 5 mm trocar is inserted in the right upper quadrant and one 12 mm trocar is inserted in the right mid-abdomen (at the approximate intersection between the mid-clavicular line and a line drawn directly laterally from the umbilicus). On the left this pattern is roughly a mirror image of the right, with the larger 12 mm port high in the left upper quadrant and the 5 mm port placed lower (*Figure 1*).

Dissection begins by taking down the falciform ligament to its insertion into the liver with a LigaSure device. An endostitch device is used to tie the base of the falciform and the tail is brought out through a separate 2 mm stab incision high in the midline to aid in retraction of the liver. The lesser sac is entered through the gastrocolic ligament and the short gastric vessels are divided along the greater curvature of the stomach in their entirety to the

left crus of the diaphragm. The posterior adhesions of the stomach to the retroperitoneum are mobilized to expose the anterior surface of the pancreas. The stomach or proximal duodenum can be divided depending on planned approach to reconstruction (we will routinely take the pylorus).

The arterial anatomy supplying the liver and head of the pancreas is identified as it runs superior and posterior to the antrum of the stomach. The common hepatic artery, gastroduodenal artery (GDA), and proper hepatic artery are dissected along their course through this region and visualized. The GDA is then skeletonized circumferentially and prepared for transection with clips or stapling device. The common bile duct is dissected circumferentially and the cystic duct is identified to facilitate cholecystectomy.

We then create a tunnel behind the gland and over the portal vein, similar to that done in open surgery. At this point, we will frequently divide the neck or body of the gland to enhance visualization and allow safe dissection of the pancreatic head and uncinate. The remainder of the dissection can be carried out as allowed by patient anatomy and operative positioning. The superior aspect of the pancreas is dissected along the neck and body of the gland to identify the splenic artery takeoff proximal to its course towards the pancreatic tail. The inferior border of the pancreas is then dissected and mobilized out of the retroperitoneum. The splenic vein laterally is identified and dissected free if able at this point. Attention is taken to identify and preserve the inferior mesenteric vein. The superior mesenteric vein's confluence with the splenic vein to form the portal vein is identified during the course of this dissection. The splenic artery and vein are transected between clips or a stapling device and the tail and spleen are dissected free using electrocautery. Finally to mobilize the gland, a laparoscopic Kocher maneuver is completed and a defect in the ligament of Trietz is created in order to deliver the jejunum up through to the superior part of the abdomen.

The head and uncinate is then separated from lateral aspect of the portal vein and the superior mesenteric artery by a combination of blunt dissection, electrocautery, and transection between clips. Approximately 20 cm of jejunum is delivered through the ligament of Treitz and the jejunum is divided with a laparoscopic stapling device. The small bowel mesentery is divided adjacent to the bowel wall and in the proximal direction toward the uncinate. This plane is carried along towards the superior mesenteric vein and the superior mesenteric artery margin until the specimen is free.

These specimens are extracted in an endocatch bag through an extension of the periumbilical 12 mm Hassan port's incision. The specimen is then passed off to the intraoperative laboratory team where the GDA and pancreatic duct are cannulated; the gland is distended with collagenase, and subsequently digested. Islet purification is carried out, at our institution, under sterile conditions in the same operating room. A good harvest is critical as transplanted cells cannot divide or replicate. When able, the pancreatic tissue is kept on ice to preserve the function of the remaining islet cells. Minimizing warm ischemia time increases the viability of islets (11), which is positively correlated with insulin independence after TPIAT (12).

While the specimen is being processed the operation continues at the patient bedside. We close the mini-laparotomy in interrupted fashion, leaving two sutures untied to facilitate re-insertion of our 12 mm port without excessive air leak. Our preferred method of reconstruction has been described in detail previously and includes hepaticojejunostomy with interrupted absorbable suture (13). A stapled side-to-side, antecolic, retrogastric gastrojejunostomy is performed with a common channel created by a single fire of a 60 mm endoscopic stapling device. The gastrostomy and jejunostomy are then closed with interrupted absorbable suture. In selected patients, a Braun jejunojejunostomy is added in an attempt to mitigate bile acid gastritis.

Once the solution containing pancreatic islet cells is ready for autotransplantation, a hollow-bore 16 gauge needle with intravenous tubing attached is introduced into the abdomen through a 12-mm port site. The needle is placed into the portal vein and the solubilized islets are infused into the liver over a period of 20–45 minutes (*Figure 2*). Direct pressure applied to the puncture site will often be all that is required to achieve hemostasis. In some cases, a single 5–0 prolene suture is used to close the venotomy. Peritoneal drains are not required following TP but can be placed through either the left and/or right 5 mm port site at the discretion of the operating surgeon (*Figure 3*).

Post-operative management

Following LTPIAT, most patients are extubated in the operating room after port-site closure. They are admitted to the surgical intensive care unit overnight with careful attention paid to glucose control. An insulin infusion is often used to keep blood glucose values between 100 and 150 mg/dL. A nasogastric tube and arterial pressure line are maintained during the first postoperative night. Typically these patients are stable for transfer to a general surgical

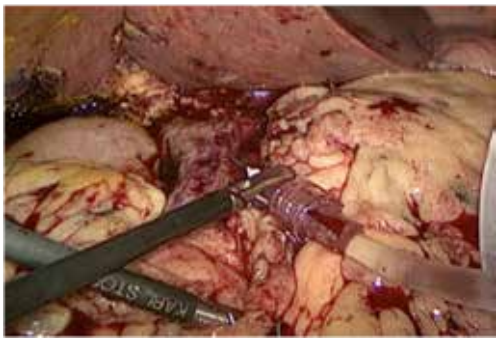

Figure 2 Laparoscopic placement of needle into portal vein for infusion of isolated islet cells.

Figure 3 Laparoscopic total pancreatectomy with islet autotransplantation (LTPIAT) for chronic pancreatitis (14). Available online: http://www.asvide.com/articles/1047

floor the following morning. Limited sips and chips diet is often initiated post operatively day 1 with slow advancement towards a goal diet of carbohydrate-limited regular food over the first week. Insulin requirements are aggressively managed over the first few days as the diet is advanced. An extensive education program, started preoperatively, is continued during the patient's hospital stay. Typically, patients require supplemental insulin injections for approximately one-month postoperatively.

Discussion

Over the last decade, a laparoscopic approach to pancreatectomy has gained popularity with increased adoption in multiple centers across the world. Studies suggest the minimally invasive approach is not only feasible but equivalently efficacious and safe: with similar perioperative morbidity and mortality (6-10,15-19). In particular, the minimally invasive approach to distal pancreatectomy has been widely accepted and clearly demonstrated advantages such as reduced blood loss, reduced overall complication rate, reduced surgical site infection and shorter hospital length of stay (7-10,17). Laparoscopic TP remains a rare procedure, but has shown recent increased use in high volume centers and similarly shown to be safe and feasible (15,16,18,19). A comprehensive review of our initial experience revealed those receiving LTPIAT had significantly shorter hospitalization with median length of stay being 10.5 compared to 14 days for open surgery as well as significant decrease in median postoperative dose of opiate on discharge in the laparoscopic group compared to open (16). With addition of additional patients to this series we have continued to show LTPIAT to be safe and efficacious with a 0% mortality and evidence of endocrine function preservation with 60% of patients postoperatively requiring <10 units of insulin a day (*Table 1*). Further detailed explanation of our experience is beyond the scope of this technical document and is to be described in a future manuscript. Additional studies are needed to further identify clinically significant outcomes between open and LTPIAT in a larger cohort of patients. Multicenter prospective data would be of benefit due to the limited yearly number of LTPIAT performed.

The learning curve and technical demands of LTPIAT limits accessibility to the hepatobiliary surgeon with advanced laparoscopic skills and isolated to high volume regional centers with the resources to offer multidisciplinary postoperative care and education to these complex patients. These limitations may impede widespread adoption of this technique.

Conclusions

At a high volume pancreatic center with experienced laparoscopic surgeons LTPIAT is feasible and safe for the management of chronic pancreatitis. As minimally invasive hepatobiliary surgery becomes more widespread, advantages of this technique may be further illuminated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by Johns Hopkins Hospital institutional review board and informed consent was obtained from the patient for intraoperative filming of surgery. Outcomes discussion is a retrospective review of deidentified information in our institution's secure pancreatic database.

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Laparoscopic radical antegrade modular pancreatosplenectomy

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Abstract: Although laparoscopic distal pancreatectomy is widely accepted for benign or borderline malignant pancreatic diseases, its application for pancreatic ductal adenocarcinoma (PDAC) remains controversial. Several recent reports have shown that laparoscopic surgery, for the treatment of PDAC, is associated with similar postoperative complications and survival outcomes compared with open surgery, and offers several advantages, particularly shorter hospital stay and less blood loss. However, potential risk of bias cannot be excluded because these results were obtained in retrospective studies. More importantly, it is unclear whether the extent of surgical resection is comparable between laparoscopic and open distal pancreatectomy. The aim of this video article is to show the technical feasibility of laparoscopic surgery to reproduce open radical antegrade modular pancreatosplenectomy (RAMPS) in terms of the extent of surgical resection.

Keywords: Distal pancreatectomy; radical antegrade modular pancreatosplenectomy (RAMPS); laparoscopy; pancreatic ductal adenocarcinoma (PDAC)

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Introduction

Laparoscopic distal pancreatectomy is a widely accepted operative procedure for treating benign or borderline malignant diseases in the body or tail of the pancreas (1-3), but its role in treating pancreatic ductal adenocarcinoma (PDAC) is poorly defined. With ongoing improvements in laparoscopic techniques, several recent reports have shown that laparoscopic surgery may be safe and effective for the treatment of PDAC (4-8). Laparoscopic surgery was associated with less blood loss and shorter hospital stay compared with open surgery. In addition, laparoscopic surgery did not compromise the oncologic outcomes in terms of the margin negative rate, the number of harvested lymph nodes, or the survival rate. However, laparoscopic and open distal pancreatectomy were generally compared in retrospective studies with a high risk of bias and, importantly, the extent of surgical resection was not specified or was heterogeneous. Standardizing the extent of resection and the surgical technique is essential to avoid false results when the oncologic outcomes are compared for two procedures such as open and laparoscopic distal pancreatectomy. In this context, radical antegrade modular pancreatosplenectomy (RAMPS), which was introduced by Strasberg *et al*. (9) to improve the tumor-free retroperitoneal margin and achieve adequate lymph node dissection, is a reference procedure for comparing laparoscopic and open surgery. This is because the dissection plane and extent of lymph node dissection are clearly defined in RAMPS. This video article describes our laparoscopic posterior RAMPS procedure.

Patient selection and workup

The indication for laparoscopic RAMPS and the decision to perform anterior or posterior RAMPS were based on abdominal computed tomographic (CT) images obtained within 1 month before surgery. Laparoscopic RAMPS is performed if the tumor lacks evidence of invasion to other organs except the left adrenal gland, spleen, and splenic vessels. As suggested by Strasberg *et al*., anterior RAMPS is chosen when the tumor is confined within the pancreas without evidence of invasion to the posterior capsule of the

Figure 1 Laparoscopic radical antegrade modular pancreatosplenectomy (RAMPS): a stepwise approach (10). Available online: http://www.asvide.com/articles/1048

pancreas whereas posterior RAMPS is chosen when the tumor has penetrated the posterior capsule of the pancreas.

Preoperative preparation

Preoperative blood tests include a complete blood count, electrolytes, renal, liver function tests, and CA 19-9. Oral glucose tolerance test and glycosylated hemoglobin (HbA1c) are checked to detect undiagnosed diabetes mellitus associated with PDAC and to be used as a baseline in evaluating postoperative changes in glucose metabolism after pancreatectomy. Patients are allowed to consume food until midnight before the operation day. Mechanical bowel preparation is not performed. Antibiotic prophylaxis is administered within 30 min of incision. Written informed consent is obtained from all patients before surgery.

Procedure

Under general anesthesia, the patient is placed in a supine, 30° reverse Trendelenburg position with left-side-up adjustment. After creation of a carbon dioxide pneumoperitoneum via a 12 mm infra-umbilical port, three or four additional trocars (12 and 5 mm trocars for the surgeon, and one or two 5 mm trocars for the assistant) were inserted. The two trocars for the surgeon are placed in the right upper abdomen, and trocars for the assistant are inserted in the left upper abdomen, as shown in the video (*Figure 1*). A three-dimensional flexible laparoscopic camera (Olympus, Tokyo, Japan) is used.

After trocar placement, the greater omentum is divided using LigaSure® (Medtronic, Minneapolis, MN, USA) from the midline towards the spleen. To maintain a good surgical field, the gastric antrum is fixed to the abdominal wall using a suture, which is pulled outside the abdominal wall. After elevating the neck of the pancreas using the grasper, the inferior pancreatic border is dissected until the superior mesenteric vein (SMV) is exposed. Small branches of the SMV encountered during dissection are controlled with LigaSure®. Thereafter, the surgeon approaches the superior border of the pancreas. The left gastric vein and artery are identified and followed toward the origin of the splenic artery. The left gastric lymph nodes are dissected until the splenic artery is exposed. The splenic artery is isolated and encircled with a vessel loop. A window is made between the pancreas and splenic vessels, and the neck of the pancreas is divided using an endoscopic stapler.

After transection of the pancreas, the splenic artery and vein are isolated and divided between Hem-o-lok clips® (Weck Teleflex Medical, Research Triangle Park, NC, USA). Lymph nodes on the left side of the celiac axis and superior mesenteric artery (SMA) are dissected. The lateral and posterior sides of the SMA are dissected further until the left renal vein is identified. After further dissection along the left renal vein, the left adrenal vein is isolated and divided between metallic clips at the junction with the renal vein. Retroperitoneal dissection continues along the anterior surface of the renal vein laterally and posteriorly behind the adrenal gland. Posterior and lateral dissection is continued to the anterior surface of the kidney. The superior and inferior attachments of the pancreas are divided as dissection proceeds towards the spleen. The short gastric vessels are then divided. Finally, the lienorenal ligament is divided. A Jackson-Pratt drain is placed near the pancreatic stump. The surgical specimen is retrieved in a vinyl bag and extracted through a small incision created by extending a port-site incision.

Postoperative management

After surgery, the patients are transferred to a general ward without intensive care unit management unless they have underlying severe comorbidities requiring careful monitoring or they experience an intraoperative event. Early ambulation is encouraged from postoperative day (POD) 1. Patients are allowed to drink water on POD 1, and have a soft blended diet from POD 2. Intravenous pain controllers are administered until POD 3–4 and oral analgesics are given thereafter if necessary. Abdominal CT is routinely performed on POD 5 to check for fluid collection around

the pancreas stump or other intraabdominal complications. The abdominal drain is removed according to the drain amount, color, and amylase level, and the results of abdominal CT on POD 5. The patient is discharged if the following criteria are met: (I) abdominal drain has been removed; (II) the patient can tolerate a diet without needing intravenous fluid infusion; and (III) postoperative pain is tolerable with or without oral analgesics.

Tips, tricks, and pitfalls

- Fixation of the stomach to the abdominal wall can avoid the need for a trocar to maintain the surgical field;
- The gastrocolic ligament should be divided close to the gastroepiploic vessels so that bulky omentum on the side of the stomach does not block the surgical field;
- To decrease the risk of pancreatic fistula, the stapler cartridge should be selected according to the thickness and hardness of the pancreas. The stapling technique is also important. The closure jaw should be clamped slowly and carefully, taking more than 3 min at a fixed speed. If the pancreatic parenchyma is too hard to safely apply the stapler, the surgeon may transect the pancreas and ligate the exposed pancreatic duct instead;
- The course of the common hepatic artery and splenic artery should be carefully noted on the preoperative CT images. Sometimes, a tortuous hepatic artery can be mistaken for the splenic artery. The splenic artery should be divided at its origin from the celiac trunk after confirming the courses of the common hepatic artery and the left gastric artery;
- During lymph node dissection, the lymphatics or soft tissue around the lymph nodes should be grasped to avoid troublesome bleeding caused by lymph node injury;
- The left renal vein can be approached after lateral and posterior dissection of the left side of the SMA or superior dissection of the duodenojejunal junction. This vessel is the landmark of the inferior border of the dissection, and guides the proper plane of posterior dissection;
- The opening of the mesocolon, if present, should be repaired to avoid postoperative complications, particularly small bowl herniation through this opening.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Laparoscopic spleen preserving distal pancreatectomy

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Abstract: Minimal invasive surgery is growing rapidly in vast fields of abdominal surgery. Nowadays, due to the development of laparoscopic instruments and improvement of surgical technique, laparoscopic pancreas surgery is becoming more widely adopted. Laparoscopic distal pancreatectomy has now become a standard procedure for the benign or borderline malignant tumor located in body or tail of pancreas, but laparoscopic spleen and splenic vessel preserving distal pancreatectomy is still a technically demanded operation. In this multimedia article, we will demonstrate our technique of laparoscopic spleen and splenic vessel preserving distal pancreatectomy.

Keywords: Spleen and splenic vessel preserving distal pancreatectomy; minimal invasive pancreatic surgery; laparoscopy

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Introduction

Minimal invasive surgery is growing rapidly in vast fields of abdominal surgery. Nowadays, due to the development of laparoscopic instruments and improvement of surgical technique, laparoscopic pancreas surgery is becoming more widely adopted (1,2). Laparoscopic distal pancreatectomy has now become a standard procedure for the benign or borderline malignant tumor located in body or tail of pancreas (3-6). Splenic preservation is associated with a reduction in perioperative infectious complications (7,8), postoperative pancreatic fistula (9), and cancer recurrence (10,11). Therefore, in patients with benign or borderline malignant tumor in the body or tail of pancreas, spleen preserving distal pancreatectomy is preferred over combined splenectomy (12). Laparoscopic spleen and splenic vessel preserving distal pancreatectomy is still technically demanded operation (13). In this multimedia article, we will demonstrate our technique of laparoscopic spleen and splenic vessel preserving distal pancreatectomy.

Patient selection and work up

The patient is a 30-year-old female who has a 2 cm mass at the pancreas body. Pancreatic tumor was detected with the abdominal sonography for health checkup. The patient does not have any symptoms. CT showed a 2 cm subtle low attenuating lesion at the pancreas body-tail junction, and MRI showed a 1.9 cm well-demarcated low signal intensity tumor in the T1 weighted image, intermediate high signal intensity in the T2 weighted image. Laparoscopic spleen and splenic vessel preserving distal pancreatectomy was planned.

Equipment preference card

The equipment used in our hospital includes HD dual monitors with Endoeye Flex 3D articulating Videoscope (Olympus®). We used The ECHELON FLEX™ Powered vascular stapler with Gold cartridge (Ethicon®), and LigaSure energy device (Covidien®).

Procedure

Under general anesthesia, patient was positioned supine. We are using four ports: one 12-mm optical port at the umbilicus, two ports in the right abdomen. An additional

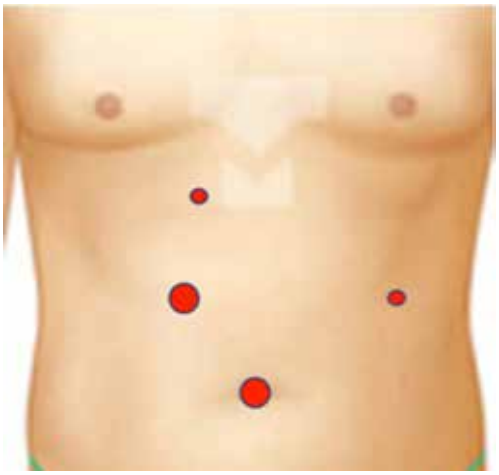

Figure 1 Trocar position.

Figure 2 Laparoscopic spleen preserving distal pancreatectomy (14). Available online: http://www.asvide.com/articles/1117

5-mm port is placed at cross point of anterior midclavicular line and left hypochondrium: it is used by the assistant surgeon (*Figure 1*).

The procedure starts with cutting of greater omentum using an energy device from middle to left until the spleen is exposed. Stomach is retracted cephalad by suturing its posterior wall and pulling out the string using a needle passer. Dissection is then continued at the inferior border of the pancreas. LigaSure is useful to control small vessel by sealing during dissection of pancreas. Medium sized vessels are clipped and divided. LigaSure and the suction tip are useful for dissecting between pancreas and splenic vein (*Figure 2*).

Then, the dissection is carried on at the superior border of pancreas in order to identify and isolate the splenic artery. After splenic artery isolation, retropancreatic space is made by dissection between pancreas and portal vein. Surgical tape is placed around the pancreas neck and gently lifted upwards by the assistant. Pancreas is transected by The ECHELON FLEX™ Powered vascular stapler (60 mm) with Gold cartridge (Ethicon®). The type of cartridge depends on the thickness and texture of the pancreas. Green cartridge is used for thick and hard pancreas or the pancreatic duct can be sutured intracorporeally. Dissection is then carried on from right to left. The LigaSure is frequently used to separate the splenic vessels from pancreatic parenchyma. Gradually, the dissection is continued all the way to the splenic hilum. Meticulous bleeding control and irrigation is done and fibrin glue is applied on the pancreatic resection margin. Specimen is pulled out through extended umbilical port by putting in the vinyl bag. Umbilical port and 10 mm port site fascia are closed by suture. Drain is placed at the pancreas resection margin through the left 5 mm port.

Role of team member

- Dr. Ho-Seong Han: Surgeon;
- Dr. Yoo-Seok Yoon: Surgeon;
- Dr. Seong Uk Kwon: Assistant Surgeon;
- Dr. Hyo Seok Na: anesthesiologist;
- Nr. Yu Jin Heo: scopist.

Tips, tricks and pitfalls

It is very important to acquire a proper view of the surgical field in laparoscopic surgery. To obtain the right surgical field, the assistant should lift the stomach at the cephalad direction as it interferes with the exposure of the pancreas and the celiac axis. So we have to add an extra port for the assistant to manipulate the stomach beforehand. Hence, if we anchor the stomach by suture and pull the string out of abdomen, the surgical field will remain stable during the whole operation time. If the stomach is large, one or two more sutures will be helpful.

Bleeding from small branches can occur easily while dissecting between the pancreas parenchyma and the splenic vessels. Using the sealing device, it is possible to control these small veins. When clips are used for small veins, it may easily fall off and bleed easily. The sealing device may be useful for secure control of small vessels and shortening operative time.

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None.

Footnote

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Total laparoscopic pancreaticoduodenectomy

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Abstract: Total laparoscopic pancreaticoduodenectomy (TLP) represents perhaps one of the most challenging abdominal operations. This procedure is gaining popularity in recent years, mostly due to the numerous reports underling its safety and feasibility in the setting of several benign and malignant pancreatic pathologies. Minimal-invasive pancreatic surgery is rapidly becoming a reality in many centers around the globe and its benefits, compared to the traditional open approach, have been extensively proven in the setting of distal pancreatic resection. The many advantages of a laparoscopic approach, such as the improved visual magnification, the theoretical improved tissue exposure, and the potential for a more delicate manipulation of tissues are reasonably expected to be applicable to other pancreatic procedures including TLP. Herein we describe a technique for a TLP; we provide some suggestions on patient selection, pre-operative preparation, equipment, postoperative management, and finally discuss some of the most common pitfalls encountered during the procedure.

Keywords: Laparoscopic pancreaticoduodenectomy; Whipple; minimally invasive pancreatic surgery; pancreas

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Introduction

Total laparoscopic pancreaticoduodenectomy (TLP) has remained a topic of controversy in the surgical literature during the last two decades. TLP was first reported in 1994 by Gagner and Pomp, who performed the procedure in the setting of chronic pancreatitis (1). Since then, several single institution series reported on the safety and feasibility of TLP in the setting of several benign and malignant pancreatic pathologies (2-4). The available literature mainly focuses on two key aspects of TLP, one being the learning curve necessary to master the procedure and the other being the comparison of overall outcomes between TLP and open pancreaticoduodenectomy (OPD) (5-7). The numerous studies that have focused on TLP learning curve have identified at least three phases: a slow difficult beginning, followed by a rapid improvement that culminates in a plateau phase characterized by a slow but continuous improvement (5-7). Moreover, most studies comparing TLP to OPD suggest that when TLP is performed in center of expertise the oncologic outcome, the complication rate, and the mortality rate are similar to OPD. Furthermore, TLP appears to be associated with decreased blood loss and hospital stay despite being associated with longer operative time (7-11).

Minimally invasive approaches to pancreatic surgery represent the most recent technical innovation in the field of pancreatic surgery and range from a laparoscopic assisted procedure, to a total laparoscopic or robotic approach.

The benefits of a minimal invasive pancreatic surgery have been extensively recognized for distal pancreatic resection and include reduced blood loss, shorter hospitalization, and reduced overall complication rates compared with the standard open approach (12-15). However, the definitive benefits of a minimally invasive approach (laparoscopic or robotic) to pancreaticoduodenectomy (Whipple procedure) continue to be debated (10,16-18). Nevertheless, it appears reasonable to speculate that some of the advantages seen with the use of a minimally invasive approach to distal pancreatectomy may be applicable to a TLP.

Herein we describe a technique for a TLP; we provide some suggestions on patient selection, pre-operative

Figure 1 The video illustrates the key steps performed during a total laparoscopic pancreaticoduodenectomy (TLP) (20). Available online: http://www.asvide.com/articles/1057

preparation, equipment, postoperative management, and finally discuss some of the most common pitfalls encountered during the procedure.

Patient selection and workup

Most patients with pancreatic, ampullary, or biliary pathologies who require a pancreaticoduodenectomy are eligible for a laparoscopic approach. One limitation is represented by patients with locally advanced pathologies (i.e., locally advanced pancreatic adenocarcinoma) with involvement of the mesenteric vasculature due to the inherent technical difficulties represented by the need for laparoscopic vascular resection and reconstruction (although a few specialized centers occasionally offer TLP in this setting) (11,19).

The authors routinely obtain preoperative multi-slice pancreas specific triple-phase (i.e., arterial, late arterial, and venous phase) computed tomography in order to properly evaluate the pancreatic gland and its spatial relation with the surrounding organs and vasculature; particular attention is given to the evaluation for any aberrant anatomy (e.g., replaced or accessory hepatic vasculature).

Additional imaging is dictated by the particular pancreatic pathology that is being addressed, and can vary from endoscopic retrograde cholangiopancreatography with or without pancreatic duct brushing, endoscopic pancreatic ultrasound with or without fine needle aspiration, and magnetic resonance imaging.

Preoperative laboratory tests are routinely obtained and include a complete blood cell count, a complete metabolic panel (CMP), a coagulation profile, and in case of a patient with known preexisting diabetes glycated hemoglobin level is assessed; specific tumors markers are obtained based on the pathology being treated.

Pre-operative preparation

Patients selected to undergo a TLP meet preoperatively with a nutritionist and a glucose management expert, this provides an initial overview on the life style and diet adjustments that are necessary following the procedure. Furthermore, this initial encounter represents an opportunity for the patient to become familiar with the available insulin treatment regimens and glycemic monitoring strategies, should the need arise.

Procedure

This section summarizes the key steps performed during a TLP as illustrated in the multimedia file supplement associated with this manuscript (*Figure 1*).

Dissection phase

The patient is placed supine on the operating table and care is taken to properly secure the patient with a thigh belt to the operating table. It is paramount to ensure proper patient positioning and stability, as the table will be tilted at different stages of the procedure to help with organ exposure during tissue dissection and reconstruction. The upper extremity bony prominences are covered with soft pads; both arms are extended to no more than a 60° degree (to avoid injury to the brachial plexus).

The surgeon is positioned on the left side of the patient, the first assistant is positioned on the right side of the patient, and the second assistant stands on the left side of the patient, next to the surgeon. However, throughout the case operating is done from both sides of the patient depending on what is being done.

The procedure can be performed using five trocars, including a Hassan optical trocar, two 12 mm trocars, and two 5 mm trocars.

The Hassan optical trocar is positioned at the umbilicus (to be used for a 10 mm 30° or 45° angled laparoscope), two 12 mm trocars are placed along both left and right hemiclavicular line approximately 2 cm below the rib cage (these are the two main working ports), one additional 5 mm trocars is placed on the right side of the umbilicus (to provide lateral traction as needed) and an additional 5 mm

trocar can be placed on the left of the umbilicus as needed.

Once the abdominal cavity is accessed, the abdomen is first explored then attention is turned to the identification of the lesser sac. An ultrasonic dissector is used to divide the gastrocolic ligament, below the gastroepiploic vessels, allowing access to the retroperitoneal area and ultimately leading to direct visualization of the pancreas.

Subsequently the assistant provides cephalad traction on the stomach (by grasping the stomach antrum or body with an atraumatic laparoscopic grasper); this will facilitate the identification of any adhesions present between the posterior surface of the stomach and the anterior surface of the pancreas. These adhesions can then be sharply divided gaining full exposure of the anterior surface of the pancreas.

The dissection of the porta hepatis is initiated and the gastroduodenal artery (GDA) lymph node is identified and removed. The removal of the GDA lymph node allows visualization of the GDA take-off that is isolated and skeletonized, care is taken to avoid avulsion of the superior anterior pancreaticoduodenal artery.

The GDA can now be ligated; the authors prefer a suture ligation of the proximal GDA that is additionally reinforced with two medium surgical clips, proximally and distally, prior to its sharp division. Care is taken to verify that the GDA is properly skeletonized and removed of all surrounding soft tissue in order to ensure full ligation with the surgical clips.

Attention is then turned to the inferior pancreatic border and care is taken to identify the superior mesenteric vein (SMV). Blunt dissection is carried on along the SMV anterior surface, progressively separating the posterior aspect of the pancreatic neck from the SMV and eventually leading to the identification of the confluence between the SMV vein and the splenic vein. During this step, the laparoscopic approach offers a magnified visualization of the "tunnel" created between the pancreatic neck and the SMV-splenic vein confluence that is a clear advantage compared to a traditional open procedure.

The hepatic flexure and the transverse colon are mobilized inferiorly after division of the colohepatic peritoneum exposing the second and third portion of the duodenum. An extended Kocher maneuver is performed to allow for medialization of the duodenum and the plane between the duodenum and the retroperitoneum is identified and dissected using either blunt or energy dissection to allow for the identification of the inferior vena cava, the aorta, and the superior mesenteric artery.

The gallbladder is identified, the Calot's triangle is exposed, and the cystic duct and the cystic artery are dissected and doubly ligated with surgical clips prior to being sharply divided. A cholecystectomy is then completed in a standard laparoscopic fashion and the dissected gallbladder is placed in the right abdomen for later removal.

The stomach can then be transected just proximal to the pylorus using a laparoscopic stapling device (the pylorus should be clearly identified prior to the transection in order to avoid accidently stapling across the pylorus). The gastric remnant can now be mobilized into the left upper abdomen allowing for improved exposure of the pancreas.

The pancreatic neck is then divided along the previously created pancreatic tunnel (with the use of electrocautery) and the pancreaticoduodenal arteries are controlled (with the use of an energy device) for hemostasis. The pancreatic duct is identified and an appropriately sized pediatric feeding tube (usually ranging from 4 to 8 French) is inserted in the pancreatic duct; this will function as a temporary stent and will aid with the subsequent reconstruction.

The common bile duct is then identified, dissected free from the surrounding tissues and its proximal aspect is secured with a surgical bulldog clamp, this will avoid spillage of bile during the remaining steps of the procedure. An energy device is then used to transect the common bile duct approximately 2 to 3 cm above the superior pancreatic border.

The authors use a laparoscopic stapler to divide the jejunum to 50% of its width at site chosen for the future definitive transection; the division of only half of the jejunum allows for easier rotation of the jejunum through the ligament of Treitz and under the mesenteric vessels. Alternatively, as shown in the video, the jejunum can be completely transected and the two jejunal free ends can be held together by a stay suture that will eventually allow for easy jejunal rotation under the mesenteric vessels.

The ligament of Treitz is identified and mobilized from its retroperitoneal attachments, using blunt dissection and an energy device. Once the dissection is completed, the duodenum and the jejunum can be safely rotated under the mesenteric vessels. A window is created in the mesentery, approximately 15 to 20 cm distal to the duodenojejunal flexure, and the jejunal vascular arcades are serially divided with the use of an energy device.

Attention is then turned to the pancreatic neck with the ultimate goal to expose and to dissect free the uncinate process. The assistant applies gentle cephalad and lateral

traction to the pancreatic head (toward the patient's right), this allows the surgeon to perform a blunt dissection along the SMV-portal vein confluence achieving complete separation between these structures and the posterior surface of the remaining pancreas.

At this stage, the uncinate process can be dissected free from the superior mesenteric artery using an energy device, however, occasionally it will require clips or suture ligature. A laparoscopic suctioning device can be used to gently retract the SMV laterally (toward patient's left side) allowing for complete visualization of the attachment between the SMA and the uncinate process. It is paramount to visualize both vessels (SMV and SMA) simultaneously during this delicate dissection in order to avoid catastrophic venous or arterial injuries.

Ultimately, the jejunum can be completely transected (at the site of the previous partial transection) using a laparoscopic stapling device.

This final step completes the dissection portion of the procedure and the specimens, including the previously dissected gallbladder, can be safely removed using a laparoscopic endo-bag and extracted through the umbilical port site.

Reconstruction phase

The reconstruction commences with the creation of a duct to mucosa pancreaticojejunostomy. The free end of the jejunum is brought in close proximity to the pancreatic remnant in preparation for an end to side, duct to mucosa pancreaticojejunostomy. The anastomosis begins with the construction of the posterior anastomotic row, which is fashioned using a single-layered running 4–0 barbing suture that eliminates the need for knots to secure suture lines. Then, a 2–3 mm jejunotomy is made to allow for a duct to mucosa anastomosis. After securing the pancreatic duct to the jejunal mucosa with a 5–0 synthetic non-absorbable suture, the pancreatic duct stent is passed through the jejunal defect and a duct to mucosa anastomosis is completed using five or six additional 5–0 synthetic non-absorbable sutures in an interrupted fashion. Finally, a single-layered running anastomosis is performed using a barbed suture on the anterior side.

The completion of a pancreaticojejunostomy is followed by the creation of an end-to-side choledochojejunostomy. The previously transected CBD is gently dilated with the use of a laparoscopic Maryland dissector instrument (by gentle separation of the instrument jaws) to allow for an easier anastomosis. Then, a jejunotomy is performed on the antemesenteric portion of the free-jejunal-end with the use of a laparoscopic electrocautery; this site is again gently dilated with a laparoscopic Maryland dissector to approximately match the size of the previously transected choledocho. An end-to-side duct-to-mucosa choledochojejunostomy anastomosis is performed using interrupted 4–0 synthetic absorbable sutures; the posterior row of the anastomosis is fashioned first and usually requires 3 to 4 interrupted sutures. Once the posterior row of the anastomosis is completed, a 6 to 8 French silicone tube (usually a pediatric feeding tube) can be customized to serve as a temporary biliary stent and inserted through the anterior opening of the choledochojejunostomy, this is followed by completion of the anterior row of the anastomosis in a similar fashion.

To minimize the tension of the choledochojejunostomy anastomosis, the authors routinely anchor the free-end of the jejunal limb to the hilar plate using one or two interrupted 3–0 synthetic absorbable sutures.

The mesenteric defect can now be closed with interrupted 3–0 silk sutures.

A jejunal loop is brought closer to the gastric remnant in preparation for an antecolic gastrojejunostomy, two 3–0 silk sutures are placed proximally and distally along the length of the future anastomosis to serve as anchoring sutures (stay-suture) so to facilitate the alignment of the jejunal segment to the stomach remnant. The assistant can now hold the tail of the proximal anchoring suture up toward the abdominal wall while applying gentle tension to the distal jejunal limb, at the same time the surgeon applies gentle cephalad tension to the stomach remnant; this maneuver stabilizes the gasto-jejunal unit and two enterotomies (a gastrotomy and a jejunotomy) can be easily created using an energy device.

A gastrojejunotomy is then completed using a stapling device; the resulting common enterotomy defect is closed with interrupted 3–0 silk sutures.

Finally the abdomen is explored for evidence of bleeding, bile leakage, or remaining enterotomy defects; one surgical drain is placed posteriorly to the pancreaticojejunostomy and one anterior to the choledochojejunostomy. The abdominal wall fascial defects are finally closed with the use of a Carter-Thomason needle suture passer.

Equipment card

The key surgical instruments and supplies necessary to

Table 1 TLP equipment card (includes key components)

Item name	Quantity
5 mm 0° and 30° laparoscopes	1
10 mm 0° and 45° laparoscopes	1
Endoscopic kittner	1
Harmonic scalpel ACE® laparoscopic 36 cm	1
Suction irrigator	2
Endoscopic catch bag 15 mm	1
Endoscopic stapler 30 mm	2
Endoscopic stapler 60 mm × 3.8 mm	2
Endoscopic stapler reload 45 mm × 2.5 mm	2
Endoscopic stapler reload 60 mm × 3.8 mm	1
Endoscopic shear 5 mm × 35 mm	1
Grasper 5 mm × 35 mm	2
Endoscopic clip applier	1
Skin stapler 35 mm wide	1
Endoscopic trocar blunt 12 mm × 100 mm	3
Endoscopic trocar 5 mm × 100 mm FIOS®	2
Endoscopic trocar threaded 15 mm × 100 mm	1
Foam pad elbow protector	1
Feeding tube (available 4-6-8 French)	2
Surgical drains 15 Fr	2
Surgical clips large and medium	2
Ligasure Maryland 37 cm	1
Endoscopic clip III 5 mm clip applier	1
Endostich sofsilk 2-0 48 inches	8
Prolene 5–0 blue 36” C-1 needle	1
Endoloop coated vicryl 18 inches	1
Surgipro II 4–0 36” CV-23 needle	2
Suture PDS 4–0 RB-1	8
Suture V LOC 3–0 P-14 18” 180	2

TLP, total laparoscopic pancreaticoduodenectomy.

perform a TLP are summarized in *Table 1*.

Role of team members

TLP is considered to be among the most complex abdominal surgeries and requires significant amount of technological and human resources both during the operative procedure as well as during the recovery phase. The procedure requires one surgeon, who will direct the execution of the operation, and two surgical assistants, a first assistant to help with the performance of the various steps of the operation, and a second assistant dedicated to maneuvering the laparoscope. The role of the anesthesiology is of fundamental importance to ensure proper anesthesia, timely monitoring of all physiology parameters, and prompt response in case of unexpected blood loos. The operative team is also composed of one scrub nurse and a circulating nurse. The postoperative role of an expert nutritionist, glucose management nurse, and an endocrinologist expert in diabetes cannot be overemphasized may the needs for insulin therapy arise following pancreatic resection. The nutritionist will guide the patient through the alimentary adjustments needed and will optimized the use of pancreatic enzymes replacement therapy to the need of the specific patients. The glucose management nurse and the endocrinologist will provide the education and the therapeutic expertise necessary to achieve safe satisfactory glycemic control.

Postoperative management

Once the procedure is completed, the patient is usually extubated in the operating room (OR) and transferred directly to intensive care unit where he or her will remain for less than 24 hrs. During the initial recovery phase the attention is mainly focused on obtaining appropriate fluid resuscitation, pain control and optimal glucose level (i.e., <180 mg/dL). On postoperative day (POD) 1, the patient is transferred to a regular surgical ward, continuous telemetry monitoring is ensured, and ambulation is strongly encouraged. A post-pancreatectomy diet, consisting of small, frequent, low-fat, high-carbohydrate and -protein meals, can usually be started on POD 4. A detailed summary of the authors’ postoperative management approach is provided in *Table 2*. In the absence of severe complications, the patient can be discharged from the hospital as soon as POD 6.

Tips, tricks, and pitfalls

- Excellent pre-operative imaging is required as palpating aberrant arterial anatomy is not possible with the laparoscopic approach. Having knowledge of this anatomy will allow success with even aberrant arterial anatomy;
- Complete dissection of the common and hepatic artery

Table 2 Postoperative management approach to TLP

Description	POD 0 (day of surgery, transfer from OR to SICU, extubate in OR)	POD 1 (transfer to surgical ward in AM if no issues)	POD 2	POD 3	POD 4	POD 5	POD 6 (possible discharge)
Laboratory tests	CBC, CMP, serum amylase ABG, attempt to minimum labs as needed	CBC, CMP, Mg, PO4, coagulation profile	CBC, CMP	No labs	CBC, CMP	Drain amylase	CBC, CMP
Medications & fluids	SSI, PCEA or PCA, PPI, LR @ 150 (unless other specific fluids needed), SQH Q8h	SSI, PCEA or PCA, PPI, LR @ 84 (unless other specific fluid needed), SQH Q8h, wean O2 as tolerated	SSI, PCEA or PCA, PPI, D5 1/2 +20 @ 20, SQH Q8h, stool softener BID, insulin coverage	SSI, PCEA, PPI, D5 1/2 +20 @ 20, SQH Q8h, stool softener BID, insulin coverage	SSI, PO pain pills, d/c PCEA or PCA after oral pain pills given, PPI, d/c IVF, SQH Q8h, Colace BID, pancreatic enzymes replacement with meals	SSI, PO pain pills, PPI, Colace BID, SQH Q8h, pancreatic enzymes replacement with meals	SSI, PO pain pills, PPI, stool softeners BID, pancreatic enzymes replacement with meals, all patients are discharged home on PPI
Diet	NPO	Sips/chips <250 cc/4 hours	Sip/chips <250 cc/4 hours	Clear liquid diabetic diet	Post-pancreatectomy diet	Post-pancreatectomy diet	Post-pancreatectomy diet
Activity	Bedrest; IS 10×/hour	OOB as tolerated, IS: 10× per hour, pulmonary toilet	OOB, laps ×3, IS: 10× per hour, pulmonary toilet	OOB, laps ×4, IS: 10× per hour, pulmonary toilet	OOB, laps ×5, IS: 10× per hour, pulmonary toilet	OOB, laps ×6, IS: 10× per hour, pulmonary toilet	OOB, home w/IS
Devices	NGT to LIWS, JP drains to bulb suction, SCDs, TEDs, Foley	Keep NGT to LIWS until POD#3, JP to bulb suction, maintain Foley, SCDs while in bed, TEDs	d/c Foley, JP to bulb suction, SCDs @HS	JP bulb to suction	JP to bulb suction, d/c Foley if epidural discontinued	d/c JP1 if appropriate (output <20 mL for 48 hours, no evidence of bile leak)	d/c JP1 (if appropriate), otherwise send home with drain
Consults and miscellaneous	PT/OT consult no CPAP postoperatively	d/c arterial line or central line if applicable. Transfer to floor with telemetry	Case management glucose management consults (all patients) diabetes educator consult	—	Change insulin to AC + HS, cover > 120 nutrition consult	Insulin AC + HS	Discharge

AC + HS, before meals and bedtime. POD, postoperative day; OR, operating room; SICU, surgical intensive care unit; CBC, complete blood count; CMP, complete metabolic panel; ABG, arterial blood gas; Mg, magnesium; PO4, phosphate; SSI, sliding scale insulin; PCEA, patient controlled epidural analgesia; PCA, patient controlled analgesia; PPI, proton pump inhibitor; LR, lactated Ringer's solution; SQH, subcutaneous heparin; NPO, nil per os; IS, incentive spirometry; NGT, nasogastric tube; LIWS, low intermittent wall suction; JP, Jackson-Pratt; SCD, sequential compression device; TED, thrombo embolic deterrent hose; PT, physical therapist; OT, occupational therapist; CPAP, continuous positive airway pressure; IVF, intravenous fluid; TLP, total laparoscopic pancreaticoduodenectomy.

is required prior to transection of the GDA as test occlusion of the GDA and palpation of the proper hepatic is not possible;
- If visualization of the bile duct for the hepaticojejunosotomy is difficult, using a looped suture around the base of a mobilized falciform ligament through a poke incision at the base of the xiphoid can lift the liver;
- Bringing the jejunum through the ligament Treitz *vs.* the meso-colon avoids twisting that can be overlooked laparoscopically and provides a tension free loop for reconstruction;
- Having a laparoscopic bulldog set with various sizes is useful to quickly control bleeding from the portal vein allowing for laparoscopic repair if necessary.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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The prospective of laparoscopic pancreaticoduodenectomy for cancer management

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Abstract: Laparoscopic pancreaticoduodenectomy (LPD) is an extremely challenging surgery. First described in 1994, LPD has been gaining a favorable position in the majority of pancreatic surgery. Now, LPD is worldwide accepted. A literature search was conducted in PubMed, and only papers written in English containing more than 26 publications of LPD were selected. Papers in distal and robotic pancreatic procedure were not included in the review of a total of 222 LPD publications. The total number of patients analyzed was 1,082 from 25 articles and the largest series. Six of these studies came from the United States, 1 from France, 5 from Republic of Korea, and 1 from India, 2 from Japan, 5 from China, 1 from Italy, 1 Germany, 2 from UK. The overall pancreatic fistula rate was 20.5%. The overall conversion rate was 10.4%. LPD seems to be a valid alternative to the standard open approach with similar technical and oncological results. LPD is a safe procedure, 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 pancreaticoduodenectomy (LPD); Whipple procedure; pancreatic cancer; review

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Introduction

Laparoscopic pancreaticoduodenectomy (LPD) remains one of the most advanced laparoscopic procedures. Owing to the evolution in laparoscopic technology and instrumentation within the past decade, LPD is beginning to gain wider acceptance. While minimally invasive approaches are more feasible and very safe, some pancreatic surgeries are still performed in an open procedure because of the location and intimate relationship of the pancreas to major blood vessels, the reconstruction complexity of a pancreatoduodenectomy and the technical difficulty in performing such a minimally invasive approach (1). Modern medicine has introduced laparoscopic surgery that has revolutionized the field of pancreatic surgery so that, by now, surgical procedures for either benign or malignant pancreatic disease can be performed laparoscopically. The general differences between an open approach and a laparoscopic surgery are the methods of access and exposure and the degree of operative trauma (2). In line with significant development and maturation of surgical technologies, the numbers

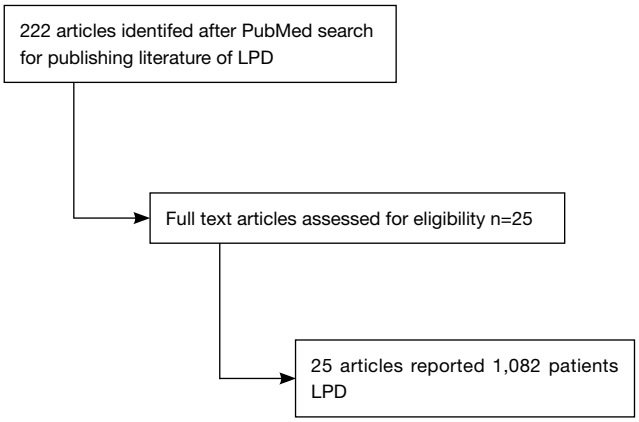

Figure 1 Literature search. LPD, laparoscopic pancreaticoduodenectomy.

of such laparoscopic pancreatic surgeries have increased each year. However, although clinical procedures were initiated around 2 decades ago, laparoscopic pancreatic surgery, specifically LPD, is still in its infancy; thus, certain innovations and novel strategies to manage this kind of procedure still need to be explored.

Methods and materials

A literature search was conducted in PubMed. Papers in laparoscopic distal pancreatectomy and robotic pancreatic procedure were not included in the review. The final search was completed on December, 2016 and revealed 222 articles and papers written in English containing more than 25 publications of LPD were selected. The total number of patients analyzed was 1,082 patients, and the largest series. Six of these studies come from the United States, 1 from France, 5 from Republic of Korea, and 1 from India, 2 from Japan, 5 from China, 1 from Italy, 1 from Germany, 2 from UK. 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, mortality. Oncologic data including number of lymph nodes removed, and resection was also recorded (*Figure 1*).

Results

LPD

The first LPD procedure was described by Gagner and Pomp in 1994 (3). Despite being first carried out 2 decades ago, it has not yet gained universal acceptance and popularity as it requires highly advanced technical skills with a lengthy learning curve, requiring a longer operative time (4). Despite the difficulty and complexity of this surgical procedure, LPD has been progressively developed in specialized centers due to the availability of newer technologies, successful application of laparoscopy in other complex abdominal surgeries and the motivation by surgeons to embrace innovation in the modern world (5). Recent reports on a large series of LPD demonstrated that the procedure might not only be feasible, but that it might have advantages as compared with open pancreaticoduodenectomy (OPD). According to Li *et al.* (6), their experience of LPD showed shortened hospitalization time and that operation time for experienced surgeons was significantly shorter than their previous attempts. Accordingly, blood loss was less, overall length of hospital was shorter, post operation pain was less and a faster recovery time were just some of the perceived benefits of LPD over open procedures (7).

Boggi *et al.* (5) has published a large review incorporating 25 articles wherein four techniques currently used for LPD (pure, hand-assisted, robot-assisted laparoscopy and laparoscopic-assisted surgery) were summarized. There were a total of 746 LPD surgeries between 1997 and 2013, with numbers generally increasing per year (based on published articles; from Boggi *et al.*, 2014) (5). Among the four techniques, pure laparoscopy gained the highest preference with more than half of the total LPD (51.7%) while the hand-assisted operation had the smallest number, around 0.6%. Not including the hand-assisted LPD, the other three operations obtained similar results with regard to the overall morbidity and mortality. However, in terms of blood loss, operative time and pancreatic fistula rates, pure laparoscopy had preferable results over the other two operations. Meanwhile, robotic-assisted LPD (RA-LPD) was also becoming popular; however, this system is not evenly available throughout the world (8), as the cost for this approach remained high and several limitations were reported for the use of this system such as the risk of malfunction and system collision (9,10), the lack of haptic feedback and the inability to move the patient after the robot has started operating (10), among others. Despite these limitations, performing this RA-LPD improves the dexterity of surgeons and surgical maneuver is easier compared to the open approach. Interestingly, using the data of all four techniques mentioned above (see *Table 1*),

Table 1 Published articles on LPD operative outcomes

Ref	Year	Country	Cases	OT (min)	EBL (mL)	Conv (%)	LOS (%)	Morb (%)	PF (%)	Mort (%)	LN	Res (%)
Jin *et al.* (11)	2016	China	66	367±49	193±126	0	18.9±12.1	36.4	4.5	0	20.3±10.9	100
Kim and Hong (12)	2016	Republic of Korea	12	411±59	118±57	0	12.5±4.5	NR	NR	NR	14.2±2.3	100
Wang *et al.* (13)	2015	China	31	515	260	9.7	12.6	NR	25.8	0	13	100
Senthilnath *et al.* (14)	2015	India	130	310±34	110±22	0.7	8±2.6	29.7	8.46	1.5	18.15±4.7	NR
Mendoza *et al.* (15)	2015	Republic of Korea	18	596.6	275	NR	13	44.4	22.2	NR	12.8±8.1	83
Liu *et al.* (16)	2015	China	21	316	240	4.9	14	24.6	4.9	NR	149	95
Dokmak *et al.* (17)	2015	France	46	342	368	6.5	25	74	48	2.1	20	60
Croome *et al.* (18)	2014	UK	108	379±93	492±519	0.9	6	NR	11	1	21.4±8.1	77.8
Lee *et al.* (19)	2013	Republic of Korea	42	404±30	374±176	7.1	17.1±9.2	35.7	7.1	2.3	16	100
Kim *et al.* (20)	2013	Republic of Korea	100	487±121	NR	4.7	15±9.7	33.3	25.7	0.9	13	100
Corcione *et al.* (21)	2013	Italy	22	392	NR	9.1	23	63.6	27.3	4.5	15	100
Asbun and Stauffer (4)	2012	USA	53	541±88	195±136	16.9	8±3.2	NA	16.7	5.7	23.44±10.1	94.9
Ammori and Ayiomamitis (22)	2011	UK	7	628	350	NR	11	29	14	0	7	NR
Kendrick and Cusati (23)	2010	USA	65	368	240	4.6	7	41.9	17.7	1.6	15	89
Zureikat *et al.* (24)	2011	USA	14	456	300	14.2	8	64.2	35.7	7.1	18.5	100
Song *et al.* (25)	2015	Republic of Korea	97	480	592	NR	14±7.7	26.8	29.9	0	12.5	90
Wellner *et al.* (26)	2014	German	40	343	NR	40	14	87	24	2.5	15	86
Gumbs *et al.* (27)	2013	USA	72	436	400	19	NR	NR	22	1.4	16	95
Paniccia *et al.* (28)	2015	USA	30	340	300	6	11	NR	50	0	NA	100
Tan *et al.* (29)	2015	China	30	513±56	NR	3.33	9.9±3.7	17.2	10	0	8.6±1.71	NR
Chalikonda *et al.* (30)	2012	USA	30	476	485	NR	10	30	7	4	NR	NR
Kuroki *et al.* (31)	2012	Japan	20	656.6	376.6	0	NR	NR	45	NR	NR	NR
Chen *et al.* (32)	2015	China	60	410	400	NR	20	NR	NR	NR	NR	NR
Lai *et al.* (33)	2012	China	20	492	247	NR	13.7	50	35	0	NR	73
Suzuki *et al.* (34)	2012	Japan	14	581	471	NR	23	33	33	0	NR	100
Bao *et al.* (35)	2014	USA	28	431	100	NR	7	NR	21	7	15	63
Jacobs and Kamyab (36)	2013	USA	5	588	136	NR	6	NR	1	NR	4–5	95
Li *et al.* (6)	2014	China	1	450	100	0	12	0	0	0	1–2	100

NR, no recorded; LPD, laparoscopic pancreaticoduodenectomy.

the number of LPD (*Figure 1*) reported in a more than a year (from January 2012 to June 1st 2013) has exceeded the LPD reported in the last 15 years and is a proof that LPD has quickly matured into an acceptable surgical procedure at least in specialized centers and in the hands of surgeons with highly advanced laparoscopic skills (5).

Comparison between LPD and the open approach

Asbun and Stauffer (4) have compared the outcomes of patients who have undergone LPD with those patients who have undergone OPD based on morbidity and mortality, in a 6-year period (between 2005 and 2011). According to the results, significant differences were observed in favor of LPD that included shorted intensive care unit (ICU) and hospital stay, lower blood loss and transfusions, and higher retrieval of lymph nodes. Although operative time was statistically longer for LPD, there were no difference in overall complications and pancreas fistula between LPD and OPD. Therefore, Asbun and Stauffer (4) have suggested that LPD is safe and feasible and the outcomes were better than OPD. Aside from this, LPD could also offer an extended long-term survival after the operation (13). However, technical difficulty and complexity of this procedure still remain a limitation (4), and other authors still contend that LPD had no significant advantages over OPD since there were no significant differences in terms of blood loss, morbidity, number of lymph nodes harvested, mortality and R0 resection rate (24), which was not in agreement with more recent reports (13,18,30,31) among others.

Kuroki *et al.* (31) made a retrospective analysis comparing the outcomes of laparoscopically-assisted pancreaticoduodenectomy (LA-PD) and OPD surgeries among 51 patients (n=20 for LA-PD while n=31 for OPD) with pancreatic and periampullary disease. According to their data, operative time and post-operative complications did not differ significantly between the two groups while blood loss was much less in the LA-PD group. This reduced blood loss in minimally invasive surgeries has also been recognized by other authors (30,37). As such, Kuroki *et al.* (38) concludes that LA-PD is safe, feasible and has an advantage of less blood loss, as is usually the case in minimally invasive surgeries. With regard to operative time, it has been shown that mean time of operation can be lessens with improved skills. For example, Kim *et al.* (20) recorded a reduction in mean operation time from 9.8 hrs (for the first 33 patients) to 6.6 hrs (for the last 40 patients). Kendrick *et al.* (23) also reported a reduction in operative time to 5.3 hrs from the previous 7.7 hrs. Because of these findings, it can also be elicited that LPD can be performed efficiently and safely by experienced and highly skilled surgeons, although the learning curve is steep. Also, standardizing LPD protocols may potentially help shorten LPD operative time (38). However, according to Corcione *et al.* (21), LPD does not provide significant benefits compared to the open approach but may do in specialized centers with surgeons who have acquired highly advanced skills in LPD.

In another study, Croome *et al.* (18) evaluated the advantages of total laparoscopic pancreaticoduodenectomy (TLPD) (n=108) over OPD (n=124) for pancreatic ductal adenocarcinoma performed from January 2008 until July 2013. The results showed that after operation, the OPD group stayed longer in the hospital (average: 9 days) compared to the TLPD group (average: 6 days). Moreover, progression-free survival was longer in TLPD compared to the PDC group. In patients administered with adjuvant chemotherapy, median time until commencement of treatment was also shorter in TLPD (48 days, ranging from 17–116 days) compared to OPD (59 days, ranging from 25–302 days) and a significantly smaller proportion of patients in the TLPD group had a delay of more than 56 days. Intraoperative transfusions and delayed gastric emptying occurred less frequently in the TLPD group. In terms of overall survival, there was no significant difference between the two. Based on these results, Croome *et al.* [2014], has emphasized that the TLPD was not only feasible but also had significant advantages over the traditional open approach. Furthermore, Jacobs and Kamyab [2013] have also evaluated the oncologic outcome of TLPD and based on their experience, complication rates were equivalent or improved in TLPS compared to the traditional Whipple procedure. The patients also had a faster recovery and shorter length of stay and a better quality of life.

Comparison between RA-LPD and OPD

Chalikonda *et al.* (30) made a comparison between the outcomes of RA-LPD and OPD among 60 patients (n=30 for RA-LPD and n=30 for OPD). Based on their case-matched data, the mean operative time for RA-LPD is longer than OPD while the blood loss and length of stay were decreased in the RA-LPD compared to the OPD. Albeit one perioperative death was experienced in the RA-LPD group that has led to emergent conversion to OPD,

the need for re-operation did not differ between the two groups. Chalikonda *et al.* [2012] has recognized surgical robots as having the potential to overcome some technical difficulties associated with laparoscopy and, with the necessary skills needed to perform such operation aligned with the proper selection of patients, good outcomes are achievable with RA-LPD. The only drawback that was mentioned was the high capital and maintenance costs of RA-LPD plus the added costs associated with longer operative time. Accordingly, the reduced morbidity after RA-LPD made it an acceptable and reasonable surgical approach, for appropriately selected patients (30).

In another study, a comparison was done between RA-LPD and OPD surgeries (Lai *et al.*, 2012) among 87 patients (n=20 for RA-LPD and n=67 for OPD) who underwent either of the two operations from January 2000 to February 2012. The results for RA-LPD were longer operative time, less blood loss and shorter hospital stay, in concurrence with the results reported by Chalikonda *et al.* (30). Furthermore, there were no statistically significant differences between the two groups in terms of complication and mortality rates and total number of lymph nodes harvested. As such, Lai *et al.* (33) has recognized the safety and feasibility of RA-LPD, although caution should be carefully observed to evaluate the appropriateness of this procedure for each patient. More recently, Parisi *et al.* (39), has also recognized the evolution of minimally invasive pancreaticoduodenectomy through robotic technology, suggesting it to be feasible, reproducible and safe.

Recently, Chen *et al.* (32), has also published a study comparing RA-LPD and OPD among 180 patients (n=60 for RA-LPD and n=120 for OPD) who underwent such operations between January 2012 and December 2013. According to the results, patients who underwent RA-LPD had lesser blood loss, longer but decreasing operative time, resumed bowel movement faster, off-bed return to activity faster and length of hospital stay shorter compared to patients who underwent OPD. Based on mortality, morbidity, and disease-free survival, there were no significant differences between the RA-LPD and OPD groups. Hence, the author suggested that RA-LPS is associated with faster recovery, but it involved a large learning curve for surgeons. *Table 1* summarizes the intra- and postoperative outcomes of different studies on LPD.

Modifications of the LPD procedure

More recently, Liu *et al.* (16) has reported a modification of the LPD procedure. With accumulated substantial experience in laparoscopy, a modified and simpler procedure, called the reverse-"V" approach, was developed to optimize LPD for appropriately selected patients. This modified approach is advantageous as it helps in avoiding pancreatic leakage and also lessens difficulty in the surgical union of tubular parts (anastomosis). The procedure was done in four ports (see Liu *et al.*, 2015, for the detailed procedure) in 21 patients. Based on the results, the median blood loss was less (240 mL) as was the operative time (368 minutes). The reported blood loss and operative time for this study is in fact lower than previous studies (22,40). There was also no perioperative mortality reported. Therefore, LPD using a reverse-"V" approach is safe, which can give good results and can be used in treating localized malignant lesions. Since this surgical procedure is feasible and simple at the same time, further investigations should be continually carried out. However, even though this procedure is simpler compared to the traditional LPD procedure, surgeons attempting should be equipped with advanced skills in pancreatic surgery and laparoscopy to avoid complications (14).

Conclusions

It is clear that benefits of LPD over OPD are relative to the respective skill and experience of the surgeon carrying out the procedure. Therefore, in order to continue the improvement of LPD techniques, it is vital to standardise surgical training and carry out further research to identify which aspects of LPD instruction most efficiently teach surgeons to reduce blood loss, tissue trauma and complications. However, when researching this we must be mindful of the extent that the skill of the surgeon has on the outcome of the operation and the differing abilities of surgeons to learn at different stages of the learning curve. Therefore, a possible avenue to achieve this would be using surgical simulation machines to assess how different instructional methods affect blood loss and trauma incurred in subsequent simulated operations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare

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Laparoscopic pancreatic resection—a review

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Abstract: Contrary to many other gastrointestinal operations, minimal access approaches in pancreatic surgery have gained ground slowly. Laparoscopic distal pancreatectomy has gained wide acceptance. It is associated with reduced blood loss and shorter duration of stay (DOS) while oncologic results and morbidity are similar to open surgery. In recent years the number of laparoscopic pancreatoduodenectomies has also increased. While oncological outcome seems comparable to the open approach, operative times are longer while DOS and blood loss are reduced. One added advantage of the laparoscopic approach to pancreatic cancer seems to be that adjuvant treatment can start earlier. Minimal access total pancreatectomy, only reported in small numbers (mostly robot assisted), has also been shown to be feasible and safe. Enucleation (EN) of small pancreatic lesions is the most common tissue sparing resection. Although no reconstruction is necessary, the risk of pancreatic fistula is high, related to excision margins equal or smaller than 2 mm to the main pancreatic duct. Compared to the open approach, laparoscopic EN has shown comparable results in terms of morbidity, pancreatic function and fistula rate, with shorter operation times and faster recovery. Experience in robot assisted pancreatic surgery is increasing. However reports are still small in numbers, lacking randomization and mostly limited to dedicated centers. The learning curve for minimal access pancreatic surgery is steep. Low patient volume leads to longer DOS, higher costs and negatively impacts outcome.

Keywords: Minimal access surgery (MAS); pancreas; pancreatic resection; laparoscopy

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Introduction

In the last decades minimal access surgery (MAS) has gained wide spread use both for benign and malignant disease in gastrointestinal surgery (1). Oncological adequacy has been shown in a variety of indications, including colonic (2,3) and gastric cancer (4). Laparoscopic pancreatic surgery, however, has been slow to gain momentum. Since the first description of minimal access cases reported in 1994 (5), the proportion of laparoscopic pancreatic resections remains low: according to the US Nationwide Inpatient Sample database from 2000 to 2011, only 5% of all resections were performed via a minimal access approach (6). However, with progress in laparoscopic equipment, increasing numbers of cases have been reported in all indications (6,7). Our aim was to review the literature concerning the major advances in minimal access pancreatic surgery.

Definitions

The International Study Group on Pancreatic Fistula (ISGPF) (8) defined postoperative pancreatic fistula (POPF) as "drain output of any measurable volume of fluid on or

Table 1 ISGPF grading of POPF (8)

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment*	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)**	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Sepsis	No	Yes	Yes
Readmission	No	Yes/no	Yes/no

*, partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage; **, with or without a drain *in situ*. ISGPF, International Study Group on Pancreatic Fistula; POPF, postoperative pancreatic fistula; US, ultrasonography; CT, computed tomographic scan.

after postoperative day 3 with amylase content greater than 3 times the serum amylase activity". Severity is graded from A to C (*Table 1*).

Distal pancreatectomy (DP)

DP accounts for about a third of all pancreatic resections (6). Indications include benign, pre-malignant and malignant lesions of the pancreatic body/tail such as chronic pancreatitis, endocrine tumors, intraductal papillary mucinous neoplasm (IPNM), pancreatic pseudocysts, mucinous and serous cystic neoplasia, metastases and also trauma with ductal injury (9-11).

MAS accounts for between 10.8% to 46.6% of DP (9,12,13). Several publications have found no statistically significant difference in operative times between laparoscopic DP (LDP) and open DP (ODP), ranging from 156 to 383 min and from 145 to 330 min in laparoscopic and open surgery, respectively (14-17). Conversion rate ranged from 0% to 34% (18,19), hemorrhage and failure to progress being the most common causes. Estimated intraoperative blood loss was found to be significantly lower in LDP (9,13,14,20,21).

Morbidity in LDP has been reported to range from 0% to 67% in single center studies (22,23). However, recent meta-analyses (9,18) described overall morbidity ranging from 34.0% to 37.4%. As morbidity is essentially related to POPF, one possible explanation for this wide range of morbidity may be the use of different definitions for POPF. Adhering to the ISGPF definition, systematic reviews have described the POPF incidence to range from 16.8% to 21.7% in LDP (9,11).

Similarly, reported mortality (range, 0.2–0.4%) (9,18) and reoperation rates (range, 2.1–6.0%) (18,24,25) did not differ from outcomes after open surgery. In spite of a variety of closure techniques available (suture, stapler, sealant, mesh), at the present time there is no proof that one closure technique is better than the other (26-30). Spleen preserving LDP has been described to be safe and feasible (10,22) and has been reported in 18.2% (16) to 60.4% (31) of LDPs.

In their 2015 meta-analysis of 34 studies, Mehrabi *et al*. (9) described a statistically significant difference in time to first oral intake (0–1.3 days) and duration of stay (DOS) (0–3.8 days). Of note, DOS after DP seemed to be shorter in the United States compared to centers outside of the United States, which might be attributed to differences in health care systems (18). More recently, Shin and colleagues (12) confirmed these reductions in their single center, propensity matched analysis.

Resection margin status was also studied in the meta-analysis by Mehrabi *et al*. (9): four studies (32-35) reported comparable R0 rates in both groups (592 patients) (OR: 1.63; 95% CI: 0.65–4.07; P=0.29), while the rate of R1 resections was lower in the LDP group (520 patients) (OR: 0.34; 95% CI: 0.14–0.83; P=0.02) (19,34-36).

The mean number of lymph nodes harvested did not differ significantly between LDP and ODP (12 to 13.8 LDP *vs*. 10 to 12.5 ODP) (12,13). However, the median number (10, range, 1–64) of lymph nodes harvested in the ODP group in one report (12) was less than 12, the recommended number for adequate disease staging (37).

Shin *et al*. observed a median postoperative survival of 33.4 months in LDP *vs*. 29.1 months in OPD (P=0.025) (12). In contrast a multicenter study by Kooby *et al*. found considerably shorter survival (16 months) in both groups (13).

While low long-term survival rates are typical for pancreatic cancer, the difference in survival between these last two studies might be attributed to the differences in median tumor size (3.0 *vs.* 3.5 cm) as well as the type of (monocenter *vs.* multicenter) study.

Pancreatoduodenectomy (PD)

Due to the anatomical position in the retroperitoneal space, the vicinity to large vessels and the need for three critical anastomoses, PD is considered one of the most challenging operations in GI surgery. Laparoscopic pancreatoduodenectomy (LPD) was described first by Gagner *et al.* over 20 years ago (5), but since then has not gained widespread use, as it was considered even more difficult (*vs.* the open approach) with questionable benefits to patients (38). However, with the advance of laparoscopic techniques and improved equipment, the number of LPD performed is continuously rising, as demonstrated by an increase of 50% from 2000 to 2010 according to Tran and colleagues (39).

Several studies have attempted to compare the operative and oncologic characteristics of open and laparoscopic pancreatic head resections, but none were randomized (38-52). Mean operative times have been reported to be significantly longer in LPD, ranging from 452 to 541 min for LPD compared to 372 to 401 min in OPD (40-42), although one center reported non-significant differences (465±86 *vs.* 465±98 min, respectively) (43). On the other hand, similar to what was observed in LDP, intraoperative blood loss has been reported to be significantly lower in LPD (492.4±519.3 to 841.8±994.8 mL in LPD *vs.* 866.7±733.7 to 1,452.1±1,966.7 mL in OPD) (43-45). DOS was significantly shorter in several comparative studies (6 to 8 *vs.* 9 to 12.4 days, respectively) (40,43,44) whereas other studies (7,41) found no statistically significant difference. Conversion to open surgery was reported in 9.1% to 30.0% of cases, mostly due to venous invasion and intraoperative bleeding (7,44,46). Overall morbidity in LPD has been reported to range from 35–52%, however this difference was not found to be statistically significant between the surgical approaches (43,47,48).

Postoperative mortality was recorded to range from 3.2% to 8.8% in LPD *vs.* 3.4% to 5.7% in OPD, difference which was not statistical significant (7,39,40,43). The reported incidences of clinical relevant POPF (grades B and C) described in several studies were fairly similar, ranging from 6.3% to 11.0% (45,49) in LPD and 5% to 9% (40,43) in open surgery. In their systematic review, Correa-Gallego *et al.* (44) described overall POPF rates of 21% (8% grade B and C) in LDP and 17% (7% grade B and C) in ODP. This is comparable with Boggi and colleagues (46), who found a 24.8% incidence (10.5% grade B and C) for POPF after LDP in their meta-analysis.

Given that the majority of PDs are performed for malignant or premalignant lesions (7,46,49), adequate oncological resection remains one of the key questions. The number of lymph nodes harvested has been reported to be similar (7,45) or even significantly higher in LPD (40,43,44) compared to PD. Comparisons of R0 resection rates showed that results between open and LPD did not differ significantly (7,40,43,45,50). Of note, however, margin status may not be the ideal parameter for comparisons because definitions of margin involvement vary and under-reporting of microscopic margin involvement has been described (51). Portal venous infiltration as such is not a contraindication for the LPD (52). Interestingly, Croome and colleagues (45) reported a significantly longer interval of progression free survival and a shorter median time to adjuvant chemotherapy in LPD. However, overall survival was not improved, consistent with what is generally observed in pancreatic cancer (43,49).

However, most results come from highly experienced centers for LPD and may not be generally applicable. Moreover, several studies (39,47,48) have indicated that the learning curve is steep, DOS is increased and total costs are higher in centers performing fewer PDs. According to Adam and colleagues in their analysis of 7,061 PD for cancer in the US from 2010–2011, 92% of LPD (14% of all PDs) were undertaken in hospitals performing 10 LPD or less over a 2-year period. They also found a significantly higher 30-day mortality rate in LPD compared to OPD, which was inversely correlated with the volume of LPD per hospital (7). This is in agreement with the OPD learning curves described by Tseng *et al.* (53) identifying a number of 60 interventions necessary for adequate experience.

Total pancreatectomy (TP)

TP is rarely performed, accounting for 5.4% to 6.7% of all pancreatic resections in high volume centers (54,55).

This may explain why only a few papers (56-60) with small numbers have been published on laparoscopic total pancreatectomy, and thus showing only that it was feasible and safe with apparently satisfactory oncologic outcome.

Parenchyma sparing resections

Parenchyma-sparing resections are indicated in small—benign or low grade malignant—lesions, thus reducing the risk of exocrine and endocrine insufficiency (61). Safety and feasibility of enucleation (EN) and middle pancreatectomy, the most common procedures performed laparoscopically, have been described (62-64).

Indications for parenchyma sparing approaches include mainly neuroendocrine neoplasms, serous cystadenoma and branch duct IPMN as well as solitary renal cell carcinoma metastasis (62,65,66). Depending on the location, tumor size should not exceed 3 to 4 cm in diameter for laparoscopic EN (67,68). Although EN does not include a reconstructive phase, the procedure is associated with a high risk for POPF. In their systematic review on 811 patients undergoing EN, Beger *et al*. found a 36.7% POPF rate, 16.3% of which were clinically relevant (ISGPF grades B and C) (64). A resection margin equal or less than 2 mm from the main pancreatic duct has been identified as a high risk factor for development of POPF (67).

Zhang and colleagues (61) found no difference between open and laparoscopic EN concerning preservation of pancreatic function, but described shorter operation time as well as lower intraoperative blood loss and faster recovery (in terms of time to first flatus and first oral intake; DOS) in the minimal access approach. A systematic review by Briggs *et al*. reported conversion rates ranging from 10.5% to 44.4% with a 29.3% POPF rate (31).

Robotic-assisted surgery

The first robotic-assisted pancreatic resections were reported in 2003 by Melvin *et al*. (69) for DP and by Giulianotti *et al*. (70) for PD. Since then several reports (71-73) have shown promising results, comparable to and at times better (conversion rate, DOS) than standard laparoscopy and open procedures. While most studies represent early experiences, there is a significant learning curve for robotic pancreatic surgery (74), as in other robotic-assisted procedures (75). Boone *et al*. (76) described a continuous learning effect with statistically significant improvement after 20 (conversion rate, blood loss), 40 (POPF incidence) and 80 (operative time) procedures.

Of note, the total cost per operation is higher in the robotic approach [$8,304 robotic DP (RDP) *vs*. $3,861 LDP; robotic PD +€6,200 *vs*. OPD] (77,78). Interestingly, however, in their single institution experience, Waters *et al*. (36) reported lower overall costs for robotic DP after adjusting for DOS ($10,588 RDP *vs*. $12,986 LDP *vs*. $16,059 ODP). Notwithstanding, hospital costs are most likely subject to substantial variations depending on different health care systems (79).

Conclusions

Laparoscopic pancreatic resections have been shown to be feasible and safe, with rising numbers being reported during the last decade. Most LPD have been performed in university and urban teaching hospitals, while DP seems to be more widely implemented (6).

Comparisons with open surgery have shown reductions in hospital stay and intraoperative blood loss as well as similar results in terms of oncological adequacy. However, none of the data included in this review derive from controlled randomized studies and often represent single center or even single surgeon's experience, thus underscoring a significant risk for bias. This stresses the need for RCTs wherever possible.

Another major issue is the steep learning curve associated with pancreatic surgery in general and specifically the minimal access approach. Low volume hospitals have been shown to be significantly associated with worse patient outcomes. Robotic assisted surgery is gaining popularity especially in the U.S.

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Footnote

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Simultaneous laparoscopic resection of distal pancreas and liver nodule for pancreatic neuroendocrine tumor

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Abstract: Laparoscopic distal pancreatectomy (LDP) with or without splenic preservation is increasingly performed for benign or border-line neoplasms of the body and tail of the pancreas. Pancreatic neuroendocrine tumors appear as an excellent indication for laparoscopic resection and this procedure is becoming the gold standard for the surgical treatment of such neoplasms. The safety and advantage of laparoscopic resection over open distal pancreatectomy (ODP) have been proven. In this video, we present a LDP with splenectomy for a neuroendocrine tumor of distal pancreas, with associated wedge resection of a liver nodule. Technical considerations were also discussed.

Keywords: Laparoscopy; distal pancreatectomy; splenectomy; liver wedge resection; pancreatic neuroendocrine tumor

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Introduction

Laparoscopic distal pancreatectomy (LDP) was first described by Cuschieri *et al*. (1) for benign diseases in 1996; in the same year, Gagner *et al*. (2) reported their early experience with eight LDP performed in patients with islet cell tumors. Nowadays, LDP is the procedure of choice for small lesions of the pancreatic body-tail of various nature.

In the literature there are many papers that demonstrate the advantages of LDP versus open distal pancreatectomy (ODP) in terms of severe complication reduction according to Clavien-Dindo classification (3), reduction of blood loss and shorter length of hospital stay (4-8). There are no differences between the two techniques in terms of postoperative pancreatic fistula (POPF) development.

Published data on oncologic radicality are limited as the mininvasive technique is mainly reserved to benign or borderline disorders, leading to relevant biases on the results.

Randomized controlled trials are needed to validate the effective advantages of LDP over ODP (9-11).

Patient selection and work-up

A 65-year-old woman, with no previous medical history, underwent a CT scan for living organ donation evaluation that showed a 3 cm hypervascular lesion in the pancreatic tail and a 3 cm slightly hypervascular nodule in segment 2 of the liver. Magnetic resonance imaging (MRI) with extracellular contrast confirmed the presence of both pancreatic and hepatic lesions (*Figures 1,2*). The pancreatic lesion was hypointense on both T1w and T2w phases, slightly hyperintense on T2w phase, high signal in DWI sequence, hyperintense on postcontrast arterial phase and isointense on venous phase. The hepatic lesion appeared isointense on precontrast T1w phase, very slightly hyperintense on T2w fs phase, hyperintense on postcontrast

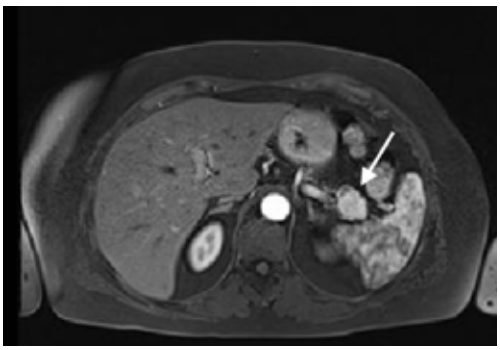

Figure 1 Magnetic resonance imaging (MRI) on postcontrast arterial phase shows a 3 cm hyperintense lesion in the pancreatic tail (arrow).

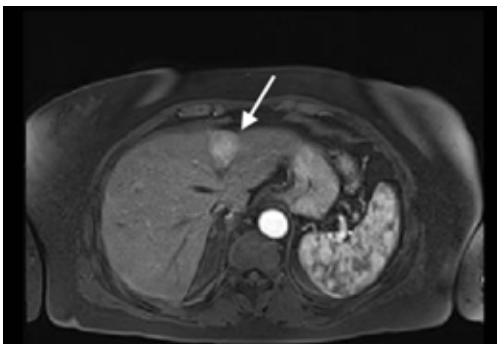

Figure 2 Magnetic resonance imaging (MRI) on postcontrast arterial phase shows a 3 cm hyperintense liver lesion in segment 2 (arrow).

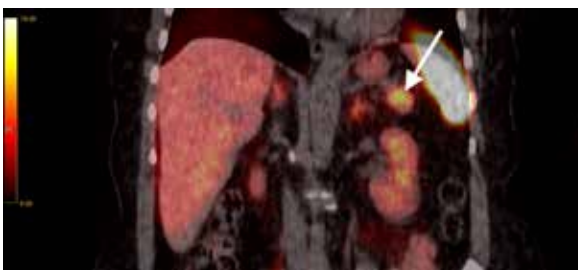

Figure 3 ^{68}Ga-DOTATOC-PET revealing the uptake of the radiotracer in a 30 mm area of pancreatic tail (arrow).

T1 phase and it showed slightly restricted diffusion. Scans were suggestive of neuroendocrine tumor of the pancreas with undetermined liver nodule. ^{68}Ga-DOTATOC-PET revealed high uptake of the radiotracer in a 30 mm area of the pancreatic tail (*Figure 3*). Laparoscopic exploration and

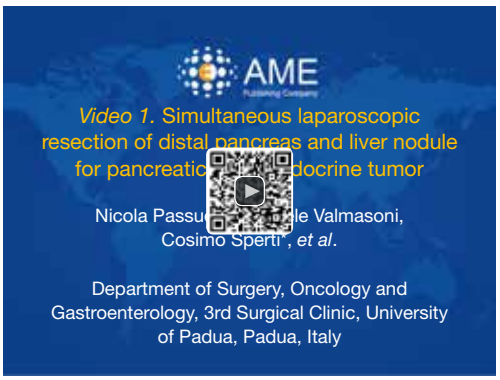

Figure 4 Simultaneous laparoscopic resection of distal pancreas and liver nodule for pancreatic neuroendocrine tumor (12). Available online: http://www.asvide.com/articles/1262

resection of both pancreatic and liver lesions was planned.

Pre-operative preparation

The patient fasted for 12 hours before surgery. The operation was performed under general anesthesia with endotracheal intubation. A 16 F gastric decompression tube and urinary catheter were placed. Prophylactic third generation cephalosporine was administered intravenously on induction.

Equipment preference card

High definition laparoscopic video system, pneumoperitoneum system, ultrasonic dissector, laparoscopic instruments including atraumatic graspers, scissors, clipping devices, surgical stapler and plastic specimen bag were prepared.

Procedure (*Figure 4*)

The patient was placed in a supine position with abducted spreaded legs. The chief surgeon stood between the legs. The first assistant and camera operator stood on the right side of the patient, the second assistant stood on the left side of the patient as well as the laparoscopy screen. A 10-mm trocar was placed in periumbilical region and pneumoperitoneum was created with open technique. The intra-abdominal pressure was maintained at 12 mmHg. The other trocars were placed at right-upper and left-upper quadrants (15 mm) and in epigastric region (5 mm).

Laparoscopic exploration was performed and the gastrocolic ligament was opened with ultrasonic dissector. An intraoperative ultrasound confirmed the body-tail lesion and the hepatic 3 cm nodule in segment 2 of uncertain nature. The peritoneum under the inferior margin of the pancreas was dissected and pancreas was mobilized, splenic vein was discovered and section was performed after clips positioning (Weck® Hem-o-lok® Teleflex Incorporated, Morrisville, NC, USA). The splenic artery was identified at the superior edge of the pancreas and sectioned after clips positioning. Furthermore the pancreas was sectioned with a laparoscopic stapler (EndoGIA Covidien Inc., Mansfield, MA, USA) and mobilized from the body to the tail. Splenic isolation completed the distal pancreatectomy. The surgical specimen was immediately put into a plastic specimen bag and retrieved through a small Pfannenstiel incision. Haemostasis of the surgical field was secured.

The hepatic lesion in S2 was entirely resected with safe margins with ultrasonic dissector with a satisfying haemostasis. Prophylactic cholecystectomy was performed.

Three drainages were placed: one in the subhepatic region, one in the splenic region and one close to the pancreatic stump.

Role of team member

- Dr. Nicola Passuello: Trainee;
- Dr. Michele Valmasoni: Surgeon;
- Dr. Gioia Pozza: Trainee;
- Dr. Elisa Sefora Pierobon: Surgeon;
- Dr. Alberto Ponzoni: Radiologist;
- Dr. Cosimo Sperti: Surgeon.

Post-operative management

Short course 3rd generation cephalosporin was administered. Gastric tube was removed on POD 2 and the patient started eating on the same day. Drain amylase levels were checked on POD 1, 3 and 5 and were always negative. Both the subhepatic and splenic drains were removed on POD 4 while the remaining was removed on POD 6. The patient was discharged on the same day.

Histopathological examination of the pancreatic specimen showed a neuroendocrine G2 tumor with no lymph node metastasis. Immunohistochemistry examination showed MIB1 3%, chromogranin A, beta-catenin and synaptophysin positivity. The hepatic nodule analysis demonstrated focal nodular hyperplasia.

Tips, tricks and pitfalls

Gastrocolic ligament opening must to be large in order to have space to insert the ultrasonic probe. Attention must be paid to right and left gastroepiploic arteries preservation, section of the short gastric vessels need to be carried out in order to mobilize the spleen from the stomach.

Ultrasound examination must be accurate in order to define the characteristics of the tumor, the relationship of the lesion with the Wirsung duct and, above all, with the splenic and mesenteric vessels.

The most challenging part of the procedure is the splenic vessels isolation: splenic vein must be isolated with caution at the inferior edge of the pancreas, and a sufficiently long portion of vein need to be dissected in order to clip the vessel in two points reducing the risks of bleeding. Furthermore, it is important to identify and section all the small single venous branches that come off the pancreas into the splenic vein.

An appropriate drainage positioning is eventually needed: in fact, a correct drainage of the pancreatic stump is a useful way of access for a radiological treatment in case of POPF development.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Staple-free robotic distal pancreatectomy and splenectomy

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Contributions: (I) Conception and design: D Galvez, J He; (II) Administrative support: J He; (III) Provision of study materials or patients: J He; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Minimally invasive surgery has slowly gained popularity in the field of hepatopancreatobiliary surgery in the last few years. This is likely due to shorter length of stay, less estimated blood loss and postoperative pain, quicker recovery, and better cosmetic results. The laparoscopic distal pancreatectomy is associated with less overall morbidity and considered as the standard of care for selected patients. Robotic distal pancreatectomy (RDP) not only maintains the benefits of the laparoscopic approach, but also adds potential benefits. In this article, we describe the operative technique of an entirely staple-free RDP with splenectomy. The method is presented in a stepwise approach along with a concise video. The patient presented is a 58-year-old male with a well-differentiated neuroendocrine tumor involving the body of the pancreas; no major blood vessel involvement.

Keywords: Robotic surgery; distal pancreatectomy; splenectomy

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Introduction

Minimally invasive surgery has slowly gained popularity in the field of hepatopancreatobiliary surgery in the last few years. This is likely due to shorter length of stay, less estimated blood loss and postoperative pain, quicker recovery, and better cosmetic results (1-7). Laparoscopic distal pancreatectomy has become the standard of care for selected patients due to the absence of anastomosis and lower morbidity comparing to open surgery (4,8-10). The technical challenges of laparoscopic distal pancreatectomy are mainly due to the retroperitoneal location of the pancreas and its proximity to major vascular structures, and the high incidence of postoperative pancreatic fistula (3,5,11-13). Robotic technology adds several advantages to the traditional laparoscopic approach, such as a three-dimensional operative view with an enhanced hand-eye coordination, reduction of natural tremors, introduction of EndoWrist® technology, and a more comfortable and ergonomic position for the surgeon to operate (4,14). Here, we describe the operative technique of an entirely robotic distal pancreatectomy (RDP) with splenectomy. The method is presented in a stepwise approach along with a concise video.

Patient selection and workup

The distal pancreatectomy procedure is indicated for patients with lesions in the pancreatic body and tail. Several factors have to be taken in to account when a minimally invasive approach is considered. These include the patient's body mass index (BMI), history of previous intra-abdominal procedures, cardio-pulmonary comorbidities and tolerance to general anesthesia. Disease specific factors include: histology (malignant *vs.* benign), size (bulky *vs.* small), and involvement of major vessels such as the celiac artery, common hepatic artery, superior mesenteric artery (SMA), and/or portal vein (PV). Involvement of the splenic vessels is not a contraindication in general.

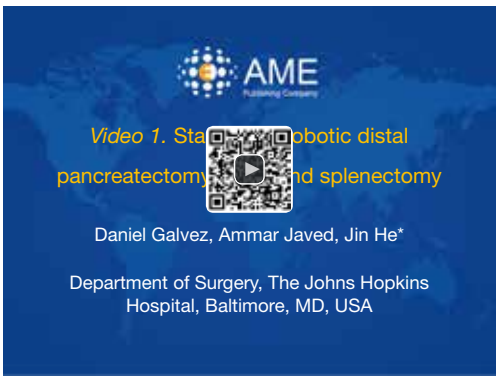

Figure 1 Staple-free robotic distal pancreatectomy (RDP) and splenectomy (15).
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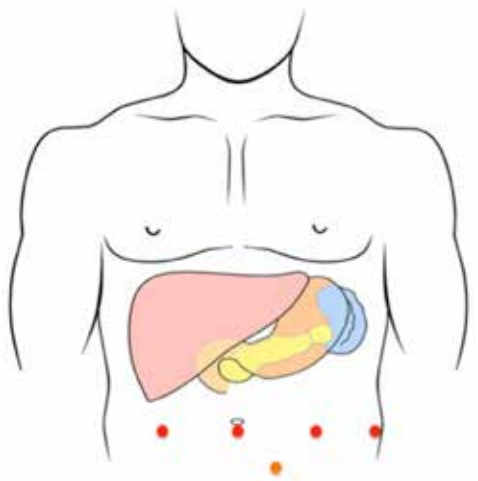

Figure 2 Trocar placement.

Preoperative workup should include a three-phase pancreatic protocol CT scan or MRI. EUS guided fine needle biopsy is often indicated to determine the histology if neoadjuvant therapy is considered as part of the treatment plan.

Preoperative preparation

Routine preoperative evaluation is required, which includes routine lab work evaluating liver and kidney function, coagulation, etc. A mechanical bowel preparation is helpful especially when the patient has a history of chronic constipation.

Equipment preference card

The robotic platform we currently use is the DaVinci Xi (Intuitive Surgical, Sunnyvale, CA, USA). The following instruments are on the tray: EndoWrist Monopolar Hook Cautery, Scissors, Maryland Bipolar Forceps, Fenestrated Bipolar Forceps, Vessel Sealer, Medium-Large Clip Applier, Large Needle Driver and Large SutureCut™ Needle Driver, Tip-Up Fenestrated Grasper ×2.

Clinical summary

A 54-year-old male presented with an incidental pancreatic mass on CT scan. Further workup revealed an 8 cm × 6 cm well-differentiated neuroendocrine tumor involving the body of the pancreas. The tumor partially encased the splenic artery and vein but both vessels remained patent. The mass also abutted the PV and superior mesenteric vein (SMV) confluence. No evidence of distant metastasis.

Procedure (*Figure 1*)

After induction of general anesthesia, the patient is placed in a split leg position. The skin is prepared and draped in a sterile fashion. An 8 mm infra-umbilical vertical incision is made and a pneumoperitoneum is established using a Veress needle. An 8 mm robotic trocar is placed and the robotic camera is introduced for exploration. Signs of carcinomatosis and/or liver metastasis are examined if intraabdominal adhesion is minimal. If nothing prohibitive is evidenced, we then place three additional 8 mm ports: one in the right upper quadrant and two in the left upper quadrant. All trocars are placed under direct visual guidance. A 5 mm bladeless trocar might be needed for the assistance. This is placed in the left lower quadrant (*Figure 2*).

All robotic trocars (red dots) are placed in a line. The robotic camera is placed in the infra-umbilical trocar. The assisting trocar (orange dot) is placed in the left lower quadrant.

After docking the DaVinci Xi system from the patient's left side, the assistant is sitting between the legs to help with instrument exchange. We use the robotic vessel sealer to divide the ligamentum teres. This is helpful for instrument exchange, especially for obese patients. We then divide the greater omentum from the great curvature of the stomach. This is carried out from the pylorus up to

the gastroesophageal junction. The arcade of gastroepiploic vessels is preserved. All short gastric vessels are divided with the vessel sealer if splenectomy is also performed. The stomach is retracted cephalad allowing entry to the lesser sac. This retraction can be facilitated by an 0 nylon suture around the body of the stomach. This nylon suture is brought out below the xiphoid using a Carter-Thompson needle. This will help suspend the left liver and stomach against the abdominal wall. A robotic hook cautery is used to dissect along the common hepatic artery and splenic artery; we then trace them back to the celiac axis and confirm the origin of the splenic artery. Lymphatic tissue along the artery can be dissected out as a separate specimen. The splenic artery is encircled with a vessel loop and divided with scissors after placing Hem-Lock clips. Then, careful dissection along the superior edge of the pancreas allows exposure of the gastroduodenal artery (GDA) and its confluence to the common hepatic artery. With the artery retracted up, the PV above the pancreas can be identified. We then dissect along the inferior edge of the pancreas to expose the SMV underneath the neck of the pancreas. A retropancreatic tunnel is carefully created bluntly between the neck of the pancreas and the PV. An umbilical tape is often used to wrap around the pancreatic neck and to lift the gland while we use the vessel sealer to divide the neck of the pancreas. Dissection is then carried out along the inferior edge of the pancreas laterally. The splenic flexure of the colon is carefully dissected off the inferior pole of the spleen. Then, with the divided end of the pancreas retracted to the left side, the dissection of the splenic vein is carried out. The splenic vein is encircled with a vessel loop and divided with scissors after placing Hem-Lock clips. We often use a 2–0 silk tie to ligate the splenic vein before we place the Hem-Lock clip. This is helpful when the tumor is bulky and the space is limited for clip placement. The tumor and pancreas are then fully mobilized from the retroperitoneum using the vessel sealer, from medial to lateral direction. The spleen is completely freed from the retroperitoneum. The specimen is placed in a large Endo-Catch bag. After confirming hemostasis, the stump of the pancreas can be closed with a 4–0 V-Lock suture in a running fashion. If a pancreatic duct can be identified, it should be suture closed with a 5–0 PDS suture. A Jackson-Pratt drain is placed near the site of pancreatic stump. Then we undock the DaVinci system from the trocars. The Endo-Catch bag with the specimen is then retrieved through a 7 cm long Pfannenstiel incision.

Postoperative management

On postoperative day (POD) 1 the nasogastric tube (NGT) was removed and diet advanced to a limited clear liquid diet (less than 60 cc/h). On POD 2 unlimited clear liquid diet was allowed. On POD 3 he was advance to a full liquid diet and the Foley catheter was removed. On POD 4 he was given a regular diet. On POD 6 his JP drain was removed and the patient was discharged home.

Tips, tricks and pitfalls

- All robotic trocars are placed in a line. This is necessary for the Xi system;
- Docking the DaVinci Xi system from the patient's left side. The assistant sits between the patient's legs to help with instrument exchange;
- The stomach is retracted cephalad by a 0 nylon suture around the body of the stomach. This nylon suture is brought out below the xiphoid using a Carter-Thompson needle. This will help suspend the left liver and stomach against the abdominal wall;
- The splenic artery has to be traced back to the celiac axis to confirm that the hepatic artery is not mistaken;
- An umbilical tape is often used to wrap around the pancreatic neck and to lift the gland while we use the vessel sealer to divide the neck of the pancreas;
- 2–0 silk tie is often used to ligate the splenic vein before we place the Hem-Lock clip. This is helpful when the tumor is bulky and the space is limited for clip placement;
- The stump of the pancreas can be closed with a 4-0 V-Lock suture in a running fashion. If a pancreatic duct can be identified, it should be suture closed with a 5-0 PDS;
- Skin needs to be prepared and draped wide enough for the Pfannenstiel incision.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Robotic transgastric cystgastrostomy and pancreatic debridement in the management of pancreatic fluid collections following acute pancreatitis

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Abstract: Pancreatic and peripancreatic fluid collections may develop after severe acute pancreatitis. Organized fluid collections such as pancreatic pseudocyst and walled-off pancreatic necrosis (WOPN) that mature over time may require intervention to treat obstructive or constitutional symptoms related to the size and location of the collection as well as possible infection. Endoscopic, open surgical and minimally invasive techniques are described to treat post-inflammatory pancreatic fluid collections. Surgical intervention may be required to treat collections containing necrotic pancreatic parenchyma or in locations not immediately apposed to the stomach or duodenum. Comprising a blend of the surgical approach and the clinical benefits of minimally invasive surgery, the robot-assisted technique of pancreatic cystgastrostomy with pancreatic debridement is described.

Keywords: Pancreatitis; pseudocyst; walled-off pancreatic necrosis (WOPN); cystgastrostomy; robotic surgery

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Introduction

Acute pancreatitis results in approximately 250,000 hospitalizations yearly in the United States (1). This diagnosis is confirmed by a history of abdominal pain, elevated pancreatic enzymes, and characteristic findings on cross-sectional imaging (1,2). Approximately 5–15% of these cases develop pancreatic necrosis, which is characterized by hypoperfusion of a portion of the pancreatic parenchyma typically associated with necrosis of peripancreatic tissue (1-4). Pancreatic necrosis may not be evident on the first imaging study and can evolve over several days (4,5). Acute peripancreatic fluid collections may be visualized on imaging at the onset of pancreatitis; however, pancreatic pseudocyst or walled-off pancreatic necrosis (WOPN) both represent delayed, matured fluid collections that typically manifest at least 4 weeks after onset of symptoms. These separate entities develop by different mechanisms and are radiographically distinguishable. A pseudocyst develops from a disruption of the main pancreatic duct or an intraparenchymal ductal branch and contains amylase-rich simple fluid; characteristics include a well-defined, non-epithelialized wall and negligible to minimal solid material within the fluid collection (2). WOPN, conversely, develops from areas of pancreatic necrosis which may have been detected initially by imaging as acute necrotic collections characterized by hypoperfusion of pancreatic parenchyma (2). WOPN contains necrotic pancreatic tissue and potentially necrotic peripancreatic tissue along with a variable amount of fluid. WOPN is differentiated from an acute necrotic collection both by time from symptom onset (>4 weeks) as well as an enhancing, matured capsule of reactive tissue.

Pancreatic pseudocysts

Intervention is typically indicated for pseudocysts that fail to resolve after 6 weeks, are larger than 6 cm, and produce compressive symptoms due to their size and location; examples include gastric outlet obstruction and biliary obstruction (6,7). Pseudocysts may be treated endoscopically or surgically depending upon location (5,6). For those pseudocysts in the retrogastric or periduodenal locations, endoscopic puncture and stenting can allow for resolution via dependent internal drainage. Large series comparing surgical and endoscopic management of symptomatic pseudocysts show high rates of overall success in drainage. Endoscopically treated pseudocysts may require additional procedures to achieve complete resolution, while surgically treated pseudocysts typically require repeat procedures only for distant recurrence or bleeding due to larger anastomoses (8).

WOPN

WOPN can occur in locations similar to those of pseudocysts; however, WOPN requires intervention more often for systemic symptoms or failure to thrive, recurrent fevers, or infection. Due to the inclusion of solid, necrotic material, WOPN is unlikely to completely resolve with passive drainage and requires debridement (5,8). Endoscopic instrumentation has improved to allow some debridement of the encapsulated necrosum with primary success rates of 50–80% (8-10); however, surgical debridement allows access to WOPN not directly opposed to the stomach or duodenum, with paracolic gutter extent, or with large amounts of necrotic tissue. Primary success rates for drainage of pseudocysts and WOPN in surgical series ranges from 85–100% (5,8,9). Additionally, surgical debridement of WOPN resulting from biliary pancreatitis allows for concomitant cholecystectomy. We follow an algorithmic treatment pathway for the surgical management of necrotizing pancreatitis that was developed according to our institutional experience and analysis of clinical outcomes (*Figure 1*).

Technique for robotic cystgastrostomy

Multiple methods for accessing pseudocysts and WOPN exist and are employed based on the location of the collection. Open, laparoscopic, and robot-assisted laparoscopic (RAL) techniques can be used; access to the necrosum can be attained via the lesser sac, through a transduodenal, endogastric, or transgastric approach or via the infracolic approach (6,7). Internal drainage procedures such as cystgastrostomy, cystduodenostomy, or cystjejunostomy with debridement are often sought to decrease the incidence of pancreaticocutaneous fistulae, as an internal enteric fistula is created to avoid transabdominal drainage (6,11).

Initial descriptions of laparoscopic transgastric cystgastrostomy were elaborated as treatment for pseudocysts (12,13); this was subsequently extended to the treatment of WOPN with inclusion of pancreatic debridement (14,15). Depending on the type of trocar used for laparoscopic transgastric pancreatic cystgastrostomy, dislodgement of trocars is feared in descriptions of the procedure. As a combination of the principles of open transgastric cystgastrostomy and the benefits of minimally invasive surgery, RAL cystgastrostomy accesses the gastric lumen via an anterior gastrotomy created with monopolar electrocautery. The superior flap of the gastrotomy can be suspended with the fourth robotic arm or sutured to the posterior surface of the anterior abdominal wall to allow freedom of all robotic arms and instruments.

The WOPN cavity has been entered classically by puncturing the point of maximum indentation into the stomach. Intraoperative ultrasound is used prior to performing a posterior gastrotomy (*Figure 2* at min 2:06) to evaluate the location and extent of the necrosum relative to surrounding anatomy. After making an initial puncture into the fluid collection (*Figure 2* at min 2:20), the posterior gastrotomy is extended to 5–6 cm in length with electrocautery linked to the robotic shears or the vessel sealer device. The interior of the WOPN cavity is then visualized. Necrotic pancreatic tissue is bluntly debrided using fenestrated graspers and irrigation (*Figure 2* at min 2:40). Meticulous debridement of tiny pockets of necrotic tissue is not required due to the continued autodigestion of residual necrotic tissue by gastric acids facilitated by the cystgastrostomy.

Once the necrotic tissue is debrided, it is removed via a laparoscopic retrieval sac at the end of the case. Alternate reports of laparoscopic debridement describe pushing the necrotic tissue toward the pylorus for natural digestion (15). The cystgastrostomy is then sutured robotically in running fashion using absorbable barbed suture (3–0 polydioxanone V-Loc™ suture; Medtronic, Minneapolis, MN, USA) taking full-thickness bites of the cyst and gastric walls (*Figure 2* at min 3:22). A stapling

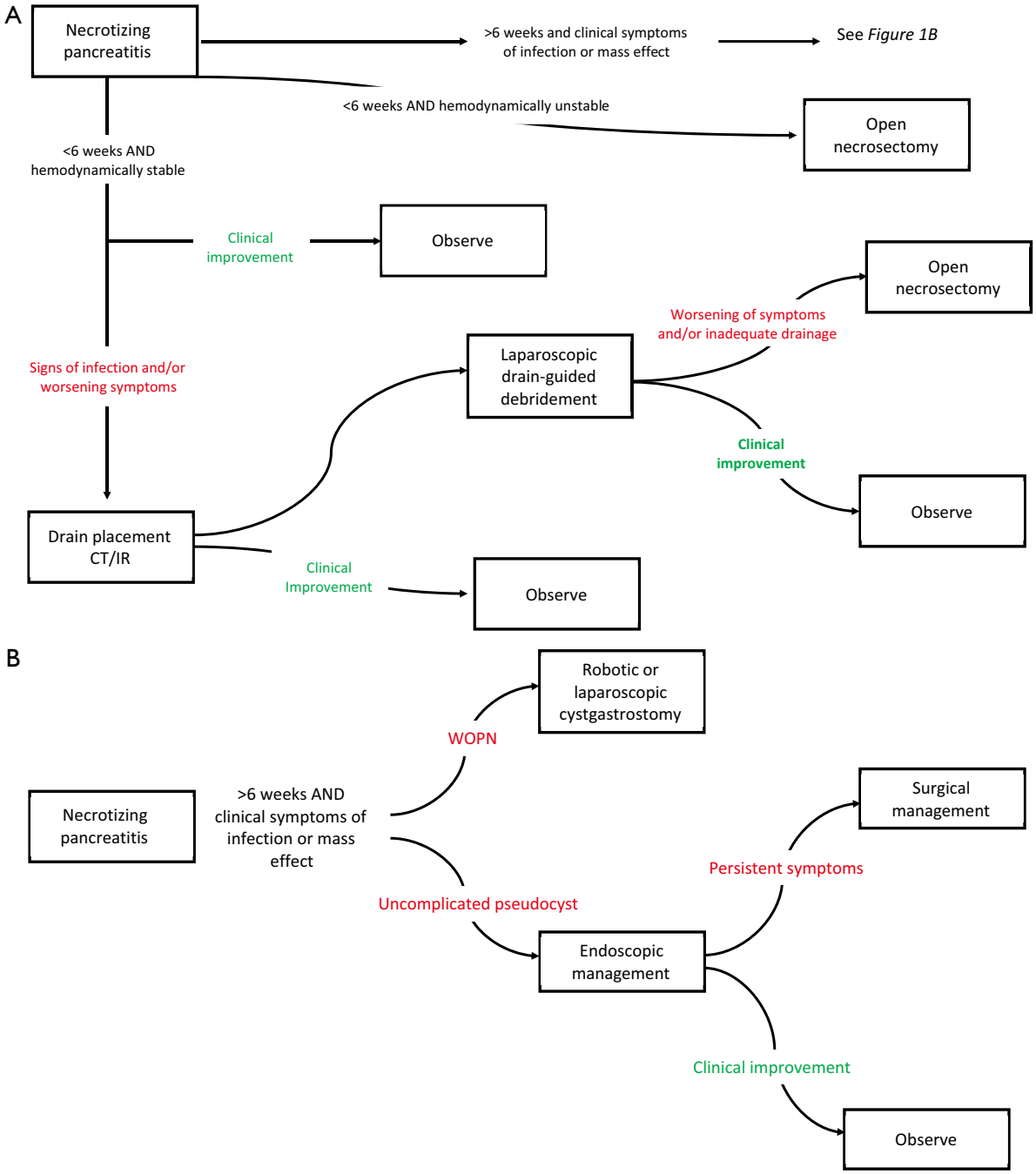

Figure 1 Treatment algorithm for the management of severe acute pancreatitis and its sequelae. (A) Treatment pathway for the management of necrotizing pancreatitis within 6 weeks of symptom onset; (B) treatment pathway for the management of necrotizing pancreatitis following 6 weeks of persistent symptoms. WOPN, walled-off pancreatic necrosis; CT, computed tomography; IR, interventional radiology.

device is not used routinely in the robotic procedure as described in laparoscopic cystgastrostomy (14). The matured cystgastrostomy prevents separation of the posterior wall of the stomach from the WOPN cavity and is performed to decrease the incidence of anastomotic bleeding from the gastric wall and cyst wall. Prior to closing the anterior gastrotomy, a nasogastric tube is directed into the WOPN cavity for use in postoperative

Figure 2 Robotic pancreatic cystgastrostomy with pancreatic debridement. A visualization of the robot-assisted technique of pancreatic cystgastrostomy with pancreatic debridement is provided (16).
Available online: http://www.asvide.com/articles/1050

irrigation of the cavity. Transabdominal drains are not routinely employed postoperatively.

To close the anterior gastrotomy, multiple techniques have been described using permanent or absorbable suture and performing the closure in running or interrupted fashion as well as in one or two layers (12-15). We close the anterior gastrotomy in a single layer using 4–0 V-Loc™ suture (Medtronic) in a single layer taking full-thickness bites of the gastric wall (*Figure 2* at min 4:02). Two sutures are routinely employed for closure, each starting at an apex and meeting at the midpoint of the gastrotomy, where a locking plastic clip is placed on the tails of the suture. The barbed suture is secured in place with the plastic clip and does not require a knot to be tied. We routinely reinforce the gastrotomy closure with an aerosolized fibrin sealant (TISSEEL™; Baxter Healthcare, Deerfield, Illinois, USA). At this time, other indicated procedures may be performed, such as cholecystectomy if the initial pancreatitis resulting in WOPN was biliary in origin. In the absence of other procedures or following their completion, the procedure is terminated. The abdomen is desufflated and robotic ports are removed.

Postoperative management

With the exception of nasogastric tube care, standardized enhanced recovery after surgery (ERAS) pathways are employed in the care of every patient undergoing robotic cystgastrostomy and pancreatic debridement. Specifically, deviation from ERAS pathways occurs in the use of the nasogastric tube to irrigate the retrogastric cavity with normal saline every 6 hours. The nasogastric tube is typically removed on the morning of the second postoperative day. An oral contrast swallow study is not performed to evaluate for anastomotic leak. Similarly, routine postoperative laboratory assessments are obtained on the first postoperative day but do not continue in the absence of clinical or postoperative laboratory evidence indicating repeated evaluations. Once the nasogastric tube is removed, the patients are given a noncarbonated clear liquid diet and advanced as tolerated to a regular diet. Typically, patients are discharged on postoperative day 3–5 depending on tolerance of diet and pain control. Patients are seen in clinic approximately 2 weeks after surgery and then 1 month after surgery, at which time an abdominal computed tomography (CT) scan with intravenous contrast is obtained to evaluate for resolution of the WOPN or pseudocyst.

Tips, tricks, and pitfalls

During creation of the cystgastrostomy, we demonstrate the use of the robotic shears with linked electrocautery. Using an energy device for this portion of the procedure has been described (13,15). Alternatively, though not performed during our robotic cystgastrostomy procedures, multiple firings of an endoscopic or robotic stapler could be used to create the anastomosis as in laparoscopic cystgastrostomy (8,14).

During debridement of the WOPN cavity and mobilization of the necrotic tissue, no haptic feedback exists as with laparoscopic debridement. Converting from laparoscopic to robotic debridement progressively develops a surgeon's visual perception of tissue strain. Only after gaining sufficient robotic experience is a surgeon able to perceive how aggressively to pull and handle the tissue. We argue that the autodigestion afforded by anastomosis to the stomach allows surgeons to leave small traces of necrotic tissue in the cavity in order to prevent tearing of the cavity wall during debridement during initial experience with robotic cystgastrostomy.

Closure of the cystgastrostomy is achieved with one V-Loc™ suture initiating at each apex of the cystgastrostomy. In the video, a locking plastic clip is placed at the midpoint of the cystgastrostomy to anchor the ends of the suture. Alternatively, to avoid opening a clip applier, these barbed sutures can be continued in their respective directions beyond the midpoint to create a double-reinforced central portion of

the gastrostomy closure. In this case, no clip or knot would be required.

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Footnote

Conflicts of Interest: Dr. Martinie serves as a consultant and proctor for Intuitive Surgical. Dr. Iannitti serves as a consultant and proctor for Medtronic. All other authors have no conflicts of interest to declare.

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Robotic pancreaticoduodenectomy

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Abstract: Pancreaticoduodenectomy (PD) is considered one of the most complex and technically challenging abdominal surgeries performed by general surgeons. With increasing use of minimally invasive surgery, this operation continues to be performed most commonly in an open fashion. Open PD (OPD) is characterized by high morbidity and mortality rates in published series. Since the early 2000s, use of robotics for PD has slowly evolved. For appropriately selected patients, robotic PD (RPD) has been shown to have less intraoperative blood loss, decreased morbidity and mortality, shorter hospital length of stay, and similar oncological outcomes compared with OPD. At our high-volume center, we have found lower complication rates for RPD along with no difference in total cost when compared with OPD. With demonstrated non-inferior oncologic outcomes for RPD, the potential exists that RPD may be the future standard in surgical management for pancreatic disease. We present a case of a patient with a pancreatic head mass and describe our institution's surgical technique for RPD.

Keywords: Pancreas; pancreaticoduodenectomy (PD); robotic surgery

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Introduction

Pancreaticoduodenectomy (PD) continues to be one of the most complex and challenging abdominal surgeries. The vast majority of PD are still performed as an open operation in the United States (1). Unfortunately, PD has been found to have a perioperative morbidity of 40% and mortality of 5% (2-4).

In 1994, Gagner and Pomp performed the first laparoscopic PD; since that time, the use of minimally invasive surgery for PD has continued to evolve (5,6). Giulianotti *et al*. (7) published the first robotic pancreatic resection in Europe in 2003; in the same year, Melvin *et al*. (8) described the first series of robotic pancreatic resection for neuroendocrine tumor in the United States. Since that time, studies have demonstrated that robotic PD (RPD) can be performed safely with low conversion rates, decreased morbidity and mortality, and a shorter hospital length of stay compared with open PD (OPD) (9-11). Other studies have also demonstrated that RPD has non-inferior oncologic outcomes compared to OPD (12-14). It should be mentioned that none of these papers represented randomized controlled studies but rather very selected individual institution case series. A recent systematic review found an open conversion rate of less than 10% for RPD and morbidity and mortality lower than those found in previous reports for OPD (15).

A review of the experience with RPD at our own institution revealed that, in selected patients, RPD resulted in less blood loss, a shorter intensive care unit (ICU) length of stay, a lower 30-day complication rate, and no difference in total cost compared with OPD even after implementation of an enhanced recovery after surgery (ERAS) pathway (16,17). Perhaps most importantly, we found that, with increasing experience, the pancreatic fistula rate could be reduced to below that of most open series, and certainly lower than most of the series for laparoscopic PD.

Patient selection and workup

A 56-year-old man presented with abdominal pain, jaundice, and acute pancreatitis. Computerized tomography (CT) and magnetic resonance imaging (MRI) identified pancreatitis with pancreatic duct and biliary ductal strictures. No obvious mass was detected; rather, a subtle area of hyperenhancement was detected in the head of the pancreas. The patient underwent endoscopic retrograde cholangiopancreatography (ERCP), which identified common bile duct (CBD) and pancreatic duct strictures, and a biliary endostent was placed. Endoscopic ultrasound (EUS) was subsequently performed and identified a pancreatic head mass. The patient's case was presented at multidisciplinary conference, and consensus among physicians was to proceed with PD. Given no vessel involvement, dilated pancreatic duct, and ideal body habitus, our recommendation was to perform RPD.

Equipment preference card

All robotic cases are performed using the da Vinci Si® robot (Intuitive Surgical, Sunnyvale, CA, USA). Robotic instruments used for RPD include monopolar curved scissors, fenestrated bipolar forceps, a vessel sealer device, and prograsp forceps. The large needle driver is commonly used for suturing as well as dissecting around blood vessels such as the gastroduodenal artery. A Hem-o-lok® Ligation System (Teleflex, Morrisville, NC, USA) is used to control vasculature. Robotic or laparoscopic staplers are used for transection of bowel. Monocryl® and V-Loc™ sutures (Medtronic, Minneapolis, MN, USA) are used for all anastomoses. A LapSac® Surgical Tissue Pouch (Cook Medical, Bloomington, IN, USA) is used for extraction of the specimen.

Procedure

The patient is placed under general anesthesia, and an arterial line and two peripheral intravenous lines are placed. We no longer routinely place central lines. A nasogastric tube and urinary catheter are placed along with sequential compression devices on the patient's lower extremities. The right arm is tucked and the left arm is extended out on an arm board for anesthesia access. The patient is positioned supine with his legs together (not in French position) and the bed is turned 90 degrees so that the left arm is extended towards the anesthesiology team. Only slight reverse Trendelenburg position is utilized.

Pneumoperitoneum is obtained with a Veress needle at the umbilicus and subsequently upsized to an initial 12-mm port. Three additional robotic 8-mm cannulas (right mid-axillary line, left midclavicular line, and left mid-axillary line) and one additional 12-mm camera port is placed in the right mid-clavicular line under direct vision. The umbilical trocar site typically serves as the assistant port during most of the resection portion of the procedure. Most cases require a total of five ports. 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 per routine institutional practice. The gallbladder is commonly sutured to the anterior abdominal wall to expose the porta hepatis without the need for a Nathanson retractor, which is used in patients with previous cholecystectomy. The inferior border of the distal gastric antrum and proximal duodenum is mobilized with care. The right gastric and right gastroepiploic vessels are dissected, sealed, and divided using the robotic bipolar vessel sealer device. The proximal duodenum is divided distal to the pylorus using a robotic or laparoscopic stapler device, and the stomach is placed into the left upper quadrant for subsequent reconstruction. The hepatic flexure of the colon is taken down to expose the duodenum, again using the robotic vessel sealer device, and the larger the colon/omentum, the more mobilization is performed. A Kocher maneuver is performed and an attempt is made to mobilize as much of the third and fourth portions of the duodenum from the right side as possible. In a patient with relatively little intra-abdominal fat, the duodenum and ligament of Treitz often can be completely mobilized from the right side. In other patients, the ligament of Treitz must be identified from below the transverse colon or by creating a window in the transverse colon mesentery. The small bowel is transected approximately 20 cm distal to the ligament of Treitz. The small bowel mesentery is divided using the robotic vessel sealer device, staying close to the jejunum towards the root of the small bowel mesentery; the jejunum is then passed through the mesenteric tunnel. It is critical for the surgeon to be capable of performing this difficult maneuver with all three techniques.

Attention is then turned to the portal dissection, where intraoperative ultrasound is always performed to identify and confirm the vascular anatomy and the proximity of the tumor to these structures. Typically, the monopolar scissors are used for this portion of the dissection, which begins with the common hepatic artery lymph node, the medial portal

lymph node package, and other nodes extending to the celiac axis. These nodes are all removed and pathologically examined as separate specimens. The gastroduodenal artery is then identified and dissected carefully, ligated with 3–0 silk ties, clipped with Hem-o-lok clips, and divided. A short stump of the gastroduodenal artery should be left on the hepatic artery to prevent the tie or clip from falling off. The inferior border and the neck of the pancreas are dissected out and mobilized, usually by identifying the superior mesenteric vein (SMV) by ultrasound or by following the middle colic vein cephalad. A tunnel is created underneath the neck of the pancreas, on top of the superior mesenteric and portal vein, to the superior aspect of the pancreas. An umbilical tape is passed underneath the pancreas for traction. Finally, the neck of the pancreas is transected using the monopolar scissors coupled with saline irrigation to minimize charring of the tissue, a technique that has been previously described (18). Once within the central portion of the gland, cutting current is also utilized to minimize thermal coagulation of the pancreatic duct.

The uncinate process is mobilized away from the SMV and the superior mesenteric artery (SMA). This must be performed with infinite precision and caution, and with complete understanding of where the SMA and branches are located. To begin, venous branches entering the uncinate coming off of a first jejunal branch of the SMV must be ligated with silk ties, rather than by energy (vessel sealer) or clips to prevent dislodgement later in the reconstruction. Ultrasound is again utilized at this point to visualize the SMA. The robotic vessel sealer is then used to take the uncinate process as close to the SMA as safely possible, but any dominant arterial branch encountered in this portion of the dissection, such as the inferior pancreaticoduodenal artery, is clipped or suture ligated. As the dissection emerges from the superior aspect of the uncinate process, posterior duodenal and portal lymph nodes typically are mobilized and included with the specimen. If not done previously, the proximal gallbladder/cystic duct dissection is performed, and these structures are clipped and divided. The gallbladder remains suspended to the anterior abdominal wall using the previously placed suture for retraction and is removed after the hepaticojejunostomy reconstruction. The common hepatic duct is transected using the monopolar scissors, although occasionally it is either clipped and divided or stapled. The entire specimen is placed into a specimen retrieval bag, removed from the abdominal cavity from the slightly enlarged umbilical trocar site, and sent to pathology for any frozen section margin analysis that may be indicated. For low-grade pathology where margin status is not of concern, the specimen is removed following reconstruction. The specimen retrieval site is partially closed using interrupted sutures around the 12-mm trocar, and the camera is moved to this location for the reconstruction phase of the procedure.

For reconstruction, the stapled end of the jejunum is brought alongside the transected surface of the pancreas, typically through a window made in the right side of 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, and a duct-to-mucosal anastomosis is created using interrupted 6–0 monofilament sutures, typically over a 7- or 5-French pancreatic duct stent. 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 5–0 monofilament suture in a running or interrupted fashion depending on the size of the duct. Small, non-dilated ducts must be anastomosed with absolute precision using interrupted monofilament sutures. Finally, an antecolic duodenojejunostomy is performed approximately 50 cm from the biliary anastomosis using absorbable monofilament suture in a running fashion. Occasionally, when the transverse colon and omentum prohibit such a reconstruction due to their bulk, a loop of jejunum is brought up through a mesenteric window made to the left of the middle colic vessels. A single closed suction drain is placed in the right upper quadrant close to the biliary and the pancreatic anastomosis. All port sites are closed appropriately.

Postoperative management

Historically, our patients have had epidural catheters placed by the anesthesiology service. We no longer routinely utilize these catheters; however, in the event the case is converted to OPD, a transversus abdominis plane (TAP) block is performed. Postoperative management includes standardized ERAS protocols for pancreatic surgery.

Figure 1 Clinical presentation and imaging of 56-year-old male with pancreatic head mass. Surgical technique of a robotic pancreaticoduodenectomy (PD) is provided in this video (19). Available online: http://www.asvide.com/articles/1051

Patients are typically discharged on postoperative day 7.

Tips, tricks, and pitfalls

- Avoid the use of epidural catheters;
- If conversion from robotic to open occurs, consider a TAP block;
- Positioning tips: turn bed 90 degrees to allow anesthesia access to extended left arm. Use only slight reverse Trendelenburg;
- Robotic cart should be positioned over patient's head, not over right shoulder;
- Take down round ligament for use as a pedicle flap for pancreaticojejunostomy (minute 1 on *Figure 1*);
- Suture gallbladder to anterior abdominal wall to avoid use of a Nathanson retractor (minute 1 on *Figure 1*);
- Always use intraoperative ultrasound to identify vascular anatomy, especially to distinguish between the middle colic vein and SMV (minute 2 on *Figure* 1);
- Couple saline irrigation during pancreatic transection to minimize charring of the tissue. Use cutting current to minimize thermal coagulation to pancreatic duct (minute 4 on *Figure 1*);
- Use a 7- or 5-French pancreatic duct stent during pancreaticojejunostomy anastomosis (minute 7 on *Figure 1*);
- If the size of the transverse colon and omentum prohibit an antecolic duodenojejunostomy a loop of jejunum is brought up through a mesenteric window made to the left of the middle colic vessels.

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Footnote

Conflicts of Interest: Dr. Martinie serves as a consultant and proctor for Intuitive Surgical. Dr. Iannitti is a consultant and proctor for Medtronic. All other authors have no conflicts of interest to declare.

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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,

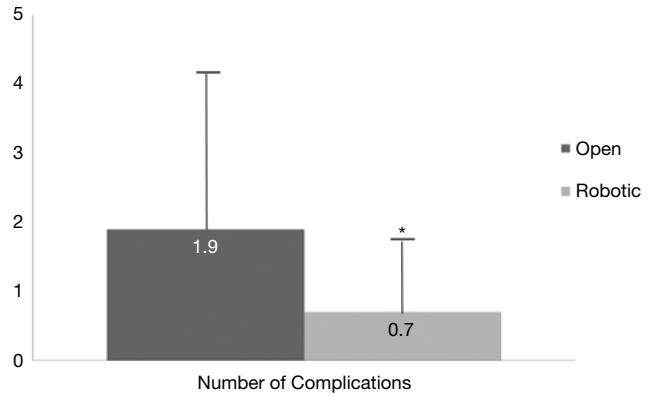

Figure 1 Overall complications. The number of complications, including, but not limited to, delayed gastric emptying, surgical site infection and pancreatic anastomosis leak rate was lower in the robotic group (P=0.008).

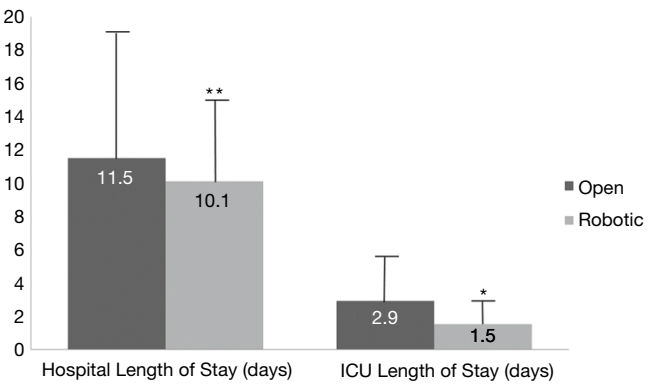

Figure 2 Length of stay. There was significant difference in ICU length of stay between the open and robotic PD group, in favor of the latter. There was a trend for shorter hospital length of stay in robotic group. However, for this observation there is potential for type II error, given the small sample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

Conflicts of Interest: Dr. Martinie serves as a consultant and proctor for Intuitive Surgical. The other authors have no conflicts of interest to declare.

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Clinical trials to reduce pancreatic fistula after pancreatic surgery—review of randomized controlled trials

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Abstract: Pancreatic fistula is one of severe postoperative complications that occur after pancreatic surgery, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP). Because pancreatic fistula is associated with a higher incidence of life-threatening complications. In order to evaluate procedure or postoperative management to reduce pancreatic fistula after pancreatic surgery, we summarized some randomized controlled trials (RCTs) regarding pancreaticoenterostomy during PD, pancreatic duct stent during PD, procedure to resect pancreatic parenchyma during DP, and somatostatin and somatostatin analogues after pancreatic surgery. At first, we reviewed nine RCTs to compare pancreaticogastrostomy (PG) with pancreaticojejunostomy (PJ) during PD. Next, we reviewed five RCTs, to evaluate the impact of pancreatic duct stent during PD. Regarding DP, we reviewed six RCTs to evaluate appropriate procedure to reduce pancreatic fistula after DP. Finally, we reviewed eight RCTs to evaluate the impact of somatostatin and somatostatin analogues after pancreatic surgery to reduce pancreatic fistula. The best way to prevent pancreatic fistula after pancreatic surgery remains still controversial. However, several RCTs clarify a useful procedure to reduce in reducing the incidence of pancreatic fistula after pancreatic surgery. Further RCTs to study innovative approaches remain a high priority for pancreatic surgeons to prevent pancreatic fistula after pancreatic surgery.

Keywords: Pancreatic surgery; clinical trial; pancreatic fistula

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Introduction

The morbidity rate after pancreatic surgery still remains high in the range of 15% to 65%, although mortality has decreased to less than 5% due to recent advances in surgical techniques and perioperative management (1-7). In particular, pancreatic fistula is one of the most severe postoperative complications after pancreatic surgery. Pancreatic fistula is reportedly associated with a higher incidence of life-threatening complications, such as intra-abdominal abscess, intra-abdominal hemorrhage, and sepsis (8-12). A strategy to decrease pancreatic fistula after pancreatic surgery is urgently required.

The various innovative techniques, including operative techniques, intensive care medicine and pharmacological agents have been utilized to prevent the incidence of pancreatic fistula after pancreatic surgery. This review summarizes the randomized controlled trials (RCTs) to prevent pancreatic fistula after pancreatic surgery.

Definition of pancreatic fistula

In 2005, an international study group of pancreatic surgeons (ISGPF) proposed a consensus definition and clinical grading of postoperative pancreatic fistula (13). Pancreatic fistula was defined by ISGPF guidelines as follows: amylase

level in drainage fluid on POD 3 that was more than 3 times the serum amylase level. Pancreatic fistula was classified into three categories by ISGPF as follows: Grade A—"transient pancreatic fistula", it has no clinical impact; Grade B—required a change in management or adjustment in the clinical pathway; Grade C—a major change in clinical management or deviation from the normal clinical pathway. Grade B and C were defined as "clinical pancreatic fistula".

RCT regarding the operative technique to prevent pancreatic fistula after pancreaticoduodenectomy (PD)

Several clinical trials regarding operative technique were performed to prevent pancreatic fistula after PD as follows: (I) pancreaticojejunostomy (PJ) versus pancreaticogastrostomy (PG); and (II) pancreatic stent.

PJ versus PG

Both PJ and PG are established reconstructive procedures in PD for pancreatic or periampullary tumors. The meta-analysis of RCTs published in 2015 revealed a higher rate of pancreatic fistula after PD in PJ, when compared to PG (14). In this meta-analysis seven RCTs were reviewed, including 562 patients who underwent PG and 559 who underwent PJ. The pancreatic fistula incidence was significantly lower in the PG group than in the PJ group (11.2% *vs.* 18.7%, OR: 0.53, 95% CI: 0.38–0.75, P=0.0003). The overall mortality rate was 3.7% in the PG group and 3.9% in the PJ group (P=0.68). No significant differences regarding overall morbidity and mortality were found between PJ and PG. PG has been thought to be safer than PJ for the following reasons: (I) the gastric acid environment inhibits the activation of pancreatic enzymes; (II) the proximity of the stomach to the pancreatic remnant decreases tension on the anastomosis; (III) the rich gastric vascular supply reduces the tendency for ischemia of the anastomosis (15-17). However, there are some limitations in this meta-analysis as follows; (I) the type of intervention and the indications for surgery which are different among seven RCTs may lead to different results; (II) the definition of pancreatic fistula varied among these RCTs may cause the different decision of pancreatic fistula among each institution. There were nine RCTs to examine that PG reduces the incidence of pancreatic fistula comparing PJ (*Table 1*) (17-25). Afterward, a multicenter prospective randomized controlled trial comparing PG with PJ from Germany was published in 2015 (25). The impact of study was the currently largest (n=440) multicenter prospective randomized controlled trial comparing PG with PJ regarding postoperative complications including pancreatic fistula and long-term pancreatic function. The incidence of grade B/C pancreatic fistula after PJ was similar to that after PG (PJ: 22% *vs.* PG: 20%, P=0.617). On the other hand, this study reported that PG was associated with a significantly increased rate of postpancreatectomy hemorrhage compared to PJ (PJ: 12% *vs.* PG: 20%, P=0.023), although there was no significant difference regarding overall morbidity and mortality between PJ and PG.

Regarding long-term pancreatic function between PJ and PG, two RCT have demonstrated that pancreatic exocrine insufficiency is more severe after PJ than PG (23,25). In contrast, one RCT has reported conflicting long-term outcomes regarding pancreatic function (24). However, pancreatic exocrine function in these RCTs was not measured directly. Alternatively, surrogate parameters including steatorrhea, body weight loss, and stool elastase level have represented pancreatic exocrine function indirectly. Moreover, surrogate parameters used for pancreatic exocrine function were different in each study. A furthermore large multicenter trial is required to evaluate long-term pancreatic function between PJ and PG.

Pancreatic duct stent in PJ

The impact of pancreatic duct stent to reduce pancreatic fistula after PD remains still controversial. There are three types for procedures of pancreatic duct stent as follows; lost stent, external stent and no stent. However, it remains unclear which is best procedure to reduce pancreatic fistula. There were five RCTs regarding pancreatic duct stent following PJ to prove the hypothesis that stent reduces the incidence of pancreatic fistula (*Table 2*) (10,26-29).

At first, three RCTs regarding external pancreatic duct stent versus no stent were reviewed. Poon *et al.* reported that pancreatic fistula occurred in 6.7% of patients with external drainage stent, and in 20% with no stent (P=0.032) in RCT which compared external drainage stent (n=60) with no stent (n=60) (10). However, this study included both soft and hard pancreatic parenchyma. Soft pancreas is well known to cause higher incidence of pancreatic fistula after PD than hard pancreas. Soft pancreas has been reported to be one of the risk factors for pancreatic fistula. In 2011, Pessaux *et al.* performed RCT to evaluate the impact of external duct stent among high-risk patients with soft pancreas or a non-

Table 1 Summary of nine randomized controlled trials regarding pancreaticogastrostomy versus pancreaticojejunostomy in PD

Authors	Settings	Years	Variable	Sample size	Definition of PF†	PF (%)	P value
Yeo *et al*. (17)	Single center	1995	PG	73	>50 mL of amylase-rich drainage fluid	12.3	NS
			PJ	72	after POD10 or pancreatic leakage	11.1	
					demonstrated radiographically		
Duffas *et al*. (18)	Multicenter	2005	PG	81	Chemically, 4 times normal serum amylase	16.0	NS
			PJ	68	level on POD3, clinically and radiologically	20.0	
					leak by fistulography		
Bassi *et al*. (19)	Single center	2005	PG	69	Any clinical significant output of fluid, rich	13.0	NS
			PJ	82	amylase confirmed by fistulography	16.0	
Fernández-Cruz	Single center	2008	PG	53	ISGPF‡	4.0§	<0.001
et al. (20)			PJ	55		18.0§	
Wellner *et al*. (21)	Single center	2012	PG	59	ISGPF‡	10.0§	0.775
			PJ	57		12.0§	
Topal *et al*. (22)	Multicenter	2013	PG	162	ISGPF‡	8.0§	0.002
			PJ	167		19.8§	
Figueras *et al*. (23)	Single center	2013	PG	65	ISGPF‡	15.0	0.014
			PJ	58		34.0	
El Nakeeb *et al*. (24)	Single center	2014	PG	45	ISGPF‡	22.2	0.796
			PJ	45		20.0	
Keck *et al*. (25)	Multicenter	2016	PG	171	ISGPF‡	20.0§	0.617
			PJ	149		22.0§	

†, pancreatic fistula; ‡, pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C. PD, pancreaticoduodenectomy; PG; pancreaticogastrostomy, PJ; pancreaticojejunostomy; NS, not significant.

Table 2 Summary of five randomized controlled trials regarding pancreatic duct stent in PD

Authors	Settings	Years	Variable	Sample size	Definition of PF†	PF (%)	P value
Winter *et al*. (26)	Single center	2006	Internal stent	115	>50 mL/day amylase-rich (3 times	11.3	NS
			No stent	119	serum level) on day 7 or more after	7.6	
					surgery		
Poon *et al*. (10)	Single center	2007	External stent	60	>10 mL/day (3 times serum level) more	6.7	0.036
			No stent	60	than 3 days after surgery	20.0	
Tani *et al*. (27)	Single center	2010	Internal stent	50	ISGPF‡	26.0	NS
			External stent	50		20.0	
Pessaux *et al*. (28)	Multicenter¶	2011	External stent	77	ISGPF‡	26.0	0.030
			No stent	81		46.0	
Motoi *et al*. (29)	Single center	2012	External stent	46	ISGPF‡	6.0§	0.040
			No stent	47		22.0§	

†; pancreatic fistula; ‡; pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C; ¶, only patients with soft pancreas and a diameter of P-duct less than 3 mm are enrolled. PD, pancreaticoduodenectomy; NS, not significant.

dilated duct less than 3 mm (28). The study has reported that external pancreatic duct stent significantly reduced pancreatic fistula compared to no stent: 20 of 77 (26%) in external pancreatic duct stent group versus 34 of 81 (42%) in no stent group (P=0.03). Moreover, the stent group significantly reduced morbidity compared to no stent group (41.5% *vs.* 61.7%, P=0.01). Similarly, Motoi *et al.* also reported that among patients with a non-dilated duct, external pancreatic duct stent significantly reduced clinically relevant pancreatic fistula compared to no stent: two of 21 (10%) versus eight of 20 (40%) (P=0.033) (29). Pancreatic duct stent may protect PJ by diverting pancreatic juice away from the anastomosis, to improve long-term pancreatic duct patency, and to facilitate precise suture placement.

On the other hands, the impact of internal pancreatic duct stent remains still unclear. Winter *et al.* has reported that internal pancreatic duct stent did not reduce the incidence of pancreatic fistula, compared to no stent (11.3% in internal pancreatic duct stenting; n=115 versus 7.6% in no stent; n=119) (26). However, in this study, the technique of PJ anastomosis was not standardized as the use of duct-to-mucosa or invagination technique. The invagination technique is chosen in PJ for a small pancreatic duct which is more difficult for duct-to-mucosa. A bias of surgeons in selecting the anastomotic technique may influence outcomes in this study. Moreover, external stent may decrease the incidence of stent migration or offer a better diversion of pancreatic juice away from anastomosis compared to internal stent. However, Tani *et al.* has reported that no difference was found between external and internal stents regarding short-outcomes including the incidence of pancreatic fistula (27). It remains still controversial which is better external stent or internal stent. Meta-analysis has reported that pancreatic duct stent did not reduce the incidence of pancreatic fistula and other complications in PD compared with no stent (30). A large multicenter randomized controlled trial for standardized anastomotic techniques for PD is required to conclusively evaluate the benefits of using pancreatic duct stents.

RCT regarding the operative technique to prevent pancreatic fistula after distal pancreatectomy (DP)

DP is a procedure for treatment both benign and malignant diseases of the body and tail of the pancreas. In an effort to reduce the incidence of PF after DP, surgeons have attempted various surgical techniques to transect pancreatic parenchyma including a hand-sewn closure, stapler closure, scalpel, electrocautery or ultrasonic devices. However, appropriate procedure to transect the pancreas during DP remains still controversial. *Table 3* summarizes RCTs regarding procedure to prevent pancreatic fistula after DP (31-36).

Stapler closure has recently become a standard technique for pancreatic stump closure. The meta-analyses on hand-sewn suture and stapler closure reported by Knaebel *et al.* showed that stapler closure (22.8%) had reduced pancreatic fistula more than hand-sewn suture (34.9%) (37) and those reported by Zhou *et al.* showed that stapler closure (22.1%) had reduced pancreatic fistula more than hand-sewn suture (31.2%) (38). These two reports of meta-analyses demonstrated that stapler closure in DP tended to reduce pancreatic fistula as compared to manual suturing, but could not prove that stapler closure was statistically useful. In 2011, the results of RCT of hand-sewn suture and stapler closure were published (31). However, the multicenter randomized DISPACT trial found that stapler closure did not significantly reduce the incidence of pancreatic fistula after DP in comparison to hand-sewn closure. In this study, 352 patients were randomized both treatment groups, 177 patients were stapler group, 175 patients were another group. The incidence of pancreatic fistula did not differ between both groups (stapler closure; 32% *vs.* hand-sewn; 28%, OR: 0.84, 95% CI: 0.53–1.33, P=0.56). Afterward, there are RCTs regarding absorbable material (32,34,35) or seromuscular patch (33) to reinforce the staple line. In 2012, it has been reported that the resection with a stapler having reinforcing absorbable materials significantly reduced clinically relevant pancreatic fistula (32). However, in two RCTs, an absorbable fibrin sealant patch (TachoSil) to stapling technique did not reduce the incidence of pancreatic fistula. Montorsi *et al.* have reported the incidence of pancreatic fistula was not significantly different between groups (with TachoSil group; 62% *vs.* without TachoSil group; 68%, P=0.267) in a multicenter, randomized, controlled trial (34). Park *et al.* also examined a similar prospective, multicenter, randomized controlled study (35). In this RCT, the incidence of clinically relevant postoperative complications (grade B and C, ISGPF) (with TachoSil group; 22.9% *vs.* without TachoSil group; 28.3%, P=0.536). These two studies demonstrated that the TachoSil patch did not reduce the incidence of pancreatic fistula after DP. TachoSil had no significant effect on the incidence of pancreatic fistula. On the other hand, a RCT has reported that covering the stapled pancreatic remnants with seromuscular patch significantly decreased the overall

Table 3 Summary of six randomized controlled trials regarding resection of pancreatic parenchyma in DP

Authors	Settings	Years	Variable	Sample size	Definition of PF†	PF (%)	P value
Diener *et al*. (31)	Multicenter	2011	Stapler	177	ISGPF‡	32.0	NS
			Hand-sewn	175		28.0	
Hamilton *et al*. (32)	Single center	2012	Stapler	46	ISGPF‡	20.0§	0.0007
			Stapler with mesh	54		1.9§	
Oláh *et al*. (33)	Single center	2009	Stapler	35	ISGPF‡	30.0	NS
			Stapler with a seromuscular patch	35		12.0	
Montorsi *et al*. (34)	Multicenter	2012	Standard closure¶	130	ISGPF‡	68.0	NS
			Standard closure with TachoSil	145		62.0	
Park *et al*. (35)	Multicenter	2015	Stapler	53	ISGPF‡	54.7	NS
			Stapler with TachoSil	48		70.8	
Kawai *et al*. (36)	Multicenter	2015	stapler	61	ISGPF‡	37.7	NS
			Pancreaticojejunostomy	62		38.7	

†, pancreatic fistula; ‡, pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C; ¶, standard closure: by stapler or by scalpel and hand-sewn suture. DP, distal pancreatectomy; NS, not significant.

rate of pancreatic-related complications, although the rates of clinically relevant postoperative complications (grade B and C, ISGPF) were comparable between two groups (33).

A multicenter randomized controlled trial has evaluated whether PJ of pancreatic stump decreases the incidence of pancreatic fistula after DP compared with stapler technique in a multicenter randomized controlled trial (36). This RCT demonstrated that PJ of the pancreatic stump during DP does not reduce pancreatic fistula compared with stapler closure. However, this study has reported that PJ of pancreatic stump in thickness of pancreas greater than 12 mm tended to reduce the incidence of clinically relevant pancreatic fistula compared to stapler closure (22.2% of the stapler closure group *vs.* 6.2% of the PJ group; P=0.080).

Efficacy the use of somatostatin or its analogues after pancreatic surgery

Somatostatin and somatostatin analogues, including octreotide and vapreotide, have well-recognized inhibitory effects on pancreatic exocrine secretion. Therefore, somatostatin or octreotide have been used as prophylactic agents to prevent pancreatic fistula after pancreas resection. *Table 4* summarizes RCTs regarding the administration of somatostatin and somatostatin analogues after pancreatic surgery. Two RCTs reported that prophylactic somatostatin or octreotide significantly reduced the incidence of pancreatic fistula after PPPD (39,40). On the other hand, four recent RCTs reported that the use of somatostatin analogues including octreotide and vapreotide, did not reduce pancreatic fistula after pancreas surgery (41-45). A meta-analysis regarding the benefit of somatostatin and its analogues reported that these agents reduced overall morbidity (P=0.003) and pancreas-specific complications (P=0.002), but did not reduce the incidence of clinically relevant pancreatic fistula after pancreatic surgery (47). In contrast, another meta-analysis report concluded that these agents didn't have advantages of utility for mortality, re-operation rate, and hospital stay, and the incidence of clinical pancreatic fistula after pancreatic surgery (48). Recently, one RCT reported that pasireotide which is another long-acting somatostatin analogue significantly reduced the incidence of pancreatic fistula after pancreatic surgery (46). As the reason to reduce pancreatic fistula, the report discussed that pasireotide has a long half-life and a strong affinity to some SSTR-subtypes compared to other somatostatin analogues. The impact of somatostatin and its analogues to reduce pancreatic fistula after pancreatic surgery remains controversial, as study design is heterogeneity by each study. Furthermore large multicenter RCTs are required to clarify the benefits of somatostatin and its analogues after pancreatic surgery.

Conclusions

Consensus on the best way to prevent pancreatic fistula after

Table 4 Summary of eight randomized controlled trials regarding administration of somatostatin and somatostatin analogues after pancreatic surgery

Authors	Years	Variable	Procedure	Sample size	Definition of PF†	PF (%)	P value
Shan *et al*. (39)	2003	Somatostatin	PD	27	>10 mL/day (3 times serum level) more	22.0	<0.050
		control		27	than 7 days after surgery	48.0	
Gouillat *et al*. (40)	2001	Somatostatin	PD	38	>100 mL/day (5 times serum level) more	5.0	0.047
		control		37	than 3 days after surgery	22.0	
Suc *et al*. (41)	2004	Octreotide	PD and DP	122	3 times serum level more than 3 days	11.0	NS
		control		108	after surgery	8.0	
Sarr (42)	2003	Vapreotide	PD and DP	135	>30 mL/day (5 times serum level) more	30.4	NS
		control		140	than 5 days after surgery	26.4	
Yeo *et al*. (43)	2000	Octreotide	PD	104	>50 mL/day amylase-rich (3 times serum	11.0	NS
		control		107	level) on day 10 or more after surgery	9.0	
Lowy *et al*. (44)	1997	Octreotide	PD	57	>200 mL/day (3 times serum level) more	12.0	NS
		control		153	than 3 days after surgery	6.0	
Fernández-Cruz	2013	Octreotide	PD	32	ISGPF‡	6.0§	NS
et al. (45)		control		30		10.0§	
Allen *et al*. (46)	2014	Pasireotide	PD and DP	152	ISGPF‡	11.0	0.002
		control		148		25.0	

†, pancreatic fistula; ‡, pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation; §, the rate of ISGPF grade B/C. PD, pancreaticoduodenectomy; DP, distalpancreatectomy; NS, not significant.

pancreatic surgery remains still controversial. However, several RCTs steadily clarify a useful procedure to reduce the incidence of pancreatic fistula after pancreatic surgery. Therefore, further RCTs to study innovative approaches remain a high priority for pancreatic surgeons to prevent pancreatic fistula after pancreatic surgery.

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Footnote

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Techniques for prevention of pancreatic leak after pancreatectomy

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Abstract: Pancreatic resections are some of the most technically challenging operations performed by surgeons, and post-operative pancreatic fistula (POPF) are not uncommon, developing in approximately 13% of pancreaticoduodenectomies and 30% of distal pancreatectomies. Multiple trials of various operative techniques in the creation of the pancreatic ductal anastomosis have been conducted throughout the years, and herein we review the literature and outcomes data regarding these techniques, although no one technique of pancreatic ductal anastomosis has been shown to be superior in decreasing rate of POPF. Similarly, we review the literature regarding techniques of pancreatic closure after distal pancreatectomy. Again, no one technique has been shown to be superior in preventing POPF; however the use of buttressing material on the pancreatic staple line in the future may be a successful means of decreasing POPF. We review adjunctive techniques to decrease POPF such as pancreatic ductal stenting, the use of various topical biologic glues, and the use of somatostatin analogue medications. We conclude that future trials will need to be conducted to find optimal techniques to decrease POPF, and meticulous attention to intra-operative details and post-operative care by surgeons is necessary to prevent POPF and optimally care for patients undergoing pancreatic resection.

Keywords: Pancreaticoduodenectomy; distal pancreatectomy; pancreatic leak; post-operative pancreatic fistula (POPF); prevention

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Introduction

Pancreatic resections, whether for benign or malignant disease processes, are some of the most technically challenging operations performed by surgeons. After pancreatic resection the potential for the development of serious complications exists. One of the most serious complications after pancreatic resection is the development of a post-operative pancreatic leak or fistula, whereby digestive pancreatic enzymes leak out of the pancreatic ductal system via an abnormal connection into the peri-pancreatic space or the peritoneal cavity, with resulting morbidity such as abdominal pain, ileus, fever, and the possibility of abscess, sepsis, and hemorrhage and consequently prolonged hospitalization. Importantly, patients with post-operative pancreatic fistula (POPF), leak, or abscess have been found to have a 90-day mortality of 5% in a single-institution report of pancreatectomy outcomes prospectively-collected over a five-year period (1). The magnitude of this complication is not insignificant; in a large worldwide literature search, the incidence of pancreatic fistula after pancreaticoduodenectomy was found to be 12.9% and 13% after distal pancreatectomy (2), and other reports detail fistula rates up to 31% for distal pancreatectomies (3).

Given the need to decrease the incidence of POPF as well as the resulting significant morbidity and mortality, various techniques have been attempted to prevent the formation of pancreatic leak and fistula. In this report we review techniques for the prevention of pancreatic leak after pancreatectomy.

Definition

A POPF is any abnormal connection between the pancreatic ductal system and the peri-pancreatic space, the peritoneal cavity or other body cavities, or externally to the skin. Leakage of enzyme-rich pancreatic fluid is typically diagnosed in the post-operative period via percutaneous drainage of a fluid collection that is found to be high in amylase content or via continued drainage of amylase-rich fluid through a drain placed at the time of surgery. In the past, varying criteria for what constitutes POPF have been published in the literature; however in an attempt to standardize the definition of POPF an international study group (ISGPF) of pancreatic surgeons convened in 2005 (4). POPF was thus defined as drain output of any volume occurring on or after post-operative day 3 with amylase content at least three times that of serum amylase levels.

In order to standardize the reporting of POPF outcomes, the authors also defined three grades of POPF: Grade A is a transient fistula that does not have any clinical impact, does not delay hospital discharge, and is managed by slow removal of peri-pancreatic drains. Grade B POPF requires a change in clinical management, such as making the patient NPO, administering TPN, or re-positioning drains, and leads to a delay in hospital discharge or to a readmission. Grade C POPF is the most severe and requires a major change in clinical management such as ICU-level care, percutaneous drainage of undrained fluid collections, or operative re-exploration for further drainage or attempted anastomotic repair. Grade C POPF causes a major increase in hospitalization time as well as increased rates of complications and the possibility of mortality (4).

Techniques to prevent pancreatic leak

Multiple trials using various operative techniques and pharmacologic agents have been conducted to evaluate for a decrease in or prevention of POPF. Herein we review the literature on techniques to decrease POPF.

Operative anastomotic construction techniques

Historical technique: ligation of the pancreatic duct

Historically the creation of a pancreatic-enteric anastomosis after pancreaticoduodenectomy was fraught with leak and complications, and thus some authors advocated simply ligating the pancreatic duct without re-creating continuity to the GI tract as a means of fistula prevention. Brunschwig reported on three cases of pancreatic duct ligation all without fistula creation in 1952 (5), and in a large report by Goldsmith and colleagues the POPF rate was equivalent between 45 patients treated with pancreatic duct ligation and 34 treated with anastomosis to the jejunum (6). Pancreatic endocrine dysfunction in the form of diabetes may develop after pancreatic duct ligation (7), and since approximately 1975 pancreatic duct ligation has been abandoned in favor of re-establishment of continuity of the pancreatic duct to the intestines (8,9).

Pancreaticojejunostomy (PJ) anastomotic techniques

Multiple techniques in anastomosing the pancreatic duct to the gastrointestinal (GI) tract after pancreaticoduodenectomy have been described in the literature. Two of the predominant methods of creating a PJ are an end-to-side duct-to-mucosa anastomosis or the invagination technique. Briefly, in the end-to-side duct-to-mucosa anastomotic technique, the jejunal limb is brought into the retroperitoneum adjacent to the pancreas in a retrocolic fashion. A two-layer anastomosis is constructed with interrupted absorbable suture material, beginning with a posterior row of seromuscular sutures securing the jejunum to the pancreas (*Figure 1*). The pancreatic duct-to-mucosa anastomosis is performed to an enterotomy in the jejunum with a second circumferential layer of interrupted sutures, taking generous amounts of pancreas and the full-thickness of the jejunum, followed by completion of an anterior layer of seromuscular sutures again securing the anterior aspect of the opened jejunum to the capsule of the pancreas. In a report by Z'graggen and colleagues using this technique, POPF was seen in 2.1% of 331 patients who underwent pancreatic head resection (10).

The goal of creating an invagination PJ is to invaginate or "dunk" all of the cut edge of the pancreatic parenchyma into the lumen of the jejunum (11). The performance of invagination PJ anastomosis begins with a posterior row of interrupted seromuscular sutures bringing the jejunum into apposition with the pancreatic capsule (*Figure 2*). The jejunum is opened, and an inner layer of running locking suture is then performed taking full-thickness jejunal bites and large bites of the pancreatic parenchyma and capsule, but not of the pancreatic duct, with the goal of invaginating all of the cut edge of the pancreatic tissue into the jejunum. An anterior layer of seromuscular sutures rolling the jejunum onto the pancreatic capsule is then performed to complete the anastomosis.

Berger and colleagues sought to compare rates of

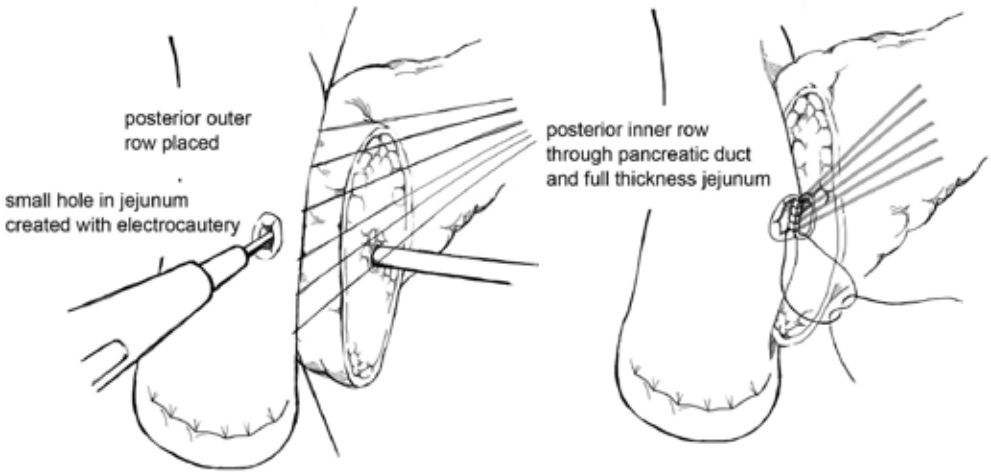

Figure 1 Duct-to-mucosa pancreaticojejunostomy.

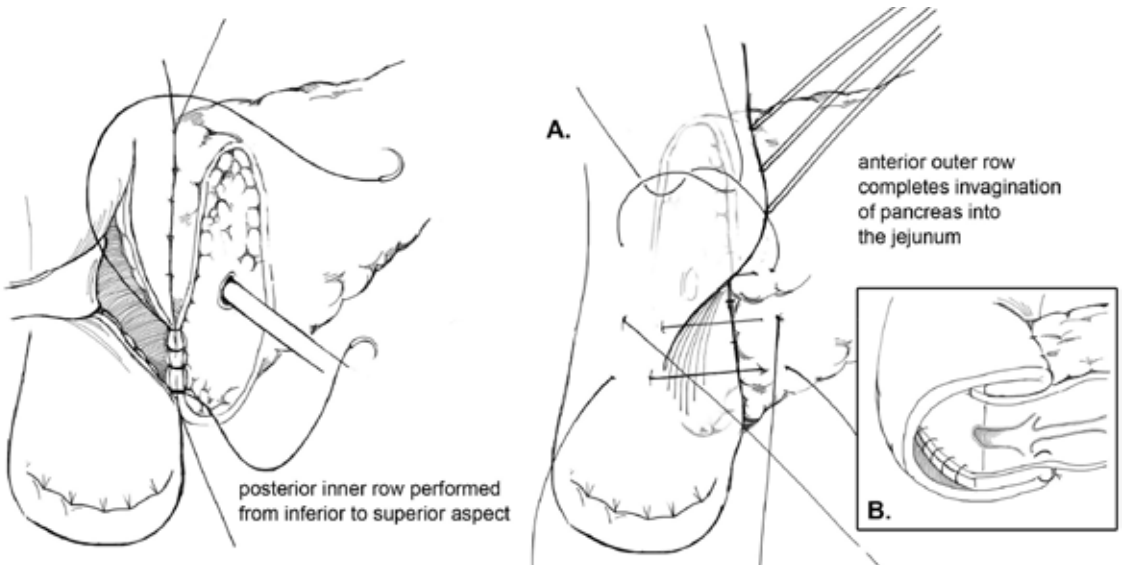

Figure 2 Invagination pancreaticojejunostomy.

POPF at the PJ with the use of the invagination technique versus the duct-to-mucosa technique to test the hypothesis that use of the duct-to-mucosa technique would lead to a decreased POPF rate (12). To this end the authors performed a randomized prospective clinical trial at two institutions and randomized 197 patients undergoing pancreaticoduodenectomy to the invagination or the duct-to-mucosa technique; patients were stratified in both groups by whether the pancreatic parenchyma was hard or soft. POPF occurred in 17.8% of all patients, with significantly more POPF seen in the duct-to-mucosa group compared with the invagination group (24% *vs.* 12%, P<0.05) and with more POPF in soft glands (27%) than in hard glands (8%). The authors concluded that the pancreatic texture was the greatest determinant in POPF and that further studies are needed to determine the optimal anastomotic technique.

Modified duct-to-mucosa PJ

One variation of the duct-to-mucosa technique that bears noting is the transpancreatic U-suture technique with a duct-to-mucosa anastomosis described by Grobmyer, Blumgart, and colleagues at Memorial Sloan Kettering Cancer Center and originally created by Dr. Leslie Blumgart (13).

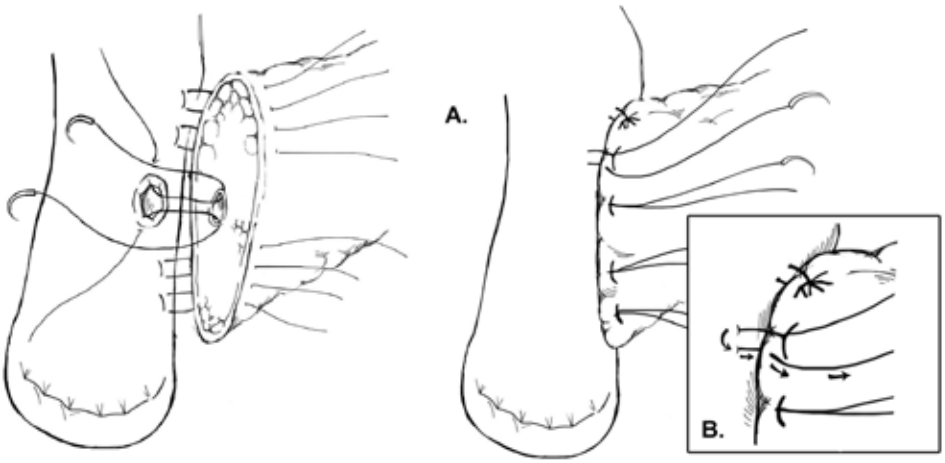

Figure 3 Modified duct-to-mucosa pancreaticojejunostomy—Blumgart anastomosis.

In this technique an outer layer of polyglactin sutures are first inserted full-thickness anterior-to-posterior through the pancreas with subsequent seromuscular horizontal mattress stitches on the jejunum, followed again by a full-thickness posterior-to-anterior bite coming up through the pancreas (*Figure 3*). Care is taken not to pass the needle through the pancreatic duct. The u-stitches are not tied yet, and a duct-to-mucosa anastomosis is then created with fine polydioxanone interrupted suture. The seromuscular sutures are then tied bringing the jejunum into close apposition anteriorly on the pancreas; however the suture is not yet cut. Lastly, the sutures with the needles still on are used to create an anterior seromuscular bite on the jejunum with the needle being brought through the pancreas under the previous knots. The sutures are then tied again, thus imbricating the jejunum over the entire pancreas. In an audit of 187 patients with PJ anastomoses constructed by this technique, the authors report an overall POPF rate of 20.3%; however most of these were ISPGF Grade A, with only 6.9% of patients with Grade B or C POPF. Soft pancreatic texture was significantly associated with leak, and patients with POPF had significantly smaller diameter pancreatic ducts compared with patients without POPF (3 *vs.* 4 mm, P=0.008). Kleespies and colleagues published their outcomes data using what they call the "Blumgart anastomosis" after their department began to use this technique for PJ and abandoned the traditional duct-to-mucosa technique (14). They found significantly decreased leak rate with the Blumgart anastomosis (13% *vs.* 4%, P=0.032), as well as significantly decreased rates of postoperative hemorrhage, complications, and length of ICU stay. Proponents of this technique argue that the transpancreatic sutures minimize radial forces on the anastomosis, and that it is relatively quick to construct and easy to teach to trainees.

Binding technique for PJ creation

Another technique for creating the PJ anastomosis is the so-called "binding" PJ reported by Peng and colleagues (15), in which the distal 3 cm of the jejunal loop to be used for anastomosis are everted and the mucosa ablated either by electrocoagulation or by topical treatment with 10% carbolic acid followed by immediate rinsing in 75% ethanol and normal saline (*Figure 4*). The proximal 3 cm of the pancreatic stump is then anastomosed to just the mucosa of the jejunum. The treated 3 cm of jejunum are then rolled out and intussuscepted back over the pancreas, sutured into place, and lastly a catgut tie is looped around the entire circumference of the anastomosis 1 cm from the cut edge of the pancreas. The authors reported a 0% POPF rate after the completion of 150 cases using this anastomosis, with an overall morbidity of 31.3% and a mean hospital stay of 19.8±5 days (16). A subsequent prospective trial conducted by Peng and colleagues randomized 217 patients undergoing pancreaticoduodenectomy to traditional PJ anastomosis or binding PJ anastomosis (17). Leak was seen in 8 of 111 (7.2%) conventional PJ patients compared with 0 of 106 binding PJ patients (P=0.014), and complications were reported in 36.9% of conventional PJ patients compared with 24.5% of binding PJ patients (P=0.048), including 6.3%

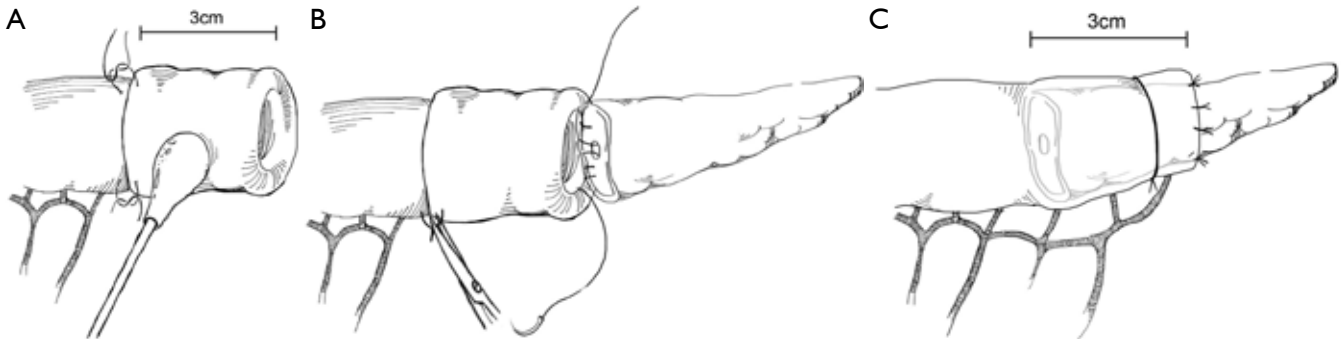

Figure 4 Binding pancreaticojejunostomy.

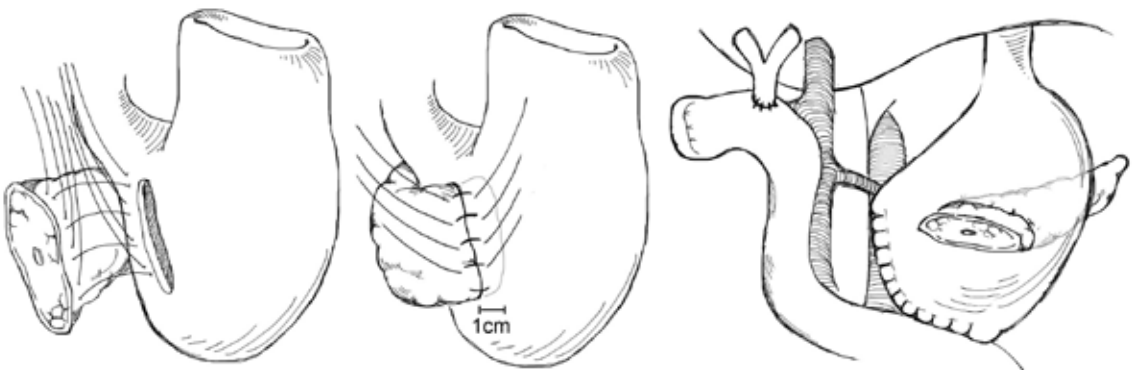

Figure 5 Pancreaticogastrostomy.

perioperative mortality in the conventional group and 2.8% mortality in the binding group (P=NS). Subsequent trials of binding PJ conducted in Europe have not replicated the impressive rate of POPF. A case-control study 22 binding PJ and 25 conventional PJ patients found no difference in the rate of POPF, with longer delay in POPF healing as well as increased postpancreatectomy hemorrhage in the binding group (18). Similarly, a recent prospective two-institution trial of 69 binding PJ patients compared to 52 conventional PJ historical control patients demonstrated significantly shorter hospital stay in the conventional PJ patients. Soft pancreatic texture was significantly associated with POPF; however no significant difference in the rate of POPF between binding and conventional PJ anastomoses was seen (19). Binding PJ remains one of many options for creation of the pancreatic-enteric anastomosis.

Pancreaticogastrostomy (PG) creation

The creation of pancreatic duct anastomosis to the stomach PG instead of to the jejunum has been studied as well, with the rationale that a PG anastomosis is easier to perform and that the stomach has a more robust blood supply compared with the jejunum. Additional rationale for PG instead of PJ in the case of pancreatic head resections that extend to the left past the midline is that the increase in distance may put the resulting jejunal limb and jejunal anastomosis under tension, with increased risk for subsequent leak; however after such a resection the stomach will be immediately adjacent to the remnant pancreas with the opportunity to create a tension-free PG anastomosis (*Figure 5*). In evaluating PG, an earlier report by Delcore and colleagues demonstrated no leaks of the PG anastomosis in 45 cases (20), and a 0% leak rate over 38 cases was also reported by Mason *et al*. (21). PG was later compared to PJ anastomosis in a prospective randomized trial conducted by Bassi and co-workers, in which 151 patients with soft pancreatic glands were randomized to PG or end-to-side PJ anastomoses (22). Pancreatic fistula occurred in 13% of PG patients and 16% of PJ (P=NS); however post-operative fluid collections, delayed gastric emptying, and biliary fistulae were significantly less in the PG group. A similar trial was conducted by Duffas

et al. who randomized 81 patients to PG and 68 patients to PJ after pancreaticoduodenectomy and found POPF in 16% of the PG group and 20% of the PJ group (23). The authors concluded that the type of anastomosis does not influence the development of POPF, and a meta-analysis of PG versus PJ trials noted that there was no superiority of either technique and surgeons should continue to use the technique with which they are most familiar (24). Interestingly, a recent prospective randomized multi-center trial by Topal and colleagues from Belgium randomizing 329 patients to PJ or PG after pancreaticoduodenectomy, in which patients were stratified by pancreatic duct diameter (≤3 or >3 mm), reported significantly more POPF in the PJ group than the PG group (19.8% *vs*. 8%, OR 2.86, 95% CI: 1.38-6.17, P=0.002) (25). The authors concluded that PG should be the preferred anastomosis after pancreaticoduodenectomy, although further data from a multi-center international trial will be needed to confirm this.

Pancreatic duct anastomotic stenting

Pancreatic duct stenting at the time of anastomosis creation has been proposed as a technique to decrease pancreatic leak and fistula, with the rationale that stenting prevents the accumulation of pancreatic secretions in the pancreatic stump and the pancreatic anastomosis is excluded from direct contact with the pancreatic juice (26). This was examined in a randomized trial by Winter and colleagues who randomized 238 patients undergoing pancreaticoduodenectomy to internal pancreatic duct stent or no-stent with the endpoint of POPF development (27). Patients were stratified by the texture of the pancreatic remnant (soft *vs*. normal/hard), with 6 cm pediatric feeding tubes were used as stents. In the hard pancreas group 1.7% stent patients and 4.8% non-stent patients developed POPF (P=0.4), and in the soft pancreas group 21.1% stent patients and 10.7% non-stent patients developed POPF (P=0.1) with the conclusion that internal pancreatic duct stenting does not alter the rate of POPF.

Pancreatic duct drainage with external rather than stents has also been studied. In a study from Hong Kong in 2007, Poon *et al*. prospectively randomized 120 patients undergoing pancreaticoduodenectomy with PJ duct-to-mucosa anastomosis to an external stent or not (28). Patients in the stented group had a significantly lower pancreatic fistula rate compared with the no stent group (6.7% *vs*. 20%, P=0.032), and on multivariable analysis absence of stenting was a significant risk factor for POPF. The authors hypothesized that use of external drains more completely diverts pancreatic secretions away from the PJ anastomosis with decreased risk for leak formation.

A recent Cochrane Review also examined the efficacy of pancreatic stents in preventing POPF after pancreaticoduodenectomy in a review of randomly controlled trials extracted the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Excerpta Medica database (EMBASE), Web of Science, and other major trials databases (29). A total of 655 patients were included in the systematic review, and the authors found that the use of external, but not internal stents was associated with a significant decrease in the incidence of POPF (RR 0.33, 95% CI: 0.11-0.98, P=0.002). These results are echoed by another systematic review of the literature and meta-analysis performed by Xiong and colleagues, who examined the literature from January 1973 to September 2011 and included 1,726 patients from five randomized clinical trials and 11 non-randomized clinical observation studies in their analysis (30). The authors found that placement of internal or external stents in the pancreatic duct after pancreaticoduodenectomy did not reduce the incidence of POPF; however on subgroup analysis placement of external stents significantly reduced the incidence of POPF compared with no stent (OR 0.42, 95% CI: 0.24-0.76, P=0.004 for randomized clinical trials and OR 0.43, 95% CI: 0.27-0.68, P<0.001 for observational studies). These recent data suggest that if one intends to stent the pancreatic anastomosis, an external stent should be considered; however more data are needed to suggest routine use of pancreatic stents, and many centers have moved away from the use of pancreatic duct stents completely.

Pancreatic stump closure after distal pancreatectomy

Pancreatic leak after distal pancreatectomy occurs in approximately 30% of patients (31,32), which is a rate higher than is seen in pancreaticoduodenectomy. Many studies have been conducted to determine the optimal method for closing the pancreatic stump in order to prevent POPF. The two main techniques for closure of the pancreatic stump after distal pancreatectomy are suture closure of the pancreatic duct or stapled closure of the parenchyma. A previous retrospective report by Bilimoria *et al*. in which the authors reviewed their institutional data of 126 patients who underwent distal pancreatectomy over a nine year period found that POPF rates in patients

who underwent suture closure of the pancreatic duct was significantly lower than patients who did not undergo suture closure (9.6% *vs*. 34%, P<0.001) (33). On multivariable analysis, failure to ligate the duct was significantly associated with pancreatic leak (OR 5, 95% CI: 2-10, P=0.001). The other most prominent technique for pancreatic transection is to use a surgical stapler. A meta-analysis conducted by Knaebel and co-workers in 2005 examined ten articles in the world literature (two randomized trials and eight observational studies) that reported techniques to decrease POPF after distal pancreatectomy (34). Six of the ten studies compared hand-sutured versus stapled pancreatic closure, and in this analysis the authors found a trend towards decreased POPF with the use of staplers; however the results were not statistically significant (OR 0.66, 95% CI: 0.35-1.26, P=0.21). Given this trend towards decreased POPF with stapled closure, Diener and colleagues designed the multicenter prospective DISPACT trial in which patients undergoing distal pancreatectomy were randomized to stapler or hand-sewn closure with the primary outcomes of POPF and mortality at one week; the authors hypothesized that standardized closure with a stapler would lead to decreased POPF (35). Of 450 patients randomized, 352 were included in the final analysis (175 hand-sewn, 177 stapler). The rate of POPF in the stapler group was 32% compared with 28% in the hand-sewn group, without any significant difference between the two groups (OR 0.84, 95% CI: 0.53-1.33, P=0.56). There was one death in the hand-sewn group and none in the stapler group. The authors concluded that stapled closure was not superior to hand-sewn closure for preventing POPF, and indeed the data demonstrate that these methods of closure have equivalent POPF rates.

Given this equivalency, other methods to decrease POPF have been investigated. A prospective randomized trial of prophylactic pancreatic duct stenting to decrease POPF was conducted by Frozanpor *et al*. with the hypothesis that more efficient diversion of pancreatic secretions into the duodenum away from the pancreatic transection line would lead to decreased POPF (36). A total of 58 patients were analyzed (29 distal pancreatectomy only, 29 distal pancreatectomy with stent); the rate of ISGPF Grade B/C POPF was 42.3% in the stent group and 22.2% in the no-stent group without a significant difference between the two (OR 2.57, 95% CI: 0.78-8.48, P=0.122). Decreasing resistance across the sphincter of Oddi with stenting does not appear to have a role in decreasing POPF rates.

Various methods of reinforcing the staple line after distal pancreatectomy have been attempted as a means of decreasing leak. In a small non-randomized single-institution trial, Jimenez and colleagues reported rates of POPF with stapled pancreatic stump closure reinforced with bioabsorbable buttress sleeves mounted on the stapler and compared a group of 13 patients treated in this manner with 18 historical controls (37). Rates of POPF were 0% in the buttress group versus 39% in the control group (P=0.025). A similar single-institution report from Thaker and others of 40 patients undergoing distal pancreatectomy and bioabsorbable mesh buttress staple line reinforcement with comparison to 40 historical controls of only stapled closure found significantly decreased rate of POPF with mesh reinforcement (3.5%) compared with staple closure only (22%, P=0.04) (38). In a subsequent single-institution randomized prospective trial of stapled pancreatic closure with or without bioabsorbable mesh staple line reinforcement, Hamilton *et al*. found significantly fewer ISGPF Grade B/C leaks in 1/53 (1.9%) mesh reinforcement patients compared with 11/45 (20%) no-mesh patients (P=0.007) (39).

Currently it appears that reinforcement of the pancreatic staple line with a bioabsorbable mesh is a feasible method of decreasing POPF; however the previous single-institution results still require confirmation in the form of multi-institution prospective randomized trials, preferably with international collaboration. Just as the rigorous methodology of the DISPACT trial appears to have provided a definitive answer to the question of stapled or hand-sewn closure, so is there a need for this methodology regarding the question of bioabsorbable mesh reinforcement.

Use of fibrin glue and other topical sealant agents

The use of fibrin glue and other topical hemostatic agents applied to the pancreato-enteric anastomosis have been proposed as adjuncts to help seal the anastomosis and prevent POPF; however results have been disappointing. In a report from 1991, Kram and colleagues used fibrin glue made from concentrated fibrinogen and clotting factors which was applied topically to pancreatic wounds, staple/suture lines, and pancreatic anastomoses in both trauma and non-trauma operations; the authors reported no pancreatic fistulae, abscesses, or pseudocysts in their series of 15 patients (40). In an early prospectively randomized trial reported in 1994 by D'Andrea, 97 patients undergoing pancreatectomy for both benign and malignant conditions

were enrolled and randomized to intraoperative fibrin sealing of the pancreas or to no sealing (41). Pancreatic fistulae developed in 13.9% of the fibrin glue patients and in 11.1% of the non-fibrin glue patients, with no significant difference seen between in two groups.

In a larger prospective randomized trial of fibrin glue conducted by Lillemoe *et al*., the authors randomized 125 patients, who were felt to be at high risk for pancreatic leak after pancreaticoduodenectomy by their operating surgeon, to either topical application of fibrin glue to the PJ anastomosis (59 patients) versus no glue (66 patients) (42). The rate of POPF was 26% in the glue arm versus 30% in the control group (P=NS), and there was no difference in length of hospital stay between the groups as well. The authors concluded that the use of fibrin glue did not decrease the rate of POPF or of other complications following pancreaticoduodenectomy. A recent large meta-analysis evaluating the effectiveness of fibrin sealants in pancreatic surgery systematically evaluated seven studies including 897 patients and found that fibrin sealants had a non-significant impact on the development of POPF (43). The authors concluded that fibrin sealants cannot be recommended routinely in the setting of pancreatic resection.

Internal occlusion of the pancreatic duct with absorbable fibrin glue after creation of a pancreatic duct anastomosis has been proposed as a way to allow the anastomosis to heal without being exposed to the enzyme-rich pancreatic fluid, although early prospective non-randomized trials did not demonstrate a decrease in POPF (44). To address this, Suc and colleagues conducted a multi-institution, single-blind, prospective randomized trial in France of pancreatic resection with or without fibrin glue occlusion of the pancreatic duct occlusion (45). The authors report an overall POPF rate of 16% in their trial; however no difference in POPF rate was seen when comparing the fibrin glue to the control group. Fibrin glue occlusion of the pancreatic duct appears to have no impact on the development of POPF.

Use of somatostatin analogues

The inhibitory peptide hormone somatostatin acts to decrease the output of secretions from the pancreas, GI tract, and biliary tract, although the half-life is short at approximately two minutes (46). Synthetic analogues of somatostatin with longer half-lives, such as octreotide (47), have been developed and have been used in pancreatic surgery in an attempt to decrease POPF, with the hypothesis that decreased pancreatic juice secretion will allow for improved healing of pancreatic ductal anastomoses and consequently decreased leak rates. The use of octreotide has been studied in multiple randomized prospective trials in the United States and Europe; however the results have been mixed. Yeo and colleagues conducted a prospective trial in which patients undergoing pancreaticoduodenectomy were randomized to saline control or octreotide 250 μg subcutaneously every eight hours beginning 1-2 hours before surgery and continuing for seven days (48). Ultimately 211 patients made up the entire study cohort; POPF was seen in 9% of control group and 11% of octreotide group. The authors concluded that octreotide does not reduce incidence of POPF and that omission of this treatment may lead to a cost savings for hospitals. Sarr and co-investigators in the Pancreatic Study Group conducted a prospective, randomized, placebo-controlled trial of the long-acting somatostatin analogue vapreotide, hypothesizing that vapreotide would decrease pancreas-related complications; 135 patients received vapreotide and 140 received placebo (49). No significant differences were seen in pancreas-related complications between the two groups (placebo 26.4% *vs*. vapreotide 30.4%, P=NS), and the authors concluded that vapreotide offers no therapeutic benefit in terms of post-operative complications. Suc *et al*. conducted a French multi-center prospective randomized trial in 230 patients undergoing pancreatectomy, with 122 patients randomized to octreotide and 108 randomized to the control arm; the primary endpoint was all intra-abdominal complications (50). Intra-abdominal complications were seen in 22% of octreotide patients versus 32% of placebo patients; however this result was not statistically significant and the authors concluded that octreotide cannot be routinely used to decrease intra-abdominal complications in pancreatectomy patients.

Recently, Allen and colleagues reported their results of a single-center, prospective, double-blind, placebo controlled trial using the long-acting somatostatin analogue pasireotide, which has a longer half-life than octreotide as well as a broader receptor binding profile (51). Patients undergoing pancreaticoduodenectomy or distal pancreatectomy were randomized to pasireotide 900 μg subcutaneously given twice daily beginning the morning of operation for seven days (152 patients) or to placebo (148 patients). The primary endpoint was incidence of grade 3 pancreatic leak, fistula, or abscess; grade 3 indicating that a radiologic, endoscopic, or surgical intervention was required, and

Table 1 Selected trials performed to evaluate rates of POPF

Study	Trial arm(s)	N	Fistula (%)	Conclusion
Berger, 2009	Duct-to-mucosa Pancreaticojejunostomy (PJ)	100	12 (12%)	Fewer POPF in invagination group
	Invagination PJ	97	23 (24%)	
Grobmyer, 2010	Modified duct-to-mucosa PJ (Blumgart anastomosis)	187	13 (6.7%) Grade B/C	
Kleespies, 2009	Duct-to-mucosa PJ	90	12 (13%)	Fewer POPF with use of Blumgart anastomosis
	Modified duct-to-mucosa PJ (Blumgart anastomosis)	92	4 (4%)	
Peng, 2007	Binding PJ	111	0	Fewer POPF in binding group
	Invagination PJ	106	8 (7.5%)	
Maggiori, 2010	Binding PJ	22	8 (36%)	No POPF difference with use of binding PJ
	Invagination PJ	25	7 (28%)	
Bassi, 2005	Pancreaticogastrostomy (PG)	69	9 (13%)	No difference in POPF rates
	PJ	82	13 (16%)	
Topal, 2013	PG	167	13 (8%)	PG decreases POPF rate
	PJ	162	33 (19.8%)	
Winter, 2006	Pancreatic duct stent	58	Hard pancreas 1.7%, soft pancreas 21.1%	No difference in POPF rates
	No stent	63	Hard pancreas 4.8%, soft pancreas 10.7%	
Poon, 2007	External pancreatic duct stent	60	4 (6.7%)	External stent decreases POPF
	No stent	60	12 (20%)	
Diener, 2011	Stapled distal pancreatectomy	175	32%	No difference in POPF rates
	Hand-sewn distal pancreatectomy	177	28%	
Yeo, 2000	Octreotide	104	11 (9%)	No difference in POPF rates
	No octreotide	107	10 (11%)	
Allen, 2014	Pasireotide	152	9%	Pasireotide decrease POPF rates
	No pasireotide	148	21%	

POPF, post-operative pancreatic fistula.

the secondary endpoint was Grade B or C POPF. In total 15% of patients met the primary endpoint; however the primary endpoint was significantly less in the pasireotide group compared with placebo (9% *vs.* 21%, RR 0.44, 95% CI: 0.24-0.78, P=0.006). In the pasireotide group 7.9% of patients had Grade B POPF, and zero had Grade C, compared with 16.9% Grade B/C in the placebo group, P=0.02; rates of adverse events were similar between the two groups. Pasireotide significantly reduced risk of post-operative fistula/leak/abscess, and may have a role in the prevention of POPF in the future.

Conclusions

Post-operative pancreatic leak and fistula are a major source of morbidity and mortality after pancreatic resection. Many trials have been undertaken to identify techniques to reduce POPF (*Table 1*); however no one technique has been shown to definitively be the solution to the problem, and indeed one of the major determinants of POPF is a factor over which the surgeon has very little control, i.e., the consistency of the pancreatic parenchyma itself. Surgeons should continue to use the pancreatic duct

anastomotic technique with which they are most familiar and comfortable, and currently there is no evidence for routine use of stents or topical sealing products. For closure of the pancreatic stump after distal pancreatectomy, a stapled closure in combination with bioabsorbable mesh buttress may represent a reliable technique to decrease POPF; however high-quality data from multi-institutional prospective trials are currently lacking. In the future, novel somatostatin analogues may play a role in decreasing POPF, but without question meticulous surgical technique and attention to detail will remain the cornerstones of decreasing pancreatic leak and patient morbidity/mortality.

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Footnote

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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.

Patients who experience any complications after pancreatic surgery are associated with a three-fold increase in costs over those without complications.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Irreversible electroporation of stage 3 locally advanced pancreatic cancer: optimal technique and outcomes

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Objective: Irreversible electroporation (IRE) of stage 3 pancreatic adenocarcinoma has been used to provide quality of life time in patients who have undergone appropriate induction therapy. The optimal technique has been reported within the literature, but not in video form. IRE of locally advanced pancreatic cancer is technically demanding requiring precision ultrasound use for continuous imaging in multiple needle placements and during IRE energy delivery.

Methods: Appropriate patients with locally advanced pancreatic cancer should have undergone appropriate induction chemotherapy for a reasonable duration. The safe and effective technique for irreversible electroporation is preformed through an open approach with the emphasis on intra-operative ultrasound and intra-operative electroporation management.

Results: The technique of open irreversible electroporation of the pancreas involves bracketing the target tumor with IRE probes and any and all invaded vital structures including the celiac axis, superior mesenteric artery (SMA), superior mesenteric-portal vein, and bile duct with continuous intraoperative ultrasound imaging through a caudal to cranial approach. Optimal IRE delivery requires a change in amperage of at least 12 amps from baseline tissue conductivity in order to achieve technical success. Multiple pull-backs are necessary since the IRE ablation probe lengths are 1 cm and thus needed to achieve technical success along the caudal to cranial plane.

Conclusions: Irreversible electroporation in combination with multi-modality therapy for locally advanced pancreatic carcinoma is feasible for appropriate patients with locally advanced cancer. Technical demands are high and require the highest quality ultrasound for precise spacing measurements and optimal delivery to ensure adequate change in tissue resistance.

Keywords: Pancreatic cancer; stage 3 pancreatic; locally advanced; irreversible electroporation (IRE); technique

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Introduction

It is estimated that of the 42,000 patients diagnosed with pancreatic adenocarcinoma 45% with have stage III (locally advanced) disease with involvement of the celiac axis or the superior mesenteric artery (SMA) (1,2). Past outcomes in these rare patients that are able to undergo resection with various systemic chemotherapies are poor: post-resection 5-year survival has been reported at 6.8% and the median survival after resection has been reported to be 10.6 months (3). This poor past prognosis has historically diminished enthusiasm for aggressive surgical resection (4).

Recent publications from Kwon *et al.* have reported superior overall survival with surgical resection with simultaneous irreversible electroporation (IRE) for margin accentuation in combination with active systemic chemotherapy and/or radiation therapy (5). IRE is a technique in which multiple (100 to 200) short (70 to 90 usec), high-voltage (1,500 volts/cm) pulses are applied to tissues (6-9) to permeabilize the

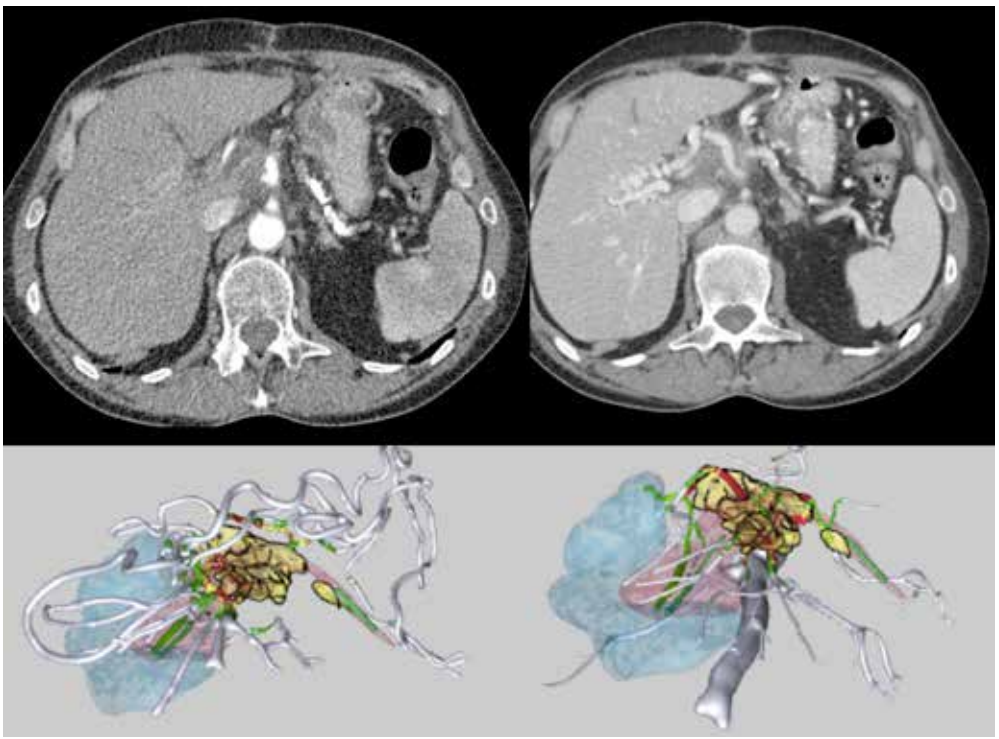

Figure 1 Representative case of locally advanced pancreatic cancer in a 68-year-old female of the pancreatic neck with celiac axis encasement and SMV-splenic vein encasement. Arterial phase with 3D reconstruction (right) and portal venous phase with 3D reconstruction (left). SMV, superior mesenteric vein; 3D, 3 dimensional.

cell membranes. IRE uses a nonthermal/electrical-based method of action and can be used to treat around vital structures such as the urethra, larger blood vessels, and nerves (7). Although irreversible electroporation for locally advanced pancreatic adenocarcinoma is a surgical palliative technique in locally advanced pancreatic disease, that has been reported and is currently standardized with the use of multiple needles (10). We have recently published our findings regarding the safety of IRE in the pancreas (11). Similarly we have also recently published superior survival rates with the use of IRE in combination with standard chemotherapy and/or chemo-radiation therapy when compared to standard of care chemotherapy or chemoradiation therapy (12).

This article describes our preferred method for the utilization of open irreversible electroporation of patients with locally advanced pancreatic adenocarcinoma.

Methods

Our standard work-up for patients with locally advanced pancreatic adenocarcinoma includes a high quality 3-phase CT scan with pancreatic protocol with 0.7 mm cuts at the time of diagnosis, which allows us to appropriately diagnose and stage patients with locally advanced pancreatic adenocarcinoma. Additional 3 dimensional (3D) imaging is also performed of these patients to better document vessel involvement and proximity (*Figure 1*). We adhere to standard diagnostic criteria of stage III pancreatic cancer such that there must be greater than 180 degree encasement of the major arterial structures (superior mesenteric and/or celiac) without evidence of any type of metastatic disease to the liver or distant lymph nodes, nor any evidence of peritoneal disease (13,14). Laboratory work-up is also performed to ensure appropriate hematologic as well as CA19-9 evaluation. Following that a staging/diagnostic laparoscopy is performed at the time of diagnosis in which peritoneal washings are obtained, as well, to ensure small occult metastases are not present that have not been visualized on CT scan. Only after this is performed do we embark on induction chemotherapy of either FOLFIRINOX-based chemotherapy (in younger patients approximately less than 75 years of age and without evidence of non-alcoholic steatohepatitis) or gemzar combination based therapy after

a thorough discussion of patient's physiologic age and performance status. The goal is for at least 3-4 months of induction based therapy (gemzar chemotherapy consists of: approximately 3-4 cycles of 2 weeks, on and 1 week off. FOLFIRINOX: is given for approximately 4-6 cycles). Following that induction chemotherapy, we repeat high-quality 3-phase CT scan, and also obtain hematologic and serologic markers to ensure locally advanced non-metastatic pancreatic adenocarcinoma still exists. The key goal of this repeat imaging is to ensure that metastatic disease has not occurred, since it is uncommon for a pancreatic cancer to truly respond or reduce in size during induction therapy (chemotherapy alone or chemo-radiation therapy) based on established RECIST criteria (i.e., reduction in size of >30% of the longest diameter). As long as the patient has not developed metastatic disease and the maximum axial diameter is not above 4 cm after induction therapy, then we do proceed with IRE therapy.

Once this is confirmed, approximately 2-3 weeks after the last dose of chemotherapy open IRE to the pancreatic tumor primary is performed. Optimal inclusion of patients who are appropriate for irreversible electroporation should include tumor sizes that are 3.0-3.5 cm in maximum diameter. Patients with metal biliary stents can be treated if that metal stent can be removed prior to or at the time of irreversible electroporation. It has been our experience that patients with the long uncovered or partially covered biliary stents are much more difficult to remove than the short (4 cm) fully covered biliary stent. In either case, removal of metal stents is critical to patient outcomes. Given that any type of metal is conductive, it has been demonstrated in our large animal model that these metal stents lead to significant deflection of energy, which can lead to incomplete ablation, high current conditions, and possible thermal injury since the degree of deflection is not consistent based on the location of the metal, the probe exposure and the fibrotic nature of the tissue to be electroporated. If metals stents are removed then a Roux-en-Y hepatico-jejunostomy is performed at the same procedure as the IRE. This procedure is performed through an open laparotomy; appropriate cardiac and pulmonary evaluation should be performed to ensure the patient can tolerate this type of procedure.

Protocol

Step 1: Upper midline incision from 4 cm below xiphoid process and to umbilicus—approximately 6-8 cm in length.

Step 2: Thorough exploration and placement of Thompson retractor using single blade underneath upper midline to lift and two bladder blades to retract midline incision.

Step 3: Ultrasound of liver to ensure no liver metastasis. Ultrasound via a transgastric technique to ensure locally advanced tumor not amenable to resection. Ultrasound of pancreatic tumor to assess 3D size (anterior-posterior, axial, and cranial-caudal planes).

Step 4: Confirm a trans-mesocolic approach optimal for lower based pancreatic head/uncinate process lesions versus mobilizing omentum and a direct pancreatic approach for superior based head lesion.

Step 5: Using continuous ultrasound at the tissue insertion site to ensure ATRAMAUTIC needle placement bracketing vital structures and tumor to insure an adequate margin.

Step 6: Using deep paralytic and adequate narcotic, IRE to all needle pairs of a total 20 pulses is delivered to assess tissue fibrosis and tissue resistance, followed by the remaining 100 pulses for efficacy.

Step 7: Confirmation of IRE efficacy through delivery of electroporation energy to verify a change in amperage draw of an amount to ensure that adequate electroporation has occurred.

Step 8: Confirmation of vital structure patency through repeat ultrasound using power Doppler imaging to confirm vital structure flow and patency.

Step 9: Consideration of prophylactic gastrojejunostomy, J-tube or hepaticojejunostomy at surgeon's discretion.

Results

Operative description (Figure 2)

Abdominal approach (*Table 1*)

The patient undergoes standard endotracheal intubation and access for open IRE is performed through a superior midline incision. A superior midline incision is utilized based on the planned needle placement performed most commonly and, I believe, in a safer manner through a caudal-to-cranial approach. In turn, the caudal-to-cranial approach is more easily facilitated through a midline laparotomy than through a bilateral subcostal laparotomy. The abdomen is thoroughly examined to rule out any type of occult solid organ liver metastases as well as peritoneal or mesenteric metastases. Intraoperative ultrasound of the liver is also performed to rule out any type of non-palpable liver

metastases that may have been missed on dynamic CT scan. Only after no evidence of metastatic disease is confirmed is intraoperative ultrasound (*Figure 3*, BK Medical Ultrasound System—Flex Focus 800, Peabody, MA) then turned to the operative assessment of the tumor. Given the lack of definitive accuracy as well as positive predictive value of CT scan alone because of volume averaging, it is important to ensure that the patient truly has greater than 180 degree encasement of the SMA before deciding on *in situ* IRE therapy *vs.* pancreaticoduodenectomy with margin accentuation with IRE along the SMA. Our optimal ultrasound technique is transgastric and is performed with placing the ultrasound probe on top of the gastric body closer to the pylorus. I recommend imaging with minimal amount of mobilization and avoiding the mobilization into the lesser sac, which further impedes optimal intraoperative imaging since this will disrupt the tissue planes with air and lead to a greater artifact. The reason for performing through a transgastric approach (*Figure 4*) is that the stomach serosa allows for a complete and clean apposition of the ultrasound crystals and provides minimal to no artifact to truly image a pancreatic head lesion and subsequent portal vein SMA as well as superior mesenteric vein (SMV). I have found this transgastric approach is also the most sensitive way to assess invasion of the SMA without the need for extensive dissection. Thus, intraoperative ultrasound imaging has become our gold standard for elucidating whether a patient has a true locally advanced tumor or a borderline resectable tumor.

Figure 2 The use of IRE in the treatment of a locally advanced pancreatic cancer (stage 3) of a pancreatic body/neck tumor (15). This video explains the rationale for the use of IRE, requirements of the need for high quality ultrasound imaging, technique for IRE needle placement, and IRE efficacy endpoint. IRE, irreversible electroporation. Available online: http://www.asvide.com/articles/501

Once local advancement is confirmed and an *in situ* IRE is then planned, imaging of the tumor and the surrounding structures is then performed in order to obtain axial, anterior/posterior as well cranial/caudal maximum tumor diameters. Vital structures that need to be included in those diameters for appropriate needle placement are also assessed. Given that a majority of pancreatic tumors' longest axis is in the cranio-caudal along the SMA for head lesions and on top of the SAM for neck lesions (approximately 4 cm),

Table 1 Indications for irreversible electroporation in locally advanced (stage 3) pancreatic adenocarcinoma

Indications
Appropriately staged pancreatic adenocarcinoma, including either 3 phase thin cut CT scan with pancreatic protocol or dynamic MRI, with diagnostic laparoscopy to rule out sub-radiologic occult metastasis
Completion of 3-4 months of induction chemotherapy with or without radiation therapy based on patients symptoms
Maximum axial and anterior to posterior tumor dimension of ≤3.5 cm (the caudal to cranial dimension can be longer since this is the plane the needles are pulled back on after initial insertion)
Relative contraindications
Axial or anterior post-chemotherapy tumor size >4 cm
Inability to undergo general endotracheal anesthesia
Atrial fibrillation
Karnofsky Performance Status <80%
Absolute contraindications
Tumor size >5 cm
Metastatic disease
Progression of local tumor >30% diameter while undergoing induction therapy
Inducible ischemia on cardiac stress test or uncontrolled angina

Figure 3 Ultrasound machine of choice given the ability for 2D biplane imaging, high definition imaging, and wireless control of all functions for easy access during the operation. 2D, 2 dimensional.

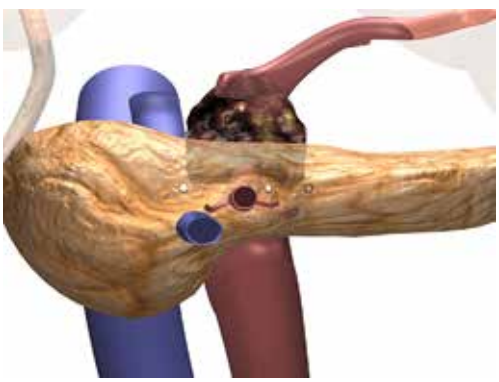

Figure 4 A trans-gastric ultrasound image is obtained, which allows for the greatest accuracy of imaging to assess resectability and target lesion size. Left—axial image of locally advanced pancreatic cancer with complete superior mesenteric vein occlusion. Right—ultrasound imaging in a sagittal plane with ultrasound crystals in cranial to caudal application.

it is not uncommon to have a tumor that is longer in the cranio-caudal plane (approximately 3-4 cm) and the maximum axial diameter between 2.5 and 3.0 cm in size. Based on the maximum axial diameter appropriate needles are placed at exactly 2.0 cm apart so that the entire tumor and an approximate 1.0 cm margin of normal soft tissue is included in the IRE plane (*Figure 5*).

As demonstrated in *Figure 5*, this most commonly requires four needles in a trans-mesocolon approach, two to three needles posteriorly to cover the retro-peritoneum and then one or two anterior to cover the anterior extent of the tumor. One to two additional probes are then placed in a more anterior approach, most commonly 1.5 cm anteriorly such that a triangle or an oblong square is then obtained (*Figure 5*).

The optimal placement of the IRE needles is performed through continuous intraoperative ultrasound from the insertion of the needle into the tissue so that the needle tip is followed at all times during needle placement. I have found that placing these needles through the transverse mesentery, with care not to damage the transverse colon vessels, is easier because it allows normal soft tissue to bracket the pancreatic head tumor as well as to allow for appropriate inferior margin to be obtained during pullbacks of the needle. Thus, the transverse mesocolon is grasped and raised anteriorly out of the abdomen by an assistant and then the surgeon's dominant hand directs the needle into the tissue, while her/his non-dominant hand utilizes the ultrasound probe to ensure accurate and appropriate needle placement. It cannot be overemphasized that an

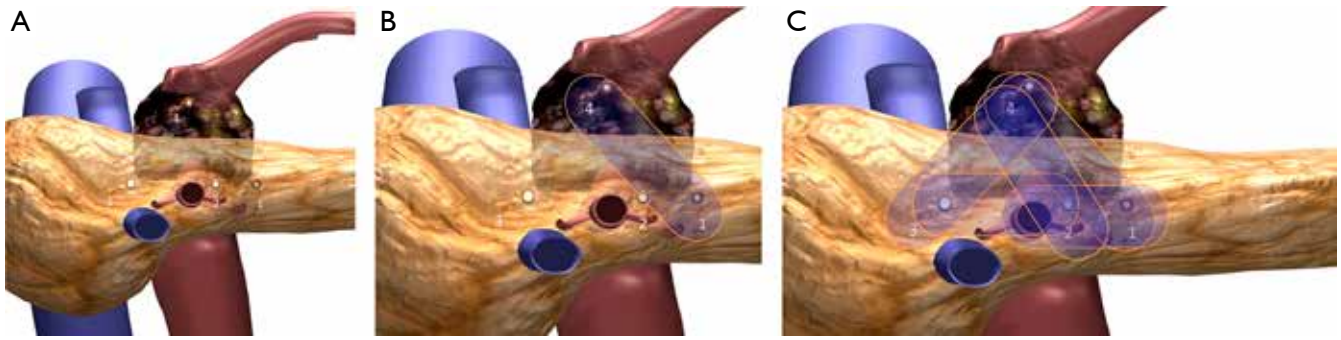

Figure 5 Axial plane with a triangle probe technique for locally advanced pancreatic tumor with a broader base in the axial plane requiring a 3-probe posterior placement technique with either one probe (or two probes) on top to create the triangle. The probe pair with the longest distance (maximum 2.3 cm) is then treated first, followed by other probe pairs to ensure a complete irreversible electroporation utilizing all probe pairs that are active. Note—probe pair 1 to 3 is not active since the distance between them is more than 2.3 cm spacing.

atraumatic needle placement should be performed to ensure that the needle does not damage the underlying vital structures, namely the SMV, portal vein, and SMA. Vascular needle trauma may induce underlying vascular thrombosis, especially given the potential hypercoagulable state in a patient with pancreas cancer.

We commonly will place the most lateral needle (probe 1—*Figure 5*) within the pancreatic at the most lateral extent. Then using spacers at 2.0 cm intervals we build off that initial needle to ensure adequate treatment margin(s). Once this margin(s) is obtained, one or two needles are then placed anterior in order to obtain complete bracketing of the tumor while allowing the normal non-tumor bearing tissue—that being the posterior aspect of the stomach anteriorly, the duodenum laterally and the transverse mesocolon inferiorly—to be left in place.

Care should also be undertaken that the maximum needle exposure to perform safe IRE of the pancreas should be 1.0 to 1.5 cm because of the significant fibrotic nature of these tumors and a larger needle exposure will not be tolerated by the gland or the underlying soft tissue to be treated. We have previously published that a greater probe exposure leads to high current conditions and the potential for thermal damage if these high current conditions are allowed to persist. Thus the maximum probe exposure should be 1.5 cm or less (16).

Following appropriate needle placement and ultrasound confirmation of appropriate spacing, those spacing measurements are entered into the energy unit's software, which allow for optimal voltage and pulse length delivery. Standard default voltage of 1,500 volts/cm is initiated with planned delivery of 90 pulses and a pulse width of 70 to 90 usec. Twenty pulses are delivered initially and then the delivery is halted in order to assess the underlying amperage draw to establish optimal voltage and pulse widths. If the current amperage draw for these first 20 pulses is less than 35 amps I believe that this is an appropriate voltage per cm and pulse widths for safe and effective electroporation. Energy is delivered between all needle pairs (*Figure 5*) and evaluation of the energy delivered is then assessed for each pair in order to demonstrate a change in current amperage draw, which has been found to be an appropriate surrogate marker of change and resistance. This change in resistance is of utmost importance to ensure against reversible electroporation, which would lead to ineffective therapy and electroporation failure. Once effective current delivery has been confirmed between all pairs the needles are pulled back the appropriate distance such that no overlapping treatments are performed. Sequential pullbacks are performed in order to obtain adequate margins both superiorly and inferiorly. Each probe pair is (*Figure 5*) then treated again following subsequent pull back and again is re-treated for a total 180 pulses, or even in a rare instance 270 pulses if the current draw does not appropriately change over each 90 pulses delivery. Following optimal pulse delivery at each needle placement and providing appropriate margins are felt to be obtained with the needle placement, the needles are removed without the need for any additional hemostatic procedures (i.e., suture ligature, etc.) in most cases. Another probe configuration using a triangle formation is sometimes needed based on a width of the axial plane of the tumor that at times narrows anteriorly (*Figure 5*).

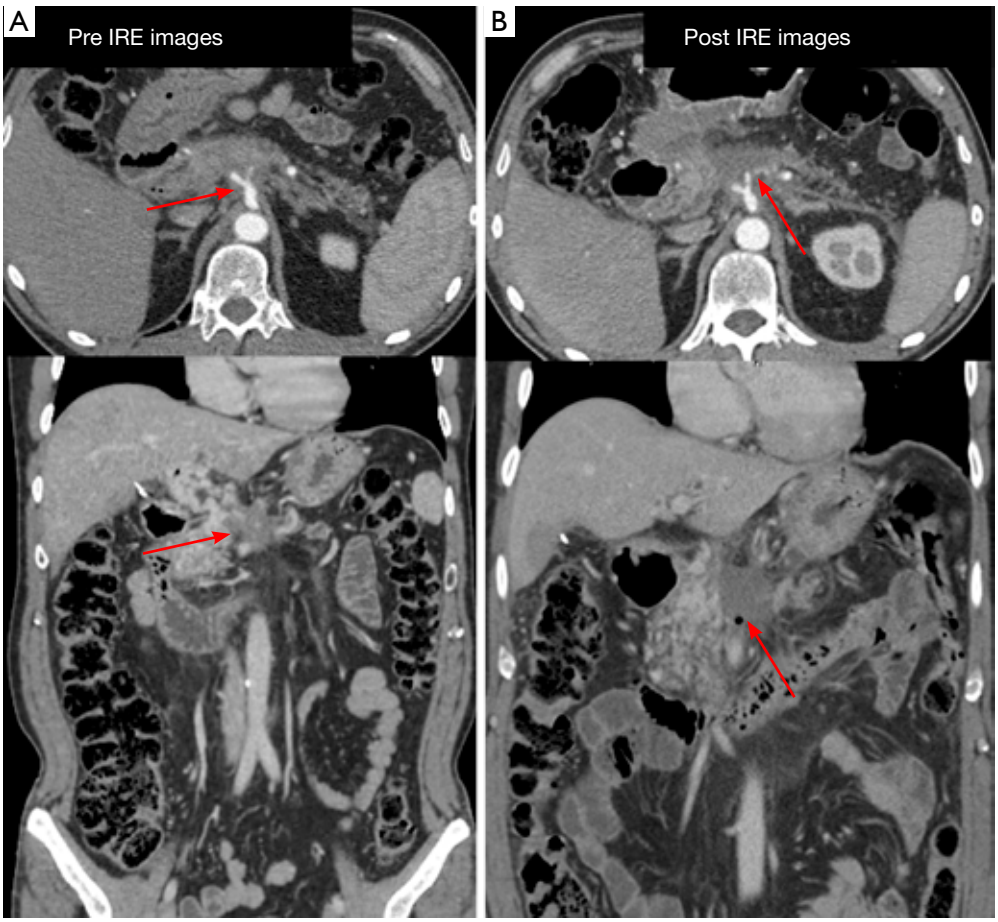

Figure 6 (A) Pre-IRE 3 phase CT of a locally advanced pancreatic cancer in the arterial and venous phase demonstrating clear SMA encasement (arrow); (B) 7 day post-operative 3 phase CT in the arterial and venous phase demonstrating normal post IRE inflammation and edema (arrow). IRE, irreversible electroporation; SMA, superior mesenteric artery.

Because of the underlying tissue edema we have not had to do any specific surgical procedures to control needle site bleeding. At most, if needle placement has punctured one of the small transverse mesocolon vessels, a suture ligature is necessary. It should be noted that continuous intraoperative ultrasound is performed during all IRE delivery in order to assess energy delivery as well as to continually evaluate vascular patency if indeed the treating surgeon feels necessary.

Following treatment a prophylactic gastro-jejunostomy is commonly performed in conjunction with a jejunal feeding tube. An abdominal drain is usually not placed in patients who undergo just *in situ* IRE.

The postoperative management of these patients is fairly standard and follows guidelines for any type of pancreatic resection. The return of gastrointestinal function and the length of stay still remain approximately 6-10 days. An initial efficacy CT scan (*Figure 6*) is not obtained until 3 months post IRE because of the protracted method of action that occurs with IRE. Imaging prior to that will be inaccurate because of the edema and ongoing apoptosis, which is the most common method of IRE induced cell death as demonstrated in large porcine model experiments (16,17). Commonly, re-initiation of systemic chemotherapy is performed before this 3-month CT scan. A patient in whom external beam radiation therapy is felt necessary (i.e., to cover regional lymph nodes) is also initiated prior to this 3-month CT scan if the multidisciplinary team feels necessary.

Discussion

The initial evaluation of this device was first published in May 2012, in which 27 patients with unresectable pancreatic cancer underwent IRE. The group comprised 13 women and 14 men, with median age of 61 years (45-80 years of age). Eight patients underwent margin accentuation with IRE in combination with left-sided resection (n=4) or pancreatic head resection (n=4) with the goal to extend the margin-negative treatment. Nineteen patients had *in situ* IRE for locally advanced unresectable lesions in the head of the pancreas. All patients underwent successful IRE, with intra-operative imaging confirming effective delivery of therapy. All 27 patients demonstrated non-clinically relevant elevation of their amylase and lipase, which peaked at 48 hours and returned to normal at 72 hours post-procedure. There has been a 90-day mortality. No patient has shown evidence of clinical pancreatitis or fistula formation. After all patients have completed 90-day follow up there has been 100% ablation success (11). There was no evidence of intra-operative bleeding, no evidence of pancreatic fistula, no evidence of damage to surrounding viscera. This initial safety profile was then reproduced in a large cohort of 54 patients treated with IRE with a similar adverse event rate and specificity (12). A total of 54 locally advanced pancreatic cancer patients have successfully undergone IRE, a group comprising 21 women and 23 men with a median age of 61 years (45-80 years). These subjects were evaluated for overall survival and propensity matched to 85 matched stage III patients treated with standard therapy, defined as chemotherapy and radiation therapy alone. Thirty-five patients had pancreatic head primary and 19 had pancreatic body tumors, with 19 patients undergoing margin accentuation with IRE and 35 undergoing *in situ* IRE. Forty-nine had pre-IRE chemotherapy alone or chemo-radiation therapy for a median duration of 5 months. Forty (73%) patients underwent post-IRE chemotherapy or chemo-radiation. The 90 day mortality in the IRE patients was one (2%). In a comparison of IRE-treated patients to those receiving standard therapy alone we have seen an improvement in local progression free survival (14 *vs.* 6 months, P=0.01), distant progression free survival (15 *vs.* 9 months, P=0.02), and overall survival (20 *vs.* 13 months, P=0.03).

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None.

Footnote

Conflicts of Interest: The author is consultant for Angiodynamics and the sole person responsible for the creation and editing of this article.

Ethical Statement: The study was approved by the University of Louisville IRB. Written informed consent was obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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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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Footnote

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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	Gem	186	34%	23	
(12,13)	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

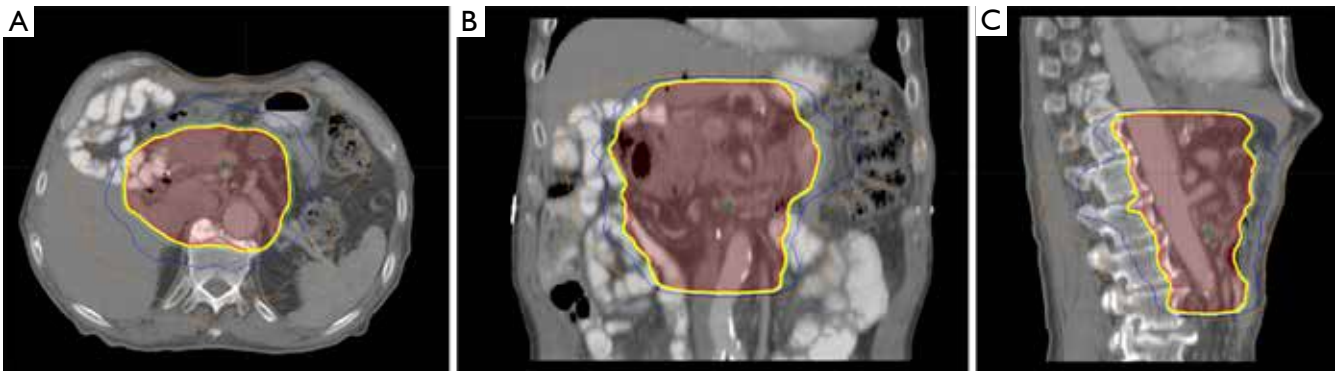

Figure 1 Representative images of an IMRT plan in a patient with PC being treated with adjuvant RT. The shaded red volume represents the target and the bold yellow line depicts the prescription isodose line. Images are (A) axial; (B) coronal; and (C) saggital. IMRT, intensity modulated radiation therapy; 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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Footnote

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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

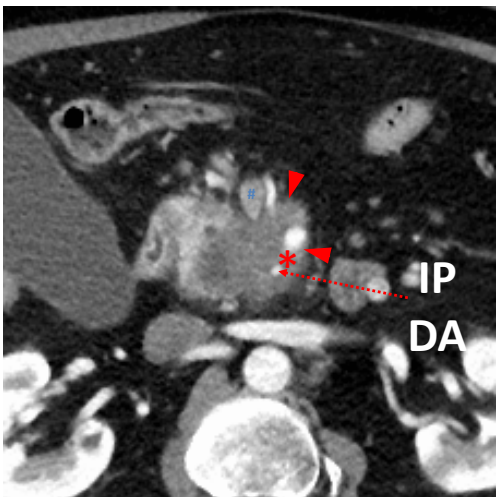

Figure 1 Locally advanced PC. SMA is labelled with * and arrows define the hypodense tumor which encases (>180 degrees) of the SMA. PC, pancreatic cancer.

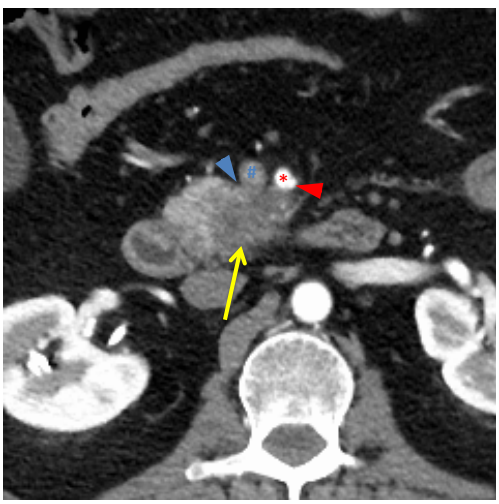

Figure 2 BLR PC. SMV is labelled with # and SMA is labelled with *. Note the hypodense tumor which abuts both the SMV and SMA. BLR, borderline resectable; PC, pancreatic cancer.

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-

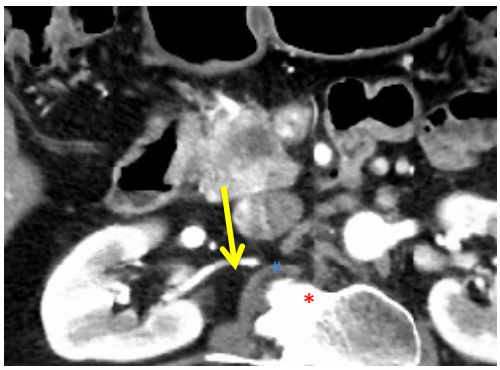

Figure 3 Resectable PC. SMV is labelled with # and SMA is labelled with *. A hypodense tumor is present in the pancreatic head with preservation of the fat plane between the pancreas and the SMV. No tumor abutment of the SMA. PC, pancreatic cancer.

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)

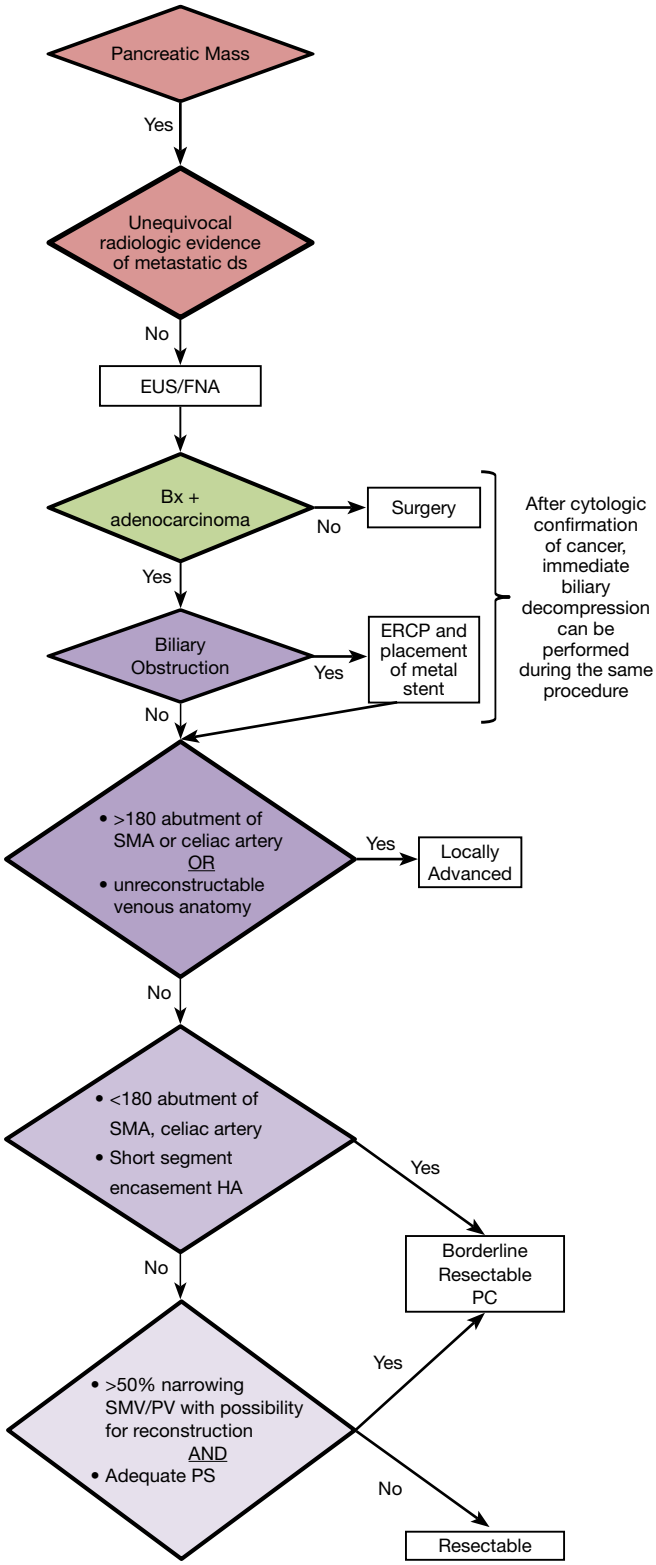

Figure 4 Algorithm for determining clinical disease stage in PC. PC, pancreatic cancer.

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

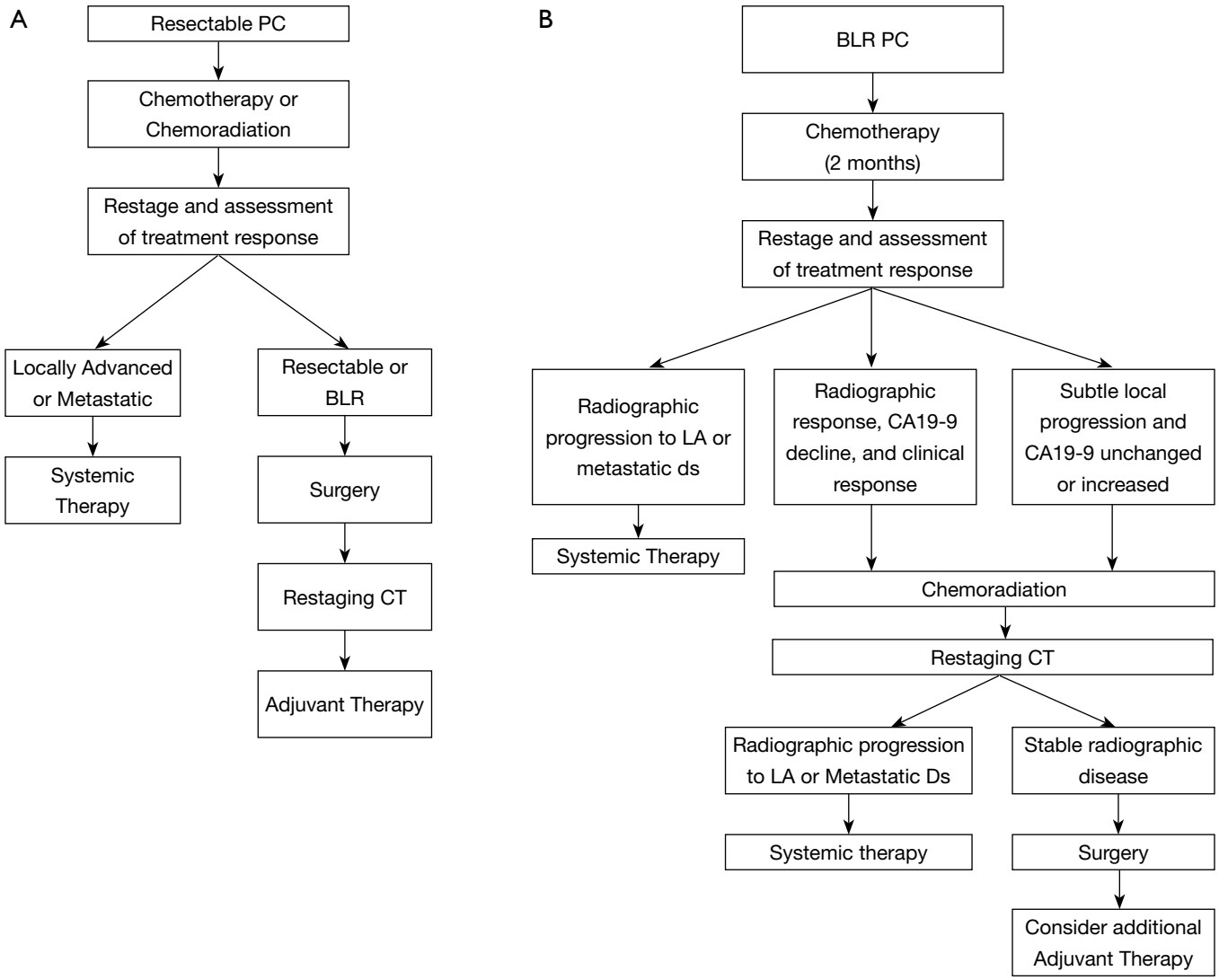

Figure 5 Treatment sequencing in (A) resectable and (B) BLR PC. CA19-9, carbohydrate antigen 19-9; BLR, borderline resectable; PC, pancreatic cancer.

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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Footnote

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Changing paradigm in pancreatic cancer: from adjuvant to neoadjuvant chemoradiation

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Background: Historically, management of pancreatic cancer has been determined based on whether the tumor was amenable to resection and all patients deemed resectable received curative intent surgery followed by adjuvant therapy with chemotherapy (CT) ± RT. However, patients who undergo resection with microscopic (R1) positive margins have inferior rates of survival. The purpose of this study is to identify patients who have undergone pancreatectomy for pancreatic cancer, determine the surgical margins, types of adjuvant therapies given and patterns of failure. Our hypothesis was that in patients who have surgery without pre-operative therapy, there is a high rate of R1 resections and subsequent local recurrence, despite adjuvant therapy.

Methods: Seventy-one patients with curative resections for pancreatic cancer between 2003 and 2015 were reviewed. Tumor stage, margin status, distance to closest margin, receipt of adjuvant therapy and length of survival were collected. Patients were divided into two groups based on whether they received adjuvant CT + RT (n=37) or CT alone (n=37). Patients were further divided based on whether resection was R1 (n=29) or R0 (n=42). Wilcoxon survival tests and Cox proportional hazards regression models were performed to determine the effects of CT + RT *vs.* CT alone, stratified by surgical margin status.

Results: Of the 29 patients (39%) who had R1, 15 received CT + RT and 14 received only CT. Patients who received CT + RT experienced a significantly longer period of PFS (13 *vs.* 7.5 mos, P=0.03) than patients who received CT alone. However, there was no significant difference found in time to death post cancer resection between CT + RT *vs.* CT alone (P=0.73). Of the 42 patients with R0, 21 received CT + RT and 21 received CT. There was a trend towards increase in PFS in patients treated with CT + RT (25 *vs.* 17 months, P=0.05), but there was no significant increase in time to death compared to patients treated with CT alone (P=0.53. Of the 36 patients with CT + RT, 21 had R0 and 15 had R1. Patients with R0 were more likely to have longer PFS (25 *vs.* 13 months, P=0.06), but there was no significant difference in time to death compared to patients with CT alone (P=0.68).

Conclusions: After curative resection, the addition of RT to CT improves PFS in both R0 and R1 settings. However, patients with R1 have significantly worse PFS and OS compared to patients with R0 and even aggressive adjuvant therapy does not make up for the difference. The paradigm has shifted and now for patients with resectable pancreatic cancers we recommend neoadjuvant CT + RT to improve RT targeting and treatment response assessment and most importantly, improve chances of obtaining R0.

Keywords: Pancreatic cancer; adjuvant therapy; chemotherapy (CT); radiotherapy

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Introduction

In 2016 an estimated 53,070 people will be diagnosed with pancreatic cancer and of those 41,780 will succumb to the disease (1). Traditionally, the management of pancreatic cancer has been determined based on whether the tumor was amenable to resection, was unresectable, or metastatic at presentation. To determine resectability of a tumor at the time of presentation is difficult, but is typically based on either computed tomography or magnetic resonance imaging of the tumor and its relationship to surrounding blood vessels. There are various definitions of surgical resectabilty from the Americas Hepato-Pancreato-Biliary Association (AHPBA), MD Anderson, National Comprehensive Cancer Network (NCCN) and Alliance, but the mainstay of resectability is a tumor that is free from contact of the major arterial and venous structures (2).

Resection status is an important prognostic factor for outcome and survival of pancreatic cancer (3,4). However, at the time of diagnosis, many patients have borderline or unresectable cancer, involving the vasculature. Even if a patient's cancer is deemed "resectable" it is possible for the patient to have positive microscopic margins on final pathology. Most commonly, the retroperitoneal margin or circumferential margin is positive, due to the technically difficult location of the tumor (5). Patients with positive microscopic margins (R1) have a poorer prognosis compared to patients with negative margins (R0) (20.3 months for R0 *vs.* 10.3 months for R1) (6).

In the United States, radiation therapy has customarily been used in the adjuvant setting for resected pancreatic cancer (7,8). However, internationally the role of adjuvant radiation is controversial as there are European studies which show no benefit to adjuvant treatment and in fact show a detriment to its use (9). Due to different patient inclusion criteria, radiation doses and schedules, these studies are difficult to compare head to head. One striking difference is that the largest study claiming a detriment to the use of radiotherapy included patients with positive margins (9).

The purpose of this study is to determine whether adjuvant radiotherapy and/or chemotherapy (CT) can compensate for microscopic positive margins at the time of resection. Our hypothesis is that in patients who have surgery without pre-operative therapy, there is a high rate of R1 resections and subsequent local recurrence, despite adjuvant therapy.

Methods

Patient Information

Under Virginia Commonwealth University (VCU) institutional review board approval, a retrospective analysis of patients treated at VCU Health for pancreatic cancer was performed to determine patient criteria and outcomes. Records for 71 patients treated with curative intent for pancreatic cancer at VCU were available in the electronic medical records from 2003 to 2015.

Tumor stage, margin status (positive, negative), distance to closest margin, receipt of adjuvant therapy and length of survival were collected and evaluated. Patients were divided into two groups based on whether they received adjuvant CT plus radiation therapy (n=36) or CT alone (n=35). Patients were further divided based on whether resection was R1 (n=29) or R0 (n=42) (*Figure 1*).

Treatment details

CT and radiation given throughout the study was consistent with few exceptions. Most patients (85.9%, n=61) received gemcitabine at standard doses given over 28 day cycles for a median of 4 cycles (range, 1–6 cycles). Other less common regimens included: gemcitabine plus cisplatin and taxotere (n=1), gemcitabine and abraxane (n=1), folfirnox (n=3), streptozocin and Adriamycin (n=1), capecitabine (n=1), cisplatin and etoposide (n=2), and 5-fluorouracil (n=1). External beam radiation therapy was given with a median dose of 50.4 Gy in 1.8 Gy fractions (range, 23.4–50.4 Gy). About half of the patients were treated with 3D conformal technique (46.5%, n=33) and the rest with intensity modulated radiation therapy (IMRT). Patients received either 5-fluoruracil or capecitabine as concurrent CT during radiation therapy.

Statistical analysis

Baseline characteristics including T and N stages were summarized by frequency and proportion per group. Patients in T stage were dichotomized into two groups: low (T 1–2) and high (T 3–4) T stages. Kaplan-Meier curves and Wilcoxon tests were used to illustrate the difference in the cumulative incidence of time to recurrence and/or death between the patients who did and did not receive radiation therapy or CT, with or without stratification of positive/

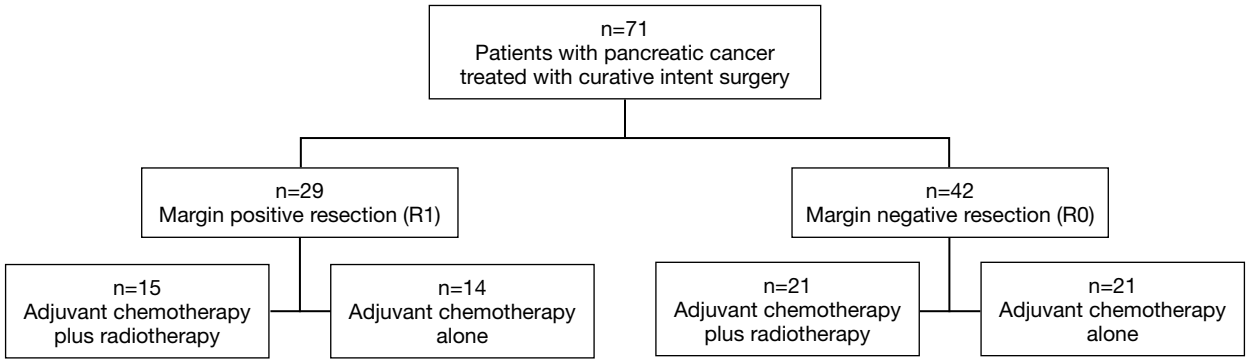

Figure 1 Treatment schema showing all patients divided based on margin status and then receipt of CT *vs.* chemoradiation. CT, chemotherapy.

negative surgical margin, respectively. Cox proportional hazards regression models were performed to model time to recurrence/death to determine the effects of radiation and CT therapy versus CT alone adjusted by potential risk factors such as T and N stages, surgical margin, and/or interaction effect between recurrence and T stage. All computations were performed using SAS® 9.4 Software.

Results

The median age of patients at the time of pancreatic surgery was 62 years old. Approximately half the patients were male (47.9%) and half female (52.1%). 71.8% (n=51) of cancers were located in the head of the pancreas, 8.4% (n=6) were located in the tail of the pancreas, 7.0% (n=5) were in the body, and 4.2% (n=5) in the neck/uncinate process, and 5.6% (n=4) were unreported. The majority (69.0%, n=49) of the cancers were moderately differentiated at final pathology, 8.5%, n=6 patients had well differentiated adenocarcinoma, 14.1%, n=10 had poorly differentiated adenocarcinoma and 8% n=6 were not reported. The median follow up of all patients was 26.6 months. The patient characteristics are outlined in *Table 1*.

Margin positive resection and outcomes

Of the 29 patients (40.8%) who had R1 margins, 15 received CT plus radiation therapy and 14 received CT only. Patients who received CT plus radiation therapy experienced a significantly longer period of progression free survival (13 *vs.* 7.5 months, P=0.03) than patients who received CT alone (*Figure 2A*). However, there was no significant difference found in time to death post cancer resection between CT plus radiation therapy *vs.* CT alone (P=0.73) (*Figure 2B*).

Margin negative resection and outcomes

Of the 42 patients (59.2%) who had R0 margins, 21 received CT plus radiation therapy and 21 received CT alone. There was a trend towards an increase in progression free survival in patients treated with CT plus radiation therapy (25 *vs.* 17 months, P=0.05), but there was no significant increase in time to death compared to patients treated with CT alone (P=0.53) (*Figures 3*).

Radiation therapy and outcomes

Of the 36 patients with CT plus radiation therapy, 21 had R0 and 15 had R1. Patients with R0 were more likely to have longer progression free survival (25 *vs.* 13 months, P=0.06), but there was no significant difference in time to death compared to patients with CT alone (P=0.68) (*Figure 4*).

All patient outcomes

Overall, patients with R0 margins were more likely than patients with R1 margins to have longer progression free survival (median 21 *vs.* 11 months, P=0.03). We did not detect a difference in overall survival between patients with R0 *vs.* R1 margins (P=0.52) (*Figure 5*).

Discussion

This study adds to the literature by showing the importance of R0 resection in patients with pancreatic cancer and

Table 1 Patient characteristics

Characteristics	All patients, n=71 (%)	R0 group, n=42 (%)	R1 group, n=29 (%)
Gender			
Male	34 (47.9)	21 (50.0)	13 (44.8)
Female	37 (52.1)	21 (50.0)	16 (55.2)
Age (years)			
Median	62.0	63.4	61.3
Range	23.6–84.2	23.6–84.2	42.0–80.9
Closest margin (cm)			
Median	0.1	0.1	0
Range	<0.01–1.1	<0.01–1.1	NA
Positive	29	0	29
Not recorded	19	19	0
T stage			
T 1–2	11 (15.5)	9 (21.4)	3 (10.3)
T 3–4	55 (77.5)	31 (73.8)	23 (79.3)
Not recorded	5 (7.0)	2 (4.8)	3 (10.3)
N stage			
LN positive (N1)	42 (59.2)	24 (57.2)	18 (62.1)
LN negative (N0)	27 (38.0)	16 (38.1)	11 (37.9)
Not recorded	2 (2.8)	2 (4.8)	0
Tumor differentiation			
Low	6 (8.5)	4 (9.5)	2 (6.9)
Moderately	49 (69.0)	25 (59.5)	24 (82.8)
Poorly	10 (14.1)	9 (21.4)	1 (3.4)
Not recorded	6 (8.5)	4 (9.5)	2 (6.9)
Tumor location			
Head	51 (71.8)	31 (73.8)	20 (69.0)
Neck/Uncinate	5 (7.0)	2 (4.8)	3 (10.3)
Body	5 (7.0)	4 (9.5)	1 (3.4)
Tail	6 (8.5)	3 (7.1)	3 (10.3)
Not recorded	4 (5.6)	2 (4.8)	2 (6.9)
Radiation therapy			
Treated	36 (50.1)	21 (50.0)	15 (51.7)
CT			
Treated	71 (100.0)	42 (100.0)	29 (100.0)

CT, chemotherapy.

demonstrates that the rate of R1 resection remains high even in carefully selected patients (6,10,11). Nearly 40% of patients considered resectable in our study had positive margins, which is consistent with the current literature (6,12). After curative resection, the addition of radiation therapy to CT improved progression free survival in both R0 and R1 settings. However, patients with R1 had significantly worse progression free survival compared to patients with R0 and even aggressive adjuvant therapy did not make up for the difference.

In other gastrointestinal malignancies such as esophageal and rectal cancers, radiation therapy is used preoperatively and has shown to improve treatment compliance, increase rates of curative surgery with down-staging, have better tumor oxygenation and decreased toxicity compared with postoperative therapy (13-15). In pancreatic cancer, the standard therapy for decades has been to resect upfront if possible and give CT and radiation therapy postoperatively. However, administering radiation postoperatively to the pancreatic bed comes with similar challenges as with other gastrointestinal sites. Treatment with adjuvant therapy is frequently delayed due to surgery and recovery time which potentially gives any residual cancer extra time to progress. Lack of receipt of some or all adjuvant treatment is also common due to decreased nutrition and overall wellness. In fact, anywhere from 25–50% of patients do not complete adjuvant therapy after pancreatic tumor resection for various reasons (16). Other challenges of using adjuvant therapy include determining the areas at highest risk of recurrence postoperatively and administering a high enough dose of radiation in the setting of R1 margins without giving a toxic dose to surrounding organs, particularly the bowel and kidneys.

A recent study from The University of Texas MD Anderson Cancer Center reported higher rates of completion of multimodality therapy in the neoadjuvant compared to the adjuvant setting; further suggesting patients are more likely to receive the full benefit of all modalities with neoadjuvant treatment of CT with or without radiation (17). One of the primary benefits of pre-operative treatment is to "test the biology" of the cancer and not put patients through the operation who have micrometastatic or rapid progressive disease at the time of diagnosis (18). Neoadjuvant therapy will delay surgery long enough that patients unlikely to benefit from the procedure will not be subject to unwanted consequences. This could save the patient from unnecessary suffering and allow for palliative care to be administered earlier.

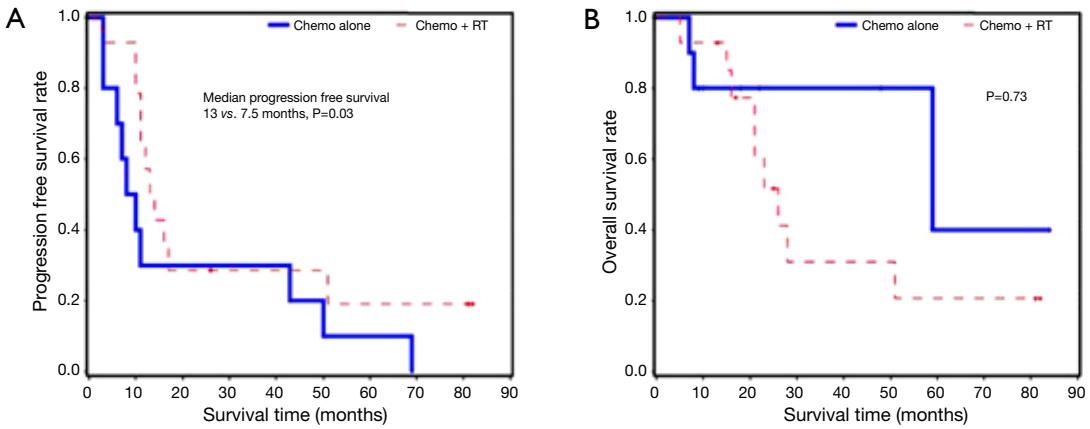

Figure 2 Kaplan-Meier curves for patients with margin positive resection. (A) Progression free survival of patients receiving CT *vs.* chemoradiation; (B) overall survival of patients receiving CT *vs.* chemoradiation. CT, chemotherapy.

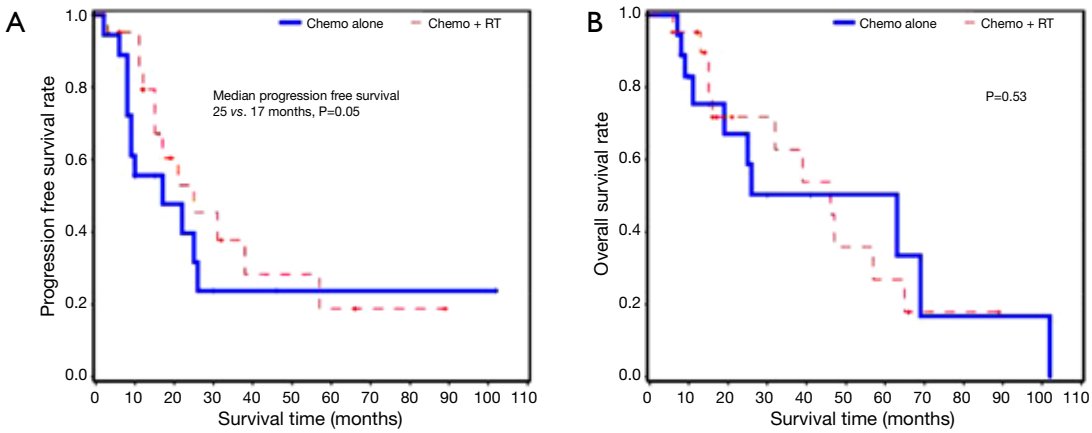

Figure 3 Kaplan-Meier curves for patients with margin negative resection. (A) Progression free survival of patients receiving CT *vs.* chemoradiation; (B) overall survival of patients receiving CT *vs.* chemoradiation. CT, chemotherapy.

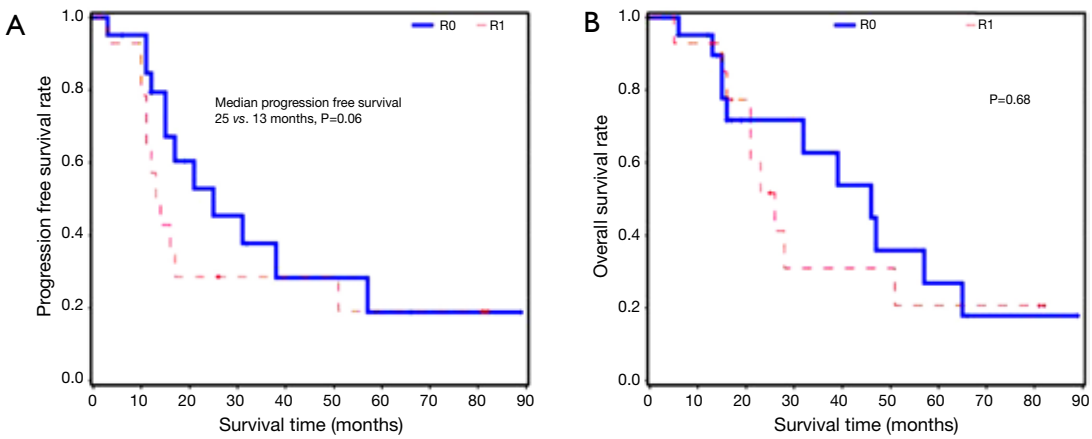

Figure 4 Kaplan-Meier curves for patients who received chemoradiation. (A) Progression free survival of patients with R0 *vs.* R1 resection; (B) overall survival of patients with R0 *vs.* R1 resection.

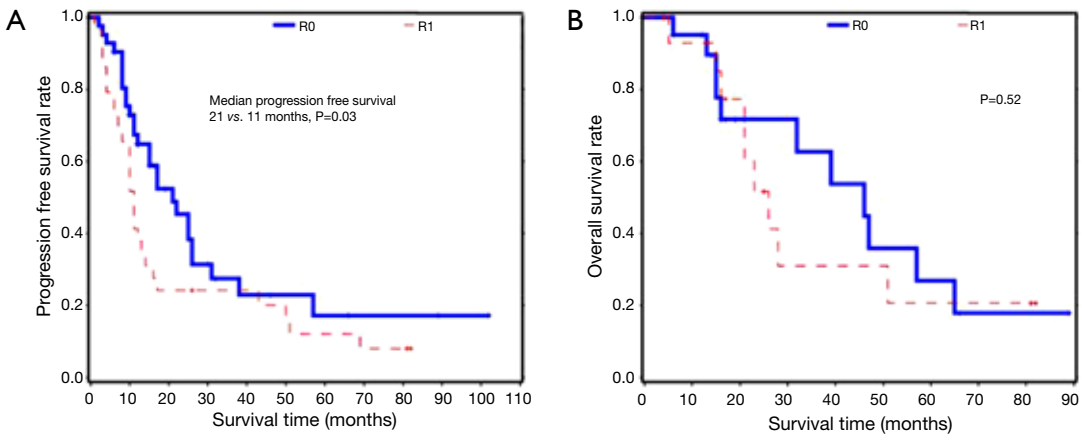

Figure 5 Kaplan-Meier curves for all patients. (A) Progression free survival of patients with R0 *vs.* R1 resection; (B) overall survival of patients with R0 *vs.* R1 resection.

For patients with a good response to neoadjuvant therapy, there are lower risks of R1 resection and their post-operative CT may be tailored to their drug susceptibility (19-21). Based on our results, it is reasonable to propose that neoadjuvant therapy be considered for all non-metastatic pancreatic cancers to increase the chances of R0 margin status. Even when patients are considered resectable they have a high risk of cancer positive margins (6). It is common for patients with borderline resectability to receive neoadjuvant therapy to help them become candidates for surgery. The literature shows that (41–47%) patients with borderline resectability can down-stage and become resectable with neoadjuvant therapy (19,20).

Concerns have been raised about delaying surgery because of the risk of the cancer progressing to unresectable status before the patient receives surgery (3). Despite this risk, the benefits of neoadjuvant therapy are hard to overlook, including increased rates of R0 resections, improved tolerance of treatment, better effect of treatment due to decreased hypoxia, and less patients receiving a morbid operation in the setting of micrometastatic disease. Using neoadjuvant therapy even for patients considered resectable is not a novel idea and is deserving of increased consideration from the medical community (22,23).

Our study has potential bias because of the lack of randomization and its retrospective nature. The power of the study is also limited due to the small sample size. Despite the limitations to our study, our results are similar to many other larger studies and show an increasing need to further investigate the use of neoadjuvant therapy for all patients with non-metastatic pancreatic cancer.

Conclusions

The traditional treatment paradigm of surgical resection followed by adjuvant chemoradiation leaves a high rate of R1 resections and adjuvant therapy is unable to compensate for residual tumor, with increased rates of progression and detriments to OS. This study adds to the growing literature in favor of pre-operative chemoradiation for all potentially resectable pancreatic adenocarcinomas in order to reduce the risk of having R1 positive margins and increase progression free survival and overall survival.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics board of Virginia Commonwealth University (VCU) (No. HM20004325) and written informed consent was obtained from all patients.

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The concept of 'borderline resectable' pancreatic cancer: limited foundations and limited future?

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is traditionally treated by a surgery-first approach. The development and adoption of the concept of borderline resectable PDAC, which extends the role of surgery, is based on the proposition that neoadjuvant therapy (NAT) will increase the resection rate, margin negative rate and overall survival. There are a number of issues with this concept and a critical review of these suggests that it is based on limited foundations and likely has a limited future.

Keywords: Morbidity; survival; mortality; outcomes; research

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Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis. The nihilism surrounding PDAC (1), the deadliest of solid cancers, is based on overall survival data that remain rooted in single digits. The best chance of survival is by surgical resection (2,3) although the chilling reality is that a curative surgical resection (i.e., negative margins or R0) is only possible in a fifth of patients of whom only 20% are alive at 5 years (4). Despite this, a surgery-first approach remains the cornerstone of curative treatment for only a minority of patients with resectable disease because resection has become more safe (5) and effective systemic treatments are still awaited (6). It is no surprise that in the drive to achieve better results some surgeons advocate more radical surgery to treat more patients (7-9). This drive has helped spawn the concept of 'borderline resectable' disease, first proposed 15 years ago (10). The rationale is easy to follow. If patients are likely to be left with residual cancer after resection and if they can be identified before resection it might be possible to down stage the disease by neoadjuvant therapy (NAT). The advantages of this approach are that a higher proportion of patients receive multimodality therapy (11), there is an increase in resection rate (12), negative margin rate (13) and overall survival. This approach also allows time for occult systemic cancer to become evident, during the course of NAT, and thus avoiding futile surgery.

There are several issues with the concept of 'borderline resectable' PDAC (BR-PDAC) and a critical examination of these calls into question the long-term viability of the concept.

Almost all patients have systemic disease when they present with PDAC

It has been calculated that over a decade is required for localised PDAC to develop subclones with metastatic potential, but at the time patients present for treatment the vast majority already have systemic disease (14). This is supported by histopathology examination of early PDAC where perineural and/or lymphovascular invasion is ubiquitous indicating a marked propensity for systemic spread at the time of treatment. This goes some way to explaining the finding that 85% of patient having a 'curative resection' succumb with systemic metastases (15,16). Other evidence that pancreatic cancer might be metastatic from the time patients present

comes from computer modelling (17) and experimental mouse models (18). While exceptions exist, for the majority of patients the 'horse has bolted' by the time they present, as treated or untreated they will die with systemic disease (16). The importance of this is that despite radical surgical resection the outcome will usually be determined by pre-existing systemic disease and whether it responds to NAT, and not the radicality of surgery.

The decision to give NAT requires accurate identification of BR-PDAC

The ability to establish whether it is possible to improve survival by treating BR-PDAC with NAT has been hampered by the 'imprecise continuum between radiologically and technically resectable and unresectable disease' (19). There are no less than seven different published definitions of BR-PDAC (20) all of which use ambiguous terms (e.g., abutment, impingement, narrowing, encasement, invasion, and adherence) and an arbitrarily determined measurement (e.g., ≥180° of circumference). Interpreting and comparing studies of NAT for BR-PDAC is difficult because they use these different definitions, chemotherapy and radiation therapy protocols and are typically small retrospective studies. Even if proponents of the BR-PDAC concept achieve consensus on accurate definitions, the prognostic relevance of the elements and reliability of their interpretation still need to be determined.

The selection of patients with BR-PDAC for NAT relies on anatomic criteria, which are not 'fit for task'

The various definitions of BR-PDAC are based on the relationship of computed tomography (CT)-detectable tumour to adjacent vessels. The problem is that the anatomic extent of tumour is often difficult to determine and the extent does not indicate the aggressiveness of the tumour, the likelihood of systemic metastases, or responsiveness to NAT. This is not to say that anatomic elements do not have some prognostic significance, but that they are not sufficient for selecting patients. It is known, for instance, that there is a worse outcome if more than 3 cm of the portal/superior mesenteric vein is involved (21,22) and if there is microscopic invasion through to the intima of the vein (23). Staging CT scanning can identify the former, but not the latter. A fresh approach to pre-operative staging is needed to provide criteria that will advance our decision-making, allow tailoring of treatment and permit more accurate prediction of outcome. In short, we need biologic and not anatomic criteria to select patients. It has been suggested that different patterns of failure in PDAC indicate distinct morphological and genetic subtypes with different patterns of metastases (24). For instance, an intact SMAD4/DPC4 gene might be used to select patients for pancreatic resection (25) as this is associated with a lower risk of distant metastases (24). Recently an integrated genomic expression analysis of 456 PDACs convincingly demonstrated that PDAC represents four distinct subtypes; squamous, pancreatic progenitor aberrantly differentiated endocrine exocrine (ADEX) and immunogenic types (26). The future of preoperative staging will involve pre-treatment tumour sampling and targeted genomic analysis to allow accurate selection of patients for tailored treatments. When this occurs the importance of anatomic criteria will rapidly fade.

It is not known if NAT improves the negative margin rate after resection

The justification for giving NAT to patients with BR-PDAC is not only to treat occult systemic disease, but also to reduce the risk of a positive resection margin (27). Confirming the latter is problematic because the risk of a positive margin in patients with BR-PDAC who do not receive NAT has not been determined. Thus the actual contribution of NAT to reducing the risk of a positive margin is not known because the available evidence is of low level and conflicting. A systematic review found that the R0 resection rates between tumours considered resectable and unresectable before NAT were not different after resection (82.1% *vs.* 79.2%) (28). This suggests that NAT did not increase the negative margin rate after resection. There is other evidence suggesting the reverse, that neoadjuvant combined therapy leads to a higher negative resection margin rate (13,29), which suggests that the addition of radiotherapy is essential to achieve a reduced R0 rate. While the objective of NAT is down-staging, the reality is that more often the effect is one of down-sizing, and this occurs in less than a third of patients (30). Neoadjuvant FOLFIRINOX has shown some promise with down-staging (31), but it is too toxic for many elderly patients. The ALLIANCE trial (32) has tested neoadjuvant chemotherapy followed by radiation therapy and failed to demonstrate an improvement in resection rates. Whether NAT increases the negative margin rate remains to be established.

It is not known if NAT improves overall outcome in patients with BR-PDAC who are resected

The ultimate proof for the concept of BR-PDAC would be to demonstrate that NAT improves overall survival. Evidence for this is not available as there have been no randomised clinical trials designed to test whether NAT in patients with BR-PDAC (or those with resectable disease, for that matter) improves overall survival (29,33). Lower levels of evidence suggest that combination NAT does not improve disease-free or overall survival (13). Therefore this question remains wide open. Whether the widespread adoption of the concept of BR-PDAC has effectively destroyed the practical equipoise necessary to conduct such trials (32) is untested. Any perceived survival advantage from NAT in patients with BR-PDAC, when compared with those with unresectable disease, might be due to other factors, including the latter harbouring more advanced stage disease, a higher incidence of preoperative arterial involvement and intraoperative incidental metastasis (34). While the primary question remains unanswered, there are considerable efforts being made to answer secondary questions such as which combinations of chemotherapy are most effective and whether radiotherapy should be included. Surely our best efforts should be directed towards determining whether NAT confers any survival advantage (35).

Accurate re-staging of BR-PDAC after NAT is not possible

Images from re-staging CT scans after NAT are difficult to interpret (36), because it is not possible to distinguish residual tumour, scarring from tumour regression, tumour desmoplasia, or inflammatory changes from NAT itself. This difficulty in accurately selecting which patients should proceed with resection means that the *a priori* decision for NAT almost inevitably commits a patient with BR-PDAC to a trial dissection after NAT, providing distant metastases do not arise in the interim. This almost certainly results in an increased proportion of patients undergoing trial dissection and synchronous vein resection (36), and probably without a reduction in the R1/R2 rate (37). Whether it is possible to more accurately stage the margins of concern with endosonography and fine needle aspiration for cytology remains to be seen (38). Whether adjunctive techniques such as 'margin accentuation' by irreversible electroporation can increase the R0 rate in this setting also remains to be seen (39,40). The inability to accurately re-stage patients with BR-PDAC after NAT remains an unsolved problem.

If NAT is indicated for patients with BR-PDAC, why is it not indicated for all those with PDAC?

The benefits of NAT, in terms of improved R0 rates and survival, might be more readily demonstrated in patients with resectable PDAC than BR-PDAC. Given the propensity for systemic spread in all patients with PDAC, the logical question is whether it should be indicated for all patients with PDAC (41). This question was vociferously debated over breast cancer many years ago. The Halsted concept of the primacy of radical local surgery, which probably retarded progress for almost a century, was successfully challenged by the Fisher concept of systemic therapy (42), using randomised controlled trials to demonstrate the importance of NAT. A similar revolution appears to be occurring in some centres that are now offering NAT for T1 and T2 PDAC. It is time to acknowledge that PDAC, even more than breast cancer, is a systemic disease at the time of presentation and that restricting NAT to a subgroup of patients (i.e., BR-PDAC) denies potential benefits for patients with resectable disease. Over-reliance on a surgery-first approach for PDAC has retarded progress. The reality is that surgery and even more radical surgery, though well intentioned, has not yielded acceptable results (9,37). And while we can be pleased that there has been a significant decrease in pancreatoduodenectomy-related morbidity and mortality over the last 3 decades (5), the efficacy of surgical treatment has reached its ceiling (5).

The foundations on which the concept of BR-PDAC has been proposed, developed and implemented are not strong. While extending the role of surgery to encompass a subgroup of patients with BR-PDAC who are down-staged by NAT has considerable appeal, the evidence to support this approach is relatively sparse. The reality is that despite our advances in staging, NAT and surgery there has been little impact on survival.

The future treatment of PDAC will be very different. NAT will become the standard of care for all patients with PDAC and will be tailored and targeted to subgroups of patients based on genomic analysis of their tumour. Patients at low risk of systemic metastases will be offered resection after NAT to confirm tumour kill and remove any residual viable cancer. Patients at high risk of systemic metastases

may not be offered surgical resection at all. While the concept of BR-PDAC has raised awareness about the importance of NAT for PDAC, the limited foundations and remaining issues suggest that it has a limited future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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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

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)

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, 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 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.

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

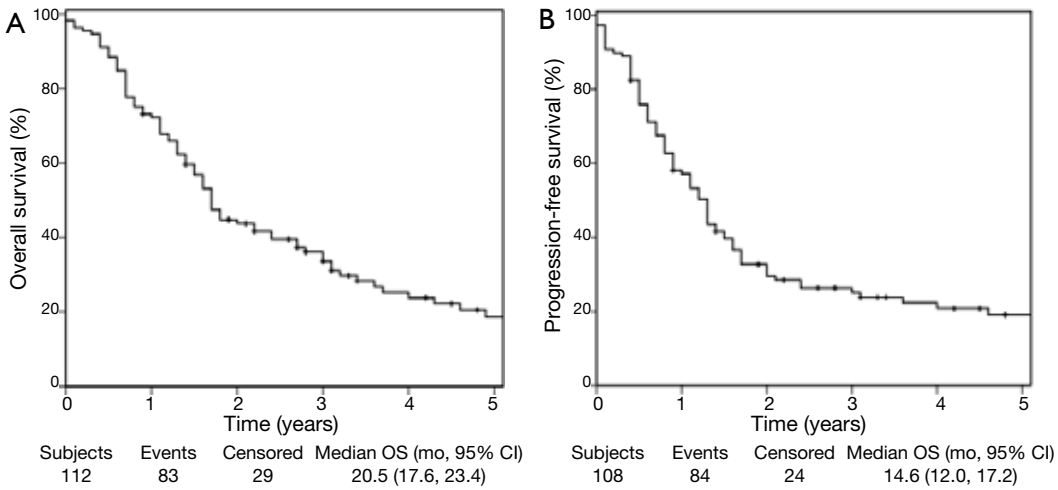

Figure 1 Kaplan-Meier survival curve of (A) overall survival (OS); (B) progression-free survival (PFS).

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).

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. 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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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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