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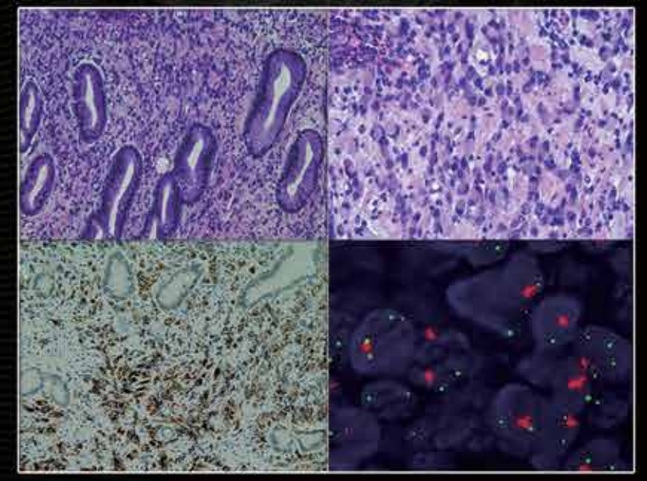

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Gastric Cancer
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Gastric cancer is still one of the most common cancers in China, though there is a remarkable decline in gastric cancer mortality in the entire population during the last two decades. The management of gastric cancer has also been evolving over the past two decades. Early diagnosis and treatment is believed to be the key to improving the prognosis of gastric cancer. However, there is no nationwide prevention project and screening program on gastric cancer now, thus early detection of gastric cancer can only rely on opportunistic screening.

Rapid development of economy in recent years has provided the opportunity to improve the poor dietary habit and some advanced progress of medical technology, making more and more novel technologies widely applied. For example, endoscopic resection has become the standard treatment for early gastric cancer and the role of laparoscopic treatment for early gastric cancer has progressively been recognized.

Although surgery is still the primary treatment option for gastric cancer, the treatment model has undergone significant changes: the previously used simple gastrectomy has been replaced by radical approaches aiming at lymph node dissection; and anatomy-based operations are giving their place to an integrated mode that combines standardized surgery and perioperative adjuvant therapies based on anatomy, tumor biology and immunology, especially the use of modulation traditional Chinese medicine to management the pre-cancer diseases of the stomach. Multidisciplinary approach plays a more and more significant role in the prevention and treatment of gastric cancer.

This new book entitled *Gastric Cancer*, edited by Prof. Jiafu Ji, was born at this point, well illustrating the up-to-date knowledge and advanced techniques in the area of gastric cancer, adding the precious experience of experts across the world. From prevention, early detection and diagnosis to treatments, from wonderful surgical video-presenting to basic researches, the book will show readers a vivid picture of the management of gastric cancer.

I'm of great honor to be invited to write this preface for this comprehensive book on gastric cancer and here would like to congratulate the editors as well as the authors on the success of this forthcoming book. I hope researchers can always find an article from this magnificent book interesting and could benefit from it.

Yan Sun, MD.
March 10, 2015

It is my pleasure to write this preface for the book on Gastric Cancer and I would first like to congratulate the authors and editors for their valuable efforts in making this comprehensive guidebook available. There is no doubt that their generous work will be rewarding.

As is known, gastric cancer is a heterogeneous disease with large variations across geographical regions.Although the global incidence of gastric cancer is declining, it remains a worldwide public health problem especially in Asia.China is one of the countries with the highest incidence of gastric cancer, and accounts for large percentage of all new cases in the world. By saying that, gastric cancer has become the third leading cause of cancer mortality in China.

However, there is currently no international consensus on the treatment regimen of gastric cancer and clinical practice varies widely across countries. With the concept of multidisciplinary treatment widely accepted, and the development of medical technologies, the strengths of various treatments based on evidence will be the key to management of gastric cancer for ultimately improving the outcomes and quality of life of these patients.

The book on gastric cancer gives an emphasis in addressing these aspects and aim to usher us into the new dawn in ongoing gastric cancer research. By putting together the experience of internationally well-known experts, the book will benefit the clinicians and researchers on gastric cancer where in-depth discussion will be initiated.

The book will never bore its reader with a progressive outline and“popup” of interesting case-series study. Also, the surgical research was consolidated by the featured Chapter of surgical videos, designed as a “how to”surgical manual. Joining the audiovisual reading experience, the reader can surely enjoy the book a lot more.

While there is still much challenge that we face today in gastric cancer, it is assured that we are embracing an optimistic future through the international cooperation and communication. Also, international conferences like the International Gastric Cancer Congress (it is excited that the12thInternational Gastric Cancer Congress will be held in China in 2017), National Gastric Cancer Academic Conference, ASCO, Best of ASCO, CSCO and others represents a good opportunity in the endeavor.

I look forward to more inspired collaboration through the academic frontier that the book opens up and I wish you delightful journey in the book.

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Controversies in the diagnosis and management of early gastric cancer

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Jiafu Ji

Early diagnosis and treatment is the key to improving the prognosis of gastric cancer. The past decades have witnessed the rapid advances in the diagnosis and management of early gastric cancer (EGC): endoscopy has played an increasingly important role, whereas laparoscopic techniques have also been introduced for EGC treatment. In China, the proportion of EGC is gradually increasing, and this condition will soon become a hot research topic. In this article, we will elucidate some major controversies in the diagnosis and management of EGC.

Ambiguities in the diagnosis of EGC

Ambiguity of definition

According to the Japanese Gastric Cancer Association, EGC is defined as a lesion of the stomach confined to the mucosa and/or submucosa, regardless of its area or the lymph node metastatic status (1). According to their morphological appearance under endoscope, EGC has been classified as type I (protruded), type II (superficial), type III (excavated), and the mixed type, among which the type II lesions are further subdivided into IIa (elevated), IIb (superficial spread), and IIc (depressed) (2). Obviously, the Japanese classification of EGC is an endoscope-based clinical diagnosis.

Currently, the most commonly used staging system for gastric cancer remains the TMN system, which is based on the post-operative pathology. The TNM system, however, does not define EGC. The EGC in the Japanese "gastric cancer" classification is roughly equal to the T1 gastric cancer in the TNM system. The prognosis of EGC and the treatment decision-making should be based on the post-operative pathology. In other words, the diagnosis of EGC need to be based on both clinical diagnosis and pathological staging.

Differences in diagnostic criteria

The criteria for the pathological diagnosis of EGC differ between China and Japan. In China, the Vienna classification of gastrointestinal epithelial neoplasia was applied, i.e., a gastric cancer is diagnosed only when the tumor at least invades deeper than the lamina propria mucosae. In Japan, in contrast, the gastric cancer is diagnosed based on cellular

atypia or structural atypia rather than the depth of invasion. Therefore, some of the EGC cases diagnosed in Japan may be the atypical hyperplasia or high-grade adenoma/dysplasia in China. Thus, special attention must be paid when citing relevant literature authored by our Japanese colleagues.

Accuracy of clinical staging

Treatment decision-making depends on the tumor stage. Currently we are unable to accurately determine the EGC. Before the initiation of endoscopic treatment, the infiltration of EGC [localized within the mucosa layer (T1a) or has already invaded the submucosa layer (T1b)] as well as the lymph node metastatic status must be accurately identified.

T staging: accurate staging by endoscopic ultrasonography and high-resolution CT

In recent years, along with the rapid advances in endoscopic treatment, particularly the optimization of endoscopic submucosal dissection (ESD), the indications of ESD for EGC has extended from T1a to some of T1b cases (3,4). Endoscopic ultrasonography remains the most reliable technique for T staging; however, its accuracy rate (roughly 80%) is still not satisfactory (5).

N staging: lymph node metastatic status

The lymph node metastatic status varies greatly among EGC patients due to the difference in the depth of tumor invasion. The lymph node metastasis rate was 3% if the tumor was localized within the mucosa layer but could reach 20% when the tumor invaded the submucosa layer (6). Identification of the lymph node metastatic status for pre-operative staging is particularly challenging and currently no satisfactory method has been available. Multiplanar reformation (MPR) has an accuracy rate of 78% for lymph node staging in gastric carcinoma patients (7); for EGC, the accuracy rate can be even lower.

The accuracies of sentinel lymph node (SLN) detection in identifying EGC were diverse and therefore its role is highly debatable (8,9). Notably, its false-negative rate (FNR) reached 15-20% in literature (10,11). Therefore, SLN detection can not be a standard technique for the screening of EGC.

Various treatment options

EGC can be cured by standard radical surgery, with the 5-year survival rate exceeding 90%. However, the radical surgery will inevitably impair the quality of life. How to minimize the surgical scope and improve quality of life has became a hot research topic in this field. Up to now endoscopic resection and modified radical surgery have been listed as the standard treatment.

Endoscopic resection

Endoscopic resection has become the standard treatment for EGC. Endoscopic mucosal resection (EMR) is feasible for differentiated mucosal cancer sized <2 cm and without any ulcer. On the contrary, ESD enables the en bloc resection of the lesion, has larger resection scope, and can be applied in patients with ulcer(s). Therefore, ESD is superior to EMR (12). In 2000, Gotoda *et al.* analyzed the clinical data of 5,265 surgically treated EGC patients and found that the risk of lymph node metastasis were low under the following conditions: there was an extremely low risk of lymph node metastasis in cases that were (I) differentiated intramucosal cancers without ulcer findings, irrespective of tumor size, (II) differentiated intramucosal cancers less than 3 cm in size with ulcer findings, and (III) differentiated minute invasive submucosal cancers less than 3 cm in size (13). Notably, endoscopic resection of EGC should be based on pre-operative examinations and post-operative pathology, during which the lymph node metastatic status, depth of lesion invasion, and size of tumors can be identified. All the postoperative specimens should underwent continuous slicing and histopathologic examinations, which are helpful to judge whether the lesion has been completely removed. Salvage surgery may be performed for patients with vascular infiltration and invasion as well as those with lymph node metastasis.

In most EGC patients, the metastatic lymph nodes are localized within the group 1 lymph nodes. About 5% of submucosal gastric cancers may be associated with the metastasis in the group 1 lymph nodes, mainly in lymph nodes 7, 8a, and 9 (14,15). Therefore, for EGC patients who are not eligible for endoscopic resection, dissection of the ablove lymph node stations are reasonable, and often can achieve good outcomes (16).

Laparoscopic surgery

The role of laparoscopic treatment for EGC has progressively been recognized. A multicenter prospective

phase III clinical study has demostrated that the laparoscopic procedures were better than the early gastric cancer surgery. As a safe and feasible technique, its short-term efficacy is better than the open surgery (17). In fact, laparoscopic wedge resection (LWR), pylorus-preserving distal gastrectomy (PPG), and vagus nerve-preserving gastrectomy have been applied in EGC patients without any risk of lymph node metastasis.

The laparoscopy-endoscopy cooperative surgery has also been applied for the treatment of EGC. It combines the endoscopic submucosal dissection with laparoscopic gastric wall resection, which prevents excessive resection and deformation of the stomach after surgery.

Challeges associated with new techniques

The proportion (about 10%) of the diagnozed EGC remains low in China. Both laparoscopy and endoscopy hath high technical requirements, and the training of medical professionals in this regard often takes a long period of time. Endoscopic or laparoscopic treatment is highly depended on accurate clinical staging and judgment, with the ultrasouic endoscope being the required equipment for the clinical diagnosis of EGC. Without ultrasouic endoscope and experienced endoscopy specialists, these new procedures could not be introduced. Also, we can not simply copy the Japanese experience, because the diagnostic criteria used in Japan and China are somehow different. Investigations on the new techniques for EGC should only be performed in major hospitals, in which some relevant clinical trials may be conducted. Finally, the implementation of these new techniques for EGC calls for the close cooperation among medical staff from the departments of endoscopy, pathology, and surgery.

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Gastric Cancer is a major public health issue and is currently ranked in the top four cancers for new cases and deaths worldwide and in both developed and developing countries. There are almost 1,000,000 new cases of gastric cancer annually and almost as many deaths around the world, with over two-thirds of these cases coming from developing countries. The majority of cases arise from Asia, Eastern Europe and South America. There is an urgent need to improve diagnostic testing and treatment options for patients with gastric cancer and to improve and expand screening programs in high risk areas of the world.

This first edition book on "Gastric Cancer" which has been edited by Professor Jiafu Ji contains articles taken from AME journals and include numerous authors with global expertise in the diagnosis and management of gastric cancer patients. The topics included in this edition are quite extensive and cover the diagnosis, multidisciplinary approach, surgical research, chemotherapy, targeted therapy, radiation therapy, and translational research. In addition, there is a novel section which includes 35 surgical video articles in the book. This book will be a great resource and update on the cutting-edge advances made in the diagnostic approaches and treatment modalities available to clinicians.

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I would like to acknowledge the great efforts made by Dr. Zhaode Bu for his assistance in putting together the book, as well as Drs. Eslick, Kim, Ahn, and all other excellent authors who have together contributed to the book. I would also like to express my gratitude to Profs. Yan Sun and Daiming Fan for their support and inspiring words. Excellent job done by editorial staffs of AME Publishing Company is also appreciated, promising the best shape of the book.

Jiafu Ji, MD, FACS
Beijing, China

Table of Contents

Multidisciplinary Approach

Surgical Research

Surgical Video

Chemotherapy

Targeted Therapy

Radiation Therapy

Translational Research

Editorial

Multidisciplinary approach for the treatment of gastric cancer

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Gastric cancer remains a worldwide public health problem especially in Asia. Over the past decade, the pattern of gastric cancer has considerably changed. Despite declining rates of distal gastric cancer, a trend of significant increasing in the incidence of proximal gastric cancer has been observed in the United States, Europe and Asia (1,2). The histology, tumor biology and clinical course are quite different between the two types of the gastric cancer. For example, diffuse histologic pattern and aggressive clinical course are frequently seen in the proximal gastric cancer. Nonetheless, the management of these two types of gastric cancer remains the same in the current practice.

The management of gastric cancer has been evolving over the past two decades. Complete surgical resection remains the corner stone for the cure of localized early stage gastric cancer. Issues investigated and debated over the past 20 years have focused on the extent of lymphadenectomy (D1 *vs*. D2 dissection) with the goal of delivering an optimal cancer operation while limiting morbidity. Although D2 dissection has been the standard practice in Japan and most Asian countries, major Western studies, the "Dutch trial" (3,4) by Bonenkamp *et al*. and The British MRC ST01 trial (5), failed to show survival benefit of D2 dissection. These trials were criticized by poor quality control of participating surgeons. Despite these negative large randomized studies, most physicians consider that D2 dissection is advantageous due to more precise staging. This notion is supported by the stage migration phenomenon first reported by Bunt and colleagues in 1995 (6). Today, extended lymphadenectomy with pancreas and spleen preservation (known as "over-D1") is generally practiced at major centers in the United States.

Adjuvant chemoradiation with 5-fluouracil (5-FU) and leucovorin has been the standard practice in the United States for the past twenty years. INT-0116 is a phase III randomized trial in which 603 patients with resected adenocarcinoma of the stomach or gastroesophageal junction (stages IB-IVM0) were randomized to either observation or combined modality therapy consisting of five monthly cycles of bolus chemotherapy with 45 Gy radiotherapy concurrent with cycles 2 and 3 (7). Patients in the INT-116 trial represented a high-risk group and 85% of the patients in both arms had lymph node involvement. After a median follow-up of 5 years, 3-year relapse free survival rates (48% *vs*. 31%; P<0.001), and hazard ratios for relapse (HR=1.52, 95% CI: 1.23-1.86) significantly favored adjuvant chemoradiotherapy. More significantly, OS rates (50% *vs*. 41%; P=0.005), hazard ratio for death (HR=1.35, 95% CI: 1.09-1.66), and median OS (36 mo *vs*. 27 mo; P=0.0005) were also significantly improved in the chemoradiation group. Outcome data in this trial was updated in January 2004 after a median follow-up of 7 years (8). The major endpoints of the trial: OS (HR=1.31, 95% CI: 1.08-1.61), DFS (1.52, 95% CI: 1.25-1.85) were unchanged from the initial analysis.

Postoperative radiotherapy is not commonly practiced in Japan and other Asian countries. Adjuvant chemotherapy trials in the US have been disappointing. Recently, Japanese adjuvant trial is most intriguing (9). A total of 1,059 patients with stage II or III gastric cancer who underwent D2 surgical resection were randomized to either observation or one year oral S-1 adjuvant therapy. S-1 (Taiho Pharmaceutical) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract) in a molar ratio of 1:0.4:1. The 3-year overall survival

was improved in the S-1 group (80.1% in S-1 group *vs.* 70.1% in the observation group; P=0.003). The toxicity profile was very favorable. Although S-1 may impact the clinical practice in Asian population, the results of this agent in Western population are rather disappointing as demonstrated in the First Line Advanced Gastric Cancer Study (FLAGS) (10). This may be due to biological differences between patient populations as to how the drug is metabolized.

Preoperative chemoradiation and perioperative chemotherapy provide benefit to down-stage the primary tumor and eliminate micrometastasis early on. In addition, the preoperative therapy is generally better tolerated. The most compelling evidence for perioperative chemotherapy is the phase III UK Medical Research Council Adjuvant Gastric (MAGIC) trial (11). A significantly better overall survival (HR=0.75; 95% CI: 0.60-0.93; P=0.009; 5 year survival rate of 36% *vs.* 23%) and progression free survival (HR=0.66; 95% CI: 0.53-0.81; P<0.001) was achieved in the perioperative group. The trial was criticized for its non-standardized surgery, potentially inaccurate preoperative staging due to the absence of laparoscopy, and a relatively poor outcome in the surgery alone group. The recent large phase III preoperative chemotherapy studies, MRC OEO2 and intergroup 8911, had complete different conclusions (12). However, these two studies population enrolled predominant esophageal cancer. In the OEO2 study, a total of 802 were randomized to either preoperative chemotherapy with 2 cycles of cisplatin and 5-FU followed by surgical resection or surgery alone. The study demonstrated a benefit of overall survival for the preoperative chemotherapy group with a 16% risk reduction (HR=0.84, 95% CI: 0.72-0.98; P=0.03). However, the intergroup 8911 did not support overall survival advantages.

Several neoadjuvant studies have demonstrated that complete pathological response (pCR) is indicative of better prognosis. Chemotherapy alone hardly achieves pCR. Preoperative chemoradiation generally produces approximately 25% pCR. Most recently, Van Hagen and co-workers published a randomized phase III study to compare preoperative chemoradiation followed by surgery to surgery alone (13). The study enrolled 368 patients that were treated with surgery alone or carboplatin and paclitaxel concurrent with radiotherapy followed by surgery. The median overall survival was 49.4 months in chemoradiation group and 24 months in surgery only group (P=0.003). A 29% pCR was achieved in the chemoradiaiton group. The study demonstrated a superior survival benefit with combined modality.

Clinical data demonstrated that multidisciplinary approach is usually required to achieve maximum clinical benefit. The current Chinese guidelines by Ji *et al*. has included the most updated and comprehensive information in diagnose and treatment of gastric cancer. The guidelines clearly endorse multidisciplinary approach in managing this disease. The guidelines will provide a standard practice in Chinese Oncology arena and minimize practice variations. Importantly, such guidelines put a step forward to bring Chinese patient population into international clinical trials, which will certainly offer a tremendous opportunity to further understand tumor biology, pharmacogenetics and epidemiological aspects of gastric cancer.

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Editorial

A current view of gastric cancer in China

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Abstract: Gastric cancer is a heterogeneous disease with large variations across geographical regions. Although the global incidence of gastric cancer is declining, it remains highly prevalent in Asia as compared to the West. China is one of the countries with the highest incidence of gastric cancer, and accounts for over 40% of all new gastric cancer cases in the world. Gastric cancer is the third leading cause of cancer mortality in China. Gastric cancer in Chinese patients is different from that occurring in the West, and is a significant health burden. Moreover, there is currently no internationally accepted standard treatment regimen and clinical practice varies widely across countries. With the development of medical technology and wide application of more and more novel technologies, evidence-based approaches in combination with the strengths of various treatments will be the key to multidisciplinary management of gastric cancer for ultimately improving the outcomes and quality of life of these patients.

Keywords: Gastric cancer; surgery; chemotherapy; radiotherapy; quality of life

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Introduction

Gastric cancer is a heterogeneous disease with large variations across geographical regions (1). Although the global incidence of gastric cancer is declining, it remains highly prevalent in Asia as compared to the West (2,3). China is one of the countries with the highest incidence of gastric cancer, and accounts for over 40% of all new gastric cancer cases in the world (4,5). Gastric cancer is the third leading cause of cancer mortality in China (6,7).

Epidemiology

In China, the latest data about national statistics of incidence and mortality on cancer was published in the beginning of this century. The incidence and mortality of cancer was derived from population-based cancer registries. In a survey of Chinese cancer registration practices in 2002, 48 population-based cancer registries were identified. They covered 5.7% of the national population. An estimate was made using data on incidence and mortality from registries. It is estimated that the five leading cancers in terms of incidence in the year 2000 were lung, stomach, liver, esophagus, and colon-rectum for men; and breast, stomach, lung, liver, and esophagus for women. In the year 2005, the second and third ranks are reversed in both sexes; the others are the same as in 2000. The total estimated number of new cancer cases increased by 11.7% in men (from 1.3 to 1.4 million) and 19.3% in women (from 0.8 to 1 million). Only cancers of the esophagus (for both sexes) and stomach (in male) showed a decline in the number of cases during these 5 years (8).

For gastric cancer, age-standardized incidence rates were 41.9 (per 100,000) for male and 19.5 for female in the year 2000. The age-standardized incidence rates were 37.1 for the male and 17.4 for the female in 2005. The age-standardized mortality rates were 32.7 for male and 15 for female in the year 2000. It is estimated to be 28.8 for the male and 13.3 for the female in 2005. In 2005, 0.3 million deaths and 0.4 million new cases from gastric cancer ranked the third most common cancer (9). The age-standardized mortality rates of stomach cancer were 40.8 and 18.6 for

males and females, making stomach cancer the leading cause of cancer death in the 1990s (10). There is a remarkable decline in gastric cancer mortality in the entire population during the last two decades. These declines were largely due to the improvements in the social-economic environment, lifestyle, nutrition, education and health care system after economic reforms started three decades ago. Nevertheless, gastric cancer remains a significant cancer burden currently and should be one of the key issues in cancer prevention and control strategy in China.

Screening and early gastric cancer

There is no nationwide screening program on gastric cancer. Early detection of gastric cancer therefore relies on opportunistic screening only (11). Now, endoscopy is widely available in urban and rural areas. The same as the western countries, most gastric cancer was diagnosed at advanced stage. Early gastric cancer rate is increasing gradually, and now the number is about 10% (12). Early gastric cancer has excellent outcomes from surgery, with a 5-year survival rate higher than 90%. In China, most surgeons consider D2 lymphadenectomy the standard and optimal surgical procedure for patients with early gastric cancer.

Advanced gastric cancer

Surgery is the crucial treatment for gastric cancer. Complete resection with adequate margin is widely considered as a standard. Most of treatment opinions in China were adopted from Japan. The margin requires >5 cm from the gross tumor. There is still controversy worldwide about whether D1 or D2 lymphadenectomy for gastric cancer is better. The western investigators have not found a survival advantage when extensive lymphadenectomy compared with a D1 resection. The Dutch Gastric Cancer Group Trial and British Cooperative Trial failed to demonstrate a survival benefit for D2 over D1 lymphadenectomy (13,14). In addition, the D2 dissection was associated with increased postoperative morbidity and mortality. Based on these results, D1 lymphadenectomy has been performed routinely for gastric cancer in Western countries. The higher morbidity and mortality rates of D2 lymphadenectomy may be due to the learning curve and higher body mass index of patient in Western countries. Conversely, in Asian countries including China, gastrectomy plus D2 lymphadenectomy is the standard treatment for curable gastric cancer.

In China, while the majority of gastric cancer occurs in the distal part of the stomach, the incidence of proximal gastric cancers is increasing. For a curative gastrectomy, it is necessary to dissect the lymph nodes in the splenic hilum and the lymph nodes along the splenic artery. Splenectomy has been recommended to facilitate lymph node dissection. The frequency of metastasis to lymph nodes at the splenic hilum or along the splenic artery ranges from 8-10% (15). Splenectomy was an important risk factor for postoperative morbidity and mortality (16). Splenectomy has not yet shown superiority on survival compared to splenic preservation. Routinely performing splenectomy is not recommended (17). For T3 proximal gastric cancer patients with No. 10 lymph node metastasis, total gastrectomy with splenectomy is recommended (18).

D2 + PALD (para-aortic nodal dissection) was once expected to be more beneficial. Compared with standard D2, D2 + PAND did not have any overall survival benefit. Even though the D2 + PALD can be performed safely by well-trained gastrointestinal surgeons, with an acceptable rate of complications, its survival benefits are not significantly better than those of standardized D2 lymphadenectomy. Therefore, D2 plus PALD is not performed routinely in China (19).

Minimally invasive technologies

Endoscopic mucosal resection (EMR) is suitable to treat early-stage gastric cancers without invasion into submucosa. Compared with conventional resection through open gastrectomy, similar long-term survival and curative effect can be achieved by EMR, preserving a good quality of life. EMR has been routinely recommended for early gastric cancer in Japan. Because of the low incidence of early gastric cancer, its applicability in China is very limited.

Laparoscopic resection is an emerging surgical approach with important advantages when compared with open surgical procedures. A few big hospitals in China began to explore the feasibility of this technique in gastric cancer (20,21). The role of this approach in the treatment of gastric cancer requires further investigation in large randomized clinical trials.

Radiation and chemotherapy

Radiation therapy is considered an integral of treatment for gastric cancer in the western hemisphere. In China, it is not recommended routinely. There are two reasons. One is most lesions in China located in distal stomach,

radiation is not reasonable approach; the other, D2 lymph node dissection is considered enough for local therapy. Chemotherapy can provide both palliation and improve survival in patients with metastatic disease. In china, most of the active agents such as taxol, docetaxel, irinotecan, oxaliplatin, capecitabine are available in urban areas.

The British medical research council performed the first well powered phase III trial for perioperative chemotherapy (22). The results of the study have established perioperative chemotherapy as a standard care for patients with operable gastric cancer. Preoperative chemotherapy is gradually accepted by physicians. In China, a phase III multi center neoadjuvant chemotherapy clinical trial on locally advanced gastric cancer sponsored by the Ministry of Science and Technology was carried out from 2006. It was the first time that national government sponsored clinical trial on gastric cancer; most of the clinical trials in China were sponsored by the drug companies.

Summary

In the last few decades, there is a notable decline in incidence and mortality rates in gastric cancer in China. Early gastric cancer rates have increased gradually. Although there is discrepancy between rural and urban areas, the treatment of gastric cancer is standardized. EUS and high resolution CT are used for staging. A multidisciplinary treatment decision-making meeting was organized before treatment. The outcome of gastric cancer improved greatly in China. In large hospital center, the 5-year survival of gastric cancer has improved from 40.1% to 57.6% (23-25). There still is considerable distance compared with the data of Japan (26). In view of the fact that most cases are in advanced stage, this is a great achievement. China has the largest population of gastric cancer in the world. It should play a more important role in the control of gastric cancer. In 2008, NCCN guidelines were introduced into China formally. Chinese physicians joined the global clinical trails (27). An increasing number of Chinese physicians are now trained in Japan and the West.

In conclusion, gastric cancer in Chinese patients is different from that occurring in the West, and is a significant health burden. Moreover, there is currently no internationally accepted standard treatment regimen and clinical practice varies widely across countries. With the development of medical technology and wide application of more and more novel technologies, evidence-based approaches in combination with the strengths of various treatments will be the key to multidisciplinary management of gastric cancer for ultimately improving the outcomes and quality of life of these patients.

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Editorial

Management of gastric cancer: the Chinese perspective

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Gastric cancer in China

Gastric cancer (GC) is a heterogeneous disease with large variations across geographical regions. Although the global incidence of GC is declining, it remains highly prevalent in Asia as compared to the West (1). China is one of the countries with the highest incidence of GC, and accounts for over 40% of all new GC cases in the world (2). GC is the third leading cause of cancer mortality in China (3).

Regional differences in patient outcomes and response to treatment in GC have also been observed. In a study comparing GC patients in the Memorial Sloan-Kettering Cancer Center in New York City (n=711) with those from Korea (n=1,646), the disease-specific survival for Korean patients was significantly better after adjusting for all known confounding factors (hazard ratio of 1.3, P=0.05) (4). Similarly in the AVAGAST trial, a phase III study of first-line chemotherapy plus bevacizumab in advanced GC, the intrinsic prognosis of Asian patients was shown to be better than Americans; however, the addition of bevacizumab to chemotherapy improved the survival of American patients only (5). Regarding safety in systemic treatment for GC, a meta-analysis of 8 Asian and 17 Western or international trials showed that geographical region (Asian *vs.* non-Asian) was an independent predictor, with Asian trials associated with lower incidence of grade 3-4 neutropenia and diarrhea (6).

There are postulations that these geographical differences in epidemiology and patient outcomes may be explained by distinct tumor biology and etiology. A number of gene polymorphisms, including those of the DNA repair gene XRCC1, were found to be associated with GC risk in the Chinese population (7-10). Other studies suggested differential prevalence of oncogene mutations in China and other parts of the world. For example, while RAS mutations were reportedly rare in Western Europe and Japan, their prevalence in China was up to 30% (11-13). The prevalence of *PIK3CA* mutations was however much lower in a Chinese cohort than generally reported (14). Furthermore, differences in GC genetic instability patterns across geographical origins may also exist, as suggested by a study comparing African patients and those from the United Kingdom (15).

The high prevalence of *Helicobacter pylori* (*H. pylori*) infection and the local circulating genotypes being highly carcinogenic (16) are of particular etiological significance in China and contribute to the geographical difference. A randomized placebo-controlled primary prevention trial in China demonstrated a reduction in GC development with eradication of *H. pylori* in the subgroup of healthy carriers without precancerous lesions at baseline, although the overall incidence of GC in the eradication and placebo groups was similar at 7.5 years (17). The association between the decline in *H. pylori* prevalence in China and the decline in gastric cancer incidence was also reported by an epidemiological study (18).

Other environmental factors such as lifestyle, diet and socioeconomic status play a role in gastric carcinogenesis. China is the largest tobacco production and consumption country in the world, consisting of more than 300 million current smokers (19), and GC risk among the Chinese population is significantly associated with tobacco smoking as shown in a meta-analysis (20). The Chinese taste for preserved, salty, fried foods and hot soup, and the low intake of certain vitamins and micronutrients are associated with risk of GC (21). Concordantly, dietary supplementation of nutrients such as vitamin C, selenium and carotene was shown in prevent GC in Chinese (22,23) but not in Caucasian populations (24,25).

On the other hand, part of the perceived geographical difference in GC may simply be related to regional variation in the prevalence of different GC subtypes and their different prognosis. While proximal tumors are more common in industrialized nations and tumors of the intestinal histology in Asia, there is no evidence that patient outcomes for particular subtypes differ between regions (26). Different patient outcomes may also be explained by variation in population screening programs; at diagnosis tumors are generally of earlier stage in Korea that in the United States (4).

Taken together, GC in Chinese patients is different from that occurring in the West, and is a significant health burden. Moreover, there is currently no internationally accepted standard treatment regimen and clinical practice varies widely across countries. An updated guideline specific for the Chinese population is therefore warranted. The *Gastric Cancer Diagnosis and Treatment Expert Panel of the Chinese Ministry of Health: Chinese guidelines for diagnosis and treatment of gastric cancer (2011 edition)* ("*the Chinese Guidelines*") *are timely published in the latest issue of Translational Gastrointestinal Cancer* (27). While the Chinese Guidelines provide a comprehensive account in the scientific area, a few points will be highlighted here.

Surgical and adjuvant treatment

Extended (D2) lymph node dissection is recommended in the Chinese Guidelines as the standard surgery for operable GC except for early disease limited to the mucosa or submucosa with no lymph node involvement. Although D2 resection is regarded as the standard of care in Asia, its role has been more controversial in the West, where previous trials failed to show any survival advantage with D2 over D1 dissection (28-31). However, more recent long-term follow-up results of a Dutch trial showed D2 surgery was associated with a lower rate of disease-related death than D1 surgery (32). Given that other reports from Western countries confirmed better outcomes with D2 surgery when performed in experienced centers (33-35), latest Western guidelines now recommend the inclusion of D2 dissection as the standard surgery for GC (36).

Adjuvant treatments currently used in the West, including peri-operative chemotherapy (37) or post-operative chemoirradiation (38), were established before D2 surgery became standard. The less aggressive surgery may explain the benefits of the more intensive adjuvant treatments. On the other hand, post-operative chemotherapy alone is effective as adjuvant treatment after D2 surgery in Asian trials (39,40). Moreover, a Korean study comparing chemotherapy with or without radiotherapy after D2 surgery did not show improved outcomes with the addition of radiotherapy (41). These findings support the choice of adjuvant therapy based on the level of surgery (D2 versus D0/1) performed, as detailed in the Chinese Guidelines.

Systemic therapy for advanced disease

Systemic options to treat advanced GC including chemotherapy and targeted therapy are similar in the East and West. In particular, the addition of trastuzumab to chemotherapy significantly improved response, progression free survival and overall survival in advanced GC patients with human epidermal growth factor (HER)-2-positive disease, defined by immunohistochemical (IHC) staining 3+ or fluorescence in-situ hybridization (FISH)-positive, in the phase III ToGA trial (42). The greatest benefit was seen in patients with higher levels of HER2 expression with either IHC3+ or IHC2+ plus FISH+. HER2-positive rate is higher in gastroesophageal junction (GEJ) than gastric cancers, and in the intestinal subtype than diffuse types (43). Although there is a lower percentage of GEJ carcinoma and a higher percentage of diffuse-type histology in Asia (6), interestingly the average HER2-positivity rate for European countries is similar to that observed in Asian countries (44). To date, trastuzumab is the first and only targeted agent in gastric cancer approved by both the United States (45) and European authorities (46). It is indicated in combination with cisplatin and capecitabine or 5-fluorouracil in the first line treatment of HER2-overexpressing advanced GC; strong HER2 expression with IHC3+ or IHC2+ plus FISH+ is required by the European and Chinese guidelines.

The development of other targeted agents in advanced GC has however made slower progress. The addition of bevacizumab to chemotherapy did not result in significant OS benefit in the phase III AVAGAST trial (5); more recently the results of the REAL-3 study in abstract form reported an inferior OS with the addition of panitumumab to chemotherapy (47). Data on other agents are still awaited. Currently, prospective biomarker-driven clinical trials dedicated to specific patient populations enriched with rational molecular targets are lacking. The population-based difference in the epidemiology and possibly biology of GC calls for international collaboration in future biomarker and clinical studies.

Alternative therapy

The Chinese Guidelines included traditional Chinese medicine (TCM) to be considered as part of supportive care for GC. TCM is a holistic system of medicine including herbal medicine, acupuncture and moxibustion, tuina, dietary therapy, and qigong (48). There has been a long history of using TCM in treating various diseases including cancer in China. It is believed that TCM may lead to potential benefits such as reducing side effects of chemotherapy and radiotherapy, improving patients' immune function, and enhancing the effects of conventional cancer treatments (49).

Despite the plethora of case reports and series on TCM in cancer care (48,50), large-scale well-designed clinical trials are lacking. Nevertheless, a recent report on 399 advanced GC patients with or without TCM treatment (51) represents the increasing effort to study TCM scientifically. Moreover, the Chinese government has approved the use of some Chinese herbal remedies in cancer treatment (49). It is therefore likely that TCM will continue to play a unique role in China.

Conclusions

The Chinese Guidelines addresses the need for population-specific recommendations on the management of GC. They help to arouse awareness of GC among the Chinese community, and to standardize clinical practices across China.

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Editorial

The first step on earth: a small step for a trial, a giant leap for mankind

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Gastric cancer is the second leading cause of cancer-related deaths worldwide (1). The 5-year survival rate is about 75% in resected patients with the early stage of the disease. However, the prognosis worsens with lymph node involvement, which predicts an increase in the probability of loco-regional and distant recurrences. As a result, there is a great interest in adjuvant therapies for resected gastric cancer patients over the last 40 years.

As a result of the INT0116 trial, a postoperative chemoradiotherapy became the standard treatment for stages II-IV in gastric cancer patients who underwent D0/D1 resections in the United States (2). The INT0116 trial found that postoperative chemoradiotherapy improved the 3-year survival from 41% to 50%, compared to surgery alone. In Europe, following the results of the MAGIC trial, perioperative chemotherapy has been accepted as standard care for gastric cancer with an improved 5-year survival from 23% to 36%, compared to surgery alone (3). Most of the patients in both the INT0116 and MAGIC trials underwent D0/D1 resections since the two large European trials that compared D1 and D2 resections failed to demonstrate any survival benefit of D2 over D1 resections (4,5). However, 15-year follow-up results of a Dutch trial showed a gastric cancer-specific survival improvement with a D2 resection (6). In Asia, a single-center Taiwanese trial found that a D2 resection led to better survival outcomes than a D1 dissection (7). As a result, the D2 resection is now recommended for gastric cancer not only in Asia but in Europe and the US as well.

The ACTS-GC trial was the first multicenter prospective randomized study that showed the benefit of adjuvant chemotherapy for gastric cancer patients who underwent D2/D3 resections. A total of 1,034 Japanese patients were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 (517 patients) or surgery alone (526 patients). The three-year survival rates were 80.1% and 70.1% in the S-1 and control group, respectively (P=0.003). The 5-year follow-up results of the ACTS-GC trial reconfirmed that 1 year of treatment with S-1 improved the OS and RFS compared to the surgery alone (8).

Moreover, the ACTS-GC trial showed the clinical significance in terms of demonstrating natural survival outcomes and a pattern of recurrence after D2/D3 resection in gastric cancer patients. However, there were some limitations in this trial. First, the ACTS-GC trial was performed only in Japan. Recently, the CLASSIC trial was performed in Asian (Korea, China, and Taiwan) (9). It is the second largest randomized trial for adjuvant chemotherapy in gastric cancer patients. It demonstrated that combination chemotherapy with capecitabine and oxaliplatin after a D2 gastrectomy improved the 3-year DFS compared to the surgery alone. The ACTS-GC and CLASSIC trial used the D2/D3 and D2 resections, respectively, for all patients since the D2 resection is the standard method of surgery in East Asia. Unfortunately, the benefits of the adjuvant chemotherapy in these trials might not be easily extrapolated to populations who commonly received D1 resections in Western countries. Second, in the subgroup analysis of the ACTS-GC trial, the more advanced stages showed a trend of decreasing benefits for adjuvant S-1 monotherapy. We therefore need to investigate more potent adjuvant regimens for advance stage gastric cancer patients, especially considering the disappointing survival outcomes in stage IIIB patients (disease-free survival rate of 37.6% at 5 years). Third, we also should consider the treatment duration and dose intensity in the ACTS-GC trial to choose a better regimen for future adjuvant trials. Only two thirds of all patients completed the 1-year treatment in the

Table 1 Survival rates

Study	3-year survival rates		5-year survival rates	
	Surgery only (%)	Adjuvant therapy (%)	Surgery (%)	Adjuvant therapy (%)
INT0116	41	50	28	43
MAGIC‡	31	44	23	36
ACTS-GC	70	80	61	72
CLASSIC	78	83	N/A	N/A

‡, The patients of the MAGIC trial received perioperative therapy rather than adjuvant therapy.

ACTS-GC, while the CLASSIC trial had a shorter duration of treatment with a higher dose intensity using doublets. Fourth, it should also be noted that the peritoneum was the most frequent recurrence site although patients with positive peritoneal fluid cytology were excluded. Previous Japanese studies have reported a treatment effect of S-1 for peritoneal metastasis, which was not definitely shown in the ACTS-GC study. S-1 adjuvant chemotherapy reduced the incidence of recurrence, but the pattern of recurrence did not change at all. It emphasizes the necessity of a new treatment strategy again for resected advanced gastric cancer. Fifth, there are some limitations of the data quality with different patient follow-up schedules between the adjuvant chemotherapy and surgery alone groups. Finally, the follow-up loss rate was relatively high (12.4%) probably due to too many participating centers.

All of the four trials (INT0116, MAGIC, ACTS-GC, and CLASSIC) demonstrated the clinical significance of adjuvant chemotherapy for gastric cancer. But overall, the survival rates of the ACTS-GC and CLASSIC trials were quite better than those of the INT0116 and MAGIC trials (*Table 1*), which mean that curative D2 surgery is the most important factor for gastric cancer.

In summary, the ACTS-GC was the first randomized prospective trial showing the benefits of adjuvant chemotherapy after D2/D3 resections in gastric cancer patients. However, it is necessary to investigate the proper adjuvant regimen for patients with more advanced stages and those who underwent D1 resection (high remaining tumor burden from non-curative surgery compared to the D2 resection) based on the limitation of the S-1 monotherapy efficacy in the ACTS-GC trial.

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Editorial

Can the ARTISTs complete the Schubert Unfinished (Sinfonie Nr. 7 in h moll D. 759 "Die Unvollendete")?

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Surgery, chemotherapy, and radiotherapy are proven treatment options for gastric cancer. D2 lymph node dissection has become a standard surgical technique after its usefulness was demonstrated by Sasako and colleagues as well as based on the findings of a 15-year follow-up in the Dutch Gastric Cancer Group assessed by Songun and colleagues (1,2).

Compared with D2 dissection alone, the survival time was prolonged in the S-1 monotherapy arm in the ACTS-GC study by Sakuramoto and colleagues and in the XELOX therapy arm in the CLASSIC study by Bang and colleagues. Both studies reported the usefulness of adjuvant chemotherapy even in patients treated with D2 dissection. The subgroup analysis in the ACTS-GC study showed the surgery/adjuvant chemotherapy combination was useful for the treatment of stage II to IIIA gastric cancer treated with S-1 alone but not for cancer of stage IIIB or higher. On the other hand, the CLASSIC study showed the usefulness of XELOX therapy in all cancer stages (II to IIIB), suggesting the combination therapy will be required for the treatment of stage IIIA or higher gastric cancer (3,4).

The Intergroup 0116 study reported a prolonged survival time in patients treated with chemotherapy in combination with radiotherapy. However, most enrolled patients were treated with D1 dissection (5). In this context, the ARTIST study, performed to evaluate the usefulness of adjuvant chemoradiotherapy in patients treated with the standard D2 dissection, is interesting (6).

The 53.2-month follow-up data from the ARTIST study revealed that the treatment completion rate was 75.4% in the XP arm and 81.7% in the XP/XRT/XP arm. While the XP/XRT/XP therapy was shown to be highly tolerable, no prolonged disease-free survival (DFS), the primary endpoint, was unfortunately demonstrated in this treatment arm. Although the subset analysis showed the DFS was longer in lymph node positive patients in the XP/XRT/XP arm, the ARTIST study has certain limitations.

First, do patients with stage IB or II cancer treated with D2 dissection really require chemoradiotherapy? These patients may be overtreated with postoperative chemoradiotherapy. Sasako and colleagues reported a 5-year DFS of 79.2% in patients with stage II cancer treated with D2 dissection followed by S-1 monotherapy only for 1 year (7). Japanese epidemiological data showed the 5-year survival rate from 80% to 90% in patients with stage IB cancer with the primary lesion in the gastric antrum and body (8).

Second, was XP appropriate adjuvant chemotherapy? The treatment completion rate was 81.7% in the XP/XRT/XP arm; however, grade 3 or higher adverse reactions were reported at much higher frequencies in the study arms compared with in patients with advanced gastric cancer treated with XP therapy (with CDDP at 80 mg/m2) in the ML17032 study reported by Kang and colleagues (9).

Based on the greater usefulness of XELOX therapy compared with adjuvant chemoradiotherapy reported by Bang and colleagues and the greater usefulness of EOX for advanced esophagogastric cancer compared with ECX suggested by Cunningham and colleagues (10), the combination of XELOX and XP therapy may be more desirable than XP alone. The combined XELOX and radiotherapy was more useful as a preoperative treatment for rectal cancer compared with adjuvant chemotherapy. A nonclinical study reported that oxaliplatin and radiotherapy upregulated thymidine phosphorylase, which converts capecitabine to 5FU in the tumor, suggesting a greater antitumor effect compared with other treatment (13,14).

Thirdly patients with diffuse type histology have poor outcome in N0116 study (15), in which chemoradiation benefited all subsets with the exceptions of women and diffuse

histology. It is obvious that no selection by histopathology, in other words, not excluding diffuse histology might have negative impact on this study.

Finally, was the duration of treatment appropriate? XP and XP/XRT/XP were used for 18 weeks in the ARTIST study. Adjuvant S-1 was used for 1 year in the study performed by Sakaramoto and colleagues (3). A JCOG study is about to start to determine the Optimal Period of Adjuvant S-1(OPAS-1, JCOG1104, UMIN000007306), to confirm non-inferiority of 4 courses (24 weeks) of S-1 adjuvant chemotherapy to 8 courses (1 year) of the same regimen in relapse-free survival in patients who underwent D1+/D2 gastrectomy and were diagnosed pathologically with stage II gastric cancer. Bang and colleagues used the XELOX therapy for 6 months. Whether the 6-month duration is recommended as it is for the adjuvant chemotherapy for colon cancer should be considered (4).

At any rate, the ARTIST study was definitely underpowered. The doctors should attempt another study based on a new protocol with more appropriate selection of patients, concomitant chemotherapy, and duration of treatment. May the ARTISTs play a beautiful harmony with perioperative chemoradiotherapy in patients with gastric cancer to complete the Schubert Sinfonie Nr. 7 in h moll D. 759 "Die Unvollendete".

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Editorial

Treatment strategies in node-negative gastric cancer

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Lymph node metastasis is the most important prognostic factor in gastric cancer (1-3). Curative resection including adequate lymphadenectomy provided the chance of a cure for localized disease. However, node-negative gastric cancer patients undergoing extensive lymphadenectomy also experience recurrence and distant metastases (4,5). In the issue of *Journal of Gastrointestinal Surgery*, Liu and colleagues (6) show that the invasion in lymphatic or vascular vessels, and depth of tumor invasion were independent prognostic factors in node-negative gastric cancer and therefore suggest considering the use of adjuvant therapies in patients with high risk for recurrence. However, it should be argued that only 234 (5.3%) gastric cancer patients undergoing curative D2 gastrectomy were free of lymph node metastasis and 67 T1 tumors (28.6%) and none of T4 tumor reported in their study. Quite different from their findings, our previous study (tumor staged according to the seventh edition of the American Joint Committee on Cancer Staging Manual) demonstrated that node-negative gastric cancer with more than 15 lymph nodes dissected accounted for 41.3% of patients undergoing radical resection and there were 358 T1 (48.4%) and 226 T4 tumors (30.5%) (5). Furthermore, our results indicated that tumor size >5 cm, T4 status and perineural invasion were independent prognostic factors in T1-4 node-negative gastric cancer (*Table 1*). Patients with T1-T3 lesions had 95.0% of 5-year overall survival rates, higher than 85.0% reported by Liu *et al.* (6). Given the fact that T1 gastric cancer without nodal involvement has an excellent prognosis and an extremely low recurrence rate, adjuvant therapy is not beneficial (5,7). In this regard, Chou *et al.* reported predictive factors for recurrence patterns in node-negative advanced (T2-4) gastric cancer and revealed that depth of tumor invasion predicted locoregional recurrence and peritoneal seeding; tumor size and perineural invasion were associated with hematogenous spread (4). Our recent study also suggested that extensive lymphadenectomy with >25 lymph nodes retrieval has survival benefit in patients with node-negative advanced gastric cancer (5). Furthermore, a recent systemic review showed that the presence of intraperitoneal free cancer cells documented by washing cytology test is associated with peritoneal recurrence and worse overall survival in gastric cancer patients (8). Taken together, adjuvant therapies should be considered in node-negative advanced gastric cancer patients with unfavorable factors for recurrence and those with inadequate lymphadenectomy to improve patient outcome (*Figure 1*).

Table 1 Multivariate analysis of prognostic factors in node-negative gastric cancer patients with >15 lymph nodes dissected

Factors	N (%)	5-year survival rate (%)	Hazard ratio (95% CI)	P value
Tumor size (cm)				
≤5	619 (85.4)	92.4	1	
>5	106 (14.6)	75.1	1.987 (1.209-3.266)	0.007
T status*				
T1	356 (48.6)	96.4	1	
T2	119 (16.3)	90.2	1.695 (0.800-3.594)	0.169
T3	36 (4.9)	97.0	0.443 (0.059-3.329)	0.429
T4	221 (30.2)	77.4	3.008 (1.602-5.647)	0.001
Location				
Upper	97 (13.3)	89.3	0.865 (0.387-1.934)	0.725
Middle	154 (21.0)	93.7	1	
Lower	469 (64.1)	89.1	1.370 (0.761-2.464)	0.294
Whole	12 (1.6)	63.6	3.865 (0.848-17.604)	0.081
Lymphatic invasion				
No	679 (95.4)	90.0	1	
Yes	33 (4.6)	80.2	1.004 (0.422-2.389)	0.992
Perineural invasion				
No	588 (17.9)	92.6	1	
Yes	128 (82.1)	76.2	1.728 (1.034-2.889)	0.037

*, according to the seventh edition of the American Joint Committee on Cancer Staging Manual; CI, confidence interval.

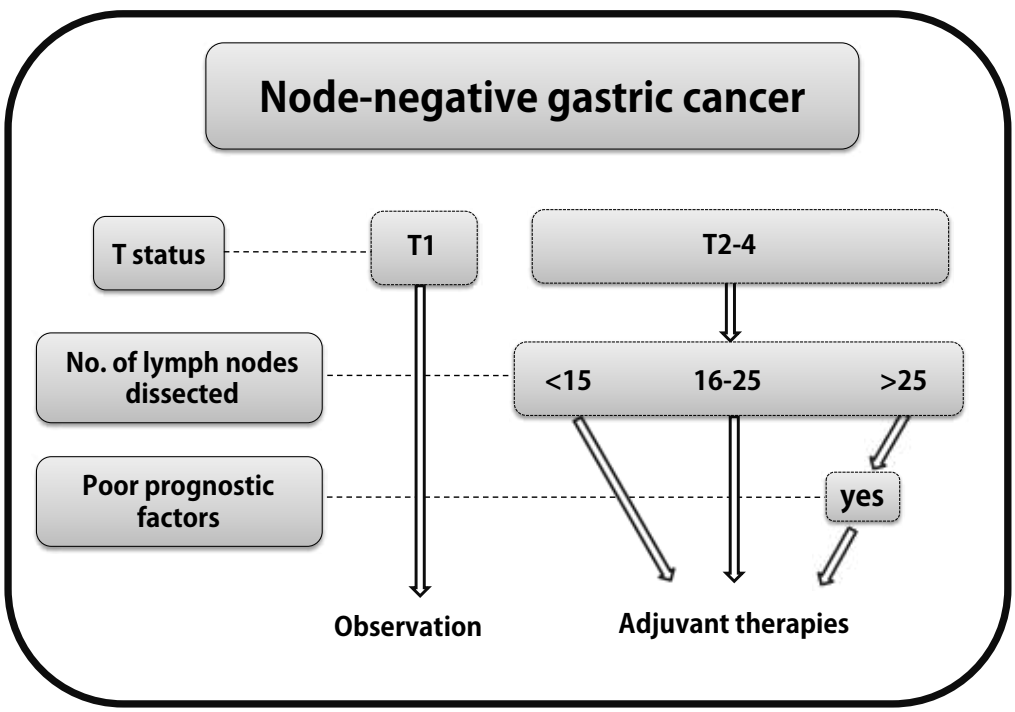

Figure 1 Strategies in managing node-negative gastric cancer

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Diagnosis

Gastric cancer: classification, histology and application of molecular pathology

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Abstract: Gastric cancer remains one of the deadly diseases with poor prognosis. New classification of gastric cancers based on histologic features, genotypes and molecular phenotypes helps better understand the characteristics of each subtype, and improve early diagnosis, prevention and treatment. The objective of this article is to review the new classification of gastric cancers and the up-to-date guidance in the application of molecular testing.

Keywords: Gastric carcinoma; classification; histology; HER2; CDH1; DPD; molecular pathology

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Introduction

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide (1-2). Although the incidence of gastric cancer has gradually decreased over the last half century, cancer at proximal stomach is on the rise (3,4). Today, gastric cancer is still the seventh most common cause of cancer-related death in the United States (5) and the prognosis of advanced gastric cancer remains poor. Gastric carcinogenesis is a multistep and multifactorial process. While the intestinal type of gastric cancer is often related to environmental factors such as Helicobacter pylori infection, diet, and life style, the diffuse type is more often associated with genetic abnormalities. Recent advances in molecular medicine have not only shed light on the carcinogenesis of gastric cancer, but also offered novel approaches regarding prevention, diagnosis and therapeutic intervention.

Classification of gastric carcinoma

Cancers at gastric cardia and gastroesophageal junction (GEJ)

Gastric carcinoma is clinically classified as early or advanced stage to help determine appropriate intervention, and histologically into subtypes based on major morphologic component. For the classification based on anatomic location, difficulty often arises when the tumor is located at proximal stomach or cardia, especially when the tumor also involves gastroesophageal junction (GEJ). It is not only because there are shared histologic features and immunophenotypes between the inflamed gastric cardiac mucosa due to Helicobacter infection and the metaplastic columnar epithelium-lined distal esophageal mucosa secondary to reflux disease, but also because there is no universal consensus regarding the anatomic definition of gastric cardia (6,7). Several classifications were proposed in order to address this issue. The scheme endorsed by the International Gastric Cancer Association separates gastric cancers into type I, type II and type III, to represent the tumors at distal esophagus, at cardia and at the stomach distal to cardia, respectively (8). This classification, however, has not clearly defined the criteria for each of these anatomic locations. Most recently, the 7th Edition of the TNM classification by American Joint Committee on Cancer (AJCC) has simplified the classification of the carcinoma at proximal stomach based on the location of tumor epicenter and the presence or absence of GEJ involvement (9). The tumor is to be stage grouped as esophageal carcinoma if its epicenter is in the

lower thoracic esophagus or GEJ, or within the proximal 5 cm of stomach (i.e., cardia) with the tumor mass extending into GEJ or distal esophagus. If the epicenter is >5 cm distal to the GEJ, or within 5 cm of GEJ but does not extend into GEJ or esophagus, it is stage grouped as gastric carcinoma (9). This classification, although easy for pathologists to follow, could still face some challenges. For example, a bulky gastric cardiac cancer with its epicenter 4 cm below GEJ will still be diagnosed and classified as an esophageal tumor if the proximal end of tumor extends into GEJ by only 0.5 cm (even if the distal end of tumor is 4 cm from the epicenter extending into the stomach). For the operating surgeon who sees the tumor *in situ*, it may be difficult for him or her to accept this tumor as an esophageal cancer. In addition, a recent retrospective study by Huang *et al*. shows that cardiac carcinoma involving GEJ or distal esophagus is more appropriately classified and staged as gastric rather than esophageal cancers, at least in the Chinese population (10). In that study, cardiac carcinomas were staged according to the depth of invasion, status of positive lymph nodes and distant metastasis, as both gastric and esophageal tumors. When the tumor stage is studied and compared with cumulative survival, the findings support that it is more appropriately to group and stage cardiac cancers as stomach in origin (10). To better separate gastric cardiac carcinoma from esophageal or GEJ malignancy, more studies are apparently needed, such as a larger patient sample, molecular profiling of the tumor, clinical follow up data, and defining the tumor location after neoadjuvant therapy as to determine whether the initially bulky tumor was more "gastric" or more "GEJ/esophagus" in origin.

Early and advanced gastric carcinoma

Early gastric carcinoma is defined as invasive carcinoma confined to mucosa and/or submucosa, with or without lymph node metastases, irrespective of the tumor size (11). Most early gastric carcinomas are small, measuring 2 to 5 cm in size, and often located at lesser curvature around angularis. Some early gastric carcinoma can be multifocal, often indicative of a worse prognosis. Grossly, early gastric carcinoma is divided into Type I for the tumor with protruding growth, Type II with superficial growth, Type III with excavating growth, and Type IV for infiltrating growth with lateral spreading. Type II tumor is further divided to IIa (elevated), IIb (flat) and IIc (depressed), as proposed by the Japanese Endoscopic Society (12). A more recent Paris classification has endorsed three gross patterns for superficial neoplastic lesions in gastrointestinal tract. Grossly and endoscopically, the tumor is classified as Type 0-I for polypoid growth (which is subcategorized to 0-Ip for pedunculated growth and 0-Is for sessile growth), Type 0-II for nonpolypoid growth (which is subcategorized into Type 0-IIa for slightly elevated growth, Type 0-IIb for flat growth, and Type 0-IIc for slightly depressed growth), and Type 0-III for excavated growth (13). Histologically, the most common forms of early gastric carcinoma are well differentiated, mostly with tubular and papillary architecture. The distinction between well-differentiated carcinoma and high grade dysplasia or carcinoma *in situ* can be challenging when only mucosal tissue is available for histologic assessment. Intramucosal invasion may not be as easily confirmed as an invasive carcinoma into submucosa where stromal desmoplasia is usually evident. The distinction between intramucosal carcinoma and carcinoma *in situ* or high grade dysplasia is important, as the intramucosal carcinoma of stomach, unlike the intramucosal carcinoma in the colon, does metastasize. Generally, the useful histologic features of intramucosal invasion are single tumor cells in the lamina propria and significantly fused neoplastic glands of various sizes. The prognosis of early gastric carcinoma is excellent, with a 5 years survival rate as high as 90% (14). In contrast, the advanced gastric carcinoma which invades into muscularis propria or beyond carries a much worse prognosis, with a 5 years survival rate at about 60% or less (15). The gross appearance of advanced gastric carcinomas can be exophytic, ulcerated, infiltrative or combined. Based on Borrmann's classification, the gross appearance of advanced gastric carcinomas can be divided into type I for polypoid growth, type II for fungating growth, type III for ulcerating growth, and type IV for diffusely infiltrating growth which is also referred to as linitis plastica in signet ring cell carcinoma when most of gastric wall is involved by infiltrating tumor cells. Histologically, advanced gastric carcinoma often demonstrates marked architectural and cytological heterogeneity, with several co-existing histologic growth patterns. The distinction between early and advanced gastric carcinoma before resection is clinically important because it helps decide if a neoadjuvant (pre-operative) therapy which has shown to improve disease free survival and overall survival (16,17) is warranted. While the macroscopic appearance is informative, the most accurate pre-operative staging information is generally obtained with endoscopic ultrasonography (EUS) and computer tomography (CT) (18).

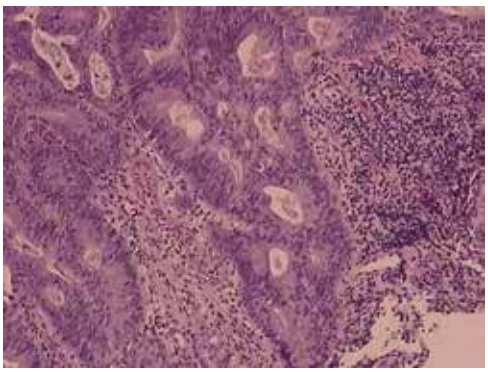

Figure 1 Tubular adenocarcinoma. Irregular-shaped and fused neoplastic glands with intraluminal mucus and debris.

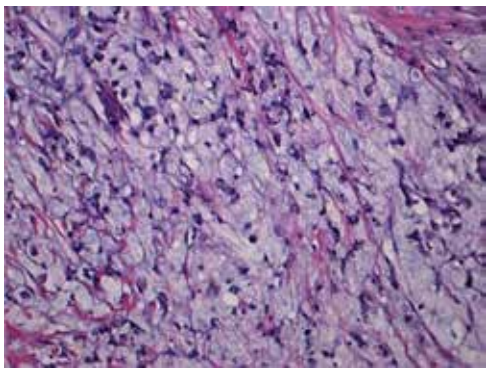

Figure 2 Mucinous adenocarcinoma. Clusters and scattered tumor cells floating in the abundant extracellular mucin pools.

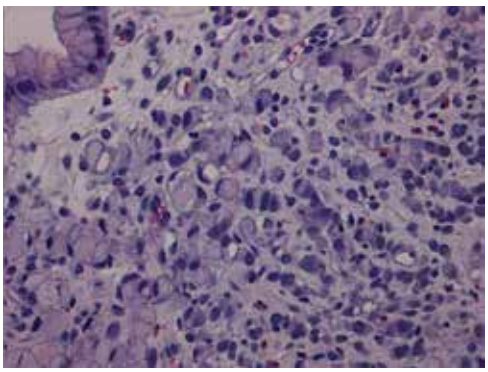

Figure 3 Signet ring cell carcinoma. Signet ring carcinoma cells are predominantly at the superficial lamina propria.

Histologic classification of gastric carcinomas

Histologically, gastric carcinoma demonstrates marked heterogeneity at both architectural and cytologic level, often with co-existence of several histologic elements. Over the past half century the histologic classification of gastric carcinoma has been largely based on Lauren's criteria, in which intestinal type and diffuse type adenocarcinoma are the two major histologic subtypes, plus indeterminate type as uncommon variant (18). The relative frequencies are approximately 54% for intestinal type, 32% for the diffuse type, and 15% for the indeterminate type (19). There are indications that the diffuse type gastric carcinoma is more often seen in female and young individuals (20,21), while the intestinal type adenocarcinoma is more often associated with intestinal metaplasia and Helicobacter pylori infection (22,23).

The 2010 WHO classification recognizes four major histologic patterns of gastric cancers: tubular, papillary, mucinous and poorly cohesive (including signet ring cell carcinoma), plus uncommon histologic variants (24). The classification is based on the predominant histologic pattern of the carcinoma which often co-exists with less dominant elements of other histologic patterns.

Tubular adenocarcinoma is the most common histologic type of early gastric carcinoma (*Figure 1*). It tends to form polypoid or fungating masses grossly, and histologically demonstrates irregularly distended, fused or branching tubules of various sizes, often with intraluminal mucus, nuclear and inflammatory debris.

Papillary adenocarcinoma is another common histologic variant often seen in early gastric carcinoma. It tends to affect older people, occur in the proximal stomach, and is frequently associated with liver metastasis and a higher rate of lymph node involvement. Histologically, it is characterized by epithelial projections scaffolded by a central fibrovascular core.

Mucinous adenocarcinoma accounts for 10% of gastric carcinoma. Histologically it is characterized by extracellular mucinous pools which constitute at least 50% of tumor volume (*Figure 2*). The tumor cells can form glandular architecture and irregular cell clusters, with occasional scattered signet ring cells floating in the mucinous pools.

Signet ring cell carcinoma (*Figure 3*) and other poorly cohesive carcinomas are often composed of a mixture of signet ring cells and non-signet ring cells. Poorly cohesive non-signet ring tumor cells are those that morphologically resemble histiocytes, lymphocytes, and plasma cells. Those tumor cells can form irregular microtrebaculae or lace-like abortive glands, often accompanied by marked desmoplasia in the gastric wall and with a grossly depressed or ulcerated surface. When it occurs at the antropyloric region with serosal involvement, the carcinoma tends to

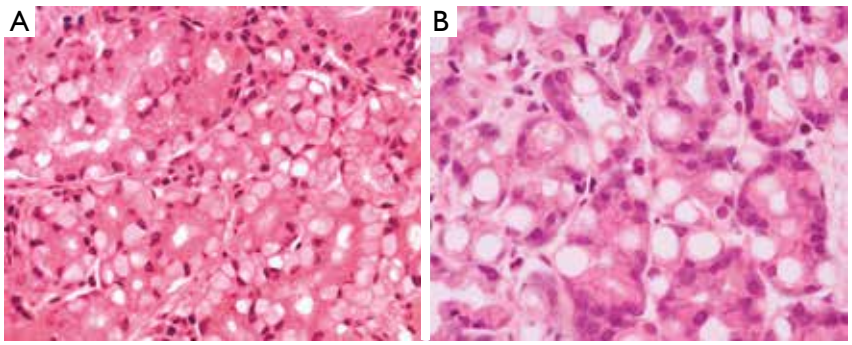

Figure 4 Pseudo-signet ring cells. The cytoplasm of pseudo-signet ring cells are vacuolated (A) and pale (B) (photos are courtesy of Dr. Caroline Hughes).

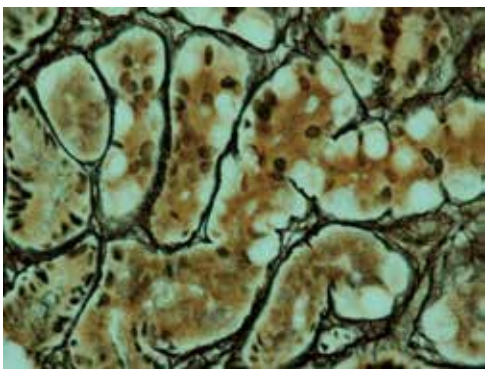

Figure 5 Pseudo-signet ring cells are confined within basement membrane and maintain intact acinar structure with reticulin stain (photo is courtesy of Dr. Caroline Hughes).

have lymphovascular invasion and lymph node metastasis. Because signet ring cell and other poorly cohesive carcinomas at antroplyoric region have a propensity to invade duodenum via submucosal and subserosal routes including subserosal and submucosal lymphatic spaces, special attention needs to be paid to those routes when a distal margin frozen section is requested at the time of surgical resection. Special stains such as cytokeratin immunohistochemistry can help detect morphologically occult signet ring cells in the lamina propria. One important differential diagnosis of neoplastic signet ring cells in gastric mucosa is benign pseudo-signet ring cells which can remarkably mimic signet ring cell carcinoma (*Figure 4*). Those pseudo-signet ring cells sometimes can demonstrate cytological atypia, even with mitoses. However, those pseudo-signet ring cells do not reveal invasive pattern with reticulin stain which highlights pseudo-signet ring cells confined within basement membrane with intact acinar architecture (*Figure 5*) (25).

In addition to the above four major histologic subtypes, WHO classification also endorses other uncommon histologic variants, such as adenosquamous carcinoma, squamous carcinoma, hepatoid adenocarcinoma, carcinoma with lymphoid stroma, choriocarcinoma, parietal cell carcinoma, malignant rhabdoid tumor, mucoepidermoid carcinoma, paneth cell carcinoma, undifferentiated carcinoma, mixed adeno-neuroendocrine carcinoma, endodermal sinus tumor, embryonal carcinoma, pure gastric yolk sac tumor and oncocytic adenocarcinoma, all listed in *Table 1*, with Lauren's classification for comparison.

Gastric carcinoma with lymphoid stroma (medullary carcinoma) is one of the uncommon subtypes. It occurs more commonly in proximal stomach and generally follows a less aggressive clinical course. Histologically, this type of carcinoma is characterized by a sharply demarcated advancing margins composed of irregular nests or sheets of polygonal tumor cells associated with a prominent lymphoid infiltrate in a non-desmoplastic stroma. It is interesting that over 80% of gastric carcinomas with lymphoid stroma are Epstein-Barr virus (EBV) positive (26,27), and EBV is only identified in the malignant and dysplastic cells but not in the normal epithelial cells (28). The finding has raised the hope for tumor cell targeting, especially after studies show that Bortezomib, a proteasome inhibitor, can induce EBV kinase by activating EBV lytic protein expression in the infected tumor cells, which in turn renders the infected cells more susceptible to killing by other agents (29). Another group of gastric carcinomas with lymphoid stroma are those that demonstrate high microsatellite instability (30,31), resulting from defective function of DNA mismatch repair proteins, usually hMLH1 or hMSH2, but rarely hMSH6 (30,32-34).

Table 1 Gastric adenocarcinoma classification systems

WHO (2010)	Lauren (1965)
Papillary adenocarcinoma	Intestinal type
Tubular adenocarcinoma	
Mucinous adenocarcinoma	
Signet-ring cell carcinoma	Diffuse type
And other poorly cohesive carcinoma	
Mixed carcinoma	Indeterminate type
Adenosquamous carcinoma	
Squamous cell carcinoma	
Hepatoid adenocarcinoma	
Carcinoma with lymphoid stroma	
Choriocarcinoma	
Carcinosarcoma	
Parietal cell carcinoma	
Malignant rhabdoid tumor	
Mucoepidermoid carcinoma	
Paneth cell carcinoma	
Undifferentiated carcinoma	
Mixed adeno-neuroendocrine carcinoma	
Endodermal sinus tumor	
Embryonal carcinoma	
Pure gastric yolk sac tumor	
Oncocytic adenocarcinoma	

The number of tumor-infiltrating lymphocytes, while significantly higher than the one in non-microsatellite instability-high cancers, is lower than that in EBV positive carcinoma (34). This group of carcinoma is usually intestinal type by Lauren's classification, and often affects the elderly, with a lower pTNM stage and a low risk of lymph node metastasis. It was suggested that microsatellite instability-high status and EBV infection were the variables which rendered the carcinoma a better prognosis. However, the claims have not been substantiated by other studies. More recent study reveals that the high number of tumor-infiltrating lymphocytes is the only favorable prognostic factor independent of EBV infection and microsatellite instability-high status (34). Also in this investigation, neither EBV positivity nor microsatellite instability-high alone was proved to be an independently favorable prognostic factor. Interestingly, EBV positivity and microsatellite instability-high status, while both share the feature of prominent tumor-infiltrating lymphocytes, are rarely concomitant, suggesting the two are unrelated and involved in distinct underlying pathways in carcinogenesis.

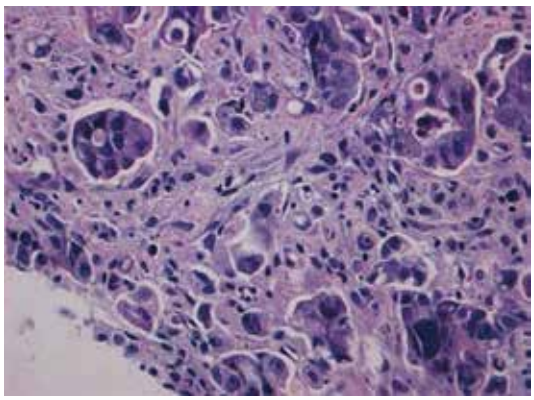

Figure 6 Micropapilary adenocarcinoma. Small papillary clusters of tumor cells devoid of fibrovascular core and surrounded by empty spaces.

Micropapillary carcinoma of stomach is a newly recognized histologic variant characterized by small papillary clusters of tumor cells without a distinct fibrovascular core (*Figure 6*). The micropapillary features are often noted in the deep advancing edge of tumor, surrounded by an empty space mimicking retraction artifact. Micropapillary carcinoma of stomach, as its counterpart at other organs, tends to form endolymphatic tumor emboli and metastasize to lymph nodes. However, the overall survival of gastric micropapillary carcinoma, unlike that in other organs, seems to be not significantly different from conventional gastric adenocarcinoma, although the result may be due to the small patient sample in that study (11 patients) (35). Because of the high incidence of lymphatic invasion and nodal metastasis (up to 82%) (35,36), it is advised that conservative treatment such as endoscopic resection not be used for gastric carcinoma with invasive micropapillary components.

Application of molecular pathology in gastric carcinoma

An accumulation of genetic and molecular abnormalities occurs during gastric carcinogenesis, including activation of oncogenes, overexpression of growth factors/receptors, inactivation of tumor suppression genes, DNA repair genes and cell adhesion molecules (37), loss of heterogeneity and point mutations of tumor suppressor genes, and silencing of tumor suppressors by CpG island methylation (38). The revelation and understanding of the molecular events and pathways have led to the application of molecular pathology

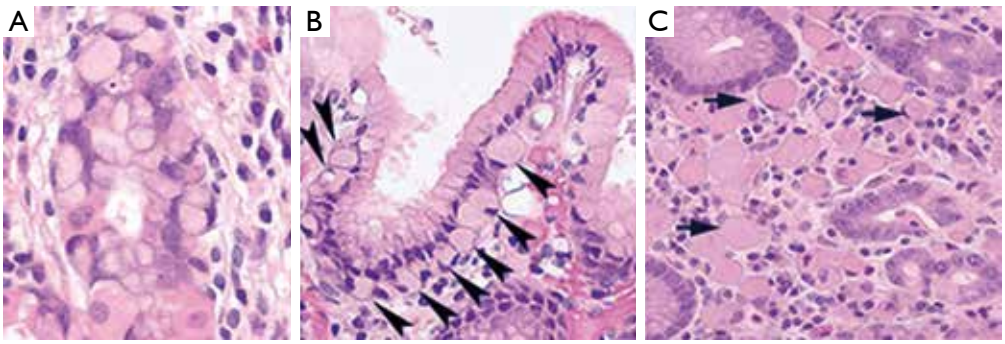

Figure 7 (A) *In situ* signet ring carcinoma cells confined within basement membrane; (B) Pagetoid spread of signet ring cells (arrow heads) below the preserved surface epithelium; (C) Focus of intramucosal signet ring cell carcinoma (arrows) in the lamina propria (all three photos are courtesy of Dr. Rebecca Fitzgerald)

in the prevention, early diagnosis, tumor classification and therapeutic intervention. The applications of molecular testing such as the testing of CDH1 gene for hereditary diffuse gastric carcinoma (HDGC) and of HER2 expression in gastric cancers have had significant impact on medical practice, and become standard patient care.

Hereditary diffuse gastric carcinoma (HDGC)

About 10% of gastric carcinomas show familial clustering but only approximately 1-3% of gastric carcinomas arise from inherited gastric cancer predisposition syndromes (39), such as hereditary diffuse gastric carcinoma (HDGC), familial adenomatous polyposis, hereditary nonpolyposis colorectal carcinoma (or Lynch syndrome), juvenile polyposis syndrome, Peutz-Jeghers syndrome, Li-Fraumeni syndrome and gastric hyperplastic polyposis (40-42). HDGC is an autosomal dominant disorder with high penetrance. Approximately 30% of individuals with HDGC have a germline mutation in the tumor suppressor gene E-cadherin or CDH1 (43). The inactivation of the second allele of E-cadherin through mutation, methylation, and loss of heterozygosity eventually triggers the development of gastric cancer (44,45). To diagnose HDGS, two or more cases of diffuse gastric carcinoma in first or second degree relatives must be documented, with at least one diagnosed before the age of 50; or there are three or more documented cases of diffuse gastric carcinoma in first or second degree relatives, regardless of the age of onset (46,47).

The histologic phenotype of HDGC in early stage includes patchy intramucosal signet ring carcinoma cells in the lamina propria and its unique feature of carcinoma *in situ* associated with pagetoid spread of tumor cells along the preserved basement membrane (*Figure* 7). The lesion can be multifocal but usually starts at the junction of antrum and body. The tumor cells often demonstrate hyperchromatic nuclei, with occasional mitoses. Because it is difficult to diagnose HDGC at an early stage both histologically and endoscopically, and because the penetrance of CDH1 mutation is high, with the carrier of this gene conferring over 80% life time risk of gastric carcinoma (47), prophylactic total gastrectomy after confirmation through CDH1 molecular testing is the only recommended way to save patients' lives. According to the updated recommendations for CDH1 testing by International Gastric Cancer Consortium, family members of the following are the candidates for CDH1 testing (48): (I) Two family members with gastric carcinoma, one of which is confirmed diffuse gastric cancer; (II) Three family members with gastric carcinoma in first or second degree relatives including one with diffuse gastric cancer; (III) One member with diffuse gastric cancer before the age of 40; (IV) Personal or family history of diffuse gastric cancer and lobular breast cancer including one diagnosed before 50.

If *in situ* signet ring cell carcinoma with pagetoid spread is identified adjacent to diffuse type gastric cancer and confirmed by expert GI pathologists, the patient should also be tested for CDH1 mutation, because the histologic features have not been reported in sporadic form of gastric carcinoma (49). The confirmation of HDGC through CDH1 mutation can help family members decide if they should consider the similar testing.

Because approximately 4% of these mutation positive families exhibit large germline deletions of CDH1 that cannot be detected by conventional DNA analysis (50), large genomic rearrangements should be sought in addition

Table 2 Human epidermal growth factor receptor 2 (HER2) scoring criteria for gastric cancer

Score	Surgical specimen-staining pattern	Biopsy specimen-staining pattern	HER2 overexpression
0	No reactivity or membranous reactivity in <10% of tumor cells	No reactivity or no membranous reactivity in any tumor cell	Negative
1+	Faint/barely perceptible membranous reactivity in >10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in >10% of tumor cells	Tumor cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in >10% of tumor cells	Tumor cell cluster with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

to conventional direct sequencing. It is also recommended that CDH1 genetic testing on blood for germline mutations should be performed in Clinical Laboratory Improvement Laboratory (CLIA)-certified molecular diagnostic laboratories or research laboratories with expertise in CDH1 gene analysis (48).

In addition to prophylactic total gastrectomy, annual mammography and breast MRI from the age of 35 years are recommended for women with HDGC, due to their increased risk of lobular breast cancer (51).

Human epidermal growth factor receptor 2

Human epithelial growth factor receptor 2 (HER2), a member of the human epidermal growth factor receptor (EGFR) family, is a proto-oncogene located on chromosome region 17q21. It encodes a 185 kD transmembrane tyrosine kinase receptor protein that regulates signal transduction in cell proliferation, differentiation and survival (52,53). HER2 gene amplification was described in gastric carcinoma after its discovery in breast cancer (54). With immunohistochemical stain, it was found that the rate of HER2 overexpression in gastric adenocarcinoma is 12% in a Japanese series (55) and 22.1% in more recent studies (56-58). HER2 overexpression is more often noted in intestinal type carcinoma (57,59) and in the carcinomas located at proximal stomach or cardia and gastroesophageal junction (24-35%) than in the remaining stomach (9.5% to 21%) (19,59,60). In addition, HER2 status in the carcinomas of stomach and GEJ is relatively homogeneous and rarely shows significant modification from primary site to metastatic foci (61).

Recently, a large scale phase III international clinical trial called ToGA showed that the humanized monoclonal antibody against HER2, Trastuzumab (Herceptin), when combined with chemotherapy (capocitabine or 5-fluorouracil and cisplatin), could effectively prolong overall survival and progression-free survival, and increases the response rate in HER2 positive advanced gastric carcinoma (57). On the basis of these findings, the regulatory approval for trastuzumab was granted in October 2010 in the United States for patients with HER2 positive metastatic adenocarcinoma of stomach or gastroesophagical junction. Now, it is recommended that all patients with gastric cancers should routinely be tested for the HER2 status at the initial diagnosis (57,62).

While HER2 positive status in gastric carcinoma is also defined as either IHC3+ or IHC2+ plus positive FISH, similar to breast cancers, there are several differences in the evaluation of HER2 status in gastric cancers. In gastric or GEJ cancers, only 5 clustered positive cancer cells in a biopsy tissue or a minimum 10% of positive neoplastic cells in a surgical resection specimen are required for defining 3+ score, on the condition that the immunohistochemical stain reveals intense complete, basolateral, or lateral membranous reactivity (62). In order to archive accurate and reproducible HER2 scoring, it is essential that the interpretation of HER2 expression is strictly based on the criteria originally reported in the Trastuzumab for gastric cancer study, which was published and listed in *Table 2* (57).

In addition, a panel of expert pathologists from the European Union and the rest of the world recommend that if immunohistochemistry is used as the initial test,

any specimen type (either surgical resection or biopsy) with <10% strongly stained tumor cells should be subjected to confirmatory *in situ* hybridization testing to preclude false-negative results (62). If the sample is poorly preserved, shows nonspecific staining at cytoplasm and nuclei of the tumor cells, or reveals staining at benign mucosa with intestinal metaplasia, the sample should be retested by FISH to exclude false positive results (62).

Based on the results from ToGA study, the levels of HER2 protein predicts well for the response of gastric carcinoma to Trastuzumab. On the other hand, the tumors with positive HER2 amplification but with low or negative HER2 expression do not respond well to Trastuzumab. Therfore, immunohistochemistry is recommended to be used as the initial testing methodology, and FISH or silver *in situ* hybridization used to retest immunohistochemistry 2+ cases (62).

Dihydropyrimidine dehydrogenase

Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in uracil catabolism, and is also the main enzyme involved in the degradation of structurally related compounds like 5-Fluorouracil (5-FU), a widely used drug in treating different kinds of tumor including gastric carcinoma. True deficiency of DPD affects approximately 5% of the overall population (63). Patients with DPD deficiency are at significantly increased risk of developing severe and potentially fatal neutropenia, mucositis and diarrhea (63-65) when treated with 5-FU or capecitabine. In addition, 3% to 5% of the population has a partial DPD deficiency due to sequence variations in DPYD gene, which potentially limits their ability to fully metabolize the drug, thereby resulting in toxicity (66-68). Many studies have addressed and identified the mutations of DPYD and epigenetic alterations of DPYD as the causes of lower levels of DPD or DPD deficiency. Subsequently, different tests have been developed in order to identify the people at risk of DPD deficiency, in the hope that the test results could eventually provide clinical guidance. One of the tests to identify the people with DPD deficiency is DPYD genotyping to detect the important mutations such as DPYD 2A (or IVS14+1 G>A) (66,69). While the individuals with positive DPYD mutation have an increased risk for DPD deficiency, DPD deficiency is also noted in the people with wild type PDYD, because epigenetic alteration, such as methylation at the regulatory region of PDYP promoter can cause lower DPD level without the mutation at DNA level (70). To make issue more complicated is that the uracil catabolic pathway involves several other enzymes such as dihydropyrimidinase (DHP) (71) and beta-urreidopropionase (BUP1) (72,73). The mutations of those genes which are at the downstream of DPD also impair uracil catabolism. Therefore, uracil breath test which involves DPD, DHP, and DUP1 may reveal more clinical information of potential toxicity in the patients who receive 5-FU treatment (74), because it evaluates the integrity of the entire catabolic pathway of uracil which cannot be archived by PDYD genotyping alone.

Despite the fact that PDYD genotyping is informative for identifying patients with an increased risk of toxicity to 5-FU treatment, and despite the large numbers of studies which attempt to identify molecular predictors of response and toxicity to treatment, none of the tests and molecular markers thus far have been proven to be reliable in prospective clinical trials, and unlike CDH1 and HER2 testing, none of those tests have been validated to permit their use as standard of care in 5-FU therapy. Many questions still remain unanswered and many components in the entire metabolic pathways of FU remain unaddressed. For example, DPD deficiency was noted only in a small percentage of patients with severe 5-FU toxicity, leaving a large numbers of patients with an unexplainable molecular basis of toxicity (75). In predicting who will develop toxicity when treated with 5-FU or capecitabine, much more work has to be done (76).

In conclusion, while gastric cancer remains a deadly disease, the discoveries of new molecular markers, genetic and epigenetic alteration, and novel pharmacogenetic traits have helped improve patients care, fostered hope and led new directions of cure. The newest WHO classification of gastric carcinoma is by far the most comprehensive, describing the morphologic characteristics of each subtype in detail. Hopefully, it will help understand the clinicopathologic entity of each subtype by correlating its histologic feature with molecular profiling and clinical behavior. It is encouraging that the discoveries of some pharmacogenetic traits have opened the door for individualized medicine, promising the future medicine to be more effective and less toxic because it is based on the molecular fingerprint not only of each tumor but of each human being. Nevertheless, many challenges remain. Some claims to attempt pharmacogenetic prediction based on the pattern of single nuclear polymorphsim (SNP) may be premature and have not been fully validated. Caution should be exercised as some of claims may be biased and could lead to harmful consequences (77,78).

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FDG PET imaging in the staging and management of gastric cancer

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Abstract: Gastric cancer is a leading cause of cancer death worldwide. Complete resection offers the only chance for permanent control, and accurate staging and evaluation of treatment response are crucial for appropriate management. Positron Emission Tomography (PET) is increasingly used to complement anatomic imaging in cancer management. PET use in gastric cancer has been limited by 1) some gastric histologies are not PET avid, 2) spatial resolution limits the ability to distinguish between primary tumor and compartment I or II lymph nodes, and 3) the lack of a unified criteria in how to interpret PET for management decisions. New criteria have been proposed establishing response metrics in the utilization of PET. More study is needed to support these criteria in routine practice and establish the place of PET in the staging and management of gastric cancer.

Keywords: Positron emission tomography; gastric cancer; tumor staging

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Introduction

Gastric cancer is one of the most prevalent cancers worldwide and is a leading cause of cancer mortality. In several Eastern countries, gastric cancer is the most common and deadly malignancy. In the Western Hemisphere gastric cancer incidence has been decreasing while esophageal and gastroesophageal junction cancers have increased (1,2). In the West, gastric cancers are typically distributed in the proximal lesser curvature, in the cardia, and in the GE junction; this distribution has been changing from a more distal distribution in the past and differs from Eastern countries with higher incidence. More than 80% of gastric cancer patients in the West are diagnosed at an advanced stage resulting in poor prognosis (3).

Complete resection of gastric cancer is the only method of achieving permanent control. However, surgeries can be morbid and futile in patients who have advanced disease, making appropriate staging and characterization of disease burden of paramount importance. Staging of gastric cancer typically makes use of a variety of imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasounds (EUS), and combined positron tomography (PET-CT), as well as laparoscopic staging and cytogenetic analysis of peritoneal fluid in appropriate patients (4-6).

The value of PET-CT has been of increasing interest among clinicians and data has supported its increased use in the detection, staging, and management of a variety of malignancies. During and after therapy, PET-CT may be useful in determining response to chemotherapy. It may be helpful for restaging and diagnosing recurrence at an earlier time or with greater certainty. This paper will address the potential uses of PET-CT specifically within the management of gastric cancer.

Background

PET is performed by injecting a patient with a radiolabeled tracer which is concentrated by the body in certain metabolically active tissues. As radioactive decay occurs, emissions are measured with a scanner and a threedimensional image representing relative uptake of the tracer is produced. 2-[fluorine 18] fluoro-2-deoxy-D-glucose

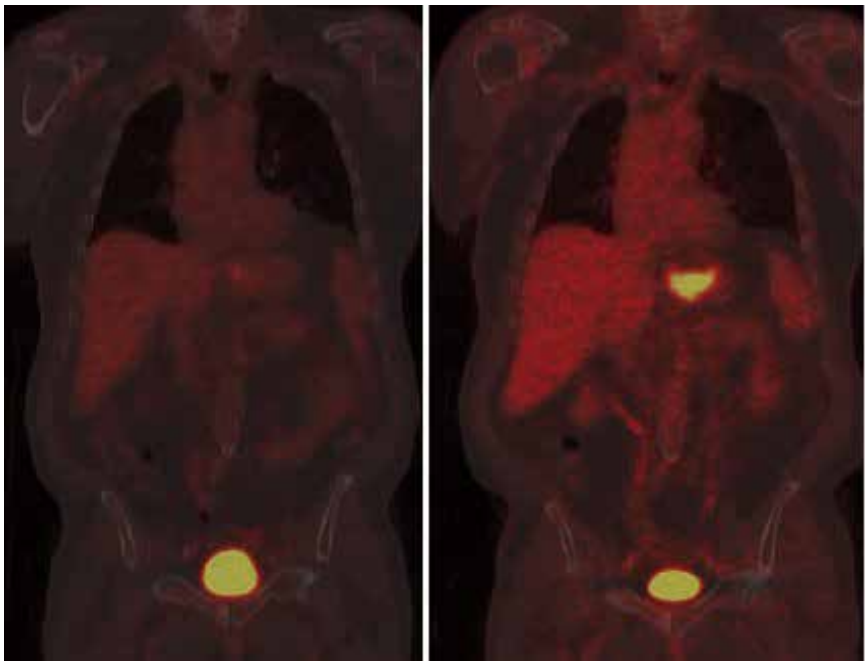

Figure 1 Registration of PET and CT imaging provides combined anatomic and physiologic information. Uptake values are relative and uptake in normal tissues (such as liver) provides a reference.

(FDG) labeled glucose is used most frequently as the tracer, and this paper will assume the use of FDG unless otherwise indicated. As f luorine-labeled glucose is transported into metabolically active cells, it is phosphorylated and trapped, ensuring that continued dissipation and transport do not dilute the signal. These biochemical properties make FDGPET a useful modality for measuring glucose demand as a surrogate for metabolically active tissues such as cancer. In several gastric cancer histologies, however, the metabolic differential between tumor and normal tissue is not as stark as with other malignancies, making the conceptual utility of PET less clear. Mucinous carcinoma, signet ring cell carcinoma, and poorly differentiated adenocarcinomas typically have less prominent FDG uptake (7,8).

Obtaining a PET scan nearly simultaneously with a CT scan using a dual gantry machine allows for registered images represent ing both anatomic and metabol ic properties. The registration is not perfect because the time of image acquisition is longer for PET than the CT portion of the imaging, but obtaining both image sets without moving the patient does provide a more accurate registration while minimizing deformation on overlay. Registration issues may be more pronounced in the GI tract considering the frequent internal daily motion of the organs (*Figure 1*).

Staging

The American Joint Committee on Cancer (AJCC) staging system is widely used for the characterization of disease burden and prognosis in gastric cancer. Based on a TNM system, the 7th edition of AJCC guidelines designate tumor characteristic staging (T) as follows: T1 when tumor invades lamina propria or muscularis mucosae, T2 when tumor invades muscularis propria, T3 when tumor penetrates subserosal tissue without further invasion, and T4 when tumor invades visceral peritoneum or adjacent structures (9). Because surgical treatment is a major prognostic factor, effort to accurately determine the invasiveness of a gastric lesion is crucial. CT-determined T staging agreed closely with pathologic staging in early studies but was subsequently shown to have disappointing accuracy. EUS is a more accurate method for determination of pre-operative T stage and was directly compared with CT in a study by Botet (10). However, evolving technologies produce ever-increasing resolution of CT imaging, and thinsection scans with multiplanar reformation and contrast suggest the comparative value between CT and EUS is not static (11).

Regardless of the imaging modality used, loss of the fat plane between a gastric mass and adjacent organs is suggestive of invasion. For this reason, PET imaging is

not particularly helpful in determining the T stage. The resolution of PET is limited by volume averaging of metabolic signal, with prominent uptake averaged across several millimeters—a distance too great to give confidence when assessing barrier invasion on the surface of organs.

N stage in the 7th edition of AJCC staging criteria is based on number of positive nodes with some changes from the previous editions. N1, N2, and N3 represent positivity in 1-2, 3-6, and 7 or more nodes respectively. Earlier staging criteria included nodal location as an objective criterion for staging. The Japanese Research Society for Gastric Cancer divides gastric nodes into four compartments, each compartment progressively more removed from the stomach (12). A D1 lymphadenectomy includes resection of compartment 1 lymph nodes (perigastric nodes at stations 1-6) while a D2 resection also removes compartment 2 (stations 7-11) and is the standard surgical procedure in high prevalence countries. D3 and D4 lymphadenectomies include their respective compartments. AJCC criteria designates involvement of hepatoduodenal, retropancreatic, mesenteric, and para-aortic nodes (i.e., compartment III and IV) as distant metastases (9).

CT criteria for lymph node metastases include size, shape, central necrosis and heterogeneity (13,14). When these characteristics are present there is a strong correlation with metastatic involvement. However, CT sensitivity suffers because a small tumor burden in a lymph node is unlikely to produce the morphological changes sufficient to satisfy CT criteria. In concept, PET seems an excellent adjunct therapy to detect these anatomically small but potentially metabolically active focuses of metastatic disease. However, the relatively poor spatial resolution of PET makes it less effective because of the difficulty of distinguishing compartment I and II nodes from the primary tumor itself. The real value of PET may be in the detection of "distant" metastatic disease in compartments III and IV and not amenable to surgical resection with a standard D2 lymphadenectomy. Identification of further spread with PET imaging may influence surgical planning for a more aggressive lymphadenectomy or the decision to avoid surgery altogether as futile and unnecessarily morbid (15).

Solid organ metastasis from the stomach occurs most commonly in the liver via hematogenous dissemination through the portal vein (16,17). Lymphatic and peritoneal dissemination are also common pathways of spread in gastric malignancy. Although distant metastases are frequently detectable using contrast CT, PET is perhaps most useful in the detection of these distant sites of solid organ metastases. A meta-analysis by Kinkel designated PET as the most sensitive noninvasive imaging modality for this purpose (18). Because radio-tracer is distributed throughout the body, larger volumes can be more easily scanned than is practical with CT.

Peritoneal dissemination is a poor prognostic factor. Detection of peritoneal metastases may change the surgical strategy from curative to palliative or deter the surgeon from laparotomy altogether. Increasingly sophisticated CT scans facilitate diagnosis of peritoneal metastases prior to visual inspection during surgery. PET may give additional sensitivity to CT. Diffuse uptake of tracer that obscures the serpiginous outline of the bowel may be an indicator of peritoneal metastases, as well as discrete areas of local uptake along areas within the peritoneal cavity that are otherwise anatomically unexplained (i.e. outside expected nodal stations or solid viscera) (11).

Response to therapy

PET may predict response to preoperative chemotherapy in gastric cancer. Ott *et al*. showed that a 35% decrease in uptake between pre-chemotherapy and PET scan taken 2 weeks after initiation of therapy predicted response with accuracy of 85%. Two year survival rate was 90% in responders and 25% in non-responders using this criteria with P=0.002 (19). Uptake decrease during therapy is a continuous variable and different thresholds have been determined by other investigators. For example, Shah *et al*. found that a 45% cutoff comparing uptake after 35 days was the best value to separate responders from nonresponders and predict outcome (20). In evaluating response to treatment for esophageal carcinoma, studies have shown marked variability (from 10-80%) in the cutoff values determined retrospectively, and it seems likely that gastric cancer may have comparable variability (21).

Wahl *et al*. have proposed a PET Response Criteria in Solid Tumors (PERCIST) analogous to and intended to eventually supercede other anatomic tumor response metrics such as the World Health Organization (WHO) criteria and multiple versions of the Response Evaluation Criteria in Solid Tumors (RECIST) (22). Wahl notes that both qualitative and quantitative approaches have been made in using PET results for response assessment. Because statistically significant variability between SUV values is typical even when tested and retested under careful control, PERCIST criteria proposes a 30% or greater decline as indicative of "medically relevant beneficial

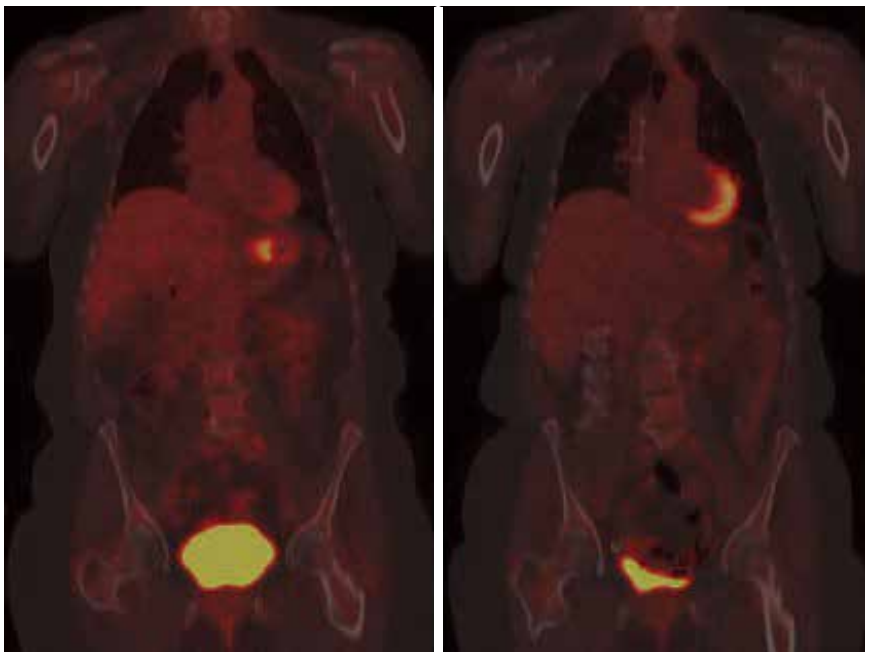

Figure 2 CT-PET at diagnosis shows uptake in the proximal stomach. After therapy, uptake is visibly reduced.

changes". Per the criteria, normal reference tissue values are designated within a scan by using a consistent protocol based on regions of interest in the liver and the most active tissues. Wahl suggests that the PERCIST criteria be used as a starting point for clinical trials and clinical reporting. This seems wise as the ad hoc approach to defining PET response has resulted in a body of work that is fragmented to the point of poor relevance.

Many gastric cancers are not PET avid and repeat imaging will not provide additional useful imaging in these patients. Wahl recommends the use of RECIST 1.1 in such cases. Ott *et al.* grouped patients with non-avid tumors as similar in prognosis to metabolic non-responders, that is, biologically unfavorable with poorer prognosis. Metabolic responders had a 69% histopathologic response rate while metabolic non-responders had only a 17% histopathologic response rate, similar to the 24% histopathologic response rate of the non-avid group. Survival was also similar between the non-avid group and the non-responding group while significantly different from the responding group (19).

In addition to suggesting responsecriteria and prognosis groupings, Kim *et al*. have compared FDG-PET to fluorothymidine (FLT)-PET with interesting results. FLT-PET had a higher sensitivity than FDG-PET and Ott suggests that it may provide a useful adjunct by providing a quantitative assessment of proliferation. While limited work using other radionuclides has been done, the potential for better clinical relevancy makes this area of investigation particularly interesting (23) (*Figure 2*).

Recurrent disease

Disease recurrence frequently occurs locally in sites that have lost characteristic anatomic features due to surgery. In such cases early detection may allow for better salvage therapy and may be assisted with the use of PET. Glucose metabolism is typically low in scar tissue and high in recurrent tumor. CT remains central in the characterization of post surgical changes and post-treatment monitoring, however, equivocal findings can be better characterized with the added metabolic information of PET. Unfortunately, the same limitations of PET previously discussed apply in this circumstance; specifically, only certain histologies exhibit sufficient uptake necessary for useful sensitivity, and spatial resolution is limited by the current technological limitations of the modality.

De Potter *et al*. found a longer survival in a cohort of patients with recurrent disease who were PET-negative than their recurrent counterparts with PET-positive disease. However, de Potter warns that the poor sensitivity and

low negative predictive value makes PET inappropriate for screening during follow up; rather, PET can provide important information regarding prognosis in patients with recurrence (24). Sim *et al*. found that the sensitivity and specificity of PET was similar to CT in all sites of recurrence except peritoneum, where it was less sensitive (25).

Conclusion

PET is a promising modalit y with increasing use across a wide variety of malignancies. It is increasingly used in GI cancers as an adjunct in both staging and management decisions. Per NCCN and other consensus guidelines, PET may be used as an option for greater specificity in characterizing suspected disease in gastric cancer; however, anatomic imaging remains the standard recommendation. Some data supports the use of PET in gastric cancer staging, particularly in characterizing distant metastases or lymphatic metastases beyond compartment I or II. Additional work is needed to refine the proposed PERCIST criteria and to find the best parameters of continuous variable for the use of PET in gastric and other GI malignancies.

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Diagnosis

Lymph node staging in gastric remnant carcinoma

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While different definitions of gastric remnant carcinoma (GRC) still exist (1,2), many accept the one proposed by Tanigawa *et al.*, which defines GRC as the cancer developing in the remnant stomach at least 10 years after distal gastrectomy, regardless of whether the resection was performed for benign or malignant disease (3).

Much interest and debate regarding the prognosis of GRC evolve over past years with different results. While some claimed the prognosis of GRC was poor because of its low resectability, extended lymph node metastasis and infiltration of adjacent organs (4-6), others found the prognosis and resectability were not significantly different between GRC and conventional primary gastric carcinoma (PGC) (7,8).

In pathophysiology, important changes in GRC include the subsequent alteration of lymphatic drainage after resection, and lower numbers of harvestable and/or metastatic lymph nodes, especially if the resection was performed for gastric malignancy with prior extensive node dissection (7,8). It remains unclear and unaddressed if less retrievable lymph nodes in GRC could potentially influence accurate nodal stage which carries a predictive power in terms of survival rate.

Li *et al.*'s recent article in the *Journal of Cancer Research and Clinical Oncology* studied the pattern of lymph node metastasis in GRC and questioned if the lymph node staging according to the Union of International Cancer Control (UICC) TNM classification (7th edition) was appropriate for GRC (9). Because the number of harvestable lymph nodes was generally less in GRC than the ones in PGC due to prior resection of stomach, Li *et al.* suggested that 15 positive lymph nodes as cutoff point for N3b in the 7th UICC N staging system may not be suitable for GRC. Based on their analysis of median survival time (MST) in 83 patients with GRC from a single institution, they concluded that the N stage would be more appropriately classified in GRC if N3a represents 7 to 9 positive nodes (instead of 7 to 15), and N3b represents 10 or more positive nodes (instead of over 15), while N0, N1 and N2 remain same as 7th UICC N staging. Their conclusion was based on the data analysis of MST from 11 patients out of a total 83. Among these 11 patients, 8 were staged as N3a and 3 as N3b per 7th UICC classification, but per Li's protocol, there would be 5 as N3a and 6 as N3b. In that very small patient sample, Li *et al.* found a statistically significant difference in MST between N3a and N3b (P=0.014) if N was staged according to their proposal, which would otherwise not exist if classified according to 7th UICC N stage (P=0.18).

Fewer retrievable lymph nodes and/or less total positive nodes in GRC have been noted in several reports. Rabin *et al.* found the mean number of lymph nodes harvested per patient was 8.3 in GRC compared with 16.7 in PGC, and mean number of metastatic lymph nodes in GRC were 0.7 per patient compared with 3.7 in PGC (P=0.03, statistically significant) (7). While no significant differences in overall 5-year survival were identified between GRC and PGC, An JY *et al.* did notice that in some patients in GRC, especially in those with prior resection of gastric malignancy, the number of retrieved lymph nodes was insufficient for accurate staging of nodal metastasis (8). While those findings support Li *et al.*'s claim in that retrievable lymph nodes in GRC are lower and therefore, it may be difficult to have 15 or more positive lymph nodes, it is too early to draw a conclusion regarding the suitability of the cutoff number of lymph nodes proposed by Li *et al.*

First, Li *et al.*'s conclusion was derived from a very small patient sample in a retrospective or post hoc study.

Therefore, no difference in MST between N3a and N3b when staged per 7th UICC scheme might have occurred because the sample was too small to reach statistic power. The effect of this underpowered study due to small patient sample is evident in that no differences in MST were noted between N1 and N2 in their analysis. In addition, the results from a retrospective or post hoc study with small patient sample such as Li's may be interpreted with bias when confounding factors are not fully addressed. Therefore, the claimed significant difference in MST between N3a and N3b per Li's protocol may not be noted among general population of the patients. It is generally accepted that the stage combining T, N and M, or TNM group stage would have much better predictive value for overall survival and MST than a single T or N stage. Yet, the study did not reveal the T stage associated with those 11 patients in their proposed N3a and N3b subgroups. Additionally, the study failed to reveal if these 11 patients had history of neoadjuvant or adjuvant therapy, because these subjects should generally be excluded from study such as this. Finally, some other studies have shown the ratio of positive to negative nodes in gastric cancer may have a better predictive value for survival (10). It remains to be tested if that finding can also apply to N stage in GRC in which it is more difficult to harvest adequate number of nodes. Therefore, studies with a much larger patient population to exclude potential confounding factors and incorporate alternative way to calculate positive lymph nodes such as the ratio of positive to negative lymph nodes are needed before the modified N stage in GRC proposed by Li *et al.* can be accepted.

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The role of ^{18}FDG-PET in gastric cancer

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Imaging with ^{18}F-fluoro-2-deoxyglucose PET (^{18}FDG-PET) is based on the increased glucose uptake of neoplastic cells, which over-express the main cell-membrane glucose transporter GLUT-1 resulting in higher uptake of ^{18}FDG as well. More than visual analysis an often-used semi-quantitative method to assess tumor ^{18}FDG uptake is the standard value (SUV), which is the measurement of ^{18}FDG up-take in a tumor volume normalized on the basis of a distribution volume.

^{18}FDG-PET has been widely used to evaluate various types of malignant tumors, including lung, oesophageal, and colorectal cancer and lymphomas (1). However, the role of ^{18}FDG PET in gastric cancer is debatable. Although ^{18}FDG-PET is clinically useful in detecting recurrent gastric cancer after surgical resection (2,3), the role of ^{18}F-FDG PET in preoperative workup is limited due to its low sensitivity for primary tumour and lymph node (LN) metastasis (4,5). Furthermore, because only a few studies with a small number of patients have been performed, the role of ^{18}F-FDG PET in predicting prognosis of patients with gastric cancer is still contentious.

The primary site detection rate of ^{18}FDG-PET is about 50% in early gastric cancer and 92% in advanced gastric cancer. Sensitivity for detecting the primary tumour varies between 47 and 96% due to the different characteristics of enrolled patients (5-12) of the studies considered. The variable and sometimes intense physiological ^{18}FDG uptake in the normal gastric wall and differences of ^{18}FDG uptake in cancer lesions according to hystopathological subtypes of gastric cancer are the most significant contributing factors for the low detection rate of gastric primary tumours.

Normal gastric wall devoid of malignant lesions can displays an SUV exceeding 2.5 and benign gastric mucosal inflammation can show focal intense ^{18}FDG accumulation, which restricts detection of gastric cancer lesions (13-15). ^{18}FDG uptake in mucinous carcinoma can be positively correlated with tumour cellularity, but negatively correlated with the amount of mucin within the tumor mass, which accounts for low detectability of ^{18}FDG-PET for undifferentiated and mucinous tumors (16). Furthermore, an infiltrative growth pattern, high content of mucus and low concentration of cancer cells lead to low ^{18}FDG uptake in poorly differentiated cancer and signet-ring cell cancer, in spite of their aggressiveness. Detection rate is higher when tumors are larger than 3.5 cm and have deeper depth of invasion, and at a later stage. In many multivariate analyses, tumor size, spread of tumor cells beyond the muscle layer (≥ T2), and lymph node metastasis were statistically significant factors in primary site detection rate.

The sensitivity, specificity, and positive predictive value of ^{18}FDG-PET to lymph node metastasis are 60%, 85%, and 80%, respectively; sensitivity being lower compared to CT while specificity and positive predictive value are higher. PET is less sensitive than CT in the detection of lymph node metastasis located near to gastric wall in the regional stations, mainly due to its poor spatial resolution, which makes it unhelpful in discriminatine between lymph nodes and the primary tumor (17). Detection of lymph node metastases in the 12, 13, 14, 15, 16 stations can change the extent of lymph node dissection or may preclude unnecessary surgery. Metastases at these anatomical sites would theoretically be easier to identify at PET because they are located away from the primary lesions. In other words, the relatively low spatial resolution of PET does not adversely affect the detection of these metastases because they are remote from the primary tumor or from areas of intense FDG uptake. Sensitivity, specificity, and positive predictive value to distant metastasis are, respectively,

65%, 99%, and 88%, similar to CT. The major advantage of [18]FDG-PET over anatomic imaging modalities is its capacity to detect distant solid organ metastases. Metastases to the liver, lungs, adrenal glands, and ovaries can be readily identified at FDG PET (18). [18]FDG PET has a little value in diagnosing peritoneal carcinomatosis, again hampered by its low sensitivity (mean 32%) but relatively high specificity (mean 88.5%). Some authors have reported that peritoneal lesions show an extensive fibrosis around relatively few malignant cells, wich could explain the low sensitivity of this imaging modalità, the small size of peritoneal nodules (<5 mm) could represent another reason for the low detection rate (19). The study of Lee *et al.* (20) demonstrated that [18]FDG uptake in gastric cancer is an independent and significant prognostic factor for predicting cancer recurrence after curative surgical resection. Patients with negative [18]FDG uptake in gastric cancer showed a significantly recurrences rate after surgical resection than patients with positive 18FFDG uptake. Furthermor, recurrence-free survival was significantly different between patients with positive and negative [18]F-FDG uptake. Therefore, although the detectability of [18]FDG-PET/CT for gastric cancer is low, preoperative 18F-FDG-PET/CT could provide effective information on the prognosis after surgical resection in patients with gastric cancer expecially in tubular and undifferenziated types. In addition, [18]FDG-PET has actually a significant role in monitorino the response to neoadjuvant chemotherapy, showing chemo-responders at early stage. It is anticipated that the use of new metabolic tracers, such as coline or methionine will improve the sensitivity of PET-CT in staging gastric cancer.

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Aberrant DNA methylation as sensitive and promising biomarkers in diagnosing of cancers

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A recent study by Yu *et al*. and co-workers have provided potential usefulness of methylation of CDH1 promoter in preoperative peritoneal washes (PPW) as a marker for prognostic indicator in gastric cancer patients (1). Epigenetic gene silencing by promoter CpG islands hypermethylation and subsequent transcriptional gene silencing are important mechanisms in the inactivation of tumor suppressor genes (2). DNA methylation has been deeply involved in the development and progression of many types of cancer and extensive researches in this field have suggested strong potentiality for the DNA methylation signatures to prognostically differentiate cancers beyond current clinical classifications (3-6). DNA methylation can also occur at the early stage of tumorigenesis in precursor lesions and aged or inflamed tissues (7-12) suggesting that epigenetic changes constitute the earliest steps toward neoplastic transformation by creating molecular diversity, which may be useful for identifying populations being at risk of developing carcinomas. Moreover, it is possible to detect very tiny amounts of methylated molecules among samples (13). Therefore, aberrant methylation can be considered as sensitive and very promising biomarkers in early diagnosing of tumors. For example, there have been studies showing the usefulness of DNA methylation analysis of mucosal wash as a tumor marker in the stomach and colon (14,15). It has been also proposed tumor cells can release DNA to peripheral blood and enriched circulating DNA level can be found in the serum of cancer patients, several times higher than cancer free subjects. Previous studies showed that methylation of multiple genes, derived from cancer tissues, were detected in blood plasma, urine, sputum and peritoneal washes in several cancers (16-21). The results suggest that examination of DNA methylaton in any source of samples could be utilized as a molecular diagnostic marker of cancer.

Yu *et al*. and co-workers evaluated this concept in gastric cancer. They collected preoperative peritoneal washes (PPW) from 92 gastric patients undergoing surgery. They chose CDH1 promoter as a candidate marker, which has been frequently methylated in gastric cancer and used real-time methylation specific-PCR, a sensitive method for measurement of methylated DNA. The result demonstrated good correlation of CDH1methylation with more aggressive clinicpathological subtypes of gastric cancer including larger sizes of tumors, infiltration type, lymphatic and venal invasion, higher T stage, lymph node and distant metastasis. There was a significant worse disease-free survival (DFS) among the patients with CDH1 methylation in their PPW. Cox regression analysis confirmed CDH1 methylation in PPW was an independent risk factor for gastric cancer patients, with a remarkable decrease in DFS after postoperative 30 months (1).

The current result supports the strong potentiality of DNA methylation as molecular diagnostic marker in universal types of samples, and opened the avenue for further researches of this field for the application of DNA methylation as a clinical test in diagnostic test in cancer treatment.

In recent years, several methods have been developed to provide a genome-wide landscape of the DNA.methylation status, highlighting the importance of unbiased approaches for DNA methylation mapping in cancer (3,4,6). Moreover, recent comprehensive genome-scale understanding of the DNA methylation loss and gain in cancer revealed

that most methylation alterations in cancer occur not in promoters, and also not in CpG islands, but in sequences up to 2 kb distant, termed 'CpG island shores', which shows tight link to gene expression (22). Advances in this field may further enable the clinical application of DNA methylation status as a diagnostic marker for cancer, and the discovery of specific methylation changes raises the possibility that specific epigenetic therapy may be useful for cancer treatment as shown in several neoplasms such as MDS and lymphoma (23).

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Diagnosis

Adenocarcinoma of esophagogastric junction requires a clearer definition

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Abstract: The past few years have witnessed two facts in gastric cancer research: the morbidity and mortality of gastric cancer has shown a significant downward trend worldwide; and the incidence of the adenocarcinoma of esophagogastric junction (AEG) has gradually increased in Western countries, which may be explained by the high prevalence of obesity and gastroesophageal reflux disease among the Western populations. AEG can be the collective name of the adenocarcinomas located in the proximal 1/3 of the stomach and in the lower part of the esophagus (within 5 cm above the Z-line). It covers the gastric cardia cancer, distal esophageal carcinoma, proximal gastric cancer, and cancer of the cardiac part of gastric fundus. A standardized definition of AEG will facilitate future scientific research and academic exchanges.

Keywords: Adenocarcinoma of the esophagogastric junction (AEG); staging; surgery

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Introduction

The past few years have witnessed two facts in gastric cancer research: the morbidity and mortality of gastric cancer has shown a significant downward trend worldwide (1); and the incidence of the adenocarcinoma of esophagogastric junction (AEG) has gradually increased in Western countries (2), which may be explained by the high prevalence of obesity and gastroesophageal reflux disease among the Western populations (3). The prevalence of gastric cancer is high in China, and the mortality of gastric cancer remains high in the rural areas; although the incidence of distal gastric cancer has slightly declined in the urban areas, the overall 5-year survival has not remarkably increased. Meanwhile, along with the rapid socioeconomic development in China, the lifestyles of many urban residents have increasingly been similar as those in the Western countries. As more people become obese, the high prevalence of AEG will also occur in China - in fact, such a trend has been reported (4). AEG has a poor overall prognosis, and its treatment needs to be improved (5).

The diagnosis and, particularly, treatment of cancers at the "gastroesophageal junction" had been highly controversial; the introduction of AEG has brought more problems and quarrels. In our opinion, defining the concept of AEG is the prerequisite for determining the research subjects, whereas more high-level clinical trials that are able to resolve these questions/quarrels are key to the improved treatment of AEG.

Defining the concept of AEG

Gastroesophageal junction is the structure that connects the esophagus and the stomach. Anatomically, it is known as the gastric cardia, which has no visible border with the other parts of the stomach. Malignancies located at this site have various names including AEG, cancer of cardia and stomach fundus, proximal gastric cancer, gastric cardia cancer, and distal esophageal carcinoma. In fact, the pathologic types of malignancies at the site also vary, which may include adenocarcinoma, squamous cell carcinoma, and, particularly, AEG. The concept of AEG, initially proposed

by German surgeon Siewert, refers to the adenocarcinomas with epicenter located within 5 cm proximal or distant to the Z-line (6). He noted this phenomenon because the prevalence of AEG was high in Western countries and is constantly growing. In fact, many Chinese doctors have noted this disease and conducted many relevant studies. However, due to its relatively confusing definition, AEG remains particularly controversial or lacks specialized research. A standardized definition will be critical for academic research on AEG. The World Health Organization (WHO) classification refuse the term "gastric cardia cancer" since it is ambiguous and sometimes misleading; rather, it recommends "proximal gastric cancer" or "gastric body cancer" based on the tumor size, although no clear definition of tumors at this site has been proposed. Similarly, the Union for International Cancer Control (UICC) tumor classification also does not distinguish the gastric cardia cancer from other gastric cancers. It has been widely accepted in China that AEG includes both the distal esophageal adenocarcinoma and gastric cardia adenocarcinoma. However, the so-called "gastric cardia adenocarcinoma" has also not clearly defined, and its relationship with the gastric cancer cannot be identified.

In our opinion, the esophageal cancer and the gastric cancer differ dramatically in terms of pathogenesis, biological behaviors, and treatment, whereas the adenocarcinomas above and below the cardia have similar biological behaviors as the proximal gastric cancer and distal esophageal carcinoma. Therefore, a uniform consideration in terms of diagnosis, treatment, and prevention will be more feasible. According to Siewert, the epicenter of AEG is located within 5 cm proximal or distant to the Z-line. We believe that the proximal edge is easy to determine, because the esophagus has relatively fixed length; in contrast, the distal edge is more likely to be affected by the stomach size. Generally speaking, in an adult, a moderately filled stomach has a mean length (from the fundus to the lower part of greater curvature) of 25-30 cm, and the size and morphology of the stomach vary as the stomach filling degree, body position, and body shape change. In addition, measurements of the *in vivo* and *in vitro* specimens often yield dramatically different results; distance alone can not reliably define the tumor type. In contrast, the Japanese Gastric Cancer Association (JGCA) gastric cancer classification is more useful in this regard. According to the Japanese Classification of Gastric Carcinoma (3rd edition), the stomach is anatomically divided into threeportions, the upper (U), middle (M), and lower (L) parts, by the lines connecting the trisected points on the lesser and greater curvatures. Therefore, we recommend that, be combining the Japanese classification and Siewert definition, AEG can be the collective name of the adenocarcinomas located in the proximal 1/3 of the stomach and in the lower part of the esophagus (within 5 cm above the Z-line). It covers the gastric cardia cancer, distal esophageal carcinoma, proximal gastric cancer, and cancer of the cardiac part of gastric fundus. A standardized definition of AEG will for sure facilitate scientific research and academic exchanges.

Unique features of AEG in China

The AEG, particularly the distal esophageal carcinoma, has shown increasingly prevalence in the Western countries. In the United States, the incidence of distal esophageal carcinoma has increased by 6 times in the past decades, and this carcinoma became the main esophageal cancer type since the late 1990s. Similarly, the proportion of the proximal gastric cancer among gastric cancers has also dramatically increased since 1970s, whereas the distal gastric cancer declined (7). The increased incidence of distal esophageal carcinoma may be related with gastroesophageal reflux disease and Barrett's esophagus; nevertheless, there is much controversy on the etiology of gastric cardia cancer (8). Esophageal squamous cell carcinoma is highly prevalent in China, similar as the gastric cardia cancer. The gastroesophageal junction connects the end of the esophagus and the beginning part of the stomach. It roughly equals to the lower edge of the lower sphincter, but is not consistent with the Z-line (i.e. the border between the squamous epithelium and cylindrical epithelium at the lower part of the esophagus). A survey conducted in a region with high esophageal and cardiac cancer incidences in Henan Province showed that, the rate of the upward shift in Z-line (≥3 cm), irregular histopathology, and unclear histopathology was 12%, 10%, and 1% under endoscope. In patients with the upward shift in Z-line, the frequencies of basal cell hyperplasia and anaplasia at the lower part of the esophagus remarkably increased. Meanwhile, the incidences of cardiac chronic superficial gastritis and chronic atrophic gastritis associated with intestinal metaplasia were significantly higher than those without upward shifted Z-line. Among the normal subjects in the highly prevalent region, the detection rates of Barrett's esophagus and reflux esophagitis were 0.5-2.4% and 5.0-6.0%, respectively. Among the cardiac cancers, the intestinal type accounted for over 60%, which was mainly seen in patients with intestinal

metaplasia, atrophic gastritis, active gastritis, or gastric cardia inflammation (9). As shown in the clinical reports, the overall proportions of proximal gastric cancer, cardiac cancer, and distal esophageal carcinoma accounted for about 30-40% of gastric cancer in China and Western countries, which were far higher than those in Japan and Korea (10,11). Therefore, AEG in China has unique etiologies when compared with the Western countries and also remarkably differs from those in Japan, Korea, and other Eastern Asian countries/regions with high prevalence of gastric cancer.

Typing of AEG and its surgical implications

AEG should be typed from the perspectives of basic research and clinical application. According to Siewert classification, tumors with the epicenter 1-5 cm proximal to the esophago-gastric junction (EGJ) was classified as type I tumor (adenocarcinoma of the distal esophagus); tumors with the epicenter 1 cm proximal to EGJ and 2 cm distal to EGJ was classified as type II tumor, which is the "true" cardiac cancer; tumors with the epicenter 2-5 cm distal to EGJ was classified as Siewert type III (in ferior cardiac cancer). This classification assumes that the tumors grow in a symmetric manner, which obviously has certain limitations. Furthermore, it is often challenging to distinguish the subtypes of an advanced tumor. Anyway, the Siewert classification remains the most commonly accepted system. As reported by Siewert *et al.* (12), the types I, II, and III accounted for 35.9%, 28.7%, and 35.4%, respectively. Bai *et al.* (13) reported 203 cases and found that the types I, II, and III AEG accounted for 14.3%, 39.4%, and 46.3%, respectively. In our series, we summarized the data of 471 patients and found that the type I AEG accounted for only 4.7% (14), which is consistent with the findings in Japan and Korea (15). It has been widely agreed that the distribution of Siewert types of AEG differs between Asian countries and the Western countries. Data have shown that the high AEG prevalence in Western countries is related with gastroesophageal reflux disease, and its risk factors include alcoholism, obesity, and smoking. The pathogenic mechanism of AGE significantly differs between the Eastern Asian countries and Western countries, although remained unclear.

In terms of survival, most studies believe that the prognosis of patients with Siewerttype I AEG is poorer than those of patients with type II and type III (16), whereas the type II and type III have similar prognoses. Fang *et al.* (17) reported that among 231 patients wtih Siewert type II and III AEG, the 5-year survival was 59.6% and 63.5%, respectively (P=0.947). Our studies have also yielded the same conclusions. Obviously, the Siewert type II and type III AGE are more alike, and meanwhile are different from type I. In fact, it has increasingly recognized that Siewert type I AGE is more similar to esophageal cancer, whereas the type II and type III close to the gastric cancer.

Also, there is no consensus on the surgical approaches for AEG. The conventional surgical procedures for AEG include Ivor-Lewis operation, transhiatal esophagectomy, surgical resection of left transthoracic approach, and thoracoabdominal approach. These methods have their unique advantages and disadvantages, and are preferred by different doctors. The surgical resection of left transthoracic approach can ensure the complete dissection of the posterior mediastinal lymph nodes and achieve negative esophageal resection margin, but has shortcomings including insufficient dissection of abdominal lymph nodes and high incidences of post-operative complications. The abdominal surgeries also have their limitations: they can not sufficiently cut off the esophagus and completely dissect the lower mediastinal lymph nodes. Siewert *et al.* (12) reported that, in patients with Siewert type I AEG, the proportion of lower mediastinal lymph node metastasis accounted for 50% of the total number of lymph node metastasis, whereas in type II and type III AEG, it accounted for 11% and 5%, respectively. According to Ichikura *et al.* (18), the rate of mediastinal lymph nodes involvement was 14% in Siewert type II AEG, while the metastasis rates in lymph nodes near the cardia, lesser curvature, and left gastric artery were 76%, 48%, and 33%, respectively. Although the metastasis rates differed among different studies, a basic fact is that abdominal lymph node metastasis remains the main finding in patients with Siewert type II and type III AEG. Therefore, a thorough dissection of abdominal lymph nodes is warranted. The JCOG9502 trial, a multi-center randomized controlled study, enrolled totally 167 patients, with am aim to compare the left thoracoabdominal approach (LTA) with the abdominal-transhiatal approach (TH) in the treatment of the gastric cancer of the cardia or subcardia. Its main follow-up endpoint was the overall survival. LTA does not improve survival after TH and leads to increased morbidity in patients with cancer of the cardia or subcardia, LTA cannot be justified to treat these tumours; it is not recommended for Siewert type II and type III AEG (19). Therefore, the following consensus has been reached concerning the surgical approaches for AEG: the Siewert type I AEG should be treated as esophageal cancer. For Siewert type

I and type III AEG, abdominal surgery is recommended; however, efforts should be recommended to ensure the complete dissection of the posterior mediastinal lymph nodes and achieve negative esophageal resection margin; meanwhile, the lower mediastinal lymph nodes should also be dissected. Compared with the surgical approaches, the D2 dissection of abdominal lymph nodes is more important, which has also been a priority in the standardized surgical treatment for gastric cancer.

The 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging criteria for gastric adenocarcinoma has included AEG in esophageal cancer, which has caused a lot of controversy. Huang *et al.* (20) retrospectively analyzed 142 AEG patients with esophageal involvement and found that the gastric cancer staging can better predict the patient's prognosis. Some Korean scholars reviewed the clinical data of 4,534 cases from a single center and found that, among 497 AEG cases (all were Siewert type II and type III), the esophageal cancer staging criteria could not provide accurate staging for AEG (21). Currently the 8th edition of AJCC TNM staging criteria for gastric adenocarcinoma is under preparation, during which this issue is expected to be further discussed.

Conclusions

In China and many other East Asian countries/regions, whether AEG should be classified as an independent cancer remains controversial in terms of pathogenesis, population differences, surgical techniques, and staging. The proportion of Siewert type I AEG is low in China; anatomically, it belongs to esophageal cancer, so does its diagnosis and treatment. The Siewert type II and type III AEG are more likely to be gastric cancer, and their clinical features, diagnosis, and treatment are similar; also, they can not be strictly distinguished from the proximal gastric cancer or cancer of the cardiac part of gastric fundus. However, most Siewert type II and type III AEGs are already in the advanced stages and large in size, and it is often difficult to accurately distinguish them. In summary, AEG can be the collective name of the adenocarcinomas located in the proximal 1/3 of the stomach and in the lower part of the esophagus (within 5 cm above the Z-line). It covers the gastric cardia cancer, distal esophageal carcinoma, proximal gastric cancer, and cancer of the cardiac part of gastric fundus. A standardized definition of AEG will facilitate future scientific research and academic exchanges.

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Updating advances and controversies on the multidisciplinary therapy of gastric cancer

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Abstract: Gastric cancer is one of the most common malignancies. In recent years, the overall treatment modality of gastric cancer has been an integrated mode that combines standardized surgery and perioperative adjuvant therapies based on anatomy, tumor biology and immunology. Reasonable staging of gastric cancer is of great significance in guiding the choice of integrated treatment programs, determination of the efficacy and prognosis. Despite more detailed and accurate staging for gastric cancer and prognosis identification in the updated staging system, more are left to be solved. At the same time, the role of free intraperitoneal cytology and laparoscopy in staging should also be given adequate attention. In terms of operations, after years of extensive debate and exploration, D2 lymph node dissection involving nodes around named branches of the celiac trunk has been considered as a standard treatment. While the development of perioperative adjuvant treatment has substantially improved the outcomes of advanced gastric cancer, altered treatment strategies have also brought new challenges. In recent years, the rapidly developed new treatment technologies and targeted therapy combined with traditional chemotherapy provide a new opportunity for breaking through the existing bottleneck in this field.

Keywords: Gastric cancer; multidisciplinary therapy; advances; controversies

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Introduction

Gastric cancer is one of the most common malignant tumors. Data show a global annual increase of about 934,000 gastric cancer patients and about 734,000 deaths worldwide, with 56% from China and Japan (1). Although surgery is still the primary treatment option for gastric cancer, the treatment model has undergone significant changes: the previously used simple gastrectomy has been replaced by radical approaches aiming at lymph node dissection; and anatomy-based operations are giving their place to an integrated mode that combines standardized surgery and perioperative adjuvant therapies based on anatomy, tumor biology and immunology. This article summarizes the latest research advances and clinical significance of the multidisciplinary management of gastric cancer in recent years as follows.

Staging of gastric cancer

Reasonable staging is the first step in the multidisciplinary management of gastric cancer, a significant link for the choice of treatment programs and determination of the efficacy and prognosis. Since its first edition in 1977, the TNM staging system has been used as a basis for the clinical staging of gastric cancer and a standard staging method in each update of the clinical diagnosis and treatment guidelines of gastric cancer. On January 1, 2010, the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) promulgated the 7th edition of TNM staging (2), including a new set of TNM staging criteria for gastric cancer. Compared with the 6th edition of TNM staging in 2003, the new system includes major adjustments regarding the identification of tumor invasion, lymph node metastasis and

other aspects of gastric cancer.

These include:

(I) T stage: (i) the original T1 is divided into T1a (tumor invasion confined to the mucosa) and T1b (invasion of the submucosa); (ii) the original T2 is divided into T2 (tumor invasion of the muscle) and T3 (invasion of serosal connective tissues); and (iii) the original T3 and T4 are respectively changed to T4a [tumor invasion through the serosa (visceral peritoneum) but no invasion of adjacent structures], andT4b (tumor invasion of adjacent structures).

(II) N stage: using a cutoff of three metastatic nodes, the original N1 was divided into N1 (metastasis of 1-2 regional lymph nodes) and N2 (3-6 regional lymph node); and The original N2 and N3 are combined as N3 (metastasis of 7 or more regional lymph nodes).

(III) M stage: Mx (distant metastasis unassessable) is removed.

The new staging system was subject to academic verification from different angles after its release. Qiu *et al.* (3) conducted a retrospective analysis of 1,000 patients with gastric cancer, and found that the 7th version was not as efficient as the 6th version in predicting the 5-year survival. Ahn *et al.* (4) compared the two staging criteria in 9,998 cases of gastric cancer, however, suggested that the new one better reflected the difference in survival between patient groups. Nevertheless, these changes signify more active and meticulous treatment strategies for gastric cancer patients with regional lymph node metastasis as developed by the international academic community, which is consistent with China's past experience in this regard. In this revision, however, the original IV stage regarding non-distant metastases has been moved forward. Whether this adjustment is reasonable remains subject to further discussion, and the relevant verification and analysis is underway. Moreover, in light of the lacking of sufficient data on individualized treatment, the modification of treatment strategies in line with the updated staging also needs to be further studied.

In Japan, anatomic classification of lymph nodes based on the location of primary lesions has been used to determine the degree of metastasis (N1-N3, M1) and staging and define the corresponding dissection scope (D1-D3) until the provision of the 13th edition. However, in view of the complexity and lacking of objective identification of the location of primary lesions and metastatic lymph nodes, these staging criteria have not been accepted by non-oncologists as well as investigators in other countries. Meanwhile, a growing number of studies have shown that classification based on the number of metastases is a better indicator of prognosis than the anatomic one. Therefore, the anatomic N stage staging has been abolished and replaced by the lymph node-based methodology in the new Japanese guidelines and management protocols. The current revision fully reflects the general applicability and objectivity of tumor staging valued by both Eastern and Western scholars.

At present, the primary means for diagnosing gastric cancer include endoscopy, endoscopic ultrasound, CT, PET-CT and MRI, where pathological diagnosis is still the gold standard. Difficulty in determining the depth of invasion and lacking the ability to identify metastases to lymph nodes and distant tissues make traditional endoscopy only a qualitative diagnostic tool, which can not be used for staging. Endoscopic ultrasound has an accuracy up to 80.3% in preoperative staging of gastric cancer, and has particularly great clinical significance in determining levels of tumor invasion. CT and MRI have a higher sensitivity for lymph node metastasis and distant metastasis. In addition, preoperative diagnostic laparoscopy enables accurate observation of the location and extent of the primary tumor, lymph nodes, peritoneal metastasis and invasion of adjacent tissues, and is thereby gaining more and more attention in recent years. Muntean *et al.* (5) conducted staging laparoscopy (SL) for 45 patients with gastric cancer and found that the tool had an overall sensitivity of 89%, specificity of 100% and diagnostic accuracy of 95.5%. It also showed 54.5% sensitivity, 100% specificity and 64.3% accuracy for lymph node metastases. On the other hand, PET/CT has been more and more valued in the assessment of resectable gastric cancer. Hur *et al.* (6) suggested in a study that a higher ^{18}FDG uptake of the primary tumor and regional lymph nodes may indicate a higher degree of local progression and lower chance for radical treatment, hence reducing the possibility of a simple laparotomy.

Treatment options for early gastric cancer

The Japan Gastrointestinal Endoscopy Society first introduced the concept of early gastric cancer (EGC) in 1962 (7). EGC is confined to the intramucosal leision, regardless of its size or lymph node metastasis. It is generally believed that lymph node metastasis may occur even in early gastric cancer, and thus D2 resection has been regarded as the standard surgery for early gastric

cancer. With deepened studies on the molecular biology and clinical pathology of EGC and gradual understanding of the pattern and biological behavior of lymph node metastasis, the treatment model has undergone great changes. Surgeries with narrowed scope of gastrectomy and lymph node dissection are introduced, including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), laparoscopic wedge resection (LWR), intragastric mucosal resection, (IGMR), laparoscopic-assisted radical gastrectomy and other surgical procedures. Many long-term follow-up results show that with appropriate surgical indications, minimally invasive surgery has benefits of less postoperative pain, faster recovery of gastrointestinal function and less blood loss without increasing postoperative recurrence of cancer.

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)

The currently accepted indications for EMR treatment of EGC include visible mucosal carcinoma (cT1a) with a size <2 cm, differentiated histological type and no formed ulcers. Studies have confirmed that lymph node metastasis is rare among cases with those indications. If pathological results confirm invasion of the superficial submucosa without involvement of vessels, gastrectomy or close follow-up may be applied. If SM1 is invaded with vascular and lymphatic involvement or infiltration of deep submucosal SM2, D2 gastric resection should be added. Introduced since 2000, ESD has the following advantages compared with EMR: (I) Resection with controllable scope and size, enabling complete removal of even large tumors; and (II) Ulcer lesions are no longer a contraindication for ESD. Therefore, ESD can achieve complete removal of larger even ulcer lesions. EMR or ESD currently facing the biggest problem is how to improve the accuracy of preoperative staging.

Laparoscopic assisted gastrectomy

In recent years, Japanese scholars put forward that laparoscopic gastrectomy is suitable for about 20% of candidates of gastric cancer surgery (8,9). So far, however, randomized controlled trials with a large sample comparing laparoscopic (assisted) surgery and open surgery are still lacking, and there are only a few small-scale controlled trials available (10,11). No high-level evidence was derived from these results to demonstrate the superiority of laparoscopic surgery, as a minimally invasive treatment, in the intraoperative bleeding volume, respiratory dysfunction, narcotic dosage, and length of hospital stay or other indicators (12). Hence, laparoscopic surgery is still considered only for IA, IB patients and as an experimental option. The recommendation grade of laparoscopic surgery for gastric cancer is merely "C" in the Japan Society of Laparoscopic Surgery Clinical Guidelines. Therefore, although it is technically feasible to perform laparoscopic surgery for a strict selection of gastric patients to achieve as effective D2 resection as open surgery, this modality needs to be further explored due to the lacking of clinical trial results with a large sample and evidence-based design.

Function-preserving minimally invasive surgery

This mainly includes the following types: (I) Laparoscopic assisted vagus-preserving radical surgery; (II) Pylorus-preserving gastrectomy (PPG); (III) Laparoscopic assisted vagus sparing segemental gastrectomy (LAVSSG). These approaches improve the quality of life by preserving the hepatic and celiac branches of the pyloric vagus and thus effectively improving postoperative digestive function and reducing the incidence of gallstones (13) and diarrhea. However, due to overlapping indications with endoscopic surgery, it is not commonly used in conventional therapy. Careful consideration should be given to older patients and those with poor body conditions. However, since function-preserving local excision provides better quality of life (14) after operation, renewed assessment may be possible as diagnostic techniques (such as sentinel lymph node detection technology) advance and standard options change.

Multidisciplinary management of advanced gastric cancer

Surgical treatment

The long-term survival in patients with advanced gastric cancer is less than 30%. Surgery has dominated in the combined treatment for long. Two preliminary consensuses are present in gastric cancer surgery: surgery alone can not provide biologically radical treatment even with extended resection and lymph node dissection; and palliative resection enables better outcomes in patients without distant metastasis than those untreated. For advanced gastric cancer, a commonly accepted practice is standard surgery for the purpose of radical resection, which requires removal of 2/3 or more of the stomach and

Table 1 Randomised trials comparing the extent of lymphadenectomy

	Arm	N	Morbidit (%)	Mortalit (%)	5-year survival (%)	10-year survival (%)	15-year survival (%)
Cuschieri *et al.* (1999) (21)	D1	200	28	6.5	35	–	–
	D2	200	46	13	33	–	–
Bonenkamp *et al.* (1995) (22); Hartgrink *et al.* (2004) (23); Songun *et al.* (2010) (16)	D1	380	25	4	45	30	21
	D2	331	43	10	47	35	29
Degiuli *et al.* (2004) (24)	D1	76	10.5	1.3	–	–	–
	D2	86	16.3	0	–	–	–
Wu *et al.* (2006) (25)	D1	110	7.3	0	53.6	–	–
	D3	111	17.1	0	59.5	–	–
Sasako *et al.* (2008) (26)	D2	263	20.9	0.8	69.2	–	–
	D2+PAND	260	28.1	0.8	70.3	–	–

D2 lymph node dissection to ensure R0 resection of the primary tumor (distance between gross margin and the original lesion >5 cm and microscopic negative margins). Correspondingly, non-standard operations may also be available with varying resection and dissection extents based on disease progression.

Scope of lymph node dissection

The scope of lymph node dissection has been a highly controversial topic in studies of gastric cancer. Most investigators from Japan, China, Korea and some from Europe and the US suggest extended lymph node dissection (ELND), which is advised against by most European and American investigators. In recent years, however, they have accepted most of the Asian opinions with the release of a series of large-scale randomized controlled trial results. A retrospective analysis of the data of 1,377 patients undergoing gastric cancer resection from the US-SEER database showed that the longest survival period of advanced patients was among those with 15 or more N2 lymph nodes or 20 or more N3 lymph nodes (15). A 15-year follow-up of the Dutch study also revealed increased survival after D2 dissection. A further analysis of the cause of death pointed out that the mortality related to gastric cancer after D2 operation was obviously lower than those undergoing D1 dissection (37% versus 48%, P=0.01), whereas higher perioperative mortality as a result of the combined splenectomy or pancreatectomy was a major cause of bias in the study (16). The Italian gastric cancer study group reported the results of pancreas-preserving D2 dissection, which confirmed that the perioperative morbidity and mortality of D2 was comparable to D1 surgery (17). Australia and Spainish studies also demonstrated that D2 surgery improved patients' quality of life without increasing their risk of perioperative mortality (18,19). Enzinger *et al.* conducted a subgroup analysis of the highly controversial INT0116, showing that D1 or D2 surgery tended to improve survival in centers with a relatively large number of gastric cancer patients (20).

Therefore, starting from the 2010 version, NCCN guidelines for surgical treatment of gastric cancer have particularly provided that "modified" D2 surgery (not combined with pancreatectomy or splenectomy) performed by experienced surgeons in larger-scale cancer centers could actually provide lower mortality and better survival benefits. Hence, "radical surgery for gastric cancer should be completed by experienced surgeons in a large cancer center, which should include dissection of regional lymph nodes-perigastric lymph nodes (D1) and lymph nodes along the named vessels accompanying the celiac trunk for the purpose of examining at least 15 or more lymph nodes". D2 lymph node dissection involving nodes around named branches of the celiac trunk has been considered as a standard treatment.

Extensive surgery

Extended radical resection is performed for primary gastric cancer or metastases that directly invade perigastric organs (T4) or those with lymph node metastasis of N2 where radical resection is still avaliable (*Table 1*). This includes: Extensive resection combined with removal of other organs; and D2 or above level lymph node dissection, such as

surgeries targeted at IIIa, IIIb and some IV lesions involving the number 16 lymph nodes.

(I) Extended resection combined with removal of the pancreas and the spleen

Since dissection of numbers 10 and 11 lymph nodes is required for D2 dissection in upper gastric cancer, some investigators suggested combined resection of the left pancreas, the splenic artery and vein and the spleen. However, this brought to a high incidence of severe postoperative complications such as pancreatic fistula, intra-abdominal infections and diabetes. Wang *et al.* (27) randomly assigned 84 patients with advanced gastric cancer to receive pancreas-preserving radical resection (38 cases) and combined pancreatic resection (46 cases). As a result, postoperative complication rates were 23.7% and 52.2%; respectively, while the postoperative 5-year survival rates were the opposite 42.4% and 35.6%, suggesting that routine combined resection of the head and tail of the pancreas should be avoid in upper and medium advanced gastric cancer. Therefore, combined pancreatectomy is often not recommended when the lesion is not invading this organ and only metastasis of the lymph nodes around the splenic artery or splenic hilum is suspected. Left pancreatic resection combined with splenectomy is only indicated for patients whose gastric cancer has directly invaded the pancreas.

For advanced gastric cancer of the upper stomach, it has been controversial as to whether splenectomy should be combined for complete dissection of numbers 10 and 11d lymph nodes. In particular, European and American investigators have regarded this combination as a high-risk modality. Recent studies have found that the occurrence of splenic lymph node metastasis is mostly associated with gastric cancer at the cardia area, with an incidence of 9.8-14%, and is mainly observed in advanced tumors that have invaded into or beyond the serosa (T4). Since direct violation of the spleen is clinically rare, prophylactic splenectomy does not provide better outcome for the treatment of gastric cancer than spleen-preserving approaches and it is therefore not routinely advised. A number of clinical trials, including the (28) Japanese JCOG0110, are underway to explore this practice. Nonetheless, the preliminary consensus for now is that splenectomy should be performed as long as the spleen is directly invaded by IIIb and IV gastric cancer at the cardia or greater curvature, or circulation metastasis and splenic lymph node metastasis is present.

In short, for gastric cancer of the upper and medium part of stomach that invades the tail and head of pancreas, total gastrectomy should be combined with spleen and pancreatic resection; in the case of metastasis of the numbers 10 and 11 lymph nodes, combined splenectomy should be considered. Prophylactic splenectomy should not be performed when there is no metastasis to numbers 10 and 11 lymph nodes.

(II) Lymph node dissection at the level of D2 or above

The significance of extended dissection is unclear. The significance of prophylactic number 16 lymph node dissection has been denied by a Japanese randomized controlled trial (JCOG9501) (26). For metastasis to the number 16 lymph nodes without other non-radical curable factors, although R0 could be achieved by D2+No.16 dissection, the outcomes remain poor. Whether D2 or D2+No.16 should be the choice following downstaging by preoperative chemotherapy is still under study.

Perioperative treatment

Perioperative chemotherapy

Changes in the trend of managing solid tumors such as breast cancer and lung cancer have in large part triggered a revolution in the field of tumor treatment. It is recognized that tumor is a systemic disease even in the early stages, which entails systemic management such as chemotherapy. Tumor recurrence and metastasis are associated with not only the completion of surgical resection and lymph node dissection, but also the presence of micrometastases and its further growth and proliferation, which play a more important role. For a long time, attempts have been made with adjuvant chemotherapy to control relapse and metastasis, though no satisfying, definite results have been produced. Adjuvant chemotherapy after the resection of primary lesions does not achieve individualized effects even applied according to the specific staging. Therefore, the concept of preoperative adjuvant therapy (also known as neoadjuvant therapy) has been introduced based on the experience of adjuvant therapy, which includes neoadjuvant chemotherapy, neoadjuvant radiotherapy and neoadjuvant chemotherapy. The introduction and application of preoperative neoadjuvant treatment has been a challenge of the new century to both cancer surgeons and physicians (*Figure 1*).

The most representative clinical trial regarding perioperative chemotherapy is the UK MAGIC study (29). In the study, three cycles of epirubicin combined with

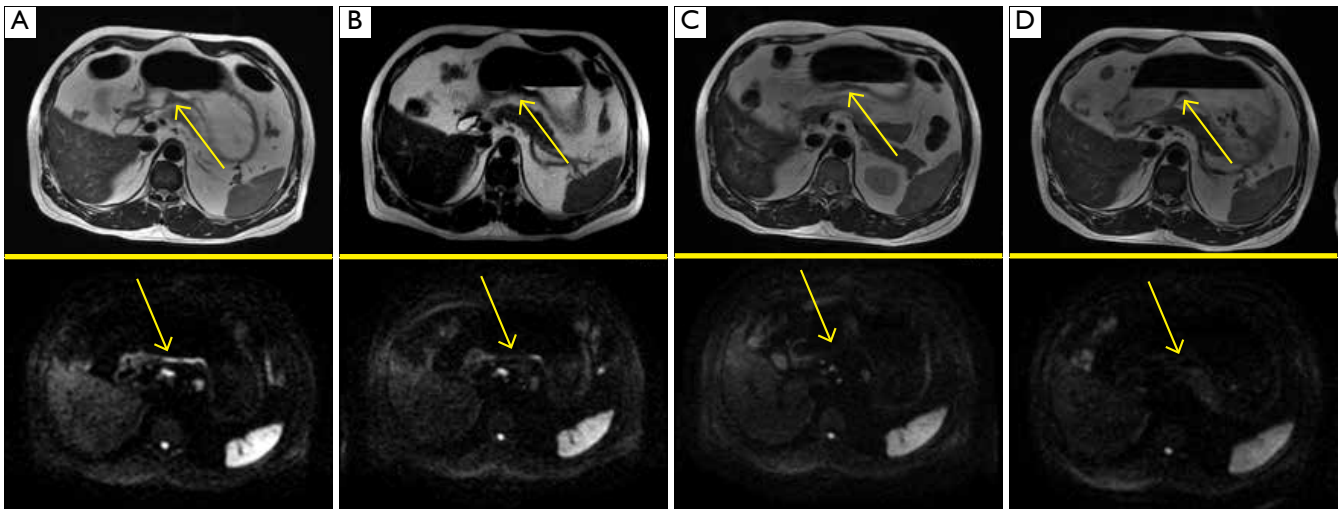

Figure 1 Metabolic response to chemotherapy. Patient with CT and EUS staged T4aN2 disease underwent laparoscopy with peritoneal washings, which was negative for M1 disease. Combined PET/CT was performed prior to the initiation of chemotherapy in the form of Oxaliplatin and TS-1 (Panel A). Repeat imaging was obtained after 2-cycles intervals. Note, the decreased metabolic uptake within the primary tumor which corresponded to a decrease in tumor size seen on CT. The patient underwent radical D2 gastrectomy and was found to have pathological complete response.

cisplatin and 5-FU (ECF regimen) chemotherapy were given respectively before and after surgery, and were well tolerated in the 86% patients who completed the preoperative chemotherapy. In the combination therapy group, 229 patients (92%) received surgical exploration, of which 69% received radical surgery, while only 66% patients received radical treatment in the surgery alone group. There was no significant difference in the postoperative mortality and surgically related mortality between the two groups. Pathological tumor size was used to evaluate the efficacy of treatment, and the results showed a significantly lower value in the combination therapy group than in the surgery alone group (P<0.001). The disease-free survival and 5-year survival rate in the combined treatment group were significantly prolonged, with a 25% decrease in the risk of recurrence and metastasis (HR=0.75, P=0.009). The results suggested that perioperative chemotherapy might improve long-term survival in patients with advanced gastric cancer, where neoadjuvant chemotherapy could downstage the T, N staging of locally advanced gastric cancer and improve the surgical cure rate.

Currently accepted principles of neoadjuvant chemotherapy necessitate control of micrometastasis in high-risk groups with locally advanced yet radically resectable cancer. The specific indications include clinical stage II-IIIb (cT3-4, cN1-2) with the use of following regimens: EEP (30), ECF (29), OLF (Oxaliplatin, leucovorin, 5FU) and so on. For cases whose lesions are not radically resectable, the objective will be downstaging III and IV advanced tumors with a larger size and extensive lymph node metastasis. The specific indications include cT3-4, cN2-, M1 (LYM) with the use of following programs: P-ELF (CDDP, etopiside, leucovorin, 5-FU), EAP (etopiside, ADR, CDDP), CPT-11 + CDDP (31), PLF (32), S-1 + CDDP, OLF (Oxaliplatin, leucovorin, 5-FU), DCF (Docetaxel, CDDP, 5-FU) and so on. Phase III clinical trial results have confirmed that radiotherapy is effective against tumors of the gastroesophageal junction (33). In addition, although there are reports that potent chemotherapy may achieve a higher negative conversion rate for patients with positive peritoneal free cells, a high level of clinical evidence is still lacking.

Regarding adjuvant chemotherapy after surgery, the INT0116 (34) study and MAGIC study (29) from the US have respectively proved the effectiveness of postoperative 5-FU/LV combined with radiotherapy and ECF (Epirubicin + CDDP + 5-FU) for preoperative/postoperative chemotherapy, though neither of them is not as effective as the overall result in the Japanese trial. The latest ACTS-GC trial has (35) confirmed that one-year TS-1 adjuvant chemotherapy after D2 radical treatment for stage II and III gastric cancer is associated with increased survival

Table 2 Randomized trials of surgery only versus surgery combined with chemotherapy or chemoradiotherapy

	Arm	N	RFS (%)	OS (%)
MacDonald *et al*. (2001) (34)	Surgery only	275	31 (3-year)	41 (3-year)
	CRT	281	48 (3-year)	50 (3-year)
Cunningham *et al*. (2006) (29)	Surgery only	253	–	23 (5-year)
	ECF	250	–	36 (5-year)
Sasako *et al*. (2011) (35)	Surgery only	530	53.1 (5-year)	61.1 (5-year)
	S-1	529	65.4 (5-year)	71.7 (5-year)
Boige *et al*. (2007) (38)	Surgery only	111	21 (5-year)	24 (5-year)
	FP	113	34 (5-year)	38 (5-year)

CRT, postoperative chemoradiotherapy (fluorouracil plus leucovorin followed by 45 Gy radiotherapy); ECF, Three preoperative and three postoperative cycles of epirubicin, cisplatin, and fluorouracil; S-1, cycles of S-1 (orally active combination of tegafur, gimeracil, and oteracil) for 1 year postoperatively; FP, 2–3 cycles of preoperative fluorouracil and cisplatin; postoperative FP was recommended for patients with a response or stable disease with pN+.

(71.7% *vs*. 61.1%, HR=0.669, 95% CI: 0.540-0.828) and decreased risk of recurrence and metastasis by 34.7% (HR=0.653, 95% CI: 0.537-0.793). The SPIRITS (36) study compared TS-1 combined with cisplatin and TS-1 single-drug treatment in 305 patients with gastric cancer from 38 centers in Japan. The results showed that the combined treatment group had significantly better overall and progression-free survival than the single-agent S-1 group. Therefore, for the initial treatment of gastric cancer patients with standard chemotherapy, Japanese investigators recommend TS-1 + CDDP36 (36), while the ECF program is still the traditional treatment recommended by western countries. Since 2009, NCCN guidelines have included paclitaxel -based chemotherapy (2B evidence level) in systemic gastric cancer chemotherapy and valued sorafenib and other targeted agents in combination with conventional chemotherapy. With the announcement of the ToGA study results (37), the therapeutic value of chemotherapy combined with trastuzumab for HER2-positive advanced gastric cancer patients has been confirmed by investigators from various countries, and this therapy has been included in the standard program for metastatic or locally advanced gastric cancer treatment (2A evidence level). Throughout the recent years, targeted drugs may have been playing a increasingly important role in the non-surgical treatment of gastric cancer, a trend shown in relevant clinical trials.

Perioperative radiotherapy

Preoperative induction chemotherapy followed by chemoradiotherapy can produce significant pathological remission and prolong the survival of gastric cancer patients (*Table 2*). MacDonald *et al*. (34) conducted a randomized controlled study (INT0116) on 556 patients undergoing surgery alone or combination of postoperative radiotherapy and chemotherapy (5-FU/LV +45 Gy radiotherapy), which showed that postoperative radiotherapy and chemotherapy was associated with prolonged survival. Since then, the program became the standard treatment in the United States. At present the CALGB80101 study is comparing it with the ECF program. However, in view of the 10-year follow-up results from the INT0116 study, the efficacy was limited in all subgroups except for poorly differentiated adenocarcinoma. The Korean randomized controlled study using capecitabine/cisplatin (XP) as a control group is also in progress.

Intraperitoneal hyperthermic chemotherapy

The postoperative recurrence rate gastric cancer is high and peritoneal recurrence is the most common form with an overall incidence up to 50% for patients with advanced gastric cancer postoperatively. Developed in recent years, the intraperitoneal chemo-hyperthermia (IPCH) is one of the highly valued therapeutic tools, which combines the anti-cancer effects of synergies from regional chemotherapy and hyperthermia. This easy-to-operate technology, showing significant effects both in the prevention and treatment of peritoneal metastasis or postoperative recurrence of advanced gastrointestinal cancer with small toxicity, has become an ideal surgical adjuvant therapy.

Gastric cancer patients with no distant metastasis that involves the liver, lung, brain or bone and no serious organic complication of the heart, lung , liver, kidney and

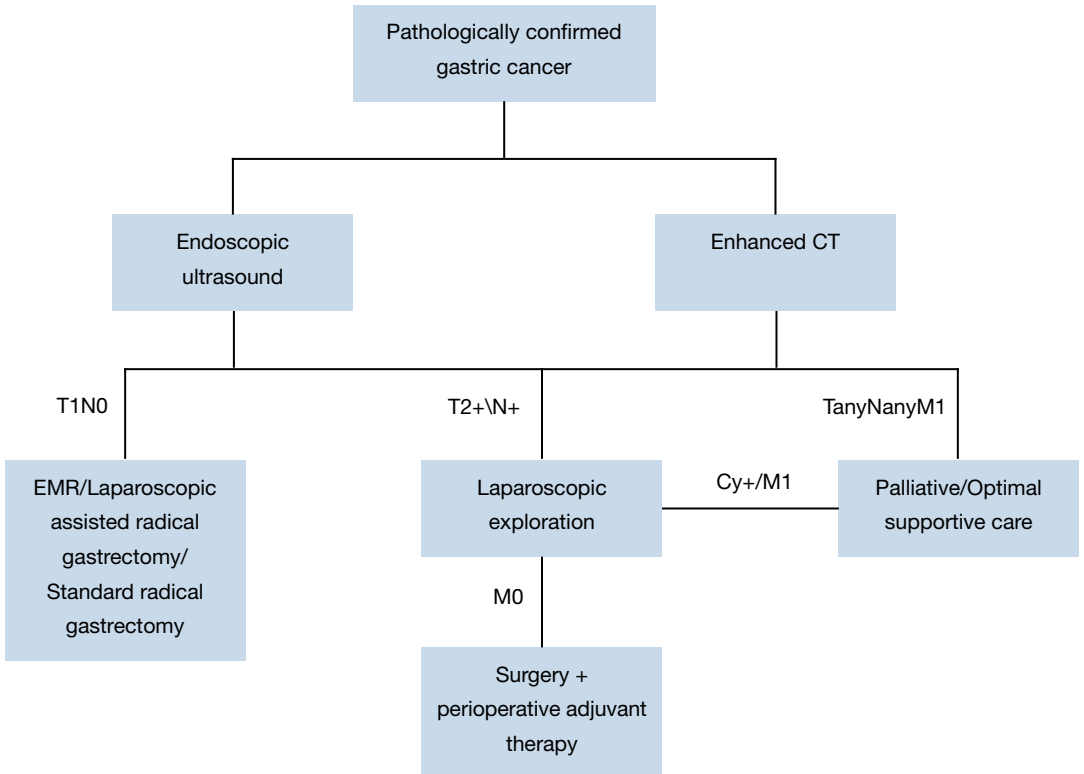

Figure 2 The multidisciplinary therapy of gastric cancer

other vital organs, who have had the primary foci cured or palliatively resected and have one of the following conditions, are eligible for IPCH treatment: (I) Positive for intraperitoneal free cancer cells (FCC); (II) Tumor invasion into or beyond the serosa, or peritoneal metastasis; and (III) Postoperative scattered peritoneal recurrence or small or moderate malignant ascites, for whom radical cytoreductive surgery is possible, i.e. surgical removal of as much visible metastases as possible, particularly nodules on the peritoneal surface. Relevant articles have noted that hyperthermic perfusion chemotherapy is only effective on nodules of 3-5 mm. Therefore, to achieve satisfying outcomes, it is recommended to perform IPCH therapy following minimization of the intra-abdominal tumor burden.

In summary, the new mode of 'surgery + perioperative therapy' has come on the stage of gastric cancer treatment (*Figure 2*). With the development of medical technology and wide application of more and more novel technologies, evidence-based approaches in combination with the strengths of various treatments will be the key to multidisciplinary management of gastric cancer for ultimately improving the outcomes and quality of life of these patients.

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Multidisciplinary approach for the treatment of gastric cancer

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In the past, gastric cancer (GC) with stage IV was considered as a terminal illness and a generalized form of cancer. Even though, patients with stage IV GC were offered a palliative chemotherapy or a best supportive care, median survival was 6 to 12 months.

In the late 1990s, TS-1, irrinotecan, taxanes and oxaliplatin (OHP) were introduced for gastric cancer treatment. The response rates after monotherapy with these drugs were around 20%. While chemotherapy in combination of two or three of these drugs have shown an excellent response rate of 42% to 74% with a prolonged survival (1,2). However, treatment failure as a result of toxicity was also reported (3,4). More recently, combination chemotherapy with an oral fluoropyrimidine (S-1 or capecitabine) and platinum (cisplatin: CDDP or OHP) has been recognized as standard chemotherapy for metastatic gastric cancer all over the world (5).

Even though high response rate to systemic chemotherapy was achieved, GC with stage IV is still dismal. Overall survival by systemic chemotherapy alone is less than 5% for 5-year, whereas, no survival benefit has been reported by cytoreductive surgery (CRS) alone.

The current state-of-the-art treatment to improve the long-term survival for GC with stage IV consists of a comprehensive management strategy using CRS and perioperative chemotherapy. The strategy is now performed in a curative intent. CRS plus perioperative chemotherapy including neoadjuvant chemotherapy, intraoperative intraperitoneal chemotherapy combined with hyperthermia, early postoperative intraperitoneal chemotherapy confers a prolonged survival period (6).

The aims of neoadjuvant chemotherapy (NAC) are stage reduction, eradication of micrometastasis outside the surgical field, and the improvement of resectability. Systemic chemotherapyis used for bulky lymph node metastasis or liver metastases. S1 plus CDDP can be given as a standard first-line chemotherapy, and the one-year survival rate of CRS after NAC with S1 plus CDDP was 75% (2).

The most frequent form of distant metastasis from GC is peritoneal carcinomatosis (PC). However, systemic chemotherapy shows little effects on the PC. Intraperitoneal (IP) chemotherapy for PC offers potential therapeutic advantages over systemic chemotherapy by generating high local concentrations of chemotherapeutic drugs in the peritoneal cavity (7,8). This concentration difference enables to eradicate small PC nodules before CRS and lowers the systemic toxicity.

Recently, bidirectional chemotherapy combined with simultaneous administrating intravenous and IP chemotherapy was developed (9). Bidirectional diffusion gradient can create a wider treatment area than single treatment. This approach was given in acronym neoadjuvant intraperitoneal and systemic chemotherapy (NIPS). NIPS is used before surgery to reduce the peritoneal surface involved by peritoneal dissemination, and to eradicate peritoneal free cancer cells. Accordingly, NIPS can increase the incidence of complete cytoreduction, resulting in the survival improvement (9). In addition, NIPS did not add to the morbidity and mortality of further surgical treatment (9).

Extensive intraoperative peritoneal lavage (EIPL) treatment is a new modality to remove peritoneal free cancer cells by the extensive washing of peritoneal cavity with saline (10). Briefly, after a potentially curative operation, the peritoneal cavity was irrigated with 1 liter of normal saline, extensively shaken and washed, then followed by the complete aspiration of the fluid. This procedure was done 10 times. According to a prospective randomized study

(RCT) in patients with intraperitoneal free cancer cells (Cy1) without overt peritoneal metastasis (P0) (P0/Cy1), the EIPL group had a significantly lower incidence of peritoneal recurrence. EIPL therapy is strongly recommended as a prophylactic strategy for patients with P0/Cy1 status (10).

An abundance of experimental and clinical evidence has indicated that malignant cells are selectively destroyed by hyperthermia in the range of 41-43 ℃. Hyperthermia impairs DNA repair, protein denaturation, and the inhibition of oxidative metabolism in the microenvironment of malignant cells and increases cell death. Hyperthermia enhances chemotherapy efficacy, and the combination of heat and anti-neoplastic drugs frequently results in increased cytotoxicity. Some chemotherapeutic agents augment cytotoxicities in combination with mild hyperthermia. Such effects have been reported for mitomycin C, cisplatinum, docetaxel, gemcitabine and irinotecan. An additional factor *in vivo* is increased drug penetration, which is observed at temperatures above 39-42 ℃ (7).

To date, intraperitoneal chemotherapy and hyperthermia have been investigated as possible treatment options for PC from ovarian (11), colorectal (12,13) and gastric cancer (14,15). In gastric cancer, two RCTs have been reported for the prevention of peritoneal recurrence after curative resection (16,17). A recent meta-analysis of RCTs for gastric cancer indicated that HIPEC with CRS is associated with an improved overall survival (18).

It is expected that the use of molecular targeting agents combined with CRS plus chemotherapy will lead to remarkable progress in the near future.

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Gastric metastasis of Merkel cell carcinoma, a rare cause of gastrointestinal bleeding: case report and review of the literature

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Abstract: Merkel cell carcinoma (MCC) is a highly aggressive cutaneous tumor of neuroendocrine origin. It is usually seen in elderly Caucasian males and occurs in sun exposed areas of the body. Diagnosis of MCC can be challenging and requires confirmation by immunohistochemical studies. It has an aggressive biological behavior with early local and distant metastasis and carries a dismal prognosis. However, metastasis of MCC to the stomach is very uncommon and rarely reported in the literature. We hereby describe a patient with gastric metastasis of MCC, who presented with upper gastrointestinal (GI) bleeding.

Keywords: Merkel cell carcinoma (MCC); gastric metastasis; gastrointestinal bleeding (GI bleeding)

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Introduction

Merkel cell carcinoma (MCC) is an uncommon and a highly malignant cutaneous tumor of neuroendocrine origin, which frequently affects elderly Caucasian males. Exposure to ultraviolet (UV) radiation and immunosuppression are important pre-disposing factors. Recently, Merkel cell polyomavirus has also been implicated in its pathogenesis (1). Histologically, MCC can appear similar to a variety of other small round blue cell tumors; hence, immunohistochemical studies play an important role in confirming its diagnosis. MCC has an aggressive biological behavior characterized by rapid growth, early distant metastasis and poor prognosis. The most common sites of metastasis of MCC include distant lymph nodes, distant skin, lungs, central nervous system and bone (2). Metastasis of MCC to the stomach is extremely uncommon and it is rarely described in the literature. In general, it is very uncommon for tumors to metastasize to the gastrointestinal (GI) tract and small intestine is the most common site of tumor metastasis followed by stomach (3). We hereby describe a patient with gastric metastasis of MCC who presented with upper GI bleeding. Also presented is a review of literature to shed a light on clinical presentation, diagnosis and management of this rare tumor.

Case presentation

A 60-year-old Hispanic male presented to the emergency room with complaints of fatigue, weakness and passing maroon colored stools for five days. Originally, he had presented to our hospital 4 months ago with a right groin mass. This lesion was biopsied and a diagnosis of MCC was made after a battery of immunohistochemical tests (*Figure 1A-D*). Positron emission tomographic (PET) scan showed diffuse skeletal involvement and patient was started on chemotherapy (cisplatin and etoposide) and radiation therapy (RT).

In his current visit, the patient denied any nausea, vomiting or abdominal pain. He denied having any history of peptic ulcer disease. He was taking aspirin and clopidogrel after stent placement for a recent event of non-ST elevation myocardial infarction. On physical examination, he was normotensive but tachycardic with pulse rate of 130/minute. His abdominal examination was unremarkable with no tenderness, guarding or rigidity.

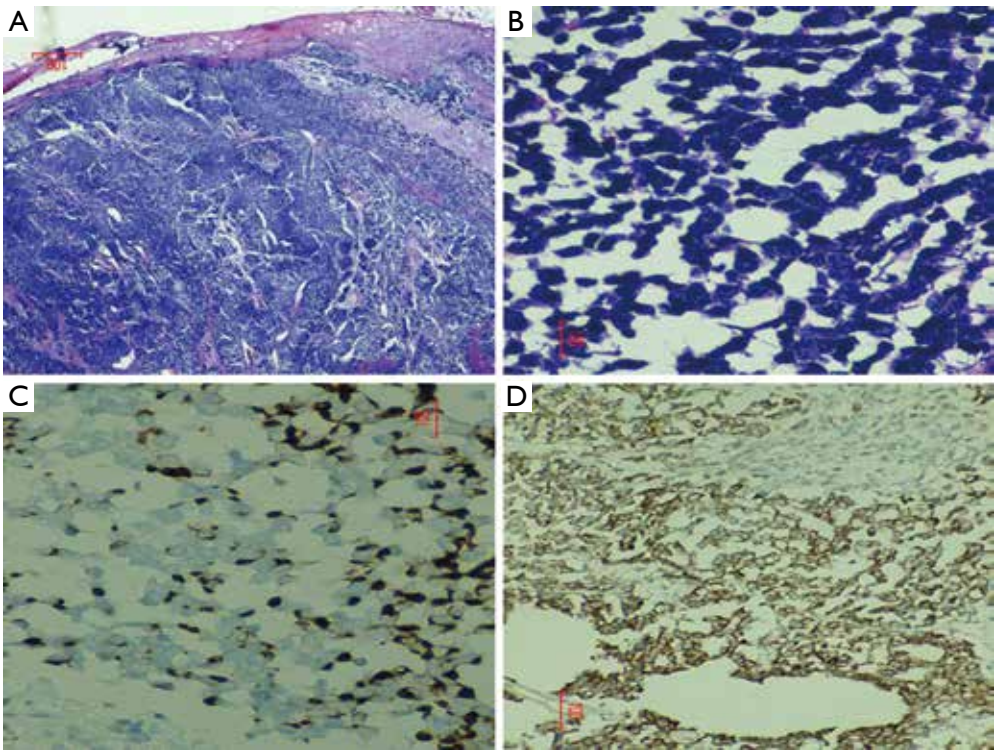

Figure 1 Histopathological images from the inguinal lymph nodes biopsy. (A,B) Hematoxylin and eosin (H&E) stained biopsy of matted inguinal lymph node showing normal tissue replaced by sheaths and nests of small round tumor cells; (C) CK-20 positive tumor cells showing a characteristic perinuclear dot-like staining pattern; (D) Tumor cells staining positive for synaptophysin. These findings were consistent with Merkel cell carcinoma.

Rectal examination showed maroon colored stools with blood clots. The rest of the physical examination was within normal limits. Laboratory studies showed pancytopenia due to ongoing chemotherapy with hemoglobin of 5.0 g/dL, platelets of 19 k/mm^3 and white blood cell count of 1.4 K/mm^3. His coagulation studies were within normal limits. Patient was resuscitated with intravenous fluids, proton pump inhibitor, packed red blood cells and platelet transfusions. Colonoscopy was unremarkable except for diverticulosis. An esophagogastroduodenoscopy (EGD) showed malignant appearing gastric folds in the fundus and the body of the stomach (*Figure 2A,B*), which were biopsied; however no active bleeding was seen. Patient responded well to the conservative treatment measures and GI bleeding was thought to be due to low platelets, aspirin and clopidogrel. Biopsy results were consistent with the diagnosis of metastatic MCC to the stomach (*Figure 3A,B*). Chemotherapy had to be held after three cycles due to severe side effects.

The patient returned one month later with similar complaints for which a repeat EGD was done. It showed a 3 cm, ulcerated mass near the lesser curvature of the stomach (*Figure 4A*) with a concurrent 4 cm ulcerated lesion in the gastric fundus with an adherent clot (*Figure 4B*). Active bleeding was seen after irrigation of the clot, which was controlled with local epinephrine injection and clipping. No further chemotherapy or RT was considered due to patient's poor performance status.

Discussion

MCC is a rare and highly aggressive cutaneous cancer affecting elderly white males (1). It was first described by Toker in 1972 as Trabecular carcinoma (4). Subsequently, electron dense neurosecretory granules were demonstrated in the tumor cells and it was classified as tumor of neuroendocrine origin (5).

According to a population based study involving 3,870 cases of MCC, males were more frequently affected than females (61.5% *vs.* 38.5%). Moreover, a majority of cases were reported in whites between 60 and 85 years of age (94.9%), whereas blacks were rarely affected (6). Excessive exposure

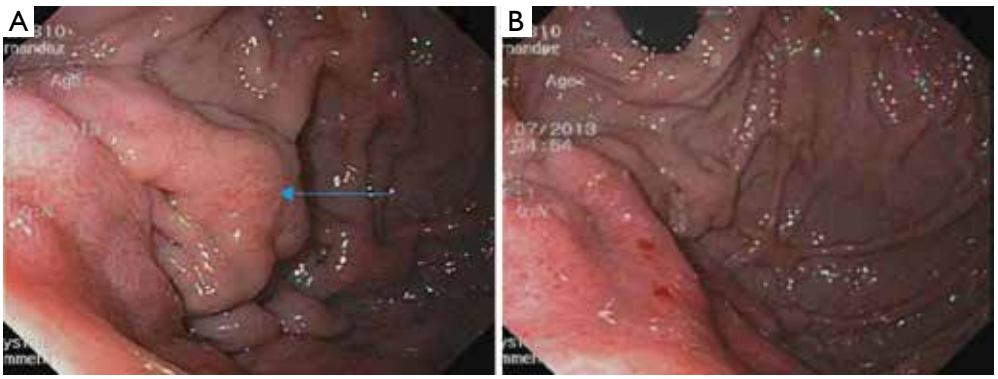

Figure 2 Images from esophagogastroduodenoscopy (EGD), (Initial presentation). (A) Malignant appearing gastric folds (blue arrow); (B) Friable appearing gastric mucosa that bled with minimal trauma.

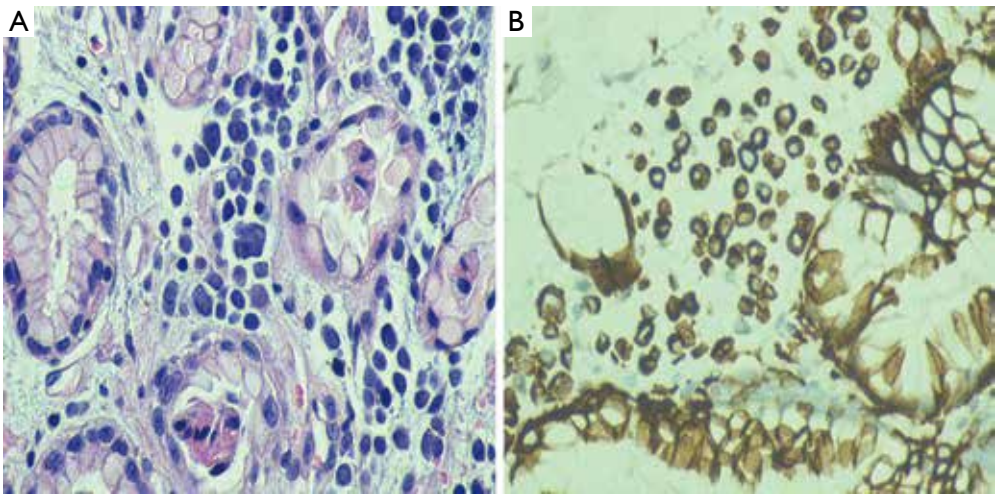

Figure 3 Gastric biopsy. (A) H&E stain showing atypical cells in the lamina propria of the gastric mucosa; (B) CK-20 positive tumor cells in the gastric mucosa.

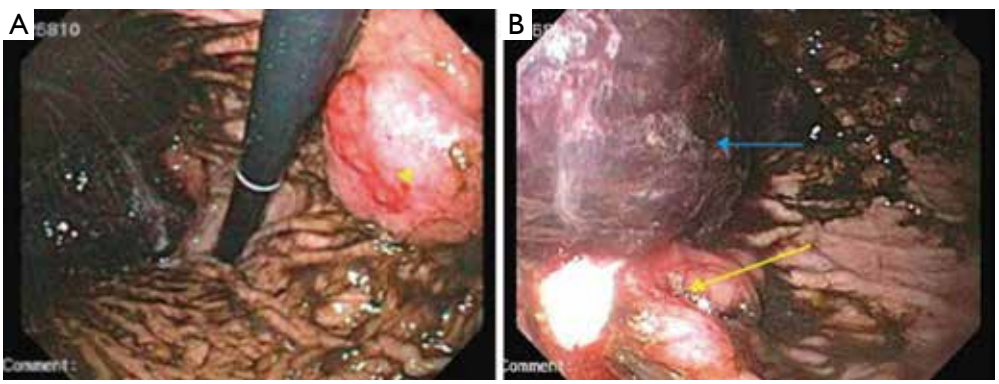

Figure 4 Endoscopic images (Repeat EGD, after one month). (A) A non-bleeding ulcerated mass on the lesser curvature of the stomach (yellow arrowhead) on retroflex view; (B) A large adherent clot (blue arrow) and a non-bleeding ulcerated mass (yellow arrow) in the gastric fundus.

to the sun light is an important risk factor for development of MCC. It is more common in immunosuppressed individuals, such as those with human immunodeficiency virus (HIV) infection, organ transplantation or lymphoproliferative malignancies (1). According to recent studies, Merkel cell polyomavirus has also been implicated to play an important role in the carcinogenesis of MCC (7,8).

MCC usually presents as a painless, firm, reddish or skin colored nodule on a chronically sun exposed area of the body (1). Highest incidence of MCC is seen in skin of the face (26.9%) followed by skin of the upper limb and shoulder (22.0%) and skin of the lower limb and hip (14.9%). MCC can also involve sun protected areas. Salivary glands, nasal cavity, lips, lymph nodes, vulva, vagina and esophagus were determined to be the most common extra cutaneous sites of involvement (6). Based on a study of 195 patients, Heath *et al.* has proposed a pneumonic "AEIOU", to describe the most common clinical features of this tumor (A = Asymptomatic, E = Expanding rapidly, I = Immunosuppressed, O = older than 50 years and U = UV-exposed skin) (9).

However, MCC does not have any classic features of presentation and it is hardly ever thought of as a primary diagnosis. If it is suspected based on initial hematoxylin and eosin staining (H&E) of the lesion, further confirmation of the diagnosis should be performed by immunohistochemical staining. Microscopically, it presents as a small round blue cell tumor, differential diagnosis for which include metastatic small cell lung cancer (SCLC), small B-cell lymphoma and anaplastic small cell melanoma. Cytokeratin-20 (CK-20) is highly sensitive marker for MCC and it is positive in about 89-100% of cases, demonstrating a characteristic perinuclear dot-like staining pattern in tumor cells. Along with CK-20, MCC often stains positively with low molecular weight cytokeratin (CAM-5), neuron specific enolase (NSE) and synaptophysin. MCC stains negatively for thyroid transcription factor-1 (TTF-1) which helps in differentiating MCC from SCLC (1,10-12). MCC does not stain for S-100 or leucocyte common antigen (LCA), which are markers of melanoma and lymphoma, respectively (13,14).

MCC is an aggressive tumor and skin lesions grow rapidly over weeks to months. It is characterized by early local, regional and distant metastasis and frequent relapses. The incidence of local recurrence is 25-30%, regional disease is 52-59% and distant metastatic disease in 34-36% of all cases of MCC (15-17). The most common sites of distant metastasis of MCC are distant lymph nodes (27-60%), distant skin (9-30%), lung (10-23%), central nervous system (18.4%) and bone (15.2%) (2). MCC rarely metastasizes to the stomach and very few cases are reported in the literature. In a recent case study of patients with gastric metastasis of MCC by Syal *et al.*, 78% of patients presented with upper GI bleeding and 67% of patients died within 4 months of diagnosis of gastric metastasis (18).

Guidelines from the National Comprehensive Cancer Network (NCCN) provide a detailed diagnostic and therapeutic approach for patients with MCC (19). In patients with asymptomatic primary MCC, sentinel lymph node biopsy (SLNB) is the most sensitive method to diagnose nodal metastasis. Positron emission tomography-computerized tomography (PET-CT) scan is preferred when distant metastasis is suspected (19-21).

Surgery is the principal modality of treatment in patients with clinically localized MCC with or without RT. SLNB should be performed in patients with clinically N0 disease. In nodal positive cases without distant metastasis, regional lymph node dissection is performed with or without RT (19,22).

RT and chemotherapy are the mainstays of treatment in patients with advanced metastasis. Interdisciplinary approach and participation in clinical trial is recommended in cases of distant metastasis. Tumor stage and tumor size are the most important prognostic factors (19). Mortality rate of MCC exceeds that of malignant melanoma and the overall five years survival rate is between 30% to 64% (15-17,23).

In conclusion, MCC is a relentless, aggressive skin tumor. It lacks any classical clinical features and it is rarely suspected as a primary diagnosis. Immunohistochemical studies play an important role in the diagnosis. Gastric metastasis of MCC is exceedingly rare and carries dismal prognosis. Given the rarity of this tumor and lack of prospective clinical trials, no clear consensus exists about the best ways of management. Surgery is the primary modality of treatment in localized stages of cancer, whereas chemotherapy and RT are the mainstay of therapy in advanced cases. Interdisciplinary approach and participation in clinical trial is recommended in the management of this rare tumor.

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Multidisciplinary Approach

Self-expandable metallic stent placement for palliation in gastric outlet obstruction

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Abstract: Malignant gastric outlet obstruction (GOO) often has a markedly adverse impact on the quality of life (QOL) of patients. Procedures in affected patients should aim to reduce obstructive symptoms and enable oral ingestion. Surgical gastrojejunostomy (GJJ) has been performed as a conventional palliative procedure. Enteral stenting has been increasingly used as an alternative to surgical palliation because of its lower invasiveness. Enteral stents used for GOO are made of a metal alloy mesh in a cylindrical shape, and are termed self-expandable metallic stent (SEMS). Of the two placement techniques, over-the-wire (OTW) and through-the-scope (TTS) deployment, TTS is easier and is now more frequently used. In general, the technical success rate is extremely high, at nearly 100%, and the clinical success rate is about 90%, but complications after placement can occur, most frequently late-developing stent dysfunction due to stent obstruction and migration. Biliary obstruction can occur concurrently with GOO, or before or after GOO, particularly in patients with pancreaticobiliary malignancies. Considering accessibility to the bile duct, biliary stenting should generally be conducted prior to enteral stenting. Transhepatic or transmural biliary stenting may be required if transpapillary stenting is not possible. Because enteral stenting is more commonly associated with late-developing stent dysfunction, it is better suited than GJJ for patients with a short life expectancy and poorer performance score. Chemotherapy may be beneficial in reducing the risk of stent obstruction, despite the possible risk of migration, particularly in patients with GOO due to gastric cancer. Many enteral stents with different structures are now commercially available, but the association between the design and mechanical properties of a stent and clinical outcomes is still poorly understood. Further, no consensus on the benefits of covered SEMS has yet been obtained. Further study to verify which types of SEMS are most suited for GOO is warranted.

Keywords: Gastric outlet obstruction (GOO); enteral stent; self-expandable metallic stent (SEMS); palliation

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Introduction

Even today, many gastrointestinal (GI) malignancies are significantly advanced and incurable at presentation. Unresectable malignancies frequently lead to luminal obstruction, and reobstruction due to local recurrence or lymph node metastasis may occur after surgical resection. Gastric outlet obstruction (GOO) particularly occurs in patients with unresectable peri-ampullary (e.g., pancreatic, ampullary, hepatobiliary cancer) or gastric cancer.

The consequences of GOO can be serious. These include intolerance of oral intake and deterioration of quality of life (QOL), with vomiting, aspiration, bloating and malnutrition. Surgical gastrojejunostomy (GJJ) has been performed as a conventional palliative procedure for GOO, but the disadvantages of this procedure include significant risks of higher morbidity and mortality (1), and a higher incidence of delayed gastric emptying (2). Enteral stenting has been increasingly used as an alternative to surgical palliation thanks to its lower invasiveness and quicker response, and the many articles related to enteral stenting for GOO show a variety of evidence. This review paper overviews the literature on enteral stenting for GOO.

General outline of gastric outlet obstruction (GOO)

GOO is usually found as a late complication and causes a variety of obstructive symptoms, including nausea, vomiting, or bloating, and usually leads to poor or no oral intake in affected patients. These symptoms tend to lead to dehydration, malnutrition and weight loss, and these are distinguished from cancerous cachexia, which accompanies advanced malignancy. Severe GOO which prevents the passage of gastric juice is often accompanied by electrolyte dehydration as well as dehydration and reflux esophagitis. These symptoms are likely to markedly harm the QOL of affected patients. The goal of palliation of GOO is to resume oral intake and improve obstructive symptoms.

Treatments for malignant GOO

The conventional palliative management for GOO is GJJ, either open or laparoscopic. This procedure provides an effective reduction in obstructive symptoms and allows the resumption of oral intake. However, enteral stent placement was developed in the early 1990's (3-6) and has been practically available for 15 years now.

In addition to stent placement and bypass surgery, other palliative procedures include chemotherapy, radiotherapy, insertion of a decompression tube (e.g., nasogastric or gastrostomy tube), and administration of somatostatin analogue. These have been used independently or in combination with stent placement or GJJ. Nevertheless, the only effective management which allows the resumption of oral intake is surgical GJJ and stent placement; in the absence of either, patients are usually unable to ingest food orally, and often require placement of a decompression tube.

Surgical palliation carries significant risks of morbidity and mortality (1), and frequently causes delayed gastric emptying (2). In addition, many patients with GOO are poor surgical candidates, because of their debilitated condition and malnutrition due to significantly advanced cancer. Against this background, stent placement is both effective in palliating GOO and minimally invasive, and is now widely used in these patients.

Types of enteral stents

Enteral stents used for GOO consist of a metal alloy (e.g., nitinol) mesh in a cylindrical shape, and are termed self-expandable metallic stent (SEMS). Most SEMS used in the gastroduodenal region have a knitted or braided wire structure. Several types of SEMS which differ with regard to mesh structure and properties (radial force, axial force, etc.) are now commercially available from various manufacturers. SEMSs can be flared at the proximal or both ends, and may be covered with a polyurethane or polytetrafluoroethylene membrane to help prevent tumor ingrowth.

For insertion, the stent is constrained and loaded into the delivery system, most of which are designed for through-the-scope (TTS) deployment. This delivery system is about 10-Fr, which allows passage through the working channel of therapeutic endoscopes. However, SEMSs with a larger introducer sheath designed for over-the-wire (OTW) deployment are also available in some countries (7). OTW deployment is usually performed by radiologists.

Placement procedure

Before the development of dedicated devices, anatomical difficulties made stent placement for GOOs a difficult and challenging procedure (3-6). The development of dedicated stents and TTS placement have markedly facilitated placement, however, even in long, tortuous strictures.

Currently, stent placement is mostly performed with the TTS deployment technique because of its significant ease of use (8) (*Figure 1*). In addition, TTS deployment technique has an advantage enabling simultaneous placement of two stents without second insertion of endoscope (*Figure 2*). However, the diameter of the delivery catheter is 10-10.5 Fr, requiring a therapeutic endoscope with a large working channel. The procedure is performed under conscious sedation and analgesia. The prone position is optimal because it avoids aspiration and allows an ideal X-ray image to be taken. The X-ray tube of the C-arm should be appropriately rotated so that side view of the stenosis can be obtained. A therapeutic endoscope with a large working channel is inserted and the stenosis is observed. It is not necessary to traverse the stenosis with the endoscope if the stenosis is tight. Negotiation of the stricture is performed using a biliary guidewire (usually "0.035" in diameter) with an ERCP catheter. Once the guidewire can be passed through the stricture, sufficient contrast is injected to define the length of the stenosis. Withdrawing the catheter/guidewire from the distal to the proximal end of the stenosis, or use of a measuring guidewire, is helpful in determining the precise length. An appropriate length of stent (usually at least 2 cm longer than the measured stricture at each end) is then chosen according to the length

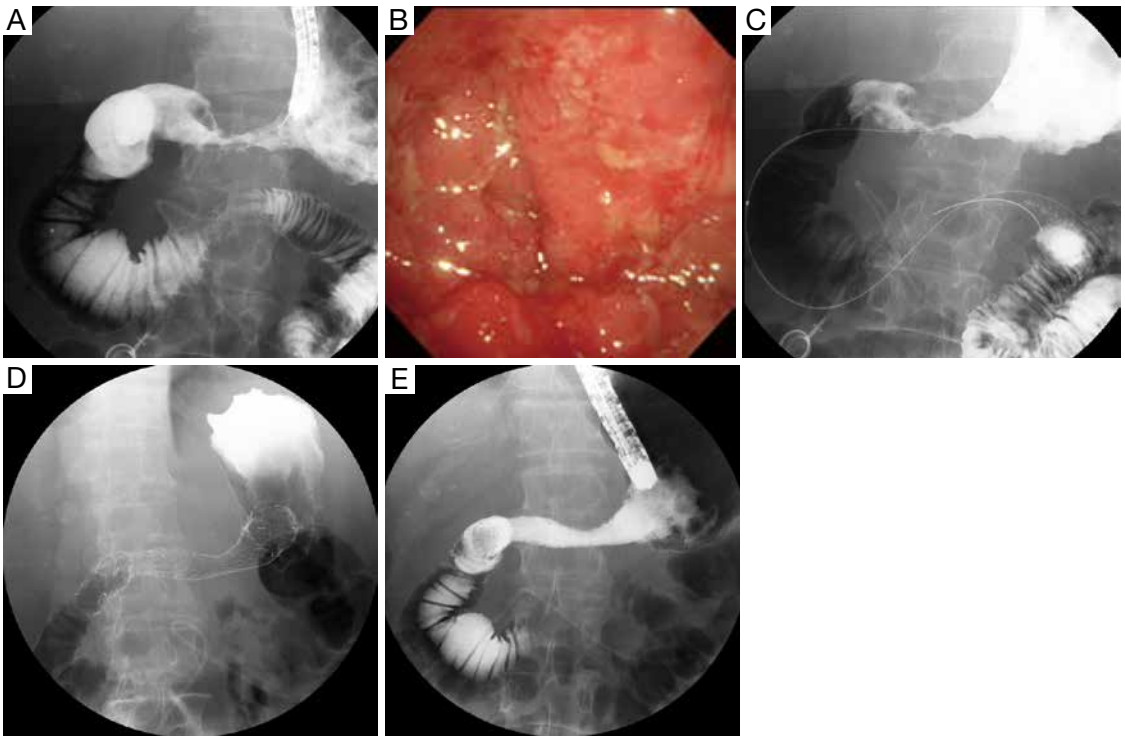

Figure 1 Stent placement in a patient with antral cancer. (A) Contrast study showing obstruction of the gastric antrum; (B) endoscopy showing gastric cancer which bleed easily; (C) a guidewire has been passed across the obstruction; (D) the stent is successfully placed at the optimal position; (E) final radiogram confirmed good passage within the stent.

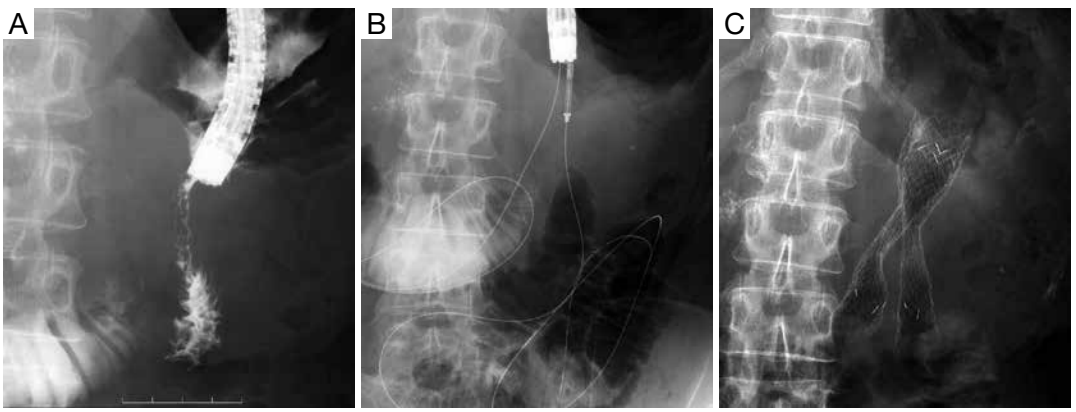

Figure 2 Stent placement for occluded palliative gastrojejunostomy. (A) Contrast study showing tumor-related obstruction of a gastrojejunostomy created for unresectable gastric cancer; (B) two guidewires have been inserted through the stricture into the afferent and efferent loops; (C) the final radiograph indicates successful placement of stents for both the afferent and efferent loops.

of the stenosis to prevent tumor overgrowth. The stent delivery system is inserted along the guidewire through the working channel of the endoscope. The stent is deployed at the stenotic region in consideration of the foreshortening ratio of the stent, which varies with stent type. The stent should be gradually deployed, with adjustment for position. After deployment, proper positioning is confirmed by a waist within the SEMS. Further, passage is determined by contrast injection via the endoscope. An abdominal plain X-ray film is taken daily to confirm stent positioning and the degree of expansion. Full expansion is usually obtained within three days.

Indications and contraindications

Placement of an enteral stent is indicated in patients with documented malignant obstruction of the pylorus and/or duodenum caused by unresectable tumors. Stent placement is frequently employed in patients who are poor surgical candidates with shortened life expectancy, poor performance status, significant comorbidities and anesthetic risk (9,10).

Contraindications of this procedure are evidence of GI perforation and documentation of multiple distal obstructions, particularly in the small bowel. Peritoneal carcinomatosis may induce multiple distal obstructions, but a study found that a diagnosis of carcinomatosis only should not be considered a contraindication to SEMS placement in patients with malignant GOO (11).

Efficacy

This procedure with TTS deployment is not difficult, and has a technical success rate of 90% to 100% (12-20). A review of 1,046 published cases reported a technical success rate of 96% (21). The most common causes of technical failure were unsuccessful transit of the guidewire through the stenosis, failed placement of the SEMS at the proper position, and migration of the SEMS during the procedure.

Clinical success, defined as the relief of obstructive symptoms and improvement in oral intake, is obtained in 58% to 92% of patients (12-20). The above review article indicates a clinical success rate of 89% (21). The discrepancies between technical success and clinical success might be attributable to underlying GI dysmotility with or without neural involvement by the tumor, distal obstruction secondary to peritoneal carcinomatosis, or general deconditioning and anorexia caused by advanced malignancy (9). A study which assessed whether stent location alters efficacy revealed that efficacy was not altered by location of the stent across the pyloric valve or within the duodenum (22).

Oral intake is most frequently assessed using the Gastric Outlet Obstruction Scoring System (GOOSS), with 0= no oral intake, 1= liquid only, 2= soft solids, and 3= low-residue or full diet (23). Many articles suggested that GOOSS score is significantly improved following stent placement (14,15,18,19,21,24-27). Most patients can continue oral intake until death. A recent study revealed that 95.9% of patients continued oral intake for the rest of their lives and that 78.4% required no further intervention until death (24). This study also revealed that many patients can resume solid food intake (GOOSS 2 or 3), with a cumulative average of 74%, ranging from 56% to 80% (15,16,24,27,28). In addition, approximately two-thirds of patients continued solid food intake until death (24). A study evaluating predictive factors of solid food intake showed that a Karnofsky performance score of 50% or less and the presence of ascites are independent poor predictive factors of ability to ingest solid food (29).

According to a functional evaluation study (30), almost 80% of patients studied had a significant improvement in gastric emptying rate. Nevertheless, another study using radionuclide scanning indicated that gastric emptying function in patients one week after stenting was significantly poorer than in healthy subjects (31).

Quality of life (QOL)

A prospective randomized trial comparing duodenal stenting versus laparoscopic GJJ by Mehta and colleagues (32) showed a significant improvement in physical health score at one month (P<0.01), but no change in pain score or mental health score at this time. No improvement in any QOL parameter was seen in the laparoscopic GJJ group. Another comparative study conducted under a retrospective design indicated that an improvement in Karnofsky performance score was more frequent in the stent group than in GJJ group (65% *vs.* 26.3%, P=0.0248) (33). Further, the median difference in performance score before and after the procedure was significantly greater in the stent group than in the bypass group (15 *vs.* –10; P=0.0149) (33). A UK study by Lowe and colleagues reported similar results, with an increase in Karnofsky score from 44/100 to 63/100 post-procedure (34). A prospective study with the WallFlex stent by van Hooft and colleagues indicated a significant improvement in post-procedural WHO performance score between the pre-stenting score and mean score up to death (14).

A study which objectively evaluated QOL score before and after stenting using the EORTC QLQ-C30 instrument to assess functional status and cancer-related symptoms and the QLQ-STO22 instrument to assess gastric-specific symptoms found that among QLQ-C30 parameters, role functioning, physical functioning, global health status, and nausea/vomiting improved after stenting, although the difference was statistically significant only for global health status (P=0.010) and nausea/vomiting (P=0.001). In contrast, however, no change was seen in other QLQ-C30 parameters, including emotional, cognitive, and social functions, or other symptoms (35). In addition, enteral stenting was associated with a significant improvement

Table 1 Comparison of three prospective studies using different stents

	Study name, authors, year		
	DUOFLEX (14), van Hooft *et al*. 2009	DUONITI (18), van Hooft *et al*. 2011	DUOLUTION (25), van den Berg *et al*. 2013
Stent used	WallFlex	Niti-S	Evolution
No. pts	51	52	46
Tech. success [%]	50 [98]	50 [96]	41 [89]
Clin. success [%]	43 [84]	40 [77]	33 [72]
Complications [%]	14 [27]	18 [35]	18 [39]
BMI	Decr (P<0.001)	NS	NS
WHO-PS	Improv (P=0.002)	NS	NS
EQ-VAS	NS	NS	Improv (P=0.005)
QL2	NS	Improv (P=0.001)	Improv (P<0.0001)

Decr, decrease; Improv: improvement; NS, not significant.

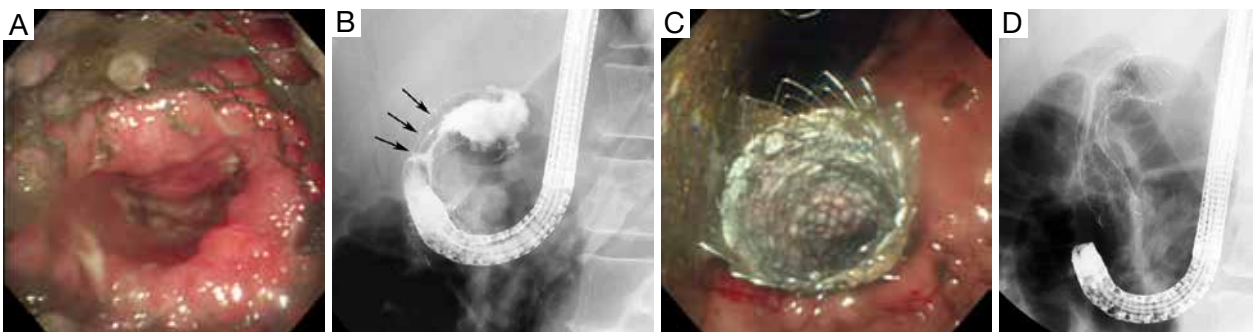

Figure 3 Placement of a second stent for occluded pre-existing SEMS due to tumor ingrowth. (A) Endoscopy reveals stent occlusion due to tumor ingrowth; (B) contrast study using endoscopy showing tumor ingrowth (arrows); (C) a covered SEMS was placed within the occluded uncovered SEMS; (D) radiograph immediate after deployment showing two overlapping SEMSs and the waist of the second SEMS. SEMS, self-expandable metallic stent.

in dysphagia (P=0.001), eating restrictions (P=0.010), dry mouth (P=0.029), and reflux (P=0.040), as assessed by the QLQ-STO22 instrument (35).

One group has recently reported three prospective studies of three different SEMSs, namely the DUOFLEX (WallFlex stent) (14), DUONITI (Niti-S stent) (18) and DUOLUTION (Evolution stent) (25) studies. The QOL score results of the three studies differed, but it is unclear whether this was due to the different structures of the stents (*Table 1*).

Complications and management

Complications are frequently classified as either early- (≤7 days) or late-stage changes (>7 days). According to a systematic review (21), major early complications, including migration and stent dysfunction, occur in 7%, and major late complications in 18%. The most common causes are stent migration, and obstruction caused by tumor in- or over-growth, hyperplasia, or food impaction. Obstruction (5-21.1%) is more frequent than migration (0-3.8%) (14-16,18,19,34). Tumor-related stent obstructions can be managed by placement of a second stent (*Figure 3*) or ablative procedures (36), while migration is often treated by placement of an additional stent. Minor complications, such as pain, nausea or vomiting, are not frequent (9%) (21), while life-threatening complications like perforation and bleeding are rare (1% or less) (9,37). SEMS with significant flexibility and blunt ends may be helpful in preventing ulcer formation and perforation (13).

Combination with biliary stent placement

Biliary obstruction can occur concurrently with GOO, or before or after GOO. Both gastroduodenal and biliary obstructions are classified into three patterns based on timing and location (*Table 2*). Mutignani and colleagues proposed a classification for the duodenal stenosis type in relation to the major papilla, with type I at a level proximal to and without involvement of the papilla; type II affecting the second part of the duodenum with involvement of the papilla; and type III involving the third part of the duodenum distal to and without involvement of the papilla (38).

Biliary obstruction usually occurs in patients with pancreaticobiliary malignancy as the underlying disease, but sometimes also in patients with other etiologies, such as gastric, duodenal or metastatic cancers. Particularly in patients with pancreaticobiliary malignancies, biliary obstruction tends to develop before the occurrence of GOO. One study reported the onset of biliary obstruction before GOO in 56%, concomitantly in 25%, and following the development of GOO in 19% (10,23). Many patients undergoing enteral stenting for GOO thus already have a pre-existing biliary stent to manage a preceding biliary obstruction. In these cases, if the pre-existing biliary stent is a plastic, it should be replaced with a SEMS, given the risk of buckling and inability to retrieve it. In type II patients with preceding biliary SEMS, concern has been expressed about the possible blockage of bile outflow with the use of a covered duodenal SEMS. A study which compared post-procedural bilirubin and alkaline between covered and uncovered SEMSs placed to bridge the papilla concluded that placement of a covered SEMS was not contraindicated (39). Nevertheless, selection of an uncovered SEMS to avoid the endoscopic inaccessibility of the bile duct may be preferable.

In cases in which biliary obstruction is concomitant with GOO, simultaneous placement of a biliary stent should be considered when placing an enteral stent for GOO, since the success rate of this procedure is comparable to that of placement of a duodenal stent alone (40). In cases with either simultaneous or two-stage placement, biliary stenting prior to duodenal stenting should be considered (*Figure 4*), because endoscopic biliary stenting is generally impossible when a duodenal stent bridges the papilla. If transpapillary biliary stenting fails even with the use of balloon dilation for duodenal stricture, a percutaneous or EUS-guided transmural approach (41) may be selected (*Figure 5*).

As stated above, development of a biliary obstruction after a duodenal obstruction is least common. Thanks to the pre-existing enteral stent, the duodenoscope can usually reach the level of the major papilla. In cases with an enteral SEMS bridging the papilla, however, a transpapillary approach is often impossible.

Table 2 Classification of gastroduodenal and biliary obstructions

Timing of development of biliary obstruction
Preceding GOO
Concomitant with GOO
Subsequent to GOO
Location of gastroduodenal obstruction
Proximal to and without involvement of the ampulla (type I*)
Adjacent to and with involvement of the ampulla (type II*)
Distal to and without involvement of the ampulla (type III*)

*, classification from type I to III was proposed by Mutignani *et al*. (38); GOO, gastric outlet obstruction.

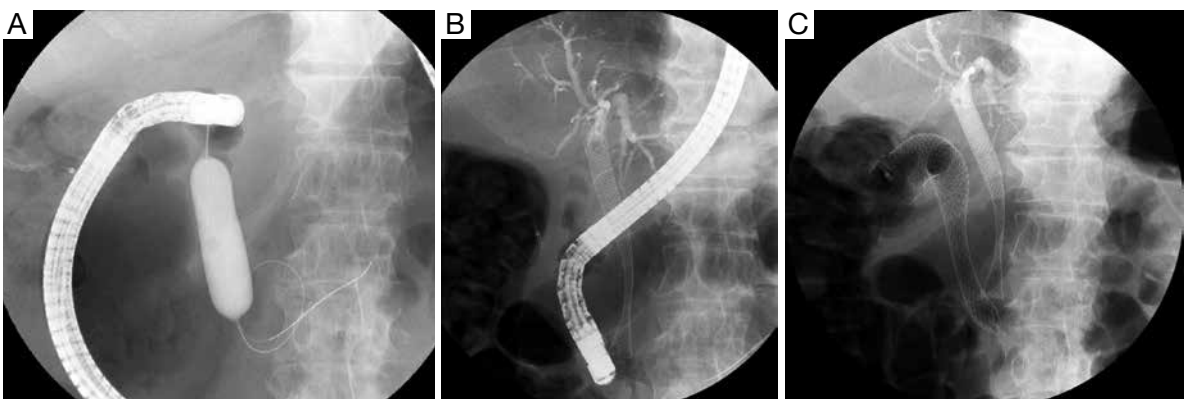

Figure 4 Stent placement for both biliary and duodenal obstruction. (A) Initially, duodenal obstruction (Pars II) was dilated with a balloon dilator; (B) next, transpapillary biliary stent placement was performed; (C) the duodenal SEMS was then placed during the same procedure. SEMS, self-expandable metallic stent.

Stent placement versus gastrojejunostomy (GJJ)

Many studies, including three randomized studies, have compared enteral stenting and GJJ (32,33,42-55). Most have suggested the superiority of enteral stenting, particularly with regard to short-term outcomes such as a shorter hospital stay and faster resumption of oral intake. The most recent systematic review reported similar results (56). Another systematic review, however, found that although stenting had a higher clinical success rate and fewer minor complications, it had a higher rate of recurrence of obstructive symptoms, suggesting that stenting may be more favorable in patients with a relatively short life expectancy, while GJJ is preferable in those with a longer prognosis (21). These authors also conducted the largest randomized study to date (53), the results of which were consistent with their previous systematic review (21). This study showed that enteral stenting was associated with poorer long-term results, with more major complications (6 *vs.* 0 cases; P=0.02) and a higher incidence of recurrent obstructive symptoms (8 *vs.* 1; P=0.02) and reinterventions (10 *vs.* 2; P<0.01), versus a better short-term outcome, with more rapid improvement of oral intake (5 *vs.* 8 days; P<0.01) and a shorter hospital stay (7 *vs.* 15 days; P=0.04) (53). There was no difference in median survival or QOL scores (53). The authors again proposed that enteral stenting should be considered in patients with a short life expectancy (less than two months). In their subsequent study evaluating possible predictors of survival, WHO score was the only significant predictor of survival in patients with malignant GOO (57). They proposed that patients with WHO score of 0-1 should be considered for GJJ, whereas those with a WHO score of 3-4 should be considered for enteral stenting (57). Similar results were reported in a recent study comparing outcomes between enteral stenting and GJJ only in patients with gastric cancer but a good performance status. That study concluded that enteral stenting was associated with more frequent late adverse events (44.4% *vs.* 12.2%; P<0.001) and reinterventions (43% *vs.* 5.5%; P <0.001), and shorter patency (125 *vs.* 282 days; P=0.001) and survival (189 *vs.* 293 days; P=0.003) (55), suggesting that enteral stenting is likely favorable in patients with a poor performance status and/or short life expectancy. However, patients with malignant GOO have a limited median survival time (49-99 days) even in many recent literatures (12,14-16,18,19,25,28,58), so many patients have a very short life span and are better served by stents.

The two modalities are compared in *Table 3*.

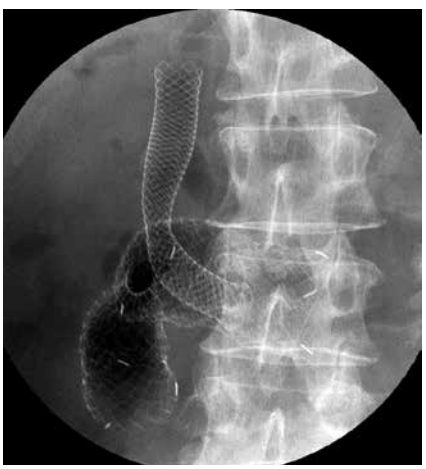

Figure 5 EUS-guided biliary stent placement in a patient with indwelling duodenal SEMS. Transpapillary biliary stenting failed because the papillary orifice was not identified due to the duodenal SEMS crossing the papilla. The EUS-guided biliary was placed through the interstices of the duodenal stent. SEMS, self-expandable metallic stent.

Table 3 Comparison between ES and GJJ

Technical success	No difference
Clinical success	Meta-analysis (5) indicates higher clinical success with ES, despite some reports showing no difference
Time to diet	Shorter time to diet by ES is a clinical consensus
Hospital stay	Shorter hospital stay by ES is a clinical consensus
Early complications	GJJ are associated with more frequent early complications, mostly related to surgery (e.g., wound infection, respiratory infection)
Late complications	ES are associated with more frequent later developing complications, mostly related to stenting procedure (e.g., stent obstruction, migration)
30-day mortality	No difference
Survival	No difference

ES, enteral stenting; GJJ, gastrojejunostomy.

Role of chemotherapy

Some reports have shown that chemotherapy is associated with a lower risk of reobstruction and more frequent migration (12,59). However, a retrospective study comparing clinical outcomes by stent type and chemotherapy for GOO due to gastric cancer revealed that patency rates are significantly improved by combining the use of an uncovered stent with follow-up chemotherapy treatment, because chemotherapy significantly lowered re-intervention rates, particularly with uncovered stents (60). According to a recent study investigating the association between the response to chemotherapy and pyloric stent outcome in patients with gastric cancer, a long time-to-progression (adjusted hazard ratio, 0.29; 95% CI, 0.13-0.67) and first-line chemotherapy (adjusted hazard ratio, 0.45; 95% CI, 0.22-0.93) were significant protective factors against reobstruction, whereas response to chemotherapy was not associated with stent migration or reobstruction (61).

Comparison between stents

Few reports have compared stent outcomes between stent types. In a retrospective study comparing Niti-S with Ultraflex, the former SEMS could be placed by a simpler and faster method, but was more frequently reobstructed (62). Although many enteral stents with different structures are now commercially available, the association between the mechanical properties of stent design and clinical outcome is still poorly understood.

Aside from stent structure or properties, several types of covered SEMS have been developed to reduce the potential risk of stent obstruction due to tumor ingrowth or mucosal hyperplasia. Five studies have compared covered or uncovered SEMS (58,63-66) (RCT, 2; prospective cohort, 1; retrospective cohort, 2). Two Korean studies showed similar results, namely less frequent reobstruction and more frequent migration for covered stents (63,65). However, a retrospective study of covered and uncovered Ultraflex stents showed that covered SEMS were associated with a higher reintervention rate despite similar outcomes in reobstruction and migration (64). A retrospective study with various covered or uncovered SEMSs in patients with pancreaticobiliary malignancies concluded that the use of uncovered SEMS may be preferable for duodenal obstruction secondary to pancreaticobiliary malignancy, since these were effective in preventing stent migration and tended to have a longer patency than covered stents (66).

The most recent prospective randomized trial reported that use of a triple-layered covered SEMS was associated with less frequent stent dysfunction at more than four weeks after stenting, despite similar short-term outcomes (58). These conflicting results may be due to differences in patient demographics, stent types, or patient survival period. In any case, they mean that a consensus on the benefit of covered SEMS has yet to be obtained. A larger randomized study is warranted.

Summary

GOO can dramatically detract from QOL. Enteral stenting is beneficial in obtaining a rapid improvement in obstructive symptoms and can be performed with a high success rate. However, it carries a higher risk of late-developing complications than surgical palliation and is therefore likely more favorable in patients with a short life expectancy. Follow-up chemotherapy may significantly lower reintervention rates, particularly with uncovered SEMSs. A consensus regarding the most suitable stent type for GOO and the significance of the use of covered SEMS has yet to be obtained.

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Surgical Research

Training as a surgeon: not just knowledge and skills

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Surgery is the combination of science, skills, and fine arts. Qualified surgeons not only operate skillfully but also can practice scientific thinking. In fact, their operations are just like the carving of a beautiful work of art by an experienced sculptor. Therefore, a surgeon must be able to use his/her hands and brain in a highly coordinated way. They must complete various procedures through superb operations to achieve the optimal effectiveness.

Obviously, the training of a young surgeon requires the self-motivation. However, it's an important fact that the encouragement, instructions, and guidance from the older generations are equally important to enable the young surgeons to become capable more quickly and take on more responsibilities.

I was often asked how to read a paper or book. "When you read a paper or a book, you should feel what the author felt, breathe what he breathed, and think in the way he thought." Only by doing so, you can focus on the questions proposed by the authors, rather then just the answers or solution. In my opinion, the questions themselves are often more informative and critical than the newly elucidated theories or the newly introduced concepts.

Then comes another question: How to be a qualified surgeon? This question is of course more difficult. Everyone has own answers. First, a qualified surgeon must be an honest people. Confucius says, "Wisdom is knowing what we know and what we don't know." Every surgeon must maintain such clean and honest virtues. I always believe that the most honest individuals are smartest. Second, a qualified surgeon should be modest. Confucius also says, "If three walk together, at least one should be my teacher." A young people, even if you have obtained an M.D. degree or became a surgeon, never think that you are superior to others. Keep a clear head, at any time. Third, respect others, especially your teachers. Respect is a two-way traffic. If someone wants to be respected they must also respect others. Finally, be tolerant. Tolerance is a required virtue. You should learn to forgive others of their shortcomings. Be open-minded and supportive, especially when you become the head of a clinical department or a senior doctor.

A qualified surgeon should also get certain achievements in scientific research. You should be well prepared for this goal. First, don't waste your time, be diligent. Successful people often have two characteristics: talent and diligence. A "talented" individual is able to learn, understand, and utilize the knowledge and skills (e.g., surgical operations) in an extraordinary way. However, without hard work and repeated practice, the so-called "talent" cannot be fully exerted, and the final achievement can be low or even zero. Therefore, diligence is somehow more important. Fortunately, it can be fully controlled by your own brain and hands. The proper integration of talent and diligence guarantees the success of a surgeon in his/her scientific research. Second, develop a deep and wide knowledge base. The rotation system should be maintained in surgery residency training program. Young residents should not be trained within a fixed specialty immediately after they leave the college. The human body is an inseparable whole. Each disease, more or less, involves the whole body. Thus, young doctors must grasp of the basic theories, basic knowledge, and basic skills of health care activities. Only deep roots can give rise to flourishing leaves. Similarly, only solid and wide knowledge base can enable a doctor to carry out effective innovations. Third, keep thinking, keep innovation. During their career training, young doctors must ask them various questions from time to time, and then try their best to find a solution. This is particularly helpful for the training of independent thinking and innovation. Mr. Hsing-chih T'ao,

a renowned 20th century Chinese educator and reformer, once wrote such a poem: "two treasures with us lifelong remain: a pair of free hands and a great brain. He who does not use his hands belongs to the dethroned king's band. He who does not use his brain has to endure hunger and pain. He who uses both his brain and hands can create a new world on exploited land." Mr. T'ao used plain language to emphasize the importance of using both brain and hands, which is particularly important for a surgeon. Fourth, scientific research must be rigorous and evidence-based, and meanwhile pay attention to research ethics. The past decades have witnessed the rapid development of medical sciences in China. However, an impetuous and utilitarian social atmosphere also spreads and even deteriorates in scientific research. Medical researchers, especially the young generation, must resist these potentially disastrous phenomena. The proper style of study, which is always evidence-based and consistent with scientific ethics, must be advocated.

I have served as a surgeon for over 30 years. During this long period of time, I have deeply recognized the importance of writing, being a qualified surgeon, and carrying out scientific research in a scientific way. I sincerely hope that the young doctors will cherish the time, work hard, keep thinking, and thus be well prepared to be an excellent doctor and an outstanding researcher. Hope you will be a qualified surgeon, a good reader, an honest person, and a serious researcher. This has long been my motto and I wish to share it with all the young doctors.

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Single-incision laparoscopic distal gastrectomy for early gastric cancer

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Introduction

Laparoscopic gastrectomy for early gastric cancer has been widely adopted as an alternative treatment option and has been reported to be beneficial for patients, with better early postoperative outcomes and also with compatible long-term oncologic outcomes to open gastrectomy (1,2).

In the meanwhile, efforts are underway to reduce the minimal invasiveness of laparoscopy. Natural orifice transluminal endoscopic surgery (NOTES) and single incision laparoscopic surgery (SILS) is the representative of this effort. While NOTES is still on the research area because of the limitation of equipment and difficulty of closure of incised lumen, there have been explosive reports on single ports surgery in the various clinical surgical fields (3).

Single-incision laparoscopic surgery (SILS) has been introduced to reduce the abdomen wall incision and trauma and the embryonic scar of the umbilicus is easily accessed to the peritoneum without any visible scar. SILS procedures decrease postoperative pain and hospital stay and lead to faster postoperative recovery than conventional laparoscopy apart from better cosmetic aspects (4). Although long-term data are still lacking to prove the outcome SILS, the reported data of oncologic patients undergoing SILS provide the technical feasibility of a single port surgery (5).

However, the feasibility of single-incision laparoscopic distal gastrectomy (SIDG) for early gastric cancer comparing with laparoscopic distal gastrectomy (LDG) has not been demonstrated in the field of gastrectomy.

There have been only 3 reports describing this procedure for patients with early gastric cancer (EGC) (6-8). Furthermore, all of these reports use 1 or 2 additional assistant ports in SIDG (*Table 1*). The technical difficulty of this operation could be showed by a long operation time comparing with conventional LDG, although the number of retrieved lymph node was not less.

Herein, we present briefly our clinical experience of SIDG in Seoul National University Bundang Hospital.

Methods

Study design and data collection

Prospectively maintained database from patients who underwent laparoscopic distal gastrectomy (LDG) due to gastric cancer were reviewed. From October 2010 to January 2013, 30 consecutive patients underwent SIDG for early gastric cancer at Seoul National University Bundang Hospital in Korea. A 2 mm assistant port was used in the initial 10 cases of SIDG. Last 20 cases of SIDG were done without any assistant port (Pure SIDG).

All 30 operations except initial 7 cases of SIDG were done by a single surgeon who had experience of 100 cases of LDG before starting the single port surgery and more than 50 cases of conventional open gastrectomy. In this study, we included patients with a preoperative diagnosis of stage I (7^{th} edition AJCC), in whom no lymph node (LN) enlargement.

Surgical technique

Pure single-incision distal gastrectomy with D1+beta lymph node dissection

The patient was placed in a lithotomy position with reverse Trendelenburg. The operator and a scopist were positioned

Table 1 Summary of previous literatures on SIDG

Year	Authors	Patients	Operation methods	Surgical outcomes	Characteristics
July 2011	Omori *et al*.	7	2.5 cm incision Two 2 mm assistant ports	Operation time: 344 min EBL 25 mL The retrieved numbers of LN: 67 No serious morbidity	First report on SIDG No pure SIDG
Mar 2012	D.J. Park *et al*.	2	2.5 cm incision One 2 mm assistant port	Operation time: 275 min EBL 85 mL The retrieved numbers of LN: 32 No complications	Case report One assistant port
May 2012	Omori *et al*.	20	2.5 cm incision Two 2 mm assistant ports	No postoperative complications including leakage and stricture	Technical report on intracorporeal Billroth I anastomosis

SIDG, single-incision laparoscopic distal gastrectomy; EBL, estimated blood loss.

between the patient's legs. A longitudinal 2.5-cm long transumbilical skin incision was made. A commercial 4-holes single port (Glove port; Nelis, Bucheon-si, Gyeonggi-do, Korea) was then placed in the umbilical incision, and the abdominal cavity was insufflated with carbon dioxide at a pressure of 13 mmHg. There was no additional assistant trocar. A 10-mm flexible high-definition scope (Endoeye flexible HD camera system; Olympus Medical Systems Corp., Tokyo, Japan) and a Harmonic Scalpel (Ethicon Endo-Surgery Inc., Cincinnati, OH) were used to visualize every corner of the operative field and facilitate dissection. We used the conventional laparoscopic grasper when operating in the greater curvature side and the curved instruments for single port surgery (Olympus Medical Systems Corp.) when operating in the lesser curvature side, including the suprapancreatic LND. Modified combined suture retraction of the falciform ligament and the left lobe of the liver was performed using 2-0 prolene on a straight needle and 5-mm hemoclips (6). Partial omentectomy was initiated distally approximately 3 to 4 cm away from the gastroepiploic arcade, which included the LN 4 d. To prevent omental infarction, the left gastroepiploic vessels were ligated distal to the omental branch. Then, the omentum was dissected and taken down from the mesocolon to the head of the pancreas and duodenum. The right gastroepiploic arcade was approached in a retrograde fashion. We first dissected the space between the duodenum and the basin including the right gastroepiploic vessels and LN station 6 and then detached these from the duodenum and distal stomach. Thus, we could easily dissect and divide the right gastroepiploic area without any significant bleeding. After dissecting LN 6, the right gastric artery and the proper hepatic artery were adequately exposed to dissect LNs 5 and 12a, and the operator exchanged the grasper for the prototype curved instruments. The right gastric artery was then divided at its origin. The duodenum was divided 2 cm distal to the pylorus using a laparoscopic linear stapler (Echelon 60 mm -3.5 and 4.5; Ethicon). LNs 8a and 9, located on the right side of the left gastric artery, were dissected along each artery. The left gastric vein and artery were exposed, individually clipped, and divided to allow dissection of LN 11p. However, we do not expose the portal vein and splenic vein for D2 lymph node dissection. LNs 1, including the vagus nerve, were dissected and the lesser curvature side was cleared up for transecting the stomach. After the transecting the stomach by linear staplers, the specimen was removed in a plastic bag from the single umbilical incision without any extension.

Uncut Roux-en Y Gastro-jejunostomy

For intracorporeal anastomosis, we used laparoscopic flexible linear stapler (Echelon flex 60-3.5 and 4.5; Ethicon Endo-Surgery Inc., Cincinnati, OH). To make an antiperistaltic gastro-jejunostomy, 2 small holes were made on the greater curvature side of the stomach and the jejunum 20 cm distal from Treitz ligament. After the formation of gastro-jejunostomy (G-Jstomy), we checked bleeding in the stapler line and lumen and the common opening was closed with a linear stapler. Next, side-to-side jejuno-jejunostomy (J-Jstomy), 25 cm below the G-Jstomy was performed in an intracorporeal fashion using 2 linear staplers. Finally, a linear stapler with no knife was applied

Table 2 Patient demographics and clinical characteristics

	SIDG (n=30)
Age	56.2±12.8
Sex (male:female)	23:7
BMI (kg/m^2)	23.4±3.7
Comorbidity	33.3% (n=10)
Previous abdominal operation history	16.7% (n=5)
ASA	
1	15
2	15

Table 3 Operative data

	SIDG (n=30)
Operation time (min)	175.5±46.6
Type of surgery	SIDG:pure SIDG =10:20
Laparoscopy or open conversion, n (%)	0
Lymph node dissection (D1+beta:D2)	28:2
Resectability (%)	
R0	100
Other organ resected, n (%)	1 (3.3)
Estimated blood loss (mL)	49.3±40.9
Reconstruction	BI:R-Y =10:20

in the afferent loop between the G-Jstomy and J-Jstomy in order to prevent bile reflux. The abdominal cavity was checked, 1 Jackson-Pratt (J-P) drainage tubes was placed through the umbilical wound around the subhepatic area, and the incision was closed.

Results

Patient demographics and clinical characteristics

The demographics of patients are described in *Table 2*. There were 23 males and 7 females in the SIDG group. The mean age of both groups was 56.2±12.8.

Operative data

All the surgeries, involving D1+beta or D2 lymphadenectomy without any laparoscopic or open conversion, were performed by a single surgeon and done in R0 status. The surgical parameters of the both group are shown in *Table 3*.

Table 4 Postoperative outcomes

	SIDG (n=30)
Postoperative hospital stays (days)	5.8±2.5
Time to first flatus	3.1±0.8
Time to first diet	3.6±1.0
Numbers of additional usage of parenteral analagesics	0.77±1.00
J-P drainage	
POD#1	105.6±90.5
POD#2	109.9±109.2
POD#3	13.8±149.3
Early complications	10.0% (n=3)
Late complications	0
Re-operation	0

The mean operation time was calculated from the start of the incision to the closure of the wound and was 175.5±46.6 in the SIDG group. The estimated blood loss was 49.3±40.9 in the SIDG group. There were initial 10 cases of SIDG with one 2 mm assistant port and 20 cases of pure SIDG without any assistant port in the SIDG group. No serious intraoperative events or complications were observed.

Postoperative outcomes

The postoperative outcomes were described in *Table 4*.

The overall early complication occurred in 3 patients (10.0%) in the SIDG group. The early complications included 1 case each of wound seroma, delayed gastric emptying and anastomotic stenosis. The wound complication was improved by conservative management. The delayed gastric emptying was improved by fasting for 5 days. A major complication, defined by a grade higher than Clavien-Dindo IIIa, was observed in 1 patient (3.3%), which was treated by temporary stent insertion.

Pathologic findings

The pathologic findings of this study are shown in *Table 5*. All the patients were diagnosed with EGC during the preoperative examinations. The number of retrieved lymph nodes was 46.9±12.2.

Operation time and learning curve

Figure 1 shows that the time taken for an operation

Table 5 Pathologic findings

	SIDG (n=30)
Size (cm)	2.49±1.88
Proximal resection margin (cm)	5.28±2.62
Distal resection margin (cm)	5.76±3.16
T-stage	
T1a	11
T1b	14
T2	3
T3	1
T4a	1
N-stage	
N0	24
N1	3
N2	1
N3a	2
Numbers of retrieved LN	46.9±12.2

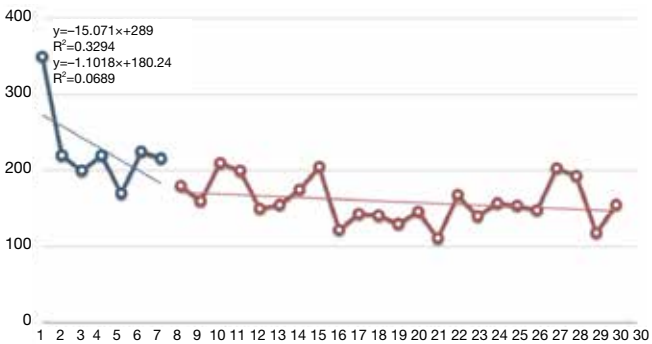

Figure 1 Operation time

gradually decreased in the SIDG group. To examine the learning process of SIDG, SIDG cases were divided into 3 groups based on the serial number of surgery (0-10, 11-20 and 21-30, respectively). The operation time in the 11-20 and 21-30 cases groups were significantly shorter than in the 0-10 cases group (P=0.007).

Conclusions

In this study, we evaluated the surgical outcomes of SIDG in 30 patients with EGC, which shows excellent postoperative outcomes. This procedure was found to have acceptable oncologic outcome, surgical time, and complications rates.

Thus, we conclude that SIDG is a likely acceptable treatment for EGC; furthermore, it is a feasible, safe, and useful method for reducing postoperative pain and facilitating cosmesis.

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Surgical Research

Mid-term results after single incision transumbilical laparoscopic sleeve gastrectomy

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Background: laparoscopic sleeve gastrectomy (LSG) is gaining large popularity as a stand-alone bariatric procedure. Single incision laparoscopic surgery (SILS) was successfully used in bariatric surgery. In 2010, we published our preliminary results of single-incision transumbilical (SITU) laparoscopic bariatric surgery including 6 cases of SITU-LSG and the short term results were perfectly acceptable. In this study, we evaluate the short- and mid-term results of (SITU-LSG) including safety feasibility, efficacy, complications and cosmetic results.

Methods: Between November 2008 and November 2012, 51 morbidly obese patients underwent SITU-LSG. Data was prospectively collected and retrospectively analyzed.

Results: The mean age was 31 years (range, 18-50 years), and the mean preoperative body mass index (BMI) was 36.3 kg/m^2 (range, 32.16-45.67 kg/m^2). Patients were 13 males and 38 females. The procedure was successfully performed in all patients without inserting additional trocars or conversion to conventional 5 ports or open surgery. The mean operative time was 72 minutes (range, 30-170 minutes). No intraoperative complications occurred. The mean hospital stay was 2 days (range, 1-5 days). No mortality, leak, stricture, wound infection and incisional hernia occurred during 2 years of follow up. The excess weight loss (EWL%) was 73.8% (range, 48.43-102.95%) and 76.1% (range, 43.35-103.16%) at 1 year and 2 years after surgery. Most co-morbidities disappeared 2 years after surgery and patients were satisfied with the cosmetic results.

Conclusions: SITU-LSG is a feasible, safe bariatric procedure with acceptable cosmetic results and effective short to mid-term weight loss and resolution of comorbidities.

Keywords: Bariatric surgery; laparoscopic sleeve gastrectomy; single incision laparoscopic surgery; single incision transumbilical laparoscopic surgery; single-incision transumbilical (SITU)

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Introduction

The prevalence of overweight and obesity has been increasing globally. Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, hypertension, obstructive sleep apnea, asthma, certain types of cancer, and osteoarthritis (1,2). It is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and authorities view it as one of the most serious public health problems of the 21st century (3). On average, obesity reduces life expectancy by six to seven years (3,4) a BMI of 30-35 kg/m^2 reduces life expectancy by two to four years (5), while severe obesity (BMI >40 kg/m^2) reduces life expectancy by ten years (5,6).

In Western countries, the Morbid Obesity is defines as: BMI ≥40 kg/m^2, or BMI ≥35 kg/m^2 with severe obesity-related morbidities. However, Asians are more prone

to develop obesity-related disease at a lower BMI than Caucasian, and in Asia-Pacific Region, we define Morbid Obesity according to the guideline from the Consensus Statement from Asia-Pacific Bariatric Surgeons Group in 2005: BMI ≥37 kg/m^2, or BMI ≥32 kg/m^2 plus Type 2 Diabetes or two obesity-related co-morbidities.

The most effective treatment for obesity is bariatric surgery. Surgery for severe obesity is associated with long-term weight loss, resolution of comorbidities, and decreased overall mortality.

Laparoscopic sleeve gastrectomy (LSG) for treatment of morbid obesity was first described as a part of the more complex operation, biliopancreatic diversion with duodenal switch (BPD/DS). Thereafter, LSG was performed as a first-stage procedure in high-risk patients with a body mass index (BMI) of more than 60 to obtain an initial weight loss with low morbidity and mortality (7).

Recently, LSG has been gaining wide popularity as a stand-alone procedure for the treatment of morbid obesity. The accelerating enthusiasm toward this procedure is driven by its relative simplicity compared with LRYGB and BPD/DS, and its promising early and long term results (8,9).

LSG has shown to provide weight loss comparable to LRYGB and LBPD-DS but with the added advantage of having lesser morbidity and along with resolution of co-morbidities such as diabetes, hypertension, and dyslipidemia (10,11). Lately, we published our 5 years experience in LSG, and the results was encouraging and comparable to LRYGB in terms of weight loss and resolution of co-morbidities (12).

Single-incision laparoscopic surgery (SILS) was first described as early as 1992 by Pelosi *et al.* performed single-puncture laparoscopic appendectomy and hysterectomy (13). Applications of SILS have expanded rapidly and various procedures including bariatric surgery have been carried out with this technique. The first SILS sleeve gastrectomy was performed by Saber *et al.* in 2008, thereafter a few reports of SILS-LSG were published with encouraging short-term results (EWL%, resolution of co-morbidities, and complication rate were comparable to that of conventional 5 ports LSG, with the advantage of better cosmetic results, less abdominal pain, and shorter hospital stay) (14-16).

In 2010 we published our preliminary results of SITU laparoscopic bariatric surgery including 6 cases of SITU-LSG and the short term results were quite satisfactory (17). Here, after 3 years of our previous study and with a larger number of patients we want to evaluate the safety, feasibility, and efficacy of SITU-LSG, and show the mid-term results regarding EWL%, resolution of co-morbidities and cosmetic outcome.

Materials and methods

Between November 2008 and November 2012, 51 morbidly obese patients had undergone SITU-LSG. The patients were fully informed about the procedures, and informed consent was obtained from them. The indications for SITU-LSG were consistent with Asian Pacific Bariatric Surgery Society guidelines for Bariatric Surgery (2005):

(I) Age between 18-65 years;
(II) BMI ≥32 kg/m^2 with obesity-related co-morbidities or ≥37 kg/m^2 irrespective of co-morbidities).

Exclusion criteria in our study were:

(I) Patients with BMI ≥50 kg/m^2;
(II) Body height ≥180 cm;
(III) Severe GERD or Barrett's disease;
(IV) History of alcohol or drugs abuse.

Each patient was preoperatively screened and evaluated by a multidisciplinary bariatric team. Preoperative pan endoscopy (OGD scopy) was routinely performed to test for Helicobacter pylori, and screen for neoplasms or peptic ulcers. Patients were admitted one day prior to surgery and were prescribed liquid diet for a day. A proton pump inhibitor (PPI) and a single dose of intravenous antibiotic (Cefazolin) were intravenously administered 1 hour before surgery. The same operative technique and perioperative protocol was used in all patients. Data was prospectively collected and retrospectively analyzed. This study was conducted with the approval of E-Da Hospital institutional review board.

Operative technique

The patient was placed in the supine position with the arms extended laterally. An anesthesiologist induced general anesthesia and performed endotracheal intubation. For most operations, the surgeon stood on the right side of the patient and the assistant on the left. A 4-cm-long omega-shaped incision was made around the upper half of the umbilicus (*Figure 1*). The incision was deepened to the linea alba after dissecting the subcutaneous fat, and a 15-mm Versaport plus V2 trocar (Covidien) was inserted after establishing pneumoperitoneum, produced by carbon dioxide insufflation at a pressure of 15 mmHg. A 5-mm-long, rigid, 30° video laparoscope was then inserted. Under direct visualization, two 5 mm Versaport plus V2 trocars (Covidien) were inserted through both arms of the omega

Figure 1 A horizontal 4-cm-long omega-shaped skin incision around the upper half of the umbilicus

Figure 2 Triangular positioning of trocars

incision (*Figure 2*). We then inserted the liver-suspension tape (LST) into the peritoneal cavity. We used our novel previously published technique in liver suspension (18). One needle was placed in a needle holder, inserted into the lateral edge of the left liver lobe, and brought out through the abdominal wall in the left upper quadrant; the other needle was inserted into the left liver lobe near the falciform ligament and then brought out through the abdominal wall in the right upper quadrant. The liver was then retracted to an appropriate position, and the sutures were suspended with clamps (18). After achieving the appropriate liver traction, we commenced the surgical procedure.

In the SITU-LSG procedure, devascularization of the greater curvature was started 4 cm away from the pylorus and continued till the angle of His, using the 5 mm Ligasure (Tyco, New Haven, CT, USA). The posterior adhesions were taken down to prevent redundant posterior wall of the sleeve, and the angle of His was completely mobilized with exposure of the left crus of the diaphragm to facilitate complete resection of the gastric fundus.

A 36 Fr orogastric tube was inserted along the lesser curvature into the pylorus and retained as a stent for vertical gastrectomy using Endo GIA. Stapling under the guidance of calibration helps to prevent stenosis, and provides a uniform shape of the sleeve. We used a green load at a distance of 4 cm from the pylorus for the first firing and subsequently blue loads were used. Care must be taken when the first stapler is fired, as a distance of about 3 cm from the incisura angularis should be left to prevent stenosis. After the completion of the main operative procedure, the LST was removed and hemostasis was achieved by cauterization. All trocars were removed and the surgical specimens were extracted via the 15-mm umbilical defect through which a trocar had been inserted. All the fascial defects were closed individually with 2-0 Vicryl sutures. Subsequently, the wound was closed and dressing applied. Patients were transferred to the postoperative recovery room and then to the ward, provided their immediate postoperative course was uneventful. They were permitted to drink water and discharged early if they did not develop any complications.

Results

51 patients underwent SITU-LSG. They were 13 males and 38 females. The mean age was 31±7.7 years (range, 18-50 years), and the mean preoperative body mass index (BMI) was 36.32+2.89 kg/m^2 (range, 32.16-45.67 kg/m^2). Preoperative comorbidities are shown in *Table 1*.

The procedure was successfully performed in all patients without inserting additional trocars, or conversion to conventional 5 ports or open surgery. The mean operative time was 72±27.91 minutes (range, 30-170 minutes). No

Table 1 Number of patients with co-morbidities

Co-morbidity	Number of patients
Type 2 DM	2
Hypertension	8
Hyperlipidemia	28
Hyperuricidemia	9
NAFLD[a]	32

[a]-Non-alcoholic fatty liver disease.

Table 2 Resolution of co-morbidities after surgery

Co-morbidity	1 year	2 year
Type 2 DM	1/1 (100%)	1/1 (100%)
Hypertension	5/8 (62.5%)	4/5 (80%)
Hyperlipidemia	5/7 (71.43%)	6/6 (100%)
Hyperuricidemia	13/17 (76.47%)	9/10 (90%)
NAFLD	11/18 (61.11%)	9/10 (90%)

intraoperative complications occurred. The mean hospital stay was 2±0.84 days (range, 1-5 days). No mortality, leak, stricture, or wound infection occurred. One patient developed wound seroma, easily treated with aspiration. Another patient required re-admission 2 weeks after surgery because of severe vomiting and dehydration, however medical management with IV fluids and PPI was successful and the patient discharged 2 days later. No incisional hernia occurred during 2 years of follow up. The excess weight loss (EWL%) was 73.86±7.511% (range, 48.43-102.95%) and 76.12±17.54% (range, 43.35-103.16%) at 1 and 2 years after surgery, respectively. Resolution of co-morbidities at 2 years after surgery was as follows: Type 2 DM (1 patient), hypertension (4 patients), hyperlipidemia (6 patients), hyperuricaemia (9 patients), hyperlipidemia (6 patients), NAFLD (9 patients). More details about resolution of co-morbidities are shown in *Table 2*. Patients were satisfied with the cosmetic results.

Discussion

The evolution of MIS provides an opportunity to successfully perform a variety of surgical procedures through a single small incision on the abdominal wall using a technique called SILS. The application of this new technique in bariatric surgery has technical difficulties due to excessive visceral fat, huge fatty liver and difficulty of the SILS procedure itself in morbidly obese patients.

To gain popularity and acceptance in the field of bariatric surgery, single incision bariatric surgery should prove its feasibility, safety, efficacy and should at least lead to similar results to those of conventional laparoscopic bariatric surgery. This study included patients with BMI between 32 and 45 kg/m^2. We followed the Asian Pacific Bariatric Surgery Society guidelines for Bariatric Surgery (2005) to define morbid obesity and include patients in our study. Saber *et al.* and Pourcher *et al.* used the National Institutes of Health consensus criteria for inclusion (BMI more than 35 with comorbidities, or more than 40 without comorbidities) (14,19). The cut-offs for obesity definition in Asian people are lower because obesity-related co-morbidities are more likely to occur with lower BMI values in these ethnicity.

We excluded patients with BMI >50 kg/m^2, because those patients will have excessive loose skin after losing weight and will mostly ask for abdominoplasty later. Also tall patients with body height more than 180 cm were excluded from our study, because even with the use of long instruments, it is still difficult to reach the angle of His, and adequate dissection around the left crus and complete resection of the fundus are difficult. We use the umbilicus as the site of the incision, because it can hide the scar, so that the cosmetic results would be better. Most previous studies used the same site and reported good cosmetic results (14,16).

The main drawback to performing advanced laparoscopic surgery via the transumbilical approach is the crowding of instruments in a small incision and the small degree of instrument triangulation. We used 3 trocars (one 15 mm and two 5 mm) through a 4 cm incision (in the first 6 cases we used a 6 cm incision). Saber *et al.* used 3 trocars through an umbilical incision (14,15), while Lakdawala *et al.*, Prourcher *et al.*, and S. Delgado *et al.* used single port device introduced through the umbilicus (16,19,20). We found that using 3 trocars -SITU-LSG technique can create some degree of triangulation and, facilitate the movement of instruments inside and outside the abdomen, and reduce its clashing.

The mean operative time in our SITU-LSG series (72 minutes) was comparable to that of conventional LSG in the other series, and to that of our recently published study about LSG (60.63 minutes). Lakdawala *et al.* also reported a median operative time of 50 minutes in his series (N=50 patients), while the mean time was 79.2, and

128 minutes in S. Delgado *et al.* (20 patients) and P. Gentileschi *et al.* (8 patients) series, respectively (16,20,21).

All operations in our study were successful and completely done without intraoperative complications and without the need for additional trocars or the conversion to conventional LSG procedure. We feel that our novel technique in liver suspension (LST) eliminated the need to use additional trocar for liver retraction. In Lakdawala *et al.* study, all the operations were completed without conversion to conventional LSG or adding additional trocars (16). S. Dalgado *et al.* used additional epigastric 2-or 3-mm miniport for liver retraction in all patients in his series (N=20), and 1 patient required conversion to conventional LSG (20). In Pourcher *et al.* series (N=60 patients), 10 patients required a second trocar and 3 patients 2 additional trocars (19).

The mean length of hospital stay in our series was 2 days, without major complications or mortality. Only one patient developed wound seroma, easily managed with aspiration. In his series, Lakdawala *et al.* reported a median length of hospital stay of 2 days, without complications or mortality (16), while Pourcher *et al.* reported a median length of 4 days, with 1 patient developed leak from the upper gastric zone, successfully treated by a covered endoscopic prosthesis (19). S. Delgado *et al.* reported postoperative hemoperitoneum occurred in 2 patients, and required early reoperation 1 day after surgery (20). To reduce complication rate and to safely perform SITU-LSG, adequate experience in conventional LSG should be available.

Although it gives better cosmetic results when compared to conventional LSG, SITU-LSG should prove its efficacy in terms of weight loss, and resolution of co-morbidities to be accepted as a bariatric procedure.

In our series, SITU-LSG was quite effective, with a mean EWL% of 73.86% and 76.12%, 1 and 2 years after surgery, respectively. These mid-term results are comparable to that of our recently published study (12) and other studies on conventional LSG. To the best of our knowledge, this is the first study that gives 1 and 2 results after SITU-LSG.

Conclusions

SITU-LSG is safe, feasible and reproducible procedure. No important wound complications occurred during a follow up of 2 years and patients were satisfied with the cosmetic results of the procedure. The mid-term results regarding weight loss, and resolution of comorbidities are encouraging, and comparable to that of conventional LSG. Based on these results, this procedure can be recommended for morbidly obese patients with BMI less than 50 kg/m^2 and body height less than 180 cm who seek better cosmetic results.

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Laparoscopy-assisted gastrectomy following neoadjuvant chemotherapy for advanced gastric cancer - strategies for development

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Abstract: The established treatment for advanced gastric cancer is open gastrectomy with D2 lymph node dissection and postoperative adjuvant chemotherapy with S-1 or capecitabine plus oxaliplatin. However, the prognosis of patients with stage III disease is not satisfactory. More intensive chemotherapy is required to improve survival. Considering the patient compliance observed with intensive doublet or triplet chemotherapy, the administration of neoadjuvant chemotherapy is an attractive and promising approach. Many phase III trials to evaluate neoadjuvant chemotherapy in eastern Asia are now ongoing. On the other hand, surgical approaches have shifted to laparoscopic surgery. Several phase III trials to evaluate the efficacy of laparoscopy-assisted distal gastrectomy (LADG) have been performed in Japan and Korea, in both patients with early and advanced disease. Therefore, the candidates for future standard treatment consist of multimodality treatments, including neoadjuvant chemotherapy and subsequent LADG, for patients with advanced tumors located in the middle to lower third of the stomach. The feasibility, safety and long-term survival of laparoscopic gastrectomy following neoadjuvant chemotherapy must be guaranteed when neoadjuvant chemotherapy is the standard of care. Based on this background, we conducted a randomized phase II trial to compare LADG and open distal gastrectomy (ODG) after neoadjuvant chemotherapy for gastric cancer.

Keywords: Gastric cancer; laparoscopy; D2; gastrectomy; neoadjuvant chemotherapy

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Why should neoadjuvant chemotherapy be developed?

Gastric cancer is the second leading cause of cancer death worldwide and is the most common malignancy in Japan, South America, and Eastern Europe (1). Complete resection is essential for curing gastric cancer (2), however, the prognosis of patients with advanced disease treated with surgery alone is not satisfactory. Since 2000, surgery combined with adjuvant treatment has become the globally accepted standard of care for advanced gastric cancer. In the US, surgery followed by chemoradiotherapy has been established as the standard treatment based on the results of the INT-0116 phase III trial (3). In the UK and some European countries, pre- and postoperative chemotherapy with epirubicin, cisplatin and 5-fluorouracil is employed based on evidence from the MAGIC trial (4). However, surgery combined with adjuvant treatment was not optimized in the phase III trials performed in the US or Europe. After a long debate (5), D2 surgery, which was originally established in Japan, has been accepted as a standard surgery in Europe (6) and the US (7). The long-term observational report of the Dutch Phase III trial comparing D1 and D2 clearly demonstrated that D2 reduces local recurrence after surgery and thereby contributes to survival (8).

In eastern Asia where D2 is the standard surgery, two pivotal phase III trials comparing D2 and D2 followed by postoperative adjuvant chemotherapy were conducted. The ACTS-GC phase III trial performed in Japan demonstrated the benefit of S-1 for 12 months after D2 (9), and the CLASSIC phase III trial performed primarily in Korea indicated the benefits of capecitabine and oxaliplatin for six months after D2 (10). Currently, D2 surgery combined with the administration of adjuvant chemotherapy is recommended as the standard treatment for advanced gastric cancer: D2 surgery followed by S-1 in Japan and D2 surgery followed by capecitabine and oxaliplatin in Korea and the US (11).

Nevertheless the survival of patients with advanced disease is not satisfactory even by means of D2 and postoperative adjuvant chemotherapy. To improve the prognosis, more effective but also more toxic treatments exceeding these regimens should be developed in the future. However, it is questionable whether a more toxic combination regimen administered after gastrectomy is feasible or safe. Concurrent doublet combination regimens including CDDP are not acceptable (12). Although S-1 induces mild toxicities, the proportion of time to treatment failure at 12 months after surgery was not satisfactory, namely it was only 65.8% in the ACTS-GC study (9). Generally, patients suffer from loss of appetite and decreased food intake following gastrectomy, which causes a loss of body weight and decreases the quality of life. These factors may influence compliance with chemotherapy. Recently, we examined the risk factors for discontinuing S-1 after gastrectomy and found weight loss after surgery to be a significant independent risk factor (13). More toxic regimens administered after gastrectomy generally lack feasibility and safety.

Different from post-operative adjuvant chemotherapy, the administration of more intensive chemotherapy is possible in the neoadjuvant setting. The MAGIC trial clearly showed a high rate of compliance of chemotherapy with chemotherapy due to low toxicities associated with neoadjuvant chemotherapy compared with post-operative adjuvant chemotherapy (4). Moreover, all patients who should receive chemotherapy can initiate chemotherapy before surgery. It is obvious that some patients are unable to start chemotherapy after surgery due to surgical morbidity and mortality. Moreover, tumor regression due to the effects of chemotherapy and the avoidance of unnecessary surgery as a result of progression during chemotherapy would contribute to high rates of substantial R0 resection.

Another reason is the theoretical advantage of neoadjuvant chemotherapy. The aim of adjuvant chemotherapy is to eradicate micrometastatic tumor cells that cannot be resected during surgery. No treatment for micrometastatic tumor cells is administered until the patient has recovered from surgery and postoperative chemotherapy is initiated. On the other hand, micrometastatic tumor cells are initially treated without delay in neoadjuvant chemotherapy regimens, which is another theoretical benefit of neoadjuvant chemotherapy.

On the other hand, over-diagnosis is a disadvantage of neoadjuvant chemotherapy. In the MAGIC trial, the target patients had clinical stage II-III disease and all patients had clinical T2-T4 disease (4). However, 8.3% of the patients had pathological T1 disease in the randomized surgery alone arm.

Current status of clinical trials for neoadjuvant chemotherapy

In Japan, a phase III trial conducted by the Japan Clinical Oncology Group (JCOG) is now on-going to evaluate the survival benefits of neoadjuvant chemotherapy consisting of S-1 plus CDDP followed by surgery and postoperative S-1 by comparing surgery and postoperative S-1 in patients with clinically resectable scirrhous type gastric cancer. More recently, several regimens and courses of neoadjuvant chemotherapy were tested among clinical T4 or clinical stage III patients in phase II trials (14,15). One of these trials is the COMPASS trial comparing neoadjuvant chemotherapy consisting of two and four courses of S-1 + CDDP, paclitaxel and CDDP for stage III gastric cancer by a two- by two-factorial design. The other is the COMPASS-D trial comparing neoadjuvant chemotherapy consisting of two and four courses of S-1 plus CDDP and S-1, CDDP and docetaxel for macroscopically resectable serosa-positive gastric cancer by a two- by two- factorial design (15).

In Korea, the PRODIGY phase III trial (NCT01515748) is now on-going to evaluate the survival benefit of neoadjuvant chemotherapy consisting of docetaxel, oxaliplatin, and S-1 followed by D2 and postoperative S-1 by comparing D2 and postoperative S-1 in patients with T2-3/N+ and T4 disease. In China, two different phase III trials are now on-going to evaluate the benefits of neoadjuvant chemotherapy by comparing surgery and postoperative S-1 plus oxaliplatin. One study is being conducted to test neoadjuvant chemotherapy consisting of

pre- and post operative S-1 plus oxaliplatin (RESONANCE phase III, NCT01583361), while the other is being performed to evaluate pre- and post operative S-1 plus oxaliplatin as well as pre- and post operative capecitabine plus oxaliplatin in three arms (the Hebei Medical University trial, NCT01516944). In the UK, perioperative bevacizumab combined with the MAGIC regimen was tested in the STO3 phase III study (NCT00450203).

Although new regimens such as S-1 followed by S-1 plus oxaliplatin, chemoradiation with S-1 or capecitabine with oxaliplatin, or S-1 plus docetaxel have been tested as post-operative adjuvant chemotherapy in phase III trials, no trials have evaluated the use of triplet regimen after surgery. In the future, it is obvious that post-operative adjuvant chemotherapy will shift to neoadjuvant chemotherapy.

Surgery combined with neoadjuvant chemotherapy

D2 gastrectomy is a feasible and safe procedure when performed by experienced surgeons. The morbidity and mortality were reported to be 20.9% and 0.8% (16), respectively, in the JCOG-9501 phase III trial performed in Japan. On the other hand, the feasibility and safety of D2 surgery following neoadjuvant chemotherapy has not been fully evaluated. In the MAGIC phase III trial, the surgical morbidity and mortality were 45.7% and 5.6%, respectively in the patients who received surgery following pre-operative chemotherapy and 45.3% and 5.9%, respectively in those who received primary surgery (4). In the FNCLCC/FFCD phase III study, the postoperative morbidity and mortality were 25.7% and 4.6%, respectively, in the patients who received neoadjuvant chemotherapy followed by surgery and 19.1% and 4.5%, respectively, in the patients who received primary surgery (17). In both trials, the surgical complications were similar regardless of whether the patients received primary surgery alone or surgery following the neoadjuvant chemotherapy, however, the surgical procedures were less than D2 in most cases in the MAGIC study and were not accurately described in the FNCLCC/FFCD phase III study.

Only one phase III study (EORTC 40954 study) has compared D2 surgery and preoperative 5-FU plus CDDP and D2 surgery (18). D2 surgery was performed in more than 90% of the patients in both arms. The overall morbidity was higher in the neoadjuvant group (27.1%) than in the surgery alone group (16.2%). Injury of a major blood vessel occurred in 4.3% of the patients in the neoadjuvant arm versus 1.5% of the patients in the surgery alone arm. In the surgery alone arm, one splenectomy was required to achieve hemostasis. Different from D1 and D0 surgery, the nodes along the pancreas and spleen should be dissected in D2 or more extended surgery. When the lymph nodes along the pancreas are enlarged, it may difficult to identify the branched arteries or drainage veins around the pancreas, which can be related to surgical difficulties.

On the other hand, several Japanese investigators have demonstrated that performing D2 or more extended surgery is feasible and safe, even after neoadjuvant chemotherapy, in single-arm phase II studies (19-21). Except for randomized studies, the complication rates in the single-arm studies are difficult to compare with other historical control data, due to differences in the population, chemotherapy regimen, duration of chemotherapy, and the terminology and definitions used to describe each complication were not strictly determined. In addition, surgical complications differ between total and distal gastrectomy.

Current status of laparoscopy-assisted distal gastrectomy (LADG)

Since Kitano reported the first case of LADG for gastric cancer in 1994 (22), LADG become widely performed in community hospitals to treat both early disease and advanced tumors. Laparoscopic surgery provides a good quality of life in addition to cosmetic benefits. LADG is often selected when the tumors are located in the middle to the lower third of the stomach. Thus far, many retrospective studies, in-house small prospective studies, and meta-analysis demonstrated the feasibility and safety of LADG for treating gastric cancer (23,24). Recently, Katai reported that the rate of Grade 3 or 4 morbidities evaluated according to the Clavien-Dindo classification was 5.1% among 176 patients and that the rate of anastomotic leakage and/or pancreatic fistula, the primary endpoint, was only 1.7% in a large-scale multicenter phase II study (25). Based on this study, Katai initiated a phase III study (JCOG-0912 study, UMIN000003319) to compare overall survival between LADG and open distal gastrectomy (ODG) for stage I gastric cancer (26). In Korea, Kim also reported that morbidity and mortality were not significantly different between LADG and ODG among 342 patients enrolled in a phase III study (KLASS-01 study, NCT00452751) (27). The KLASS-01 study has recently completed patients recruitment (n=1,415) and will be opened in September

2015 (28). The JCOG-0912 and KLASS-01 studies will clarify that LADG exhibits non-inferior survival compared with ODG for early gastric cancer.

Moreover, a phase II/III trial is now on-going for advanced gastric cancer in Japan (JLSSG0901 trial, UMIN000003420). The phase II part of this trial has been completed, and the feasibility and safety of LADG with D2 dissection were confirmed for patients with advanced disease. In Korea, Lee also reported that performing LADG with D2 was found to be feasible and safe in a single-arm phase II study (29). In Korea, the KLASS-02 trial (NCT01456598) is also now on-going to compare D2 gastrectomy using the laparoscopic or open approach for T2-T3 gastric cancer. The JLSSG0901 and KLASS-02 studies will clarify whether LADG exhibits non-inferior survival compared with ODG for advanced gastric cancer.

Unlike LADG, performing total gastrectomy under the laparoscopic approach remains challenging and the technique has not been standardized.

Strategy to develop LADG following neoadjuvant chemotherapy

Considering the current status of the development of neoadjuvant chemotherapy and laparoscopic surgery for advanced disease as a primary treatment, the candidates for future standard treatment include multimodality treatments, such as neoadjuvant chemotherapy and subsequent LADG, when advanced tumors are located in the middle to lower third of the stomach. However, the efficacy of LADG following neoadjuvant chemotherapy has not yet been established. The feasibility, safety and long-term survival of laparoscopic gastrectomy following neoadjuvant chemotherapy must be guaranteed when neoadjuvant chemotherapy is the standard of care. This procedure has repeatedly been presented to be safe and feasible in some Japanese medical meetings (30). However, the use of LADG following neoadjuvant chemotherapy has not yet been tested in prospective clinical trials.

What should be evaluated in trials and how?

Surgical difficulties are affected by the extent of gastrectomy, the extent of dissection, disease progression, body composition, the duration and regimen of neoadjuvant chemotherapy and the approach of laparoscopy or open surgery. One ideal trial would be to evaluate whether safety and feasibility differ between LADG and ODG under the same conditions. Randomized trials to compare LADG and ODG following the same regimen of neoadjuvant chemotherapy would clarify this hypothesis. Another hypothesis is that the LADG following neoadjuvant chemotherapy is equally as feasible and safe as primary open surgery without neoadjuvant chemotherapy. Because a morbidity of 20.9% and a mortality of 0.8% were observed in the patients receiving primary D2 surgery (16), LADG following neoadjuvant chemotherapy must have either equivalent of lower rates of lower morbidity and mortality than these values. The hurdles for LADG appear to be too high in this setting. Based on this background, we conducted a randomized phase II trial to compare LADG and open distal gastrectomy (ODG) after neoadjuvant chemotherapy for gastric cancer (31).

LANDSCOPE trial

The purpose of this study was to evaluate the safety and efficacy of LADG compared with ODG for gastric cancer that is macroscopically resectable via D2 gastrectomy and to determine whether LADG can be used in a test arm in a future phase III trials to evaluate the non-inferiority of overall survival compared with ODG in patients who receive neoadjuvant chemotherapy. To minimize variability in chemotherapy regimens, we restrict to the subjects to the patients enrolled in a randomized phase II trial of neoadjuvant chemotherapy comparing a regimen of S-1 plus CDDP (SC) and S-1/CDDP/Docetaxel (SCD) as well as the duration of two and four courses of chemotherapy (COMPASS-D trial, UMIN000006378) (15).

This study is an open-label, randomized phase II clinical trial. The protocol has been approved by the Protocol Review Committee of the Kanagawa Standard Anti-cancer Therapy Support System (KSATTS). The primary endpoint is the 3-year progression-free survival (PFS) rate. The secondary endpoints are the overall survival, surgical morbidity and mortality, R0 resection rate, R0R1 resection rate, conversion rate, efficacy and safety in patients who complete the surgery and the efficacy and safety in each subset.

The key eligibility criteria for the 1st enrollment before neoadjuvant chemotherapy included histologically proven adenocarcinoma of the stomach, clinical T4aN0-N3M0 disease, confirmed on upper gastrointestinal endoscopy or an upper gastrointestinal series, and abdominal CT and laparoscopy according to the method of Haberrmann (32), an age ranging between 20 and 80 years and the patients who were enrolled in the COMPASS-D phase II trial.

The key eligibility criteria for the 2nd enrollment included patients who received two or four courses of SC or SCD, as defined by the COMPASS-D trial, and the presence of gastric tumors that are macroscopically resectable via distal gastrectomy with D2 lymph node dissection. Resectability was evaluated using upper gastrointestinal endoscopy and CT seven to 21 days after the date when the anti-cancer drugs were administered.

Following the completion of neoadjuvant chemotherapy or when the tumors progress during treatment, the patients will proceed to surgery. The patients enrolled in this study will receive open or laparoscopic distal gastrectomy. In both groups, the intraperitoneal cavity will be assessed to determine whether R0 or R1 surgery is possible via D2 distal gastrectomy. When performing R0/R1 surgery is impossible, the protocol treatment will be stopped. After confirming resectability, dissection will be started.

For laparoscopic surgery, the number of trocars will be limited to five or six. Reduced port surgery is prohibited. The length of the skin incision is limited to <6 cm. When a longer skin incision is required, the case will be regarded to require conversion to open surgery. The protocol prohibits the use of laparoscopic total gastrectomy and laparoscopic extended surgery such as lymphadenectomy exceeding D2 and combined resection of other organs. When these types of surgery are necessary to achieve R0/R1 resection, the surgeon must convert to open surgery. The operators of laparoscopic surgery will be limited to surgeons whose skills for laparoscopic distal gastrectomy are qualified by the Japan Society for Endoscopic Surgery.

The present study is a randomized phase II trial to evaluate the efficacy and safety of LADG compared to ODG. This study is primarily designed to evaluate the 3-year DFS rate of LADG and to demonstrate that it is not inferior to that of ODG. LADG will be considered promising for a subsequent phase III trial if the Bayesian posterior probability of "the difference in the 3-year disease-free survival (DFS) rate is less than a non-inferiority margin of 8%" is at least 50% (33). For safety, the point estimate of treatment-related death (TRD) is expected to be <5% in each group.

The planned sample size is 80, with 40 cases per arm. This sample size provides a 76% chance of satisfying the above criteria, under the hypothesis that the expected 3-year disease-free survival rate in each arm is 50%. The primary analysis in this study aims to estimate the 3-year DFS rate. The DFS curves are constructed as time-to-event plots by using the Kaplan–Meier method, and the 3-year DFS and its 95% confidence interval will be estimated. The 3-year DFS will be compared based on the normal approximation of the 3-year DFS rate (z test). The overall survival will also be analyzed in the same manner. The surgical morbidity and mortality, R0 resection rate, R0R1 resection rate, and conversion rate, will be calculated as proportions with exact confidence intervals, and compared using Fisher's exact test.

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Surgical Research

Laparoscopic D2 dissection for locally advanced gastric cancer in China

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Minimally invasive surgery has become one of the most important concepts during the development of surgery in the 21st century, among which the laparoscopic technique represents a major advancement in this field. Since Kitano *et al.* first performed laparoscopy-assisted distal gastrectomy for early gastric cancer in 1991 (1), the laparoscopic surgeries for gastric cancer have rapidly developed in the past two decades and became widely applied worldwide. Some published clinical trials have confirmed that, in addition to minimal invasiveness, the laparoscopic surgeries are also equally effective in treating early or locally advanced tumors as the open procedures (2-4). These studies were mainly conducted in patients with early gastric cancer, and therefore the laparoscopy-assisted surgery has been regarded as one of the standard approaches for gastric cancer. However, its role in the management of locally advanced gastric cancer is still to be further ellucidated from the results of some large-scale randomized controlled trials (RCTS) including JCOG0912, KLASS-02, and CLASS-01.

The number of gastric cancer patients in China accounts for about 40% of the global total cases, and over 80% of them are already in the advanced stages, showing a fairly large gap when compared with those (over 50% are in the early stages) in Japan and Korea (5). As a result, alternative of treatment strategy is also directly affected. Therefore, the challenges faced by laparoscopic surgeries for gastric cancer are somehow different from those in other countries. When medical centers in Japan and Korea had already carried out RCTs on the role of laparoscopic surgeries for early gastric cancer, few Chinese hospital adopted this technique (6). Today, some RCTs on the effectiveness of laparoscopic surgeries for locally advanced gastric cancer are being carried out in Japan and Korea; fortunately, the laparoscopic gastric surgeries have increasingly been applied in China (*Video 1*). More than one Chinese centers have performed over 1,000 laparoscopic gastric operations. Pioneers in this field have demonstrated the features and advantages of laparoscopic surgeries, inspiring the surgeons, particularly the young doctors, to actively learn and apply this technique. Nevertheless, enthusiasm and confidence cannot be easily converted into the adoption and popularization of the new technique. Laparoscopy technology is featured by enlarged field of view and refined dissection, which are particularly important for the radical surgery of gastric cancer and may also exert certain advantages in the training and learning. However, the indications of laparoscopic surgeries for the locally advanced gastric cancer remain controversial. Findings from large-scale RCTs may provide more convincing evidences. In some clinical conditions such as obesity, fusion of lymph nodes, and pre-operative chemotherapy that may make the open surgeries more challenging, will the laparoscopic surgeries be more feasible or more advantageous? Many similar questions are among the hottest research topics in this field in the past few years (7-9). All the beginners must receive intensive training and exercises before they are involved in the clinical practices. The learning curve should be started by managing patients with early gastric cancer.

Although the Chinese doctors were the “learners” during the introduction of laparoscopic surgeries for the early gastric cancer, nowadays some RCTs in patients with locally advanced gastric cancer have also been carried

out in China. Notably, the CLASS-01 is the first multi-center, large-scale, prospective clinical study in this filed in China. Since patients with locally advanced gastric cancer in China is still the main body of sick people, this study will for sure improve the health care quality and maintain the best interests of these patients. However, the surgeries for locally advanced gastric cancer are often more difficult than those for the early ones, and some issues (e.g., the appropriate method for dissecting the splenic hilar lymph nodes in patients with proximal gastric cancer) still have not been addressed. Therefore, currently the laparoscopic surgeries for locally advanced gastric cancer should only be performed in the context of clinical trials. The clinical application of laparoscopic surgeries should advance gradually in due order, with the patients' interests being the top priority. By carrying out active exchanges with domestic and global partners, we will gradually establish and optimize the learning, training and certification of laparoscopic surgeries for gastric cancer in China, enabling the robust and sound application of this technique.

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Surgical Research

Perfect-results after laparoscopic surgery for gastroesophageal reflux - are they achievable?

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Abstract: In the quest for the perfect outcome following antireflux surgery, Nissen's original fundoplication has undergone many modifications. The original procedure achieved good reflux control, but this was offset by a relatively high incidence of troublesome side effects. The modifications which have been proposed as solutions to the problem of troublesome side effects have now all been tested in randomized trials. Outcomes from these suggest that division of the short gastric vessels during Nissen fundoplication is unnecessary, and that partial fundoplications are associated with less side effects. However, there is a trade-off between the risk of side-effects *vs*. the risk of recurrent reflux across the spectrum of antireflux procedures ranging from Nissen fundoplication at one end to lesser degrees of partial fundoplication at the other. Whilst a perfect outcome is almost certainly not achievable following antireflux surgery, the trade-off between the risk of reflux vs. the risk side effects needs to be considered during work-up, and the fundoplication can be tailored to the preoperative esophageal motility and individual patient preferences to achieve better outcomes.

Keywords: Perfect-results; laparoscopic surgery ; gastroesophageal reflux

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The era of surgery for gastro-esophageal reflux began in the 1950's following Nissen's original description of a 360 degree wrap of gastric fundus around the distal esophagus (1). In an earlier time when acid suppressing medication was not available, this procedure offered the only effective treatment opportunity for individuals who experienced significant symptoms of gastro-esophageal reflux. Nissen's original fundoplication entailed surgery via an open transthoracic approach with the construction of a 5 cm long, fairly tight circumferential wrap of gastric fundus around the distal esophagus. Both the anterior and posterior walls of the fundus were used for the fundoplication and the short gastric blood vessels were not divided. However, it soon became apparent that even though this operation controlled reflux well, in many individuals it was associated with troublesome side effects, such as dysphagia, abdominal bloating and flatulence, and in some individuals reflux returned later, even though the operation was initially effective.

Across the 1960's to 1980's, in an attempt to reduce the risk of side effects yet still control reflux, a range of modifications to Nissen's original procedure were proposed. Rossetti simplified the construction of the fundoplication so that only the anterior wall of the fundus was used for fundoplication (2). Donohue *et al.* (3) advocated division of the short gastric vessels to enable a very loose wrap to be constructed, and DeMeester *et al.* (4) also loosened the wrap and shortened its length progressively from 5 cm to 1-2 cm. Partial fundoplications, during which the fundus was wrapped only part way round the esophagus; e.g., Toupet -posterior placement (5), Dor or Belsey - anterior placement (6,7), were also devised. At the same time, to reduce the morbidity associated with surgical access, surgeons also moved from an open transthoracic approach via a left postero-lateral thoracotomy to an open abdominal approach via an upper midline incision, and then in the 1990's to the current laparoscopic approach (8).

The proponents of each of these technical variations all reported good outcomes, and surgeons in various parts of the world modified their techniques accordingly. However, until the late 1990's the quality of the evidence base underpinning these variations was poor, and the evidence predominantly entailed reports of good outcomes from retrospective case note reviews, or prospective studies without control groups. Furthermore, opinion was largely led by what the "experts" recommended, even when this conflicted with the evidence derived from well constructed randomised controlled clinical trials.

In considering how to best perform surgery for gastro-esophageal reflux disease, several questions should be asked:

- What is the "perfect" outcome following an intervention for reflux?
- Does high quality evidence inform the quest for a "perfect" outcome?
- Is a "perfect" outcome achievable?

What is the "perfect" outcome for the treatment of gastro-esophageal reflux?

Symptoms of gastro-esophageal reflux develop when excessive regurgitation of gastric contents into the esophagus occurs. This is a mechanical problem, and it only happens when the valve mechanism at the gastro-esophageal junction fails to prevent excessive regurgitation of gastric content. Medical therapy addresses the symptoms of gastro-esophageal reflux by blocking the production of acid in the stomach, and consequently reducing the amount of acid exposure which enters the esophageal lumen. However, it fails to physically stop reflux from occurring, and the physical reflux of gastric content continues. If this contains other substances such as bile salts and pancreatic secretions which can also injure the esophageal mucosa, then reflux symptoms may not be well controlled, as medication only suppresses acid production. Surgical fundoplication is effective as it reconstructs the valve mechanism at the gastro-esophageal junction, and physically stops gastric content from entering the esophageal lumen.

Arguably, the "perfect" treatment for gastro-esophageal reflux should meet the following criteria:

(I) The intervention is a "one-off" - i.e. a single treatment cures the patient;
(II) The treatment is 100% successful;
(III) The problem never returns - i.e. the cure is permanent;
(IV) There are no complications;
(V) There are no side effects;
(VI) Treatment does not require any surgical incisions;
(VII) Treatment can be performed on an outpatient basis - i.e. does not require hospital admission.

Unfortunately, no currently available treatment meets all of these criteria. Medication fails to meet the first 5 criteria, although side effects and complications are usually uncommon, and are reversible when medication is ceased. A range of transoral endoscopic antireflux procedures (9-12) were trialed in the late 1990's to mid 2000's, and do address criteria 6 and 7, but these have all failed to deliver reliable long term control of reflux, and have now been abandoned in many parts of the worlds. Surgical fundoplication also fails to meet all the criteria, but some of the modifications and variations to Nissen fundoplication arguably better meet the criteria for the "perfect" treatment, when compared to non-surgical options or Nissen's original procedure.

Assessing treatment outcomes

When considering outcomes following fundoplication, it is important to realize that surgeons, and patients often have different perspectives about what a good outcome actually is, for example, surgeons often focus on technical success following antireflux surgery, i.e. objective measures of reflux control and improvements in esophageal physiology. Normalization of objective measures of gastro-esophageal reflux such as endoscopic evidence of healing of esophagitis, normalization of intra-esophageal acid exposure measured by 24-hour ambulatory pH monitoring, or improvements in lower esophageal sphincter pressure measured using esophageal manometry are all issues surgeons focus on, and provide objective evidence of reflux control.

However, patients are usually more concerned about subjective outcomes, i.e. symptoms, and less concerned about objective outcomes which demonstrate reflux has been prevented. For the individual patient the issue of importance is long term symptom control with minimal side effects. They tend to look at the overall outcome following antireflux surgery, and hope to be better off after surgery. In assessing outcome from this perspective, there is often a balance between the control of reflux symptoms *vs.* the risk of post-fundoplication side effects. This balance can lead to patients reporting good or bad outcomes which don't make sense to the operating surgeon. For example, a patient can develop recurrent reflux following antireflux surgery, yet still consider the operation to be a success! This may occur when surgery is performed in individuals with symptoms

of gastro-esophageal reflux that are poorly controlled by proton pump inhibitor medication before surgery, but in whom some reflux symptoms return at a later stage. If these recurrent post-operative reflux symptoms are fully controlled by a proton pump inhibitor then the patient might still be happy with the outcome following surgery, as the patient is effectively symptom free. Other scenarios which can be acceptable, include full control of reflux symptoms following a fundoplication, but with the patient needing to modify his diet to some extent to avoid post-fundoplication dysphagia. If the original reflux symptoms were particularly troublesome, then some individuals might consider a trade-off such as mild dysphagia for solid food to be very acceptable.

In determining the overall outcome, individuals who undergo fundoplication will often balance the efficacy of reflux control against side effects, and consider this balance in the context of the extent of the preoperative problem to determine whether the overall outcome is acceptable or not. Hence, to measure outcome from the individual patient's perspective, global satisfaction measures that integrate the overall balance of symptom control *vs.* side effects are arguably more important than apparent technical success measured by objective tests.

What evidence is available to determine the best way to deliver a "perfect" outcome?

Since the 1990's a range of prospective randomised controlled clinical trials have been reported evaluating outcomes following antireflux surgery. Collectively these trials address technical issues and provide a good evidence base to determine how to best perform antireflux surgery.

Laparoscopic versus open fundoplication

Ten prospective randomised trials have been reported which compare laparoscopic versus open fundoplication, 9 evaluating Nissen fundoplication and one evaluating laparoscopic *vs.* open posterior partial fundoplication (13-17) and follow-up has been reported at up to 10-15 years in some trials. These trials enrolled between 40 and 192 patients and in general have shown benefits for the laparoscopic approach over the open approach. Early outcomes at follow-up up to 12 months demonstrate advantages for the laparoscopic approach, with shorter postoperative stays (3 *vs.* 4 days median), and less postoperative complications following laparoscopic fundoplication. Reoperation rates for reflux and side effects such as dysphagia were similar for both procedures, although there was a higher incidence of late incisional hernia formation following open surgery in some trials (14). However, in these trials these advantages of the laparoscopic approach were offset by somewhat longer operating times (approximately 30 minutes).

Division of short gastric vessels during Nissen fundoplication

Originally Nissen's fundoplication entailed a 360° fundoplication during which the short gastric blood vessels were left intact (1). However, following reports of troublesome postoperative dysphagia, routine division of these vessels to better mobilize the fundus and ensure a loose fundoplication, was promoted in the 1970's and 1980's by Donahue (3) and DeMeester (4), and this maneuver has entered common practice. The evidence supporting this was based on outcomes from case series. More recently, 6 randomised trials have been reported that enrolled a total of 438 patients and compared Nissen fundoplication with *vs.* without division of the short gastric blood vessels (18-21). The results of these studies have been remarkably consistent, and have shown no difference in reflux control or post-operative dysphagia for division *vs.* no division of the short gastric vessels. However, the larger trials demonstrated that division of the short gastric blood vessels during Nissen fundoplication is associated with an increased risk of flatulence and gas bloat-type symptoms, and more difficulty with belching. A recent meta-analysis which combined data for 201 patients from Australia and Sweden confirmed this analysis and the finding of more abdominal bloating after division of the short gastric vessels (22). The randomized trials do not support the widely held belief that dividing the short gastric vessels improves the outcome following Nissen fundoplication. Further, these trials actually suggest that dividing the vessels leads to a poorer outcome.

Nissen versus posterior partial fundoplication

Eleven prospective randomised trials have compared Nissen *vs.* posterior partial fundoplication (23-26). Study size has ranged up to 200 patients, with 6 trials enrolling more than 100. The larger studies have all demonstrated that posterior partial fundoplication achieves equivalent reflux control, but with a reduced incidence of flatulence and

bloating. Dysphagia was less common following posterior fundoplication in 2 of the larger studies. Meta-analyses have confirmed the reduction in wind-related side effects and dysphagia following posterior partial fundoplication, and also confirm equivalent reflux control (27).

Arguably the most informative study was conducted by Lundell and colleagues (23). They reported the outcomes of a randomized trial of Nissen *vs.* posterior partial fundoplication in a series of publications detailing follow-up across nearly 2 decades (23). 137 patients were enrolled. Reflux control and dysphagia symptoms were similar, but flatulence was commoner after Nissen fundoplication at early to medium-term follow-up. At 18 years follow-up outcomes were similar in terms of reflux control, side effects and overall outcome, with success rates of more than 80% were reported for both procedures. This trial suggested that the earlier side effects that occur more often following Nissen fundoplication actually improve with very long term follow-up, although the outcomes across the first 5 years were in favour of posterior partial fundoplication.

Anterior versus Nissen fundoplication

Six prospective randomised trials have been reported that compare an anterior partial fundoplication variant *vs.* Nissen fundoplication. Four evaluated an anterior 180° partial fundoplication *vs.* Nissen fundoplication (28,29), and two an anterior 90° partial fundoplication (30,31). These studies all demonstrated a reduced risk of post-operative side effects (dysphagia and wind related problems) following anterior partial fundoplication. In addition, in these trials anterior 180° partial fundoplication achieved equivalent control of reflux symptoms, whereas anterior 90° partial fundoplication was associated with a slightly higher incidence of recurrent reflux at up to 5 years follow-up. Overall satisfaction with the outcome in these trials was similar for all fundoplication types. A recently reported meta-analysis confirms these conclusions (32). The trial of anterior 180° partial *vs.* Nissen fundoplication from Watson and colleagues has reported longer term follow-up at up to 10 years (29), and at late follow-up the earlier outcome differences for the two procedures disappeared, due to a progressive decline in the prevalence of dysphagia following Nissen fundoplication across the first decade of follow-up.

Anterior versus posterior partial fundoplication

Two trials have compared anterior *vs.* posterior partial fundoplication (32,33). Both report better reflux control following posterior partial fundoplication, less side effects after anterior partial fundoplication and similar outcomes for overall satisfaction. The overall results from the randomized trials comparing Nissen *vs.* posterior, Nissen *vs.* anterior and posterior *vs.* anterior partial fundoplication demonstrated similar overall satisfaction as measured by global outcome score, but a trade-off between the risk of troublesome side-effects *vs.* the risk of recurrent reflux symptoms across the spectrum of procedures ranging from Nissen fundoplication at one end to anterior 900 partial fundoplication at the other.

Is a "perfect" outcome following surgery for reflux achievable?

The short answer to the question posed is that a perfect outcome is actually not achievable following surgery for reflux. The trade-off between the risk of recurrent gastro-esophageal reflux *vs.* the risk of post-fundoplication side effects needs to be considered during the work-up and planning for antireflux surgery. However, the data from the randomised trials does suggest that at up to five years follow-up partial fundoplication variants generally achieve a better outcome, with less side effects and better satisfaction measures following partial fundoplication in many of the trials. However, the two trials reporting data beyond ten years (23,29) suggest equivalent outcomes for Nissen versus partial fundoplication of whatever type are eventually achieved, but this can take up to 10 years!

A pragmatic approach to surgery for gastro-esophageal reflux

In the clinical practice in my Department we never divide the short gastric blood vessels and we currently construct a partial fundoplication in approximately 80% of the patients who undergo antireflux surgery (34). Our standard approach is to dissect the esophagus and the esophageal hiatus, followed by routine posterior hiatal repair irrespective of whether or not a hiatus hernia is evident, and then we construct a fundoplication. In patients with disordered or poor esophageal motility demonstrated at preoperative esophageal manometry, we always construct an anterior 180° partial fundoplication, whereas in patients with adequate esophageal motility we discuss the advantages and disadvantages of Nissen *vs.* partial fundoplication with each patient and offer a choice between the Nissen

fundoplication with a lower risk of recurrent reflux *vs.* partial (usually anterior 180°) fundoplication with a lower risk of side effects, and the patient is encouraged to make a choice. Following this discussion, approximately 2/3's choose to undergo an anterior 180° partial fundoplication.

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Surgical Research

Future perspective of laparoscopic surgery for gastric cancer: sentinel node navigation function-preserving surgery for early gastric cancer

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Abstract: After the introduction of laparoscopic surgery in gastric cancer, the short-term surgical outcome is improved regarding the quality of life (QOL) with the equivalent morbidity comparing to the conventional open surgery. However, there is controversy concerning the long-term improvement of QOL after laparoscopic gastric cancer surgery. This might be due to the same resection range of stomach and lymph node dissection between laparoscopic surgery and open surgery. To improve the long-term QOL without impairing recurrence and survival in gastric cancer surgery, stomach preserving surgery with minimal lymph node dissection through the laparoscopic approach should be considered without residual tumor in the stomach and surrounding lymph nodes. The sentinel node biopsy (SNB) concept can be adopted for this purpose. The SNB results in terms of sensitivity from individual institutions are unsatisfactory and heterogeneous among practicing surgeons. However, recently performed multicenter study from Japan offers the optimism of SNB in gastric cancer. Currently, SENORITA (Sentinel Node Oriented Tailored Approach) study group in Korea is preparing the phase III trial for stomach preserving surgery with SNB. Before the phase III trial, quality-control study of participating institutions is underway for the standardization and overcoming the learning curve of SNB. If the SNB and stomach preserving surgery can be verified by this phase III trial, it might be a good surgical option instead of standard gastrectomy and lymphadenectomy resulting in improved long-term QOL without hampering the recurrence and survival in the subgroup of early gastric cancer.

Keywords: Early gastric cancer (EGC); sentinel node biopsy; stomach preserving surgery

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Introduction

As the screening program for gastric cancer has been developed in Korea, the proportion of early gastric cancer (EGC) has been increased and the survival from the gastric cancer was improved (1,2). The standard surgical option for these EGC patients is gastrectomy with enough resection margins and the lymph node dissection according to the Japanese guideline except the absolute indication for endoscopic resection (ER) (3). Such surgical treatment makes the survival of EGC increase more than 90% but the short-term surgical outcomes are still morbid and postoperative quality of life (QOL) was impaired due to the resected stomach and destroyed nerves system during the lymph node dissection. As a consequence, the need for the minimally invasive approach is required for potential long-term survival of EGC.

After the application of laparoscopic surgery in gastric cancer, the short-term surgical outcomes are improved regarding QOL with the equivalent morbidity comparing to the conventional open surgery and the final survival

results are waiting from the prospective trials in Korea (4,5). However, there is controversy of long-term improvement of QOL after laparoscopic surgery. This might be due to the same resection range of stomach and lymph node dissection between laparoscopic and open surgery. To improve the long-term QOL without impairing recurrence and survival in gastric cancer, stomach preserving surgery with minimal lymph node dissection through the laparoscopic approach should be considered without residual tumor in the stomach and surrounding lymph nodes.

Several organ-preserving or function-preserving surgeries such as proximal gastrectomy (PG), pylorus preserving gastrectomy (PPG) and vagus nerve preserving surgery were tried but the results are still controversial (6,7). The essential factor for preserving stomach function is not only the remaining gastric volume but also preserving the nerve innervation, esophagogastric junction (EGJ) and pylorus as well. Therefore, these essential factors should be saved during the surgical treatment for the preservation of stomach function. ER is probably the best therapeutic option as the stomach preserving surgery. However, indication of ER is very limited and application of it is only for absolute indication (3). Several retrospective studies were investigated to expand the indication of ER but the clinical application was still not acceptable due to the risk of potential lymph node metastasis (8,9).

Sentinel node biopsy (SNB) concept was initially applied in penile cancer and it is already clinically applied to prevent the lymphedema in breast cancer and melanoma. It has been supposed that the SNB can be applied for organ-preserving or function preserving surgery in gastric cancer if the SNs are free of metastasis.

Review of literatures

During more than decade of years a lot of feasibility studies of SNB in gastric cancer were reported in the literature. Most of series were small in number of patients, single institution based and there was no standard definition or technique for SNB. The details of SNB method were variable in terms of indication, biopsy method, tracers, injection site and pathologic evaluation among studies. Fortunately, several review articles and meta-analysis were already reported about the SNB in gastric cancer (10-12). The pooled estimate of detection rate was more than 90% but the sensitivity is of just around 80% with heterogeneity between the studies. The important factors improving sensitivity were the number of SN, EGC, double tracers, submucosal injection and more precise pathologic method. Meta-analysis of SNB in gastric cancer concluded that the result of SBN is unsatisfactory and heterogeneous between practicing surgeons. Therefore, clinical application of SNB in gastric cancer should be cautious and more studies are warranted to improve the sensitivity of SNB in gastric cancer. Recently, the feasibility study of SNB in gastric cancer is rarely published but more challenging methods are investigated.

Past and current trials

Two Japanese feasibility multicenter trials for SNB in gastric cancer were performed. One is the Japan Clinical Oncology Group trial (JCOG0302) and the other is Japanese Society for Sentinel Node Navigation Surgery (SNNS) trial. Both studies were a little bit different in the protocols and the final results were greatly different. The JCOG0302 was terminated midway before the goal because of the unexpected high false negative rate and its cause was believed to be the simple pathologic evaluation method and the learning curve of participating institutions (13). On the other hand, SNNS trial was finished and reported in the proceedings of medical congress (14). The detection rate was 97.5% with average 5.6 SNs and the sensitivity was 93% with four cases of false negative. Two cases of them were T2 lesions and missing metastatic nodes were located at the same sentinel basin in 3 cases. These results suggested the optimism of SNB if the indication was limited with T1 and sentinel basin dissection was done harvesting more than 5 SNs.

Single institution's phase II trial from Japan was reported and the result of limited gastrectomy with SNB was satisfactory for short term outcome and recurrence during the observation period (15). Another single center phase II trial from Korea is ongoing and the result is waiting (16).

Even the controversies remaining about the SNB in gastric cancer, many experiences were accumulated in the academic society and several knowhows were suggested that how the SBN result can be improved from studies. What's more important is that the serious academic question that the clinical application of SNB in gastric cancer is possible or not. Until now, there is no identified phase III trial of SNB in gastric cancer in the world. Recently a study group named SENORITA (Sentinel Node Oriented Tailored Approach) was launched in Korean academic society including surgeons, gastroenterologists, pathologists and nuclear medicine doctors to solve this question by phase III trial (17-19). The protocol of SENORITA multicenter

phase III trial was made after several consensus meetings between co-investigators and expert seminars (20).

As many previous studies have pointed out, the essential and indispensible requirement of SNB in gastric cancer is the standardization and overcoming the learning curve. The preceding quality control study for phase III trials is now ongoing (21). The measurement of quality control was checked by performance of critical 7 steps of SNB consisting of endoscopic, surgical and pathologic procedures. If the SNB was performed perfectly in ten patients by completion of this 7 steps, that institution can participate the phase III trials.

Conclusions

Laparoscopic SNB and organ-preserving surgery in gastric cancer could offer the improved short-term surgical outcomes in terms of postoperative M&M and QOL. It could also improve the long-term QOL by minimizing the gastric resection and lymph node dissection in the EGC survivors without impairing recurrence and survival. To validate this hypothesis, multicenter phase III trial is warranted and this new procedure will benefit the subgroup of EGC patients.

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Surgical Research

Rationale of oncological follow-up after gastrectomy for cancer—the Consensus Conference

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Sir:

At present, there is no scientific evidence supporting any definite role for follow-up after gastrectomy for cancer and albeit many retrospective series have clearly demonstrated that early diagnosis of tumor recurrence in the asymptomatic phase has not resulted in a survival improvement, compared to late diagnosis (1-4), still the clinical practice in most high volume centers implies that after surgery patients are submitted to repeated clinical and instrumental checks.

We feel that it is certainly needed that follow-up schedules are based on a more solid evidence, by identifying tests and examinations with the best reliability and sensitivity, by limiting them to a period of time when recurrence is likely and concentrating clinical efforts and expenses on those recurrences whose diagnosis shows a notable impact on survival and quality of life.

Randomized Controlled Trials (RCT) are considered as the most rigorous tool for determining whether a cause-effect relationship exists between one intervention and its outcome; nevertheless, RCT's are unlikely to be rewarding in this peculiar field since excessively large sample sizes and huge amount of money and time would be needed to clearly demonstrate the efficacy of follow-up. Another mean of dealing with conflicting or scarce scientific evidence relies in Consensus methods. The focus of Consensus lies where unanimity of opinion does not exist owing to a lack of scientific evidence or when there is contradictory evidence on an issue. Consensus methods overcome some of the disadvantages normally found with decision making in groups or committees, which are commonly dominated by one individual or by coalitions (5).

On June 19th-22nd 2013 in Verona (Italy), during the 10th International Congress (IGCC) of the International Gastric Cancer Association (IGCA) organized by the Italian Research Group for Gastric Cancer, a Consensus Conference entitled "*Rationale of oncological follow-up after gastrectomy for cancer*" will take place, with the ultimate purpose to produce a CHARTER. Aim of this SCALIGER CHARTER is to present an ideal prototype of follow-up after gastrectomy for cancer, based on shared experiences and also taking into account the need to rationalize the diagnostic course and not to lose the chance to catch a recurrence at its earliest stage. Other factors to be considered are: (I) need of reliable data on surgical outcome; (II) patients' desire not to be abandoned; (III) psychological stress induced by unuseful controls; (IV) cost/benefit ratio of instrumental examinations; (V) side effects of invasive diagnostic procedures; (VI) possibility of causing a premature "diagnosis of death".

The process of construction of the International Consensus Conference started in December 2012 when a Restricted Working Group (RWG) was established: the RWG reviewed the literature, formulated 7 unresolved issues (*Table 1*), shared a proposal STATEMENT for each of them, submitted to the Scientific Committee of 10th IGCC a list of international experts including surgeons, oncologists, radiation oncologists, gastroenterologists, statisticians and methodologists with a geographical distribution reflecting different health cultures worldwide, therefore from "emerging" and highly developed Countries. Forty-eight of these experts have agreed to participate in an Enlarged Working Group (EWG) which—according to the dictates of the Delphi method—

Table 1 Questions to be answered
1. Should patients be clinically abandoned after curative surgery (and adjuvant chemotherapy)?
2. Should follow-up be exclusively managed by GP instead of surgeon, oncologist, gastroenterologist?
3. Should follow-up be differentiated on the basis of recurrence risk?
4. Should only clinical checks be performed during follow-up?
5. Should advanced imaging techniques be regularly prescribed during follow-up?
6. Should upper GI endoscopy be regularly prescribed during follow-up?
7. After how many years follow-up should be stopped?

to date is already working blindly to create an online preliminary consensus on the 7 statements. A revised version of the statements will be presented in a plenary session at the 10th IGCC and offered for signature. Thereafter, on the basis of the Consensus Conference results, the RWG will draw a final CHARTER draft, which will be displayed on the IGCC/IGCA website, through December 31st 2013; all the participants in the Consensus Conference will be invited to apply the resulting follow-up guidelines in their daily practice.

The CHARTER is expected to be re-evaluated every two years.

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Surgical Research

Laparoscopic total gastrectomy with spleen-preserving splenic hilar (No. 10) lymph node dissection for gastric cancer is still a challenging procedure

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Abstract: To perform the laparoscopic surgery for locally advanced gastric cancer located in proximal third of the stomach, laparoscopic lymphadenectomy for splenic hilar lymph nodes is essential procedure. The important point of this procedure is how to perform it without injuring the splenic vessels and parenchyma of the spleen and pancreas. This video presentation shows meticulous dissection of the lymph nodes around the distal pancreas and spleen without bleeding. The laparoscopic technique in this video can provide insight into the challenge for surgeons. However, laparoscopic total gastrectomy for locally advanced gastric cancer still needs confirmative clinical evidence. Therefore, it should be performed for selected patients by the experienced surgeons.

Keywords: Gastric adenocarcinoma; total gastrectomy; laparoscopic surgery

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The dissection of splenic hilar lymph nodes in gastric cancer surgery is indispensable for treating gastric cancers located in the proximal third of the stomach. According to the treatment guidelines suggested by the Japanese Gastric Cancer Association, extended lymphadenectomy (D2) for total gastrectomy should include the No. 10 lymph nodes around the splenic hilum (1). However, one randomized controlled clinical trial comparing D1 and D2 lymph node dissection in gastric cancer surgery showed increased mortality and morbidity rates in the D2 group, and the splenectomy for D2 lymph node dissection was presumed to be one of the reasons for this difference (2). In addition, splenectomy for lymph node dissection may increase the postoperative transfusion and infection rates, contributing to the poor prognosis of cancer patients (3). Theoretically, the best option for a patient with advanced gastric cancer requiring total gastrectomy is to undergo D2 lymph node dissection without splenectomy. However, spleen-preserving D2 lymph node dissection is not a simple technique, even under open laparotomy, because of the tortuous splenic vessels and the high possibility of injury to the parenchyma of the spleen and pancreas. During laparoscopic surgery, the surgeons depend on the monitor and lack tactile sensation, and the movement of the laparoscopic instruments is limited. As such, this technique, which was introduced by Li *et al*., is very challenging (4).

The critical point of this procedure is how to perform the laparoscopic en-block dissection of the lymph nodes around the distal splenic arteries and splenic hilum without injuring the splenic vessels and parenchyma of the spleen and pancreas. There are wide variations in the distribution of the splenic vessels and the shape of the pancreatic parenchyma among patients. This variation may increase the likelihood of bleeding from branches of the splenic vessels and the postoperative leakage of pancreatic juices. As such, en-block dissection of LN 11d (lymph nodes around distal splenic artery) and LN 10 without splenectomy is thought to be not easy. Prompt control of intraoperative bleeding during the dissection of lymph nodes around splenic vessels is more difficult in laparoscopic surgery than in open laparotomy. Therefore, meticulous traction of the soft tissues around the splenic vessels is required to identify the precise plane for dissection that is required to prevent

bleeding. The video in this report details these techniques. Another report recommended that the traction of splenic vessels using strings could make it easier to dissect the lymph nodes around the splenic vessels (5). Surgeons who want to try laparoscopic dissection for splenic hilar lymph nodes should consider the various methods available.

In the present case report, the patient was diagnosed pathologically with stage IIIC (T4aN3M0). Although the surgeon had reasonable laparoscopic technique for D2 lymph node dissection accompanied by total gastrectomy, the use of laparoscopic surgery for treating advanced gastric cancer should be carefully evaluated to confirm its safety and efficacy relative to open conventional surgery. The efficacy of laparoscopic surgery for gastric cancer is currently being evaluating in randomized, controlled clinical trials, such as the KLASS trial by Korean surgeons (registered in www.clinicaltrials.gov as NCT00452751), which only includes patients with early gastric cancer. However, three studies using meta-analysis have already reported the advantages and the non-inferiority of laparoscopic surgery compared to open laparotomy (6-8), and then several retrospective studies have present about the possibility of laparoscopic extended lymph node dissection (9-11). Based on these results, clinical studies investigating the efficacy of laparoscopic extended lymph node dissection for advanced gastric cancer have been recently launched by Korean and Chinese groups (registered in www.clinicaltrials.gov as NCT01456598 and NCT01609309). However, the application of laparoscopic total gastrectomy for advanced gastric cancer has other unresolved issues, such as the dissection of LN 11d and LN 10 and laparoscopic esophagojejunostomy for reconstruction. Accordingly, the inclusion criteria for a recent prospective clinical study for total gastrectomy was limited to patients with clinical stage I disease (registered in www.clinicaltrials.gov as NCT01584336). Therefore, an experienced surgeon should perform the laparoscopic total gastrectomy, which includes the dissection of LN 11d and 10, and it has to be limited to selected patients until clinically proven in a wider patient population. Nevertheless, the laparoscopic technique presented by Dr. Li in this video can provide insight into the challenges involved in this type of surgery.

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Surgical Research

Totally laparoscopic stapled anastomosis after distal gastrectomy

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Abstract: There is wide variation in technique for anastomosis in laparoscopic gastrectomy. Du *et al*. report a novel stapled method for gastrojejunal using a circular stapler, applied in 34 patients. Compared to an intracorporeal handsewn anastomosis, this technique was equally effective and safe, but required less operative time (239 *vs*. 203.6 minutes). Whilst laparoscopic distal gastrectomy is undertaken commonly in some Asian countries, Western surgeons deal with a smaller gastric cancer case load, and face significant challenges if considering this approach for their practices.

Keywords: Gastrectomy; gastric cancer surgery; anastomosis; surgical technique

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Restoration of gastrointestinal continuity after laparoscopic gastric cancer resection is challenging. While there are numerous large series reporting the feasibility of laparoscopic gastrectomy, the wide variation in techniques used to perform either esophago-jejunal or gastro-jejunal anastomosis suggests that surgeons are continuing to look for the optimal method.

Du *et al*.'s article in *Journal of Gastrointestinal Surgery* (1) reports a novel method of stapled gastrojejunal anastomosis for laparoscopic Billroth II gastrectomy. Essentially the anvil of a circular stapler is introduced via a gastrotomy on the greater curvature of the residual proximal stomach and the rod tip of the anvil is withdrawn through the anterior wall of the stomach with the assistance of a suture attached to the rod tip. The gastrotomy is then stapled closed. A circular stapler is then introduced via the abdominal wall incision through which the gastrectomy specimen was removed and inserted into a jejunal enterotomy 10 cm distal to the planned jejunal anastomosis site. The stapler is then fired to create a gastrojejunal anastomosis, and withdrawn. An endoscopic linear stapler is subsequently introduced via the jejunotomy to perform a Finney type stricturoplasty before a second firing of the linear stapler is used to close the jejunotomy.

In a series of 70 patients, the stapled anastomotic technique was performed in 34 patients and compared to a non-randomised comparison group of 36 patients who had an intracorporeal handsewn double layer gastro-jejunostomy performed by the same surgeon. Operative, post-operative, in hospital stay and 90 days follow-up outcomes were assessed, with the only significant difference being a shorter operative time (239 *vs*. 203.6 minutes) for the stapled anastomosis group. This difference is somewhat at odds with the reported 40 minutes time for a hand sutured anastomosis and a 20-25 minute time for stapled anastomosis. No complications were reported for the patients with a stapled anastomosis and the technique is clearly a feasible way of performing a laparoscopic Billroth II anastomosis.

There are a number of ways of restoring gastrointestinal continuity after a distal gastrectomy. Billroth I, Billroth II and Roux-en-Y reconstruction techniques are all used. Whether performed open (2,3) or laparoscopically (4), the anastomoses are more quickly constructed with stapling devices than hand-sewn techniques and with otherwise equivalent results. More commonly circular stapling devices have been used, but linear stapled anastomoses have also been reported (5).

The majority of series of laparoscopic distal gastrectomy variants utilise a Billroth type reconstruction rather than a Roux limb. This avoids the need for a jejuno-jejunal anastomosis and thus perhaps simplifies and shortens the

procedure. However the use of Billroth I and II procedures does seem somewhat at odds with the superior outcomes in terms of decreased bile reflux and/or gastric food stasis associated with the Roux limb, seen both after ulcer (6) and cancer (7,8) resectional surgery. Although the same rationale of ease of completion with a Billroth reconstruction was applied by some surgeons performing open surgery, the principles of reconstruction should not be lost purely to facilitate completion of a procedure laparoscopically. Meta-analysis (9) suggests that use of a Roux limb is not associated with increased operative complications but is associated with decreased reflux and increased quality of life.

It is clear on reviewing the laparoscopic gastric cancer literature that it is almost entirely based on Eastern experience, particularly Korean and Japanese. Given the very high incidence of gastric cancer, the relative bias towards both early gastric cancer, and gastric cancer presenting predominantly in the distal stomach, surgeons in these countries have an enormous experience in distal gastrectomy. These countries have established the feasibility of performing a D2 type lymphadenectomy laparoscopically and hence the resectional component of the surgery has not changed with minimally invasive surgery. Laparoscopic resection has thus become a standard of care in many Eastern centres.

Western surgeons do not deal with anywhere near the same volume of gastric cancer, and the challenges of performing a D2 resection safely and thoroughly have perhaps been prioritized ahead of the application of minimally invasive surgery to gastric cancer resection. While it is performed by some in the West, the difficulties of overcoming a learning curve in a low volume environment are apparent. However, the obesity epidemic in the West means there are high volume bariatric surgeons for whom the application of a Roux-en-Y reconstruction after laparoscopic gastric bypass is now standard. Perhaps rather than evolving different techniques for Billroth reconstructions, the challenge is to combine the Eastern experience of laparoscopic gastric cancer resection with the Western experience of laparoscopic Roux-en-Y reconstruction.

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Surgical Research

Safe, simple & efficient totally laparoscopic Billroth II gastrectomy by only stapling devices

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Gastric cancer is the fourth most common cancer diagnosis worldwide in men with an expected incidence of 640,000 cases and the fifth most common in women with an expected incidence of 350,000 cases in 2011 (1). Approximately, 8% of total cases and 10% of annual cancer deaths worldwide are attributed to this dreaded disease. Surgical resection offers the only durable cure from gastric cancer (2). Since the introduction of Billroth's procedure of gastrectomy and reconstruction in 1881, surgical techniques in gastric surgery has progressed gradually. Since Azagra *et al*. performed the first laparoscopic distal gastrectomy with Billroth II reconstruction for gastric cancer in the early 90's, laparoscopic approach has become a promising method of surgical treatment for patients with gastric cancer proving to own several advantages over open surgery (3,4).

Most surgeons prefer laparoscopy-assisted gastrectomy rather than totally laparoscopic procedures due to the technical difficulties associated with intracorporeal anastomosis. However, recent advancement in surgical stapling technology enables an entirely laparoscopic approach in the treatment of gastric cancer (5). Compared to laparoscopy-assisted gastrectomy, this approach appears to have several advantages which include shorter incision, less pain, and earlier recovery (6). Studies have also suggested the feasibility, safety and efficiency of totally laparoscopic gastrectomy when performed by high volume laparoscopic surgeons, albeit with a relatively prolonged operating time (7,8).

Intracorporeal gastrojejunostomy (GJ) anatomosis following Billroth II gastrectomy can be performed by either hand-sewn technique, using stapler devices or a combination of both. Du J *et al*. reported their experience of intracorporeal gastrojejunal anastomosis using a two layer hand-sewn technique (9), whereas Ruiz *et al*. described a 4-layer closure using continuous absorbable sutures (10). Hand-sewn anastomosis requires advanced laparoscopic skills and is considered to be time-consuming, but has the advantage of avoiding the risk of wound infection and hernias, which occur as a result of manipulation by a circular stapler. It also has a lower risk of gastrointestinal bleeding at the GJ site and lower operating costs (11). However, totally hand-sewn GJ anastomosis is technically demanding, with a steep learning curve. Experience at the beginning can be discouraging, even for surgeons with extensive training in advanced laparoscopic surgery. Though it will lengthen the operating time during the initial learning period, constant training develops the surgeon's skills and will significantly shorten the operating time as experience accumulates (9-11).

Nevertheless, totally hand-sewn anastomosis has been considered extremely difficult and has been avoided by most laparoscopic surgeons. Authors have reported intracorporeal reconstruction of the digestive tract following gastrectomy using linear stapler devices combined with a hand-sewn technique (12,13). Lee *et al*. performed an end-to-side GJ with an endo GIA stapler and closure of the stoma with intracorporeal hand-sewn technique in 2 layers (12). It is important to ensure that both gastrotomy and enterotomy are small, just large enough to accommodate the jaws of the stapler so that subsequent suture closure of the hole is not time consuming.

In a comparison study with open Bill Roth II gastrectomy, the operating time was significantly longer

and this was attributed to performing the intracorporeal anastomosis. However, over time they were able to improve their technique and perform the surgery faster (12). Although more technically demanding compared to open distal gastrectomy, Wong *et al*. reported that the combined laparoscopic procedure with stapled and hand sewn anastomosis had less blood loss, fewer inflammatory reactions, rapid return of gastrointestinal function, and shorter hospital stay without compromising operative curability (13).

Circular staplers are also widely used for reconstruction following Billroth II gastrectomy for gastric cancer. Seo *et al*. compared the hand-sewn method to the circular stapling method for anastomosis in patients who underwent laparoscopy assisted distal gastrectomy (LADG) (14). No significant differences were observed in the clinicopathologic parameters and post operative outcomes. However, the operating time and anastomosis time were significantly shorter in the stapler group (14). Therefore, the circular stapling method could be applied safely and efficiently for GJ anastomosis in LADG.

Recently, Du *et al*. described a novel method for performing Billroth II gastrectomy by only using circular and linear stapling devices without any hand sewn anastomosis (15). Most surgeons avoided linear staplers in favour of hand-sewn anastomosis for closure of the enterotomy that was used to introduce the shaft of the circular stapler. A stapled enterotomy closure here was believed to cause postoperative intestinal stricture (16). However, Du *et al*. were able to prevent stricture formation by an additional side-to-side anastomosis using a linear stapler at the site of enterotomy to enlarge the lumen. In a comparative study of patients undergoing laparoscopic Billroth II distal gastrectomy with only hand-sewn anastomosis and stapling device anastomosis, Du's method seemed also safe and feasible while associated with decreased operative time and may be associated with shorter learning curve (15).

Intracorporeal GJ anastomosis could also be performed using a two linear stapler technique (17-19). When using linear staplers, care must be taken to avoid stricturing of the efferent loop of the jejunum, when the entry hole is closed with a stapler. Ahn *et al*. reported that in experienced hands, the complication rate following intracorporeal reconstruction using linear staplers was significantly lower than that of the extracorporeal group (17). They also concluded that intracorporeal reconstruction after laparoscopic distal gastrectomy was feasible and safe after a learning curve of 20 cases, if the surgeon had already sufficient experience in extracorporeal reconstruction. In a study by Lee *et al*., the mean operating time and post operative hospital stay was statistically shorter in the laparoscopic distal gastrectomy group using linear staplers compared to LADG group (18). Anastomosis related complications were not significantly different in both groups. However, bleeding from the anastomosis site in the intra-corporeal procedure tended to be higher than that of the extra-corporeal method (18).

In intracorporeal anastomosis, a linear stapler has some advantages over a circular stapler. In order to use a 25 mm circular stapler intraabdominally, a 33 mm trocar is needed or the incision has to be extended and this requirement could jeopardize the merit of a minimally invasive procedure. Moreover, it may be tedious and complicated to perform an intracorporeal purse-string suture and anvil placement (19). In contrast, a linear stapler only requires a 12 mm trocar for introduction, thereby resulting in better cosmetic outcome. Furthermore it is much easier to handle a linear stapler intraabdominally (18,19).

In spite of the obvious benefits, laparoscopic gastrectomy has not yet met with widespread acceptance and it still is limited to only a few centers. This slow acceptance is not only related to the major concern about the difficulty of intracorporeal reconstruction. In addition, operative cost is obviously higher because of the additional laparoscopic instruments and stapling devices (13,20). In a cost analysis study by Song *et al*., operation related costs and total costs were greater in the laparoscopic distal gastrectomy group compared to open and LADG groups (21). These differences resulted mainly from the cost of materials that were used in the operation theatre. Some surgeons have attempted to lower the cost spent on staplers, by closing the entry hole of the stapler in GJ anastomosis using an intracorporeal hand-sewn technique (19,21). Others have reduced the expenses further by performing a totally hand-sewn anastomosis (11).

Another important factor that could increase the operative cost is prolonged hospital stay due to complications. In the Eight Nationwide survey of endoscopic surgery [2006] in Japan, the rate for the postoperative complications after laparoscopic distal gastrectomies was 9.2%, and more than half of those complications were related to the anastomosis (54.0%) including leakage, stenosis and obstruction of the anastomotic site (20). In a recent meta-analysis of published trials, laparoscopic distal gastrectomy was associated with significantly lower overall complications, estimated blood loss and hospital stay despite having longer operative times (22).

Similarly, a study comparing LADG and laparoscopic Billroth II distal gastrectomy showed the latter to be a more feasible procedure that could be safely performed in less time producing better cosmetic results (18). Therefore as the surgical technique matures without significant complications, which could lengthen the hospital stay, totally laparoscopic distal gastrectomy is believed to be apparently a cost-effective approach (13).

Reports of laparoscopic techniques for treating patients with early gastric cancer in the world literature have shown oncologic equivalency to that of open technique, with much benefits of minimally invasive approach, including less pain, earlier recovery, shorter hospital stay, and better quality of life (23). In advanced gastric cancer, Shuang *et al*. performed D2 lymph node dissection in both LADG and open gastrectomy groups. There was no significant difference between the two groups in the number of resected lymph nodes, yielding similar oncologic outcomes (3). In a case-controlled study of 30 patients undergoing laparoscopic subtotal gastrectomy with 30 matched open gastrectomy patients for gastric cancer, Strong *et al*. reported on the technical feasibility and equivalent short-term recurrence-free survival of laparoscopic subtotal gastrectomy when compared with the open procedure (24).

In conclusion, intracorporeal Billroth II anastomosis using stapling devices has been shown to be safe, feasible and efficient. Using this approach, surgeons embarking in laparoscopic distal gastrectomy may have a shorter learning curve with better outcomes. However cost remains a major factor in its widespread utilization.

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Surgical Research

What is the best reconstruction after totally laparoscopic distal gastrectomy if the delta-shaped gastroduodenostomy cannot be performed?

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Totally laparoscopic distal gastrectomy (TLDG) means that all the processes are performed laparoscopically without a mini-laparotomy on the epigastrium for the reconstruction in laparoscopy-assisted distal gastrectomy (LADG) (1). Delta-shaped gastroduodenostomy is a representative type of intracorporeal anastomosis. It has been reported that early postoperative outcomes, such as estimated blood loss, return of bowel function, postoperative pain and hospital stays are significantly improved in TLDG compared with LADG. Furthermore, especially in obese patients, the overall complications rate is significantly lower in TLDG than in LADG because direct visualization by laparoscopy gives a better operation view and minimizes unexpected surgical trauma (2,3). Recently, Kanaya *et al.* have reported that the short and long-term outcomes of the 100 consecutive patients with a mean follow-up period of 54.9 months. They concluded that the delta-shaped anastomosis is safe, simple, and provides satisfactory postoperative outcomes (4).

However, intracorporeal Billroth-II anastomosis has been rarely reported until now. There is only one report about intracorporeal Billroth-II (5). Intracorporeal Billroth-II anastomosis is usually performed using a linear stapler. When using a linear stapler, theoretically, a stricture in entry hole could be a problem (6).

To solve this problem, in the issue of *Journal of Gastrointestinal Surgery* (2012;16:738-43), Jianjun Du *et al.* reported a series of 36 patients with a novel, safe, simple, and time-saving Billroth II anastomosis by only stapling devices after laparoscopic distal gastrectomy. The results grossly appear to be excellent, with good postoperative outcomes and appropriate conduct of the operative procedures. However, we think that this report raises several questions. Firstly, does the entry hole closure by a linear stapler truly cause a stricture? Jianjun De and colleagues assumed that intracorporeal reconstruction of Billroth II was mostly performed by using laparoscopic linear stapler combined with hand-sewn technique. Recently, it is a general trend that the entry hole is usually closed by a linear stapler and this is the most simple and time-saving procedure when intracorporeal gastro-jejunostomy was performed. In experienced hands, it can be finished within 5-10 minutes. The reasons for the hand-sewing closure of the entry hole are a problem of cost and concern for stricture of the efferent loop. Leaving the expense aside, this kind of stricture problem could be avoided if the entry hole is made on the afferent loop side (7). And also with the proper stapling technique, the amount of sacrificed tissue after linear stapling could be even lower than that of hand-sewing manner, which means a proper linear stapling technique do not cause a stricture in the jejunum.

Secondly, Billroth II reconstruction is not a recommendable method in the current situation. There is much concern about gastric remnant carcinoma and worse postoperative quality of life due to alkaline reflux gastritis (8), although Billroth II gastro-jejunostomy is still widely used as a reconstruction after distal gastrectomy. In this point of view, Roux-en Y type reconstruction has been reported as a better option with the advantage of less bile reflux into the remnant stomach or reflux esophagitis than Billroth

II anastomosis (9). And also Roux-en Y reconstruction is thought to be more natural and simple way to make gastro-jejunostomy using a circular stapler.

Thus, what is the best reconstruction after totally laparoscopic distal gastrectomy if the delta-shaped gastroduodenostomy cannot be performed? We cautiously recommend Roux-en Y gastro-jejunostomy rather than Billroth II anastomosis. It has been reported that Roux-en Y anastomosis is superior to Billroth II anastomosis in terms of frequency of bile reflux. Furthermore, it can be performed without concern about the stricture in the common entry hole. However, we need more solid evidence from further clinical trials to determine the best anastomosis after TLDG.

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Surgical Research

Node-negative gastric cancer: a good occasion for studying new prognostic factors

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Dr. Liu and Colleagues (1) present an interesting study that adds data to those already available in the literature from both Western (2-4) and Eastern series (5-7). The sense of all these papers, analyzing prognostic factors significantly related with survival in patients correctly staged as N0 (more than 15 lymph nodes removed at surgery), is that of trying to understand in depth if staging whether or grading is more important in determining the fate of patients with gastric cancer. In fact, analyzing the N0 patients may reveal that these patients have simply been treated at an earlier stage of their disease, and this would lead to stress once more the importance of screening practices, or on the contrary, the same analysis could reveal as other parameters that are actually kept in minor consideration (what might be called grading), significantly influence the biological behavior of the disease, which would lead to the need for better molecular characterization of a single tumor in a single patient.

The majority of studies investigating the clinicopathologic features and prognostic indicators of node-negative gastric carcinoma patients come from Eastern centers. Limits of many published studies are the presence of different surgical approaches, namely in terms of lymph node dissection, a follow-up too short for cancers whose recurrence if often late, the inclusion of cancers at very low risk of recurrence, such as T1 cancers, and finally the inclusion of patients that may be understaged as node-negative, as less than 15 nodes were retrieved and analyzed after surgery. The paper by Liu and Colleagues examined a remarkable series (4,426 patients in 12 years, i.e. almost 400 patients per year), in which, however, it appears unusual that the number of N0 cases is relatively low: in fact, the series focuses on only 234 patients (5.3%), a percentage much lower than reported in the literature, where N0 patients represent over 30% of all cases. This discrepancy is not clearly explained. All patients were correctly staged with more than 15 harvested lymph nodes, and the average number of examined nodes is 21.1, slightly lower than the limit considered optimal for a D2 lymphadenectomy, which is 25 lymph nodes. Another fact which deserves to be commented is a distribution of the degree of differentiation clearly biased in favor of medium and poor differentiation (G2+G3>95% of cases, while in most N0 studies it is around 50%). In addition, about 30% of cases of T1 cancers (Early Gastric Cancer), which should be excluded because at almost no risk of recurrence, are included. On the other hand, the pathological study appears accurate, and the oncological follow-up is intensive and long-term (51 months on average): we can therefore expect that this study provides reliable data for analysis.

Overall, 33 out of 234 N0 patients had a recurrence, representing a small treasure for pathologic analysis, looking for biological parameters that indicate a potential for an increased biological aggressiveness regardless of staging. However, in this paper a thorough analysis of biomolecular features is not performed: all the parameters taken into consideration belong to histology rather than to molecular biology, and they are easily detectable in the context of a basic pathologic assessment. This could be an advantage, as they provide useful elements for prognosis that are available in daily clinical practice.

The results seem to indicate that, between grading and staging, the latter is the most important factor: in fact,

out of 3 factors significantly related with prognosis in multivariate analysis, none is clearly correlated with the degree of cell differentiation or biological parameters, while all 3 show that patients who have relapsed would not have remained yet N0 for long term, since they had neoplastic emboli in peritumoral vessels and lymphatics, meaning that the process of metastasis had likely already started. It would be interesting to know the type of recurrence of these 33 patients having worse prognosis, but this data is not provided by the study.

Future lines of research should take into account both our ability to investigate the stage of the disease in greater depth (probably through research of micro-metastases in the lymph nodes apparently negative at hematoxylin-eosin staining (8,9), and the research for biological parameters able to explain a greater aggressiveness of tumors apparently low-stage (for example, a study is in progress under the Italian Research Group for Gastric Cancer auspices, evaluating HER 2 overexpression, chemochines receptor expression, TP53, KRAS, CTNNB1, APC and PI3CA).

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Surgical Research

Completely laparoscopic reconstruction following distal gastrectomy: what is the best method?

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The number of laparoscopic gastrectomies (LG) has increased since the first LG was performed in the early 1990s (1,2). LG is widely accepted as an option for early gastric cancer in Korea and Japan, where many cases are diagnosed at an earlier stage because the numerous advantages of LG over open gastrectomy, such as less pain, earlier recovery, and improved cosmesis. Most early LG operations were "laparoscopy-assisted" distal gastrectomies, in which reconstruction was performed through a mini-laparotomy after gastrectomy had been completed laparoscopically (2). The laparoscopy-assisted technique has the advantage that surgeons can perform anastomosis in a similar fashion to that employed in open surgery. However, the procedure is still difficult in obese patients, or in cases requiring transection at a more proximal site, because of the limited work space, even under a larger laparotomy.

Totally laparoscopic distal gastrectomy (TLDG) with intracorporeal anastomosis was introduced to solve these problems. Although the first successful case was reported in 1992 by Goh *et al.* (1), it was not widely accepted in the 1990s because of the technical difficulty. Intracorporeal linear-stapled anastomosis for Billroth-I reconstruction, which is the most preferred type of reconstruction in Japan, was reported as the delta-shaped anastomosis by Kanaya *et al.* in 2002 (3). The method is quite simple and can be done quickly using only linear staplers. Reports of TLDG have gradually increased through the late 2000s (4-7). The main objectives of the introduction of TLDG were to minimize the surgical scar and to establish a standardized reconstruction method that can be safely applied to obese patients. However, the increasing popularity of TLDG has revealed several other advantages in comparison to the laparoscopy-assisted technique. Those include faster bowel recovery, less pain, fewer complications, earlier hospital discharge, and longer safety margins (6-8). These data strongly support the superiority of TLDG over laparoscopy-assisted distal gastrectomy.

The reconstruction method in open surgery is chosen mainly based on the surgeons' preference, because either the Billroth-I, Billroth-II, and Roux-en-Y methods have their own advantages. Several types of Billroth-I and Roux-en-Y intracorporeal anastomosis have been reported for TLDG (9). More surgeons currently seem to prefer Billroth-I anastomosis in TLDG, because the laparoscopic Roux-en-Y method is more complicated and requires longer time. Du and colleagues have published totally laparoscopic Billroth-II gastrectomy using only staplers (10). They reported that both hand-sewn and stapled methods are safe and feasible, but the stapled method is simpler and less time-consuming, and probably associated with a shorter learning curve.

Billroth-II reconstruction is not preferred by many surgeons, because it can cause more severe bile reflux, which may lead to increased risk of metachronous cancer development (11,12). However, recent findings suggest that helicobacter pylori infection is a stronger risk factor. There is no clear clinical evidence that remnant cancer develops more frequently following Billroth-II procedures, than after other methods (13). Furthermore, the mean time interval between Billroth-II gastrectomy and detection of a stump cancer can be as long as 20 to 30 years (13,14). Therefore, Billroth-II anastomosis could be used as a standard method at least for older patients, when a simple and easy laparoscopic method is available. Billroth-II

anastomosis was done within 20-25 min by using the new stapling method reported by Du *et al*., which is shorter than that with the hand-sewn method (10). They experienced no postoperative complications. Their data shows that Billroth-II reconstruction is another feasible choice for TLDG.

A simple and easy anastomosis technique is a key factor in expanding the use of TLDG. Although the outcome reported by Du *et al*. was excellent, the anastomotic time was a little longer than those with the recently reported linear-stapled Billroth-II technique (10 min), or the delta-shaped anastomosis (13 min) (9,15). The difference might be the learning period; they reported 34 cases, while the latter two case series included 130 and 100 cases, respectively. Another difference is that the latter two methods use only linear staplers. Using either a hand-sewn, circular stapler or linear stapler method can yield excellent outcomes when performed by experienced laparoscopic surgeons. The clinical outcome of TLDG with Billroth-II gastrectomy with their matured technique is awaited.

Minimizing the specific complications, such as afferent loop syndrome, internal hernia, and duodenal stump leakage, is also important for the general use of TLDG with Billroth-II anastomosis. Internal hernia occurs in 2-5% of patients during the long follow-up period after laparoscopic gastrectomy with Roux-en-Y reconstruction (16,17). The frequency is higher than in open surgery, because less adhesion occurs. It is a rare complication, but it could lead to massive strangulation and risk the life of patients. Therefore, closure of the potential defect is recommended when Roux-en-Y or Billroth-II reconstruction is chosen in TLDG, and careful long-term follow-up of patients is necessary.

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Surgical Research

Emergency surgery for perforated gastric malignancy: an institution's experience and review of the literature

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Background: The aim was to evaluate the outcome of patients who underwent surgery for perforated gastric malignancies.

Methods: A review of all patients who underwent surgery for perforated gastric malignancy was performed.

Results: Twelve patients (nine gastric adenocarcinoma and three B-cell lymphoma) formed the study group. Ten (83.3%) had subtotal gastrectomy performed, while two (16.7%) underwent total gastrectomy. All eight patients with adenocarcinoma who survived the initial operation fared poorly. The two patients with lymphoma who survived the surgery underwent subsequent chemotherapy has no disease recurrence currently.

Conclusion: Surgery in perforated gastric malignancy is fraught with numerous challenges.

Keywords: Emergency, surgery, perforation, treatment outcome, malignancy

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Introduction

Perforated gastric malignancy is a surgical emergency fraught with numerous challenges. Although the diagnosis of a perforation can be easily achieved, the differentiation between a malignant and benign aetiology remains elusive (1,2). This has serious implications as it often determines the extent of the operation.

The aims of surgery in these patients are two-fold: to manage the peritoneal contamination and the underlying malignancy. While managing the peritoneal contamination could be easily handled, the ideal operation in treating the malignancy is perplexing as it is dependent on various factors such as the haemodynamic stability of the patient, the surgical expertise and the stage of the malignancy (3-6). To perform a complete oncologic resection may be too hazardous for the patient, whereas a limited procedure could significant impact the long-term survival of these patients.

The short-term outcome in these patients is often poor due to the septic complications from the perforation and may be further contributed by any concurrent resection surgery (3-6). Moreover, the long term outcome in these patients may be unfavourable due to the likely advanced stage of the gastric malignancy and the possibility of tumour seeding of the peritoneal cavity through the perforation (3-6).

Due to the relative rarity of this topic being discussed in the literature, this review was performed to evaluate the presentation and the short- as well as the long-term outcome of patients who underwent urgent surgery for perforated gastric malignancies.

Methods

Study population

Tan Tock Seng Hospital is a 1400 bed hospital, the second largest in Singapore and provides secondary and tertiary medical care for about 1.5 million people. A retrospective review of all patients who underwent emergency surgery for perforated gastric malignancy from October 2003 to March 2009 was performed. Patients were identified from the hospital's diagnostic index and operating records. All

Table 1 Classification of surgical complications (8-10)

Grade I: Any deviation from the normal postoperative course without the need for pharmacolog ical treatment or surgical, endoscopic, and radiological inter ventions
Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III: Requiring surgical, endoscopic or radiological inter vention
Grade IV: Life-threatening complication(s) requiring ICU management (including organ dysfunction)
Grade V: Death of a patient

Table 2 Characteristics of the 12 patients who under went surger y for perforated gastric malignancy

	Adenocarcinoma group, n=9	Lymphoma group, n=3
Median Age, range (yrs)	76 (30-83)	47 (41-84)
Male gender	5	3
ASA score		
1	0	0
2	1	1
3	6	1
4	2	1
Premorbid condition		
Hy pertension	5	0
Diabetes mellitus	4	0
Hyperlipidaemia	3	0
Ischaemic heart disease	3	0
History of cerebrovascular accident	0	0
Known malignancy pre-operatively	2	1
Pre-operative CT scan performed	5	3

malignancies were confirmed upon histological evaluation.

The data collected included age , gender, ASA (American Society of Anesthesiologists) score and comorbid conditions. In addition, operative findings and inter ventions, length of surgery, peri-operative complications, mortality and length of hospital stay were also documented.

Prior to the surgery, fluid resuscitation, nasogastric tube, parenteral antibiotics and proton pump inhibitor would be administered to every patient. Intra-operatively, all patients underwent copious lavage of the peritoneum and mass closure of the fascia. The extent of resection was determined by the primary surgeon intra-operatively and all cases were operated by a surgeon of at least Consultant grade.

Disease recurrence was confirmed through radiological and/or pathological evaluation, while the overall survival duration was documented from the date of surgery until the date of death. All gastric cancers were staged according to the guidelines of the American Joint Committee of Cancer (AJCC) (7). The grades of complications (GOC) were in concordance to the classification proposed by Clavien and group (8-10) (*Table 1*).

Results

During the study period, twelve patients (n=8, 66.7% males) underwent surgery for perforated gastric cancer. Gastric adenocarcinoma and B-cell lymphoma were responsible for the perforation in nine (75.0%) and three (25.0%) patients respectively. Three had their gastric malignancy diagnosed prior. The median age of the study group was 75 (30~84) years, with the majority (n=10, 83.3%) having an ASA score of 3 or 4.

All patients presented with severe abdominal pain. Pneumoperitoneum on erect chest radiographs was seen in five (41.7%) patients while emergency confirmatory computed tomographic (CT) scans were performed in the rest. Majority (n=9, 75.0%) of patients underwent surgery within 24 hours of presentation. *Table 2* highlights the various characteristics of the study group.

Intra-operatively, seven (59.3%) patients have severe peritoneal contamination. Ten (83.3%) had partial or subtotal gastrectomy performed with Bilroth II anastomosis, while the remaining two (16.7%) underwent total gastrectomy with a resulting Roux-en-Y anastomosis.

Two patients died from septic complications contributed by pneumonia and intra-abdominal sepsis, one of whom had a duodenal stump leak which necessitated a subsequent laparotomy, drainage of the intra-abdominal collections

Table 3 Surgical obser vations and outcome of the study group

	Adenocarcinoma group, n=9	Lymphoma group, n=3
Site of perforation		
Prox imal stomach: Cardia or Lesser curve	7	3
Distal stomach: Incisura or A ntrum	2	0
Surgical ty pe		
Partial or subtotal gastrectomy	7	3
Total gastrectomy	2	0
Staging of malignancy		
Tumour	A ll are T3	A ll are high grade
Nodal status	N0: 1 N1: 2 N2: 2 N3: 3	A ll have metastatic lymph nodes
Metastatic disease	3 M1 disease	None
Grade of complications		
No complications	0	0
Grade I	0	1
Grade II	3	0
Grade III	0	1
Grade I V	5	0
Death or grade V	1	1
Specific complications		
Duodenal stump leak	3	1
Pulmonar y-related	7	2
Cardiovascular-related	4	1
Wound infection/ dehiscence	5	0
Median length of stay (days)	24 (11-100)	16 (8-32)

and repair of duodenal stump dehiscence. The remaining ten patients were discharged well after a median length of stay of 16 (range: 8~100) days. *Table 3* illustrates the surgical observations, procedure and outcome.sification proposed by Clavien and group (8-10) (*Table 1*).

Apart from the duodenal stump leak above, three other patients had duodenal stump leaks that were managed conservatively. Almost all the patients had either pulmonary or cardiovascular complications post-operatively.

Adenocarcinoma

Nine patients had adenocarcinoma. All had T3 disease and the only patient with N0 disease was one of the fatalities, the rest of the patients all had involved lymph nodes. Three patients had metastatic disease diagnosed concurrently with peritoneal (n=3) and liver (n=1) involvement.

Eight patients survived the initial operation. In the three patients with metastatic disease, one foreign patient defaulted follow up and went back to his home country. The other two passed away from their advanced disease at three and ten months post-operatively, respectively. Both did not undergo any palliative chemo- or radio-therapy.

In the remaining five patients, one defaulted three months after the surgery. Two other patients had disease recurrence in the peritoneum causing intestinal obstruction within eight months of the initial surgery. Both perished within a few months subsequent to that. Both did not undergo any adjuvant chemo- or radio-therapy.

Only two patients in this group underwent adjuvant chemo- and radio-therapy in whom one had hepatic and pulmonary metastases ten months post-operatively and passed away seventeen months after. The other patient had spinal metastases diagnosed sixteen months after the surgery. He declined further chemo and radio-therapy and defaulted follow up subsequently.

Lymphoma

Two patients survived the initial surgery and both underwent subsequent chemotherapy and are still on strict surveillance under the medical oncologist. Currently, both are well with no evidence of disease recurrence.

Discussion

Even though the incidence of malignant gastric perforation remains low, the consequences are considerable (1,2). Our series affirmed the dismal peri-operative outcome following surgery in these patients. Two patients (16.7%) died with another six (50.0%) having severe complications (GOC III and IV). Similar to other reports, the majority of these complications are attributed to cardio-respiratory and septic causes (11-15).

Though malignancy has been quoted as an independent factor predicting worse outcome in gastric perforation, other more commonly associated adverse factors would include pre-operative shock, poor pre-morbid condition, advanced age, delayed presentation and resection surgery (11-16). Over the years, several scoring systems have been advocated in the prognostication of patients with gastric perforation, with Boey score being commonly adopted and validated in several reports (15,16).

Boey score utilized three independent factors of concomitant severe medical illness, pre-operative shock and long-standing perforation with predicted mortality rate of over 80% if all three factors are present. However, one of its main criticisms has been its inability to consider other physiological and intraoperative parameters. This has resulted in the numerous other scoring systems such as the Mannheim peritonitis Index (MPI), ASA score and APACHE II being adopted, each with its advantages and limitations. Suffice to say, the outcome in these patients are dependent on a combination of patient, disease and surgeon factors.

To make matter worse, in the absence of a known pre-operative gastric malignancy, it may be difficult to accurately diagnose the presence of malignancy in any gastric perforation (1,2). Mistaking a benign ulcer perforation as malignant is not impossible given the significant surrounding induration and enlarged inf lammatory lymph nodes. This may subject the patient to an unnecessary extensive and resection surgery with its numerous associated complications (1-6,17). Some of the clues suggestive of a malignant perforation would include advanced age, size of ulcer > 6 cm and size of perforation > 0.5 cm, raised white cell counts and longer duration of symptoms (1). The importance of frozen section intraoperatively has been emphasised to clinch the diagnosis but it may not be always available and false negative is also possible. In our series, frozen section was not performed in any patients as it was either not available or deemed not necessary by the primary surgeon because of the size of the ulcer and perforation, or if the malignancy was clinically suspected or already diagnosed. These would have supported the decision for gastrectomy regardless of the outcome of frozen section.

Even when the malignant perforation could be accurately diagnosed, the surgical procedures of choice in these patients are often dependent on various factors. These would include the presence of metastatic disease, expertise of the surgeon in performing an oncologic resection, the degree of contamination and perhaps most importantly, the intra-operative haemodynamic status of the patient.

At one stage, malignant gastric perforation has been deemed as terminal disease due to the associated peritoneal dissemination and early recurrences (18-20). This had led to the practice of simple closure of the perforation (21,22). However, this technique has been associated with unacceptable peri-operative complications and hence abandoned. Perhaps this should only be considered when the patient is extremely haemodynamically unstable to withstand any resection.

Over the years, the morbidity following emergency gastrectomy has been improving due to improving surgical technique and advancement in critical care (23). This has become the preferred surgical option in patients with malignant gastric perforation. Not only is it able to tackle the perforation, it can also remove the underlying pathology. However, the extent of radical oncologic surgery is perhaps dependent on the aforementioned factors. While it may be dangerous to embark on a major radical oncologic resection, the implications of a limited procedure may seriously impact the long term survival in patients with potentially curable gastric malignancy. This had led to the adoption of a two-stage procedure in handling this perplexing situation (3,24). While the first stage aimed to tackle the peritoneal contamination and the gastrectomy, the second procedure would be performed at a later date to ensure adequate lymph node clearance. However, the problems of such a staged procedure would include the significant postoperative adhesions from the first surgery, and also the fitness of the patient to withstand another extensive surgery. In addition, this could delay the commencement of any chemo- and radio-therapy, especially if any complications were encountered.

Recent data have disproved the notion that gastric perforation often resulted in increased risks of recurrences and peritoneal disease. The long term survival of patients with per forated gastric adenocarcinoma is actually comparable to patients performed electively (3-6). The only factor determining long term survival is the stage of the malignancy. As seen in our series, the majority of our patients had very advanced disease on diagnosis and fared badly subsequently with almost all the patients developing disease recurrences. Though several of our patients developed peritoneal disease subsequently, it could be related to the advanced staging and progression of the primary malignancy rather than contributed by the perforation. Unfortunately, large series is not available in the literature to shed more light into this.

The role of surgery in gastric lymphoma has been addressed by numerous reports and should only be performed as a primary radical treatment, palliative procedure or when emergency complications such as massive bleeding or perforation are encountered (25-28). The implications of the gastric perforation in the long term survival of these patients appear minimal with no reports of associated recurrence reported. The most important factor determining the long term survival is again the stage of the lymphoma. None of our patients had any systemic or peritoneal recurrence and both are currently well upon completion of their chemotherapy.

Conclusion

Surgery in perforated gastric malignancy is fraught with numerous challenges. Short-term outcome is dismal and is dependent on the various patient and disease factors. Long-term survival in these patients is dependent on the underlying stage of the malignancy.

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Surgical Research

Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction-a systematic review and meta-analysis of randomized and non-randomized trials

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Background: Open surgical gastrojejunostomy (GJ) has been the treatment of choice, but it has high morbidity and mortality rates. During the last decade, endoscopic self-expandable metal stents (SEMS) have been used. This meta-analysis aimed to compare surgical GJ and endoscopic stenting in palliation of malignant gastric outlet obstruction (GOO).

Methods: A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science. The search identified 3 randomized controlled trials (RCTs) and 14 non-RCTs reporting on patients who underwent surgical GJ or endoscopic stenting for malignant gastroduodenal outflow obstruction

Results: The results of the three RCTs demonstrated that SEMS resulted in comparable major [odds ratio (OR): 0.62, 95% confidence intervals (CI): 0.021-18.371] and minor (OR: 0.32, 95% CI: 0.049-2.089) complications in a shorter time to tolerating an oral intake (SEMS: 3.55 days and GJ: 7.15 days) and shorter hospital stay (SEMS: 5.1 days and GJ: 12.13 days, however, statistical insignificant P value =0.11). Among the non RCTs: SEMS resulted in a shorter time to tolerating an oral intake (SEMS: 1.48 days and GJ: 8.07 days, P value <0.01), similar rate of complications (OR: 0.33, 95% CI: 0.1-1.08), lower mortality (OR: 0.5, 95% CI: 0.21-1.20, P value <0.01) and a shorter hospital stay (SEMS: 7.61 days and GJ: 19.04 days, P value <0.0001). There was no significant difference between median survival times among RCTs and non RCTs.

Conclusions: These findings suggest that stent placement is associated with better short-term outcomes and hence, duodenal stenting is a safe means of palliating malignant gastric outflow obstruction. However, a large RCT is needed to systematically compare stent placement with GJ with regard to medical effects, quality of life and costs.

Keywords: Endoscopic stenting; gastrojejunostomy (GJ); malignant gastric outlet obstruction (GOO)

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Introduction

Gastric outlet obstruction (GOO) is a recognised complication of malignancies of the upper gastrointestinal (UGI) tract. The most common causes are pancreatic and gastric malignancies, with lymphomas, ampullary carcinomas, biliary tract cancers and metastases also contributing. In patients with pancreatic cancer, it is estimated that 15-20% of patients develop GOO (1). The majority of patients have locally advanced or metastatic cancer with dismal prognosis and median survival of only 3-6 months (2). The aim in palliating patients with malignant GOO is to re-establish an oral intake by restoring gastrointestinal continuity. This ultimately improves patients' quality of life in the advanced stages of cancer. Traditionally, surgical gastrojejunostomy (GJ) has been the standard treatment approach for these patients. Although

GJ relieves symptoms in almost all patients, the procedure is associated with morbidity of 10-16% and mortality of up to 7% (3-5). Also, post-operatively, most patients suffer delayed gastric emptying that is often associated with longer hospital stay (6). Although laparoscopic GJ has been introduced as a less invasive alternative to open GJ, the technique still carries substantial risk and is not widely available (7-10).

Endoscopic placement of self-expandable metal stents (SEMSs) has emerged as an alternative means for palliation of GOO. Multiple uncontrolled case-series studies have demonstrated SEMSs to be safe and effective with technical success of 90-100% and clinical success of 67-100% (11-17). Randomized trials have shown mixed results, with two trials favouring endoscopic SEMS (18,19) and one favouring surgical GJ (20). Therefore, it is currently unknown whether patients with GOO are best palliated with endoscopic SEMS placement or GJ. Also, SEMS are expensive and it is unclear whether their use is less costly when compared with surgical GJ. Although direct cost studies have shown that SEMS placement is less costly than surgery, the general applicability of the data is debatable given the small number of patients enrolled in each of these single-institution trials (7,21,22).

Hence we performed this meta-analysis to compare outcomes of endoscopic stenting (ES) with GJ. The primary goal of this study is to the compare the overall complication rate and effectiveness (ability to tolerate oral intake) of SEMS and GJ in patients with GOO. The secondary objective is to identify predictors of clinical outcomes [reintervention rate, length of hospital stay (LOHS), hospitalization charges, and complications].

Methods

Study protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses PRISMA guidelines where possible in performing our systematic review (23). We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to January 2013. The search terms included "gastric outlet, gastroduodenal or duodenal obstruction", "gastrojejunostomy, gastroenterostomy or surgical bypass", and "endoscopic and stent", which were searched as text word and as exploded medical subject headings where possible. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with GOO who underwent GJ or SEMS.

Data extraction

We performed the data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data. The event rate and confidence intervals (CI) were calculated.

Statistical analysis

Pooled event rate and 95% CI were calculated using a random effects model (24). We tested heterogeneity with Cochran's Q statistic, with $P<0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively (25). The quantified publication bias using the Egger's regression model (26), with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P<0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n+10$, with n being the number of studies included in the meta-analysis (27). All analyses were performed with Comprehensive Meta-analysis (version 2.0).

Results

The original search strategy retrieved studies (*Figure 1*). The abstracts were reviewed and after applying the inclusion and exclusion criteria, articles were selected for full-text evaluation. Of the articles selected, only 20 met

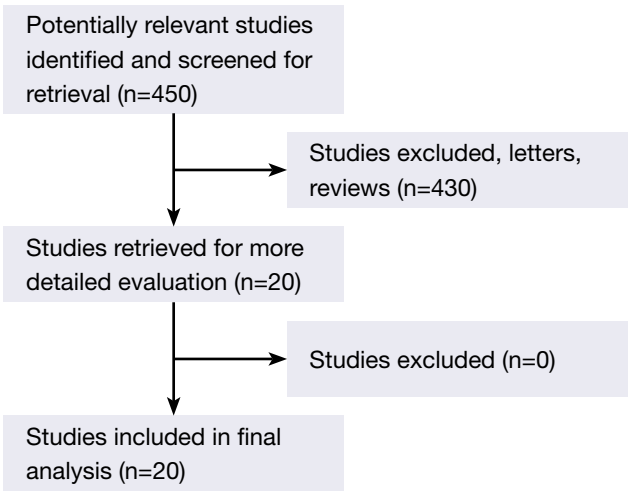

Figure 1 Flow of included studies.

full criteria for analysis and are summarised in *Table 1*. The years of publication ranged from 2001 to 2013.

The results of the three randomized controlled trials (RCTs) demonstrated that SEMS resulted in lower major [odds ratio (OR): 0.62, 95% CI: 0.021-18.371] and minor (OR: 0.32, 95% CI: 0.049-2.089) complications in a shorter time to tolerating an oral intake (SEMS: 3.55 days and GJ: 7.15 days) and shorter hospital stay (SEMS: 5.1 days and GJ: 12.13 days). Among the non RCTs: SEMS resulted in a shorter time to tolerating an oral intake (SEMS: 1.48 days and GJ: 8.07 days), lesser complications (OR: 0.33, 95% CI: 0.1-1.08), lower mortality (OR: 0.5, 95% CI: 0.21-1.20) and a shorter hospital stay (SEMS: 7.61 days and GJ: 19.04 days). There was no significant difference between median survival times among RCTs and non RCTs (*Tables 2* and *3*).

Heterogeneity and publication bias

No publication bias was detected using the Egger's regression model.

Discussion

GOO secondary to unresectable primary or metastatic malignancy is a challenging aspect of patient care. The main objective of a palliative procedure in patients with malignant GOO is to restore their ability to eat.

A comprehensive review of 32 case series including 606 patients was conducted by Dormann *et al.* (41) 94 % of the patients were unable to take food orally or were mainly ingesting liquids. Stent placement and deployment were successful in 589 of the patients (97%). Clinical success was achieved in 526 patients in the group in which technical success was reported (89%; 87% of the entire group undergoing stenting). Disease-related factors accounted for the majority of clinical failures. Oral intake became possible in all of the patients in whom a successful procedure was carried out, with 87% taking soft solids or a full diet, with final resolution of symptoms occurring after a mean of 4 days. There was no procedure-related mortality. Severe complications (bleeding and perforation) were observed in seven patients (1.2%). Stent migration was reported in 31 patients (5%). Stent obstruction occurred in 104 cases (18%), mainly due to tumor infiltration. The mean survival period was 12.1 weeks.

Current literature included three RCTs that compared ES with GJ (18-20). These three trials combined consist of a total of 84 patients. Confounding variables could not be studied in most of the published trials to avoid overfitting. However, if factors, such as chemoradiation therapy, carcinomatosis, age, comorbidities, etc., are not accounted for, results may be biased.

Johns Hopkins, Baltimore (39) recently published a cohort of 347 patients. Technical success was higher for GJ (99% *vs.* 96%, P=0.004). Complication rates were higher in the GJ group (22.10% *vs.* 11.66 %, P=0.02). Reintervention was more common with ES (adjusted OR 9.18, P<0.0001). Mean LOHS was shorter (adjusted P=0.005) in the ES compared with the GJ group. However, mean hospital charges, including reinterventions, were greater in the ES group (US34,250 *vs.* US27,599, P=0.03). ES and GJ had comparable reintervention-free time in patients who had reintervention (88 *vs.* 106 days, respectively, P=0.79). Chemotherapy [adjusted hazard ratio (HR) 3>0.57, P=0.04] and radiation therapy (adjusted HR 0.35, P=0.03) were associated with significantly longer duration of oral intake after ES or GJ.

Boston Scientific Corporation (31) evaluated 425 stenting and 339 GJ hospitalizations. Compared with GJ, median LOS (8 *vs.* 16 days; P<0.0001) and median cost (US15,366 *vs.* US27,391; P<0.0001) per claim were both significantly lower for stenting. Stenting was more commonly performed at urban versus rural hospitals (89% *vs.* 11%; P<0.0001), teaching versus non-teaching hospitals (59% *vs.* 41%, P=0.0005), and academic institutions (56% *vs.* 44%; P=0.0157). The institutional patient data analysis included 29 patients who underwent stenting and 75 who underwent surgical GJ. While both modalities were technically successful and relieved GOO in all cases, compared with surgical GJ, the median post-procedure LOS was

Table 1 Characteristics of the studies included in the systematic review and meta-analysis

Author	Year	Country	Study type	Procedure	No of patients
Jeurnink *et al.* (28)	2007	The Netherlands	Retrospective cohort	ES	53
				OGJ	32
				LGJ	10
Mittal *et al.* (7)	2004	New Zealand	Retrospective cohort	ES	16
				OGJ	16
				LGJ	14
Schmidt *et al.* (29)	2009	USA	prospective observational study	ES	24
				OGJ	16
Chandrasegaram *et al.* (30)	2012	Australia	Retrospective cohort	ES	
				OGJ	
Roy *et al.* (31)	2012	USA	Retrospective cohort	ES	425
				OGJ	339
El-Shabrawi *et al.* (32)	2006	Austria	Retrospective cohort	ES	22
				OGJ	17
Espinel *et al.* (33)	2006	Spain	Retrospective cohort	ES	24
				OGJ	17
Yim *et al.* (22)	2001	USA/Singapore	Retrospective cohort	ES	12
				OGJ	15
Wong *et al.* (34)	2002	USA	Retrospective cohort	ES	6
				OGJ	17
Maetani *et al.* (3)	2004	Japan	Retrospective cohort	ES	20
				OGJ	19
Maetani *et al.* (35)	2005	Japan	Retrospective cohort	ES	22
				OGJ	22
Del Piano *et al.* (36)	2005	Italy	Retrospective cohort	ES	24
				OGJ	23
Mejía *et al.* (37)	2006	Columbia	Retrospective cohort	ES	15
				OGJ	15
Jeurnink *et al.* (20)	2010	Netherlands	Randomized controlled trial	ES	20
				OGJ/LGJ	17
Mehta *et al.* (18)	2006	United Kingdom	Randomized controlled trial	ES	13
				LGJ	14
Fiori *et al.* (19)	2004	Italy	Randomized controlled trial	ES	9
				OGJ	9
Guo *et al.* (38)	2010	China	Prospective cohort	ES	13
				OGJ	21
Johnsson *et al.* (21)	2004	Sweden	Prospective cohort	ES	21
				OGJ	15
Khashab *et al.* (39)	2013	USA	Retrospective cohort	ES	120
				OGJ	227
No *et al.* (40)	2013	Korea	Retrospective study	ES	72
				OGJ	41

ES, endoscopic stenting; OGJ, open gastrojejunostomy; LGJ, laparoscopic gastrojejunostomy.

Table 2 Pooled odd ratio and 95% CI of randomized trials and non-randomized trials

Outcome	Pooled odds ratio	95% CI	I^2	P value
RCT				
Major complications	0.62	0.021-18.37	74.04	0.02
Minor complications	0.32	0.049-2.089	45.20	0.16
Non RCT				
Number of patients tolerating a diet	4.01	1.4-11.46	46.17	0.08
Mortality	0.5	0.21-1.20	34.50	0.14
All complications	0.33	0.1-1.08	75.85	<0.0001

RCT, randomized controlled trial; CI, confidence interval.

Table 3 Outcomes of randomized trials and non-randomized trials

	Means		P value
	ES	GJ	
RCT			
Time to oral intake (days)	3.55	7.15	0.11
Hospital stay (days)	5.1	12.13	<0.01
Non RCT			
Time to oral intake (days)	1.48	8.07	<0.01
Hospital stay (days)	7.61	19.04	<0.0001
Total medical costs ($)	8,629.5	17,842	0.09
Survival (days)	96.05	103.31	0.59

RCT, randomized controlled trial; ES, endoscopic stenting; GJ, gastrojejunostomy.

significantly lower for enteral stenting (1.5 *vs.* 10.7 days, P<0.0001). There was no difference in rates of delayed complications between stenting and surgical GJ (13.8% *vs.* 6.7%; P=0.26).

Memorial Sloan-Kettering Cancer Center (29) performed a prospective observational study examining quality of life in patients with malignant GOO. Median overall survival was 64 days. A shorter hospital stay and trend to lower mortality were observed after stent placement; solid food intake and rates of secondary intervention were comparable. Both stent and surgical bypass were associated with acceptable QOL outcomes. Fifteen patients refused participation at 1 month and 28 died of disease before 3 months, so ten patients completed all surveys.

Conclusions

In conclusion, while the technical and clinical outcomes of GJ and stent placement appear comparable in relieving obstruction, stent placement is associated with shorter LOS. This endoscopic approach is also in line with the minimally invasive goals of palliation, namely minimizing pain, hospitalization, and physiologic stress to the patient.

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Surgical Video

Intracorporeal laparoscopic esophagojejunostomy using endoscopic linear staplers: the experiences of 293 cases

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Abstract: Although several investigators have suggested their method to perform a totally laparoscopic total gastrectomy (TLTG), even experts on laparoscopic gastrectomy, it is very hard to perform a safe TLTG in practice because of the complexity of procedure. We developed a secure technique for intracorporeal laparoscopic esophagojejunostomy (EJ) using endoscopic linear staplers and successfully performed the TLTG method. Between September 2006 and January 2013, total of 293 patients with early gastric cancer in the upper third of the stomach underwent TLTG using endoscopic linear stapler in one institution. The laparoscopic EJ was successfully performed in all patients; none of the patients required conversion to open surgery or other laparoscopic anastomosis techniques. All the operations were curative. The intracorporeal EJ procedure can be performed easily and safely, and this method of TLTG may become a powerful alternative procedure for intracorporeal EJ after laparoscopic total gastrectomy.

Keywords: Laparoscopic total gastrectomy; intracorporeal anastomosis; esophagojejunostomy

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Introduction

Due to its safety and efficacy, laparoscopic gastrectomy is becoming a widely used surgical method for treating early gastric cancer (EGC) (1-5). After its introduction in 2002, several types of totally laparoscopic gastrectomy using intracorporeal reconstruction have been made to improve early surgical outcome of laparoscopic gastrectomy (6-10). Recently, we also reported that early surgical outcomes of totally laparoscopic distal gastrectomy using an intracorporeal reconstruction (TLDG) are superior to those of laparoscopic assisted distal gastrectomy using an extracorporeal reconstruction (LADG) (11,12).

More recently, some investigators reported various types of totally laparoscopic total gastrectomy using an intracorporeal reconstruction (TLTG) (13-18). In practice, however, it is very hard to perform or try TLTG. Unlike TLDG method, TLTG demands a high level of surgical technique. Therefore, we introduce more practical TLTG method from our experiences.

Surgical techniques

Each patient was placed in the reverse Trendelenburg position. A carbon dioxide pneumoperitoneum was formed from the umbilical port, and pressure was maintained between 12 and 15 mmHg. Five trocars were placed in a U-shape. To retract the liver, the attachment site of the lesser omentum to the right diaphragmatic cruse was intracorporeally sutured, and then a thread pulled by a suture-passer was tied onto the skin in the xyphoid process area. If the operating field was not sufficient, an additional 5-mm trocar was inserted into the epigastric area to retract the liver.

Dissection was begun by dividing the greater omentum, from the mid-portion of the gastroepiploic arcade to the left gastroepiploic vessel. The lymph nodes around the left gastroepiploic, and short gastric vessels were dissected. After dissecting the lymph nodes around the short gastric area, the infrapyloric area was dissected. After lymph nodes around the suprapyloric area were dissected, the duodenum

was transected just below the duodenal bulb using an endoscopic linear stapler (ECHELON FLEX™ 60) (*Video 1*). And then, lymph nodes around common hepatic, proximal or distal splenic, celiac, and left gastric arteries; and right paracardial and lesser curvature areas were dissected in that order.

After having cleared all lymph nodes, nearly two-thirds of the esophagus diameter was transected 2 cm above the gastroesophageal junction using the endoscopic linear stapler (ECHELON FLEX™ 60) and the first intracorporeal suture was placed at the end of the stapled line to retract the esophageal stump and this suture was cut 15 cm from the esophageal stump, which it was retracted by first assistant during reconstruction of esophagojejunostomy (EJ). The unstapled esophageal stump was then transected with laparoscopic scissors after grasping the remnant stomach with a laparoscopic intestinal clamp to avoid cancer cell spillage (*Video 1*). To make the lumen of esophagus easier to detect, a second round of intracorporeal suture was placed at the small esophagostomy of the esophageal stump and it was extracted outside the abdomen through the right lower trocar to retract it, which prevented slipping of the esophageal mucosa and submucosa during reconstruction of EJ. The specimen was subsequently removed through another suprapubic incision that was approximately 3-4 cm long. After removing the specimen, the suprapubic incision site was closed by continuous suture to reinstate the pneumoperitoneum. The proximal resection margin of the specimen was examined pathologically.

The jejunum was then divided 20 cm below the ligament of Treitz by using an endoscopic linear stapler (ECHELON FLEX™ 60), and an efferent loop was turned in a counter-clockwise direction to reconstruct the EJ. An enterostomy of jejunum was made in the antimesenteric side of the Roux-en-Y limb by using laparoscopic scissors, and an endoscopic linear stapler (ETS STRAIGHT™ 45) with closed staple height of 1.5 mm was inserted into esophagostomy and enterostomy of jejunum to form an EJ (*Video 1*).

Postoperative management

Gastrografin studies were performed on postoperative day 3 to evaluate leakage after certain intraoperative events that occurred in nine patients during reconstruction of the esophagojejunostomy. A soft diet was commenced on the day when each patient felt comfortable enough to eat soft foods. The patients were discharged when they had no problems eating a soft diet and were generally comfortable, and inflammatory conditions, including leukocytosis, unstable vital signs, and abrupt onset of abdominal pain, were absent. The final decision about discharge was made by the patient.

Clinical analysis of early surgical outcomes of TLTG

The study sample included 185 men (63.1%) and 108 women (36.9%) with mean age 57.0 years (range, 22-84 years). The average body mass index was 24.8 kg/m^2 (range, 16.6-32.4 kg/m^2). Intracorporeal esophagojejunal anastomosis using an endoscopic linear stapler was successful in all patients. None of the patients required conversion to open surgery or other laparoscopic anastomosis techniques. All the operations were curative. The mean operation time was 141.8±43.9 min. The mean time to first flatus was 3.47±0.9 days and the mean post-operative day on which patients commenced a soft diet with no morbidity was 4.52±8.0 days. The mean length of hospital stay of patients with no morbidity was 7.80±3.6 days. *Table 1* shows the postoperative complications and managements of the patients who underwent TLTG. The overall postoperative complication rate was 15.7%, the mild postoperative complication rate was 11.3%, and the severe postoperative complication rate was also 4.4%.

Discussion

Recently, several types of totally laparoscopic gastrectomy using intracorporeal reconstruction were introduced. We also reported the benefits of totally laparoscopic distal gastrectomy with gastroduodenostomy using endoscopic linear staplers. Despite several articles about experiences for totally laparoscopic total gastrectomy using intracorporeal reconstructions reported, however there are few reports to evaluate early surgical outcomes of totally laparoscopic total gastrectomy. In practice, TLTG is rarely performed because of the complicated procedures. Therefore, we would like to introduce our method to perform TLTG safely and reduce the possibility of cancer cell spillage from our experiences.

In practical procedures, it is needed to prevent the slipping of esophageal stump during reconstruction of EJ because the resected esophageal stump moves easily into the thoracic cavity. To prevent the slipping of esophageal stump and perform the anastomosis in abdominal cavity during the reconstruction, we had devised improved techniques

Table 1 Postoperative complications and treatments of TLTG

Type	Morbidity	N (%)	Treatment
Major	Internal herniation	3 (1.02)	3 Laparoscopic hernia reductions
	Extra luminal bleeding	2 (0.68)	1 Laparoscopic management
			1 Interventional pig-tail catheter insertion + antibiotics
	Anastomotic leakage	1 (0.34)	1 Long-term parenteral nutrition + interventional pig-tail catheter insertion + antibiotics
	Duodenal stump leakage	2 (0.68)	1 Laparoscopic surgical dranage
			1 Laparoscopic tube duodenostomy insertion + conservative therapy
	Anastomosis structure	2 (0.68)	2 Stent insertion
	Intra-abdominal abscess	2 (0.68)	2 Interventional pig-tail catheter insertion + antibiotics
	Post-operative ileus	1 (0.34)	1 Laparoscopic adhesiolysis
Minor	Intra-luminal bleeding	1 (0.34)	1Conservative treatment
	Extra-luminal bleeding	1 (0.34)	1Conservative treatment
	Anastomotic leakage	10 (3.41)	10 JP Drainage + antibiotics
	Anastomosis structure	5 (1.71)	5 Conservative treatment
	Intra-abdominal abscess	2 (0.68)	2 JP Drainage + antibiotics
	Post-operative ileus	8 (2.39)	8 Conservative treatment
	Wound infection	3 (1.02)	3 Conservative treatments
	Other	3 (1.02)	3 Conservative treatments

TLTG, totally laparoscopic total gastrectomy; JP, Jackson-Pratt.

as follows. Two intracorporeal suturing using black silks were in the end of stapled line and opened esophagostomy of esophageal stump. To prevent slipping of esophageal slipping during the reconstruction, first assistant pulled first thread toward operator side in abdominal cavity and second assistant pulled second sutured thread outside the abdominal cavity through right lower troca. This retraction would have enabled operator to prevent falling of the anastomosis into thoracic cavity and confirm the safety of anastomosis. And, operator could insert without great difficulty an endoscopic linear stapler between opened hole of esophageal stump and jejunal stump to make common channel. As a result, we could minimize the size of remnant anterior hole of common channel. After completion of the EJ, we could confirm the safety of posterior and anterior side of the anastomosis.

In conclusion, we strongly believe that TLTG could be a best way to improve early surgical outcomes in gastric cancer patients. However, inexperienced surgeons for laparoscopic gastrectomy should be careful in performing TLTG because TLTG is made up of complex processes. Therefore, it is conceivable that our TLTG method from high volume center experiences can help surgeons decrease or overcome the learning period.

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Surgical Video

Reducing the number of abdominal ports used for laparoscopic distal gastrectomy using the "MiniLap" grasper

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Laparoscopic gastrectomy is widely accepted as a good alternative to open surgery for the treatment of early gastric cancers, and has several advantages including less abdominal wound, reduced pain, quicker recovery, and better postoperative quality of life (1,2). Conventional laparoscopic distal gastrectomy usually requires 4 to 5 abdominal ports for an operator and assistant, and an additional umbilical port for laparoscope insertion. With advances in laparoscopic instruments and surgical technique, many surgeons are trying to perform laparoscopic gastrectomy reducing the number of abdominal ports used. Single port laparoscopic surgery, also called single incision laparoscopic surgery, in which all the procedures are performed via a single umbilical port, has been recently introduced by some experts (3). Unlike other surgical procedures, however, laparoscopic gastrectomy via a single abdominal port is still technically challenging because of the technical difficulties regarding manipulation of laparoscopic devices and intracorporeal anastomosis through a single abdominal port, as well as the lack of appropriate laparoscopic devices for this procedure (4-6).

In this video (*Video 1*), we introduce "reduced ports laparoscopic distal gastrectomy" using the "MiniLap" grasper (Stryker, CA, USA). "MiniLap" grasper is 2.3 mm in diameter and can be inserted into the abdominal cavity without conventional abdominal laparoscopic port. It leaves little abdominal scar and does not require suturing of its insertion site. During laparoscopic distal gastrectomy, it can be used as an assistant device to retract the stomach and secure operating field or to retract the liver. Also, it can be used for an additional assistant port when performing single incision laparoscopic gastrectomy. In this procedure, it enables surgeons to reduce conventional two assistant laparoscopic ports without significant disruption of the operative procedures. Only two abdominal ports for an operator are needed for laparoscopic distal gastrectomy when "MiniLap" graspers are used. In addition, it would benefit patients from reducing costs, minimizing surgical pain and scarring.

In our experience, the procedures of gastric and lymph node dissection was feasible and safe using the "MiniLap" graspers. "Mini-Lap" grasper could do the nearly same function as conventional laparoscopic devices through abdominal ports. After gastric dissection, reconstruction is usually performed with intracorporeal Billroth II anastomosis using linear staplers. From June 2012 to March 2013, we performed this procedure on 25 patients with gastric cancer. The mean operating time was 135 min (range, 90 to 180 min), and there was no conversion to open surgery. Postoperatively, two patients had postoperative complications (one case of pneumonia and one case of gastric stasis). No hospital mortality occurred. The mean hospital stay was 7.7 days. In conclusion, "MiniLap" grasper is useful reducing the number of abdominal ports used during laparoscopic distal gastrectomy. Laparoscopic gastrectomy using the "Mini-Lap" grasper is technically feasible and safe. Also, it could reduce the costs and benefits patients from surgical pain and scarring.

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Surgical Video

Functional end-to end esophago-jejunal anastomosis using linear staplers following laparoscopic total gastrectomy

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Introduction

Technical difficulty of laparoscopic Roux-en-Y reconstruction is a major reason of less prevalence of laparoscopic total gastrectomy (LTG). Reconstruction-related complications, such as anastomotic leakage or stenosis were reported in higher rate than in distal gastrectomy (1). To overcome the technical obstacle and establish a standardized reconstruction method, we introduced intracorporeal functional end-to end (FETE) esophago-jejunal anastomosis using endoscopic linear staplers in September 2006 (2,3). This video article demonstrates our standard laparoscopic procedure of Roux-en-Y reconstruction using endoscopic linear staplers following total gastrectomy (*Video 1*).

Surgical technique

After completion of total gastrectomy, a jejunal loop about 20 cm distal to the ligament of Treitz is marked with dye, and the jejunal mesentery is divided to create a 50-cm Roux-en-Y limb. Marginal vessels are always divided so that Roux-en-Y limb could reach the esophagus without tension. Jejunal branches are also divided, if necessary. Side-to-side jejunojejunostomy is performed using a 45 mm linear stapler. After the entry hole is closed by continuous suture with 3-0 Vicryl®, the jejunal mesenteric defect is also closed with 3-0 continuous suture with non-absorbable thread.

Then, the Roux-en-Y limb was brought up via the antecolic route to create an esophagojejunostomy. Small holes are made at the end of the Roux-en-Y limb on the antimesenteric side, and on the left dorsal side of the esophageal stump. To make the lumen of the esophagus easier to detect, a nasogastric tube was advanced through the hole. Through the left lower trocar, a 45 mm endoscopic linear stapler is inserted. The anvil fork is inserted into the Roux-en-Y limb, and then the cartridge side is inserted into the esophageal lumen using the nasogastric tube as a guide. After the entry hole is roughly closed with staplers that is used for fixation of mesh in hernia repair, closure is completed with a linear stapler through the right lower trocar. An air leakage test is performed to confirm the tightness of the anastomosis. Hand-sewn closure of the Petersen's defect is done using non-absorbable thread.

Results

From September 2006 to December 2012, LTG with FETE esophagojejunostomy were planned in 119 patients. LTG was accomplished in 117 patients (98.3%). Reasons of two conversion were, bleeding from the splenic hilum and involvement of a naso-gastric tube during esophagojejunal anastomosis. Postoperative complications occurred in 27 patients (22.6%). Among them, reconstruction-related complications were opserved in five patients (4.3%): two anastomotic leakage of esophagojejunostomy (1.7%), two Roux stasis (1.7%), and one duodenal stump leakage (0.9%). Median postoperative hospital stay was 14 days. During median observation period of 30 months, adhesive ileus occurred in 5 patients (4.3%), and internal hernia through the jejunal mesenteric defect occurred in three patients (2.6%). No anastomotic stenosis was observed. While all patients with adhesive ileus were successfully treated with fasting and/or decompression, all three patients with internal hernia required emergent operation. Mesenteric defects had not been closed during initial LTG in all three patients.

Conclusions

Intracorporeal FETE esophago-jejunal anastomosis was safely performed with less postoperative reconstruction-related complications. The advantages of FETE esophagojejunostomy include safe anastomosis under better visualization, and less anastomotic leakage or stenosis. Mesenteric defects should be closed to prevent internal hernia.

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Surgical Video

Laparoscopic total gastrectomy with spleen-preserving splenic hilar (No. 10) lymph nodes dissection

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Abstract: Laparoscopic total gastrectomy with spleen-preserving splenic hilar (No. 10) lymph nodes dissection is challenging due to the tortuous splenic vessels and possibility of parenchymal injury to the spleen or pancreas. Based on our anatomical understanding of peripancreatic structures, we combined the characteristics of laparoscopic surgery and developed a strategy using retro-pancreatic approach for laparoscopic spleen-preserving No. 10 lymph nodes dissection.

Keywords: Stomach neoplasm; laparoscopy; lymph node excision; splenic hilar

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Guoxin Li

Splenic hilar (No. 10) lymph nodes (LN) metastasis was identified as an important prognostic factor in previous studies for gastric carcinomas (1,2). Dissection of No. 10 LN should be conducted in laparoscopic total gastrectomy with D2 lymphadenectomy for treatment of advanced proximal gastric cancer (3). Traditional No. 10 LN dissection was mainly achieved through combined resection of pancreas and/or spleen. However, due to the increased postoperative morbidity and mortality, spleen-preserving gastrectomy was subsequently suggested (4). In laparoscopic total gastrectomy, spleen-preserving No. 10 LN dissection is challenging and technically demanding and was only reported by a small number of skilled laparoscopic surgeons in high-volume specialized centers (5).

In 2012, a 54-year old male patient with upper abdominal pain was incharged in our department. Gastrofiberoscopy with biopsy identified an adenocarcinoma with a diameter of 9.5 cm located at the middle-third of the stomach near the lesser curvature. Abdominal high-resolution multi-directional computed tomography (CT) showed no distant metastasis, gross involvement of the gastrosplenic ligament or LN number 4sb, at the splenic hilar or along the splenic artery (SA).

The surgery was performed with laparoscopic ultrasonic shears [Laparoscopic Coagulation Shears (LCS); Ethicon Endo-Surgery, Cincinnati, OH] (*Video 1*).

Under general anesthesia, the patient was placed in the supine position with legs set apart in a reverse Trendelenburg position. The surgeon stood on the patient's left side; the assistant surgeon took the patient's right side; and the camera operator stood between the patient's legs. After pneumoperitoneum was established with carbon dioxide insufflated at a pressure of 12 mmHg, five working ports were introduced (6). Exploration of abdominopelvic cavity was conducted to exclude distant metastasis and carcinomatosis.

In this video, the greater omentum was divided along the border of the transverse colon

Video 1 Laparoscopic total gastrectomy with spleen-preserving splenic hilar (No. 10) lymph nodes dissection.

toward the inferior pole of the spleen and then rightward toward the duodenum. By dividing the gastrocolic ligament, the less sac was entered. The stomach was then overturned cephalad, the right gastroepiploic vein was identified by dissecting the mesogastrium inferior to the gastric antrum off the transverse mesocolon, which was then ligated and divided at its origin. The right gastroepiploic artery was usually identified next to the vein, which was also divided to allow the removal of LN 4d and 6. The gastropancreatic fold could be exposed, and the gastroduodenal artery was located in the groove between duodenum and pancreatic head, which served as a clue to trace the celiac trunk and its branches. By pressing the top of the pancreatic arch, the left gastric vein and artery could be identified, which were both ligated at origin. By following the common hepatic artery, the proper hepatic artery could be traced. The right gastric artery was located in the hepatoduodenal ligament as a small branch running from the proper hepatic artery to supra-pylorus. By ligating the right gastric artery and dissecting the tissues around the proper hepatic, common hepatic artery and celiac trunk, the right side of supra-pancreatic LN (5, 7, 8a, 9, 12a) were removed en-block.

By retracting the pancreas meticulously in the caudal direction, the soft tissue was dissected off the superior margin of the pancreatic body and tail in order to enter the retropancreatic space, thus uncovering the proximal SA. By opening the artery and vein sheath and skeletonizing the SA from proximal portion towards the distal portion, LN 11p could be removed. When the bifurcation was reached, two secondary branches of the SA could be seen. The superior branch coursed towards the superior pole of the spleen and the inferior one coursed directly towards the splenic hilar. The pancreatic tail was mobilized using the infra-pancreatic approach to re-enter the retropancreatic space. The superior and inferior branches of the SA were then skeletonized until they reached the spleen parenchyma. Meanwhile, the left gastroepiploic vessels and the short gastric vessels originating from the SA were ligated and divided. By skeletonizing the SA, fatty tissues bearing LN 10, 11d, 4sa and 4sb were removed and all vessels in the splenic hilar area were saved with the preservation of the spleen.

The duodenum was transected 2 cm distal to the pylorus using an endoscopic linear stapler (Echelon 60 Endopath Stapler; Ethicon Endo-surgery, LLC, Guaynabo, Puerto Rico 00969, USA). Subsequently, the phrenoesophageal and both vagus nerves were divided and the LN 1 and 2 was dissected. The Roux-en-Y esophagojejunostomy and jejunojejunostomy were carried out extracoporeally through a 4-5 cm midline minilaparotomy just below the xiphoid process using a circular stapler and hand-sewing.

The operating time was 201 min and estimated blood loss was 80 mL. Pathological findings suggested the TNM stage was T4aN3M0 (IIIC) according to AJCC cancer staging manual-7th edition. The numbers of total retrieved LN and No. 10 LN were 40 and 4 respectively. The number of total metastatic LN was 15 and there was 0 positive No. 10 LN. Postoperatively, the patient experienced the first flatus on day 4, began oral intake of liquid diet on day 4, semi-liquid diet on day 5 and discharged on day 6. Within 30 days after surgery, no complication was observed. At the last follow-up of 8 months, the patient didn't experience recurrent disease.

In conclusion, laparoscopic total gastrectomy with spleen-preserving splenic hilar lymph nodes dissection through retro-pancreatic approach could be technically safe and feasible. The procedure might be helpful for experienced laparoscopic surgeons to extend the surgical indication to advanced proximal gastric cancers.

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Surgical Video

Standard lymph node dissection (D2 surgery) for antral carcinoma

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Han Liang

Gastric cancer is one of the most common cancers in China, and most are already at an advanced stage when they are diagnosed. Although the range of lymph node dissection for gastric cancer remains controversial in the East and the West, a consensus in eastern Asia is: the standard lymph node dissection should reach D2. Take antral carcinoma as an example. Lymph node stations 1, 3, 4, 5, 6, 7, 8, 9, 11, 12a, and 14 should be dissected. The standard dissection should be based on the anatomical characteristics of the stomach. Dissection should be performed in the spaces between tissues. The corresponding vessels should be ligated at their roots to ensure the complete dissection of lymph nodes.

The video of the standard lymph node dissection (D2 surgery) for antral carcinoma is described as follows (*Video 1*).

(00:00:00-00:00:50): dissection of lymph node station 15

The first step is to remove the first three lobes of greater omentum and dissect the lymph node around colonic vessels (i.e., lymph node station 15). The assistant extends the transverse colon to find the correct anatomic layer, so as to completely remove the lymph nodes and soft tissues without causing unnecessary injury and bleeding. The power of electric knife is typically set at 50 Hz, which helps to avoid injuring the adjacent vessels and solidify the small blood vessels around the lymph nodes to keep the field clear in operation. The operator uses tweezers (or the assistant uses hemostatic forceps) to hold the lymph nodes and soft tissues that are to be removed, to form certain tension after moderate traction, which helps to automatically expose the tissue gaps and avoid the electric knife to injure the colonic vessels. Dissection of lymph node station 15 must maintain the integrity of transverse mesocolon.

(00:00:51-00:02:04): dissection of lymph node station 14v

After the dissection of lymph node station 15, the surgeon then divides along the colonic vessel towards the lower edge of the pancreas. The dissection must be performed layer by layer, with vessels as the axes. Dissection of lymph node station 14 is a challenging and dangerous step in the radical resection of gastric carcinoma. For new surgeons, the operation should be performed step by step until the origin of the superior mesenteric vein is exposed. The new surgeons should set their electric knife at low power to avoid the accidental injury of the superior mesenteric vein. The operator uses clamps or tweezers to hold the lymph nodes and soft tissues that are to be removed to form certain tension, which helps to expose the anatomic gaps and avoid accidental injury.

Video 1 Standard lymph node dissection (D2 surgery) for antral carcinoma.

(00:02:05-00:02:58): dissection of lymph node station 4sb at the greater curvature of the stomach

Lift the spleen with gauze pads to alleviate the tension of vessels at the hilus of spleen. During the dissection, the assistant must cautiously protect the spleen. Beginning from the splenic lower pole, the operator dissects individual lymph node from left to right towards the greater curvature of stomach. If condition allows, ultrasonic scalpel can be used to completely remove lymph nodes and soft tissues without causing excessive bleeding. Finally, the lymph node station 4sb is removed en bloc. When distal subtotal gastrectomy is performed, the lymph node station 4d is also removed.

(00:02:59-00:04:43): dissection of lymph node station 13 via Kocher incision

After the Kocher incision is opened, the assistant lifts the head of the pancreas and duodenal loop to the right side of the patient, and the operator dissects the lymph nodes along the gaps at the vascular archs. There are many vessels behind the head of the pancreas and should be carefully protected. The lymph node station 12b near the common bile duct is not within the range of standard radical treatment. Injury of common bile duct (and thus biliary fistula) should be avoided during the dissection of lymph node station 12b. Excessive peeling of tissue from the common bile duct surface should be avoided to affect its blood supply. In addition, during the skeletonization of common bile duct, portal vein, and hepatic artery, any damage to the vena cava (beneath) or portal vein (left rear) should be avoided.

(00:04:45-00:06:12): dissection of lymph node station 12a (i.e., lymph nodes near the proper hepatic artery)

The anatomic relationships among common bile duct, portal vein, and hepatic artery inside the hepatoduodenal ligament should be carefully considered to avoid the accidental injury of the portal vein. The skeletonization of common bile duct, portal vein, and hepatic artery should be performed by an experienced operator; however, attention should be paid to protect the nerves and blood supply of the gallbladder, so as to avoid post-surgical cholecystitis and cholelithiasis. Accidental injury of the cystic artery may cause the necrosis of the gallbladder.

(00:06:14-00:06:32): dissection of lymph node station 12b

Dissection of lymph node station 12b is not within the range of standard D2 dissection. Accidental injury of the portal vein and common bile duct should be avoided during the operation.

(00:06:33-00:06:58): dissection of suprapyloric lymph node

After the lymph nodes and soft tissues around the right gastric vessels are dissected, ligate the right gastric artery at the root. One or two pyloric veins should be preserved.

(00:06:59-00:07:56): dissection of lymph node station 8a (lymph nodes near the common hepatic artery)

The first assistant pushes down the pancreas, and the second assistant pulls up the residual stomach and liver with S-hooks. The operator looks for the inter-tissue gaps along the upper edge of the pancreas. The lymph node station 8a is typically distributed along the common hepatic artery. It has rich blood supply; after having been completed removed, the bleeding naturally stops.

(00:07:58-00:08:39): transection of duodenum

The duodenum is transected at the proper site using purse-

string clamp. Place circular stapler into the screw base.

(00:08:40-00:10:18): dissection of lymph nodes around the left gastric artery

This is one of the most common lymph node metastasis locations. Therefore, with the left gastric artery as the anatomic marker, lymph nodes in this location must be completely dissected. The lymph nodes at the front, left back, and right back of the left gastric artery should be dissected firstly. Then, from the left or right approach, the lymph nodes behind the left gastric artery should be dissected. After lymph node dissection, the left gastric artery should be ligated at the root (typically double ligated with a 4-0 silk suture.

(00:10:20-): dissection of lymph node station 9

After the dissection of lymph node station 7, the lymph node station 9 (lymph nodes around the celiac trunk) is then dissected along the root of left gastric artery. The left gastric artery is ligated.

(00:11:26-00:11:35): dissection of lymph node station 11p

The operation continues along the upper edge of the pancreas, and, at the left side, the lymph node station 11p surrounding the splenic artery is dissected. The splenic artery is coil-shaped and tortuous, and therefore must be carefully identified. Otherwise it may be mistakenly ligated as lymph nodes. In addition, about 60% of patients have posterior gastric artery arising from the splenic artery. It should also be cautiously identified and ligated.

(00:11:36-00:11:46): dissection of lymph node station 12p

Any injury to the portal vein should be avoided.

(00:11:58-00:12:12): dissection of lymph node stations 1 and 3

Finally, the lymph nodes at the right side of the cardia and the lesser curvature of stomach are dissected. Ultrasonic scalpel can easily achieve the complete resection of lymph node stations 1 and 3. When performing ligation, the operator must ligate vessels at the anterior and posterior walls of the lesser curvature of stomach layer by layer to achieve the complete resection of lymph nodes in this region and the proper hemostasis.

Digestive tract reconstruction

B-1 Digestive tract reconstruction is performed after the specimen removal. The surgical field after dissection is displayed.

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Surgical Video

Laparoscopic spleen-preserving splenic hilar lymph node dissection for proximal gastric cancer

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Abstract: The video shows the operation of laparoscopic spleen-preserving splenic hilar lymph node dissection for advanced proximal gastric cancer in left approach, in order to achieve the effect of en-bloc resection. The technique simplifies the complicated operation procedure of laparoscopic spleen-preserving splenic hilar lymph node dissection and leads to popularization and promotion.

Keywords: Laparoscopic; spleen-preserving; splenic hilar lymph node dissection; proximal gastric cancer

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Chang-Ming Huang

Case report

A 47-year-old man (BMI 21.26 kg/m^2) was referred to our hospital for operation of gastric cancer. Endoscopic biopsy confirmed a histologic diagnosis of moderately differentiated adenocarcinoma. Abdominal computed tomography (CT) scan showed a thickening of gastric body and cardiac wall with perigastric lymph nodes enlarged. Laboratory testing revealed alfa-fetoprotein level of 1.81 ng/mL, carcino-embryonic antigen level of 1.8 ng/mL, carbohydrate antigen (CA) 199 level of 966.26 U/mL and CA 125 level of 80 U/mL. The patient was underwent laparoscopic spleen-preserving splenic hilar lymph node dissection for proximal gastric cancer in left approach in February 21, 2012. The final pathological diagnosis was advanced proximal gastric cancer with pathologic stage IIb (pT3N1M0). The patient recovered well after operation. First drip feeding occurred after 3 postoperative days, first oral fluid feeding occurred after 5 postoperative days and semi-liquid feeding occurred after 7 postoperative days. The patient left the hospital after 9 postoperative days and the hospital stay was 12 days. The patient is still alive with no evidence of recurrence.

Surgical technique

Patient is placed in the reverse trendelenburg position with head elevated about 15-20 degrees, and tilted left side up about 20-30 degrees. The surgeon stands between the patient's legs, the assistant and the camera operator are both on the patient's right side. At the start of the operation, the assistant places the great omentum behind the stomach to keep the visual field clear and pulls up the body of stomach toward upper right and tenses the splenogastric ligamen, the surgeon gently presses the tail of pancrea toward lower left, splenic hilum will be able to be show. The surgeon opens the pancreatic envelope, separates the membrane of body and tail of pancrea by ultrasonic to reach the posterior pancreas

Video 1 Laparoscopic spleen-preserving splenic hilar lymph node dissection for proximal gastric cancer.

space at the superior border of the pancreas and opens the vascular envelope of the end of the splenic artery. The surgeon dissects the lymphatic fatty tissue on the surface of inferior splenic lobar artery towards the lower pole of the spleen. The left gastroepiploic artery which issues from the inferior splenic lobar artery is vascularized, clamped with its origin cut. At this time, the assistant gently pulls up the lymphatic fatty tissue at the surface of the inferior splenic lobar artery. Surgeon's ultrasonic scalpel's non-function face closes the surface of the inferior splenic lobar artery. Starting from the root of left gastroepiploic artery, the surgeon uses the ultrasonic scalpel by the separation method of blunt and sharpness alternately, pushing, peeling and cutting, carefully dissects the lymphatic fatty tissue and vascularizes the inferior splenic lobar artery. With the inferior splenic lobar artery revealed gradually, 2 branches of short gastric arteries which issue from inferior splenic lobar artery are skeletoned and divided in their roots. As a result, the inferior splenic lobar artery is vascularized completely. Then, the fatty tissues and the gastric tissues are pulled up by the assistant; the surgeon dissects the lymphatic fatty tissue on the surface of the superior splenic lobar artery starting from the root of the artery towards the upper pole of the spleen, just as the procedure of vascularizing the inferior splenic lobar artery. 1 branch of short gastric artery which issues from superior splenic lobar artery is skeletoned and divided in its root. After the above procedure, the lymph node dissections in the front of splenic vessels are finished. Then the assistant pulls up the root of the inferior splenic lobar artery towards upper right. The lymphatic fatty tissue behind splenic vessels will be able to show and be pulled up by the surgeon towards lower left in order to keep in tension. The lymphatic fatty tissue behind splenic vessels will be dissected. Finally, a piece of gauze will be put behind splenic vessels at splenic hilum to indicate that the vessels are vascularized and the lymph nodes are dissected completely.

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Surgical Video

Radical proximal gastrectomy with modified double tracks anastomosis after preoperative chemotherapy for gastric cancer

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Abstract: A 65-year-old female patient with advanced gastric cancer received post-chemotherapy surgery. Gastroscopy showed a cauliflower-like mass was present at the lesser curvature of the gastric cardia, with its surface being damaged. An ulcer-like lesion was located from the lesser curvature of the lower cardia to the lesser curvature of the middle portion of the gastric body. The lesion was fragile and easy to bleed. Abdominal CT showed thickened walls of cardia, which was consistent with the diagnosis of "carcinoma of the gastric cardia". The TNM stage was considered to be T4aN2M0. He received chemotherapy before surgery. The cancer was down-staged after chemotherapy. The response evaluation was categorized as partial response (PR) according to RECIST criteria. Radical proximal gastrectomy with modified double tracks anastomosis were performed three weeks later. The intra-operative blood loss was little. Mild edema and adhesion of the local tissue were observed, but did not affect the surgical operation or prolong the surgical duration. No significantly enlarged lymph node was detected during intra-operative exploration. A limited number of small lymph nodes were dissected. The anastomotic tension was low, and the blood supply was good. Mild hypoproteinemia was detected after surgery and successfully corrected. No other complication occurred. The post-operative recovery was smooth. The postoperative pathology was ypT2N0M0 IB, and the tumor regression grade (TRG) was TRG 1.

Keywords: Gastric cancer; gastrectomy; jejunal interposition; preoperative chemotherapy

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Yong Li

A 65-year-old female patient experienced abdominal bloating, intermittent abdominal pain, and anorexia two weeks ago (January 31, 2012) without obvious causes. In a local hospital, she was diagnosed as "chronic gastritis" and received traditional Chinese medicine-based treatment. However, she responded poorly to the treatment, although her spirit and sleep were good and the urination and defecation were normal. No obvious weight change was found. ECOG score: grade I; body surface area =1.24 square meters. Routine blood, urine, and stool tests as well as biochemical tests at admission showed no abnormality. Tests for tumor markers showed: CA50, 15.19 IU/mL; CEA, 1.05 ng/mL; CA19-9, 675.2 IU/mL; and CA72-4, 6.89 U/mL. Electronic gastroscopy showed that a cauliflower-like mass was present at the lesser curvature of the gastric cardia, with its surface being damaged. An ulcer-like lesion was located from the lesser curvature of the lower cardia to the lesser curvature of the middle portion of the gastric body. The lesion was fragile and easy to bleed. It was covered with white fur, with its edge showing dam-like structures. The patient was diagnosed as with "adenocarcinoma" by gastroscopic biopsy (*Figure 1*). Abdominal CT showed thickened walls of cardia, which was consistent with the diagnosis of gastric cancer. The

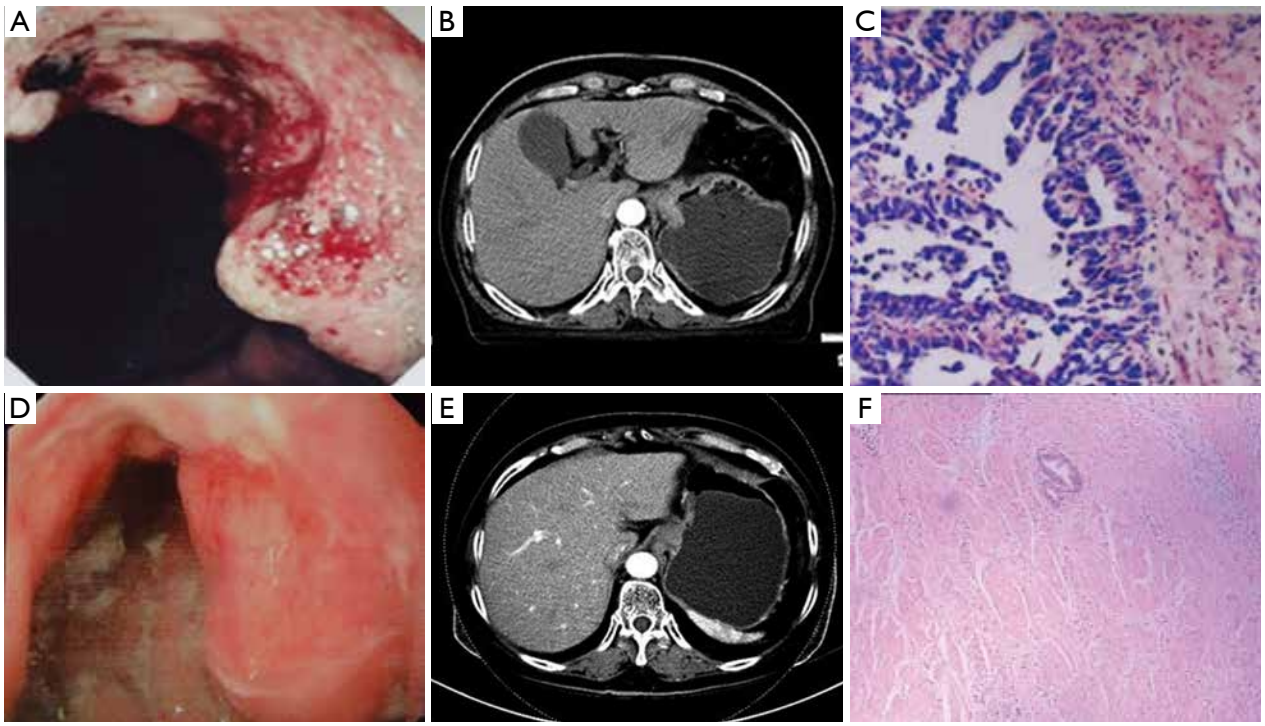

Figure 1 (A) Gastroscopic findings before chemotherapy; (B) CT findings before chemotherapy; (C) gastroscopic pathology before chemotherapy; (D) gastroscopic findings after chemotherapy; (E) CT findings after chemotherapy; (F) pathologic findings after surgery.

TNM stage was considered to be T4aN2M0 (*Figure 1*). After Multidisciplinary team (MDT) discussion, the patient was clinically diagnosed as cT4N3M0, phase IIIB, and Siewert type II. Since the lesions (locally advanced gastric cancer) were relatively large, pre-operative chemotherapy was provided employing the XELOX protocol (intravenous oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 1,000 mg/m^2 on day 1-14, for two cycles).

One week later, tests for tumor markers showed: CA50, 9.12 IU/mL; CEA, 2.58 ng/mL; CA19-9, 58.76 IU/mL; and CA72-4, 3.58 U/mL. A second gastroscopy was performed, which showed superficial ulcer at the gastric cardia. The ulcer was fragile and easy to bleed. The diagnosis was gastric cardia cancer, which was pathologically confirmed (*Figure 1*). CT performed one week after chemotherapy showed post-chemotherapy changes including the thickened gastric walls. The TNM stage was T4N0M0 (*Figure 1*).

The gastric cancer was down-staged after chemotherapy. The response evaluation was categorized as PR according to RECIST criteria. The surgery was actively prepared. Radical proximal gastrectomy with modified double tracks anastomosis were performed three weeks later (*Video 1*). An abdominal median incision was routinely made. No ascitic fluid, peritoneal planting, or liver metastasis was found during intra-operative exploration. The tumor (sized 2 cm × 3 cm × 1 cm) was located at the lesser curvature of the gastric cardia, invading the serous membrane. After the removal of greater omentum, gastrocolic ligament, and the anterior lobe of the transverse mesocolon, ligate the left gastroepiploic artery and the short gastric arteries; dissect lymph node stations 4sa and 4sb; ligate the right gastroepiploic vein, and dissect lymph node stations 6 and 4d. The greater curvature of stomach was dissociated. During the treatment of the lesser curvature of stomach, dissect lymph node station 12a; divide the right gastric vessels; and dissect lymph node station 5. The lesser curvature of stomach was dissociated. The stomach was cut at the one third of the line drawn between the larger and lesser curvatures of stomach, and the specimen from the residual tissue was collected. Dissect lymph node stations 8a, 9, 11p, and 11d. Divide the left gastric vein and the left gastric artery, and meanwhile dissect lymph node stations 7, 3, and 1. Dissociate cardia and esophagus, and dissect lymph node station 2. Divide esophagus about 4 cm above the dentate line. Place a T-25 circular stapler into the screw base. Jejunum, mesenteric membrane and its adjacent blood vessels were transected about 30 cm away from the ligament

Video 1 Radical proximal subtotal gastrectomy and jejunal interposition after preoperative chemotherapy for gastric cancer.

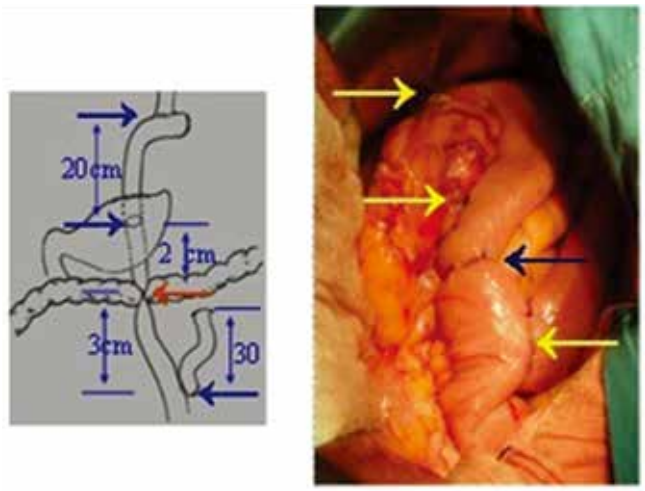

Figure 2 After digestive tract reconstruction.

of Treitz. The #29 and #24 stapler were inserted at the distal jejunum about 15-20 cm away from the esophageal-jejunum anastomosis and 5-10 cm away from the antimesenteric border. End-to-side anastomosis was performed between the distal jejunum and esophageal stump across the anterior side of the colon. The jejunal stump was closed using the stump stapler. The seromuscular layer was suture-buried. The lesser curvature of the residual stomach was sutured. Side-to-side anastomosis was performed between the posterior wall of the larger curvature and the distal jejunum using the stapler about 15-20 cm away from the esophageal-jejunum anastomosis. Braun's anastomosis was performed between the proximal jejunum and the distal jejunum about 5-10 cm away from the gastrointestinal anastomosis. After the jejunal stump was closed using the stump stapler, the seromuscular layer was suture-buried. The intestinal tract 3 cm below the gastrointestinal anastomosis was ligated with a 4-0 silk suture to close the access. All the edges of the anastomosis made by the stapler were continuously sutured. The mesenteric gap was also closed. The surgery was smooth. Mild edema and adhesion of the local tissue were observed. Exudate at the cutting site increased after electric knife or HIFU treatment. The intraoperative blood loss was little. No significantly enlarged lymph node was detected during intra-operative exploration. A limited number of small lymph nodes were dissected. D2 lymphadenectomy was smoothly completed. Satisfactory anastomoses were achieved. The anastomotic tension was low, and the blood supply was good (*Figure 2*).

Mild hypoproteinemia was detected after surgery and successfully corrected after symptomatic management. No other surgery-related complication occurred. She recovered well and was smoothly discharged. Post-operative pathology: Morphology: a 2 cm × 3 cm × 1 cm superficial ulcer was visible at the lesser curvature of cardia. Its cutting plane was gray and fragile. Histochemistry: CK(+). A small number of degenerative cell variants deep inside deep muscle layer were seen in the tumor bed, and the tumor regression grade (TRG) was TRG 1. Clinically, the lower stump was negative. Detection for positive lymph node showed: CK, negative; station 1, 0/1 (the remaining three were soft tissues); station 2, 0/3; station 6, 0/6; station 11p, 0/2; station 9, 0/1 (the remaining one was soft tissue); station 4sa, 0/5; station 4sb, 0/2; station 3, 0/4 (the remaining one was soft tissue); station 8a, 1; station 11d, 3; station 5, 1; station 19, 1; station 20, 1; station 7, 1; station 4d, 1; station 12a, one soft tissue (*Figure 1*).

After the treatment, the patient received 6 cycles of adjuvant XELOX, during which mild myelosuppression was observed, which was improved after active interventions. Currently, her quality of life is good, and no relapse or metastasis has been noted.

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Surgical Video

Totally laparoscopic distal gastrectomy reconstructed by Roux-en-Y with D2 lymphadenectomy and needle catheter jejunostomy for gastric cancer

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Abstract: A case of 69-year-old male patient with gastric cancer was reported in this article, who previously received endoscopic submucosal dissection (ESD) suspected as early gastric cancer and then underwent totally laparoscopic distal gastrectomy with D2 lymphadenectomy after the pathologic result of ESD showed positive resection margin. Roux-en-Y reconstruction was used in this patient with Type 2 diabetes mellitus, which was demonstrated to be helpful for maintaining glucose homeostasis in diabetes. Needle catheter jejunostomy (NCJ) was carried out together, which was used for nutrition support therapy in early postoperative period and during expected chemotherapy after surgery.

Keywords: Totally laparoscopic distal gastrectomy; Roux-en-Y reconstruction; D2 lymphadenectomy; needle catheter jejunostomy (NCJ); gastric cancer

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Jian-Chun Yu

Patient information

A 69-year-old male patient was admitted to Department of General Surgery, who complained for continuing dull pain in subcostal area accompanied by anorexia and emaciation for five months. Gastroscope (*Figure 1*) carried out when the patient came to see gastroenterology physician in our hospital one month ago showed an apophysis lesion on the front wall of gastric antrum along lesser curvature with central depression and overlying white moss and no infection of helicobacter pylori. Biopsy (*Figure 2*) showed chronic inflammation in gastric mucosa accompanied by mucosal erosion and severe intestinal metaplasia and high grade intraepithelial neoplasia in partial epithelial. Endoscopic ultrasonography (EUS) (*Figure 3*) showed middle and low echo changes and 0.6 cm thickness in the mucosal layer of the lesion with a complete submucosa. Early gastric cancer was suspected. PET-CT (*Figure 4*) showed increased metabolism in gastric antrum with the SUV value of 1.0-1.5 and no tumor metastasis. Tumor markers including CEA, CA199 and CA724 were normal. The patient was first admitted to Department of Gastroenterology two weeks ago and endoscopic submucosal dissection (ESD) (*Figure 5*) was carried out. Pathologic result (*Figure 6*) showed a moderately differentiated gastric adenocarcinoma involving the submucosa and cancer cells seen in the bottom margin with a negative circumferential margin. Then the patient was transferred to Department of General Surgery for surgical

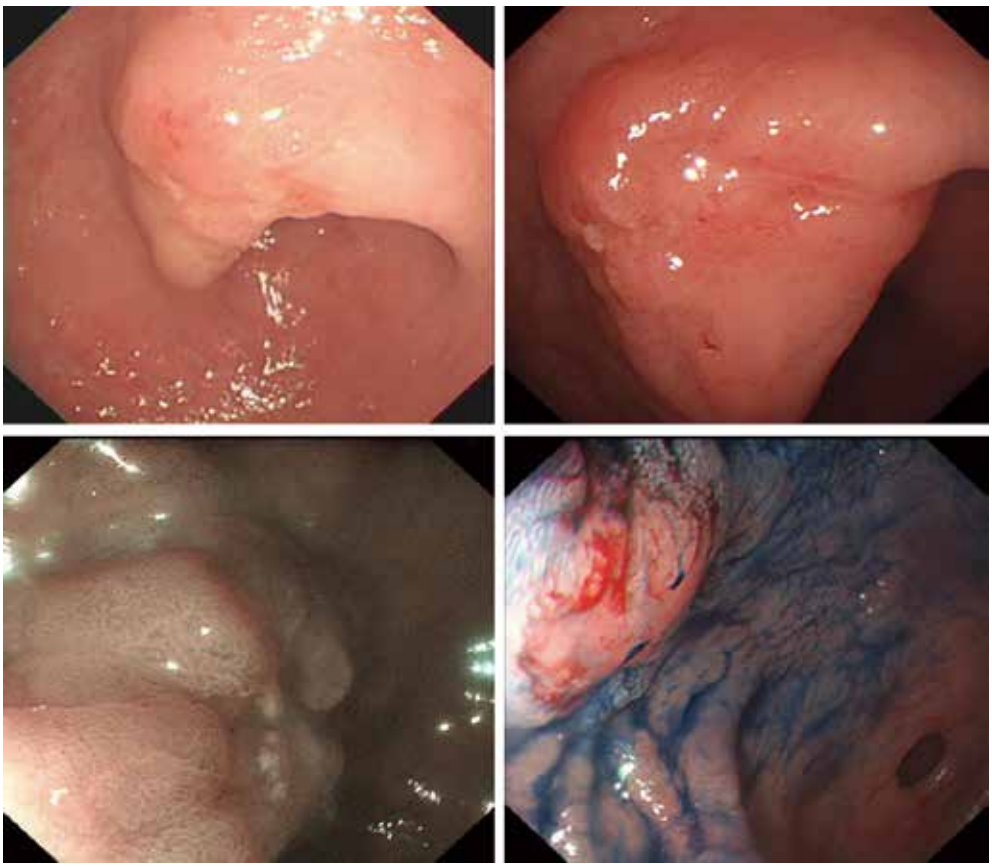

Figure 1 Gastroscope showed an apophysis lesion on the front wall of gastric antrum along lesser curvature with central depression and overlying white moss.

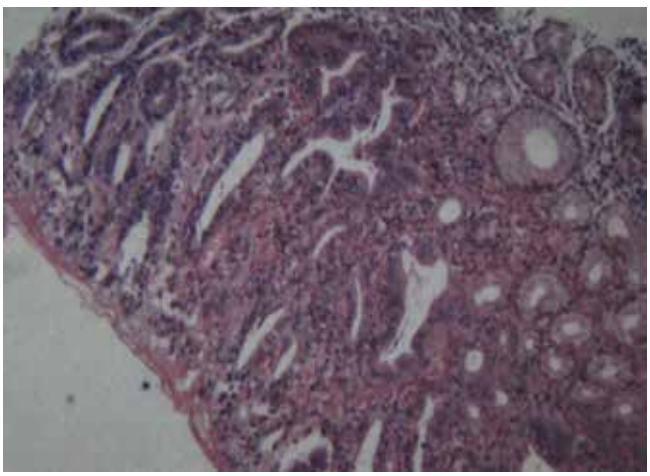

Figure 2 Gastroscopic biopsy showed chronic inflammation in gastric mucosa accompanied by mucosal erosion and severe intestinal metaplasia and high grade intraepithelial neoplasia in partial epithelial.

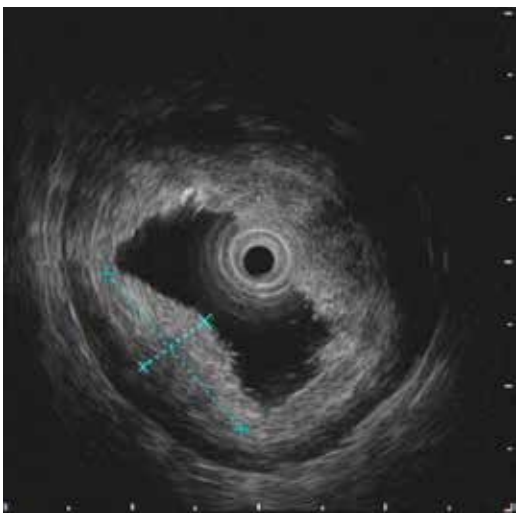

Figure 3 Endoscopic ultrasonography (EUS) showed middle and low echo changes and 0.6 cm thickness in the mucosal layer of the lesion with a complete submucosa.

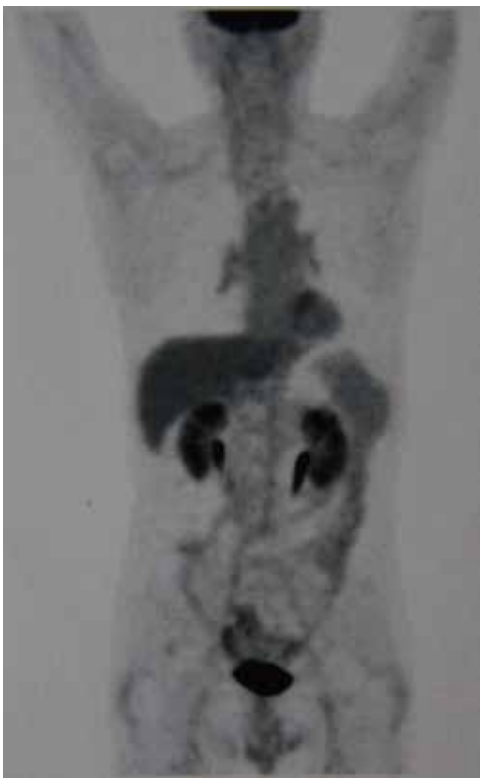

Figure 4 PET-CT showed increased metabolism in gastric antrum with the SUV value of 1.0-1.5 and no tumor metastasis.

treatment. The patient's past history included hypertension for 20 years controlled well by oral drugs and Type 2 diabetes mellitus for 11 years controlled well by insulin. There was no positive finding in physical examination. Further examinations were carried out after the admission for the preparation of surgery. Routine blood test showed hemoglobin of 119 g/L. Fecal occult blood test was positive. Biochemical tests and coagulation function test were normal. Echocardiography showed enlargement of both atriums and right ventricle and mild tricuspid regurgitation with mild pulmonary hypertension. Lung function test showed obstructive ventilatory dysfunction and decreased diffusion function. Three-dimensional reconstructive CT (*Figure* 7) showed thickened wall in gastric antrum and visible enlarged lymph nodes along lesser curvature.

Plan of surgical strategy

According to the pathologic result of ESD which showed tumor invasion to submucosa or perhaps more deep and suspected lymphatic metastasis from CT scan, laparoscopic distal gastrectomy with D2 lymphadenectomy was arranged. Intraoperative gastroscope was also planned to help locate the tumor position accurately and confirm the extent of resection because of relatively early T staging of tumor.

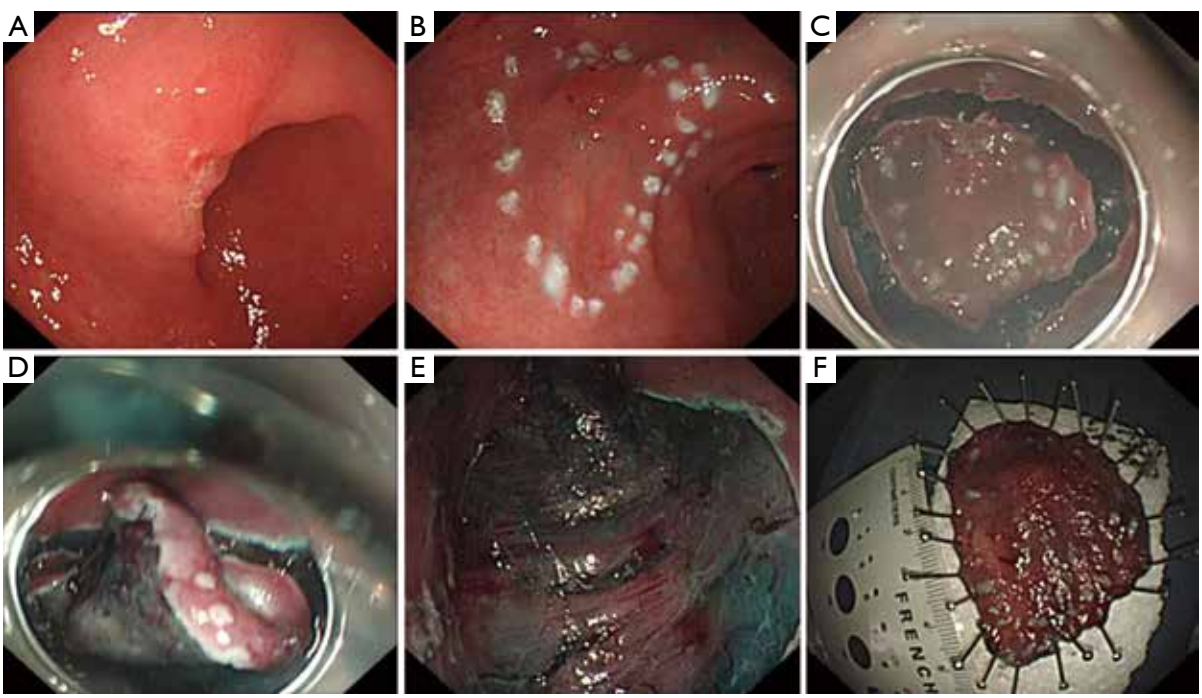

Figure 5 The process of endoscopic submucosal dissection (ESD).

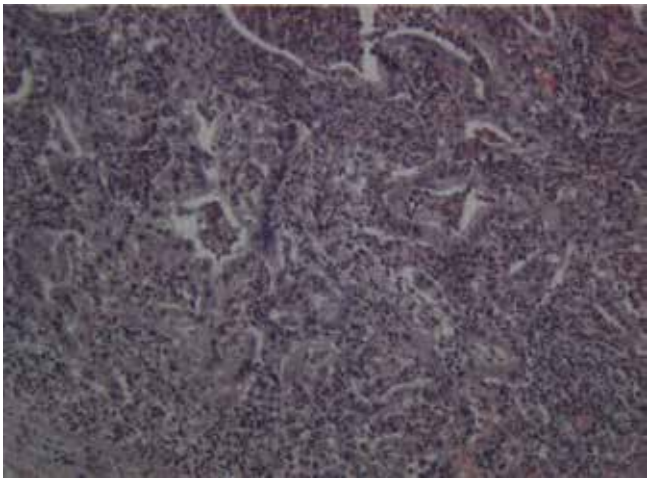

Figure 6 Pathologic result of ESD showed a moderately differentiated gastric adenocarcinoma involving the submucosa and cancer cells seen in the bottom margin with a negative circumferential margin.

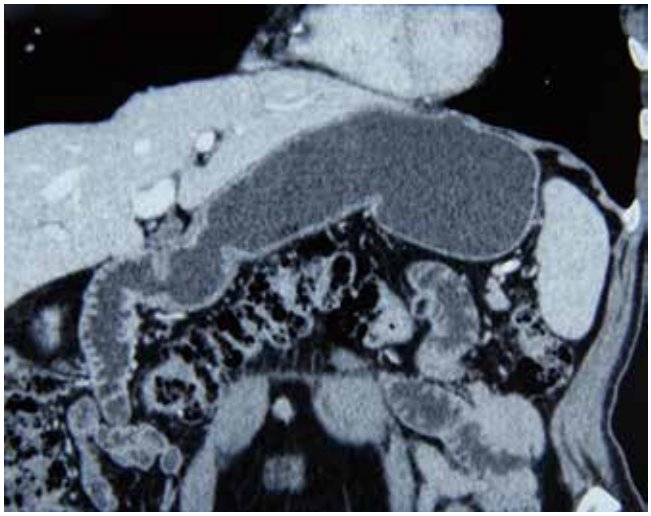

Figure 7 Three-dimensional reconstructive CT showed thickened wall in gastric antrum and visible enlarged lymph nodes along lesser curvature.

Video 1 Totally laparoscopic distal gastrectomy reconstructed by Roux-en-Y with D2 lymphadenectomy and needle catheter jejunostomy for gastric cancer.

Roux-en-Y reconstruction was demonstrated to be helpful for maintaining glucose homeostasis in diabetes (1), so it was chosen in this patient with Type 2 diabetes mellitus. NCJ was arranged for nutrition support therapy in early postoperative period and during expected chemotherapy after surgery according to suspected lymphatic metastasis from CT scan (2).

Operating procedure (*Video 1*)

The operation was performed in a regular way. After establishment of pneumoperitoneum and placement of laparoscopic instruments, adhesion between gastric antrum and gallbladder was revealed and no organic or peritoneal metastasis was seen during exploration. There was no gastric serosal involvement due to the tumor. Enlarged lymph nodes were detected along lesser curvature. ESD wound was located at the gastric angle by intraoperative gastroscope and distal gastrectomy was confirmed. Gastrocolic ligament was divided toward the splenic flexure of colon until cutting some of short gastric arteries and then toward the liver flexure until 3 cm distal to pylorus. Anterior lobe of transverse mesocolon and capsula pancreatic were removed until the superior margin of pancreas. The right gastroepiploic vessels were dissected and No.6 and No.14 lymph nodes were removed. The hepatoduodenal ligament was then dissected and No.12 Lymph nodes were cleaned. The right gastric artery was exposed and cut off and No.5 and No.8 lymph nodes were dissected. The left gastric vessels were exposed and cut off and No.7, No.9 and No.11 lymph nodes were removed. The soft tissues along lesser curvature and the right side of cardia including No.1 and No.3 lymph nodes were removed. The omentum along greater curvature including No.4 lymph nodes was divided. Gastroscope was used again to help

determine the proximal cutting edge. Duodenum was cut off at 3 cm distal to pylorus by an endocutter. Jejunum was cut off at 40 cm distal to the ligament of Treitz. A precolonic anastomosis was made between the distal stump and posterior wall of stomach by an endocutter. The distal stomach with omentum was cut off at 6 cm proximal to the tumor. An anastomosis was made between the proximal stump of jejunum and the distal jejunum at 40 cm distal to the gastrojejunal anastomosis. NCJ was performed at 40 cm distal to the jejunojejunal anastomosis through the port on left upper quadrant. The whole resected specimen was got out of abdomen in a specimen bag through the prolonged 3 cm incision on right upper quadrant. The abdomen was irrigated with distilled water and no evidence of bleeding noted. A drainage tube was positioned adjacent to the gastrojejunal anastomosis through the incision on right upper quadrant. All the wounds were closed carefully.

Postoperative management

Postoperative treatment included fasting, fluid infusion and acid suppression. The blood pressure and sugar levels were monitored and controlled well. A small amount of enteral nutrition was given through NCJ tube on the first day after surgery. The volume of enteral nutrition was increased gradually and fluid infusion was reduced. The patient began to drink and eat on the fifth day after surgery and the drainage tube was removed. The patient recovered well and was discharged one week after surgery. The final pathologic result showed no residual cancer or lymph node metastasis. Inflammatory cells infiltration was seen in the ESD area. There was lymph node reactive hyperplasia in totally twenty-five resected lymph nodes (No.1 0/3, No.3 0/2, No.4 0/4, No.5 0/0, No.6 0/3, No.7 0/3, No.8 0/1, No.9 0/0, No.11 0/0, No.12 0/5, No.14 0/4). Immunohistochemical stain showed AE1/AE3(-), CD68(+), CEA(-) and Ki-67 index 15%. The final pathologic staging is pT1bN0M0 according to the pathologic result of ESD which showed tumor invasion to submucosa. Chemotherapy was not recommended and the patient followed up regularly in outpatient clinic.

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Surgical Video

Laparoscopy-assisted D2 radical distal gastrectomy

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Abstract: This video presents the whole process of treating a patient with early gastric cancer (T1N0M0) with laparoscopy-assisted D2 radical distal gastrectomy. A 36-year-old male patient was admitted due to "dull pain and discomfort in the upper abdomen". Gastroscopy indicated a poorly differentiated adenocarcinoma (1 cm × 1 cm in size) in gastric antrum. A diagnosis of "early gastric cancer" was made. On October 24, 2012, he received laparoscopy-assisted D2 radical distal gastrectomy under general anesthesia. The surgical procedures included exposure and disconnection of perigastric vessels, dissection of gastric lymph nodes, and gastrointestinal (GI) tract reconstruction. The surgery was smooth, and the patient recovered well from the surgery. By presenting this video, we wish to share our knowledge and experiences in endoscopic techniques with all the colleagues.

Keywords: Gastric cancer; laparoscopy-assisted; D2 radical distal gastrectomy

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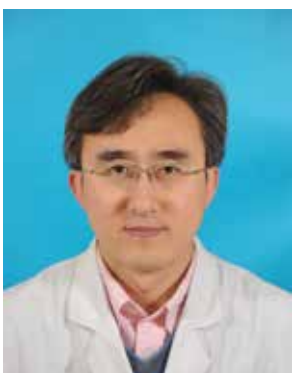

Cheng-Xue Dang

Video description

The first case of radical resection of gastric carcinoma was completed in Japan in 1991. The past two decades have witnessed the advances in gastric cancer research, improvement of laparoscopic equipment, training in laparoscopic surgery, and increased awareness of cancer among the general public. Up to now the endoscopic techniques have been successfully introduced in the surgical treatment of cancer. Compared with the conventional open D2 radical gastrectomy, the laparoscopy-assisted D2 radical gastrectomy has many advantages: clear microscopic anatomy; less blood loss, small abdominal trauma, and quick post-operative recovery. However, due to the use of equipment, the doctor's hands do not touch the human body directly, which requires a better anatomic knowledge. Currently, laparoscopy-assisted radical gastrectomy for gastric cancer has become increasingly common. Along with the scientific development and the increased demand among the patients for better quality of life, minimally invasive endoscopic techniques will play more important roles.

General data

A 36-year-old male patient was admitted due to "dull pain and discomfort in the upper abdomen". Gastroscopy indicated a poorly differentiated adenocarcinoma (1 cm × 1 cm in size) near gastric antrum. A diagnosis of "early gastric cancer" was made. Preoperative examinations showed that there were no definite contraindications for surgery.

Video 1 Laparoscopy-assisted D2 radical distal gastrectomy.

Laparoscopy-assisted radical distal gastrectomy was then scheduled.

Surgical procedures

Routine preparation for laparoscopy was made after the patient was satisfactorily anesthetized. Abdominal exploration showed that the abdominal parietal and visceral layers were not obviously adhered, no metastasis was found in pelvic/abdominal aortic lymph nodes or mesenteric lymph nodes, and the liver surface was smooth. Since the findings were consistent with the pre-operative diagnosis, laparoscopy-assisted D2 radical distal gastrectomy was performed (*Video 1*): the gastrocolic ligament was divided along the left border of the transverse colon to expose the transverse mesocolon. After the anterior lobe of the transverse mesocolon was resected from left to right, dissect the anterior lobe of pancreas envelope, during which the middle colic artery must be carefully protected. Superior mesenteric artery and vein was found through the middle colic artery, and the gastrocolic trunk of Henle was exposed. After the right gastroepiploic vein and artery were exposed and divided, the Group 6 lymph nodes were dissected. After the gastroduodenal artery was dissociated, the gastroduodenal artery, right gastric artery, and common hepatic artery and its branches were further dissected. The right gastric artery and vein were then exposed and divided. The portal vein was dissociated inside the hepatoduodenal ligament, and the groups 5 and 12a lymph nodes were dissected. The gastric antrum and the inferior-posterior wall of duodenal posterior wall were dissected, during which damage to structures within the hepatoduodenal ligament due to surgical instrument should be avoided. Celiac trunk can be found along the common hepatic artery. After the transection of left gastric artery and vein, the groups 7, 8, and 9 lymph nodes were dissected, followed by the dissection of group 11p after the dissociation of splenic artery and vein, during which any variation of celiac artery and splenic artery should be considered. Beginning from the lower pole of the spleen, divide the greater curvature of stomach to the right upper side. After the left gastroepiploic vein was divided and ligated, open the gastrosplenic ligament, transect one or two short gastric arteries inside the ligament with HIFU and then dissect group 4sb lymph node. Divide the hepatogastric ligament and the anterior lobe of hepatoduodenal ligament, dissect the groups 1 and 3 lymph nodes, and then thoroughly dissociate the upper wall of duodenum and gastric antrum. A 4-6-cm upper abdominal median incision was made at the beginning of the operation. A specimen retrieval bag was used to protect the incision. Transect the duodenum under the pylorus. Radical distal gastrectomy was performed after the distal stomach was pulled out of the peritoneal cavity. Billroth-I anastomosis was performed for the residual stomach and the duodenal stump. Stop the bleeding, indwel the drainage tube, and then suture the incision.

Post-operative pathology and staging

The dissected lymph nodes included: lymph nodes at lesser curvature of the stomach, 14; lymph nodes at greater curvature of stomach, 4; supra-pyloric lymph nodes, 2; and sub-pyloric lymph nodes, 6. The TNM stage was $T_1N_0M_0$.

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Surgical Video

Laparoscopic assistant distal radical gastrectomy

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Abstract: As a minimally invasive procedure for gastric cancer, laparoscopy-assisted radical gastrectomy has increasingly been accepted, particularly when applied for the early gastric cancer. While its long-term effectiveness for the advanced gastric cancer remains unclear, its technique has become mature enough to meet the requirements of open surgery. In this video, laparoscopic assistant distal radical gastrectomy was performed on a 32-year male patient. The post-operative pathology confirmed that 8 of 25 lymph nodes were positive. The final TNM stage was pT3N3M0 and the pathologic stage was IIIb. The operation lasted 3 hours and 10 minutes. The intra-operative blood loss was about 50 mL and the incision length was 7 cm.

Keywords: Gastric cancer; laparoscopy-assisted radical gastrectomy; minimally invasive procedure

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Yingwei Xue

Video description

As a minimally invasive procedure for gastric cancer, laparoscopy-assisted radical gastrectomy has increasingly been accepted, particularly when applied for the early gastric cancer. While its long-term effectiveness for the advanced gastric cancer remains unclear, its technique has become mature enough to meet the requirements of open surgery.

In this video laparoscopic assistant distal radical gastrectomy was performed on a 32-year male patient (*Video 1*). He had a body mass index (BMI) of 26. The pre-operative routine examinations showed a gastric antral cancer located at the lesser curvature. The pre-operative stage was $cT_{1\text{-}2}N_{1\text{-}2}M_0$. The intra-operative exploration showed that the cancer did not penetrate the serosal layer, and no distant metastasis was found. During the surgery, the principles of open surgery were followed: no touch, en bloc, and extracapsular resection (dissociation of the larger/lesser omental bursa and pancreatic capsule). The extended (D2) lymph node dissection was performed. Furthermore, based on the patient's specific condition, the lymph node stations 14v and 18 were dissected. Therefore, the final dissected lymph nodes included stations 1, 3, 4sb/4d, 5, 6, 7, 8a, 9, 11p, 12a, 14v, and 18. The post-operative pathology confirmed that 8 of 25 lymph nodes were positive. The final TNM stage was pT3N3M0 and the pathologic stage was IIIb. The operation lasted 3 hours and 10 minutes. The intra-operative blood loss was about 50 mL and the incision length was 7 cm. He was able to ambulate 12 hours after surgery, and anal exhaust occurred 41 hours later. After 80 hours, He began taking liquid diet. He was discharged 8 days after surgery; two weeks later, he began to receive adjuvant chemotherapy.

Video 1 Laparoscopic assistant distal radical gastrectomy

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Our experiences from this case are: (I) Upon the beginning of the surgery, open the lesser omental bursa under the gastric cardia immediately to place grasping forceps to fence off the left hepatic lobe; if needed, dissect the celiac trunk region from the posterior approach to make the dissociated stomach hung in the abdominal wall. (II) During the dissection of lymph nodes in the the hepatoduodenal ligament region, the combination of the posterior approach with the anterior approach will make the dissection simpler and safer.

Acknowledgements

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Surgical Video

D2 distal subtotal gastrectomy for antral carcinoma

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Abstract: A 53-year-old Chinese man was pre-operatively diagnosed with adenocarcinoma of gastric antrum (moderately differentiated). The tumor was preoperatively assigned to $T_{2\text{-}3}N_{1\text{-}2}M_0$. Preoperative evaluation of the patient allowed him to undergo surgical treatment. In advanced gastric cancer, D2 lymphadenectomy was needed. Therefore, distal subtotal gastrectomy with D2 lymphadenectomy was adopted. During surgical exploration, abdominal or pelvic metastasis was not found and local invasion was not observed. The distal gastrectomy with Billroth I reconstruction was performed, two thirds of the stomach was resected. Lymph nodes of group 1, 3, 4, 5, 6, 7, 8, 9, 11P, and 12 were dissected. The whole operation lasted about 3 hours and intraoperative blood loss was about 100 ml. The patient recovered well after the surgery.

Keywords: D2 distal subtotal gastrectomy; antral carcinoma

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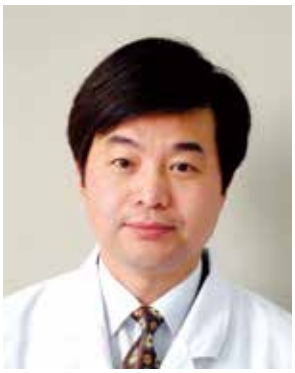

Bing Xiong

Video description

A 53-year-old Chinese man presented to the Department of Surgical Oncology in Zhongnan Hospital with 2-months history of upper abdominal pain and discomfort. He underwent endoscopy with biopsies. Endoscopic visualization of the gastric antrum revealed an ulcer about 5cm in diameter. Pathological biopsy confirmed that was gastric carcinoma. The patient was then hospitalized for treatment on April 16, 2013. At admission, physical examination showed upper abdominal lighter tenderness. Jaundice was not observed. No enlarged lymph nodes were noted; the liver and spleen was impalpable; abdominal mass was not palpated. Laboratory evaluation included a complete blood count, urine and stool test, the liver and renal function test, all of which were normal. EKG was normal. Serum tumor marker test showed that CEA was 84.5 ng/mL, CA19-9 was 61.6 μ/mL. Several imagine procedures were performed; the results of chest computed tomography (CT) and pelvic B ultrasound were normal; upper abdominal CT plus three-dimensional reconstruction showed: gastric antrum and wall thicken, tumor possibly had invaded the gastric muscularis; meanwhile, enlarged perigastric and retroperitoneal lymph nodes were observed (*Figure 1A*, *B*). The preoperative TNM stage was T2 or T3N1 or N2M0. During surgical exploration, no metastasis was found in pelvic cavity, abdominal cavity and liver; the tumor located in the gastric antrum, sized about 3 cm in diameter; the serous membrane was normal. After exploration, distal subtotal gastrectomy with D2 ymphadenectomy was performed (*Video 1*, *Figure 1C*, *D*, *Figure 2*, *Figure 3A*, *B*, *C*). Postoperative pathological examination showed: the tumor sized about 5 cm × 4 cm × 3 cm, protruded into the gastric cavity and infiltrated the deep muscularis(*Figure 3D*); pathological classification was gastric adenocarcinoma

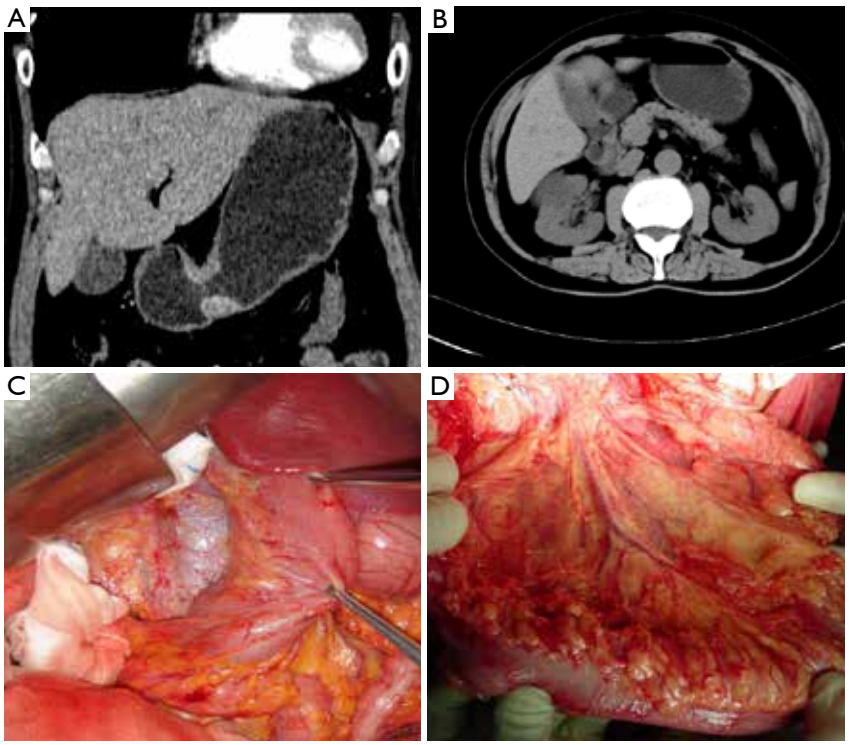

Figure 1 (A) Three-dimensional reconstruction revealed that the tumor was located at gastric antrum and invaded the muscular layer; however, no enlarged perigastric lymph node was observed; (B) sectional view showed the relationship between the pancreas and the stomach. No enlarged lymph node was found behind the peritoneum; (C) COX incision; (D) removal of the anterior lobe of transverse mesocolon.

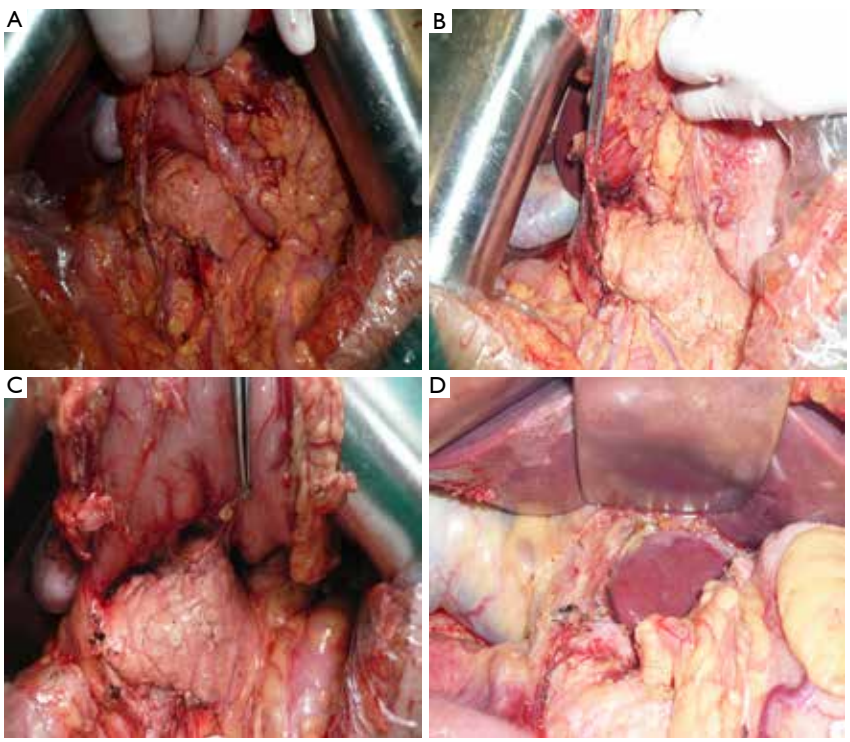

Figure 2 (A) Ligation of right gastroepiploic vein to dissect lymph node station 6; (B) decortication of the pancreas; (C) ligation of the right gastroepiploic artery; (D) dissection of lymph node stations 5 and 12.

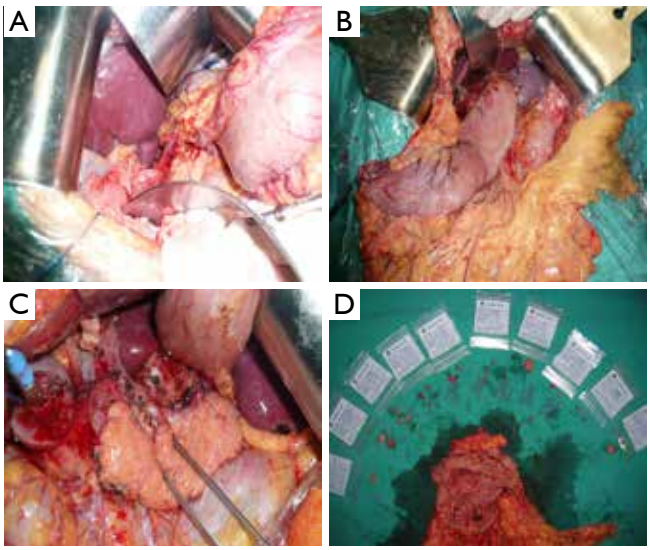

Figure 3 (A) Dissection of lymph node stations 7, 8, 9, and 11P; (B) dissection of lymph node stations 1, 3 and 4; (C) the surgical field following dissection; (D) postoperative specimens.

Video 1 D2 distal subtotal gastrectomy for antral carcinoma.

(moderately differentiated); Immunohistochemical test showed CerbB2 was positive (3+) and ki67 was about 95% positive; all the surgical margins were negative. Metastasis was found in several groups of dissected lymph nodes (group 7 4/4, group 6 1/2 and group 12 1/1). Group 5 was fiber adipose tissue without findings of carcinoma. According to the results of the postoperative pathological examination, the pathological stage was assigned to T2N2M0. The patients recovered well after surgery. Post-operative adjuvant therapy was provided.

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Surgical Video

Laparoscopy-assisted radical total gastrectomy plus D2 lymph node dissection

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Abstract: The process of laparoscopic radical total gastrectomy plus D2 lymph node dissection for a patient with gastric body cancer was recorded in this video. This was a female patient with gastric body cancer in the preoperative stage of CT2N0M0. The laparoscopic radical total gastrectomy plus D2 lymph node dissection was performed on October 13, 2011 after no operative contraindication was found. The operation process included several steps: surgical exploration, gastrocolic ligament separation, subpyloric lymph node dissection, dissection of superior margin of pancreas, gastrocolic ligament separation, perisplenic hilar dissection, and digestive tract reconstruction. The operation was successful and the postoperative recovery was good. The post-operative pathology reported pT3N0M0.

Keywords: Gastric cancer; gastrectomy; D2 lymph node dissection

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Chaohui Zheng

Case report

A 59-year-old woman name was admitted to our hospital due to repeated oppressive pain in upper abdomen for half a year. No melena, vomiting, hematemesis and distension were reported by the patient. The outpatient gastroscopy in our hospital indicated gastric body cancer one week ago. The patient was scheduled to be hospitalized as with "gastric cancer". She had high spirit, with normal appetite, good sleep, and normal urination and defecation. No obvious weight change was found with T 36.8 ℃, P 78/min, R 18/min, BP 120/80 mmHg. She was conscious, without any appearance of emaciation and anemia. No left supraclavicular superficial lymph nodes were palpable. Cardiopulmonary auscultation showed normal results. The abdomen was flat. Gastrointestinal type was not seen. There was no rebound tenderness on abdomen. No mass was palpable. The liver and spleen were not palpable under the ribs. The Murphy's sign was negative. Shifting dullness was negative. Bowel sounds were heard 4-5 times/min. Digital rectal examination: No abnormality was seen in the anus. Rectal mucosa was smooth and no mass was touched. No mass was touched in the rectouterine fossa. No bloodstain was seen on the fingertip. Three routine examinations and full set of blood biochemical tests showed normal results. Ultrasound gastroscopy: poorly differentiated adenocarcinoma of ulcer type in the high position of lesser curvature, sized 1.0 cm; the cancer invaded the muscle layer. Chest X-ray film: no obvious consolidation was seen in lungs. Color Doppler ultrasound of abdomen: mild fatty liver; no enlarged lymph nodes were seen around the stomach. CT scan: thickening of the gastric wall in the high position of lesser

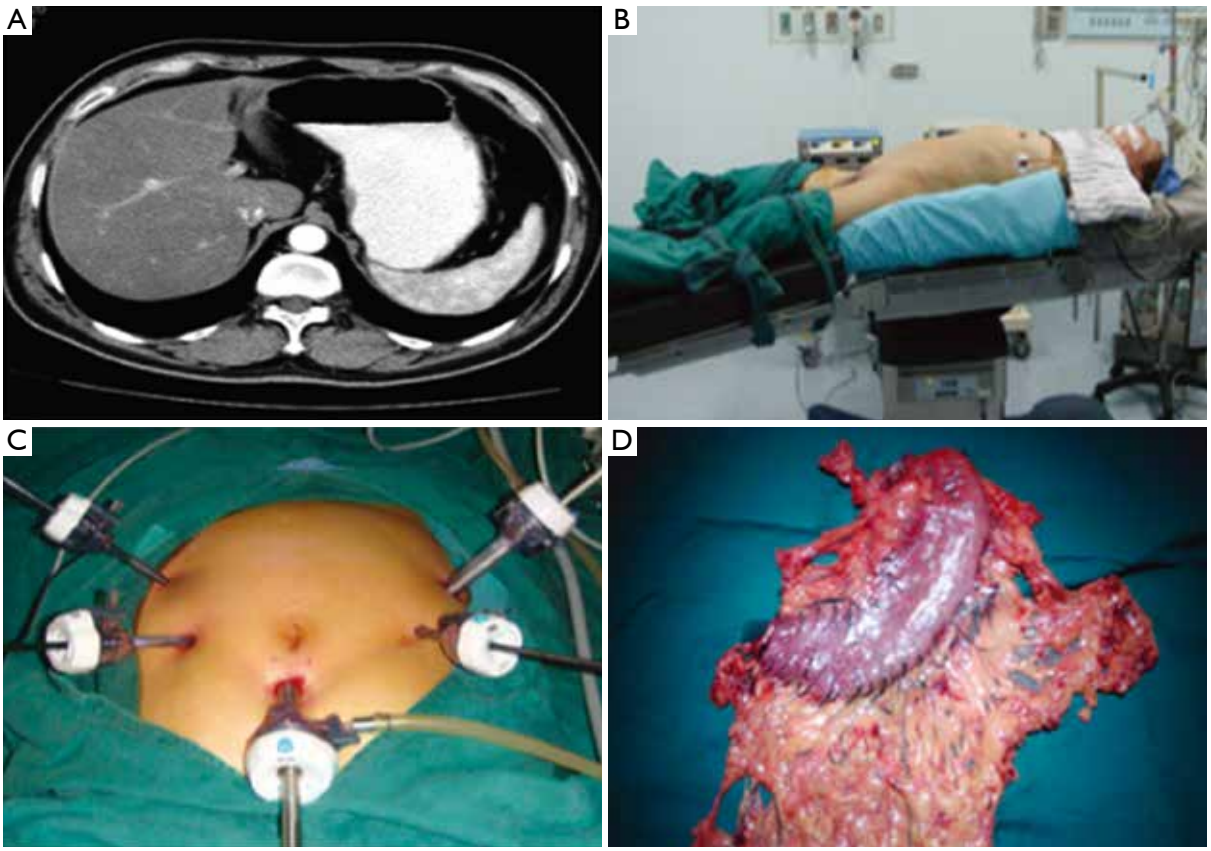

Figure 1 (A) Preoperative CT scan; (B) patient's position; (C) trocar location; (D) postoperative specimen.

Video 1 Laparoscopy-assisted radical total gastrectomy plus D2 lymph node dissection.

curvature (about 1.0 cm); no enlarged retroperitoneal lymph nodes were seen (*Figure 1*). Preoperative diagnosis: gastric body cancer (stage: cT2N0M0). The patient was indicated for surgical treatment and had no surgical contraindications. The laparoscopy-assisted radical total gastrectomy + D2 lymph node dissection was then performed on October 13, 2011.

Video description

Patient's position

The patient was placed supine and in a split-legged position, with the head slightly higher of 15° (*Video 1*).

Operator's positions

The surgeon stood at the left side of the patient, the assistant at the right side of the patient, and the camera holder between her two legs.

Trocar location

Five-hole method was adopted. An annular tube about

10 mm in diameter was placed 1 cm under the umbilicus as the observation hole; a 12-mm cannula is inserted 2 cm to the left anterior axillary line under the costal margin as the main operation hole, and a 5-mm cannula is placed in the left midclavicular line 2 cm above the umbilicus as the traction hole. Two annular tubes about 5 mm in diameter were placed respectively on the right collarbone midline 2 cm above the umbilicus and on the right axillary front 2 cm under the costal margin as the operation holes for the assistant.

Surgical steps

Exploration and separation of gastrocolic ligament

No ascites was found in abdominal cavity and no implantation metastasis nodule was seen in pelvic cavity, omentum and mesentery. No metastatic lesion was found on the liver surface. The tumor was located in the lesser curvature and did not invade the serous membrane. The greater omentum was put on the transverse colon, lifted by the assistant using two non-invasive grasping forceps and simultaneously unwrapped to both sides. The transverse colon was pulled to the opposite direction by the operator using a non-invasive grasping forceps with the left hand to form a triangle traction and keep the tension of the greater omentum. The greater omentum was cut in the avascular zone of superior colon margin near the central part of the transverse colon using an ultrasonic scalpel. After that, the incision was extended to the splenic flexure of colon on the left side and to the hepatic flexure of colon on the right side. The transverse colon margin of the greater omentum was then completely transected.

Separation and dissection of inferior regions of the pylorus

The greater omentum was lifted by the assistant and the transverse mesocolon was pressed by the operator to form certain tension between them and reveal the space formed by the loose connective tissue between the anterior lobe and posterior lobe of the transverse mesocolon. The blunt separation and sharp separation were alternatively used to separate the anterior lobe of the transverse mesocolon using an ultrasonic scalpel along the space from the right margin of the transverse colon to the descendant duodenum on the right side, to the splenic flexure of colon on the left side and to the inferior margin of pancreas on the head side. The middle transverse colon vein was exposed by separating the anterior lobe of the transverse mesocolon. The point of middle colon vein joining the superior mesenteric vein was exposed by separating along the surface of the middle colon vein to the inferior margin of pancreas. The adipose and lymphoid tissues were separated along the anatomic space on the surface of the superior mesenteric vein by the ultrasonic scalpel to the inferior margin of pancreas on the head side. After the retro-pancreatic space was found, the lymphoid tissue was then separated to the left margin of pancreas on the left side and to the point of joining the superior mesenteric vein on the right side. After that, the separation was continued with the ultrasonic scalpel along the anatomic space on the surface of Henle's axis on the right side to expose the point of the right gastroepiploic vein joining the right/auxiliary right colon vein. The gastric antrum was turned over to the head side and the separated adipose and lymphoid tissue was lifted up by the assistant. And then the separation was continued with the ultrasonic scalpel from the point of the superior pancreas-duodenal vein joining the right gastroepiploic vein to the level of superior margin of pancreatic head along the surface of the right gastroepiploic vein. The completely isolated right gastroepiploic vein was then pulled to the lateral side to be separated from the pancreas by the assistant. The right gastroepiploic vein was transected by the operator on the superior side of the point of super-anterior pancreas-duodenal vein joining the right gastroepiploic vein. The right gastroepiploic vein was then transected after the vascular clamp was used. After that, the gastric antrum was pulled to the head side and the duodenal bulb was pushed to the lateral side by the assistant. The pancreas was lightly pressed by the operator to expose the avascular space between the posterior pancreatic wall and the pancreatic head. And the gastroduodenal artery was exposed by the separation with the ultrasonic scalpel along the space. The root of right gastric artery was exposed after the terminal of gastroduodenal artery was isolated. At this point, the adipose and lymphoid tissues on the surface of the right gastroepiploic artery were pulled by the assistant. The separation was continued along the anatomic space on the arterial surface to the direction of pylorus to isolate the right gastroepiploic artery and cut it at the root after the vascular clamp was used. Here, the inferior pyloric artery from the gastroduodenal artery should also be transected, and damage to the arteries and bleeding should be avoided during the dissection of lymph node station 6. Subsequently, the whole piece of adipose and lymphoid tissue was removed by the ultrasonic scalpel adhering to the duodenal wall from the broken end of the right gastroepiploic arterial

root to the isolated duodenal wall to complete the dissection of lymph node station 6. At this point, the dissection of the inferior pyloric lymph nodes was completed.

Dissection of the superior margin of pancreas

The greater omentum was put on the anterior gastric wall in the left and upper stomach and the greater curvature was turned over by the assistant. At the same time, the pancreatic capsule was lifted and tensioned. The transverse mesocolon was pressed under the inferior margin of pancreas by the operator and the pancreatic capsule was then separated carefully by the ultrasonic scalpel adhering to the pancreatic surface to the level of superior margin of pancreas. The gastropancreatic folds were grasped and lifted up by the assistant with the left hand using the grasping forceps and the pancreatic capsule separated to the level of superior margin of pancreas was lifted and tensioned with the right hand. A small gauze was used on the top surface of the pancreas and the pancreas was gently pressed down by the operator to tension the gastropancreatic folds, straighten the left gastric artery and unwrap the superior margin of pancreas. The retro-pancreatic space was entered by opening the gastropancreatic folds with the ultrasonic scalpel along the superior margin of pancreas and usually the splenic artery was firstly exposed. The initiation part of the common hepatic artery could be exposed by separating along the anatomic space on the surface of splenic artery. The adipose and lymphoid tissue on the surface of splenic artery was lifted by the assistant with the right hand using the grasping forceps after the orientation of splenic artery on the superior margin of pancreas was generally understood. The splenic artery was carefully separated along the orientation of splenic artery to the retro-gastric artery branches nearby. After the en bloc removal of the adipose and lymphoid tissues in the proximal splenic artery, the lymph node station 11p was dissected. The dissection of No. 9 lymph node started from the initiation part of splenic artery. The adipose and lymphoid tissue was lifted by the assistant and dissected by the ultrasonic scalpel along the anatomic space on the surface of artery to the direction of the celiac artery. And then the root of the left gastric artery accompanied with the coronary vein was exposed. After that, the adipose and lymphoid tissues around the coronary vein were dissected by the ultrasonic scalpel and the coronary vein was isolated at the level of superior margin of the common hepatic artery followed by the transection. Subsequently, the assistant softly clamped the left gastric artery and pulled it to the head side. The left gastric artery was isolated and transected by the ultrasonic scalpel along its surface to complete the dissection of lymph node stations 7 and 9. The gastropancreatic folds were loosed and the posterior wall of gastric antrum was pulled to the head side by the assistant. And the pancreas was gently pressed by the operator continuously. The separated adipose and lymphoid tissue on the surface of the common hepatic artery was gently lifted by the assistant after the orientation of the common hepatic artery on the superior margin of pancreas was understood. The whole piece of adipose and lymphoid tissue on the superior side of the common hepatic artery was dissected after the separation by the ultrasonic scalpel along the anatomic space on the surface of the common hepatic artery to the direction of duodenum until the point of the common hepatic artery bifurcating gastroduodenal artery and proper hepatic artery to complete the dissection of lymph node station 8a. The posterior wall of the gastric antrum was raised to the head side, and at the same time the duodenal bulb was pushed to the lateral side by the assistant. The pancreas was gently pressed near the bifurcation of common hepatic artery to tension the hepatoduodenal ligament and completely expose the superior region of pylorus from the back. The root of the right gastric artery could be exposed during the process of isolating the proper hepatic artery by the ultrasonic scalpel along the surface of the proper hepatic artery to the direction of porta hepatis. The right gastric artery was gently lifted and isolated carefully by the assistant. And then the vascular clamp was used on the root of the artery for transection. Subsequently, the separation was continued to the right and a "window" was opened on the right side of the anterior lobe of the hepatoduodenal ligament to provide an accurate pointcut for the transection of the hepato gastric ligament. The separated adipose and lymphoid tissue on the surface of the proper hepatic artery was gently lifted by the assistant. The separating was continued by the ultrasonic scalpel to the head side along the anatomic space and the adipose and lymphoid tissues in the anterior reign of the proper hepatic artery and near the root of the right gastric artery were dissected to complete the dissection of lymph node stations 5 and 12a. At this point, the dissection of lymph nodes in the superior margin of the pancreas was completed.

Separation of the hepatogastric ligament

The stomach was turned over to the original place and the transected greater omentum was put in the inferior reign

of the colon. The hepatic left lateral lobe was lifted by the assistant and the gastric angle was pressed by the operator to tension the hepato gastric ligament to expose the anterior lobe of the hepatoduodenal ligament. The separation was continued by the operator through the opened "window" of the right anterior lob of the hepatoduodenal ligament to the first porta hepatis. Then the hepato gastric ligament was cut along the inferior margin of the liver to the direction of gastric cardia to complete the dissection of lymph node station 1 and 3.

Separation and dissection of the splenic hilar region

First, it was necessary to change the patient's and the operator's stance for the dissection. The patient was in a position of 15-20º head-high and leg-low and 20-30º right inclined. The operator stood between the patient's legs, and both the assistant and camera holder were on the right side of the patient.

The removed omental tissue was put on the right side in the abdominal cavity, the gastric body was pulled to the right upper side and the left side of the greater omentum was lifted by the assistant. The left transverse colon was pulled to the inferior side and the greater omentum was separated by the ultrasonic scalpel along the superior margin of the transverse colon to the splenic flexure of colon on the left side. The splenogastric ligament was lifted by the assistant and the transverse mesocolon on the splenic flexure was gently pressed to the left and lower side to fully expose the splenogastric ligament and the splenic hilar region. The retro-pancreatic space on the superior margin of the pancreas was entered after the separation of the capsule by the ultrasonic scalpel to firstly expose the splenic vein at the pancreatic tail. The adipose and lymphoid tissues on the surface of the splenic vessels were lifted by the assistant. The separation was continued by the ultrasonic scalpel adhering to the splenic vein to the direction of the splenic hilar and the root of left gastroepiploic vessel could be exposed near the pancreatic tail and the lower pole of spleen. The left gastroepiploic vessel was gently lifted by the assistant and the adipose and lymphoid tissues near the left gastroepiploic vessel were carefully separated by the ultrasonic scalpel. And after the left gastroepiploic vessel was isolated, the vascular clamp was used to block the vessel for the final transection. Then the lymph node station 10 was dissected to the direction of splenic hilar region. The dissection started from the broken end of the left gastroepiploic vessel. The posterior wall of the gastric fundus was pulled and turned over to the right upper side to tension the splenogastric ligament by the assistant. The splenic hilar was then exposed the pancreatic tail and was further pressed by the operator. The adipose and lymphoid tissues on the surface of splenic vascular branch in the splenogastric ligament were gently lifted by the assistant, and the separation was continued carefully by the ultrasonic scalpel adhering to the anatomic space on the surface of the splenic lobar artery. At this point, there were 4-6 short gastric arteries bifurcated from the splenic lobar artery in the splenic hilar region passing through the splenogastric ligament. The short gastric arteries were clamped and pulled to the head side by the assistant. And the adipose and lymphoid tissues were carefully dissected by the ultrasonic scalpel close to the roots of the short gastric arteries. The short gastric arteries were isolated and the vascular clamp was used to block the vessel for the final transection after the passing path was confirmed to the gastric wall. The anterior and posterior regions of splenic lobar artery were isolated continuously and the adipose and lymphoid tissue in the splenic hilar region was fully dissected to complete the dissection of lymph node station 10. It was necessary to notice the variation of the splenic lobar artery branch in the dissection and avoid the bleeding caused by the injury. The transected splenogastric ligament was moved to the anterior wall of the gastric body by the assistant and the gastric fundus was pulled and turned over to the right and upper direction. The trunk of splenic artery in the retro-pancreatic space was exposed after the pancreas was pressed by the operator. The isolated adipose and lymphoid tissue on the surface of the splenic artery was lifted by the assistant. And the adipose and lymphoid tissue around the distal end of the splenic artery was fully dissected along the anatomic space on the surface of the splenic artery from the initial end of the splenic lobe artery to the trunk of splenic artery by the ultrasonic scalpel. At this time, 1-2 posterior gastric arteries bifurcated from the splenic artery were often found. The assistant should clamp the posterior gastric vessels to the upper side for the transection at the roots by the ultrasonic scalpel close to the trunk of splenic artery. The dissection of lymph node station 11d was then completed. Finally the dissection of lymph nodes in the splenic hilar was completed. Subsequently, the gastric fundus wall was pulled to the right and lower sides and the gastrophrenic ligament was separated from the upper pole of the spleen to the esophageal hiatus. The cardiac part of gastric fundus was pulled to the right and upper side by the assistant to expose the left diaphragmatic crus to separate

the adipose and lymphoid tissue in the esophageal cardia when the separation continued to the region around the left diaphragmatic crus. It was necessary to notice that there was gastric fundus branch bifurcated from the left inferior diaphragm artery. And it should be isolated at the root to complete the dissection of No. 2 lymph node.

Digestive tract reconstruction

The left and right diaphragmatic crus were isolated and the posterior reign of the esophagus and the right side of the cardia were dissociated. The anterior and posterior branches of vagus nerve were cut and the esophagus was dissociated about 6 cm. The duodenum was cut 3 cm off the pylorus with 60 mm blue nail Endo-Gia stapler closure under the laparoscope and the broken end was closed then. The esophagus was cut 3 cm off the superior margin of the cardia with 60 mm blue nail Endo-Gia stapler closure under the laparoscope and the broken end was closed. The catheter in the OrVil^{TM} stapler resisting the nail seat was slowly delivered to the esophagus stump through the oral cavity with the help of experienced anesthetist. A small incision was made by the ultrasonic scalpel in the corresponding part of the catheter balloon perpendicular to the closed esophageal stump only suitable for the catheter; the catheter was pulled out through the small incision to the abdominal cavity until the white plastic rubber ring was fully exposed. The stitch between the anvil head and catheter was cut to make the anvil head fit the esophagus stump. The catheter was then removed through the main operation hole. A 3 cm longitudinal incision was made under xiphoid in the center of the upper abdomen and the incision protector was implanted. The whole stomach was removed for the pathological examination. The upper jejunum was transected 15 cm below the Treitz ligament through a small incision and the proximal opening hole was closed. The OrVil^{TM} 25 mm stapler was implanted through the distal opening hole of the jejunum. And then the upper abdomen was entered through the small incision. The pneumoperitoneum was reconstructed and the nail seats in the esophageal were anastomosed monitored by the laparoscopy to complete the end-to-side esophageal-jejunum anastomosis. The 60 mm Endo-Gia blue nail was used to close the distal jejunum opening hole. Then the side-to-side esophagus-jejunum anastomosis was performed in the proximal jejunum about 45 cm to the esophagus jejunum. After the abdominal cavity was washed, a drainage tube was placed near the esophagus-jejunum stoma and spleen nest respectively and elicited from the left and right upper abdominal puncture hole to suture the incisions. The post-operative pathology reported pT3N0M0.

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Surgical Video

Laparoscopy-assisted radical total gastrectomy plus D2 lymph node dissection/dissection of lymph node station 16

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Abstract: Laparoscopy-assisted D2 radical resection for gastric cancer has been carried out in quite a few Chinese hospitals. However, the techniques that are feasible for the dissection of lymph node station 3, particularly for lymph node station 16, under the laparoscope require further investigation. We have successfully employed the "middle approach" under the laparoscope for the implementation of D2+No.16 dissection in 18 patients with advanced gastric cancer. This video (*Video 1*) describes the process of laparoscopy-assisted radical total gastrectomy (D2 + No. 16 dissection). In conclusion, upon the completion of laparoscopy-assisted radical D2 surgery for gastric cancer, laparoscopic dissection of lymph node station 16 is feasible for carefully selected patients with advanced gastric cancer.

Keywords: Advanced gastric cancer; laparoscopic surgery; D2+No. 16 dissection; total gastrectomy

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Feng Qian

Introduction

While D2 radical resection remains the "gold standard" treatment for the advanced gastric cancer, whether the lymph node station 3 should be dissected remains controversial (1,2). It has been proposed that a moderately extended radical resection can improve the long-term efficacy for the advanced gastric cancer (3). Zhan *et al.* (4) analyzed the aortic lymph node metastasis in patients with advanced gastric cancer and found the dissection of lymph nodes around the abdominal aorta can improve the 5-year survival in patients with positive lymph node station 16 less than 3 (or negative). For gastric cancer patients with suspected lymph node station 2 involvement, the lymph node station 16 should be actively dissected. In recent years, laparoscopy-assisted D2 radical resection for gastric cancer has been carried out in quite a few Chinese hospitals (5,6). However, the techniques that are feasible for the dissection of lymph node station 3, particularly for lymph node station 16, under the laparoscope require further investigation. We have successfully employed the "middle approach" under the laparoscope for the implementation of D2+No.16 dissection in 18 patients with advanced gastric cancer. This video (*Video 1*) describes the process of laparoscopy-assisted radical total gastrectomy (D2 + No. 16 dissection).

Video 1 Laparoscopy-assisted radical total gastrectomy plus D2 lymph node dissection/dissection of lymph node station 16.

Surgical methods

Patient characteristics

A 65-year-old male patient (body height: 168 cm; body weight: 58 kg) was clinically diagnosed as poorly differentiated adenocarcinoma of the gastric body, with a pre-operative pathologic stage of $T_3N_2M_0$.

Body position and five-hole method

The patient was placed supine and in a split-legged position after general anesthesia. The surgeon stood at the left side of the patient, the assistant at the right side of the patient, and the camera holder between his two legs. A "curved 5-hole method" was applied: the CO_2 pneumoperitoneum was created by umbilicus puncture, maintaining the pressure at 12 mmHg. A 10-mm trocar was placed in the left anterior axillary line below the costal margin as the working port; a 5-mm auxiliary port was created slightly above and 5 cm to the left of the umbilical fossa; a 5-mm port was created in the right anterior axillary line below the costal margin; and finally, a 10-mm port was created in the right midclavicular line slightly above and 10 cm to the umbilical fossa.

Dissection of lymph node stations 1 and 2

After the abdomen was opened, the tumor location was routinely explored to identify the lesions, lymph node involvement, and intra-abdominal metastasis. Open the greater omentum to the head side; transect the greater omentum using an electric hook from the middle of transverse colon and then enter the lesser omental bursa. After the left gastroepiploic vein was divided and ligated, the lymph node stations 4d and 4sb were dissected. After the gastrosplenic ligament and posterior gastric arteries were transected using HIFU along the splenic hilum, the lymph node stations 4sa and 10 were dissected. The separation continued to the left side of the gastric carida, and then the lymph node station 2 was dissected. After the greater omentum was flipped and raised, the operator stretched the transverse colon, and separated the omentum along its attachment to the hepatic flexure of the colon. Then the anterior lobe of the transverse mesocolon was removed. After the middle colonic artery and its branches were separated, the superior mesenteric vein, right colic vein, and right gastroepiploic vein were exposed. After the right gastroepiploic vein was cut off at its root, the lymph node stations 15, 14v, and 6 were dissected. The separation continued along the deep surface of the anterior fascia of pacreaticodudenum till the duodenum. Isolate the right gastroepiploic artery and cut it at the root. The lower edge of the duodenum bulb was exposed. Dissect the pancreatic capsule. After the splenic artery was separated and exposed along the upper edge of the pancreas, the lymph node station 11 was dissected. After the celiac artery was exposed along the splenic artery and cut off with titanium clip at the root of left gastric artery, the lymph node stations 7 and 9 were dissected. The separation continued before the hepatic artery and along its upper edge, and then the lymph node station 8a was dissected. Then the capsule of the hepatoduodenal ligament was cut open, and the lymph node station 12a in front of and at the external side of the proper hepatic artery was dissected. The lymph node station 5 was dissected at the root of right gastric artery. The hepatogastric ligament was cut open using HIFU, and then the dissociation continued closely along the lower edge of liver till the right side of esophagus, where the lymph node station 3 was dissected. Cut open the serosal surface of the esophagus till the separation site at the left side; after the esophagus was thoroughly exposed till 5 cm above the gastric cardia, the lymph node station 1 was dissected. Thus, the dissection of lymph node N1 and N2 levels were completed, reaching the level of D2 radical treatment. Make a 5-cm median longitudinal incision on upper abdomen (depending on the tumor size) and then drag the stomach and greater and lesser omentums out from the abdominal cavity and remove the tumor.

Dissection of lymph node station 16

With the pancreas and transverse colon as the borders, the level 3 lymph nodes were dissected in the upper and lower regions: in the upper region, the lymph node stations 8p, 12p, 12b, 16a. The lymph node stations 8p, 12p, and 12b are located behind the common hepatic artery and proper hepatic artery. The arteries must be exposed and lifted to effectively remove the lymphatic/adipose tissues behind the arteries. Although the lymph node station 16a is located at the surface of the abdominal aorta between the celiac artery and the left renal vein, the common hepatic artery and the proximal portion of the splenic artery must be lifted before these lymph nodes could be thoroughly dissected. Therefore, the offending artery suspension method was applied: The assistant gently lifted the common hepatic artery with a separation clamp in her right hand. The operation pressed the upper edge of the pancreas with a separation clamp in his left hand; then, the operator divided hepatic common artery from the portal vein along the lower edge of the hepatic common artery. After the hepatic common artery was lifted with a sling, the lymph node station 8p behind the hepatic common artery was dissected. The operation continued to the distal side along the hepatic common artery, during which the proper hepatic artery was divided and hung. Then, the lymph node stations 12p and 12b behind the proper hepatic artery and before the portal vein were dissected. The operator pressed the pancreatic body downward with his left hand; the assistant lifted the hepatic common artery and splenic artery using a sling with the forceps in her right hand; the operator then dissected the lymph node station 16a2 that is located between the celiac artery and the lower edge of the left renal vein using HIFU in his right hand. The "middle approach" was applied for the dissection of the lymph node station 16b1. The transverse colon was lifted to the head side. The patient's body position was changed to "left high and right low". The assistant lifted the small intestine to the right abdominal cavity to expose the lower portion of the abdominal aorta. The operator lifted the peritoneum at the surface of abdominal aorta using a separation clamp in his left hand, and then separated the peritoneum longitudinally along the tissue between the abdominal aorta and inferior vena cava using an electric hook or HIFU in his right hand. Beginning from the root of the inferior mesenteric artery, the lymph node station 16b1 (located in the anterior and lateral sides of tissues between the abdominal aorta and inferior vena cava and inside the fossa) was dissected upwards till the lower edge of the left renal vein. Then, the lymph node station 16 was dissected.

Results

Laparoscopy-assisted radical total gastrectomy plus D2 lymph node dissection/dissection of lymph node station 16, followed by oesophagus-jejunum Roux-en-Y reconstruction, were successfully performed. The surgical operation lasted 260 min, and the intraoperative blood loss was about 110 mL. Post-operative pathology showed that the tumor had invaded the serosal layer. Thirteen of 33 positive lymph nodes were detected, among which 3 of 5 lymph nodes in station 16 were positive. The clinicopathological diagnosis was poorly differentiated adenocarcinoma of the gastric body, T3N3M0, and IIIb stage. He recovered well and was smoothly discharged 8 days after surgery. No complication was noted.

Discussion

The lymph nodes near the stomach are divided into three levels: the first level includes stations 1, 2, 3, 4, 5, and 6, which are close to the gastric tissue; the second level include stations 7, 8a, 9, 10, 11, and 12a, which are on the surface of the specific arteries; and the third level, which include stations 8p, 12b, and 12p (which are on the posterior side of the specific arteries or behind these arteries) and stations 16a2 and 16b1 (which are near the abdominal aorta). The D2 radical resection for gastric cancer requires the en bloc removal and resection of the first and second lymph node levels along with the gastric tissue. However, the lymph nodes of the third level are located in deeper anatomic layers and are not mutually connected; also, they are located among arteries and the deep portion of trunk vein and therefore need to be removed separately, which is challenging even via open surgery.

The lymph node stations 2 and 4sa belong to the third-level lymph nodes for tumors in the lower stomach but are the second-level lymph nodes for tumors in the upper stomach. On the contrast, the lymph node stations 5, 6, and 12a belong to the third-level lymph nodes for tumors in the upper stomach but are the second-level lymph nodes for tumors in the lower stomach. Therefore, the absolute third-level lymph nodes only include stations 8p, 12p, 12b, 14v, 16a2, 16b1, 19, and 20 (7).

For the dissection of lymph node stations 16a2 and 16b1 (i.e. paraaortic lymph nodes), the lateral approach is often

employed during open surgery: separate the right colon or left colon from the lateral abdominal wall and then lift it to the opposite side (8). After the retroperitoneal tissues are thoroughly exposed, dissection is performed. However, this approach is not feasible for the laparoscopic surgeries: the workload will be heavy for either left approach or right approach, because it roughly equals the additional work needed for right hemicolectomy or left hemicolectomy; in addition, the colon relaxation is not helpful for the exposure of abdominal aorta and inferior vena cava. Therefore, for laparoscopic surgeries, the middle approach was adopted in our serials: The assistant lifted the transverse colon to the head side and the small intestine to the right side to expose the lower portion of abdominal aorta. The operator separated the peritoneum using an electric hook or HIFU, and then can easily dissect the lymph node station 16b1 located from the root of the inferior mesenteric artery to the lower edge of the left renal vein.

When performing laparoscopic lymph node dissection for gastric cancer, the following issues must be carefully considered: (I) its main indications include gastric cancer at stage IIIa, stage IIIb, or stage IV without distant metastasis. Less experienced surgeons should operate on slim young and mid-aged patients firstly; (II) When dissecting the lymph node stations 8p, 12p, 12b, and 16a2, the hepatic common artery, splenic artery, and proper hepatic artery must be completely exposed and then lifted before the lymph nodes can be completely dissected; (III) The lymph node stations 16a2 and 16b1 are close to the deep and fragile splenic vein, portal vein, left renal vein, and inferior vena cava and are also adjacent to the chylous pool. These structures can be easily injured and bleed during the dissection, resulting in postoperative lymphatic leakage. Therefore, efforts should be made during the dissection to avoid any possible deep vein damage and lymphatic leakage; if the presence of any lymphatic tube is suspected, it should be clamped with titanium clip or slowly transected with HIFU; (IV) Before the dissection of the third-level lymph nodes, the omentum, gatric tissues, and tumor should be removed firstly, so as to keep surgical field clear; meanwhile, an abdominal incision should be preserved for emergency treatment.

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In conclusion, upon the completion of laparoscopy-assisted radical D2 surgery for gastric cancer, laparoscopic dissection of lymph node station 16 is feasible for carefully selected patients with advanced gastric cancer.

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Surgical Video

A case of laparoscopy-assisted radical distal gastrectomy

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The past decades have witnessed the rapid development of laparoscopy in radical treatment of gastric cancer since its first application in distal gastrectomy in 1992. Currently, laparoscopy-assisted radical distal gastrectomy is one of the standard operations for early gastric cancer in Japan. We have been applying this technique since 2011, and a summary of our operation and findings for a recent case is presented below:

A 58-year-old man, surnamed Guan, was admitted to our hospital due to gastric cancer. Preoperative examination confirmed a cT2N0M0 stage, and laparoscopy-assisted radical gastrectomy was performed on April 18, 2013.

Surgical procedure

The patient was placed supine and in a split-legged position, followed by general anesthesia via endotracheal intubation (*Video 1*). A 10 mm incision was made to establish CO_2 pneumoperitoneum, with the pressure maintaining at 13 mmHg. A port for observation was then inserted below the umbilical edge with a 12 mm trocar at an angle of 15 degrees above the horizontal plane of the organs. A 30-degree laparoscope was used for abdominal exploration. A 12 mm trocar was placed in the left anterior axillary line 2 cm below the costal margin as the working port; a 5 mm trocar was inserted within the left midclavicular line parallel to umbilicus for elevating certain structures; and two 5 mm trocars were placed within the right anterior axillary line 5 mm below the costal margin and within the right midclavicular line parallel to umbilicus, respectively, for elevating operations by the assistant. The surgeon stood on the left side of the patient by routine.

The gastrocolic ligament was transected. With the greater curvature and the transverse colon elevated to the opposite side, the left part of the gastrocolic ligament was cut with an ultrasonic scalpel near the transverse colon, and then divided to the splenic flexure. The attachment of the greater omentum to the transverse colon was extended and stretched tightly, and then separated to enter the greater sac, along which the division was continued into the anterior and posterior space of the transverse mesocolon near the splenic flexure, until the lower edge of the tail of the pancreas was exposed. The gastrosplenic ligament was transected. The gastric body was flipped towards the head side and withdrawn to the right along with the greater omentum, and the splenic flexure to the left inferior side to create a vertical tension against the gastrosplenic ligament. The posterior wall of the gastric fundus was thus pulled aside to expose the splenic hilum and the tail of the pancreas. The capsule of the pancreas was opened from the lower to the upper edge of the pancreatic tail with an

Video 1 A case of laparoscopy-assisted radical distal gastrectomy.

ultrasonic scalpel. A Hem-o-lok clip was used to close the upper edge at the root. The left gastroepiploic artery and vein were cut (with due caution to avoid necrosis of the lower splenic pole by preserving the supplying branches). Meanwhile, lymph node stations 4sb and 4d were dissected. The separation was continued towards the upper region, in which a branch of the short gastric vessels was dissected.

The right segment of the gastrocolic ligament was cut near the transverse colon using the ultrasonic scalpel, and separated through the hepatic flexure, and the colon was isolated from the descending part of the duodenum and from the duodenal bulb. The mesogastrium and the mesocolon were separated along the joining line between the posterior wall of the gastric antrum and the mesocolon. The posterior wall of the gastric antrum was pulled to the left anterior side, and the colon and its mesentery to the right inferior side, revealing fully the underlying loose fascial space at the junction between the two. The right portion of the transverse colon and its mesentery were freed from the descending part of the duodenum and the duodenal bulb, along the surface of the head of the pancreas and the lower edge of the pancreatic neck. At this point, the right gastroepiploic vein, the right colic vein and their convergence, the gastrocolic trunk, were completely exposed. The right gastroepiploic vein was transected above the point where it joined the anterior superior pancreaticoduodenal vein. With the pancreas as a starting point, the pancreatic capsule was lifted and tissues were separated from the lower edge of the pancreas along the anterior pancreatic space on the surface of the pancreas towards the external superior region, until the origin of the right gastroepiploic artery at the gastroduodenal artery was reached. The right gastroepiploic artery was then clamped with a Hem-o-lok clip and cut. The posterior inferior wall of the duodenal bulb was dissociated near the surface of the pancreatic head along the anterior pancreatic space. The 6th station lymph nodes were dissected.

As the stomach was put back into place, the antrum was pulled to the right inferior side, and the liver to the right superior side, maintaining a tension over the hepatogastric ligament. After the hepatogastric ligament was dissected, the lesser sac was cut open along the left lobe of the liver, until the right side of the cardia was reached. The whole stomach was lifted. The separation of the pancreatic capsule was continued until the gastroduodenal artery, common hepatic artery, pyloric vein, proper hepatic artery, right gastric artery, portal vein, coronary vein, left gastric artery, splenic artery, and posterior gastric artery and vein were exposed. The prepyloric vein, right gastric artery, coronary vein, and left gastric artery were clamped with Hem-o-lok clips and cut. Lymph node stations 5, 8a, 9, 12a, 7, and 11p were dissected along the course. The right crus of the diaphragm feet was divided from right to left to the lower esophageal cardia region; and stations 1a and 1b were dissected. The separation was continued along the lesser curvature into the cardia, extending closely along the gastric wall to the feeding vessels of the lesser curvature, while dissecting stations 3a and 3b.

The distal portion of the stomach was resected and removed as a specimen, and the reconstruction of the digestive tract was completed, through the auxiliary port. An incision of about 5 cm was made in the midline over the xiphoid for pulling out the removed stomach and omentum, while the adjacent tissues were covered by an incision protector. The duodenal bulb was closed with purse-string suture with an anvil placed.

A stapler was triggered at the posterior wall of the residual greater curvature to complete the gastroduodenal anastomosis.

Findings and recommendations

Gastric cancer mainly spreads across local lymph nodes via the lymphatic vessels, which forms the theoretical basis of radical gastrectomy. Therefore, removal of sufficient stomach tissues and thorough dissection of the gastric lymph nodes can achieve complete remission for patients with gastric cancer. At present, the widely recognized principles for the radical treatment of gastric cancer include: (I) en

bloc resection of the lesion; (II) surgical margins of ≥5 cm from the tumor; (III) complete dissection of lymph nodes; (IV) non-contact and complete elimination of tumor cells shed in the abdominal cavity. Most gastrointestinal surgeons in China have accepted D2 lymph node dissection as the standard operation for radical gastrectomy. Laparoscopy-assisted radical resection must comply with the same principles as for traditional open surgery, including the requirement for tumor-free margins and en bloc resection, where lymph node dissection is always the key and challenging link. Due to the differences in the field of vision and instrumental operation, laparoscopy-assisted surgery employs unique procedures of lymph node dissection. Despite a limited number of reports on laparoscopy-assisted radical resection of advanced gastric cancer, the currently available data show improved short-term efficacy and comparable long-term outcomes in favor of the technique compared with open surgery. Lymph node dissection begins from the peripheral normal tissues, not along the common hepatic artery, by gradually exposing the various vessels and branches. The lymph nodes are harvested by bundle, rather than individually, for elimination of all stations as well as the pathways for tumor metastases. No fat or lymph node residue can be found in the lesser curvature region after the dissection. In theory, this technique combines tumor-free radial margins with en bloc resection, which is a genuine embodiment of the oncologic principles for radical gastrectomy. With the beneficial larger field of view, laparoscope allows more detailed presentation of small vessels, nerves, fascia and other structures, facilitating the creation of the gastric fascial space by vaporization using the ultrasonic scalpel. All these contribute to a more refined process of lymph node dissection under laparoscope compared with open surgery.

As with traditional operations, the laparoscopic technique follows the same requirements with higher demand on the operating skills. There is no shortcut to expose the vascular roots and dissect lymph nodes—a series of steps should be followed to complete the operation on a layer-by-layer basis so that all vascular structures are clearly revealed in a proper order.

When dealing with lymph nodes within dense or fragile structure layers, rupture and bleeding of small blood vessels seem to be inevitable, particularly in a surgeon's first several operations. Most of these cases can be properly handled with adequate caution by the surgeon in a calm and confident manner, thus avoiding transition to open surgery.

For a blood vessel smaller than 5 mm in diameter but with high probability of bleeding, coagulation can be applied to the proximal stump of the vessel at small power with the ultrasonic scalpel before cutting off. When dividing any blood vessel, the operating surface of the ultrasonic scalpel should always be pointed towards the external side of that vessel to avoid injury.

The use of ultrasonic scalpels during an open gastrectomy following the same surgical approach as in the laparoscopic technique will considerably shorten the learning curve for laparoscopic gastric surgery. In addition, a designated cooperation team is also indispensable for the smooth implementation of laparoscopic radical gastrectomy.

To sum up, laparoscopy-assisted radical gastrectomy with lymph node dissection is a practical treatment for gastric cancer in better compliance with the oncologic principles, with the advantages of minimal invasiveness, reduced organ exposure, and rapid postoperative recovery.

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Surgical Video

Laparoscopy-assisted D2 gastrectomy plus laparoscopic bursectomy in locally advanced gastric cancer patients

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Abstract: Laparoscopy-assisted gastrectomy has been well practised in eastern countries for early gastric cancer. A Japanese trial on bursectomy has demonstrated the trend of improving long-term survival outcomes in serosa-positive gastric cancer patients. We have preliminarily investigated and documented the feasibility and safety of laparoscopic bursectomy in laparoscopy-assisted D2 gastrectomy for locally advanced gastric cancer. However, in spite of this, this technique is still quite controversial and requires further high-qualified trials due to inadequacy of long-term outcomes.

Keywords: Gastric cancer; laparoscopy; bursectomy; lymphadenectomy; surgery

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Laparoscopy-assisted gastrectomy for gastrectomy cancer has started more than 20 years and been well spread and developed in Mainland China for nearly a decade (1,2). In Japan and Korea, the stage I diseases compose more up to 50-60% in population and laparoscopy-assisted gastrectomy has been well accepted for predictive early gastric cancer (3,4). According to the latest treatment guideline by Japanese Gastric Cancer Association, most of the GI surgeons accepted the selected candidates with early diseases to be considered for laparoscopic surgery. However, in China, the majority of gastric cancer is advanced diseases, while by many high-volume hospitals' experiences the proportion of early gastric cancer is only 10-20% in operated patients. Thus the stage I diseases only composed of 30% in laparoscopic surgeries in Mainland China, and D2/D2+ lymphadenectomy was performed in 69% laparoscopy-assisted gastrectomies (2).

Interestingly, among previous Chinese literatures, the reported incidences of complications (10.9%), mortality (0.4%), reoperation (1.1%) and conversion-to-open (4.1%) were similar with those among Japanese and Korean reports (2,5). The Chinese Laparoscopic Gastric Surgery Study (CLASS) group was established at 2009, and numerous Chinese laparoscopic GI surgeons were participated in and aimed to promote the level of Chinese studies on laparoscopic gastric surgery (2). As known, previous evidence based on open surgery indicated the D2 lymphadenectomy as a standard procedure for resectable advanced gastric cancer patients in common practice (6,7). What's more, for locally advanced gastric cancer, laparoscopy-assisted distal gastrectomy plus D2 lymphadenectomy was demonstrated to be a technically feasible and safe procedure by experienced hands (8,9). However, by now, we are still lack of the data of long-term survival outcomes by laparoscopy-assisted gastrectomy for advanced gastric cancer. After a multicenter retrospective case control study, CLASS group started its first multicenter randomized controlled trial "Multicenter Study on Laparoscopic Distal Subtotal Gastrectomy for Advanced Gastric Cancer (CLASS-01)", to compare long-term outcome (3-year overall survival and recurrence outcomes) between laparoscopic and open distal subtotal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer patients (10).

Many GI surgeons are familiar with and practise the surgical technique of bursectomy for advanced gastric

Video 1 Laparoscopy-assisted D2 gastrectomy plus laparoscopic bursectomy in locally advanced gastric cancer patients.

cancer. Nevertheless, there is still the controversy on bursectomy whether it could bring survival benefits to advanced gastric cancer patients. Japanese Gastric Cancer Association only recommended it as an under-investigated technique for the serosa positive (sT4a) patients, but not for sT1-2 diseases (11). The major risk of bursectomy should be the potential iatrogenic injury of colonic vessels or pancreatic solid. Therefore, it's easy to understand that bursectomy is complex and difficult to be performed in laparoscopic gastric cancer surgery.

A Japanese multicenter randomized trial involving 11 hospitals and enrolling 210 sT2-4aN0-1 resectable gastric cancer patients compared bursectomy to conventional non-bursectomy procedure (12,13). As its reports, the overall postoperative complication rates were 14.4% and 14.2% in bursectomy and non-bursectomy groups, respectively. The risks of pancreatic fistula were rare around 2.9% and 6.6%, respectively. Its interim analysis showed that bursectomy group had a trend of lower peritoneal recurrence (8.7% *vs.* 13.2%). Survival curvature analysis also showed a trend of better 3-year overall survival rate of bursectomy group in serosa-positive subset (69.8% *vs.* 50.2%, P=0.081) (12,13). Therefore, this trial demonstrated that bursectomy might be feasible and safe, as well as with potential of improving long-term survival outcomes. Another high-qualified multicenter randomized trial (JCOG-1001) has launched from 2010 to enroll 1,000 sT3-4sa patients till 2020. The later one may give more robust evidence on estimating the surgical technique of bursectomy.

Therefore, based on the background stated above, we thought of the feasibility and safety of laparoscopic bursectomy and performed a preliminary study to investigate its feasibility and safety of complete bursectomy in laparoscopy-assisted gastrectomy for advanced gastric cancer. It meant based on laparoscopy-assisted gastrectomy plus D2 lymphadenectomy, additional laparoscopic bursectomy required complete dissection of anterior layer of transverse mesocolon and pancreatic capsule. Finally, we reported 16 patients (7 distal and 9 total gastrectomies) with resectable advanced gastric cancer underwent complete laparoscopic bursectomy (*Video 1*) from Jan 2011 to Apr 2012 (14). There was no incidence of intraoperative vascular or visceral injury, and also no case converted to open surgery or died. The length of laparoscopic bursectomy was 45.3±20.1 min, and mean total operation time was 287.3±31.2 min, which was even shortened against that in our earlier stage of learning curve without bursectomy (293.5±31.6 min) (14,15). Mean volume of blood loss was 75.5±12.3 mL and mean postoperative hospital stay length was 11.3±6.0 d (4-32 d) (14). The overall complication rate was 31.3%, concerning 6.3% peritoneal cavity infection, 6.3% wound infection, 12.5% pneumonia and 6.3% urinary tract infection (14). Besides, there was no case of pancreatic fistula, anastomotic leakage and adhesive intestinal obstruction. Laparoscopy-assisted D2 gastrectomy plus bursectomy for advanced gastric cancer appears feasible and safe.

Through our experiences, firstly, we believe well understanding the anatomy of bursa omentalis and the extension of complete bursectomy (inner layer) must be most important. The difficulty of laparoscopic bursectomy should be the dissection of anterior layer of transverse mesocolon and pancreatic capsule. Secondly, the operator needs a large amount of experiences of laparoscopic gastric cancer surgery to avoid iatrogenic injury of colonic vessels and pancreas solid. Thirdly, the team work should be paid enough attention to, so that both assistant and camera holder are required to well understand the operation procedure and practical anatomy. Especially, the assistant must try to expose the potential or masked space appropriately for the sake of facilitating operator to identify important structure correctively.

Additionally, yet, we should learn that there were some retrospective studies not to support the survival benefits of bursectomy. Yoshikawa T *et al.* found that in a serosa-positive series, bursectomy didn't have better 3-year and 5-year survival outcomes in posterior wall invaded group than those in others (16). Kochi M *et al.* reported 254 consecutive series of stage IA to IIIC diseases, and the 5-year

overall survival rate was 85.8% in the bursectomy group and 80.8% in the nonbursectomy group (hazard ratio =0.82; 95% CI, 0.37-1.74, P=0.60) (17).

In a short, the laparoscopy-assisted D2 gastrectomy plus complete bursectomy for locally advanced gastric cancer might be technically feasible and safe. However, in spite of this, this technique is still quite controversial and requires further high-qualified trials due to inadequacy of long-term outcomes.

Acknowledgements

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Surgical Video

Radical total gastrectomy plus D2 dissection for gastric cancer

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A 78-year-old male was presented in our hospital. His pre-operative CT and B-mode ultrasound showed no liver or lung metastasis. Enlarged lymph nodes (1-2 cm in diameter) were found around the stomach and near the common bile duct. These masses invaded the serous layer. However, no enlarged lymph node was detected after peritoneum or near abdominal aorta. Pre-operative chemotherapy was not feasible for such an elderly patient. Radical surgery was then scheduled. Due to the presence of non-tender swollen lymph nodes near the common bile duct, radical total gastrectomy plus D2 dissection was performed (*Video 1*). In addition to the routine dissection of groups 1, 2, 3, 4, 5, 6, 7, 8a, 9, 12a, 11p, and 11d, groups 12b, 12p, 8p, and 13 lymph nodes were also selectively dissected. Intrathecal decollement was employed to ensure the surgical completeness. The post-operative pathology showed that this was an ulcerative adenocarcinoma of the stomach. The mass sized 7 cm × 4.5 cm, invading the serous layer. Tumor thrombi were visible inside the vessels. No residual cancer was found at the upper and lower cutting edge. No obvious nerve invasion was observed. Metastases were detected in: group 1, LN0/4; group 2, LN0/3; group 3, LN5/10; group 4, LN4/9; group 5, LN2/5; group 6, LN0/5; group 7, LN0/4; group 8a, LN2/6; group 8p, LN1/3; group 9, LN0/3; group 10, LN0/4; group 11p, LN0/3; group 11d, LN0/2; group 12a, LN2/4; group 12b, LN1/4; group 12p, and LN1/3; group 13, LN0/3. No relapse was found during the 23 months of follow-up.

Video 1 Radical total gastrectomy plus D2 dissection for gastric cancer.

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Surgical Video

Radical surgery for cardia carcinoma: total gastrectomy, D2 + No.10 dissection, esophagojejunal Roux-en-Y anastomosis

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Abstract: A 71-year-old man with cardia carcinoma (cT4NxM0) suggested was scheduled for a primary radical resection of the lesion. Intraoperative exploration revealed no ascites, no suspicious palpable metastatic nodes in the pelvic cavity, liver, small intestine/colon, or the mesentery; the tumor, an ulcerated mass of about 10 cm × 8 cm, was located in the cardia, involving the body of the stomach; enlarged lymph nodes were palpable at the lesser curvature side. A Kocher incision was made for exploration, which showed enlargement of station 12b lymph nodes, though no metastasis was indicated by frozen section pathology. No obvious enlargement of station 16 lymph nodes was detected. A radical surgery was then planned, and routine total gastrectomy with D2 lymph node dissection was performed. Due to the nature of proximal advanced gastric cancer, the spleen and the pancreatic body and tail were isolated retroperitoneally, and pulled outside the abdominal cavity for dissection of lymph node stations 4sa, 10, 11d, and 4sb. Esophagojejunal anastomosis was then performed routinely on a Roux-en-Y loop. The postoperative recovery was uneventful. Imaging of the anastomosis showed no complication four days after the surgery, and a regular diet was resumed gradually. Postoperative chemotherapy was delivered from the third week after surgery using the DOF regimen. The patient was in a satisfactory general condition eight months after surgery, without signs of recurrence or metastasis.

Keywords: Radical surgery; cardia carcinoma; total gastrectomy; D2 + No.10 dissection; esophagojejunal Roux-en-Y anastomosis

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Data of the patient

Medical history

The patient was a 71-year-old man, admitted for "upper abdominal discomfort for over 3 months, and gastric neoplasm found 2 months ago". He had no history of surgery, trauma, hypertension, diabetes, and/or heart disease.

Admission examination

No palpable enlargement of the supraclavicular lymph nodes was found. The abdomen was flat and soft, without visible peristalsis, tenderness or rebound tenderness. There was no muscle guarding. The liver and spleen were not palpable under the ribs. Murphy's sign was negative, and no percussion pain on the hepatic or renal regions was found. Bowel sounds were heard 4 times/min; and shifting dullness was negative. Digital rectal examination: a finger was inserted smoothly; the mucosa was smooth; no palpable or obvious mass was detected, and there was no blood on the glove after the examination.

Preoperative routine examination

Blood routine [2012-08-28]: WBC count: 4.73×10^{9}/L, RBC count: $\downarrow3.93\times10^{12}$/L, hemoglobin: ↓97 g/L, neutrophils: 66.8%, lymphocytes: 21.6%, platelets: $\uparrow367\times10^{9}$/L; liver

Video 1 Radical surgery for cardia carcinoma: total gastrectomy, D2 + No.10 dissection, esophagojejunal Roux-en-Y anastomosis.

function [2012-08-28]: ALT: 7 U/L, AST: 16 U/L, ALP: 50 U/L, GGT: 14 U/L, TBA: ↑12 μmol/L; renal function [2012-08-28]: urea nitrogen: 3.8 mmol/L, creatinine: 65 mol/L, uric acid: 0.255 mmol/L; blood glucose [2012-08-28]: glucose: 5 mmol/L; clotting function [2012-08-28]: PT: 10.5, APTT: 23.9 seconds, FIB: ↑366.3 g/L; hepatic immune parameters [2012-08-28]: HBsAg: negative, HBs-Ab: 7.26, HBeAg: negative, HBe-Ab: negative, HBc-Ab: positive (+), HBcAb-IgM: negative, HCV-Ab: negative, anti-HAV IgM: negative; tumor markers [2012-08-28]: AFP: 4 μg/L, CEA: 2.22 μg/L, CA199: 17.05 U/mL.

Other tests before surgery

Preoperative endoscopy: neoplasm at the cardia; pathology: adenocarcinoma, moderately differentiated. Whole abdomen CT (performed in another hospital, no image data available): signifcantly thickened gastric wall at the cardia region, and gastric cancer was considered; chest X-ray: no obvious abnormalities.

Preoperative diagnosis

Cardia cancer (Siewert type III, preoperative staging: cT4N+M0).

Treatment protocol

Primary radical resection and postoperative adjuvant chemotherapy.

Surgery procedure (Video 1)

Exploration

An incision of about 20 cm was made in the middle of the upper abdomen and around the umbilicus, to gain access to abdominal cavity layer by layer. Abdominal exploration: a small amount of ascites was found. No obvious nodes were palpable in the pelvic cavity and the liver. No enlargement or nodes were detected in the small intestine, colon and their mesenteries. The tumor was an ulcerated mass of about 10 cm × 8 cm, located in the cardia, involving the body of the stomach. Enlarged lymph nodes were palpable at the lesser curvature side. A Kocher incision was made. After the duodenum and the head of the pancreas were isolated, enlargement of station 12b lymph nodes was found, though pathology of the frozen section pathology of the resected specimen showed “no metastasis”. No obvious enlargement of stations 3 and 16 was detected.

Isolation and dissection

The gastrocolic ligament was cut close to the transverse colon, and the anterior lobe of the transverse mesocolon was fully isolated to expose the lower edge of the pancreas. Station 14v lymph nodes were dissected along the surface of the SMV. As the gastrocolic trunk was exposed, the right gastroepiploic vein was cut and lymph nodes around the head of the pancreas were dissected. The right gastroepiploic artery was ligated and cut. Stations 4d and 6 were dissected. The separation was continued upwards until the pancreatic capsule was completely dissected to reach the upper edge of the pancreas. The duodenum was isolated to 3 cm below the pylorus. A 80 mm dividing stapler was triggered to closed and cut the duodenum. The hepatoduodenal ligament was cut open from the left edge of the common bile duct. The lymph nodes were dissected from left to right: the hepatogastric ligament was cut and lymph nodes around the proper hepatic artery (station 12a) were dissected until the hepatic portal was reached; the right gastric artery was ligated and cut (station 5), and lymph nodes to the left and posterior side of the portal vein were dissected (station 12p). The dissection was continued to the celiac trunk (station 9) along the common hepatic artery (station 8). The left gastric artery (station 7) and coronary vein were ligated at their roots. The small omentum was divided close to the liver, and stations 3 and 1 at the lesser curvature side were dissected.

The diaphragm-esophageal fascia was open; both vagus nerves were cut, and lymph nodes (station 2) to the left of the cardia were dissected. An approximately 7 cm portion of abdominal esophagus was isolated, cut, and placed into the distal end of a 25 mm circular stapler (Weike). Pathology of the frozen section of the resected margin suggested "no tumor involvement". The splenorenal, phrenicosplenic and splenocolic ligaments were separated. The spleen was flipped and raised; the dorsal tissues of the pancreas were divided, and the pancreatic tail and spleen were lifted. Lymph nodes along the upper edge and dorsal side of the pancreas were dissected along the splenic artery. The short gastric vessels (station 4sa) were cut, and the left gastroepiploic vessels (station 4sb) were divided at the roots. Lymph nodes of stations 11 and 10 were then dissected along the splenic artery, vein and their branches. The specimens were completely removed.

Reconstruction

The small intestine was cut 20 cm from the Treitz ligament. An end-to-side anastomosis was made between the distal small intestine and the esophagus using a 25 mm circular stapler (Johnson). A side-to-side anastomosis was made between the proximal intestine and the small intestine 50 cm below the previous esophageal anastomosis using a 25 mm circular stapler (Weike). The stumps were closed using a 80 mm linear dividing stapler (Weike). All stumps and anastomoses were consolidated with absorbable interrupted suture. Holes on the small bowel mesentery were closed using interrupted sutures

Postoperative pathology

(Gastric) ulcerative adenocarcinoma, Grade II, mostly mucinous adenocarcinoma, which invaded all of the layers. No involvement was found in the upper and lower surgical margins. One metastatic lymph node was found out of 22 lymph nodes at the lesser curvature. Multiple tumor nodules were observed. No metastasis was detected in the five lymph nodes from the greater curvature, one lymph node from station 13, and three lymph nodes from station 10 (1/31).

Postoperative chemotherapy regimen

DOF: docetaxel 100 mg/2 h ivgtt + oxaliplatin 200 mg/2 h ivgtt + calcium leucovorin 300 mg ivgtt + 5-FU 0.5 IV, 5-FU 4.5 g civ × 48 h q3w × 6 times.

Prognosis

The patient was followed up regularly three months after surgery. The patient was in a satisfactory general condition by eight months after surgery, without signs of recurrence or metastasis.

Instructions for key steps of the procedure

Kocher incision

The Kocher incision was made at the external side of the duodenum to expose the duodenum and the head of the pancreas (*Figure 1A*). This does not only facilitate the exploration of lymph node stations number 12b, 13 and 16 for intraoperative staging and guiding treatment strategies, but also make it easier to completely remove the greater omentum from its rightmost attachment (*Figure 1B*). In addition, it is also helpful for reducing the anastomotic tension in Billroth I reconstruction following distal subtotal gastrectomy.

Lymph node stations 12b, 13, and 16 are explored

In the present case, enlarged lymph nodes were found in station 12b, lymph nodes around the common bile duct. According to the latest criteria in Japan, a metastatic lymph node in this location should be construed as a staging of M1, making the radical surgery unjustified. Hence, pathology of the frozen section was obtained, and the results suggested no tumor metastasis (*Figure 1C*). No significant enlargement was detected in stations 13, posterior to the pancreatic head, and 16, aside the aorta (*Figure 2A,B*).

Anatomical structures anterior to the pancreatic head and dissection of station 14v

There are multiple variations of the veins anterior to the pancreatic head. In the present case, the right gastroepiploic vein entered the middle colic vein, rather than the Henle trunk. Therefore, caution should be paid when the subpyloric lymph nodes were dissecting, and the anterior superior pancreaticoduodenal vein should be preserved (*Figure 2C*). Dissection of station 14v has remained controversial. Despite the proximal location, the tumor was large and involving the gastric body, so this lymph node station was dissected as well (*Figure 3A*).

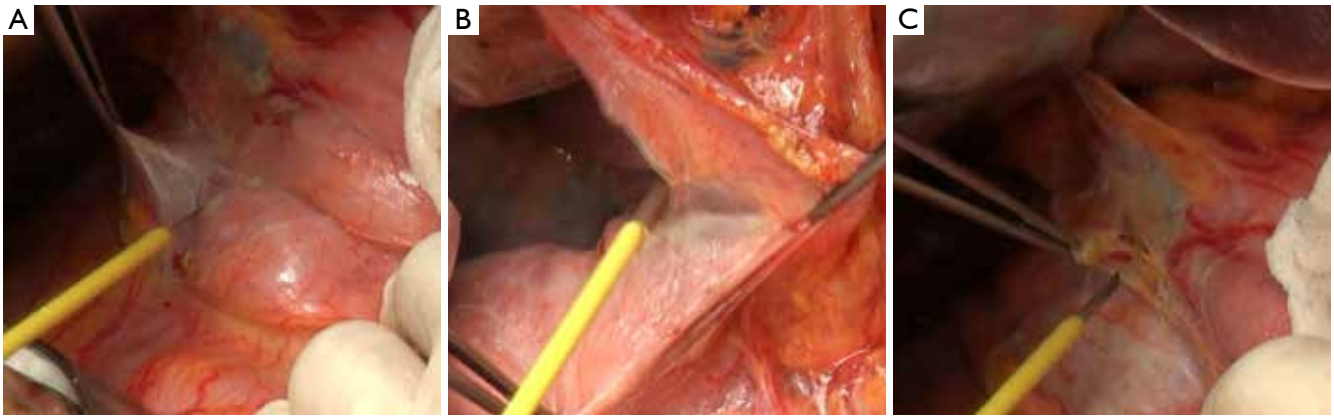

Figure 1 (A) Kocher incision; (B) isolating the attachment point of the greater omentum, followed by complete removal; (C) biopsy of lymph node station 12b.

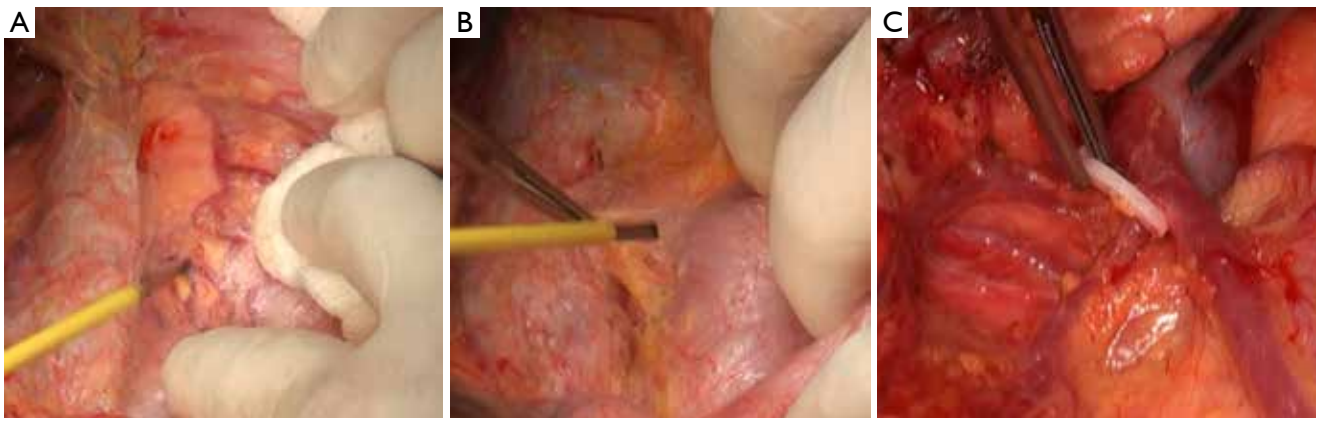

Figure 2 (A) Exploration shows negative results for lymph node station 13; (B) exploration shows negative results for lymph node station 16; (C) anatomy of veins anterior to the pancreatic head (clip: stump of the right gastroepiploic vein).

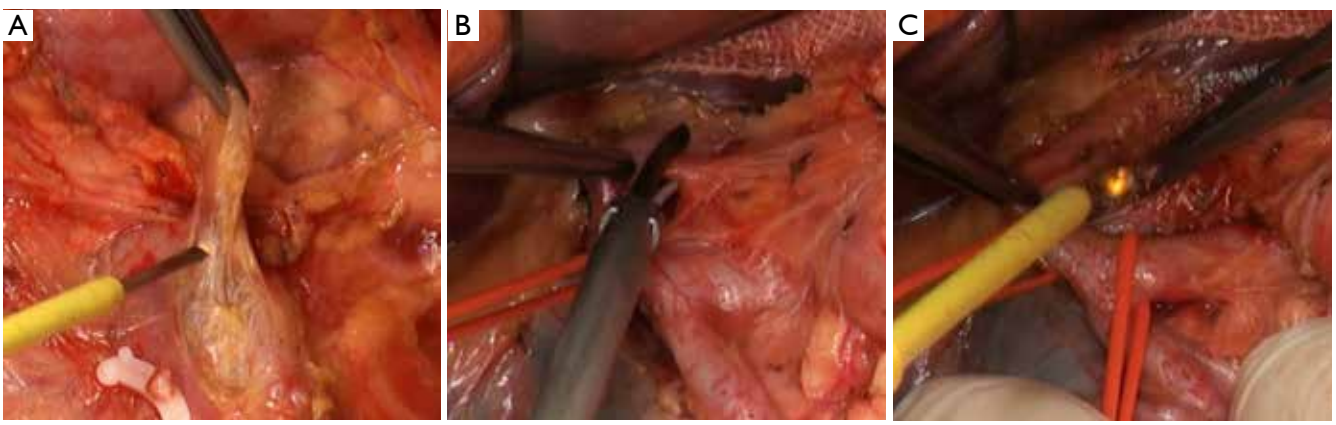

Figure 3 (A) Dissection of lymph node station 14v; (B) color-coded tube pulling PHA in dissection of station 12a; (C) color-coded tube pulling PHA and CHA in dissection of station 12a.

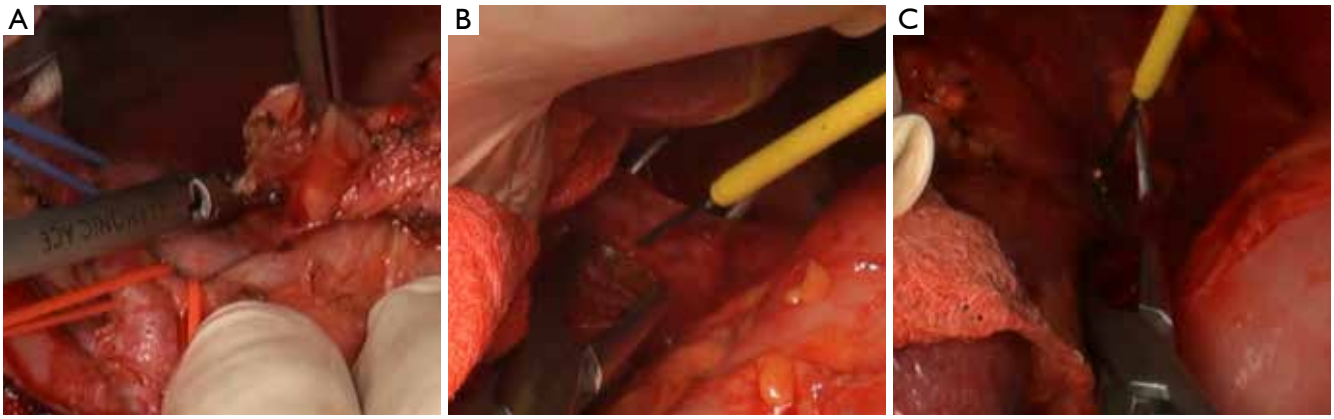

Figure 4 (A) Color-coded tube pulling PV in dissection of station 12p; (B) transecting the splenocolic ligament; (C) dividing the posterior pancreatic space.

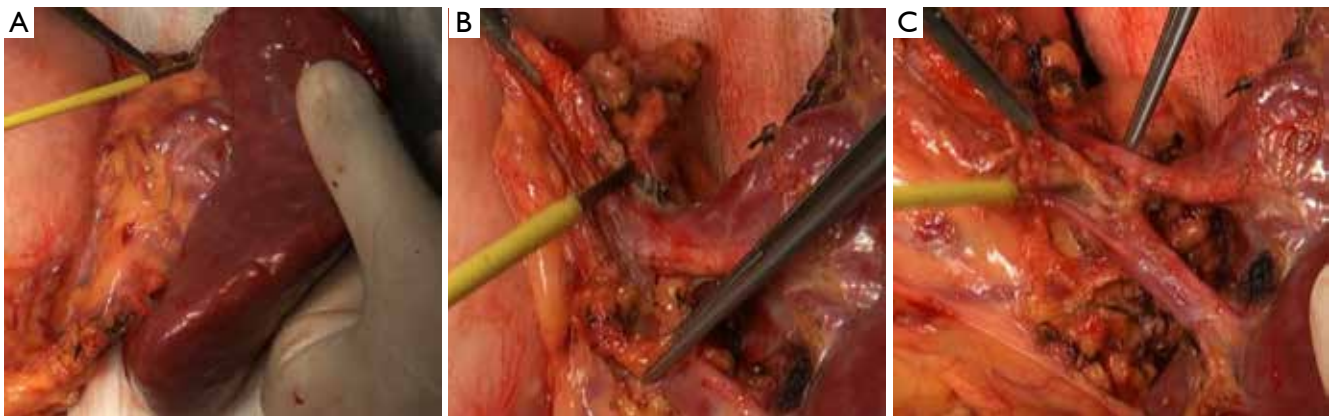

Figure 5 (A) dissection of splenic hilum lymph nodes *in vitro*, part 1; (B) dissection of splenic hilum lymph nodes *in vitro*, part 2; (C) dissection of splenic hilum lymph nodes *in vitro*, part 3.

About dissection of lymph node station 12

There were many lymph nodes in station 12a, and some were posterior to the PHA, making it difficult to dissect. Hence, CHA and PHA were individually isolated, and pulled with the color coded tubes to create a facilitating field under tension (*Figure 3B,C*). In addition, caution should be given to protect the common bile duct during the dissection. Enlarged lymph nodes were also found near the portal vein. To achieve R0 resection, PV was isolated and pulled in the same way for dissection of station 12p (*Figure 4A*).

About dissection of lymph node stations 4sa, 4sb, 10 and 11

Splenic hilum lymph node dissection was performed in this case of advanced proximal gastric cancer. This can be done using *in vitro* or in situ approaches. Based on our experience, we prefer cutting the splenorenal, phrenicosplenic and splenocolic ligaments, and separating the posterior pancreatic space (*Figure 4B,C*), so that the spleen and pancreatic head can be pulled out of the abdominal cavity for ease of dissection. This method is advantageous in that: (I) It allows safer and more thorough dissection under direct vision (*Figure 5*); (II) It is easier to identify the gastric and splenic branches of the splenic vessels, enabling preservation of the intact blood supply to the spleen when dissecting station 4sa (*Figure 6A*); (III) Compared with the *in vivo* and in situ methods, our approach enables better exposure of the root of the left gastroepiploic vessels, leading to thorough dissection of station 4sb (*Figure 6B*); (IV) The tail of the

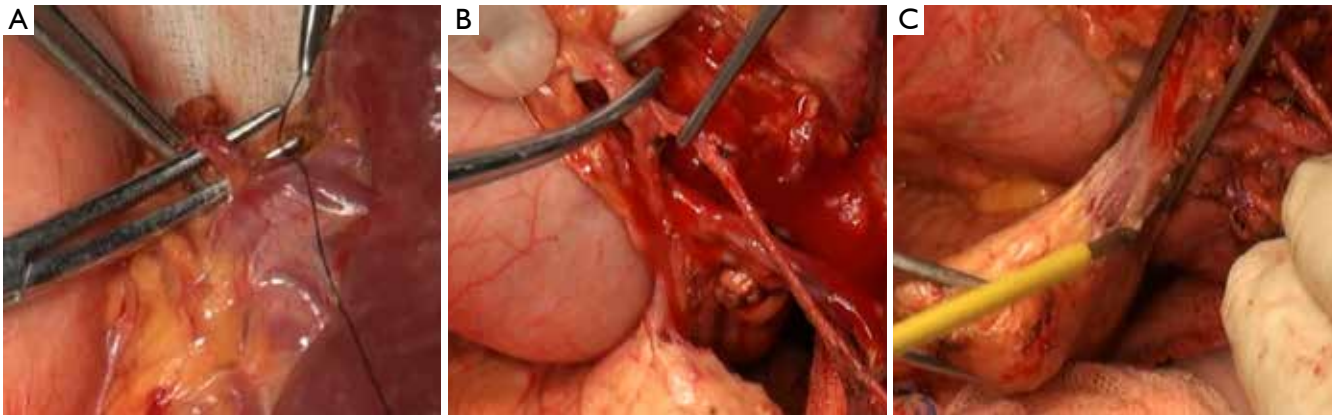

Figure 6 (A) Cutting the short gastric vessels, followed by station 4sa lymph node dissection; B. transecting the left gastroepiploic vessels at the root, followed by lymph node station 4sb dissection; C. isolating and protecting the tail of the pancreas.

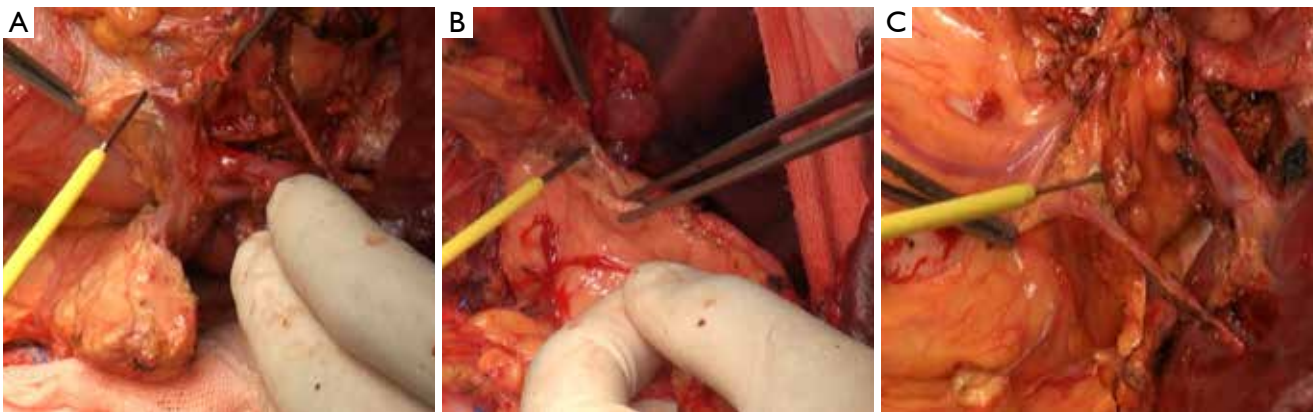

Figure 7 (A) Dissecting lymph nodes station 11d; (B) dissecting lymph nodes station 11p; (C) isolating and protecting the vessels to the lower splenic pole carefully.

pancreas is better protected, avoiding pancreatic injury and postoperative pancreatic fistula (*Figure 6C*); (V) It provides good exposure in favor of the dissection of lymph nodes station 11 (*Figure 7A,B*); (VI) Dissection should be carefully performed to protect the vessels to the lowest splenic pole, as they are often thin and emerge early from the gastroepiploic artery. In situ dissection of station 4sb is associated with a high risk of lower pole ischemia because the vessels are often cut during the procedure. In the present case, these vessels were carefully isolated and protected (*Figure 7C*). The surgical field upon completion of dissection is shown in *Figure 8A*. After that, the spleen and the pancreas were put back in place without the need for fixation. A supine position for 24 hours would be sufficient as splenic torsion is very rare (*Figure 8B*).

Surgical field after dissection (Figures 8C-9B)

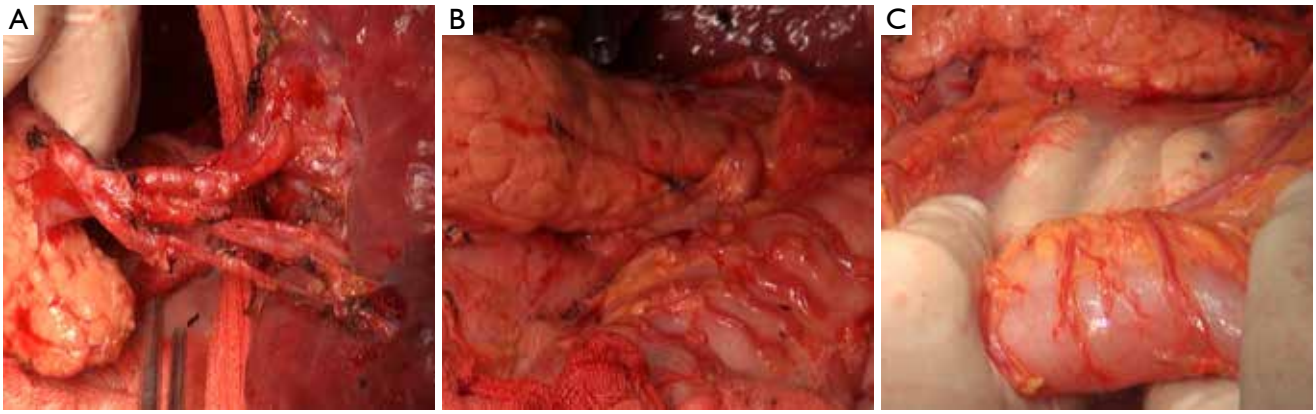

Figure 8 (A) Stations 10 and 11d after dissection; (B) spleen and the pancreatic body and tail were placed back after dissection; (C) transverse mesocolon area.

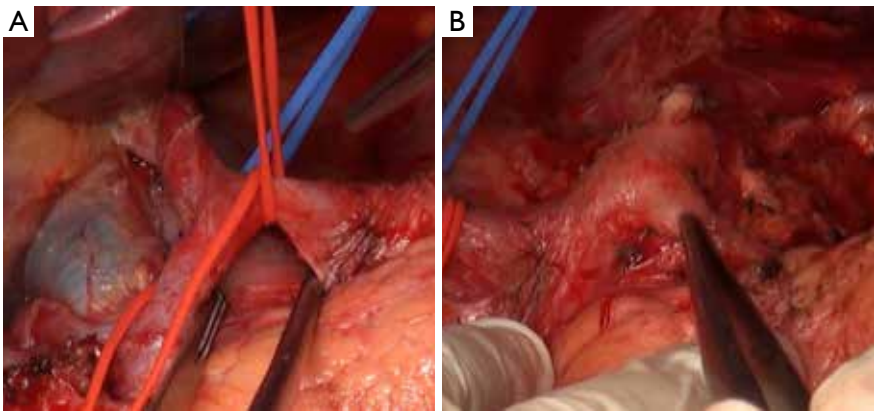

Figure 9 (A) Lymph nodes Station 12; (B) Lymph nodes stations 7, 8a and 9.

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Surgical Video

D2 surgery for a gastric cancer patient after neoadjuvant chemotherapy

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Abstract: This video demonstrates the surgical procedure for a gastric cancer patient who had responded well to pre-operative chemotherapy. Gastric cancer was pre-operatively confirmed by endoscopy. CT showed that the distal gastric cancer directly invaded the head of the pancreas and meanwhile was associated with metastasis in lymph node stations 3, 6, 7, 8, 9, and 11p. The pre-operative pathological stage was $T_{4b}N_2M_0$. The patient responded well to pre-operative chemotherapy. Post-chemotherapy CT showed that a gap appeared between the cancer and the head of the pancreas and the lymph node metastases disappeared. D2 surgery was then performed. Surgical features: the metastatic lymph nodes located at vital sites before chemotherapy as well as the primary tumor may form scar tissues after necrosis and cover the major organs and vessels. The disappearance of the metastatic lymph nodes on CT can not rule out the possibility of cancer, which may be detected by pathology. Therefore, these lymph nodes must be dissected. The surgical operation is challenging.

Keywords: Gastric cancer; neoadjuvant chemotherapy; D2 surgery

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A 36-year-old male patient was admitted due to "upper abdominal discomfort for over one month and vomiting after eating for one month". He was confirmed to be with gastric antrum carcinoma by gastroscopy and biopsy. CT at admission showed that the gastric cancer directly invaded the head of the pancreas and meanwhile was associated with metastasis in lymph node stations 3, 6, 7, 8, 9, and 11p. The cancer was closely involved with the hepatic common artery, root of the splenic artery, abdominal arteries, and root of the left gastric artery. Surgical resection can be challenging. Therefore, a pre-operative FLEEOX chemotherapy was applied. The FLEEOX regimen consisted of a slow intravenous infusion of 5-fluorouracil (5-FU) 370 mg/m^2 over 5 days and an intravenous infusion of leucovorin (calcium folinate) 200 mg/m^2 over 5 days, then oxaliplatin 120 mg/m^2, epirubicin 30 mg/m^2, and etoposide 70 mg/m^2 were injected into the tumor site on days 6 and 20. Each cycle lasted 5 weeks.

After two cycles of treatment, a second CT showed that the metastatic lymph nodes completely disappeared, and only scar left at the primary lesion. He received D2 surgery ten days after the chemotherapy was completed (*Video 1*).

Video 1 D2 surgery for a gastric cancer patient after neoadjuvant chemotherapy.

The metastatic lymph nodes located at vital sites before

chemotherapy may form scar tissues after necrosis and cover the major organs and vessels. Therefore, these scar tissues must be peeled off from the vital vessels during the D2 surgery. The surgery, particularly when lymph node stations 6, 5, 8, 9, 11p, and 7, are dissected involving with multiple sites, can easily cause bleeding and therefore is quite difficult.

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Surgical Video

Laparoscopy-assisted D2 radical distal subtotal gastrectomy

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Abstract: The laparoscopic surgery for gastric cancer has been a hot spot in the development of gastric cancer surgery during recent years. The perigastric lymph nodes were divided into five regions and then dissected by laparoscopy in our hospital, according to the extent of lymph node resection of D2 gastric cancer surgery specified in the *Japanese Surgical Guidelines for Stomach Cancer* and the *Japanese Gastric Cancer Treatment Protocols* (14th edition): (I) the peripheral lymph nodes of gastro-omental vessels in the left and lower region of the stomach (stations 4d and 4sb); (II) the peripheral lymph nodes of the inferior pylorus and superior mesenteric vein in the right and lower stomach (stations 15, 14v, and 6); (III) the lymph nodes in the right and upper stomach (station 5 in the superior pylorus and station 12a in the hepatoduodenal ligament); (IV) the lymph nodes distributed in the central region of the pancreatic body, celiac axis and three branches (stations 7, 8a, 9, and 1lp); and (V) the lymph nodes distributed along the lesser curvature (stations 1, 3 and 5). The lymph nodes were dissected and the stomach was dissociated from the lower side to the upper side and from left to right. The duodenal stump, greater curvature and lesser curvature were transected and closed with Endo-GIA. The specimen was collected through a small incision under xiphoid. The digestive tract was reconstructed by RouX-en-Y gastrojejunostomy under direct vision, followed by incision suture.

Keywords: Gastric cancer; laparoscope; radical distal subtotal gastrectomy

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Clinical data

General data

A 54-year-old male patient was admitted to our hospital due to repeated oppressive pain and discomfort in upper and middle abdomen for 3 months. The oppressive pain and discomfort in upper and middle abdomen occurred without significant causes 3 months prior to the admission, which manifested persistent, dull pain. Gastroscopy performed in our hospital 5 days ago showed ulcerative cancer in gastric angle (*Figure 1*); pathology: tubular adenocarcinoma grade II (*Figure 2*). He was then admitted as with "gastric cancer".

Treatment

Abdominal CT after admission showed (*Figure 3*): (I) The stomach cavity was not fully distended with irregular gastric wall thickening in the gastric antrum, gastroscopy was then advised; (II) some small lymph nodes in the hepatogastric space were detected; (III) possibility of mild expansion of biliary system due to the muddy stones associated with inflammatory change in the lower part of common bile duct was considered; and (IV) bilateral renal multiple small cysts. CA199 12.0 U/mL, CA724 0.9 U/mL, CEA 5.67 ng/mL, AFP 1.8 ng/mL. Preoperative diagnosis was tubular adenocarcinoma in lesser curvature of gastric antrum with a pT1N0M0 stage. After relevant examinations were completed, D2 laparoscopy-assisted radical distal subtotal gastrectomy was performed on January 28, 2013, followed by anti-infection, acid resistance, and rehydration and nutrition support. The patient was discharged on postoperative day 7, with stitches removed.

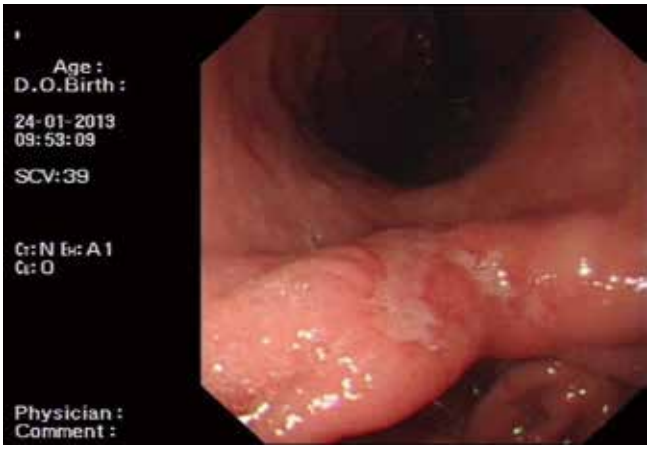

Figure 1 Gastroscopy showed an ulcerative lesion (about 1 cm in diameter) at the lesser curvature of gastric angle.

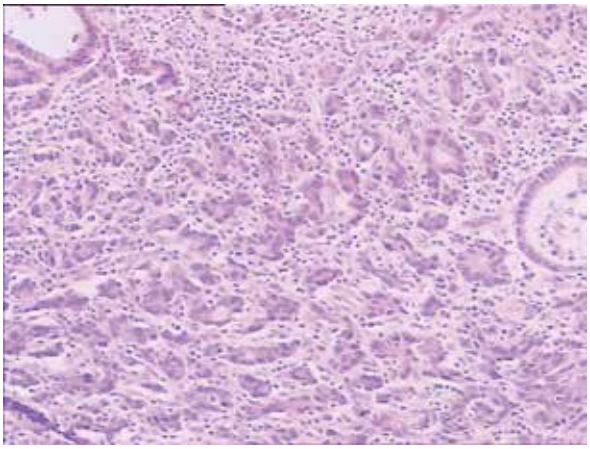

Figure 2 Pathology: tubular adenocarcinoma (grade 2).

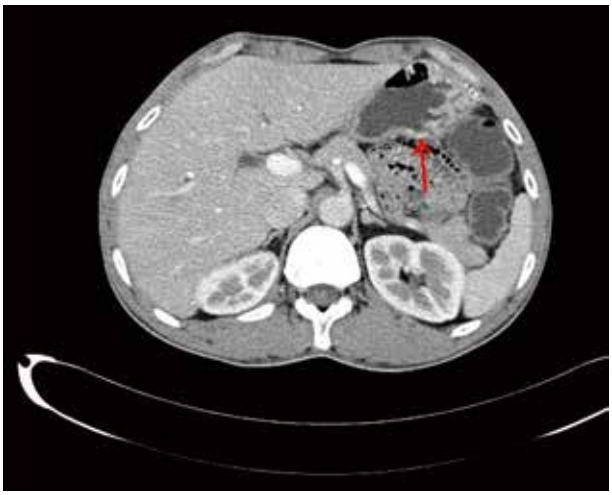

Figure 3 CT showed the irregular thickening of the stomach wall in the gastric antrum.

Video 1 Laparoscopy-assisted D2 radical distal subtotal gastrectomy.

Post-operative pathology

(I) Early grade II tubular adenocarcinoma (IIc) in lesser curvature of gastric antrum with mucosal muscle layer invaded; no cancer infiltration was found in the upper and lower incised margin of surgical specimen and the upper incised margin of the specimen additionally sent for examination. Cancer metastasis: 0/24 in the lymph nodes in lesser curvature, 0/5 at greater curvature, 1/2 at pylorus, and 0/12 under the pylorus; (II) (station 14): the specimen was a fat and vascular tissue. Immunohistochemistry: CK18 (+++) and Ki67 (+90%).

The approach of laparoscopy-assisted radical gastrectomy and lymph node dissection (*Video 1*)

(I) Dissociation of the left and lower region of the greater gastric curvature: The greater gastric curvature was clamped by the assistant using intestinal clamp with the left hand to lift gastrocolic ligament to the head side to expose the surgical field. The greater omentum was separated along the colon from the central region of transverse colon to the splenic flexure of colon with an ultrasonic scalpel to separate the left gastro-omental vessels. The lymph node stations 4d and 4sb

Figure 4 Dissection of lymph node station 4sb.

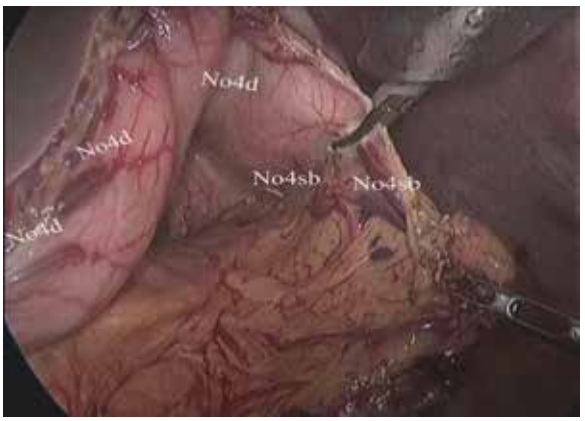

Figure 5 Dissection of lymph node station 4d and 4sb.

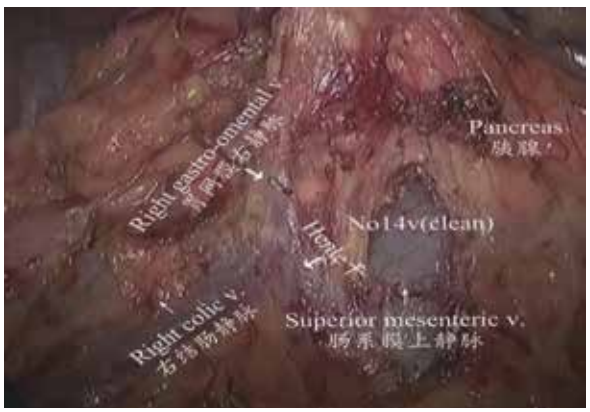

Figure 6 Dissection of lymph node station 14v; dissection of lymph node station 14v after the transection of right gastroepiploic vein.

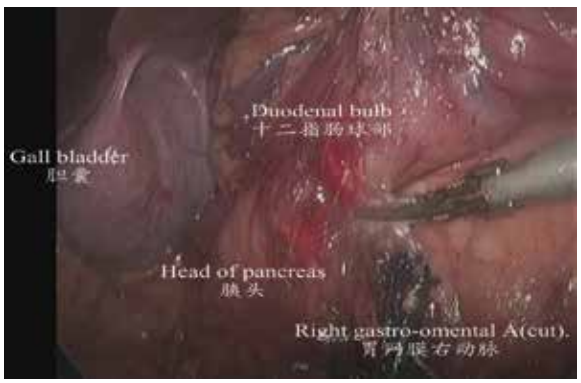

Figure 7 Dissociation of the duodenal bulb after the division of the right gastroepiploic artery at its root.

were dissected as shown in *Figures 4,5*.

(II) Dissociation of the gastric antrum and the lower region of pylorus: The gastric antrum was clamped by an assistant using an intestinal clamp with the left hand to the head side. The transverse mesocolon was pulled to the caudal side by the operator with the left hand and separated along the middle colic vein to the inferior margin of pancreas using an ultrasonic scalpel with the right hand to expose the superior mesenteric vein. The lymph node station 14v was dissected from the inferior side to the superior side. The right colic vein and right gastro-omental vein were exposed by separating the deep surface of the anterior fascia of pacreaticodudenum. The lymph node station 6 was dissected after the right gastro-omental vein was transected at the point it joined the Hennel axis. After that, the right gastro-omental artery root was transected to separate the duodenal bulb as shown in *Figures 6,7*.

(III) The upper and left region of stomach: the gastric and pancreatic folds were clamped by the assistant using an intestinal clamp with the left hand to roll to the head side, pressing the pancreatic head with the right hand. The middle region of pancreas was gently pressed by the operator using an intestinal clamp with the left hand and the gastroduodenal artery; common hepatic artery, proper hepatic artery and right gastric artery were dissected and exposed using an ultrasonic scalpel closely along the margin of the gastric and pancreatic folds. Parts of the lymph node stations 8a, 5, and 12a were dissected as shown in *Figure 8*.

(IV) The region of the upper margin of pancreatic body: The gastric body was clamped by the assistant using an intestinal clamp with the left hand to roll to the head side, pressing the pancreatic body with the right hand. The pancreatic body was gently pressed by the operator

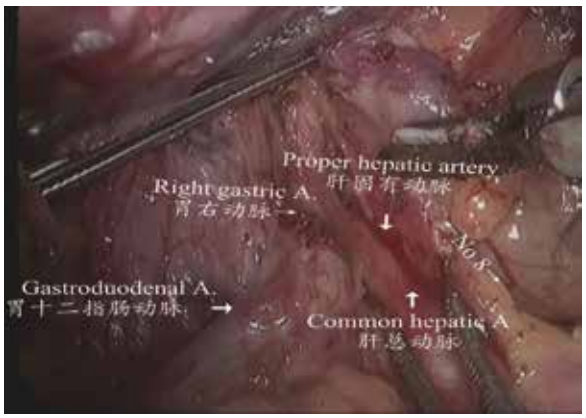

Figure 8 Dissection of lymph node stations 8a, 5, and 12a after the gastroduodenal artery, common hepatic artery, proper hepatic artery, and right gastric artery were exposed.

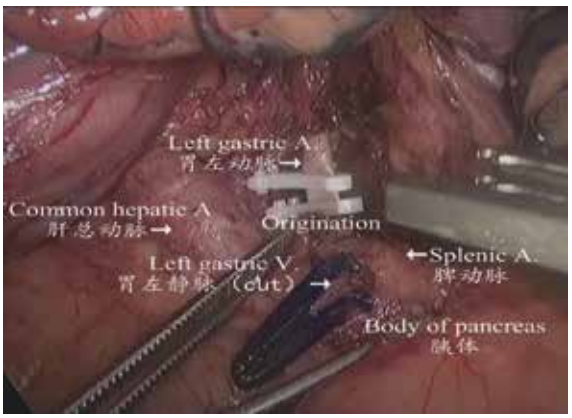

Figure 9 Dissection of lymph node stations 8a, 11d, 9, and 7 after the common hepatic artery, splenic artery, and celiac trunk were exposed.

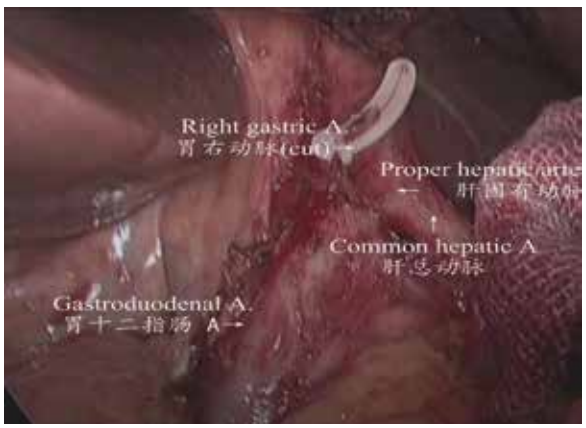

Figure 10 The lymph node station number 12a was dissected from the upper side to the lower side along the anterior side of the proper hepatic artery. The right gastric artery was transected at the root segment to dissect the lymph node station 5.

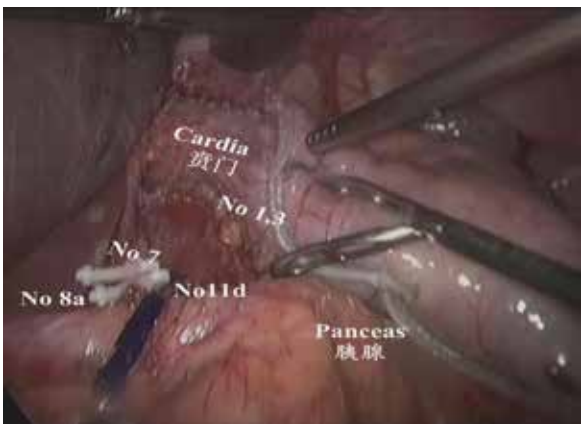

Figure 11 The lymphatic adipose tissue on the right side of the cardia was separated using an ultrasonic scalpel to the middle-upper 1/3 segment of lesser curvature to dissect the lymph node station number 1 as shown in *Figures 10,11*.

using an intestinal clamp with the left hand and the upper margin of the pancreatic capsule was lifted. The common hepatic artery, splenic artery, celiac artery axis and left gastric blood vessels were separated using an ultrasonic scalpel along the anterior side and upper margin of the common hepatic artery from the lower side to the upper side and right to left. The lymph node stations 8a, 11d, 9, and 7 were dissected as shown in *Figure 9*.

(V) Dissociation of the region of the gastric omentum: The liver was lifted by the assistant using an intestinal clamp with the left hand and the stomach was pulled to the lower abdomen using a clamp with the right hand. The operator tracted the hepatoduodenal ligament using an intestinal clamp with the left hand and transected the hepatogastric ligament along the liver to the cardia using an ultrasonic scalpel with the right hand. The lymph node station 12a was dissected from the upper side to the lower side along the anterior side of the proper hepatic artery. The right gastric artery was transected at the root segment to dissect the lymph node station 5. The lymphatic adipose tissue on the right side of the cardia was separated using an ultrasonic scalpel to the middle-upper 1/3 segment of lesser curvature to dissect the lymph node station 1 as shown in *Figures 10,11*.

Figure 12 The surgical field was inspected and the specimen was withdrawn through a 5 to 6 cm small abdominal incision under xiphoid (after suture).

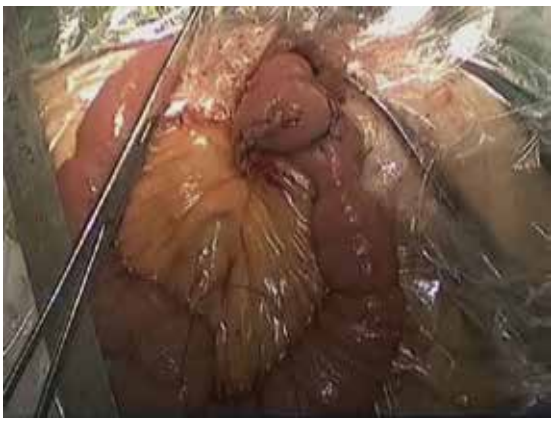

Figure 13 End-to-side anastomosis under direct vision was performed between the proximal jejunum about 15 cm to the Treitz ligament and the jejunum 45 cm to the stump.

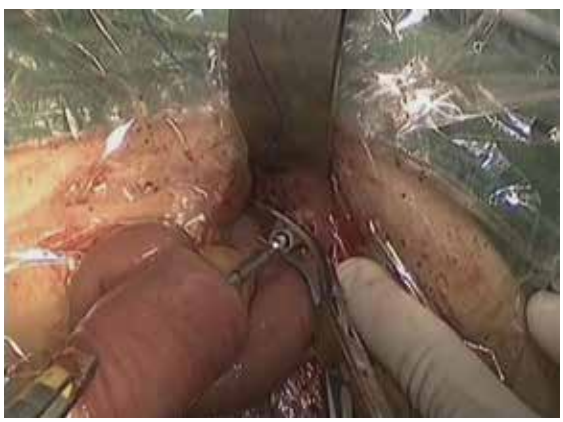

Figure 14 End-to-side anastomosis under direct vision was performed between the distal jejunal stump and stomach to reconstruct the digestive tract.

(VI) The duodenal stump, greater curvature and lesser curvature were transected and closed with Endo-GIA and the stomach was transected then for the local irrigation. The surgical field was inspected and the specimen was withdrawn through a 5 to 6 cm small abdominal incision under xiphoid. The digestive tract was reconstructed by RouX-en-Y gastrojejunostomy as shown in *Figures 12-14*.

Conclusions

The newly updated Japanese gastric cancer treatment guidelines has defined D2 radical treatment as the standard radical treatment for gastric cancer, with its indications including stage IB, stage II and some stage III cases. In 1991, Japanese surgeons for the first time reported the application of laparoscopy-assisted distal gastrectomy for early gastric cancer, which showed similar short- and long-term efficacies like the conventional open surgery (1-3). However, few studies with large number of cases have explored the role of D2 surgery in treating advanced gastric cancer. The key to a successful radical resection is the complete dissection of perigastric lymph nodes. Although this can be challenging, the relevant technques have became optimized, and many studies have demonstrated that D2 surgery can remarkably prolong the survival of patients with advanced gastric cancer. Some clinical trials have also confirmed that laparoscopy-assisted D2 radical resection can achieve the same efficacies as the open surgery in patients with early gastric cancer and part of patients with advanced gastric cancer (4-6). According to our clinical experiences, laparoscopy-assisted D2 radical resection, when we are performing dissociation and dissection in the separate regions, it is superior to the conventional open surgery in terms of surgical trauma, pain, recovery, and abdominal wall scar.

Acknowledgements

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Surgical Video

Radical proximal gastrectomy for gastric carcinoma

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Abstract: Radical proximal gastrectomy is one of the most commonly used conventional surgeries for gastric carcinoma. Its indications include: small early cancer of the upper stomach; localized cancer in the upper stomach; gastric cancer without metastasis; and gastric cancer with only lymph node station 1 metastasis. When the tumor stage was basically confirmed after the corresponding pre-operative examinations, radical proximal gastrectomy was scheduled in this case. With an attempt to share our experiences with colleagues in our hospital and in Qinghai province, we briefly describe this procedure performed in our department in this video, with its main contents including name of surgery, time, key steps, and post-operative pathology.

Keywords: Radical proximal gastrectomy; gastric carcinoma; surgery procedure

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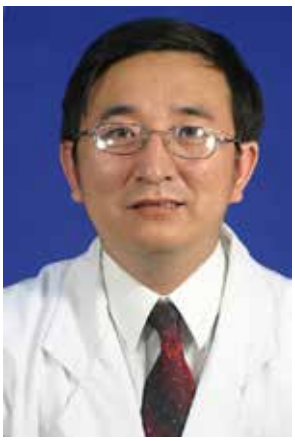
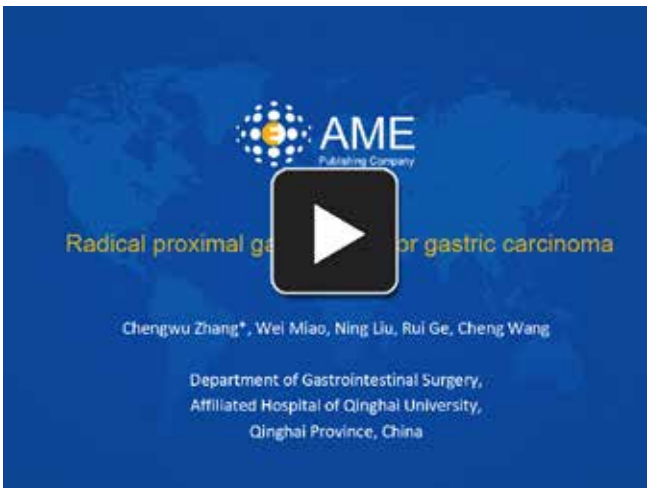


Chengwu Zhang

Video description

The patient was placed supine and in a split-legged position after general anesthesia. After routine disinfection, the surgical field was covered with a sterile surgical towel. An abdominal median incision of about 14 cm was made to gain access to abdominal cavity. After the exploration of the abdominal cavity, radical proximal subtotal gastrectomy was planned (*Video 1*, *Figures 1*-7). The adjacent tissues around the incision were covered by an incision protector. After the greater omentum was flipped and raised, the operator stretched the transverse colon, and separated the omentum along its attachment to the transverse colon with an electric knife. Meanwhile, the anterior lobe of the greater omentum was separated. Along the greater curvature of stomach, splenocolic ligament, gastrosplenic ligament, Huschke's ligament and the left gastroepiploic artery, short gastric artery, and left gastric artery inside it were dissociated, double ligated, and cut. Furthermore, the anterior lobe of the transverse mesocolon was separated, and the adhesion between stomach and pancreatic capsule were dissociated, whereas the gastric branches of the right gastroepiploic vein and the right gastric artery were preserved. After the hepatogastric ligament was cut along the liver edge (up to the right side of the esophagus), both sides of the esophagus and its anterior and posterior walls (about 5 cm) were dissociated. The gastric body was pulled down. The gastric tube was inserted into the esophagus. Purse-string device was placed 3 cm above the cardia. After the esophagus was transected, the stapler was inserted and the purse string was tightened to cut away about three-fourths of the stomach. The body of stomach was transected at 6 cm to the lower border of the tumor. The residual stomach at the lesser curvature was closed with a surgical stapler. The stump was buried with purse, and the seromuscular layer was sutured. After the residual stomach was lifted up, the incision was opened to insert the stapler,

which reached out the posterior wall of stomach. The staple (domestic 26# stapler) rod was attached to the staple body. The stapler and flip the switch was tightened to complete the anastomosis between stomach and esophagus. Efforts must be made to ensure the accuracy and patency of the anastomosis. The integrity of the anastomosis ring should be checked. After the placement of the feeding tube and the gastric tube, the greater curvature of stomach was closed using a stapler. The stump was similarly buried as in the seromuscular layer. The esophagogastric anastomosis was sutured in a continuous manner. The anastomosis tension was decreased. 5-fluorouracil was intraperitoneally injected, which would be released at a constant concentration in 500 hours. A drainage tube was placed at the left side of the esophagogastric anastomosis to check whether there was any active bleeding. After the gauzes and surgical instruments were carefully checked off, the peritoneum was closed, and the muscles and skins were sutured. The surgery was successful, during which the anesthesia was satisfactory. The intraoperative blood loss was about 180 mL. The patient was taken back to the ward after she had regained consciousness. After communication with the patient's family, the specimens and lymph node stations were sent for pathological examination.



Video 1 Radical proximal gastrectomy for gastric carcinoma.

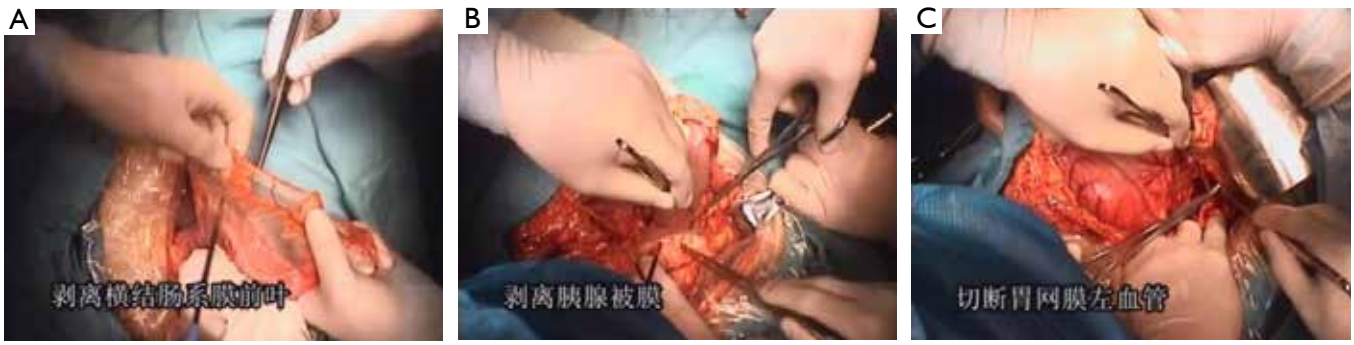


Figure 1 (A) Dissection of the anterior lobe of the transverse mesocolon; (B) dissection of pancreatic capsule; (C) transection of left gastroepiploic vein.

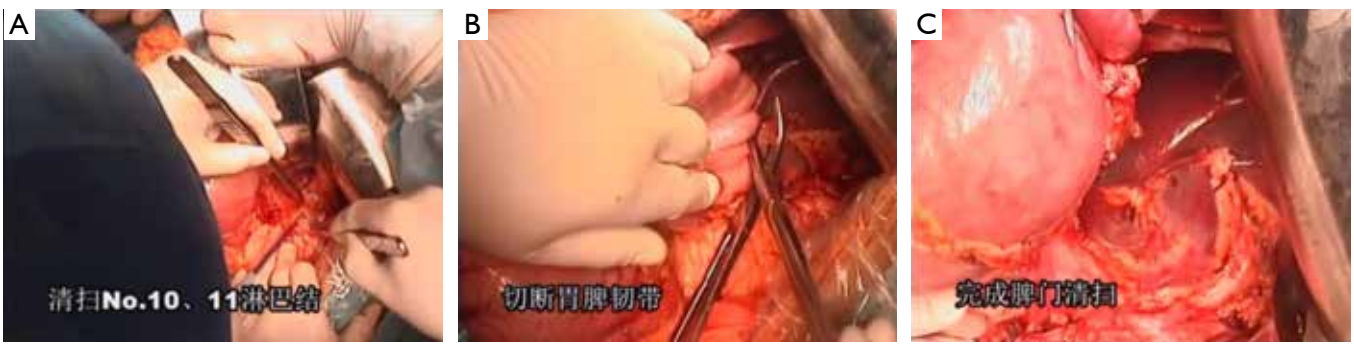


Figure 2 (A) Dissection of lymph node stations 10 and 11; (B) transection of gastrosplenic ligament; (C) dissection of splenic hilar lymph nodes.

Figure 3 (A) Dissociation of abdominal esophagus; (B) incision in lesser omentum; (C) dissection of lymph node station 5 and transaction of right gastric vessels.

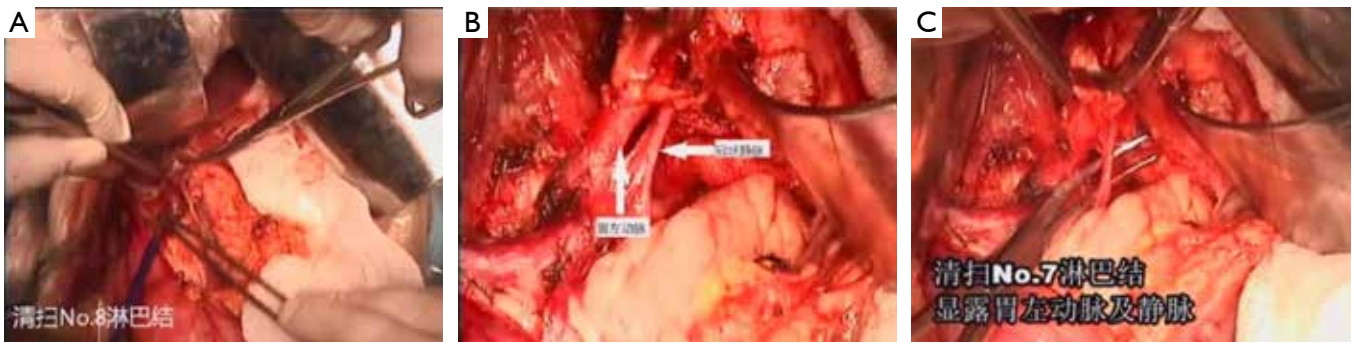


Figure 4 (A) Dissection of lymph node station 8; (B) left gastric artery; Coronary vein; (C) dissection of lymph node station 7; the left gastric artery and vein were exposed.

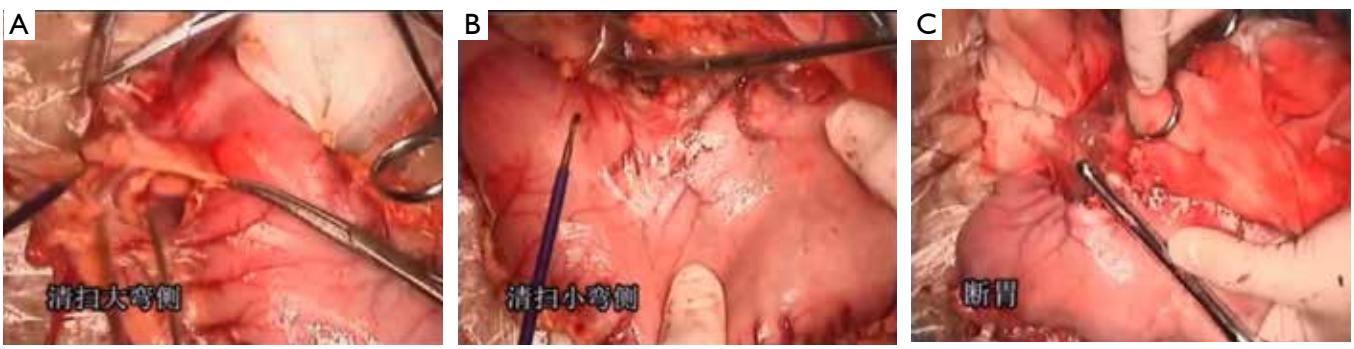


Figure 5 (A) Dissection of lymph nodes in the greater curvature of stomach; (B) dissection of lymph nodes in the lesser curvature of stomach; (C) isolating the stomach.

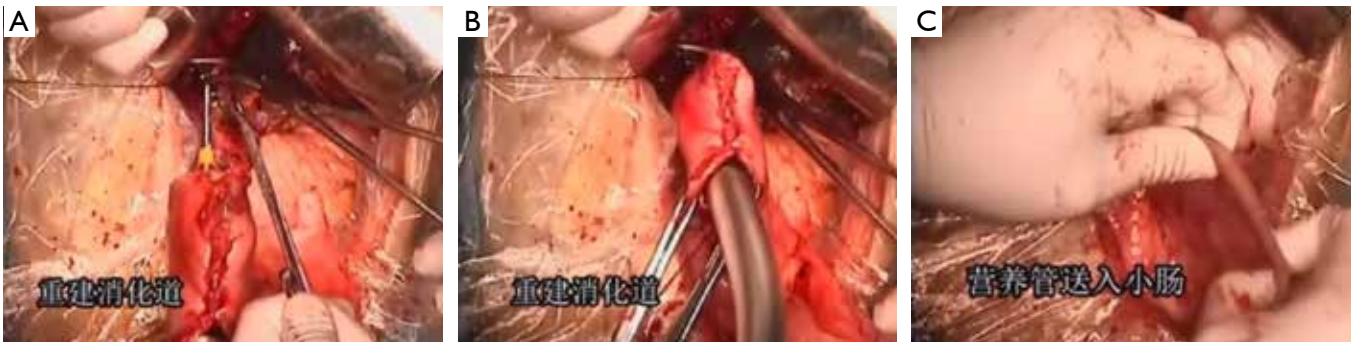


Figure 6 (A) Digestive tract reconstruction; (B) digestive tract reconstruction; (C) placing the feeding tube into the small intestine.

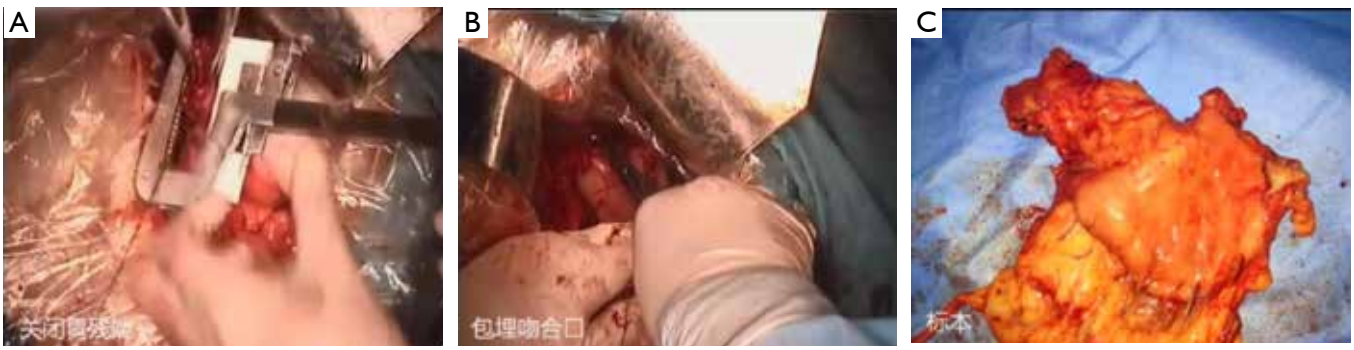


Figure 7 (A) Closure of the gastric stump; (B) buried suture of the anastomosi; (C) specimens.

Acknowledgements

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Surgical Video

Laparoscopic D2 dissection for gastric cancer

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Since laparoscopy-assisted gastrectomy (LAG) was initially reported in 1994, laparoscopic gastrectomy has been widely accepted especially in patients with early-stage gastric cancer. However, LAG for the treatment of advanced gastric cancer (AGC) has remained controversial, mainly due to its technical difficulties in systematic lymph node dissection and doubts about the effectiveness of lymphadenectomy compared to conventional open gastrectomy. Now we share a case of laparoscopic D2 dissection for gastric cancer to confirm the feasibility and efficacy of laparoscopy-assisted gastrectomy (LAG) for advanced gastric cancer (AGC) without serosal exposure, which can achieve the same radicalness as open gastrectomy by the experienced surgeon. (*Video 1*, *Figures 1-8*)

Video 1 Laparoscopic D2 dissection for gastric cancer.

Figure 1 (A) The greater omentum was first dissected, using the ultrasonicactivated scissors, along the border of the transverse colon; (B) the gastrosplenic ligament was divided and No. 4Sb, and 4Sa were dissected; (C) the superior leaf of the mesocolon and the anterior leaf of the pancreas rightward the pylorus was resected.

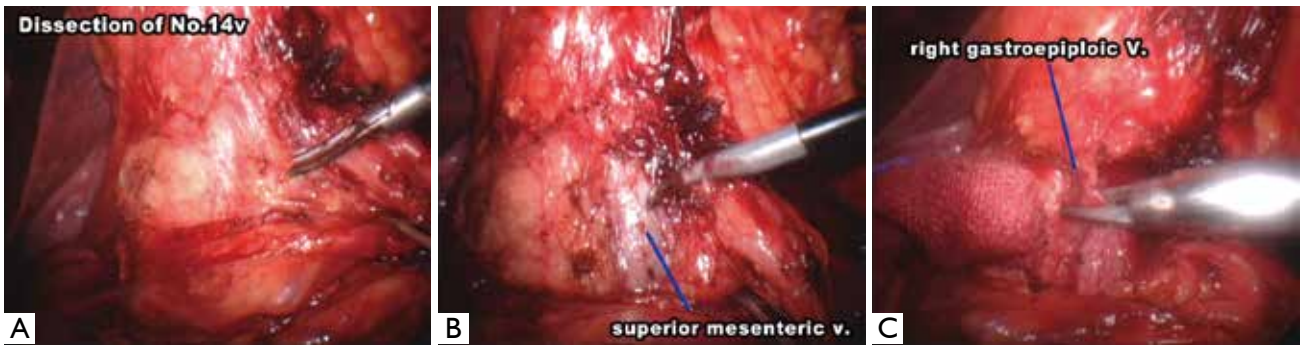

Figure 2 (A) The No.14v lymph nodeswere dissected; (B) the superior mesenteric vein was exposed; (C) the right gastroepiploic vessel was exposed and clamped at its origin.

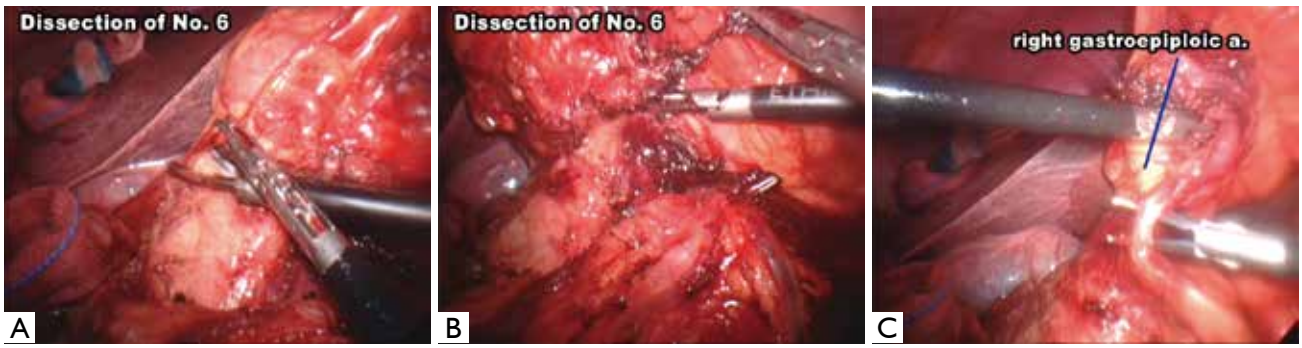

Figure 3 (A) No.6 lymph nodes were dissected; (B) No. 6 lymph nodes were removed; (C) the right gastroepiploic artery was dissected.

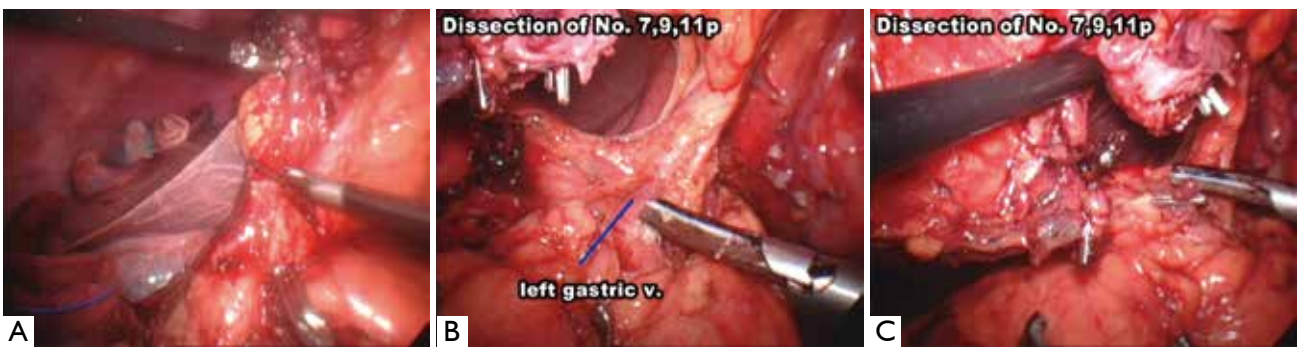

Figure 4 (A) The right gastroepiploic artery was clamped at its origin; (B) No. 7, 9, 11p lymph nodes were dissected; (C) the left gastric vein was clamped at its origin.

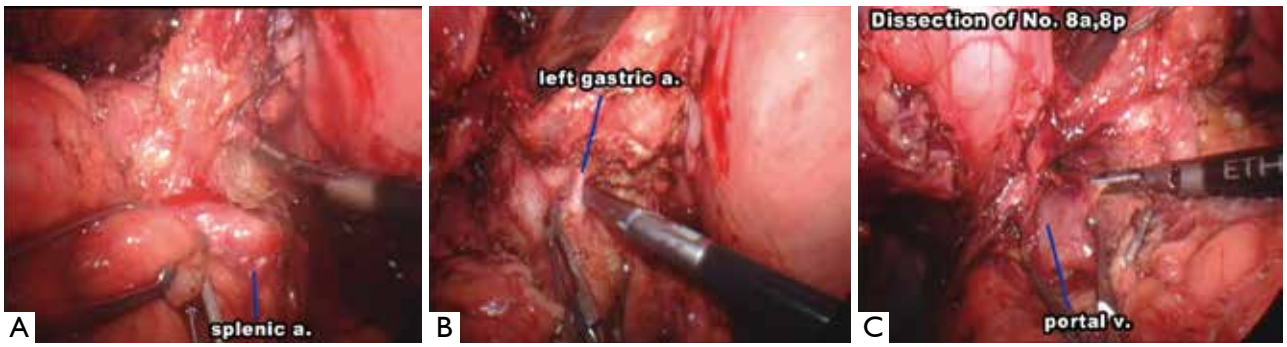

Figure 5 (A) The gastrosplenic ligament was divided and resected along the edge of spleen; (B) the left gastric artery was divided and cut from the celiac trunk; (C) No. 8a, 8p was dissected.

Figure 6 (A) The common hepatic artery was skeletonized along the gastroduodenal artery; (B) No. 12a, 12p, 5 lymph nodes were dissected; (C) the right gastric artery was divided.

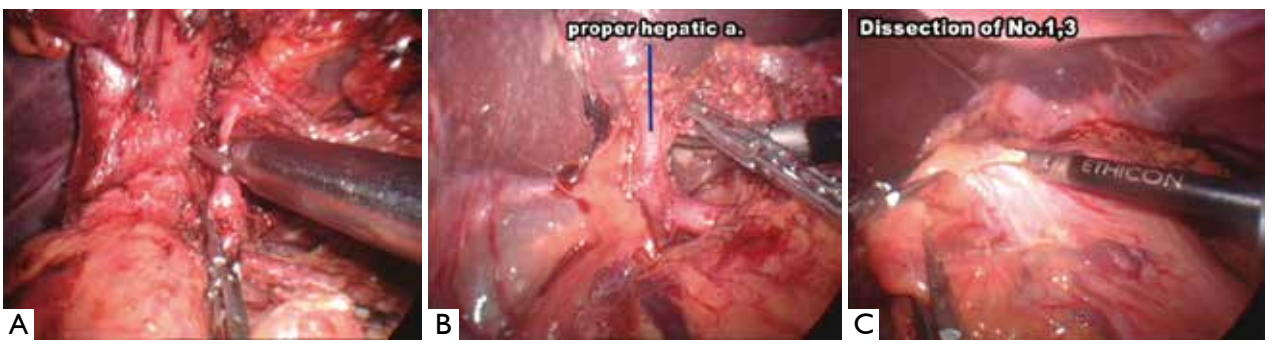

Figure 7 (A) The right gastric artery was cut at its origin; (B) the proper hepatic artery was skeletonized and No. 12a lymph nodes were dissected; (C) the lesser omentum could be resected with dissection of No. 1 and 3 lymph nodes.

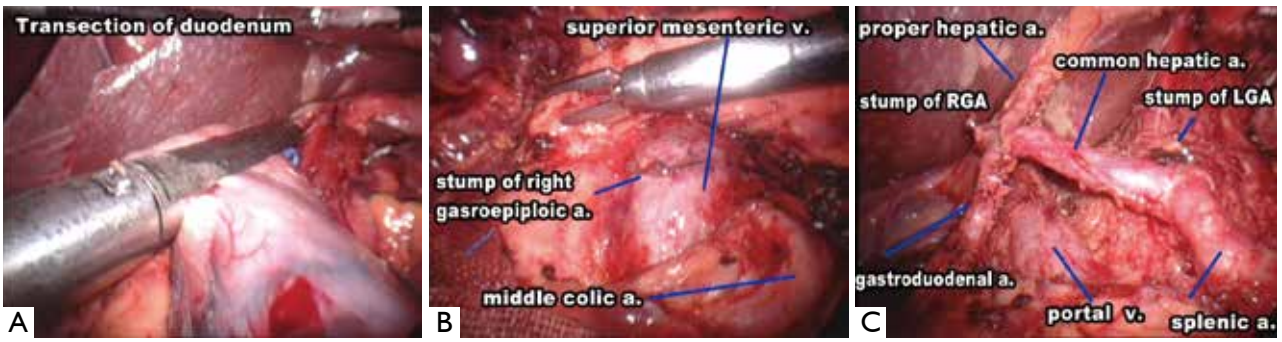

Figure 8 (A) Transection of duodenum; (B) view of skeletonized vascular (superior mesenteric vein, stump of right gasroepiploic artery, middle colic artery); (C) view of skeletonized vascular (proper hepatic artery, stump of RGA, common hepatic artery, stump of LGA, gastroduodenal artery, portal vein, splenic artery).

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Surgical Video

Anatomy of laparoscopy-assisted distal D2 radical gastrectomy for gastric cancer

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Abstract: Laparoscopic gastrectomy has been widely accepted both in China and abroad. Due to the local complex anatomy of stomach and high demand for lymph node dissection, this approach is still hard to be widely performed in primary hospitals. We have begun the laparoscopic gastrectomy since 2009. So far we have completed 349 cases of laparoscopic distal gastric D2 radical surgery.

Keywords: Laparoscopic gastric surgery; anatomy

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Laparoscopic gastrectomy has been widely accepted both in China and abroad. Due to the local complex anatomy of stomach and high demand for lymph node dissection, this approach is still hard to be widely performed in primary hospitals. We have begun the laparoscopic gastrectomy since 2009. So far we have completed 349 cases of laparoscopic distal gastric D2 radical surgery sand summarize the surgical anatomy ideas as follows.

Subjects and methods

General data

The study enrolled 349 patients with gastric cancer undergoing laparoscopy-assisted D2 radical distal gastrectomy from January 2009 to January 2012 in our department, including 180 men and 169 women, aged 29-86 years, with an average age of 57 years. All patients were confirmed as having cancer of the lower gastric body and the antrum by preoperative endoscopy and multi-detector enhanced CT scan. Based on the NCCN guidelines on the pathological staging of gastric cancer (second edition, 2011), there were 70 cases with stage IA, 30 cases with stage IB, 58 cases with stage II, 68 cases with stage IIIA, 73 cases with IIIB, and 50 cases with stage IV.

Methods

Laparoscopy-assisted D2 radical distal gastrectomy was performed on all patients. Under general anesthesia, each of the patients was placed in a supine position with the legs apart. The surgeon stood at the left side of the patient, the assistant at the right side of the patient, and the camera holder between his two legs. Trocar placement: the first port was created in the edge of the umbilical fossa for laparoscopic observation (port A); a 10 mm trocar was placed in the left anterior axillary line below the costal margin as the working port (port B); a 5 mm auxiliary port was created slightly above and 5 cm to the left of the umbilical fossa (port C); a 5 mm secondary auxiliary working port was inserted in the right midclavicular line parallel to umbilicus (port D); and the last 5 mm auxiliary port was created in the right anterior axillary line below the costal margin (port E) (*Figure 1*).

The surgery involved seven anatomical regions, focusing on proper exposure and dissection of layers of structures based on surface markers throughout the procedure.

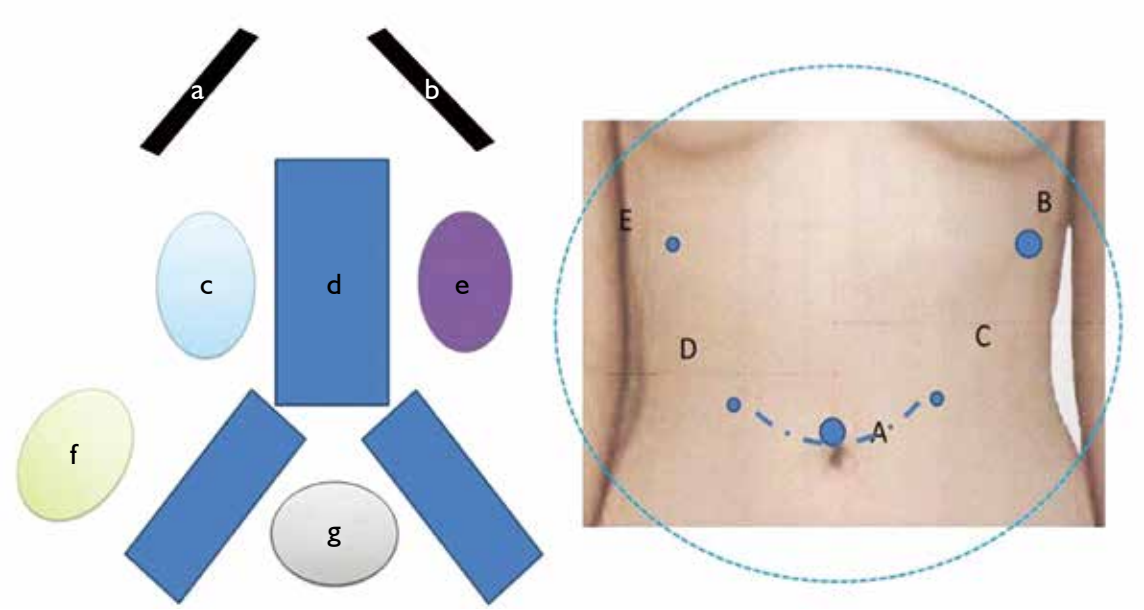

Figure 1 Positions of the patient, operators and trocar placement (the smiley-face configuration). a. Primary monitor; b. Second display; c. Assistant; d. Operating table; e. Surgeon; f. Nurse; g. Camera holder.

Results

Procedures and experiences

The surgery fields involved seven anatomical regions, including the greater omentum-transverse colon field, colon-spleen lower field, antrum-pylorus lower field, right anterior pancreas plane field, central upper pancreatic edge field, lesser curvature posterior wall field, and subhepatic lesser curvature anterior wall field. In each of the regions, the structures readily visible without surgical dissection were referred to as "surface markers", in opposite to deep structures, which had to be exposed by proper separation of anatomical spaces. Proper exposure and dissection of various structural layers based on surface markers throughout the procedure was the key to successful lymph node dissection (*Figure 2A*, *Table 1*).

Greater omentum-transverse colon field

The assistant lifted and extended the greater omentum to maintain mild tension at its attachment to the transverse colon. The operator stretched the transverse colon with forceps in the left hand, and separated the omentum along its attachment to the transverse colon with an ultrasonic scalpel or hook-type electrotome in the right hand. The operation started from the middle of the transverse colon, extending to the splenic flexure on the left and the hepatic flexure on the right (*Figure 2B*). The anterior and posterior lobular spacing of the transverse mesocolon was explored and identified. The goal in this region was to fully divide the gastrocolic ligament into the lesser sac and expose the deeper structures such as of the posterior wall of the stomach and pancreas (*Figure 2C*).

Colon-spleen lower field

The assistant pulled the omentum to the right side of the abdomen as far as possible, pushed the posterior gastric wall to the upper right with the left forceps to fully expose the pancreatic tail, and stretched part of the greater omentum with the right forceps. Using an ultrasonic scalpel, the surgeon divided along the anterior space of the pancreas between the capsule and the tail of the pancreas (*Figure 2D*) until the upper edge, exposing the splenic artery and vein around the splenic hilum. Lymph nodes No. 10 and No. 11 were dissected along the spleen vascular trunk to the splenic hilum, exposing the roots of the left gastroepiploic vessels. The gastroepiploic left blood vessels were clamped and cut. After some of the short gastric vessels were divided, the greater omentum was cut along the greater curvature to expose the greater curvature. Lymph nodes No. 4 were dissected (*Figure 2E*).

Antrum-pylorus lower field

The assistant lifted the gastric wall from the antrum and greater curvature side with the left forceps, and extended

Figure 2 (A) Dissection sequences by region; (B,C) surface markers and deep structures in the greater omentum-transverse colon field; (D,E) surface markers and deep structures in the colon-spleen lower field; (F,G) markers and deep structures in the antrum-pylorus lower field; (H,I) surface markers and deep structures in the right anterior pancreas plane field; (J,K) surface markers and deep structures in the central anterior pancreas plane field; (L,M) surface markers and deep structures in the lesser curvature posterior wall field; (N,O) surface markers and deep structures in the subhepatic lesser curvature anterior wall field.

Table 1 Specific regional fields and dissection scope

Region	Surface marker	Deep structures	Separating plane	Dissection involvement
Greater omentum-transverse colon field	Greater omentum and transverse colon	Posterior wall of the stomach, anterior plane of the pancreas, and lesser curvature	Attachment of greater omentum to the transverse colon	Greater omentum
Lower spleen pole-transverse colon-splenic flexure field	Splenic flexure of the colon and spleen tail of the pancreas and stomach wall left gastroepiploic vascular pedicle	Pancreatic parenchyma Splenic artery & vein left gastroepiploic vessels short gastric vessels	Space anterior to the pancreatic tail	No. 4 No. 10, 11
Antrum-pylorus lower field	Transverse mesocolon Antrum, duodenal bulb, pancreatic head, pancreatic neck, and right gastroepiploic vascular pedicle	Superior mesenteric vein gastrocolic vein trunk right gastroepiploic artery and vein duodenal wall pancreatic parenchyma	Anterior and posterior lobular space of transverse mesocolon, posterior space of pancreatic neck, and anterior space of pancreatic neck	Transverse mesocolon anterior lobe No. 6 No. 14v, 15
Right anterior pancreas plane field	Antrum and posterior duodenal wall pancreatic head and pancreatic neck right gastric vascular pedicle	Gastroduodenal artery common hepatic artery proper hepatic artery right gastric artery	Anterior space of pancreatic head and posterior space of the upper pancreatic edge posterior space of hepatoduodenal ligament	No. 5 No. 8, 12
Central anterior pancreas plane field	Posterior wall of the gastric body pancreas neck and pancreatic body left gastric vascular pedicle	Left gastric artery and vein splenic artery common hepatic artery	Anterior space of pancreatic body and posterior space of the upper pancreatic edge	No. 7, 8, 9 No. 11
Posterior gastric wall-lesser curvature field	Posterior wall of the gastric body lesser omentum liver surface	Posterior gastric wall with the lesser curvature exposed	Attachment of lesser omentum to the lesser curvature	No. 1, 3
Anterior gastric wall-lesser curvature subliver field	Anterior wall of the gastric body lesser omentum liver surface hepatoduodenal ligament	Gastric wall with the lesser curvature exposed proper hepatic artery upper edge of the exposed duodenal bulb	Attachment of lesser omentum to the lesser curvature attachment of lesser omentum to the liver surface	No. 1, 3, 5

the remaining part of the greater omentum with the right forceps to fully expose the anterior and posterior lobular spacing of the transverse mesocolon. The surgeon then divided along this space along the mesocolon (*Figure 2F*) to gradually expose the middle colic vessels and right colic vein. Lymph nodes No. 15 were dissected. The trunks of the gastrocolic vein and right gastroepiploic vein were clamped at their intersection, and the latter was cut. The separation continued on the right side, involving the anterior mesocolon and omentum, until the posterior outer side of the duodenal bulb. As separation continued along the posterior pancreatic space under the pancreatic neck, the superior mesenteric vein was exposed and lymph nodes No. 14 were dissected. After the root of the right gastroepiploic artery was exposed during the course, the vessel was clamped and cut. The posterior medial wall of the duodenal bulb was exposed. Dissection of lymph nodes No. 6 was completed (*Figure 2G*).

Right anterior pancreas plane field

With the assistant holding the gastric body and the antrum up with two pairs of forceps, making the duodenal bulb straightened and slightly extended towards the right side, the operator separated the anterior pancreatic space between the capsule of the pancreatic head and neck and the pancreatic parenchyma towards the patient's head (*Figure 2H*) to expose the gastroduodenal artery. The upper edge of the pancreas was then separated to divide the hepatopancreatic fold, entering the posterior pancreatic space and exposing the common hepatic artery. The separation continued towards the right side along the anterior space of the common hepatic vessels to the intersection with the gastroduodenal artery, entering the posterior space of the hepatoduodenal ligament on the head side to expose the trunks of the proper hepatic artery and the right gastric artery. The latter vessel was clamped and cut. The ligament was dissected along the surface of the proper hepatic artery. Some of the lymph nodes of No. 12, 5 and 8a were dissected in this region. (*Figure 2I*)

Central anterior pancreas plane field

The assistant lifted the gastropancreatic fold with forceps in the left hand to maintain a certain tension, flipped the greater curvature forward to make it under the liver, and held up the antrum or pressed down the pancreas with forceps in the right hand to fully expose the upper edge of the pancreas. The surgeon lifted the pancreatic capsule and separated the anterior pancreatic space to that upper edge (*Figure 2J*), divided the gastropancreatic fold along the edge, and entered the posterior pancreatic space to expose the trunks of the common hepatic artery the abdominal artery. The left gastric artery and vein, splenic artery, and part of the common hepatic artery were exposed. The left gastric artery and vein were clamped and cut. Lymph nodes No. 7, 8 and 9 were dissected. Group No. 11p was dissected along the anterior space of the splenic artery from the posterior pancreatic space towards the splenic hilum. The gastrophrenic ligament was partially separated to expose both crura of diaphragm (*Figure 2K*).

Lesser curvature posterior wall field

The assistant lifted the gastric wall on the greater curvature side with the left forceps, and extended the lesser omentum with the right forceps to expose its attachment to the lesser curvature. The operator divided individual layers of the lesser omentum from left to right along the lesser curvature to expose its gastric wall (*Figure 2L,M*).

Subhepatic lesser curvature anterior wall field

With the assistant holding up the liver, the surgeon dissected the lesser omentum along its attachment to the lesser curvature to expose the corresponding gastric wall, resected the lesser omentum along the hepatic surface, and removed the tissues on the surface of the hepatoduodenal ligament. The upper edge of the duodenum bulb was exposed and lymph nodes No. 3 and No. 5 were dissected (*Figure 2N,O*).

Surgical outcomes

The operative time ranged from 120 to 210 mins in the observed patients, with intraoperative bleeding of 50-200 mL. Transition to open surgery was required in five patients, mainly due to large BMI and the consequently unclear surgical field. No death due to the surgery was reported. Postoperative pathologic staging confirmed 60 cases with stage IA, 33 cases with stage IB, 62 cases with stage II, 60 cases with stage IIIA, 62 cases with stage IIIB, and 72 cases with stage IV. As for postoperative complications, there were five cases with duodenal stump leakage, two cases with gastroparesis, and three cases with small bowel obstruction. All of them were improved by conservative treatment.

One patient with intraperitoneal bleeding from small branches at the splenic hilum was improved via a second operation.

Discussion

The application of laparoscopic techniques in D2 radical distal gastrectomy for advanced gastric cancer has been gradually recognized (1). A full understanding of the complex anatomical structure around the stomach, as well as a refined procedure protocol, is the key to the success of a high quality operation (2). We have summed up some experience of laparoscopy-assisted D2 radical distal gastrectomy for advanced gastric cancer based on the anatomical characteristics of the stomach, in accordance with the principles of laparoscopic operation.

Subregional operations following the principles of laparoscopic operation

Compared with traditional open surgery, laparoscopic surgery enables larger view of a local field, and presents the anatomical structures more clearly. However, the vision

under laparoscope is not sufficiently broad, and it is not as easy to switch across different fields as it would be in an open surgery. Therefore, sub-regional operations, in which the operating field is not switched before all possible operations have been done in a given region, become the inevitable choice for laparoscopic radical gastrectomy, because it is the only way to avoid the inconvenience of repeated switch between fields and improve the operation efficiency. This requires the operator take the following aspects into account: (I) what are the main tasks to be accomplished in each region; (II) what are the starting and ending points in each region; (III) what quality standard is achieved upon completion of each region; and (IV) what are the challenging points for each region. Qian *et al.* divided the entire field into five regions during laparoscopic gastric surgery (3), and Li *et al.* employed six subregions (4). These are innovative improvements for the confined field in laparoscopic surgery. Based on our surgical experience, we have developed a seven-subregion configuration for laparoscopy-assisted D2 radical distal gastrectomy, involving local separation and lymph node dissection in the clockwise order from the greater omentum-transverse colon field, to the colon-spleen lower field, the antrum-pylorus lower field, the right anterior pancreas plane field, the central anterior pancreas plane field, the lesser curvature posterior wall field, and the subhepatic lesser curvature anterior wall field.

Exploration of deep structures based on surface markers

Despite the lack of tactile feedback, laparoscopic operation is highly advantageous in the visualization ability compared with traditional open surgery.

We refer to the structures directly visible without dissecting in a fixed field as surface markers. Correct identification of these markers sets a good foundation for accurate surgery. Identification of anatomical structures under laparoscope is also different than the case with open surgery. The camera holder needs to be familiar with the correct distance, direction, and angle.

We use the greater omentum and transverse colon as the surface markers in the greater omentum-transverse colon field, where the operation begins from their attachment point. As soon as the gastrocolic ligament is separated to explore deeper structures, identification of the posterior gastric wall and surface of the pancreas or other structures in the lesser sac indicates the end of operation in this region.

In the colon-spleen lower field, the splenic area of the colon and the pancreatic tail are the surface markers. Although the lower pole of the spleen can be seen in certain patients, it is covered by the greater omentum due to adhesion, making operation in this particular region a challenge during the entire treatment. To deal with the difficulties, we suggest paying attention to the following technical aspects: (I) When the spleen pole is covered by the omentum, the operation should be carried out carefully while exposing it by dividing from shallow to deep individual layers of the greater omentum that is attached to the lateral abdominal wall and the splenic flexure. Clamping of excessive omental tissues with the ultrasonic scalpel should be avoided, so as to prevent splenic injuries by the scalpel tip in a non-visualized area; (II) The tail of the pancreas serves as the essential marker in this region. Separation is carried out from here to the upper edge of the pancreas and the splenic hilum to expose the splenic artery, left gastroepiploic vessels and other structures in depth; (III) After the separation, vessels supplying the spleen from the hilum should be protected and should not be clamped. Otherwise, it can result in focal necrosis of the spleen; (IV) Misidentification of the trunk or main branches of the splenic artery as the left gastroepiploic vessel should be avoided, or extensive necrosis of the spleen may be resulted. In the antrum-pylorus lower field, the surface markers include the antrum, the duodenal bulb, and the head and neck of the pancreas. This part is a continuation of the separation along the anterior and posterior lobular space of the transverse mesocolon from the previous field. The critical area involves this region to the lower edge of the pancreas. The separation is carried out at two levels—the posterior pancreatic space and the anterior pancreatic space—to expose the trunks of the superior mesenteric vein and gastrocolic vein so that lymph nodes No. 14 can be dissected, and to expose deep structures such as the right gastroepiploic artery, respectively.

In the right anterior pancreas plane field, the surface markers include the posterior wall of the duodenal bulb, posterior wall of the antrum, head and neck of the pancreas, and the hepatopancreatic fold. The deep structures to be exposed include the gastroduodenal artery, common hepatic artery, proper hepatic artery, and right gastric artery. The key to the operation in this region is to identify the two vascular converging points—one between the gastroduodenal artery and the common hepatic artery, and the other the right gastric artery and the proper hepatic artery, particularly the latter one. Caution should be paid to identify and avoid the proper hepatic gastric artery when

the right gastric artery is clamped, thus preventing liver injury.

In the central anterior pancreas plane field, the surface markers include the posterior wall of the gastric body, the body of the pancreas, and the gastropancreatic fold. Deep structures to be exposed include the celiac trunk, left gastric vein, left gastric artery, and splenic artery. Identifying the left gastric vein is difficult in this region due to its variations. Typically, the left gastric vein is located in the head side of the common hepatic artery and will enter the portal vein trunk, while some will enter the portosplenic confluence or directly into the splenic vein (5). Those variations are located in the foot side of the common hepatic artery. When it is divided along the upper edge of the pancreas, it is easy to directly cut the left gastric vein without being able to locate the stumps. Hence, caution should be paid during this operation.

Operations in the lesser curvature posterior wall and the subhepatic lesser curvature anterior wall fields are carried out to expose the lesser curvature and dissect the lesser sac, aiming mainly to dissect lymph node groups 1, 3 and 5.

Anatomical spaces provide the proper operating pathway

With less control of bleeding compared with open surgery, and in view that bleeding may obscure the surgical field and make it difficult to proceed, laparoscopic surgery has a higher demand for blood-free operation, and separation along the correct anatomical spaces is the key to guaranteeing this. To sum up, laparoscopy-assisted D2 radical distal gastrectomy involves the following anatomical spaces: the anterior and posterior lobular space of transverse mesocolon, the posterior pancreatic space, the anterior pancreatic space, and the anterior vascular space of major branches of the celiac trunk (common hepatic artery and splenic artery). The pancreas serves as a central marker for identifying these spaces (2).

Subregional operation on a layer by layer basis facilitates understanding of the procedure and standardized dissection, which is essential for increasing the operational efficiency, shortening the learning curve, and improving the quality of surgery.

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Surgical Video

Laparoscopic radical gastrectomy for gastric cancer

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Laparoscopy-assisted distal gastrectomy for gastric cancer was first reported by Kitano *et al*. in 1994, but only for early gastric cancer. In 1997, laparoscopy-assisted D2 radical gastrectomy was performed for the first time by Goh *et al*. for the treatment of advanced gastric cancer and achieved good short-term efficacy, thus dramatically expanded its indications from early gastric cancer to advanced gastric cancer. Up until 2004, roughly 7,800 gastric cancer patients had received laparoscopy-assisted surgery in Japan. Currently, the role of laparoscopic techniques for early gastric cancer has been widely recognized by surgeons. In China, the low early diagnosis rate of gastric cancer has limited the application of laparoscopic radical operations for gastric carcinoma. However, the development of minimally invasive techniques in recent years has facilitated the application of laparoscope in gastrointestinal surgery, and laparoscopic radical gastrectomy has become a promising procedure for gastric cancer. Compared with the conventional open surgery, this approach offers bigger visual fields and larger local magnifications. However, because the gastrointestinal tract is easy to move, it is relatively hard to dissect the lymph nodes and reconstruct the gastrointestinal tract. Therefore, laparoscopic radical gastrectomy remains the most difficult procedure among laparoscopic gastrointestinal operations and therefore can not be widely applied.

Radical resection for gastric cancer includes the following three aspects: (I) Complete resection of the primary tumors and the adjacent tissues involved by these tumors; (II) standardized dissection of the involved lymph nodes; and (III) clearance of the exfoliated cancer cells in the abdominal cavity. Using the high-intensity focused ultrasound (HIFU), the laparoscopic surgery can easily remove the primary tumors and their surrounding tissues. As the stomach is a hollow organ attached with flaky greater and lesser omentums, the gastric tumors and their adjacent tissues can be lifted outside the body via a 4-6 cm abdominal incision and resected under direct vision. Gastrointestinal tract reconstruction is generally completed in vitro. During laparoscopic surgery, lymph nodes are often dissected en bloc, together with their surrounding connective tissues, in order to maintain the integrity of lymph nodes and their lymphatic vessels and reduce cancer cell exfoliation and seeding. As the perigastric lymphatic drainage patterns generally go in parallel with the main arteries of the stomach and lymph nodes of perigastric group 16 (station 3) are mainly distributed adjacent to the various gastric blood vessels, the contextualized dissection of arteries is equally important in laparoscopic surgery. Laparoscopic surgery also demonstrates mange advantages in effectively eliminating exfoliated cancer cells in the abdominal cavity: wide field of vision, polytropical angles of view, and its effectiveness in flushing the various parts of the abdominal cavity. Laparoscopic surgery is comparable and even superior to the open surgery in terms of the distance between the surgical margin and the reactive zone of the tumor and number of lymph nodes (stations) dissected.

Distribution of gastric lymph nodes

Figure 1 is the distribution of gastric lymph nodes.

Indication

Early and locally advanced gastric antral cancers.

Contraindications

(I) Patients with advanced gastric antral cancer, on whom the metastatic lymph nodes can not be easily dissected.

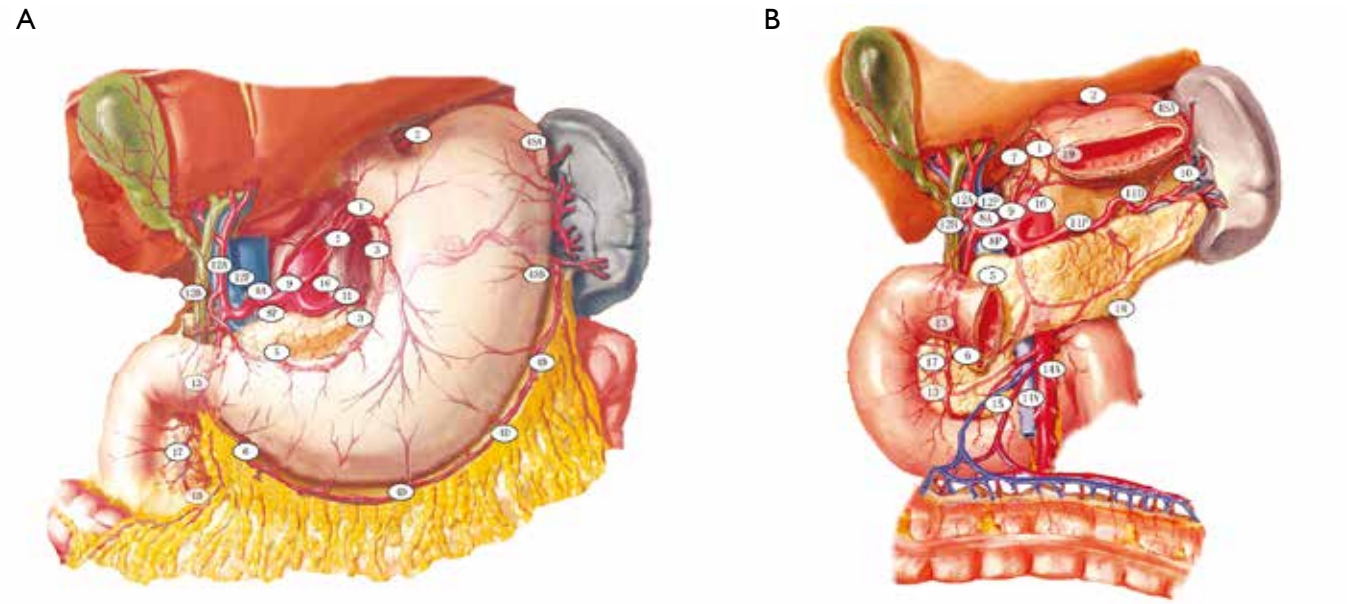

Figure 1 (A) Anterior gastric lymph nodes; (B) posterior gastric lymph nodes.

(II) Patients accompanied with heart and lung diseases and unable to receive tracheal intubation under general anesthesia.
(III) Patients with a history of upper abdominal surgery and/or extensive upper abdominal adhesion.

Surgical instruments

HIFU Ace's exambusters, linear cutter stapler, and circular stapler (diameter: 28-31 mm).

Preoperative preparations

(I) Treat anemia and hypoproteinemia, supplement vitamins, and adjust water and electrolyte balance.
(II) Perform normal saline enema once one night before surgery.
(III) Indwel the gastric canal and urinary canal in the morning on the operation day.

Anesthesia

Tracheal intubation under general anesthesia.

Position and cannula placement

The patient lies on the table in the supine position, with legs apart, or in the modified lithotomy position. A 10-mm cannula is placed at the level of the inferior umbilical margin as the observation hole, and the intra-abdominal pressure is maintained at 13 mmHg. A 12-mm cannula is inserted 1cm to the left anterior axillary line under the costal margin as the main operation hole, and a 5-mm cannula is placed in the left midclavicular line at the level of umbilicus as an adjunct hole. Two 5-mm cannulas are inserted in the symmetrical position on the right side of the above-mentioned operation cannulas. The operator stands on the left of the patient, assistant on the right, and scrub nurse between the legs of the patient (*Figures 2,3*).

Surgical procedures

Surgical procedures of laparoscopic radical gastrectomy for gastric antral cancer(*Figures 4; Videos 1,2,3,4,5,6,7,8*).

Open the greater omentum to the head side; divide the gastrocolic ligament along the avascular zone at the upper border of the transverse colon (*Figure 5*), rightward to the hepatic flexure of colon (*Figure 6*) and leftward to the splenic flexure of colon; ligate and divide left gastroepiploic vessels (*Figure 7*) and dissociate the greater curvature of stomach to the second vascular branch of the left gastroepiploic artery. Expose the middle colic artery to dissect the anterior lobe of the transverse mesocolon until the lower border of the pancreas. Divide the superior mesenteric vein at the lower

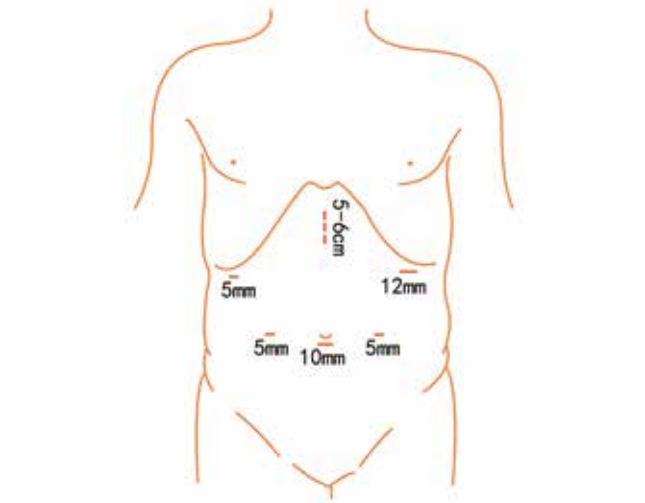

Figure 2 Cannula positions for laparoscopic radical gastrectomy for gastric antral cancer.

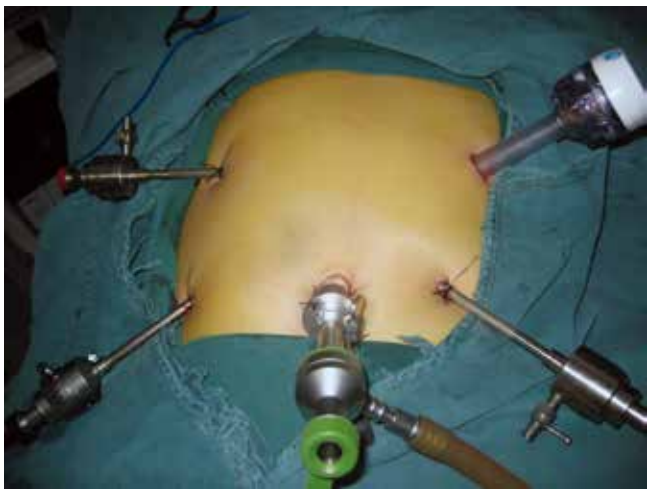

Figure 3 Cannula positions for laparoscopic radical gastrectomy for gastric antral cancer (sample).

border of the pancreas and then dissect group 14v lymph nodes (*Figure 8*). Divide and expose right gastroepiploic artery and vein along the surface of the head of the pancreas for ligation and transection at the root, and then dissect group 6 lymph nodes (*Figure 9*). Divide the loose tissue among the duodenum, gastric antrum and pancreas along the root of the right gastroepiploic artery to expose the gastroduodenal artery (*Figure 10*). Dissect the encapsulated structure that envelops the pancreas from right to left and from bottom to top till the upper border of the pancreas (*Figure 11*). Peel off the retroperitoneal membrane along the upper border of the pancreas to expose the coronary vein, which is ligated and transected near its basilar part (*Figure 12*). Expose the common hepatic artery along the upper border of the pancreas (*Figure 13*) and then divide it along the arterial sheath; meanwhile, dissect the group 8 lymph nodes (*Figure 14*). Expose the celiac trunk, proximal splenic artery and left gastric artery, and then ligate and transect the left gastric artery at the root; meanwhile, dissect group 7, 9 and 11p lymph nodes (*Figures 15*,*16*,*17*). Upward along the gastroduodenal artery, ligate and transect the root of the right gastric artery to dissect group 5 lymph nodes (*Figure 18*). Open the hepatoduodenal ligament to expose the proper hepatic artery and dissect group 12a lymph nodes (*Figure 19*). Dissociate the lesser omentum along the lower border of the liver to the right side of the cardia (*Figure 20*), and then downward along the lesser curvature to 3-4 cm above the tumor to dissect group 1 and 3 lymph nodes (*Figure 21*). Dissociate the duodenal bulb to 2 cm under the pylorus, and then transect the duodenum using a linear cutter stapler (*Figure 22*). Lift the transverse colon upward to find the beginning part of the jejunum (Treitz ligament) and mark the jejunum 12 cm to the Treitz ligament with a cloth (*Figure 23*). Make a 5-6 cm median longitudinal incision on upper abdomen (*Figure 24*) and then drag the stomach and greater and lesser omentums out from the abdominal cavity after the placement of the incision protective film (*Figure 25*) and remove the tumor at the scheduled plane. Lift the proximal jejunum out of the abdomen and place the stapler anvil (diameter 28-29 mm) of the circular stapler at the marking site to perform Billroth II (B-II) IIgastrojejunostomy in the posterior surface of stomach via the gastric cavity using the stapler (*Figures 26*,*27*); then, inspect the anastomotic bleeding (if any) and stop bleeding by suture if necessary. Place the gastric canal into the afferent loop of the jejunam via anastomosis from the gastral cavity, and then close the gastral cavity by suturing or using the linear cutter stapler 2 cm outside anastomosis. Gastrointestinal tract reconstruction can also be performed using B-I anastomosis; namely, put the stapler anvil of the circular stapler into the duodenal stump to perform end-to-side anastomosis with the duodenum in the posterior wall of gastric body via the gastric cavity using the stapler. Suture the small incision to reconstruct pneumoperitoneum, and then inspect the abdominal cavity for bleeding or anastomosis (*Figure 28*). Rinse the surgical wound thoroughly with distilled water. Routinely place the drainage tube at the surgical wound for drainage from the upper

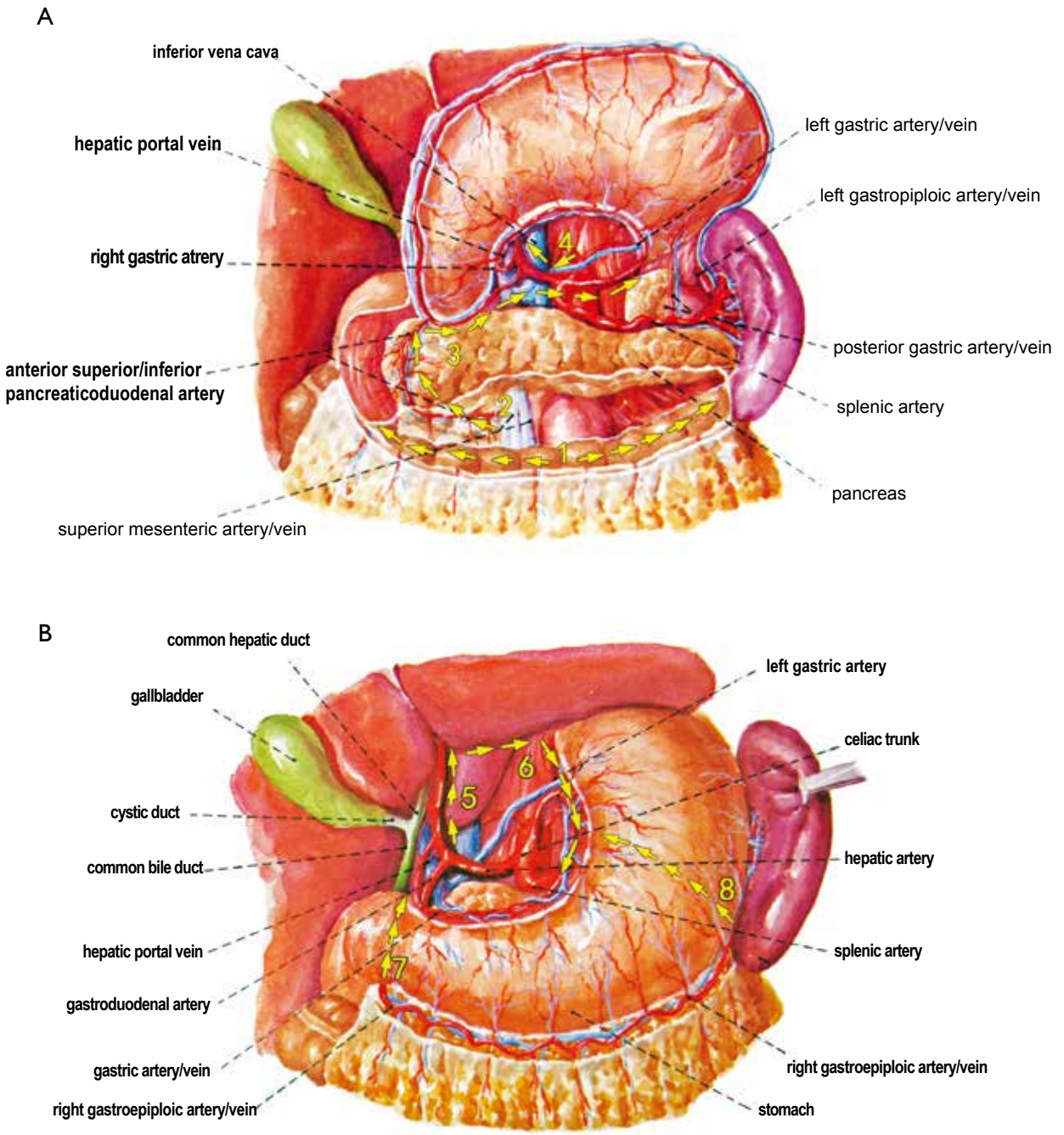

Figure 4 1. Dissociate the gastrocolic ligament; 2. Dissect lymph nodes surrounding the superior mesenteric vein (group 14v); divide the right gastroepiploic artery and dissect the infra-pyloric lymph nodes (group 6); 3. Dissect lymph nodes adjacent to the left gastric artery (group 7), adjacent to the common hepatic artery (group 8) and celiac artery (group 9); 4. Divide the left and right gastric arteries at their roots; 5. Lymph nodes in the hepatoduodenal ligament are dissected along the proper hepatic artery (group 12a); 6. The lesser omentum is divided along the lower border of the liver, downward from the right side of the cardia along the lesser gastric curvature, to dissect lymph nodes on the right side of the cardia (group 1) and the lesser gastric curvature (group 3); 7. Transect the duodenum at the level of the inferior pylorus; and 8. Transect the body of stomach at 6cm to the upper border of the tumor.

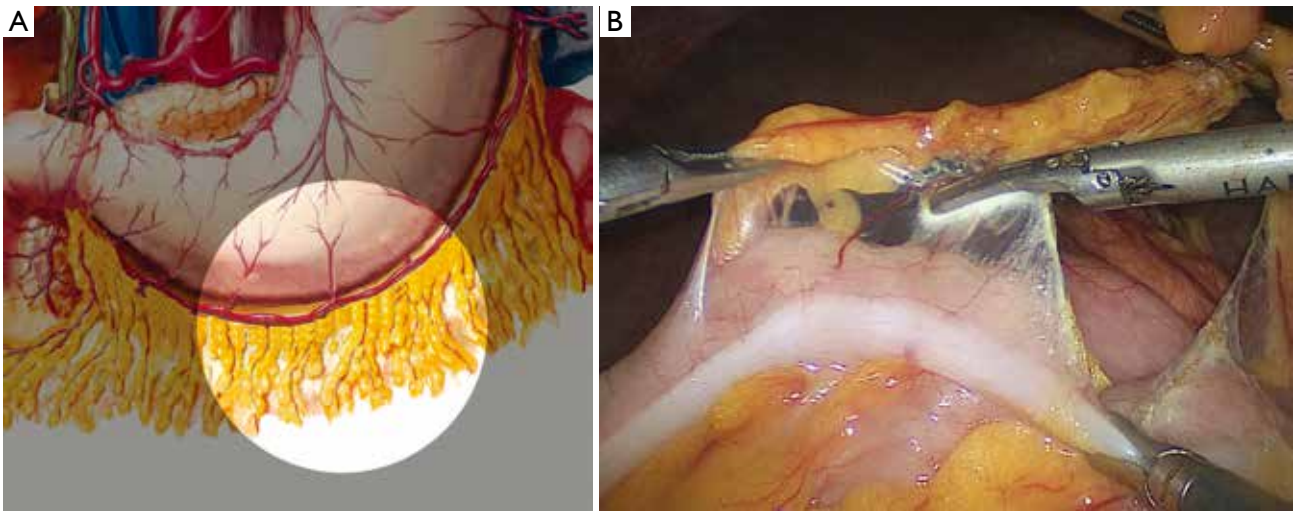

Figure 5 Divide the gastrocolic ligament along the avascular zone at the upper border of the transverse colon.

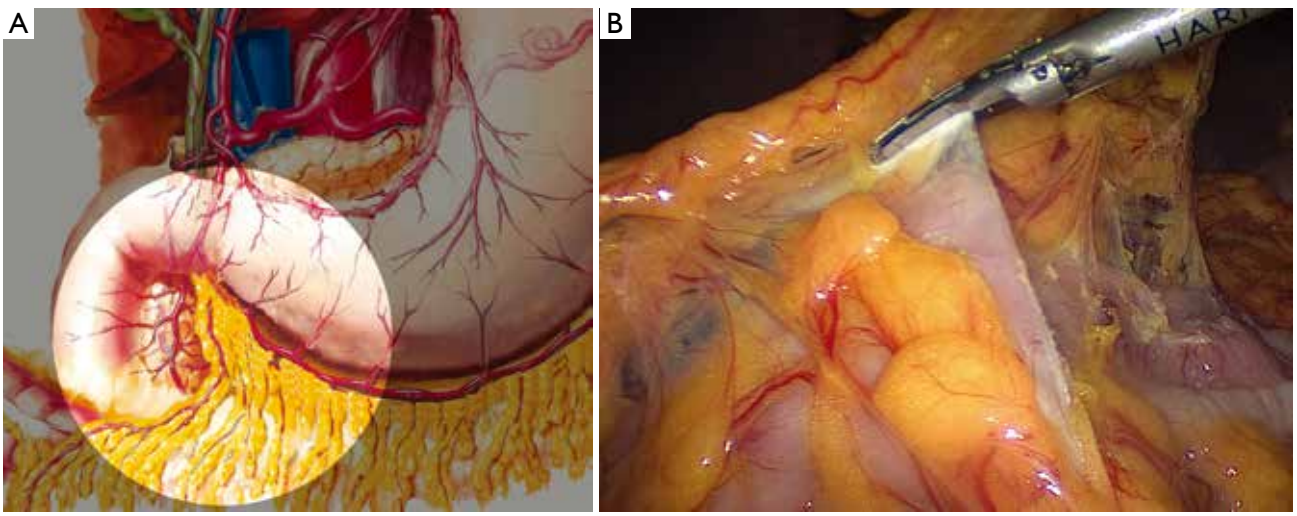

Figure 6 Divide along the avascular zone till the hepatic flexure at the right side.

left cannula. Exhaust pneumoperitoneum and pull out the cannula to gradually suture the cannula mouth at the level of umbilicus layer by layer to end the procedure. Specimens are shown in figures as follows (*Figures 29,30*).

Comments

(I) The scrub nurse must be well prepared during a laparoscopic surgery for gastric cancer due to the wide resection range and long operation interval. When the telescope moves along the operation sites, the The general view of the operative field and the quick detail view should be appropriately navigated. Meanwhile, such navigation should be performed in a smooth way to avoid the seasick sense due to unstable lens. When moving the lens in a large angle, retract the lens to the opening of its casing tube, and then slowly turn it.

(II) The inverted visual fields of local sites should be considered. An inverted visual field refers to the visual angle between laparoscopic view and equipment operation when the operator is standing at the left side of a patient to treat the greater omentum in the region of the splenic flexure. The operator must adapt to this situation and adjust his/her sensations to ensure the

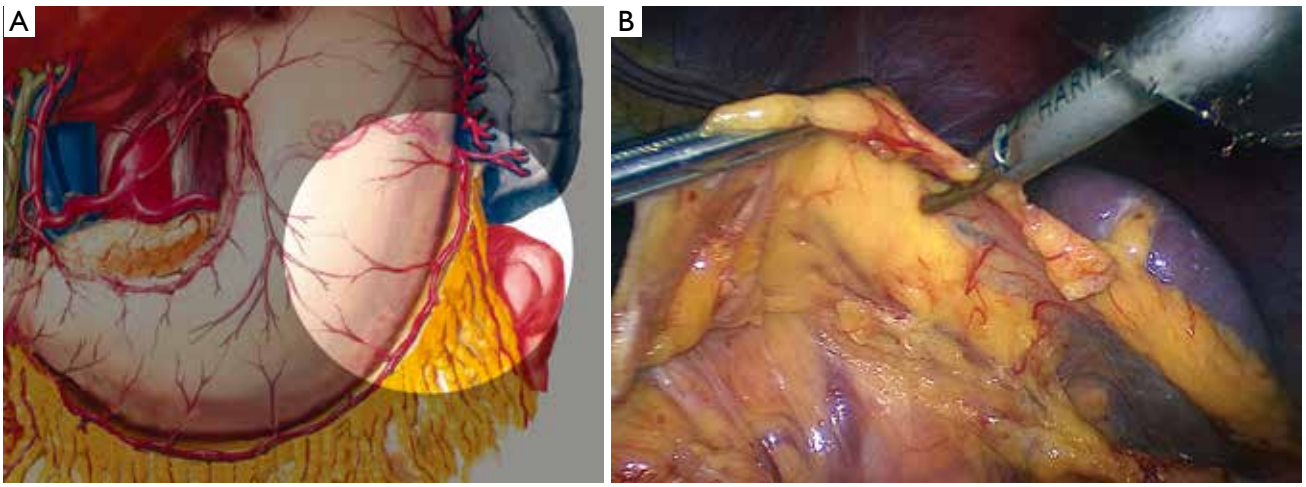

Figure 7 Divide along the avascular zone till the lower spleen pole at the left side to ligate and transect the left gastroepiploic vessels

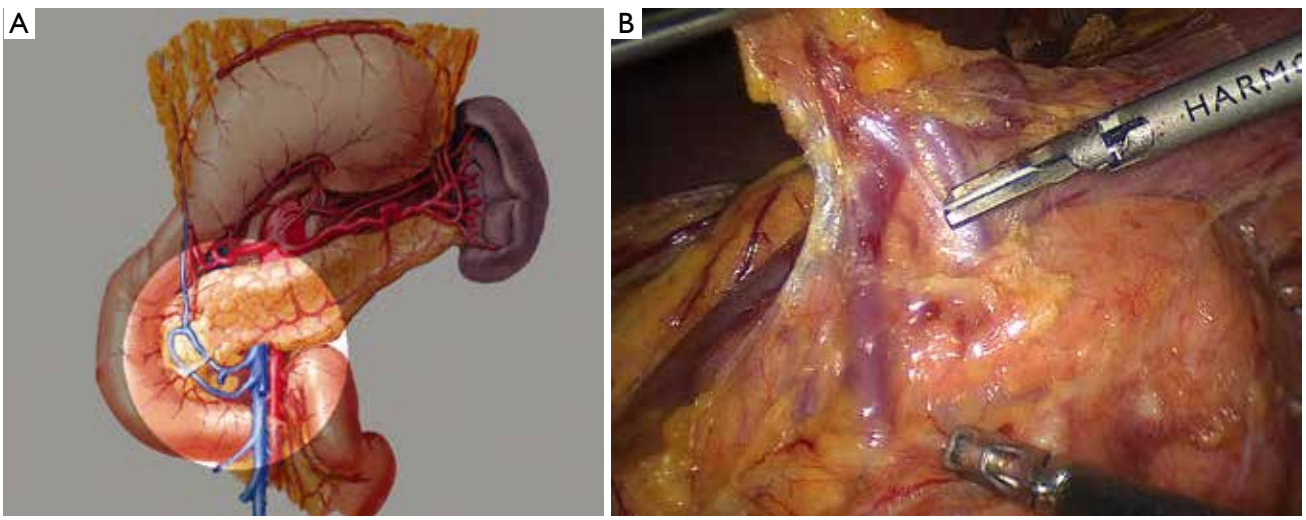

Figure 8 Dissociate the tissues along the middle colic vein in the posterior lobe of the transverse mesocolon. Here the superior mesenteric vein is visible. Dissect the superior mesenteric vein (group 14v) lymph node after the gastrointestinal venous trunks are exposed.

accuracy of operation. The assistant standing on the right side of the patient also faces the same problems when treating the hepatic flexure of colon.

(III) Unlike an open operation, the laparoscopic surgery has a visual line virtually horizontal with the anatomical layer of abdominal organs. During the surgery, tissues are often lifted upward to expose the surgical field; therefore, the relationship between local anatomy and visual direction must be properly addressed. During the laparoscopic surgery, when the lower border of the greater gastric curvature is lifted upwards to expose the posterior wall of stomach and the head of the pancreas, divide and skeletonize the right gastroepiploic artery and vein along the surface of the pancreatic head; the vessels are ligated at or near their roots to dissect the group 6 lymph node. On the contrary, the right gastroepiploic artery and vein are treated under pylorus in open surgeries. Therefore, if the vascular sources can not be determined during the laparoscopic operations, bring the stomach back into its original position; compare the change of its positions before and after lifting, so as to identify its vascular anatomy and avoid any faulty penetration.

(IV) The assistant plays an important role during the

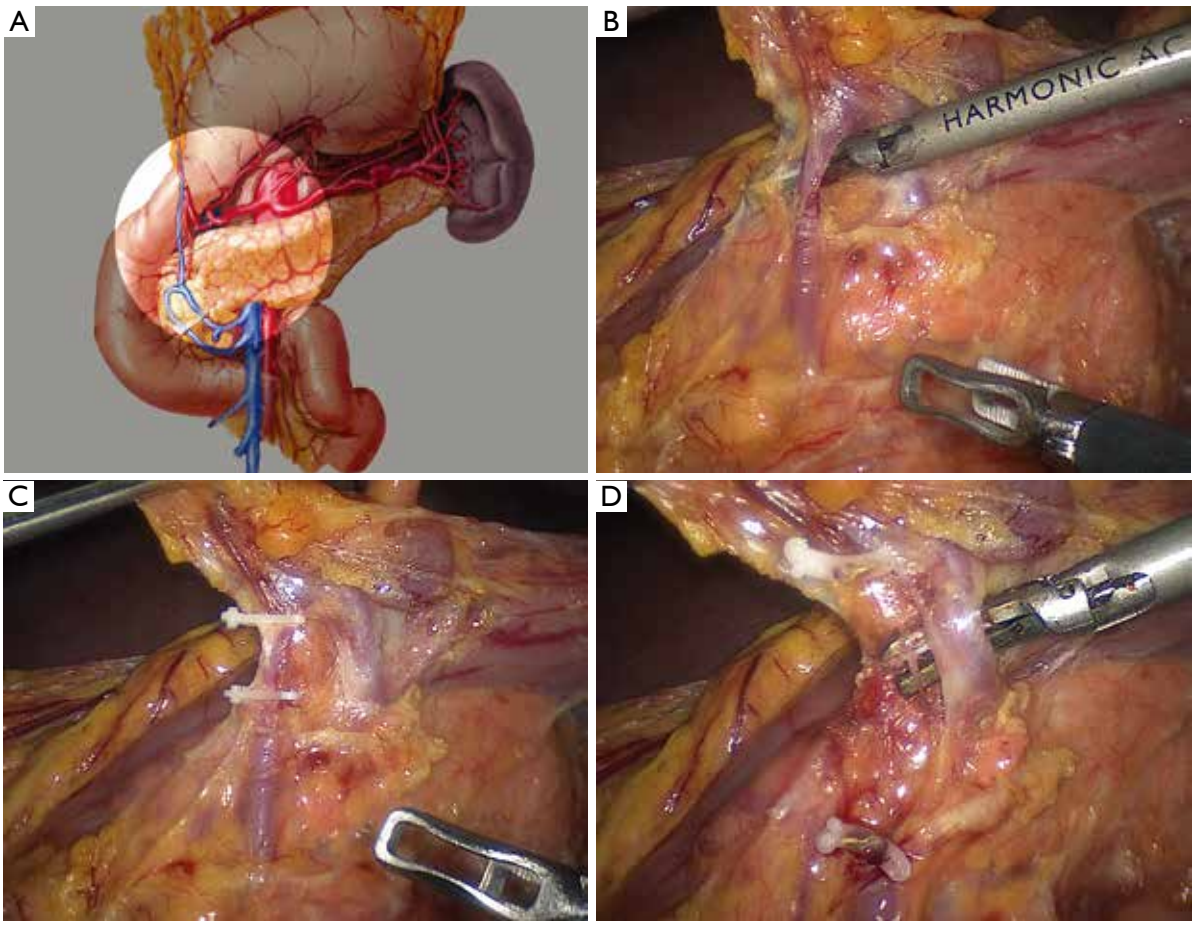

Figure 9 Ligate and transect the right gastroepiploic vein and artery near the surface of the head of the pancreas and dissect group 6 lymph node.

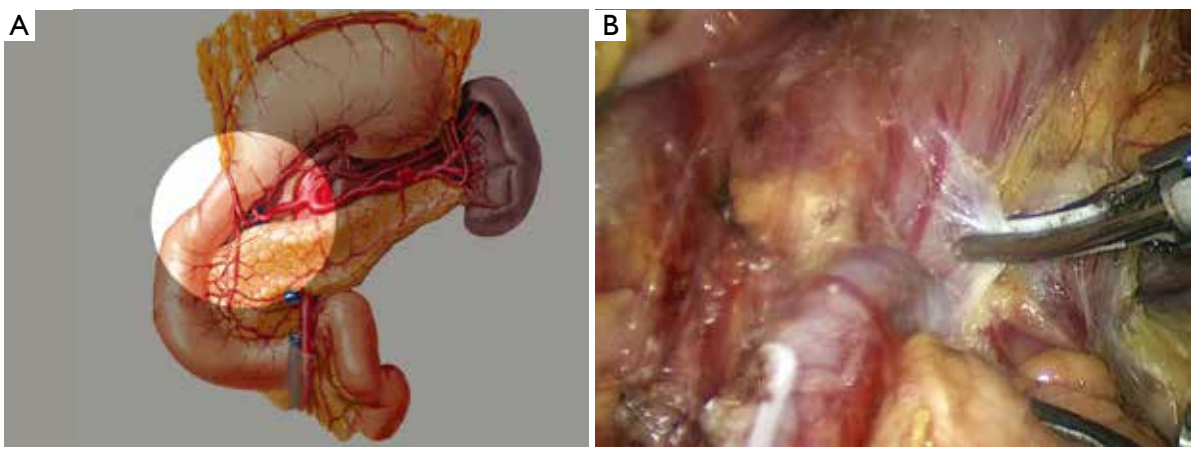

Figure 10 Divide the loose tissue among the duodenum, gastric antrum and pancreas along the root of the right gastroepiploic artery to expose the gastroduodenal artery.

Figure 11 Dissect the encapsulated structure that envelops the pancreas from right to left and from bottom to top.

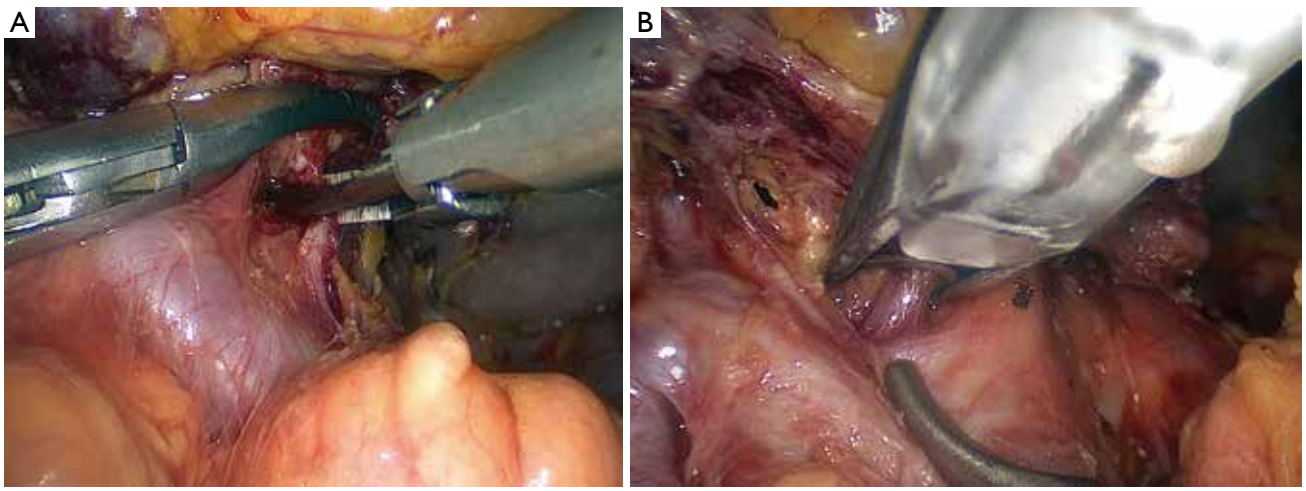

Figure 12 Peel off the retroperitoneal membrane along the upper border of the pancreas to expose the coronary vein, which is ligated and transected near its basilar part.

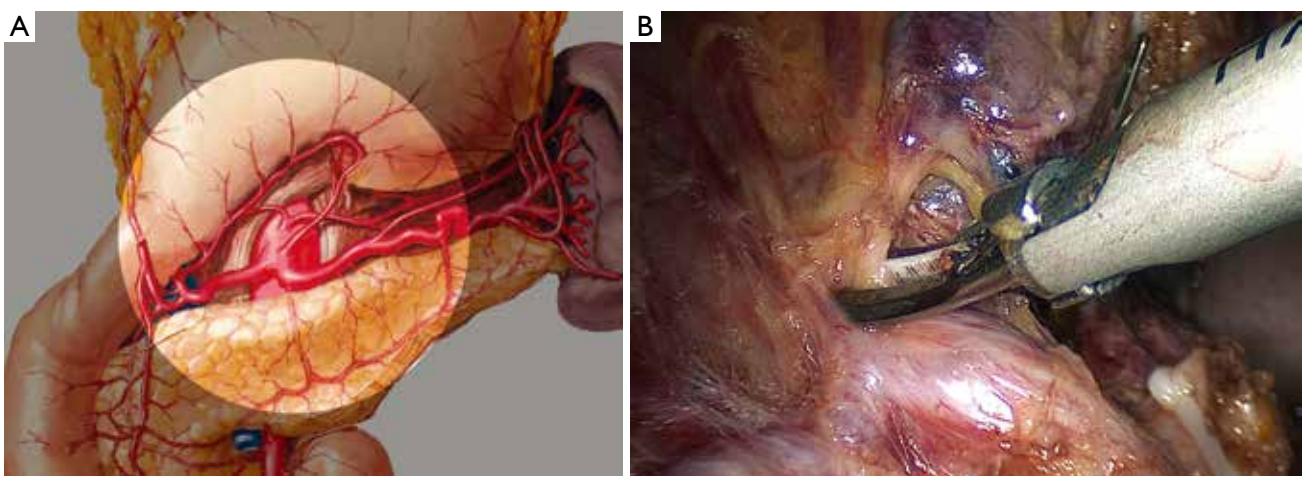

Figure 13 Expose the common hepatic artery along the upper border of the pancreas.

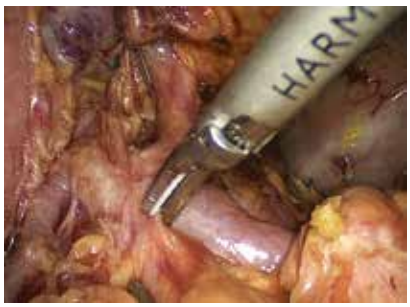

Figure 14 Expose the common hepatic artery and then divide it along the arterial sheath; then, dissect the group 8 lymph nodes after the arterial wall is skeletonized.

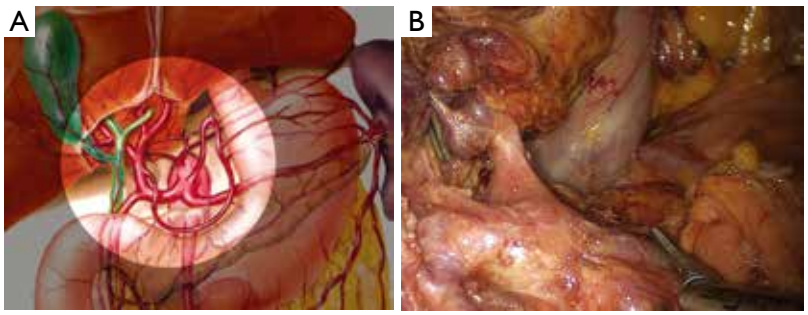

Figure 15 Divide the sheath of the common liver artery upwards and expose the left gastric artery. Meanwhile, expose the root of the splenic artery towards the left side.

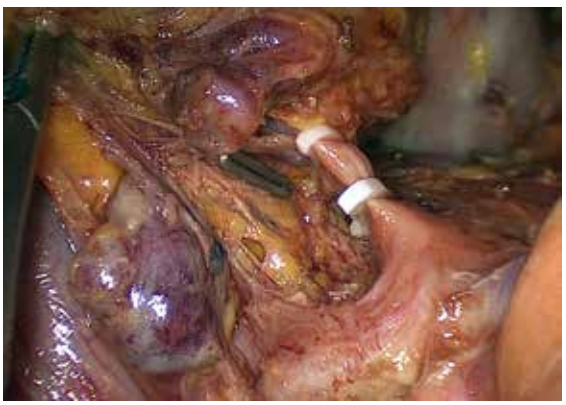

Figure 16 Expose the left gastric artery, and then ligate it at the root.

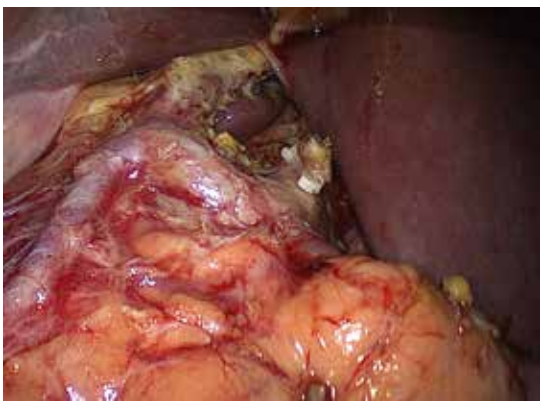

Figure 17 Transect the left gastric artery at the root; meanwhile, expose the celiac trunk to dissect group 7 and 9 lymph nodes.

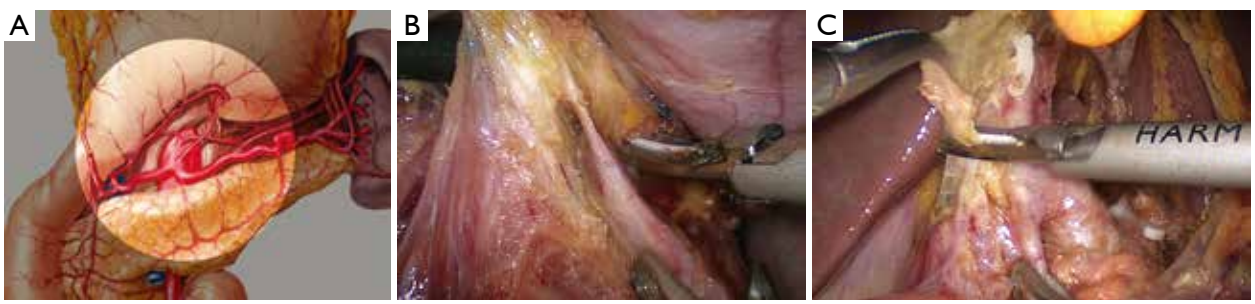

Figure 18 Upward along the proper hepatic artery, ligate and transect the root of the right gastric artery to dissect group 5 lymph nodes.

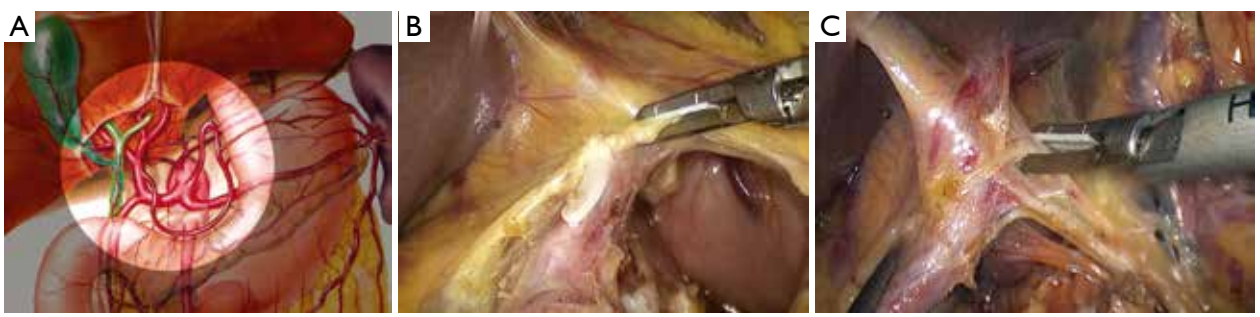

Figure 19 Dissociate the hepatic artery inside the hepatoduodenal ligament and dissect group 12a lymph nodes.

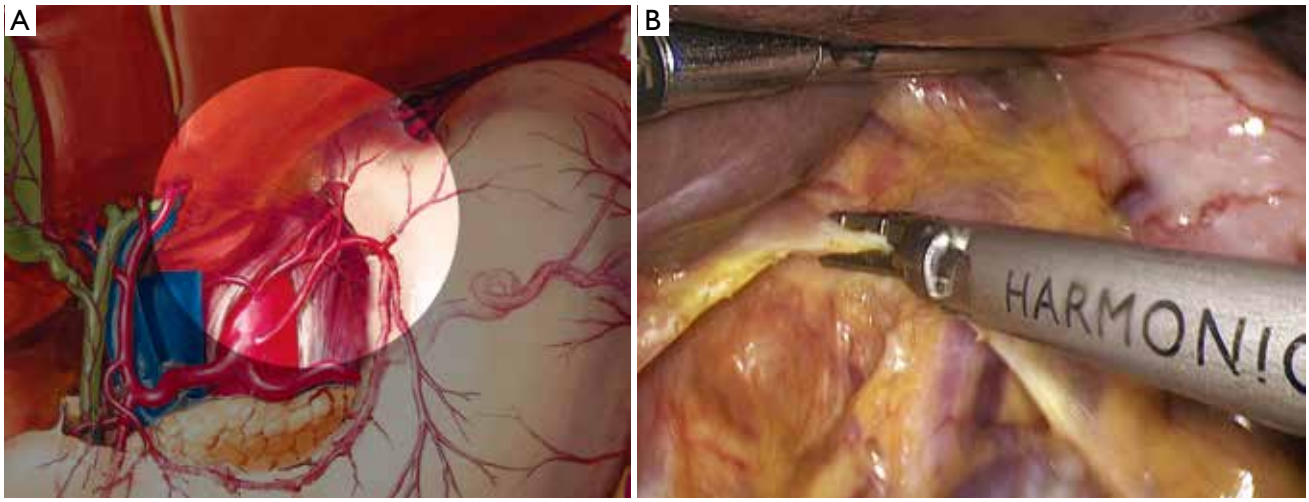

Figure 20 Dissociate the lesser omentum along the lower border of the liver.

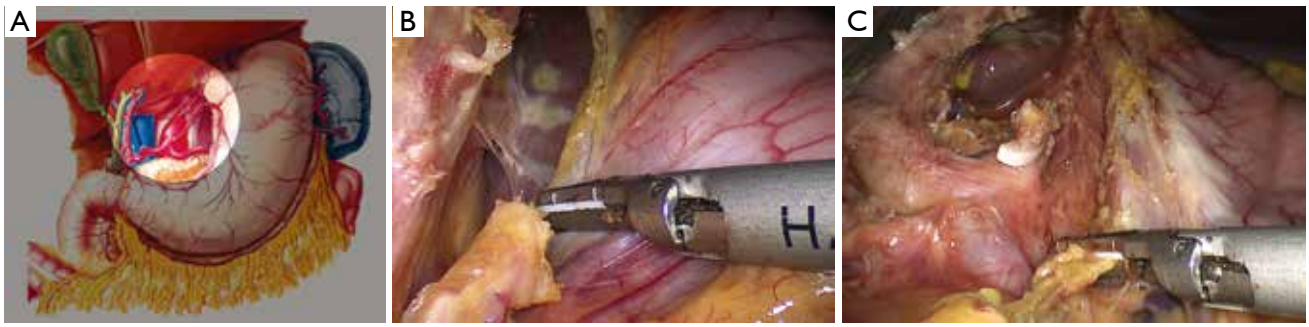

Figure 21 Dissociate the lesser omentum beginning from the right side of cardia and then along the lesser curvature to dissect group 1 and 3 lymph nodes.

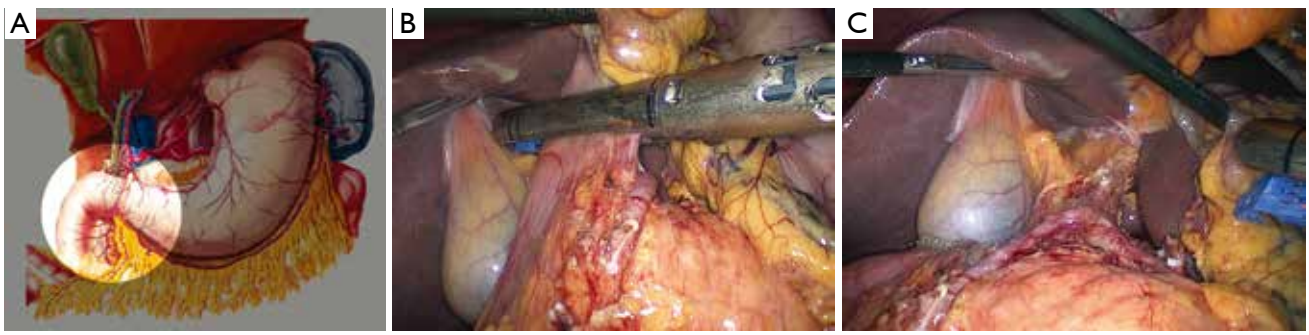

Figure 22 Transect the duodenum 2 cm under the pylorus using a linear cutter stapler.

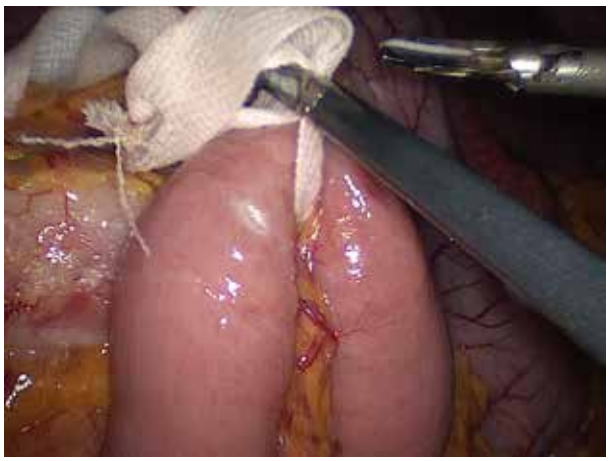

Figure 23 Mark the jejunum 12 cm to the Treitz ligament with a cloth.

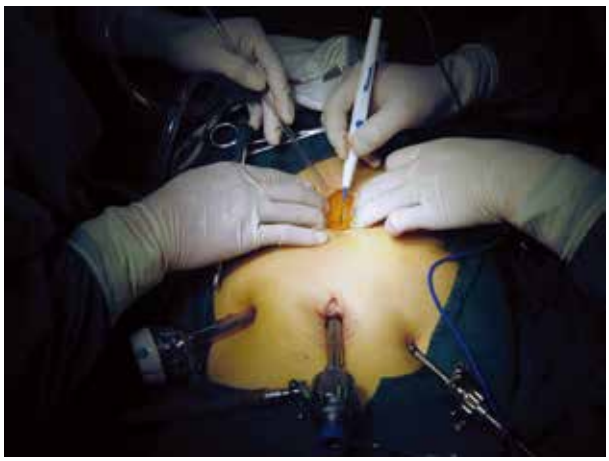

Figure 24 Make a 5-6 cm median longitudinal incision on upper abdomen.

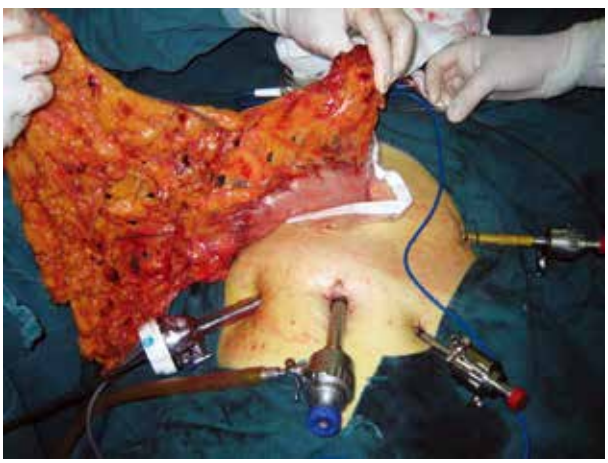

Figure 25 Drag the stomach and its surrounding lymph tissues as well as the greater and lesser omentums out from the abdominal cavity via the incision.

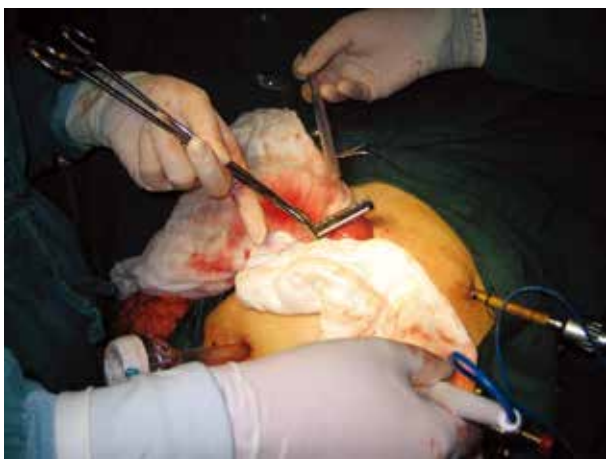

Figure 26 Lift the proximal jejunum out of the abdomen and place the stapler anvil at the marking site.

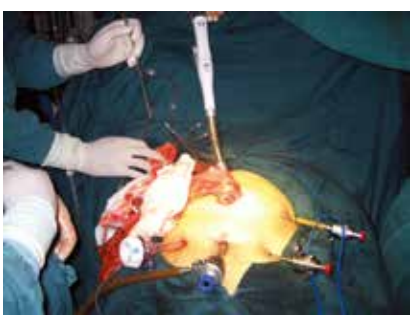

Figure 27 Perform Billroth II (B-II) gastrojejunostomy in the posterior surface of stomach via the gastric cavity using the circular stapler.

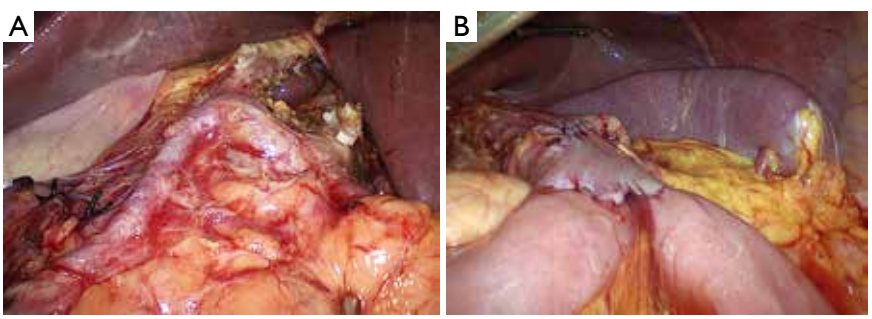

Figure 28 Inspect the abdominal cavity for bleeding or anastomosis before the surgery ends.

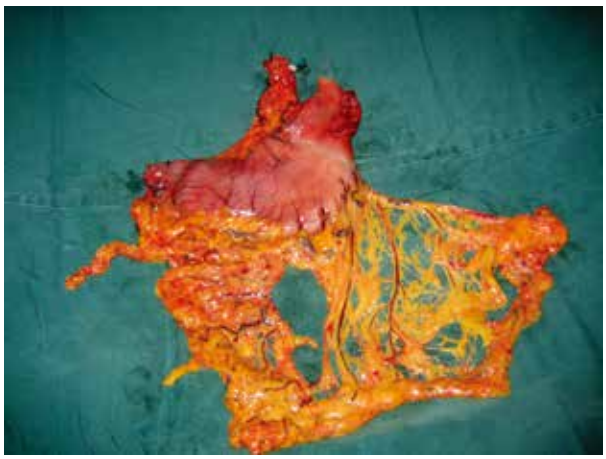

Figure 29 The resected distal stomach, greater/lesser omentums, and their surrounding lymph tissues.

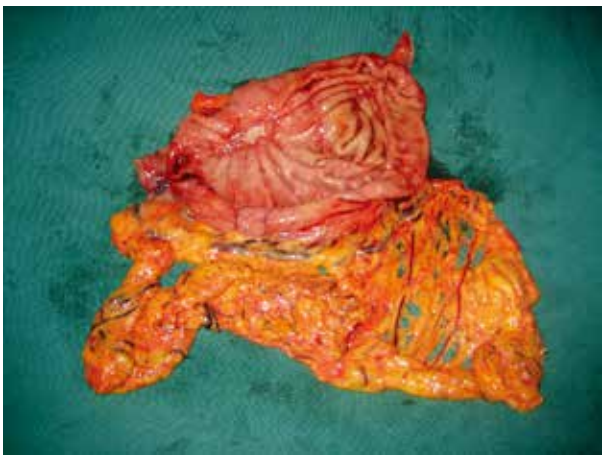

Figure 30 Gastric tumor is visible after the specimen is dissected.

laparoscopic operations for gastric cancer. Since stomach and its gastroepiploic tissues are easy to move, the assistant must prevent their movement and assist to maintain tissue tension at local sites, so as to facilitate the surgical operation. When dividing the anterior lobe of transverse mesocolon, the assistant should exert traction on the larger omentum to its head side using bowel clamp in his/her left hand and lift the omentum near the transverse colon; meanwhile, the assistant lifts the omentum on another side of the intestine, allowing the avascular zone in the mesentery of the upper edge of the anterior lobe of transverse colon expanded thoroughly. Thus, this region can be easily divided using an ultrasonic scalpel. Also, when removing the capsule in front of pancreas, the assistant must grasp the lesser curvature and lifts it upwards to expose the pancreatic surface. Since a radical stomach surgery often involves a large region, the tubular visual field of laparoscope has a contradiction with the overall operative field, which requires the assistant to be able to operate skillfully outside the visual field of laparoscope. During the operation, the visual field is mainly focused on the instrument for the operator and only few shots are available for the assistant; therefore, the assistant must be able to operate skillfully in the "indirect visual field" based on his/her good endoscopic sensations. Otherwise, operations without visual field can easily cause damage and even death.

(V) The stomach has a rich blood supply. Its small blood vessels distributes irregularly, and can easily bleed during division. Therefore, the operator must have solid knowledge about the vascular anatomy around the stomach. Most perigastric lymph nodes are attached around the main artery and must be thoroughly dissected. It is usually a challenging task to dissect lymph nodes in arterial sheath with HIFU, because the operator must carefully maintain the integrity of the arterial wall when dissecting the lymph nodes. Another difficult task is to dissect lymph nodes near the venous wall, such as dissections of lymph node along the superior mesenteric vein (No. 14v) and along the portal vein (No. 8). The vein wall is thin and fragile, and difficult to be repaired. The injury of the above key veins means the failure of the whole laparoscopic surgery, and the patient must be transferred for open surgery. Therefore, the vein walls must be clearly identified during lymph node dissection before division.

Post-operational management

(I) Gastrointestinal decompression: continuous decompression through a gastric tube is conducted until anal exsufflation happens.

(II) Analgesia: the pain can be relieved through continuous epidural catheter infusion. Injection of analgesics may be applied when appropriate.

(III) Position: after the patient fully wakes up from anesthesia and his/her blood pressure becomes stable, a semirecumbent position is recommended to facilitate breathing and reduce risk of respiratory infection.

(IV) Massage: venous return to heart from lower limbs is often affected during the long-duration

pneumoperitoneum surgery. Interrupted limb massage after surgery can prevent deep vein thrombosis.

(V Supportive care: patients after radical gastrectomy often have varying degrees of malnutrition. Overall parenteral nutritional support should be provided after surgery. Meanwhile, adjust the water and electrolyte balance and use antibiotics to carry out symptomatic management for gastrointestinal discomforts.

(VI) Diets: avoid drinking water during the first three days following surgery. Drink warm water (10-20 mL every two hours) until anal exsufflation happens. Increase the water consumption on a daily basis, gradually followed by salt water/sugar water, rice soup, and broth. Give liquid diet 8 days after surgery and semi-liquid diet 9 days after surgery.

Complications and their management

(I) Bleeding: the stomach has complex blood supply and highly variable anatomy. The vessels are often injured during surgery due to unclear anatomical structures or laparoscopic vision. The larger arteties and veins should be ligated using ligature clamps, and the smaller vessels should coagulated and dissected using HIFU. A clear vision should be maintained during surgery. Avoid rude lifting/division or violent traction; the operation must be gentle.

(II) Spleen injury: during the dissociation of the greater curvature of stomach, violent maneuvers can tear the lower pole of the spleen. If the spleen bleeding can not be effectively controlled, splenectomy should be performed. Open surgery may be performed when necessary.

(III) Patients with bile duct or portal vein injury should also be transferred for open surgery.

(IV) Post-operative complications: duodenal stump fistula or anastomotic leakage often occurs 4-6 days after surgery. Fistulas occurring 1-2 days after surgery are often due to anastomotic technique, whereas those occurring 4-6 days after surgery are often due to poor blood supply in local tissues, increased tension, and edema. In either condition, whether surgical exploitation and/or drain cleaning is required is mainly based on the clinical signs of peritonitis, volume of fistula drainage, and presence of uncontrollable fever.

(V) Long-duration pneumoperitoneum surgery may increase the risk of deep vein thrombosis. The lower limbs should be lifted appropriately after surgery. Wearing stockings or interrupted massage can also be helpful.

(VI) Veress needle or puncture cannula can cause the damage of intestinal canal and/or tissues, causing intra- and post-operative bleeding and intestinal fistula. Standardized procedures can minimize the occurrence of these complications.

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Surgical Video

Laparoscopy-assisted D2 radical distal gastrectomy for gastric cancer (Billroth II anastomosis)

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Abstract: Laparoscopic radical gastrectomy has been increasingly applied in China. However, how to reduce surgery-related trauma, shorten operative time and achieve the long-term prognosis equal to the conventional open surgery is still hot research topics. Along with the change in learning curve and the optimization of endoscopic techniques, laparoscopic lymph node dissection can achieve or even exceed the extent that can be achieved in open surgery. Therefore, it has gradually replaced the conventional digestive tract reconstruction using an auxiliary incision. By completing the laparoscopic digestive tract reconstruction with EndoGIA, we describe the laparoscopy-assisted D2 radical distal gastrectomy for gastric cancer (Billroth II anastomosis).

Keywords: Laparoscope; radical gastrectomy; Billroth II anastomosis

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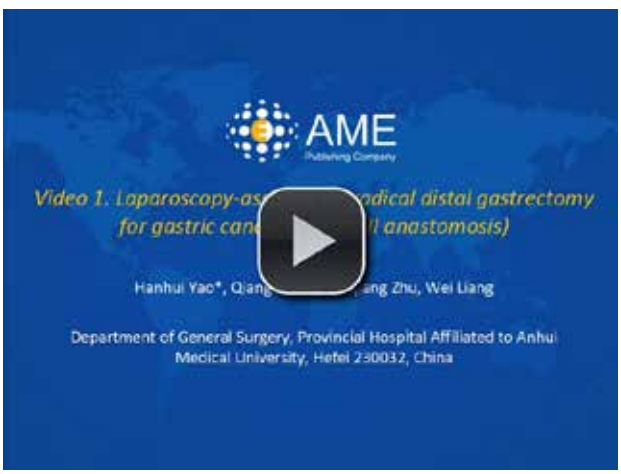
A 64-year-old female patient was admitted due to "upper abdominal discomfort accompanied with belching for half a year". Gastroscopy confirmed the presence of adenocarcinoma of gastric antrum (moderately differentiated). No evidence of distant metastasis was found during the preoperative imaging. The preoperative TNM stage was T3NxM0.

During the surgery (*Video 1*), the patient was supine and in a split-legged position after endotracheal general anesthesia. The surgeon stood at the left side of the patient, the assistant at the right side of the patient, and the camera holder between her two legs. The CO_2 pneumoperitoneum was created, and its pressure was maintained at 12 mmHg. The umbilicus was used as the observation hole. Four ports were symmetrically established at the left and right sides of the axillary line and midclavicular line, with the port at the left side of the axillary line as the main working port. Abdominal exploration showed that the tumor was located in the gastric antrum and invaded the serosal layer, while no distant metastasis at liver or pelvic floor was found. The tumor surface was blocked with biological glue to avoid cell shedding during the surgery.



Video 1 Laparoscopy-assisted D2 radical distal gastrectomy for gastric cancer (Billroth II anastomosis)

After the greater omentum was flipped and raised by the assistant, the operator stretched the transverse colon and separated the gastrocolic ligament along the colon

attachment to enter the omental bursa. After the removal of greater omentum, the operation continued leftwards to the lower pole of the spleen and rightwards to the duodenum. The greater omentum was rolled under the liver, withdrawing the stomach towards the head side to expose the pancreas thoroughly. The pancreatic capsule was disassociated along the pancreatic upper space. Then, the splenic vein was exposed at the tail of the pancreas. Along the splenci vein, the tail of the pancreas was dissociated to expose the left gastroepiploic artery and the vessels at the lower splenic pole; meanwhile, the station N4sb lymph nodes were dissected. While the vessels to the lower splenic pole were preserved, the left gastroepiploic artery was transected. The gastric greater curvature was exposed downwards; meanwhile, the station N4d lymph nodes were dissected. Pancreatic head and loop of Henle were exposed between the two lobes of transverse mesocolon; meanwhile, the station N14v was explored to identity whether it had became swollen. The right gastroepiploic vein was found by "climbing" the pancreas; it was dissociated along the loop of Henle, and then transected. Meanwhile, the station N6 lymph nodes between the arteries and veins were dissected. After the gastric body was uplifted by the assistant, the pancreas was gently pressed by the operator to lift the pancreatic capsule and expose the common hepatic artery, splenic artery, and the root of left gastric artery; meanwhile, the stations N11p and N7 were dissected. After the left gastric artery and coronary vein were exposed and transected, the station N9 was dissected till the diaphragmatic crus. The station N8a was dissected along the common hepatic artery. The right gastric artery was exposed from the lower approach and then transected. After the assistant continued to pick on the gastric body, the operator divided the posterior lobe of the hepatogastric ligament along the lesser curvature of the stomach, so as to prepare for the dissection of stations N1 and N3. Thus, after the gastric body was pulled downwards, the assistant uplifted the left liver, and the operator transected the hepatogastric ligament via the upper gastric approach. Since the right gastric artery and the proper liver artery had already been exposed via the lower gastric approach, the dissection of stations N12a and N5 became relatively easy. The anterior lobe of the hepatogastric ligament was divided along the lesser curvature of the stomach, and then the stations N1 and N3 were completely dissected. Thus, the D2 lymph node dissection was completed.

The duodenum was closed 2 cm below the pylorus using an endoscopic linear stapler (3.5 mm blue cartridge EndoGIA, Covidien) and then the stomach was transected. Using the green stapler cartridge (height: 4.8 mm), the operator clamped the gastric body 5 cm above the tumor and then transected it. Upon removal, the specimen was placed in an endobag and extracted. The tumor was carefully protected to avoid shedding. Holes were made in the residual greater curvature of stomach and in the jejunum 15 cm away from the ligament of Treitz, respectively. The EndoGIA™ Universal staplers were applied to complete the anastomosis between the residual stomach and the jejunum. The common openings were closed by EndoGIA system. The anastomosis was further sutured under laparoscope. The surgical wound and anastomosis were explored to identify any active bleeding. Thus, the reconstruction of the gastrointestinal tract was completed.

One drainage tube was placed in the right upper abdomen. After the laparoscope was removed, the puncture hole around the umbilicus was extended by 3 cm, and then the specimen was harvested.

The duration of operation was 190 min, and the intra-operative blood loss was about 100 mL. No blood was transfused during the surgery. The post-operative pathological stage was T3N2aM0. The first anal exhaust after surgery occurred 48 hours after surgery. Five days after the surgery, she began taking liquid diet. She recovered well and was smoothly discharged 7 days after surgery.

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Surgical Video

Laparoscopic gastrectomy for distal gastric cancer

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Abstract: This video presents a standard D2 laparoscopic-assisted gastrectomy for distal gastric cancer. The lymph node dissection of each station is performed as required in the standardized procedure of distal gastrectomy, followed by the Billroth II anastomosis through a small incision.

Keywords: Laparoscopy; radical gastrectomy; lymph node dissection

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Laparoscopic radical gastrectomy is indicated in patients with early gastric cancer. Laparoscopic-assisted D2 radical gastrectomy is the standard surgical approach in the management of such condition, particularly in early gastric cancer. For lymph node dissection, the second station should also be included during the treatment of early gastric cancer.

The patient is a 54-year-old man admitted for "repeated epigastric pain for one year which worsened for one week". Physical examination revealed no positive signs or palpable lymph node enlargement. Laboratory tests showed no abnormalities in the blood testing. Gastroscopy showed a 1 cm ulcer at the gastric angle, and indicated reflux esophagitis. Gastroscopic pathology showed mucosal erosion at the gastric angle complicated with high-grade intraepithelial neoplasia, and localized cancer.

In this video (*Video 1*), as the early gastric cancer is not readily located via palpation with laparoscopic instruments, an additional astroscope is used to identify the lesion and mark it with Hemo-lock on the gastric wall. After the tumor is located, the greater omentum is separated from the middle part of the transverse colon using an ultrasonic scalpel along the left half of the transverse colon towards the splenic flexure. After the omentum at the splenic flexure is divided, the separation is continued towards the splenic hilum, and the left omental vessels are clamped at the roots with Hemo-lock clips and cut. Station number 4sb lymph nodes are dissected, and the gastrosplenic ligament is then divided with Ligasure. The first branches of the short gastric vessels are transected, and station number 4sa lymph nodes are dissected. The greater omentum is then separated along the greater curvature. Station number 4d lymph nodes are dissected. After dissection of the left side, the greater omentum and the right half of the anterior lobe of the transverse mesocolon are separated towards the right side to expose the gastrocolic trunk, and the right gastroepiploic vein at the root is transected. This process is completed with caution to avoid injury to the anterior superior pancreaticoduodenal vein. Following separation of the right omental vein, the right omental artery is divided upwards along the surface of the pancreatic head. The head of the pancreas is located at a significantly higher position in this patient, so caution is needed to avoid mistaking the pancreas for lymph nodes during dissection. Therefore, the posterior wall of the duodenum and the pancreatic capsule are first separated to expose the gastroduodenal artery before dividing the right gastroepiploic artery. The right gastric artery is transected at the root, and station number 6 lymph nodes are dissected. The division is continued towards the anterior edge of the pancreas along the surface of the gastroduodenal artery to expose the common and proper hepatic arteries. With further division in the space over the surface of the gastroduodenal artery using separation forceps, the right gastric vein is cut with an ultrasonic scalpel. The right gastric artery is then exposed at the anterior region of this space and transected. Station number 12a lymph nodes are dissected. Station number 8a lymph nodes are dissected along the surface of the common hepatic artery. The celiac trunk and the splenic artery are

Video 1 Laparoscopic gastrectomy for distal gastric cancer

exposed, and stations number 9 and 10 lymph nodes are dissected. The gastric coronary vein and the left gastric artery are cut at their roots. Station number 7 lymph nodes are then dissected. Tissue in the posterior pancreatic space is divided along the upper edge of the pancreas. Fat and lymph nodes posterior to the common and proper hepatic arteries are dissected, and stations 8p and 12p are removed en bloc. After the hepatogastric ligament is separated along lower edge of the liver, the tissue over the surface of the proper hepatic artery is divided through to the upper edge of the duodenum. Stations number 5 and 12 lymph nodes are dissected. Stations 1 and 3 are then dissected along the lesser curvature. The duodenum is transected using an ENDO-GIA stapler. A central incision of 6 cm is made to the upper abdomen, and the gastric wall 5 cm away from the ulcer is transected. Billroth II anastomosis of the stomach to the jejunum is conducted.

Postoperative pathology showed moderately to poorly differentiated adenocarcinoma at the gastric angle (superficial depressed type), with invasion to the submucosa. No tumor tissue was present in the surgical margin. Metastases were found in lymph nodes of the lesser curvature (2/11), but not in those of the greater curvature (0/5). No metastasis was detected in the other lymph nodes (0/6). pTNM stage: (T1bN1M0, IB).

The patient got off the bed after the gastric tube was removed the second day after surgery, and began normal diet from the third day. He was discharged on the sixth day after surgery.

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Surgical Video

Total laparoscopic-assisted radical gastrectomy (D2+) with jejunal Roux-en-Y reconstruction

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Abstract: Total laparoscopic-assisted radical gastrectomy and the jejunal Roux-en-Y anastomosis were performed to treat cancer of the upper gastric body and fundic region. In the case of open anastomosis during total laparoscopic-assisted radical gastrectomy, an incision of 6-8 cm would be required due to the need for placing the stapler anvil. If using the Roux-en-Y procedure, however, the incision could be reduced to as small as 4-5 cm without increasing the length of operation and intraoperative bleeding that favors postoperative recovery.

Keywords: Gastric cancer; laparoscopy; gastrectomy; gastrointestinal anastomosis

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A 42-year-old woman was admitted for "repeated abdominal pain and discomfort for more than a month." Gastroscopic pathology showed adenocarcinoma of the "gastric angle and gastric body" (NO: 13-10963). CT indicated gastric cancer and abdominal lymph node metastases. Ultrasound showed a solid mass in the lower gastric body and the lesser curvature side of the gastric angle (gastric cancer was suspected, which had protruded the serosal layer, Borrmann III type), complicated with multiple enlarged lymph nodes close to the lesser curvature suspected of metastases. The preoperative diagnosis was gastric cancer, stating T3N1M0IIB. "Total laparoscopic-assisted radical gastrectomy (D2+) and jejunal Roux-en-Y reconstruction" was performed under general anesthesia on May 3, 2013.

In this surgery (*Video 1*), the patient is placed in supine position with legs apart. Routine disinfection and draping of the surgical area is performed after successful endotracheal and intravenous anesthesia. The surgeon stands on the left side of the patient, the first assistant on the right side, and the camera assistance between the patient's legs. A 1-cm incision is made above the umbilicus for placement of a trocar. Pneumoperitoneum of 12 mmHg is established, and a 30-degree laparoscope is inserted. Abdominal exploration shows no ascites, and no evident mass of the liver, parietal peritoneum, or greater omentum. An infiltrative, ulcerative tumor is visible at the lesser curvature of the gastric body (Borrmann III), about 5 cm × 3 cm in size, which is solid and invading the serosa. Stations 1, 2, 7, 8, 11 and 12 lymph nodes are enlarged in a diameter of about 0.8 cm, which are moderately solid without fusion. Trocars are inserted using the 5-port technique. An ultrasonic scalpel is used to cut the greater omentum and the anterior lobe of the transverse mesocolon. The right gastroepiploic artery and vein are ligated at their roots and cut. Station number 6 lymph nodes are dissected, and the pancreatic capsule to the upper left area is cut. The left gastric vein and artery are successively transected. Stations number 7, 9 and 8 lymph nodes are dissected, through to the station 11d, and the dissection is continued to stations 4sh, 10, 4sa and 2 lymph nodes at the left upper region. In the anterior region, the small omentum is resected, and stations 3 and 1 lymph nodes are dissected. The duodenum is transected using a linear stapler, and stations 12p and 8p lymph nodes are dissected. The abdominal segment of the esophagus

Video 1 Laparoscopic-assisted radical gastrectomy (D2+) with jejunal Roux-en-Y reconstruction

is cut with the linear stapler, and one suture is made for retraction. The transverse mesocolon is open, and the jejunum is dissociated by an ultrasonic scalpel 20 cm away from the Treitz ligament. The wall at the mesangial side is denuded. A hole is made to the esophagus with the scalpel, and a 60 mm linear stapler is inserted with the two ends at the distal stumps of the esophagus and the jejunum to establish the end-to-side anastomosis. Two sutures are made to the common opening at the side of the anastomosis for retraction, and the 60 mm linear stapler is again inserted to cut the tissue to complete the anastomosis. The stomach and the omental bursa are completely resected. A small hole is made using the ultrasonic scalpel about 40 cm below the opening of the anastomosis at the mesenteric edge for placement of the two firings of a 60 mm linear stapler through the proximal stump. Upon completion of the anastomosis, the two jejunal segments with a common opening are held with harmless forceps, and a 60 mm linear stapler is inserted to complete the jejunal Roux-en-Y anastomosis. When no anastomosis stenosis and bleeding is detected, a central incision of 4 cm is made to the upper abdomen to collect the total gastrectomy specimen, and the laparoscopic resection and anastomoses are completed.

The surgery was uneventful. The operation time was 192 minutes, with intraoperative blood loss of about 60 mL. A feeding tube was inserted, in conjunction with antibiotics and nutritional support. A small dose of Peptison was administered through the nasogastric tube on the first day. Flatus and little bowel movement occurred on the morning of the third day. As the blood testing results and temperature gradually returned to normal, the nasogastric amount was increased as well. Semi-liquid food was given from the fifth day, and the patient was discharged on the eighth day after surgery. No obvious complication was observed after 30 days. Postoperative pathology showed: total gastrectomy specimen: (gastric lesser curvature) ulcerated moderately differentiated adenocarcinoma (tumor size 5.5 cm × 4 cm), involving the serosal fat and nerve; tumor vascular thrombosis was found; the upper and lower margins of the specimens, as well as the separate "upper resected margin" were negative for tumor tissue. Metastases were observed in the lesser curvature LN2/2, greater curvature LN1/3，"Station 1" LN0/8, "Station 2" LN0/2, "Station 3" LN0/14, "Station 6" LN0/4, "Station 7" LN0/2, "Station 8" LN1/3, "Station 9" LN0/2, and "Station 10" LN0/1. No LN was detected in "stations 5, 11 and 12." IHC: tumor cells CgA (-), Syn focal (+), CD56 (-), CK8/18 (+), CK7 (-), Ki-67 20% (+). Pathologic staging was T4aN2MoIIIB.

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Surgical Video

Pylorus- and vagus-nerve-preserving partial gastrectomy (D2 dissection)

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Abstract: Pylorus- and vagus nerve-preserving partial gastrectomy is important in improving the prognosis of early gastric cancer surgery, reducing surgical complications and improving the quality of life for such patients. In the present case, pylorus- and vagus nerve-preserving partial gastrectomy was performed using the bipolar electrocautery dissection technique combined with D2 dissection along the lesser sac.

Keywords: Gastric cancer; gastrectomy; vagus nerve; pylorus

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With the development of the management strategies for gastric cancer and continuous assessment of surgical outcomes since the introduction of pylorus-preserving partial gastrectomy (PPG) for treating early gastric cancer (1), pylorus- and vagus nerve-preserving partial gastrectomy, as a successor, has become the standard option for the treatment of early gastric cancer (2,3). The indications include early gastric cancer located in M or SM layer of the M or L region, with the tumor of more than 4.5 cm away from the pylorus and without metastases to stations number 1 and 5 lymph nodes. As the key steps, the perigastric lymph nodes are dissected and the gastric branch of the vagus nerve is transected, while the hepatic branch of anterior vagus nerve and the celiac branch of its posterior trunk and the hepatic plexus, as well as the antral region more than 2.5 cm at the pyloric ring are preserved. In addition to the radical treatment, the advantages of this procedure include rapid postoperative recovery, and decreased incidence of bile reflux, dumping syndrome and cholelithiasis, as well as good gastric emptying (4-6). In the present case, we performed pylorus- and vagus nerve-preserving partial gastrectomy using the bipolar electrocautery dissection technique combined with D2 dissection along the lesser sac.

The patient is a middle-aged man who visited the Department of Gastrointestinal Surgery of the First Affiliated Hospital of Dalian Medical University for upper abdominal pain and discomfort for weeks. Preoperative fiber gastroscopy and endoscopic ultrasound confirmed superficial ulcers of the M region in a diameter of 1.0 cm. Pathology suggested adenocarcinoma, though there was no evidence of upper abdominal metastasis on CT scan. Pylorus- and vagus nerve-preserving partial gastrectomy combined with D2 dissection was performed under general anesthesia.

After the commencement of anesthesia, the patient was placed in a supine position. During the surgery (*Video 1*), a central incision of 2.0 cm was made from the xiphoid of the upper abdominal region to below the umbilicus. Abdominal exploration was then conducted layer by layer to confirm the absence of metastasis and identify the location of the tumor (based on the preoperative titanium clip marker under gastroscopy).

The hepatic branch of the anterior vagus nerve running inside the lesser omentum at the lower edge of the left liver lobe was identified, and the lesser omentum was cut at the foot of the branch. Station number 5 lymph nodes were dissected medial to the right gastric vein inside the hepatoduodenal ligament through to the gastropancreatic fold. The peritoneum was cut on the upper edge of the pancreas to expose the thin mesh- or bundle-shaped nerve

Video 1 Pylorus- and vagus-nerve-preserving partial gastrectomy (D2 dissection)

plexus on the surface of the common hepatic artery. Station number 8a lymph nodes were dissected anterior to this region through to the abdominal cavity. As the left gastric vein and splenic artery were revealed, station number 11p lymph nodes were dissected along the splenic artery to medial side of the posterior gastric artery while dividing the celiac trunk and dissecting stations number 7 and 9. The yellowish-white celiac branch of the vagus nerve was revealed to the left side of the left gastric artery. The crura and esophageal hiatus were exposed, and the posterior vagus nerve was retracted with suture. Stations number 1 and 3 lymph nodes were dissected along the left gastric artery and its branches, while preserving the ascending branch of the left gastric artery. The anterior vagus nerve was then retracted, and the gastric branch of the left gastric artery and vein and the gastric branch of the vagus nerve were ligated and cut. The right gastric vessels and their branches were transected 3.0 cm from the pylorus. Tissue of the lesser curvature side was thus completely dissected and the vagus nerve was preserved.

The greater omentum was transected 4.0 cm away from the arch near the greater curvature to expose the attachment of the omentum to the mesentery at the right side. The auxiliary colic vein was separated and exposed, and the root of the right gastroepiploic vein was then exposed at the lower edge of the pancreactic head during the separation. Station number 14v lymph nodes along the superior mesenteric vein were dissected, followed by station number 6, to expose the right gastroepiploic artery. The inferior pyloric artery was preserved, and the right gastroepiploic artery and vein were ligated and transected. At the left side, the greater omentum was cut until the lower pole of the spleen to expose the tail of the pancreas. The blood supply to the omentum was preserved, and the left gastroepiploic artery and vein were ligated and cut. Station number 4d lymph nodes were dissected through to the junction of the omental vascular arcade.

As soon as the lesion was identified, the stomach was transected towards the lesser curvature at the greater curvature from the terminal branch of the left gastroepiploic artery with a 100 mm linear stapler. The antrum was transected 3.0 cm away from the pyloric ring with a 100 mm linear stapler, and the partial gastrectomy was completed. A side-to-side anastomosis between the proximal and distal gastric ends was achieved using full-thickness suture. There was no tension and the blood supply was favorable. A nasogastric feeding tube was placed at the distal end of the anastomosis.

After the bleeding was stopped, a drainage tube was placed beneath the liver. The number of instruments and gauze was counted and confirmed, and the abdomen was closed with full-thickness interrupted suture. The patient returned to the ward safely.

The length of operation was 120 min, with bleeding of 30 mL. The patient had flatus on the third postoperative day, and felt epigastric fullness after fluid diet on the fifth day, which was relieved by one fasting day. The patient has been followed up for one year so far. The pathological status of the 20 resected perigastric lymph nodes was IIc PT1N0M0 7th AJCC.

Pylorus- and vagus nerve-preserving partial gastrectomy for early gastric cancer provides significantly satisfying clinical outcomes and postoperative quality of life. It has become one of the standard surgical options of early gastric cancer.

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Surgical Video

Laparoscopic-assisted radical gastrectomy for distal gastric cancer

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Abstract: A 48-year-old female patient was diagnosed with a superficial depressed type early gastric cancer (type IIc) of 1.0 cm at the gastric angle as indicated by gastroscopy. Laparoscopic-assisted greater omentum-preserving D2 radical gastrectomy was performed in combination with Billroth I reconstruction under general anesthesia for the distal gastric cancer on April 5, 2013. The postoperative recovery was satisfying without complications. The patient was discharged seven days after surgery.

Keywords: Early gastric cancer; gastrectomy; laparoscopic-assisted; D2 lymph node dissection

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As a novel minimally invasive surgical technique, laparoscopic radical gastrectomy is associated with such advantages as less injury, reduced postoperative pain, lower impact on immune function, rapid recovery of gastrointestinal function, and short hospital stay. In 1997, Goh and coworkers conducted D2 radical gastrectomy for advanced gastric cancer under laparoscope, which demonstrated the safety and feasibility in terms of the technique. In their reviews, Topal (1) and Huscher (2) also confirmed the above conclusion, and they suggested that the long-term survival outcomes of laparoscopic-assisted radical gastrectomy were similar to those of open surgery. Laparoscopic-assisted radical gastrectomy has now been recognized for treating gastric cancer with an invasion depth of T2 or less, without evidence of lymph node metastases in preoperative examination (3). On April 5, 2013, we conducted laparoscopic-assisted gastrectomy for a patient with early gastric cancer (type IIc). The postoperative recovery was satisfying. The details are as follows:

A 48-year-old woman was admitted to our hospital due to "upper abdominal dull pain with acid reflux for more than a month". Gastroscopy suggested a superficial depressed type early gastric cancer of 1.0 cm at the gastric angle. Biopsies indicated adenocarcinoma at the gastric angle. Endoscopic ultrasound indicated disordered structure of the submucosal layer of the gastric lesion at the gastric angle. CT scan suggested slightly thickened gastric wall at the gastric angle, without enlargement of lymph nodes around the stomach or liver metastasis. Preoperative staging: T1bN0M0. On April 5, 2013, laparoscopic-assisted D2 radical gastrectomy was conducted under general anesthesia for the distal gastric cancer.

During the surgery (*Video 1*), the patient was placed in a supine position with legs apart. Following general anesthesia, CO_2 pneumoperitoneum was established at 12 cm water column. Laparoscopic exploration showed no peritoneal dissemination or liver metastasis nodules, so the surgeons decided to perform D2 radical resection while preserving the greater omentum. The gastrocolic ligament was cut open 2-3 cm away from the greater curvature through to the lower pole of the spleen. The left gastroepiploic vessels were denuded, and the left gastroepiploic artery was ligated and cut at the root. The station number 4sb lymph nodes were dissected. The greater curvature was denuded, and station number 4d lymph nodes were dissected.

The lymph nodes in the inferior area of the pylorus were then dissected. The station number 14v lymph nodes were typically not dissected in the standard D2 radical surgery. The anterior pancreaticoduodenal fascia was stripped close

Video 1 Laparoscopic-assisted radical gastrectomy for distal gastric cancer

to the head of the pancreas to reveal the right gastroepiploic vein. During the separation, the non-working face of the ultrasonic scalpel was pointed towards the pancreas. Caution was made to avoid injury to the small vessels on the surface of the pancreas, particularly to the anterior superior pancreaticoduodenal vein. The right gastroepiploic vein was denuded, and transected before its junction with the pancreaticoduodenal vein. The right gastroepiploic artery was then denuded. The small vessels and subpyloric vessels emerging from the gastroduodenal artery and entering the posterior wall of the duodenum were treated first. This could reduce bleeding when separating the right gastroepiploic artery. After the right gastroepiploic artery was denuded, ligated and cut, the lower edge of the duodenum was denuded, and the station number 6 lymph nodes were dissected. The gastroduodenal artery was stripped to its root in an inverse direction. The common hepatic artery was dissected, and the right gastric artery was separated near the bifurcation, but was not transected for the moment.

A piece of sterile gauze was placed on the lesser sac to flip the stomach downward. The pylorus and the superior region of the duodenum were denuded, then the small omentum was opened, and the gauze was clearly visible. The duodenum was first transected, and the stomach was flipped to the left side to reveal the structure more clearly from the upper edge of the pancreas to the posterior wall of the lesser sac.

The anterior hepatoduodenal capsule was opened and the proper hepatic artery was divided. The right gastric artery was further denuded, ligated and cut at the root. The station number 5 lymph nodes were dissected. With the assistant gently lifting the gastropancreatic fold, the surgeon began to separate the superficial fascia on the upper edge of the pancreas. The gastropancreatic fold was dissected, and the coronary vein and the left gastric artery were denuded. After the coronary vein was denuded, a clamp was applied to the root and the vessel was transected. The left gastric artery was denuded from the periphery. An absorbable clamp was applied to 0.5 cm above its root and the vessel was transected so that the clamp would not slip off. The station number 7 lymph nodes were dissected.

The lesser sac was opened until the right edge of the cardia. The peritoneal reflection was opened to the anterior part of the right crus of the diaphragm to provide an accurate anatomic plane for the subsequent dissection of the station number 9 lymph nodes. The station number 12a lymph nodes were then dissected. The proper hepatic artery was gently pulled to the right side, and the fascia to the left was separated to naturally reveal the left anterior wall of the portal vein. The separation was continued along the upper edge of the fascia from the left side of the portal vein to the celiac artery, during which the stations number 12a and 8a lymph nodes were dissected en bloc. After the dissection, the entrance of the portal vein, splenic vein and coronary vein was clearly visible. The two stations were gently retracted to the left side, and the lymph nodes to the right of the celiac artery were dissected along the plane established anterior to the crus in the above steps, and the anterior region of the celiac artery was then dissected.

Afterwards, the lymph nodes proximal to the splenic artery were then dissected (number 11p). The fascia at the upper edge of the pancreas was separated towards the pancreatic tail to expose the splenic artery. It should be noted that there were several curves along the splenic artery to the splenic hilum, especially the largest one of 3 to 4 cm to the root, which was hidden behind the pancreas with lymph nodes inside that should not be omitted. Hence, we dissected the lymph nodes surrounding the splenic artery from both the anterior and the posterior directions. The dissection from posterior to anterior areas beginning from the left crus of the diaphragm would help ensure that the lymph nodes at the curves were not omitted. The supplying vessels along the lymph nodes around the splenic artery could be directly transected with the ultrasonic scalpel. After dissection, the lymph nodes were lifted to the anterior right side. The separation was then continued towards the cardia so that lymph nodes to the posterior and right of

the cardia could be dissected. The right side of the cardia and the lesser curvature of the stomach were denuded, and the stations number 1 and 3 were dissected. At this point, the laparoscopic operation was is complete. An auxiliary incision of about 5 cm was made inferior to the xiphoid for the removal of the entire specimen. A Tyco 25# circular gastrointestinal stapler was used to complete the Billroth I anastomosis.

The whole operation lasted 3 hours and 10 minutes, with intraoperative blood loss of 20 mL, and no blood transfusion was delivered. The patient was able to ambulate three days after surgery. Liquid diet was prescribed on the 5th day and semi-liquid diet on the 6th day. The patient was discharged seven days after surgery without postoperative complications. Postoperative pathology showed a superficial depressed type moderately to poorly differentiated adenocarcinoma with superficial ulceration at the junction of the antrum and the gastric body on the lesser curvature side (size 1 cm × 1 cm × 0.2 cm), invading the submucosa. Chronic inflammation was noted in 2 (suprapyloric), 1 (subpyloric), 5 (lesser curvature), 3 (greater curvature), 2 (close to the left gastric artery), 1 (close to the common hepatic artery), 2 (close to the splenic artery), 2 (close to the celiac artery), 1 (12a), 1 (4sb), and 2 (to the right of the cardia) lymph node. Both upper and lower margins were negative. Postoperative pathological staging was T1bN0M0.

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Surgical Video

Delta-shaped anastomosis in totally laparoscopic D2 radical distal gastrectomy

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Abstract: With less injury and faster postoperative recovery, laparoscopic techniques have been widely applied in D2 radical gastrectomy for distal gastric cancer. Billroth I anastomosis is a common reconstruction procedure in D2 radical gastrectomy for distal gastric cancer. The delta-shaped anastomosis, an intra-abdominal Billroth I reconstruction, has been increasingly applied by gastrointestinal surgeons. This surgical video demonstrates the delta-shaped anastomosis in laparoscopic-assisted D2 radical gastrectomy for distal gastric cancer.

Keywords: Gastric cancer; delta-shaped anastomosis; laparoscopy

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In 2002, Professor Seiichiro Kanaya from Japan Himeji Medical Center first introduced the delta-shaped anastomosis (1), which was a Billroth I side-to-side anastomosis of the posterior walls of the remnant stomach and the duodenum using a laparoscopic linear stapler. During the anastomosis, the staple line was in a "V" shape, which would turn into a triangular shape after the anastomosis was closed, hence the name "delta-shaped anastomosis". With increasing application of laparoscopic techniques in the D2 radical treatment of distal gastric cancer, the delta-shaped reconstruction has been gradually adopted in China.

In April 2013, a 54-year-old woman presented with dull abdominal pain for three months was diagnosed with adenocarcinoma of the gastric angle by gastroscopic biopsy. The lesion had a diameter of about 3 cm. After routine preoperative preparation, total laparoscopic D2 distal gastrectomy was performed; the delta-shaped anastomosis was used to reconstruct the gastrointestinal tract during operation. An ultrasonic scalpel (Johnson & Johnson, U.S.) was used for anatomical separation, and the anastomosis was completed with a gastroscopic linear stapler (Tri-Staple).

After general anesthesia, the patient was put in supine position with the head elevated and legs apart. During the surgery (*Video 1*), five trocars were inserted. CO_2 pneumoperitoneum of 12 mmHg was established. Standing on the left side of the patient, the surgeon divided the stomach and duodenum using an ultrasonic scalpel, and dissected the related lymph nodes according to the 2002 edition of the Gastric cancer treatment guidelines in Japan (2). A 60 mm gastroscopic linear stapler was inserted through the left upper trocar, which was used to transect the duedenum by rotating 90° from back to front. This would help to ensure the blood supply for anastomotic stoma. The stomach was then resected by successively transecting from the greater curvature to the lesser curvature with the stapler. A small incision was made to the remnant stomach and the edge of the duodenum respectively by the ultrasonic scalpel. The upper and lower anvils of a 60 mm linear stapler were inserted into one end respectively to close the posterior walls of the stomach and the duodenum. The stapling length was adjusted to 45 mm. Then the anastomosis of both ends was triggered. Upon confirmation of no leakage and bleeding of the anastomosis, the gastric tube was inserted into the distal anastomotic end of the duodenum. Finally, the common opening of the stomach

Video 1 Delta-shaped anastomosis in totally laparoscopic D2 radical distal gastrectomy

and the duodenum was closed with the linear stapler.

Throughout the surgery, the delta-shaped anastomosis procedure lasted about more than 10 minutes. Both resected specimens had negative margins. A total of 30 lymph nodes were dissected. Pathological staging was T2N0M0. Flatus occurred three days after the surgery. Liquid diet was started on the fourth day, and the patient was discharged on the eighth day. Based on the follow-up so far, the patient has been free of postoperative complications.

In short, the application of delta-shaped anastomosis with a linear stapler as part of the intraperitoneal Billroth I reconstruction is safe and feasible (3), allowing satisfying postoperative recovery and outcomes.

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Surgical Video

Station 10 lymph node dissections in laparoscopic-assisted spleen-preserving radical gastrectomy for advanced proximal gastric cancer

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Abstract: D2 gastric resection has been increasingly recognized as the optimal surgical treatment for advanced gastric cancer. Dissection of the station 10 splenic lymph nodes is required in the treatment of advanced proximal gastric cancer. Based on vascular anatomy and anatomical plane of fascial space, integrated with our experience in station 10 splenic lymph node dissection in open surgery and proven skills of laparoscopic operation, we have successfully mastered the surgical essentials and technical keypoints in laparoscopic-assisted station 10 lymph node dissection.

Keywords: Stomach neoplasm; laparoscopy; lymph node excision; splenic hilar

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The incidence of station 10 lymph node metastases is 9.8-20.9% in advanced proximal gastric cancer (1). The thoroughness of resection is an important prognostic factor. With further research, the critical role of the spleen as an immune organ in protecting the body against infection and tumors has been increasingly recognized (2). Meanwhile, the spleen-preserving station 10 lymph node dissection has also been accepted (3) since its first report by Hyung and colleagues in 2008 (4). In view of the complicated anatomical structures of the adjacent vessels, anatomical variations, limited space and deep location of the splenic region, as well as the bleeding-prone splenic parenchyma and the difficulty to manage splenic or vascular bleeding, the station 10 lymph node dissection is a technically demanding challenge for surgeons. Thus, a skilled and cooperative team of surgeons with experience in open surgery, solid grounding in anatomy and proven laparoscopic techniques will be needed to complete the task.

Appropriate patient selection

Surgical indications should be strictly observed: patients are eligible only when they had a preoperative stage of c (T2, T3, T4a) N1M0 as confirmed by preoperative pathological diagnosis, endoscopic ultrasound and CT scan, without evidence of fusion of the station 10 lymph nodes or spleen involvement, or potential adhesion. At the preliminary stage, patients who were obese, had surgery history or were elderly should not be considered.

In the present video (*Video 1*), the patient is a 53-year-old man confirmed as poorly differentiated adenocarcinoma by preoperative gastroscopic biopsy, with a preoperative staging of cT4aN1M0.

Procedure

Patient positioning

The patient is placed in a supine position with the head raised and legs apart. The surgeon stands on the left side of the patient, with the first assistant on the right side and the camera assistance between the patient's legs.

Surgical procedures

The omentum is lifted to expose the gastrocolic ligament.

Video 1 Station 10 lymph node dissections in laparoscopic-assisted spleen-preserving radical gastrectomy for advanced proximal gastric cancer

The anterior lobe of transverse mesocolon is separated to expose the anterior pancreatic space. The right gastroepiploic vein is ligated and cut above the anterior inferior pancreaticoduodenal vein. The right gastroepiploic artery to the left posterior region is then ligated and cut, followed by dissection of the station 6 lymph nodes. The gastropancreatic ligament is cut towards the posterior wall of the duodenal bulb along the right gastroepiploic artery, and the location of the gastroduodenal artery is confirmed. The gastroduodenal artery is the total trigger to locate the common hepatic artery, proper hepatic artery, and right gastric artery above the upper edge of the pancreas. The hepatopancreatic ligament is cut along the upper edge of the pancreas to expose and denude the common hepatic artery, which is in a shape of transverse arch. The right gastric artery to the upper left, mostly emerging from the proper hepatic artery, is ligated and cut. The proper hepatic artery is denuded towards the superior area. Stations 8, 5 and 12a lymph nodes are dissected. The gastric coronary vein joins the portal vein mostly at the upper third of the tip of the common hepatic artery, and is thus prone to injury as it is not easily exposed during retraction. Dissection is performed towards the pancreatic tail along its upper edge to enter Toldt's space at the posterior pancreatic area, and is continued towards the left upper region along the common hepatic artery to expose the celiac trunk, left gastric artery and the root of the splenic artery. Stations 7, 9 and 11p lymph nodes are dissected.

The dissection of station 10 lymph nodes is completed from both sides into the central region. The Toldt's space is enlarged along the pancreatic artery above the pancreatic upper edge, and the pancreatic artery is denuded towards the left side. Since the non-I pancreatic artery is partly embedded in the pancreatic tissue, caution is needed to avoid injury to the pancreas to prevent postoperative pancreatic leakage. Dissection is continued to the junction between the body and tail of the pancreas. The divided omentum and greater curvature are retracted towards the upper right direction, and the splenocolic ligament is transected to expose the gastrosplenic ligament. The pancreatic capsule is cut open at the lower edge of the tail of the pancreas to expose the anterior pancreatic space. The left gastroepiploic artery is ligated and cut at the upper edge of the lower splenic pole artery, and the pancreatic capsule is separated towards the right until the end. The splenogastric ligament is then divided towards the superior area. The lymph nodes along the trunk of the splenic artery and the splenic lobar arteries are dissected. Due to the considerable variations and tortuosity of branches of the splenic lobar artery, as well as the thin venous wall, the non-functional surface of the ultrasonic scalpel should be as close to the surface of the terminal branch of the splenic artery and the branches of the splenic vein as possible during the alternate sharp and blunt stripping, cutting and separation with extreme caution. During the dissection, as the posterior gastric artery mostly emerges from the splenic artery, the ligation should be carefully carried out to avoid injury to the upper splenic lobar artery emerging from the splenic artery to prevent ischemia of that lobe. There are around two to six branches of the short gastric artery emerging from the terminal branch of the splenic artery, denudation should be performed at their roots where the ultrasonic scalpel is directly used to cut off. The gastrosplenic ligament is cut along the surface of the spleen through to the left side of the cardia and the left crus of the diaphragm. Stations 4sb, 11d, 10, 4b and 2 lymph nodes are dissected in this area. The stomach and the omentum are retracted towards the left lower direction, and the hepatogastric ligament is transected along the surface of the liver through to the right side of the cardia and the right crus of the diaphragm. Station 1 lymph nodes are dissected.

Results

The length of operation was 220 min with bleeding of about 90 mL. Postoperative pathology suggested poorly differentiated adenocarcinoma, pathological stage

T4aN2M0 (IIIB). The overall lymph nodes were 5/34 (+), station 10, 0/3 (+). Postoperative recovery was uneventful without any significant complication. Flatus was present three days after surgery. Liquid diet was given on the fourth day, and the patient was discharged on the seventh day.

Conclusions

Laparoscopic-assisted radical gastrectomy with station 10 lymph node dissection is a safe and feasible treatment for gastric cancer. Proper patient selection and experience in surgical techniques is the key to successful operation.

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Surgical Video

Radical gastrectomy for D2 distal gastric cancer

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Patient's information

The patient is a 56-year-old man who visited our hospital for "repeated epigastric pain for more than two months." Physical examination showed nearly pale appearance; abdomen was soft and no mass palpable; left supraclavicular lymph node (-); and digital rectal examination (-). Gastroscopy revealed a bulging ulcerative lesion of the antrum at the lesion lesser curvature side, which had dirty appearance and was solid, fragile and prone to bleeding. Ultrasonic gastroscopy suggested myometrial invasion. Biopsy indicated adenocarcinoma. CT and MRI showed no obvious abnormalities. Therefore, the diagnosis of gastric cancer was definite for this patient. The preoperative staging was T3N0M0, and radical gastrectomy was considered (distal stomach, D2). The radical gastrectomy was performed under general anesthesia on April 21, 2013. The operation was uneventful, with intraoperative blood loss of about 250 mL. The length of operation was 180 minutes. Postoperative pathology suggested moderately differentiated adenocarcinoma of the "gastric antrum" with invasion to the serosa, and 2/35 of lymph nodes were positive. Postoperative staging: T3N1M0, stage III A. The patient was discharged 12 days after surgery and began chemotherapy (oxaliplatin + CF + 5-FU) at the department of oncology. The treatment course has been uneventful.

Surgical procedures

The main surgical instrument used in the operation is a Peng's multifunction operative dissector (PMOD) invented by Professor Shuyou Peng, which enables scraping, suction, cutting, coagulation and other operations. In view of the important role of lymph node dissection in gastric cancer surgery (*Figure 1*), we have divided the procedure into three steps. The overall operation is conducted "from right to left and bottom to top" when denuding the lymph nodes for dissection and en bloc resection (*Video 1*).

Step one

Gerota's fascia and Kocher's incision (*Figure 2*): the right renal fascia and the right fatty renal capsule are resected through a Kocher's incision, and the right renal vein, inferior vena cava, right reproductive vein and abdominal aorta are gradually exposed. The head of the pancreas is then revealed (station 13), and the duodenum is freed during this process.

Treatment of the greater omentum and transverse mesocolon: the surgeon lifts the greater omentum with vascular forceps in the left hand, and the assistant retracts the transverse colon downward to form tension. With a PMOD in the right hand, the surgeon divides the greater omentum from the hepatic to the splenic region of the colon, and the anterior lobe of the transverse mesocolon through to the lower edge of the pancreas to reveal gastrocolic venous trunk, joined by the right colic vein and right gastroepiploic vein, and the superior mesenteric vein. The surrounding fat and lymphoid tissue is dissected (station 14), and the right gastroepiploic vein is separated and cut from its root. The surrounding fat and lymphoid tissue, as well as the pancreatic capsule, is lifted upwards together. The pancreatic capsule is separated from the middle to the right to expose the entire course of the gastroduodenal artery. The right gastroepiploic artery is then divided along this vessel and transected at the root. The surrounding fat and lymphoid tissue is dissected (station 6).

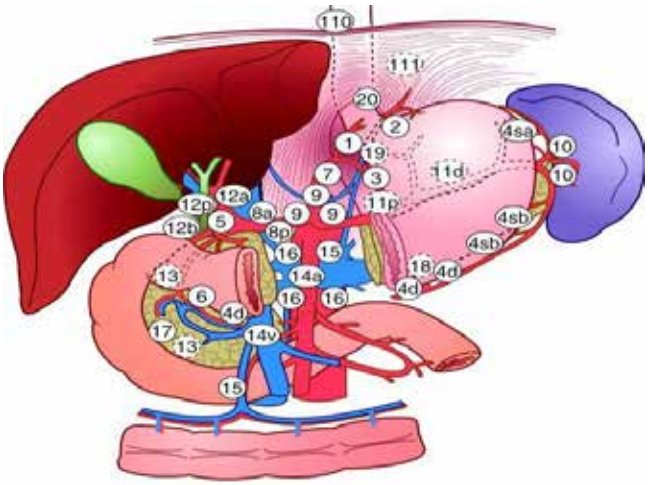

Figure 1 Distribution of lymph nodes in gastric cancer

Video 1 Radical gastrectomy for D2 distal gastric cancer

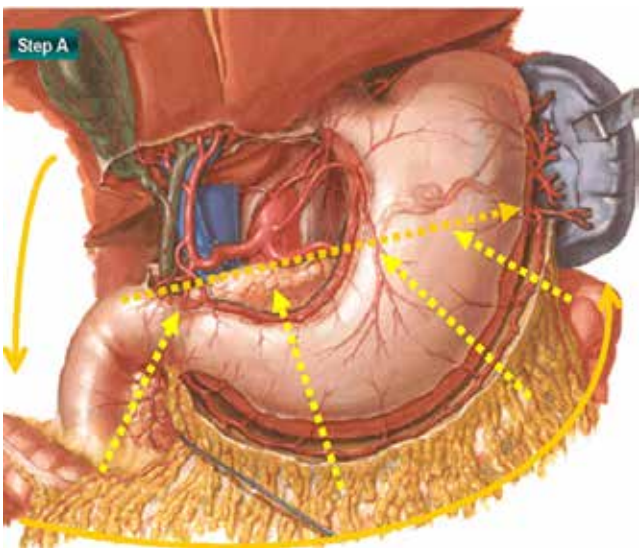

Figure 2 Step 1. Gerota's fascia and Kocher's incision omentum and transverse mesocolon

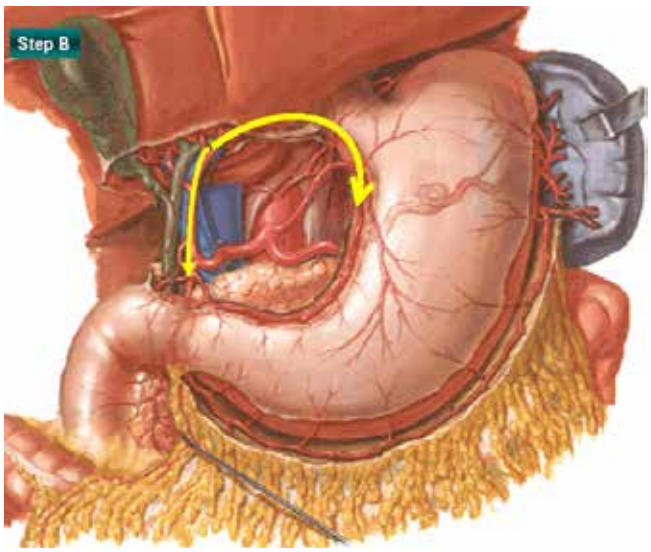

Figure 3 Step 2. Treatment of the lesser omentum

Step two

Treatment of the lesser omentum (*Figure 3*): after transection of the duodenum 2 cm inferior to the pylorus, the stomach is flipped upwards and cut longitudinally at the left edge of the common bile duct to expose the proper hepatic artery and portal vein. The separation is continued upwards to the bifurcation of the common bile duct and downwards to the common hepatic artery where the gastroduodenal artery emerges. The fat and lymphoid tissue anterior to and at the right side of the proper hepatic artery is dissected towards the left direction (station 12a), in which the root of the right gastric artery is revealed and transected. The surrounding lymph nodes as well as the entire right gastric artery are dissected towards the left (station 5), and the hepatogastric ligament is freed 1 cm beneath the liver upwards to the right diaphragm crus (stations 1 and 3).

Step three

Treatment of the structures of the celiac trunk and the

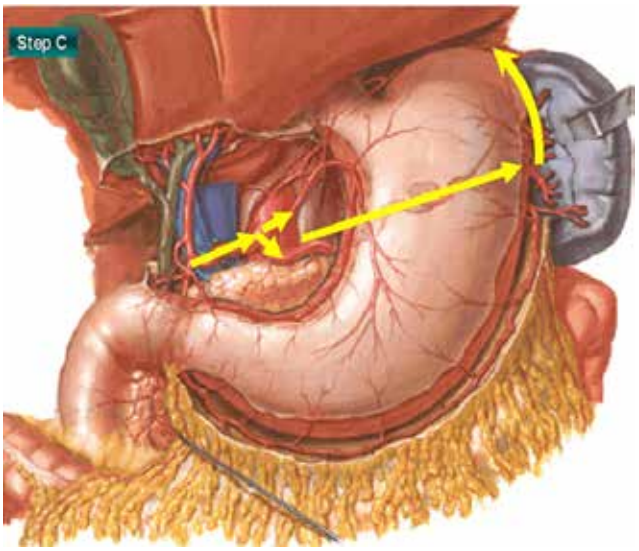

Figure 4 Step 3. Treatment of the structures of the celiac trunk and the greater curvature region

greater curvature region (*Figure 4*): using the proper hepatic artery as a landmark, the dissection is performed towards the celiac trunk to reveal the entire common hepatic artery, the initial region of the splenic artery and vein, and the left gastric artery and vein. The left gastric vessels are ligated at their roots, during which stations number 8a, 7, 9 and 11p are dissected. While dissecting stations 8 and 11p lymph nodes, feeding vessels from the pancreas often can be noted. With appropriate scraping and stripping with the PMOD, these small vessels can be rapidly separated and coagulated to ensure a clear surgical field while minimizing bleeding and avoiding potential injury to the pancreatic tissue due to redundant clamping. The stomach is flipped up to reveal the emerging point of the splenic artery from the celiac trunk. The fat and lymphoid tissue is then dissected (station 11) along the trunk of the splenic artery towards the splenic hilum. The gastrosplenic ligament is separated. During this step, it is necessary to ligate the left gastroepiploic artery and vein at their roots for dissection of station number 4sa lymph nodes.

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Surgical Video

Curettage and aspiration in splenic hilar lymph node dissection for spleen-preserving radical D2 gastrectomy

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Abstract: D2 radical gastrectomy is the standard procedure for gastric cancer in the middle or upper part of the stomach. According to the latest Japanese treatment guidelines for gastric cancer, dissection of the splenic hilar lymph nodes is required during the radical treatment for this condition. This study reports a D2 radical total gastrectomy employing the curettage and dissection techniques, in which the resection of the anterior lobe of transverse mesocolon, vascular denudation and splenic hilar lymph node dissection were successfully completed.

Keywords: Gastric cancer; gastrectomy; lymph node dissection; curettage and dissection

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Introduction

Although the global incidence of gastric cancer is declining, it remains highly prevalent in Asia as compared to the West (1). China is one of the countries with the highest incidence of gastric cancer, and accounts for over 40% of all new gastric cancer cases in the world (1,2). Gastric cancer is the third leading cause of cancer mortality in China (1). D2 radical gastrectomy is the standard procedure for gastric cancer in the middle or upper part of the stomach. According to the latest Japanese treatment guidelines for gastric cancer, dissection of the splenic hilar lymph nodes is required during the radical treatment for this condition. This study reports a D2 radical total gastrectomy employing the curettage and dissection techniques.

Materials and methods

Materials

The patient was a 44-year-old man with gastric ulcer on the lesser curvature of approximately 25 mm × 28 mm as confirmed by gastroscopy. The preoperative diagnosis was gastric carcinoma (proximal, poorly differentiated adenocarcinoma, cT3N0M0, Bormann II type). Intraoperative exploration revealed that the tumor was located in the lesser curvature near the cardia of the gastric body, about 30 mm × 25 mm in size, not protruding the serosa. The intraoperative diagnosis was proximal gastric carcinoma sT3N0M0 (EGA Siewert classification III type).

Surgical methods

In this video (*Video 1*), the surgery is performed under general endotracheal anesthesia with the patient in a supine position. A central incision of approximately 12 cm is made in the upper middle abdomen to access the abdominal cavity and explore the lesion. The incision is protected with sterile pads and retracted with an automatic ring retractor for better exposure.

Separating the greater omentum and the anterior lobe of transverse mesocolon: with the second assistant retracting the transverse colon downward with the left hand, the surgeon and the first assistant retract its anterior lobe with forceps in the left and right hands, respectively, the surgeon separates

Video 1 Curettage and aspiration in splenic hilar lymph node dissection for spleen-preserving radical D2 gastrectomy

the anterior lobe from left to right with a Peng's multifunction operative dissector (PMOD) in the right hand to completely transect the anterior lobe of the transverse mesocolon.

Dissection of station number 14v lymph nodes: with the transverse colon retracted downward, the lower edge of the pancreas and the middle colic artery and vein are divided. The lymphoid tissue around the lower edge of the pancreas, the superior mesenteric vein and the root of the middle colic vein are removed together.

Dissection of station number 6 lymph nodes: as the gastrocolic trunk is exposed anterior to the pancreatic head, its root is ligated with the Impact vascular ligation bundle (COVIDIEN LF4200) to separate from the right gastroepiploic vein. The surrounding fat and lymphoid tissue is dissected. The right gastroepiploic vein is divided from the deeper area of the right gastroepiploic artery, and separated from its root. Station number 6 lymph nodes are dissected as well.

Dissection of station number 5 lymph nodes: the liver is pulled away with an S-shaped retractor to expose the hepatoduodenal ligament and the lesser omentum. The lesser omentum is transected near the liver to expose the hepatic artery, and the right gastric artery and vein. The right gastric artery and vein are cut near the root of the hepatic artery. Station number 5 lymph nodes are dissected.

Transection of the duodenum and resection of the pancreatic capsule: the duodenum is freed and cut 2 cm away from the pylorus. Its distal end is closed. The gastric body is retracted towards the upper left direction to expose the pancreas, and the pancreatic capsule is completely resected.

Intrathecal dissection of stations number 7, 8 and 9 lymph nodes: with the pancreas retracted downward to reveal the hepatopancreatic fold and gastropancreatic fold, the vascular sheaths of the common hepatic artery, celiac trunk, proximal end of the left gastric artery, and proximal end of the splenic artery are opened from the bifurcation of the gastroduodenal artery and the common hepatic artery with a PMOD. With retraction by the vascular retracting bundle, the left gastric artery is ligated and cut at the root, and stations number 12, 8, 9 and 7, as well as part of the station 11p, are completely dissected from right to left. The coronary vein is transected at the junction of the left gastric vein into the portal vein posterior to the common hepatic artery with an Impact.

Dissection of stations number 1 and 2 lymph nodes followed by transection of the esophagus: the fat and lymphoid tissue around the abdominal segment of the esophagus and both sides along the cardia is completely dissected with an Impact. The esophagus is transected about 4 cm above the upper edge of the tumor. The disinfected esophageal stump is placed in the anvil of a 25# curved stapler.

Spleen-preserving dissection of the splenic hilar lymph nodes v the antegrade approach after the spleen is retracted: while holding the spleen fixed with the left hand, the assistant denudes the splenic hilar vessels with a PMOD close to the spleen, and transect the left gastroepiploic vessels and short gastric vessels at their roots. The gross specimen is then removed.

The splenic artery sheath is open close to the upper edge of the pancreas. The splenic artery and vein are denuded from distal to proximal. The perivascular lymphoid tissue is dissected and removed en bloc. Caution is given to avoid accidental injury to the spleen, pancreas and splenic vessels. The spleen is replaced into the spleen nest.

Esophagojejunal Roux-en-Y anastomosis: the jejunum is transected 15 cm below the Treitz ligament. A Roux-en-Y intestinal loop is freed for the end-to-side anastomosis between the esophagus and the jejunum anterior to the colon with a stapler (COVIDIEN DST EEA™ end-to-end stapler). The proximal jejunum is stapled in a side-to-side jejunal anastomosis 45 cm distal to the previous anastomosis. Upon confirmation that the anastomoses are free of stenosis, the mesangial holes are closed.

Results

The length of operation was 270 min, with intraoperative

bleeding of 100 mL. The patient remained supine for 48 hours after surgery. The resected specimen was 21 cm long on the greater curvature side and 12 cm on the lesser curvature side. The closest distance from the lesion to the surgical margin was 3 cm. The tumor did not protrude the gastric wall, and the gastric and duodenal margins were both negative. A total of 46 lymph nodes were dissected, including eight from station 14v, two from station 10, and three from station 11. No evidence of metastasis was found. The pathological diagnosis was pT3N0M0. The patient had flatus and began to ambulate on the third day after surgery. There was no pancreatitis, pancreatic fistula, intra-abdominal bleeding, subphrenic infection or other complications. The patient was discharged on the eighth day after surgery.

Discussion

Whether the dissection of lymph node stations 10 and 11 in conjunction with splenectomy is feasible for patients with advanced upper gastric cancer remains controversial. Research has shown that the conjunction with organ resection did not significantly increase the post-operative survival; rather, it increased the incidences of post-operative complications (1). Radical treatment of gastric cancer with "curettage and aspiration" technique is featured by accurate anatomy, timely hemostasis, and clear surgical field; also, it can shorten the operative time, reduce bleeding, and facilitate the removal of lymph nodes, which is particularly helpful for the spleen-preserving splenic hilar lymphadenectomy (2). One decade ago, Schwarz *et al.* proposed that the conjunction of pancreatectomy and splenectomy, when applied as an approach to the dissection of lymph nodes around the splenic hilum and splenic vessels, could not extend the survival (3). Ji *et al.* argued that the spleen-preserving splenic hilar lymphadenectomy was feasible when performed by highly skilled surgeons (4).

We believe that spleen-preserving hilar lymph node dissection should be considered as long as the tumor has not invaded the splenic hilum or the spleen. Enabling sharp and blunt scraping, suction, cutting, coagulation, pushing and other functions, a curettage and aspiration dissector can access to narrow space and significantly reduces the length of operation, as well as intraoperative injury, thus improves the resection rate and cure rate.

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Surgical Video

Laparoscopic distal gastrectomy with D2 dissection for advanced gastric cancer

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Abstract: The successful application of the laparoscopic distal gastrectomy with D2 dissection for gastric cancer requires adequate understanding of the anatomic characteristics of peripancreatic and intrathecal spaces, the role of pancreas and vascular bifurcation as the surgical landmarks, as well as the variations of gastric vascular anatomy. The standardized surgical procedures based on distribution of regional lymph node should be clarified.

Keywords: Gastric cancer; gastrectomy; laparoscopy

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The D2 lymph node dissection has been widely applied in traditional open surgery for locally advanced gastric cancer with curative intent (1). However, the feasibility of this procedure in laparoscopic surgery has only been reported in a few conclusive studies around the world (2,3). That is because of the technical threshold for laparoscopic lymph node dissection derived from the perigastric anatomical complexity (4), which is an important factor of the surgical performance and the indicator of prognosis (5). Since the inception of this technique in our department in 2004, we have clinically accumulated proven experience in laparoscopic lymph node dissection for advanced gastric cancer. We believe that it is a combination of proper arrangement of surgical procedures and skilled application of laparoscopic techniques based on complete understanding of the perigastric space (6), surgical landmarks and variations in blood vessels.

The key step in the radical treatment of distal gastric cancer lies in the regional lymph node dissection. The extent of D2 dissection for distal gastric cancer defined in the Japanese Gastric Cancer Surgery Guidelines and the Treatment Guideline for Gastric Cancer in Japan (7) involves stations number 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a and 14v lymph nodes, while station 14v is excluded in the latest guidelines.

According to the distribution of perigastric lymph nodes and the characteristics of laparoscopic techniques, especially the perigastric anatomical features of the gastric body and antrum flipped towards the head under laparoscopy, the scope of D2 lymph nodes can be divided into five regions: (I) lower left region (stations number 4sb and 4d around the left gastroepiploic vessel); (II) lower right region (mainly including station number 6 inferior to the pylorus, and at the root of the right gastroepiploic artery; station number 14v around the superior mesenteric vein in the former version); (III) upper right region (station number 5 superior to the pylorus and number 12a in the hepatoduodenal ligament); (IV) central region posterior to the gastric body (stations number 7, 8a, 9 and 11p surrounding the celiac artery and along its three branches); and (V) hepatogastric region (stations number 1 and 3 along the lesser curvature).

Based on the above classification, we have established the standard procedure for laparoscopic D2 lymphadenectomy for distal gastric cancer in our department (*Video 1*):

(I) The left side of the gastrocolic ligament is dissected near the transverse colon through to the lower splenic pole and the pancreatic tail. The key steps include extending and stretching the attachment of the greater omentum to

Video 1 Laparoscopic distal gastrectomy with D2 dissection for advanced gastric cancer

the transverse colon tightly, and then separating from the greater sac into the anterior and posterior space of the transverse mesocolon near splenic flexure, until the lower edge of the tail of the pancreas is exposed;

(II) The origin of the left gastroepiploic vessels are ligated. The key steps include extending and stretching the gastrosplenic ligament and fending off the posterior wall of the gastric fundus to expose the splenic hilum and the tail of the pancreas, and thereby the pancreatic capsule can be flipped from the lower edge to the upper edge of its tail. During this process, the left gastroepiploic artery and vein are ligated at the roots near the upper edge of the pancreatic tail, and division is continued from the greater curvature towards distal gastric body. The goal is the dissection of stations number 4sb and 4d lymph nodes;

(III) The right side of the gastrocolic ligament is cut near the transverse ligament through to the hepatic flexure, the hepatic flexure of the colon is separated from the duodenal bulb and the surface of the pancreatic head. The key steps include cutting the mesogastrium and the mesocolon along the attachment line between the posterior wall of gastric antrum and mesocolon, and retracting the posterior wall of the sinus to the left anterior direction and the colon and its mesentery to the lower right direction to expose the underlying loose fusion fascial space. Take time to divide the vessels. In the process, the anatomical layer should be fully exposed to separate the right side of the transverse colon and its mesentery from the duodenal descending part, the surface of pancreatic head and the lower edge of pancreatic neck it is attached to. In this way, the gastrocolic trunk (variations may be present in certain patients) formed by the right gastroepiploic vein, right colic vein and their confluence has been completely revealed;

(IV) The right gastroepiploic vessels are transected. The key steps include fully exposing the lower edge of the pancreatic neck, the pancreatic head and the duodenum, so that the right gastroepiploic vein can be transected above the point where the anterior superior pancreaticoduodenal vein joins. Using the pancreas as a starting point, the pancreatic capsule is lifted and the tissue is separated from the lower edge of the pancreas along the anterior pancreatic space on the surface of the pancreas towards the external superior region, until the origin of the right gastroepiploic artery from the gastroduodenal artery is reached. The right gastroepiploic artery is then cut. The posterior inferior wall of duodenal bulb is denuded near the surface of the pancreatic head along the anterior pancreatic space. The goal is the dissection of stations number 6 lymph nodes;

(V) The gastroduodenal artery is exposed and the right gastric artery is transected. The key steps include transecting the duodenum only after dissecting the tissue around the pancreatic head and the upper part of the pancreatic neck from inferior to superior along the gastroduodenal artery in the posterior region of the duodenal bulb on the surface of the pancreas and on the plane of the anterior pancreatic space, in which the bifurcation of the common hepatic artery is exposed at the upper edge of the pancreatic edge for the access to the inner layer of arterial sheath, and the proper hepatic artery is denuded along the adventitia through to hepatoduodenal ligament, where the right gastric artery is cut at its root. The goal is the dissection of stations number 12a and 5 lymph nodes;

(VI) The three branches of the celiac trunk are divided and the left gastric artery is transected. The key steps include stretching the left gastric vascular pedicle in the gastropancreatic fold and fending the gastric body towards the anterior superior region while pulling the pancreas downwards to fully expose the upper edge of the pancreas for access to the posterior pancreatic space. The three branches of the celiac trunk are denuded here and the left gastric artery is transected at the root. The division is continued upwards in the space until the crura of the diaphragm. The goal is dissection of stations number 7, 8a, 9 and 11p lymph nodes;

(VII) The hepatogastric ligament and the anterior lobe of the hepatoduodenal ligament are transected close to the

lower edge of the liver, and the right side of the cardia and the lesser curvature are fully separated. The key steps include retracting the liver upwards and the gastric downwards to stretch the hepatogastric ligament so that the hepatogastric ligament and the anterior lobe of the hepatoduodenal ligament can be transected and the division can continue towards the right to reach the anterior surface of the proper hepatic artery, which has been separated previously, and towards the left to reach the right side of the cardia, where the lesser curvature is fully divided and denuded. Stations number 1 and 3 lymph nodes are dissected;

(VIII) The distal subtotal gastrectomy, and reconstruction of the digestive tract were completed through minilaparotomy.

The above surgical procedure is designed to accommodate the characteristics of laparoscopic techniques by organizing the sequence of operations from proximal to distal, inferior to superior, and posterior to anterior. More importantly, it has incorporated with our understanding of the anatomical structures under laparoscopy, so that we can make full use of the advantages of visual amplification to identify the relevant anatomical landmarks based on the shape, color and other features, and always proceed at the correct surgical plane while minimizing bleeding.

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Surgical Video

Spleen-preserving splenic lymph node dissection in radical total gastrectomy

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Abstract: Radical gastrectomy has been recognized as the standard surgical treatment for advanced gastric cancer, and essentially applied in a wide variety of clinical settings. The thoroughness of lymph node dissection is an important prognostic factor for patients with advanced gastric cancer. Splenic lymph node dissection is required during D2 radical gastrectomy for upper stomach cancer. This is often accompanied by removal of the spleen in the past few decades. A growing number of investigators believe, however, that the spleen plays an important role as an immune organ, and thus they encourage the application of a spleen-preserving method for splenic hilum lymph node dissection.

Keywords: Gastric cancer; D2 radical resection; lymph node dissection; splenic hilum

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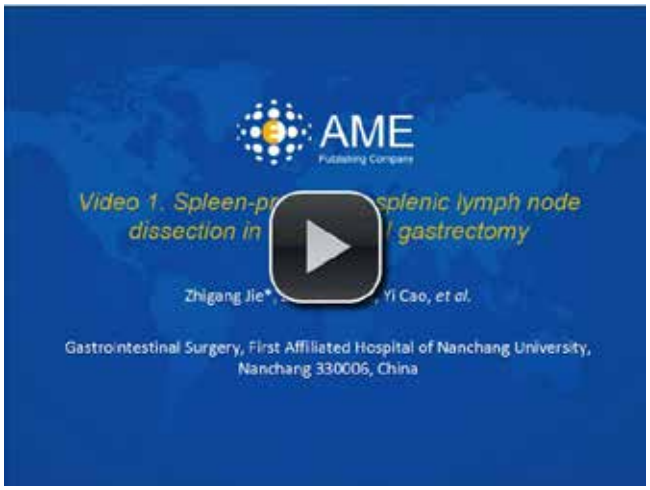
According to the Japanese Gastric Cancer Treatment Guidelines, the splenic hilar lymph nodes (No. 10) are the station 2 lymph nodes in gastric cancer of the upper and middle stomach (cardia, fundus, and gastric body). In a typical D2 gastrectomy, this group must be dissected. In order to achieve a thorough dissection, there has been controversy as to whether the spleen is preserved or removed.

In April 2013, a 51-year-old female patient visited our department due to "upper abdominal swelling with nausea and vomiting for more than a month". Gastroscopy and endoscopic ultrasound showed a mucosal nodular bulge at the gastric body and the fundus. The diagnosis was stomach cancer. Pathology suggested diffuse-type, poor cohesive cancer (gastric body), HP (–). Abdominal CT showed that the tumor was located at the junction of the gastric body and fundus, invading through the serosa and into the pancreatic capsule, with lymph node metastases. The cTNM staging was T4aN2M0. With adequate preoperative preparation, we performed spleen-preserving D2 radical total gastrectomy (*Video 1*) for the patient.

Following the routine procedures for D2 resection, we removed the anterior lobe of transverse mesocolon, and separated the pancreatic capsule. After the Kocher incision was made, we found lymph nodes around the inferior vena cava, so dissection of the station 16 was conducted, followed by dissection of the station 13 posterior to the pancreatic head.

The gastrosplenic ligament was cut, and the spleen hilum was resected. The station 10 lymph nodes were dissected. It is much easier to resect the spleen than preserving it. Iatrogenic splenic injury can often occur during gastrectomy, especially when dissecting the lymph nodes around the splenic artery, fat and connective tissue around the spleen, and denuding the splenic artery, which is associated with a high risk of injury to the spleen and blood vessels. In this case, when major bleeding was present due to splenic vascular injury, we use 5-0 proline suture to close the vascular wounds effectively. The lesion was transected 3 cm above the cardia, and the specimen was removed. Roux-en-y esophagojejunal anastomosis was conducted.

Ikeguchi and coworkers (1) reported that splenectomy was needed in advanced gastric cancer complicated by serosal invasion and local lymph node metastases. The rate of metastases to splenic hilar lymph nodes was 20.19%, and failure to dissect the lymph nodes was associated with



Video 1 Spleen-preserving splenic lymph node dissection in radical total gastrectomy

poor prognosis, while the prognosis in patients undergoing successful dissection was comparable to those without metastasis. Zhang *et al*. (2) studied 108 cases with gastric cancer and the cardia and fundus to compare the prognoses with and without splenectomy. The 5-year survival rates were 38.17% in the spleen-preserving group, and 16.19% in the splenectomy group (P=0.1008), suggesting a worse prognosis in those undergoing splenectomy. Therefore, the spleen should be preserved as long as it is unaffected by the lesion.

The length of operation was 153 minutes, with an estimated blood volume of 80 mL. According to the staging criteria described in the seventh edition of AJCC, the postoperative pathologic stage was T4aN3M0 (IIIc). Liquid diet was started from the 4th day after surgery, and the patient was discharged on the 8th day. No evidence of complications or tumor recurrence and metastasis has been found in the ongoing follow-up.

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Surgical Video

D2 plus radical resection combined with perioperative chemotherapy for advanced gastric cancer with pyloric obstruction

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Abstract: A patient with advanced gastric cancer complicated with pyloric obstruction was treated using D2 + radical resection combined with perioperative chemotherapy, and had satisfying outcomes. The perioperative chemotherapy regimen was Taxol and S1 (tegafur, gimeracil, and oteracil). Three cycles of neoadjuvant chemotherapy were delivered before surgery, and three cycles of adjuvant therapy after surgery. PR was achieved after chemotherapy. D2 + dissection of stations 8p, 12b, 12p, 13 and 14v lymph nodes was performed on September 10, 2012.

Keywords: Advanced gastric cancer; pyloric obstruction; D2 + lymph node dissection; perioperative chemotherapy

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D2 lymph node dissection has become the standard surgical approach for advanced gastric cancer (1-3). However, in the case of lower stomach cancer complicated by pyloric obstruction, the lymphatic drainage and pattern of metastases are different due to the anatomical restriction, and a higher rate of metastases into the hepatoduodenal ligament and the posterior area of the pancreatic head are often seen (4). Perioperative chemotherapy can significantly improve the survival of patients (5,6). This video describes the procedure of D2 + radical resection combined with perioperative chemotherapy for a patient with lower gastric cancer complicated by pyloric obstruction, as follows. The treatment was successful.

A 53-year-old woman was admitted on June 3, 2012 due to "upper abdominal fullness with dull pain for 3 months, with intermittent nausea and vomiting for 10 days." Gastroscopy suggested a huge, solid ulcer at the antrum close to the pylorus, involving the pylorus and resulting in pyloric stenosis. Endoscopic biopsies suggested poorly differentiated adenocarcinoma of the gastric antrum. CT: huge tumor in the antrum, considered as gastric antral carcinoma, infiltrating through the serosa with metastases to multiple lymph nodes surrounding the stomach and superior area of the pancreas. Tumor markers: CA199 402.15 U/mL. Clinical diagnoses: cancer of the gastric antrum involving the pylorus, complicated by partial pyloric obstruction, staging T4aN2M0. Three cycles of preoperative chemotherapy were delivered on June 9, July 2 and July 28, 2012, using the regimen of Taxol 240 mg/dL and S1 60 mg bid po d1-14, repeated for three weeks. After the chemotherapy courses, the CT scan suggested significantly reduced volume of the antral tumor, and lymph nodes around the stomach and the pancreas were not as obvious as before. PR was achieved following chemotherapy. Radical gastrectomy with D2 + lymph dissection was performed under general anesthesia for the distal gastric cancer resection on September 10, 2012.

During the surgery (*Video 1*), the patient was placed in a supine position. Following general anesthesia, a middle upper abdominal incision of 3 cm was made from the xiphoid down to the umbilicus. The wound was well protected, and abdominal exploration was conducted to

Video 1 D2 plus radical resection combined with perioperative chemotherapy for advanced gastric cancer with pyloric obstruction

confirm that there were no peritoneal and liver metastases. A piece of gauze was gently padded posterior to the pancreas to prevent tearing. Kocher's separation: the peritoneum was divided at the lateral border of the duodenum and the duodenum was freed. The incision continued downwards to the hepatic flexure of the colon to expand the surgical field. Sharp dissection was performed along the posterior region of the duodenum and the pancreas to reveal the inferior vena cava, the beginning part of the left renal vein, and the right ovarian vein. The anterior lobe of the transverse mesocolon and the pancreatic capsule were completely separated to the hepatic flexure of colon on the right side and to the lower pole of the spleen on the left side, so that the omental bursa could be completely removed.

The lymph nodes in the inferior area to the pylorus were dissected along the course of the middle colon vein towards its root, and the superior mesenteric vein (SMV) anatomy, as well as the gastrointestinal vein trunk and accessory right colic vein, was freed from the inferior region of the pancreatic neck. The station 14v lymph nodes were dissected around the SMV. The separation continued towards the pylorus to free the right gastroepiploic vein and the anterior superior pancreaticoduodenal vein. The structure of the gastrointestinal vein trunk formed jointly by the right gastroepiploic vein, anterior superior pancreaticoduodenal vein and accessory right colic vein was clearly visible. The right gastroepiploic vein was ligated and cut before its junction with the pancreaticoduodenal vein. The gastroduodenal artery was isolated at the junction of the duodenum and the pancreatic head. The separation continued towards the pylorus to free the right gastroepiploic artery, which was then ligated and cut at the root. The inferior pyloric artery from the gastroduodenal artery was then separated. The inferior pyloric artery was ligated and cut, and the lower edge of the duodenum and the pylorus was completely denuded to for the complete dissection of the station number 6 lymph nodes.

The left gastroepiploic artery was separated, ligated and cut from the lower pole of the spleen, followed by dissection of the station number 4sb lymph nodes. The fascia over the upper edge of the pancreas was opened to reveal the splenic artery, for the dissection of the station number 11p lymph nodes. It should be noted that there were several curves along the splenic artery to the splenic hilum, especially the largest one of 3 to 4 cm to the root, which was hidden behind the pancreas with lymph nodes inside that should not be omitted. After dissection of the station number 11p lymph nodes, the separation was continued towards the left diaphragmatic muscle to dissect the lymph nodes to the left of the celiac artery.

The stomach was flipped down to the inferior side, and the anterior peritoneum of the hepatoduodenal ligament was opened. The proper hepatic artery and the right gastric artery were divided, and the latter was ligated and cut at the root. The station number 5 lymph nodes were dissected. The supraduodenal vessels were transected, and the upper edge of the duodenal bulb was completely denuded. The duodenum was transected 3 cm below the pylorus (with a Tyco 60 mm linear stapler), with the duodenal stumps closed with reinforced stitching.

Denuding and dissection of the hepatoduodenal ligament: the lymph nodes surrounding the proper hepatic artery (number 12a) were dissected, and the artery was retracted with retraction bands to divide the left and right hepatic arteries. Since the hepatic branch and plexus of the vagus nerve were completely removed, there would be an extremely high risk of cholecystitis and gallstones after surgery, so gallbladder was removed as well. The common bile duct was separated, and the surrounding lymph nodes were dissected (number 12b). Caution was made to protect the supplying vessels to the common bile duct. The portal vein to the posterior area was separated, and the surrounding lymph nodes (number 12p) were dissected.

Dissection of lymph nodes posterior to the pancreatic head (number 13): these lymph nodes often attached closely to the pancreatic head in a flat shape. An electrocautery was required in the sharp separation, with caution to avoid the retroduodenal artery. In some cases, these lymph

nodes would be closely adhesive to that small artery, so it could be separated first to prevent bleeding. The stations number 13, 12b and 12p were pushed to the right through the Winslow's hole and retracted from the left side of the hepatoduodenal ligament. These lymph nodes were then separated along the common hepatic artery and the upper edge of the splenic vein towards the celiac trunk. The stations number 8a and 8p were dissected en bloc. The coronary vein was divided from the posterior region close to the root of the common hepatic artery, and then ligated and transected. The lymph nodes to the right of the celiac artery (number 9) were then dissected along the plane of the right crus of the diaphragm. The left gastric artery was denuded from the periphery, ligated and cut at the root, and station number 7 lymph nodes were dissected. The separation was continued along the right crus of the diaphragm towards the cardia to dissect the lymph nodes on its right and posterior side (number 1). The greater and lesser curvatures of the stomach were denuded using Ligasure (Tyco, energy platform), and the stations number 3 and 4d lymph nodes were dissected. The stomach was then transected 5 cm from the upper edge of the tumor with a Tyco 100 mm linear stapler, and 2/3 of the distal stomach was removed together with the lymph nodes.

Reconstruction: Billroth II gastrojejunostomy (Tyco 25 mm circular stapler) was performed in combination with Braun's anastomosis.

The whole operation lasted 2 hours and 50 minutes, with intraoperative blood loss of 100 mL and no blood transfusion. The patient was able to ambulate four days after surgery. Liquid diet was prescribed on the 5th day, and semi-liquid diet was prescribed on the 7th day. The patient was discharged eight days after surgery. Postoperative pathology: chronic inflammation with ulceration in the mucosa of the posterior wall of the antrum, with a small amount of degenerated adenocarcinoma with interstitial fibrosis in the mucosal and serosal layers; lymph nodes 0/36 (subcomplete remission).

Three cycles of adjuvant chemotherapy were delivered on October 26, November 22 and December 16, 2012 after surgery, using the regimen of Taxol 240 mg/dL and S1 60 mg bid po d1-14, repeated for three weeks. No sign of recurrence was observed during the nine months of postoperative follow-up. The tumor marker CA199 has remained at a low level.

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Neoadjuvant chemotherapy for gastric cancer

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Surgery remains the cornerstone of curative treatment for gastric cancer (GC). However, randomised controlled trials (RCTs) have established a multi-disciplinary approach in the treatment of resectable GC. Interestingly, trials conducted in different parts of the world have given rise to varying standards of care. Generally, except patients with T1N0 or intramucosal tumour, all patients with resectable GC should be considered for a multi-modality treatment plan, preferably decided by a multi-disciplinary team.

Three treatment strategies are now considered standard treatment options - adjuvant chemotherapy, adjuvant chemoradiation (CRT) and peri-operative chemotherapy. Whereas several studies evaluated the use of neoadjuvant chemotherapy alone in gastric cancer, RCTs that demonstrated a survival benefit utilised both pre-operative and post-operative chemotherapy. Nevertheless, as the delivery of post-operative chemotherapy was generally suboptimal, due to patients' poor tolerance, clinicians often interpreted these studies as proof of concept for neoadjuvant chemotherapy for gastric cancer. Nevertheless one could not clearly separate out the proportional benefit of each treatment component, thus one should not exclude the routine use of post-operative chemotherapy after neoadjuvant chemotherapy.

For peri-operative chemotherapy, two RCTs demonstrated almost identical survival benefit with the use of cisplatin, 5-fluorouracil (5-FU) ± epirubicin resulting in an absolute improvement in 5-year survival of 13%. The MAGIC trial used epirubicin, cisplatin and 5-FU (ECF) (1) whereas the FNLCC ACCORD 07- FFCD 9703 trial utilised cisplatin and 5-FU (FP) (2). Both studies included GC and oesophagogastric junction (OGJ) cancers, therefore this treatment strategy is employed in both GC and OGJ cancers. Oral fluoropyrimidines have been shown to be non-inferior in survival compared to infused 5-FU in advanced GC (3) and they have also been tested in the adjuvant setting in the CLASSIC (4) and ACT-GC trials (5), thus capecitabine is readily used in the peri-operative setting.

To improve on the efficacy of neoadjuvant chemotherapy, two main avenues have been pursued - (I) addition of post-operative CRT and (II) newer drugs such as biologicals. However, one needs to stress the importance of quality control for surgery in the pursuit of better efficacy from neoadjuvant chemotherapy. With D2 dissection, 5-year survival rate in the Japanese ACT-GC study was 61.1% for surgery alone (5) and in the Dutch study this was only 47% (6). Better baseline staging, establishment of high volume surgical centres and incorporation of surgical protocols in current RCTs are supposed to mitigate against poor surgical outcome. It would be interesting to see the adherence to surgical protocols in the current generation of RCTs for pre-operative therapy in gastric cancer. One concerning observation from the recently reported CALGB 80101 (7) was that the survival outcome from the control arm, bolus 5-FU/leucovorin plus radiation, was identical to that of Intergroup 0116 published more than a decade ago (8). Although no details on surgery are available yet for CALGB 80101 study, it appeared that no progress has been made in the last 10 years despite better staging and focus on high volume surgical centres. These factors will all come under close scrutiny with the recently completed UK OEO5 as well as the ongoing UK STO3 and Dutch CRITIC trials.

The addition of post-operative CRT is currently being evaluated in the Dutch CRITIC study where 788 patients will be randomly allocated to either peri-operative epirubicin, cisplatin plus capecitabine (ECC) or pre-operative ECC followed by post-operative CRT. Aside from surgical quality control, radiation quality assurance will also be of importance in this study. Indeed in the recently reported CALGB 80101 study, 15% of the radiotherapy treatment plans were found to contain major deviations (7).

The integration of biologicals is currently being assessed in the UK STO3 study. One thousand and one hundred patients will be randomised to peri-operative ECC ± bevacizumab. Maintenance bevacizumab is given for a further 18 weeks after the completion of post-operative chemotherapy. Some reservations have been made about the likely success of the STO3 study based on the negative overall survival results of the AVAGAST study in advanced gastric cancer (9) as well as the adjuvant trials in colon cancer including NSABP-C08 (10) and AVANT (11) studies. In the AVAGAST study there was a statistically significantly improved radiological response rate and progression free survival with the addition of bevacizumab. This may allow more curative surgery to be performed and this is often cited as the important secondary outcome leading to the success of the MAGIC and the FFCD studies (1,2). Furthermore, the relapse rate after gastric cancer surgery is considerably higher than colon cancer surgery. Potentially there may be more established micrometastatic disease to gain benefit from the use of bevacizumab, more akin to the setting of ovarian cancer after optimal debulking surgery (12,13). Safety results from the first 200 patients recruited into STO3 study did not demonstrate any clinically increased bevacizumab-related toxicities. Perforation rates were similar between the two treatment arms. Cardiac monitoring within the study also alleviated the concern of combined cardiac toxicity of epirubicin and bevacizumab with recovery of cardiac function after cessation of trial drugs (14).

The recent introduction of trastuzumab in metastatic HER2 positive gastric cancer calls for evaluation of HER2 targeted agents in the peri-operative setting (15). Lapatinib, TDM-1 and pertuzumab are other clinically proven HER2 targeted agents in breast cancer. However, recent studies suggested that <15% of resected gastric cancer was indeed HER2 positive. Furthermore, often the magnitude of benefit over standard treatment is less pronounced in the operable compared to the metastatic setting. The implication would potentially be a screening requirement in excess of 5,000 operable gastric cancer patients to recruit into an adequately powered RCT to evaluate HER2 targeted agents. Such trials will likely require multi-national collaboration.

Whereas the traditional TNM staging allows some selection of patients based on pre-treatment characteristics, much more individualised biomarkers are required. This does not necessarily apply to the novel biologicals only and indeed, if possible, this should also be applicable to the standard platinum/fluoropyrimidine that we are currently using for neoadjuvant chemotherapy. Recent genomic profiling of gastric cancer cell lines identified two major intrinsic subtypes: G-INT and G-DIFF (16). This gene signature was then mapped onto two independent cohorts of gastric cancer patients and was found to have prognostic significance with G-DIFF having a poorer survival. More importantly, G-INT was found to be more sensitive to 5-FU and oxaliplatin where G-DIFF was more sensitive to cisplatin. This may pave the road for the future to better select patients for neoadjuvant chemotherapy based on pre-treatment biomarkers.

In view of the poor prognosis after surgery alone and poor tolerance to post-operative therapy, neoadjuvant chemotherapy appears to be an attractive option for gastric cancer. Integration of biologicals and radiotherapy may improve survival further. However, pre-treatment biomarkers, either tissue-based or imaging-based, would be key to identify patients who would benefit most from this treatment strategy.

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Gastric cancer: toward a cisplatin-free disease?

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Abstract: Historically, the cornerstone of treatment of advanced gastric cancer (GC) is 5-fluorouracil (5-FU)-based chemotherapy that increases median overall survival (OS) compared to best supportive care by some months. The addition of cisplatin (CDDP) to chemotherapy doublets showed a limited but significant benefit in term of OS according to a Cochrane meta-analysis. However, the recent individual patient-data GASTRIC meta-analysis, confirms this benefit in term of progression-free survival (PFS) but not OS, in randomized eight trials that include or not CDDP. The substitution of CDDP with a modern agent (oxaliplatin, irinotecan or taxanes) has been poorly evaluated in the literature. The REAL-2 phase III trial confirmed the equivalence of oxaliplatin and CDDP-based triplets, and a meta-analysis of three oxaliplatin-based randomized trials demonstrated that these combinations are better that CDDP-based doublets or triplets, improving both PFS (HR =0.88) and OS (HR =0.88). In particular, oxaliplatin-based chemotherapy was associated with less neutropenia and thromboembolic events, but with worse neurotoxicity. Given that the role of chemotherapy in advanced GC is palliative, CDDP-free regimens, and in particular oxaliplatin-based chemotherapy, may be considered for both CDDP-fit and unfit patients (that are those with poor renal function, older age, bad performance status or who cannot tolerate forced hydration for example). The limited absolute survival benefit of chemotherapy in advanced GC (few weeks at best), the cumbersome vascular toxicity of CDDP and the activity of several new drugs such irinotecan, oxaliplatin, taxanes and oral fluoropyrimidines make nowadays possible to consider CDDP-free regimens for the treatment of this incurable disease.

Keywords: Cisplatin (CDDP); gastric cancer (GC); oxaliplatin; overall survival (OS); toxicity; first line

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The treatment of advanced gastric cancer (GC), including gastro-esophageal junction cancer, has evolved little over the years, with the exception of the treatment of human epidermal growth factor receptor-2 (HER-2) positive disease. Historically, the cornerstone of treatment of advanced GC is 5-fluorouracil (5-FU)-based that increases median overall survival (OS) compared to best supportive care by some months (1-3).

The combination of continuos infusion of 5-FU + cisplatin (CDDP) was investigated extensively since three decades ago, and it remains still now a reference regimen of almost all contemporary investigations, in metastatic disease (4,5).

In 2006, a meta-analysis of advanced GC (6), published in the *Journal of Clinical Oncology*, established the role of multidrug combinations (triplets) including CDDP, compared to two-drug combinations with significant survival benefit [hazard ratio (HR) for survival 0.83]. The addition of one or two agents to monochemotherapy obviously added toxicities to single-agent arms. Overall, treatment-related side effects, although not significantly different in the individual trials, were greater in combinations arms. Three studies, adopted a platinum-free combination of irinotecan-5-FU, which was compared to CDDP-5-FU or etoposide-leucovorin-5-FU (ELF).

The pooled HR for OS was 0.88 in favor of the irinotecan-containing regimens that translated into an insignificant benefit in median OS of approximately 1 month for the irinotecan-containing regimens.

The Cochrane meta-analysis of 2010 (7) confirmed the survival benefit with the addition of CDDP to 5-FU/anthracyclines doublets. However, both irinotecan-(HR 0.86; 95% CI, 0.73 to 1.02; 639 participants) and docetaxel-containing regimens (HR 0.93; 95% CI, 0.75 to 1.15; 805 participants) showed a not significant OS gain in favor of the not-irinotecan and not-docetaxel-containing regimens.

In recent years, oxaliplatin, which is more extensively studied in colorectal cancer, emerged as a valid alternative option in lieu of CDDP in stage IV GC (8). In 2011, Montagnani and colleagues published a meta-analysis of three trials comparing CDDP to oxaliplatin regimens in advanced GC (9). Two phase III and one smaller phase II trials were included. Oxaliplatin significantly improved progression-free survival (PFS) (HR =0.88, P=0.02) and OS (HR =0.88, P=0.04). In particular, oxaliplatin-based chemotherapy was associated with less neutropenia and fewer thromboembolic events, but with worse neurotoxicity. This analysis confirms that a CDDP-free chemotherapy could represent a less toxic approach, and may be more active as a first-line treatment for advanced GC. Recently, the first results of a phase III trial comparing S-1 + CDDP (SP) to S-1 + oxaliplatin (SOX) were presented at the 2013 Gastrointestinal Cancer Symposium (10). Six hundred eighty-five patients with advanced or recurrent GC were randomized to SOX (oral S-1 40 mg/m^2 bid. for 14 days plus oxaliplatin 100 mg/m^2 iv on day 1, q3 weeks) or SP (oral S-1 40 mg/m^2 bid for 21 days plus CDDP 60 mg/m^2 iv on day 8, q5 weeks). The study confirmed the noninferiority of PFS between the two platinum-based combinations. However, serious adverse events occurred in 29.3% of patients for SOX and 37.9% of patients for SP. Eight treatment-related deaths were reported in SP (2.4%) and four in SOX (1.2%). Overall, this study confirmed once again that oxaliplatin plus an oral fluoropyrimidine represents one of the referent regimens for the treatment of this disease.

With the present data in mind, it can be affirmed that oxaliplatin, irinotecan and eventually taxanes, could be adequate substitutes for CDDP in multidrug combination according to four considerations.

First, the 3-drug combination TCF, whose use is substantially limited for the toxicity profile, could be resumed by replacement of CDDP with oxaliplatin. For example, in the randomized phase II trial GATE, led by Van Cutsem *et al.* (11), the triplet combination of docetaxel, oxaliplatin and 5-FU (TEF) obtained a 46% response and more than 14 months of OS; Second, oxaliplatin has been demonstrated to be equivalent and even not cross resistant with CDDP *in vitro* (12); Third, the FOLFOX-regimen, for example, is now worldwide one of the preferred choices as an up-front treatment for both esophageal and GC (with or without radiotherapy) with similar, if not even better, outcome and safety compared to CDDP/fluoropyrimidine schedules (13,14); Fourth, a systematic review and meta-analysis (15) of randomized controlled trials (1,837 patients included from ten trials) demonstrated that irinotecan-containing regimens significantly improved OS (HR 0.86; 95% CI, 0.78-0.94; P=0.002) and PFS (HR =0.82; 95% CI, 0.69-0.97; P=0.026) compared to not-irinotecan-containing ones.

Recently, an individual patient-data meta-analysis was published (16), which included 22 out of 55 potentially eligible trials. Compared to control arms, chemotherapy reduced overall the hazard of death by 12% and of progression by 19%. When analyzing the contribution of individual agents, only CDDP (eight trials included) and irinotecan led to a benefit in PFS but not in OS. On average, the benefit with palliative chemotherapy from this meta-analysis is limited to about 3-4 months for both PFS and OS.

A confirmatory meta-analysis, published by Petrelli and colleagues, confirmed the goodness of non-CDDP over CDDP polychemotherapy in advanced disease (17). Among 14 randomized trials, including about 3,000 patients, chemotherapy regimens without CDDP significantly improved OS (HR 0.79; 95% CI, 0.68-0.92; P=0.003), PFS (HR 0.77; 95% CI, 0.66-0.90; P=0.001), and response rate (RR) (OR 1.25; P=0.004) when compared to CDDP-containing regimens.

The amount of cardiovascular risk linked to CDDP administration was revealed by a meta-analysis that compared patients with neoplastic diseases, treated or not, with CDDP (18). The incidence of venous thromboembolic events (VTEs) was 1.92% in patients treated with CDDP-based chemotherapy *vs.* 0.79% in patients not treated with CDDP-containing chemotherapies. Patients receiving CDDP-based regimens suffered from significantly increased risk of VTEs (relative risk 1.67; 95% CI, 1.25 to 2.23; P=0.01). In the setting of GC, the REAL-2 study showed an overall rate of thromboembolic events significantly lower in the oxaliplatin grvoups than in the CDDP groups (7.6% *vs.*

15.1%, P<0.001).

If we consider the activity of oral agents [capecitabine (X) and S-1] and the administration of agents such as oxaliplatin, paclitaxel, docetaxel and irinotecan, whose infusion duration and possibly worrisome toxicities could be reduced compared to CDDP, the treatment of this disease can be more convenient and feasible for patients by using CDDP-free regimens. In addition the described regimens, and in particular oxaliplatin-based chemotherapy, may be likely offered to both CDDP-fit and unfit patients (that are those with poor renal function, older age, bad performance status or who cannot tolerate forced hydration for example)

In HER-2 positive disease, however, the registration of trastuzumab, according to TOGA trials, limits the use of doublets other than CDDP-5-FU or CDDP-X (19). However, some literature evinces significant activity of oxaliplatin-based chemotherapy plus trastuzumab (20,21). The case of breast cancer is emblematic; in this setting, in fact, trastuzumab is effective and synergic (or additive) when coupled with various cytotoxic agents (e.g., vinorelbine and gemcitabine) but more cardiotoxic when associated with the most active agents taxanes and anthracyclines (22,23).

Is the paradigm of GC treatment shifting to a new era where old and toxic drugs (e.g., CDDP, anthracyclines, mytomicin C) replaced by modern and more effective agents? Is the cost of toxicities and time spent well balanced by a significant and clinical therapeutic effect of CDDP-based regimens in GC? We are not sure of this. OS of stage IV GC is near 12 months; a true gain in survival has not been demonstrated up to today with the addition CDDP as opposed to no CDDP in addition to other agents, and quality of life should still remain one of the co-primary endpoints of palliative treatments.

The duration of treatment in responders with advanced GC has not been specifically studied. There are no data about the discontinuation of a treatment regimen prior to disease progression. In general, chemotherapy is given until the patient has a progressive disease or cannot tolerate further treatment. In this case, the potential cumulative toxicity of platinum salts (allergic reaction and neurotoxicity) has to be carefully taken into account when deciding on a first-line regimen. As for now, cumulative sensorial neuropathy due to oxaliplatin can be safely attenuated without compromising efficacy, with calcium/magnesium infusions (24).

Finally, in neither an adjuvant nor a neoadjuvant setting has a clear (CDDP-based) winner regimen been declared. Platinum-based chemotherapy still remains the cornerstone of treatment in this setting, but a referent regimen has not been discovered. In locally advanced settings, ECF-like regimens are the most frequently implemented in Western countries according to MAGIC trial (25). In advanced settings, however, the REAL-2 phase III trial affirmed the superiority of X-based and the equivalence of oxaliplatin-based schedules. In the adjuvant setting, a limited but significant benefit has been demonstrated with adjuvant polychemotherapy according to GASTRIC meta-analysis (26). Most of the post operative randomized trials were mitomycin C/5-FU plus or minus anthracyclines regimens, and limited data exist with CDDP-based schemes. One of the larger trials comparing chemotherapy to no chemotherapy after D2 gastrectomy adopted however an X + oxaliplatin regimen that obtained a 44% lower risk of progression or death (27).

In conclusion, as in other neoplastic conditions (ovarian or small cell lung cancer) other platinum analogues and some new drugs, have obtained the recognition of less toxic and equi-effective systemic agents. In a GC setting, other potentially active chemotherapies have been demonstrated to safely replace CDDP as the cornerstone of up-front treatment of metastatic or unresectable disease.

A correct selection of patients and their preference, coupled with the judicious application of the more effective agents, can probably, step by step, extend a benefit to those with this incurable disease.

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The role of taxanes in the management of gastroesphageal cancer

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Abstract: Upper gastrointestinal cancers commonly referred to as gastroesophageal carcinomas encompass cancers of the esophagus, stomach and gastroesophageal junction. Although the number of newly diagnosed cases of gastric cancer has decreased in the United States, the whole burden of upper gastrointestinal carcinomas on society remains significantly high, with only a small improvement in overall survival achieved over the past two decades. Traditionally, therapeutic agents used to treat gastroesophageal cancers have been platinums and fluoropyrimidines. Taxanes are di-terpenes produced by the plants of the genus Taxus (yews). As their name suggests, taxanes were first derived from natural sources, but now they are all synthesized artificially. Interfering with cellular microtubular function during cell division is the main mechanism of action for currently available taxanes. Since their introduction into therapeutic oncology, many different other taxane-derivatives have been manufactured and are being developed. Changing the formulation of the drug to improve delivery such as liposomal encapsulation, and target deliver with antibody-drug conjugation, as well as introducing new class of cytotoxic agents that can overcome taxane-resistance. The two most commonly used taxanes are paclitaxel and docetaxel. Taxane is a class of cytotoxic agents more commonly administered in patients with breast and lung cancers. However, the regulatory approval of docetaxel to treat patients with metastatic or advanced gastroesophageal cancers in 2006 established the role of taxanes in the management of upper gastroesophageal cancers. This paper will review the current data of taxanes in the management of patients with upper gastrointestinal cancers.

Keywords: Taxanes; gastric; esophageal; gastroesophageal junction; chemotherapy

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Introduction

Upper gastrointestinal cancers, also refer to as gastroesophageal carcinomas (GECs) consist of cancers of the esophagus, stomach and gastroesophageal junction (GEJ). GECs are the fourth most frequently diagnosed cancer worldwide, and they are the second most common cause of cancer-related mortality (1). Since the late 1990s, the anatomic location of upper gastrointestinal carcinomas has shifted and this anatomic shift has varied geographically. In most Western countries, there has been an epidemiological shift: there has been a decrease in the incidence of GECs, but a steady increase in the incidence of cancers of the gastroesophageal junction (GEJ) (2,3). Over the past 10-15 years, the anatomic primary site of upper gastrointestinal carcinomas in the West has shifted to the GEJ (2). An explanation for this phenomenon remains elusive, but speculation is that environmental factors common in Western countries, particularly the higher frequency of obesity, gastroesophageal reflux disease, and Barrett's esophagus, are the likely culprits. On the other hand patients in Eastern countries with a high prevalence of GECs, GECs are still primarily located in the distal gastrum and proximal esophagus (1). Complete surgical resection remains the only treatment option for long-term disease control and cure. However, because of the high rate of recurrence and the inaccuracy of clinical staging, surgery alone is associated with a 5-year overall survival (OS) rate of only 20-30%

(4,5). Multimodality therapy with concurrent chemotherapy, chemoradiotherapy (CRT), or both is commonly used to improve the duration of disease-free survival after complete surgical resection. Several recent randomized trials have shown improved survival outcomes when surgery is combined with another therapy (4-7). Unfortunately, more than 50% of newly diagnosed GECs are locally advanced (unresectable) or metastatic at the time of diagnosis. Among patients presenting with locoregional disease, less than 30% will have potentially resectable disease (8).

Randomized controlled trials have reported that a statistically significantly survival benefit can be attained with chemotherapy plus supportive care compared with supportive care alone, even in patients with locally advanced (unresectable) or metastatic GECs (9). However, patient selection is crucial to enhance the potential survival benefit in patients with advanced GECs. Antimetabolites, such as methotrexate, and alkylating agents, such as mitomycin, were a mainstay of early therapy for advanced GECs. While these agents remain important in the treatment of patients with other malignancies, their narrow therapeutic index of significant side effects and minimal improvement of outcomes, minimize any potential benefit for patients with advanced GECs. Until 2000, the only chemotherapeutic agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of GECs included platinums (cisplatin, carboplatin), anthracyclines (doxorubicin, epirubicin), and pyrimidine analogs (5-fluorouracil [5-FU]). During that time span, treatment with chemotherapy resulted in only marginal survival improvement for patients with GECs (10). The combination of limited therapeutic options and narrow therapeutic indices of available agents resulted in disappointing treatment outcomes in patients with GECs. Until mass screening programs for GECs become available in Western countries, such as those already available in Japan, most GECs will continue to be diagnosed at more advanced stages. Overall, the prognosis of patients with GECs is poor, and it is particularly dismal for those with unresectable disease. To improve surgical outcomes or meaningful survival benefits, new effective cytotoxic or biologic targeted systemic therapies are needed for both resectable and unresectable or metastatic GECs.

Since 2006, the FDA has added a new indication for GECs to several cytotoxic agents. The main benefit of modifying older cytotoxic agents is an improved toxicity profile; examples of modified cytotoxic agents include oxaliplatin, which is a third-generation platinum, and capecitabine and S-1, which are modified or newer formulations of 5-FU. Prior to 2007, paclitaxel and docetaxel were already being used to treat patients with other solid tumor malignancies, but they did not have an FDA-approved indication for treating patients with GECs. In this paper, we will review the current roles taxanes in the management of GECs and discuss the future directions of their use.

Taxanes

Paclitaxel and docetaxel belong to the Taxane family because of their chemical structures contain a common three phenols ring. The clinical application of taxanes in the management of GECs predates their approval by the FDA for such an indication. It was not until 2006 that docetaxel received FDA approval for use as a first-line treatment in therapy-naïve patients with advanced GECs (11).

Taxanes are di-terpenes produced by the plants of the genus Taxus (yews). As their name suggests, taxanes were first derived from natural sources, but now they are all synthesized artificially. The two most commonly used taxanes are paclitaxel and docetaxel. Although all taxanes are currently used to treat patients with GECs, only docetaxel has an FDA-approved indication for use in combination with cisplatin and 5-FU to treat patients with GECs. Paclitaxel and docetaxel both have therapeutic indications for many solid tumor malignancies. However, only docetaxel has an FDA-approved indication for the treatment of advanced GECs. Paclitaxel has FDA-approved indications as a single agent for second-line therapy for metastatic ovarian cancer (12-16), for adjuvant treatment of node-positive breast cancer (17), and for second-line therapy for metastatic breast cancer (18), as well as for second-line therapy for Kaposi's sarcoma (19). In combination with cisplatin, paclitaxel is also indicated as first-line therapy for metastatic non-small cell lung (20) and ovarian (21,22) cancers. Docetaxel was introduced at the end of the 1990s; it was first approved in 1996 for the treatment of refractory metastatic breast cancer (23-25). Additional FDA indications for early breast cancers (26,27) and for advanced non-small cell lung cancer (28,29), prostate cancer (30,31), and metastatic head and neck cancers came later (32).

Paclitaxel

Paclitaxel was originally isolated from the bark of the Pacific yew tree, Taxus brevifolia. Its chemical structure was determined in 1971, and its mechanism of action was elucidated in 1979 (33). Paclitaxel is an anti-microtubule

agent that irreversibly binds specifically to the subunit of the protein tubulin and promotes the assembly of microtubules. The stabilization of microtubules prevents normal mitotic spindle formation and function. This disruption of normal spindle function, which is the primary mechanism of action of paclitaxel (34,35) ultimately results in chromosome breakage and inhibition of cell replication and migration. Therefore, paclitaxel inhibits cell replication by blocking cells in the late G2 and/or M phases of the cell cycle(35). Another important mechanism of action of paclitaxel includes induction of apoptosis via binding to and subsequently blocking the function of the apoptosis inhibitor-protein, bcl-2. Pharmacokinetics studies with paclitaxel have demonstrated that its distribution is a biphasic process, with values for α and β half-lives of approximately 20 minutes and 6 hours, respectively (33). True nonlinear pharmacokinetics may have important clinical implications, particularly in regards to dose modification, because a small increase in drug exposure and hence toxicity (33). More than 90% of the time, paclitaxel binds to plasma proteins. Approximately 71% of an administered dose of paclitaxel is excreted in the stool via the enterohepatic circulation (33). Renal clearance is minimal, accounting for 14% of the administered dose(33). In humans, paclitaxel is metabolized by cytochrome P-450 (CP-450) mixed-function oxidases. Specifically, either isoenzymes CYP2C8 and CYP3A4 of CP-450 will metabolize paclitaxel to hydroxylated 3' phydroxypaclitaxel (minor) and 6α-hydroxyplacitaxel (major), as well as to other forms of dihydroxylated metabolites. Paclitaxel is typically administered intravenously at a dose of 135-175 mg/m^2 every 21 days (33,36).

Docetaxel

While paclitaxel is a natural product, docetaxel is a semi-synthetic product. Docetaxel inhibits microtubule disassembly and promotes microtubule stabilization, leading to disruption of microtubule-mediated cellular function during cell division, cell cycle arrest at G2/M transition, and cell death (37). Like paclitaxel, docetaxel induces the activation of several molecular pathways leading to cellular apoptosis by disorganizing the microtubule structure (38). However, another proposed mechanism of action of docetaxel is related to its effect on phospholipase-D (PLD) (38). PLD has been implicated in several physiological processes, such as membrane trafficking, cytoskeletal reorganization, cell proliferation, differentiation, survival, and apoptosis (38). Pharmacokinetics studies with docetaxel have demonstrated a linear pharmacokinetic behavior with a 3-compartment model. Docetaxel binds to plasma proteins more than 95% of the time. Its metabolism also occurs via the CYP3A4 isoenzyme CP-450, and within 7 days of administration, 75% is eliminated in feces (38). Because most docetaxel is broken down in the liver, a reduced dose is recommended for patients with hepatic dysfunction, particularly those with elevated total bilirubin above the upper limit of normal (ULN) or alkaline phosphatase greater than 2.5 times ULN plus ALT and/or AST greater than 1.5 times ULN (38). Renal impairment or age greater than 75 years are an indication for docetaxel dose adjustment (38). Docetaxel is typically administered intravenously at a dose of 60-100 mg/m^2 every 21 days (33,39).

The most frequent dose-limiting toxicities (DLTs) of both paclitaxel and docetaxel include myelosuppression, hypersensitivity reactions, neuropathy, and musculoskeletal effects. Myelosuppression is both dose- and schedule-dependent, but it is not cumulative, where neutropenia is the principal DLT. The nadir of myelosuppression is usually on the 8th-10th day and complete bone marrow recovery is expected on the 15th-21st day (40). During its early development and in the initial phase II studies, docetaxel was administered at a dose of 100 mg/m^2. In these early studies, neutropenia reached its nadir on the 8th day and resolved on the 15th-21st days of docetaxel infusion, and febrile neutropenia requiring hospitalization was observed in 10-14% of treated patients (38). Since its early development, docetaxel is now administered at a modified dose of 75 mg/m^2. A significant reduction in febrile neutropenia frequency was observed with this dose (38).

Taxane hypersensitivity reactions can be categorized as type 1 (anaphylactoid) or type 2 (anaphylaxis). Symptoms of an anaphylactoid reaction include dyspnea, flushing, chest pain and tachycardia, where the cause is a surge of histamine release within 2-3 minutes after the administration of the drug. Anaphylaxis is more severe and can even be fatal; symptoms of anaphylaxis include hypotension, angioedema, and urticaria. Both types of reaction occur during the first two courses, and typically begin during the first 15 minutes of the infusion and resolve 15 minutes prior to the completion of the infusion. Along with antihistamine premedication, the administration of a prophylactic regimen consisting of 3-5 days of steroids beginning 1-2 days prior to treatment can reduce the frequency and severity of a hypersensitivity reaction (38,40). Once patients have experienced either type of severe hypersensitivity reaction, the drug is further

Table 1 Rare side effects associated with taxanes

	Paclitaxel	Docetaxel
Dermatologic	Phlebitis	Phlebitis
	Painful red or swollen mouth	Erythema multiforme
	Abscess	Toxic epidermal necrolysis
	Allergic and giant hives	Stevens-Johnson syndrome
Cardiovascular	Bradycardia	Hypertension / hypotension
	Hypotension	Myocardial ischemia
		Heart failure
		Unpredictable severe constricting chest pain / tightness
		Paroxysmal atrial tachycardia, atrial flutter, sinus tachycardia, arrhythmia
Respiratory	–	Adult respiratory distress syndrome
		Respiratory insufficiency
		Drug-induced pneumonitis
Gastrointestinal	Elevated transaminases	–
Vascular	–	Venous thromboembolism (pulmonary emboli, deep venous thrombosis)
		Vascular insufficiency (ischemic colitis, ileitis)

contraindicated. Fortunately, the incidence of anaphylaxis is low, occurring in only 2% of patients receiving paclitaxel and in 13% of patients receiving docetaxel.

Peripheral neuropathy resulting from both axonal degeneration and demyelination (40) is a DLT that is dose-dependent and cumulative. Mild symptoms relating to sensory loss usually improve or resolve completely within several months after discontinuation of therapy. Pre-existing neuropathies are not a contraindication to treatment. Central neurotoxicity may occur and may be severe especially with paclitaxel. Myalgia and/or arthralgia typically appear 2-3 days after drug administration, resolve within a few days, and are unrelated to dose (41,42). Docetaxel-associated neuropathy occurs less frequently and with less severity than paclitaxel-associated neuropathy (42).

Reversible fluid retention syndrome (42,43), which is characterized by edema and third-space fluid retention, is a unique side effect of docetaxel. Bowel wall edema and pleural and peritoneal fluid retention are common manifestations of this syndrome, which is caused by a docetaxel-induced increase in capillary permeability. The most serve end-organ complication of third-space fluid collection is heart failure. This severe complication can be ameliorated and prevented with prophylactic administration of corticosteroids, along with aggressive and early administration of diuretics (43).

No less important, but less frequently reported, toxicities associated with taxanes include fatigue, mucositis, gastrointestinal symptoms, phlebitis, drug-induced adult respiratory distress syndrome (for docetaxel), and bradycardia plus swollen, red, painful mouth (for paclitaxel). Fatigue is observed in 58-67% of the patients treated with docetaxel, and it is occasionally severe enough to cause a modification in dose (33). Mucositis typically results from slow infusion, and it occurs more frequently in patients treated with docetaxel than with paclitaxel. Although less-severe gastrointestinal toxicityties, such as nausea, vomiting, and diarrhea, also occur more frequently with docetaxel, grade 3/4 gastrointestinal toxicities are uncommon (42). *Table 1* summarizes the rare adverse effects associated taxanes.

Clinical use of taxanes in the treatment/ management of advanced gastroesophageal cancers

For many solid tumors, tumor responses and survival outcomes are higher with CRT than with radiotherapy (RT) alone (44-49). For patients with solid tumors, CRT is used to palliate symptoms, treat definitively, and contribute significantly to multimodality therapy. Chemotherapeutic agents have been successfully used as radiosentisizers; platinums, fluoropyrimidines, and taxanes are the most commonly used chemotherapeutic agents.

The results of the Radiation Therapy Oncology Group (RTOG) 85-01 trial (49) established that local disease control and survival outcome were both improved with

CRT (RT combined with cisplatin and 5-FU) compared with RT alone. Therefore, most large randomized studies of CRT in GECs have been designed with either 5-FU, cisplatin, or both as radiosensitizers. Although taxanes are used as part of CRT for GECs, their use as radiosensitizers has been limited to phase II single-arm studies of patients with both resectable and locally advanced (unresectable) disease (50). Both paclitaxel and docetaxel are recognized to be potent radiosensitizers, and their effectiveness in GECs is demonstrated by the increased rates of curative resection, cancer down-staging and pathologic complete response (pCR) (51,52). Many single-institutions, as well as cooperative, studies have suggested that taxane-based CRT is feasible, tolerable, and efficacious in patients with resectable GECs in either the preoperative or postoperative setting (51,52). Preoperative paclitaxel-based CRT has demonstrated promising rates of pathologic responses, with observed pathCR rates of approximately 15-39% (53-57). Similar promising outcomes have been observed with preoperative docetaxel-based CRT (58-61). However, most of the efficacy data on taxane-based CRT come from small phase II studies because of what had been established as standard of care chemotherapeutic radiosensitizers by RTOG 85-01 (49). Results of the CROSS (51) study highlight taxane-based CRT and establish taxane-based CRT as a major contributor in a large phase III pivotal clinical trial of GECs. Patients with resectable esophageal cancer were randomly assigned to paclitaxel and carboplatin plus concurrent RT followed by surgery or to surgery alone. A total of 363 patients with resectable ($T_{2/3}$ $N_{0/1}$ M_0) esophageal and GEJ cancers were enrolled. Preoperative CRT consisted of weekly administrations of paclitaxel 50 mg/m^2 and carboplatin (AUC =2) for 5 weeks and concurrent RT (41.4 Gy in 23 fractions, 5 days per week). Preoperative CRT did not affect surgery rates (86% *vs.* 90%) or in-hospital mortality rates (4% *vs.* 4%). However, R0 rates (92% *vs.* 65%) and pathCR rates (33% *vs.* 0%) improved after completing CRT. OS was significantly better (P=0.011) in the group of patients treated with CRT (hazard ratio [HR] =0.67; 95% confidence interval [95% CI], 0.50-0.92) likely establishing a new standard of care for patients with resectable GECs. The fact that the chemotherapy regimen used for CRT in the CROSS study did not include cisplatin and 5-FU is a significant departure from RTOG 85-01 (49).

The cytotoxic activity and survival benefit of both paclitaxel and docetaxel have been demonstrated by many pivotal phase III clinical studies, with each positive study gaining these taxanes new FDA-approved indications for use in many different malignancies. V-325 (11) is a multi-institutional, international phase III study in which therapy-naïve patients with advanced or metastatic GC/GEJ cancers were randomized to receive either docetaxel (D) and cisplatin (C) plus 5-FU (DCF) or CF. Patients in the treat arm received DCF (docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, plus infusional 5-FU 750 mg/m^2/24 hours days 1-5) intravenously every 3 weeks. The primary end point was time to progression (TTP). A total of 457 patients (DCF 227, CF 230) were treated. Ajani *et al.* reported a more favorable TTP (5.6 *vs.* 3.7 months; HR =1.47 [95% CI, 1.19-1.82]; P=0.001) and OS (9.2 *vs.* 8.6 months; HR =1.29 [95% CI, 1.0-1.6]; P=0.02) in patients treated with DCF than with CF. Despite its promising results, V-325 (11) was severely criticized for its moderate toxicity; patients treated with DCF experienced more neutropenia (82% *vs.* 57%) and febrile neutropenia (29% *vs.* 12%) than those treated with CF. An ad hoc comparison of patients' benefits in terms of quality of life between the two arms concluded that DCF significantly prolonged time to definitive worsening of performance status versus CF (median, 6.1 *vs.* 4.8 months; HR=1.38 [95% CI, 1.08-1.76]; P=0.009) (62,63). The results of this study led to FDA approval of docetaxel for gastric and GEJ cancers, but every-3-weeks DCF should be reserved for highly selected groups of patients.

Because docetaxel was found to be an active agent in GECs, many subsequent studies have offered modified and alternative docetaxel combinations in order to reduce toxicity and improve tolerance. In a randomized phase II study (64), Shah *et al.* observed moderate hematologic toxicity with DCF despite primary prophylaxis with growth colony-stimulating factor. Despite dose changes, modified DCF was noted to be much better tolerated while maintaining the same efficacy as its parent DCF.

In addition to dose and schedule modification of DCF regimens, many other docetaxel-based chemotherapy regimens have been evaluated. For instance, docetaxel has been combined with irinotecan, oxaliplatin, and S-1. S-1 is not currently available outside of clinical trials in the United States. The use of S-1 in advanced GECs in Western countries had been tempered by the negative results of the FLAGS (First Line therapy in Advanced Gastric cancer Study) study (65), comparing cisplatin plus 5-FU to cisplatin plus S-1.

Selecting between paclitaxel and docetaxel remains an art rather than science. Though commonly practiced, there are no convincing data in the medical literature on

Table 2 Taxane-based chemotherapy regimens: comparative phase II/III

Phase	Studies	N	Regimens	ORR (%)	mPFS (mOS)
Completed studies					
III	Van Cutsem *et al*. (2007) (11)	224	DCF q3weeks	37	5.6 mo (9.2 mo)
		221	CF	25	3.7 mo (8.6 mo)
III	Roth *et al*. (2007) (69)	61	mDCF	37	4.6 mo (NR)
		59	DC	25	4.9 mo (NR)
		58	ECF	18	3.6 mo (NR)
II	Tebbutt *et al*. (2010) (70)	50	wDCF	47	5.9 mo (11.2 mo)
		56	wDX	26	4.6 mo (10.1 mo)
II	Thuss-Patience *et al*. (2005) (71)	50	ECF	36	5.3 mo (9.7 mo)
		50	DF	38	5.5 mo (9.5 mo)
II	Park *et al*. (2006) (66)	38	PF	42	3.6 mo (9.9 mo)
		39	DF	33	4.2 mo (9.3 mo)
II	Im *et al*. (2008) (67)	60	FLTaxol	32	3.1 mo (10.5 mo)
		66	FLTaxotere	26	5.0 mo (8.4 mo)
II	Sym *et al*. (2009) (72)	24	wDC	38	4.8 mo
		21	wDO	38	4.1 mo
II	Lind *et al*. (2008) (73)	35	DF	40	NR (10.5 mo)
		37	FOLFIRI	46	NR (10.5 mo)
II	Shah *et al*. (2010) (64)	30	mDCF	50	NR (14.9 mo)
		31	DCF+GCSF	33	NR (12.5 mo)
III	Ridwelski *et al*. (2008) (74)	112	DC	30	6.3 mo (9.4 mo)
		123	FLC	29	6.6 mo (10.2 mo)
Ongoing studies					
III	Japan-JACCRO GC 03 (NCT00287768)	314	S1		
		314	D+S1		
II	Ireland ELECT Trial (NCT00806949)	70	EOX		
		70	DO		

N, number of patients; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; mo, month; NR, not reported; D, docetaxel; C, cisplatin; F, 5-fluorouracil; X, capecitabine; E, epirubicin; P, paclitaxel; L, leucovorin; O, oxaliplatin; FOLFIRI, folinic acid, fluorouracil, irinotecan; m, modified; GCSF, granulocyte colony-stimulating factor.

GEC to support the interchangeability between docetaxel and paclitaxel. In two randomized phase II studies (66,67) from Asia comparing 5-FU combined with either paclitaxel or docetaxel, no statistically significant difference in therapeutic efficacy or survival outcomes was observed. It remains unclear if there is a significant difference between DCF (11) and ECF (68) or other standard regimens, or between docetaxel triplet and doublets. *Table 2* summarizes selected randomized phase II or III studies with taxane-based chemotherapy regimens as first-line therapy for metastatic GECs.

Conclusion and future direction

Taxanes are a class of cytotoxic agents commonly administered in patients with breast and lung cancers. Both paclitaxel and docetaxel, two commonly used taxanes, have many indications as both single agents as well as in combination therapy for many solid tumors. They have also been shown to contribute significantly to the management

Table 3 Combination taxane-based + targeted therapy

Phase	Studies	N	Treatment	R0, pathCR (%)	Survival (mo)
Completed Studies					
III	CROSS(51)	188	S	65, 0	26
		175	PB+RT → S	94, 33	49
Ongoing Studies					
III	NCT00005060	120	DCF → S		
		120	S → DCF		
IV	NCT00525200	85 (p53 normal)	D → S CF → S		
		85 (p53 mutant)	D → S CF → S		
II	NCT00911820 (VEGF/R)	43	PCA		
		43	TPCA		
III	NCT01107639 (EGFR)	150	DC+RT		
		150	EDC+RT		
III	NCT01196390 (HER2)	240	PB+RT → S		
		240	TPB+RT → S		
III	NCT00655876 (EGFR)	210	PC+RT		
		210	EPC+RT		
III	NCT00517829 (EGFR)	75	DO		
		75	EDO		
II	NCT00683787 (VEGF/EGFR)	30	D		
		30	VD		

N, number of patients; R0, rate of curative resection; pathCR, pathologic complete response; mo, month; S, surgery; P, paclitaxel; B, carboplatin; RT, radiotherapy; D, docetaxel; C, cisplatin; F, 5-fluorouracil; PCA, cisplatin,irinotecan,bevacizumab; TPCA, docetaxel,cisplatin,irinotecan,bevacizumab; E, cetuximab; T, trastuzumab; O, oxaliplatin; V, vandetanib; VEGF/R, vascular endothelial growth factor/receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2.

of patients with both localized and advanced GECs. Direct evidence for their use in the management of GECs is derived from the results of several phase II studies. Phase III studies with taxanes in GECs are limited. V-325 (11) and CROSS (51) are pivotal studies that not only changed how we treat GECs, but also validated the role of taxanes in the management of GECs. The V-325 (11) study is a pivotal randomized study that demonstrated that docetaxel-based chemotherapy improved TTP and OS in patients with advanced GEC. The CROSS (51) study demonstrated improvements in surgical outcomes and survival in patients treated with preoperative CRT with paclitaxel and carboplatin. *Tables 2* and *3* summarize completed and ongoing clinical trials with taxanes-base chemotherapy, administered either alone or combined with targeted therapy.

The future development of taxanes for use in GEC will require establishing optimal taxane-based chemotherapy regimens to further develop with targeted therapy, evaluating possible ways of overcoming mechanisms of resistance to taxanes, and identifying molecular biomarkers that are predictive of response. This effort will require the collaborative efforts of many scientific disciplines.

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A pilot study evaluating the safety and toxicity of epirubicin, cisplatin, and UFT (ECU regimen) in advanced gastric carcinoma

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Background: Best response rates have been achieved with three-drug regimens containing 5-FU in the treatment of advanced gastric cancer (AGC) and oral fluoropyrimidines are the best alternatives as substitutes for infusional 5-FU. This study aimed to evaluate the safety and toxicity of epirubicin, cisplatin, and UFT (ECU regimen) regimens in AGC outpatients.

Materials and methods: Forty-one patients with AGC received epirubicin, cisplatin, and oral UFT plus leucovorin. Epirubicin 50 mg/m2 and cisplatin 60mg/m2 were administered on Day 1. Three hundreds (300) mg/m2/day UFT was administered with leucovorin at a fixed oral dose of 90 mg/day for 21 days, followed by a 7-day rest period. Cycles were repeated every 4 weeks. Performance status was either as 0 and 1.

Results: Among the 41 patients enrolled, complete and partial response was achieved in 7.3% and 36.6% of patients, respectively, with an overall response rate of 43.9%. Stable disease was observed in 34.1% of patients and 22% showed disease progression. Median time to progression was 5.2 months and median survival was 12.3 months. A median of 4 cycles (range: 1-6) of chemotherapy were administered. The main grade III-IV toxicities were nausea/vomiting (19.4%) and neutropenia (12.1%). Grade IV toxicities were gastric perforation and renal failure.

Conclusion: ECU appears to be an effective regimen in the treatment of AGC, with acceptable tolerability and manageable toxicity. In three-drug regimens, substitution of infusional 5-FU by UFT offers the possibility of increased AGC outpatient compliance.

Keywords: Advanced gastric carcinoma, cisplatin, epirubicin, UFT

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Introduction

Gastric cancer is one of the most challenging diseases among all cancer types. It is the fourth most common cancer worldwide, with an estimated 934 000 new cases per year in 2002 (9% of new cases globally), and occurs nearly twice as often in men (1). In the United States, mortality due to gastric cancer has declined and five-year relative survival rates improved from 16% to 24% between 1975 and 2002 (2). In Turkey, gastric cancer is the second leading cause of death in men and the third leading cause of cancer mortality in women (3). The anatomical site of origin of gastric cancer among Turkish patients differs from that reported for Western countries, with 48.1% and 41.2% of cancers in Turkish patients occurring at the antrum and corpus, respectively, and 51.6% of patients having a pathological grade III cancer (4).

Surgery is the main treatment modality for gastric cancer. Only in Japan, the majority of patients are surgically treated at stage I (5). The reported median survival benefit in AGC patients receiving chemotherapy is approximately 6 months (6), and the reported benefits of novel

chemotherapy regimens for AGC have been shown to not exceed 12 months in recent Phase III trials in Western countries (7,8).

Fluorouracil- (5-FU) based chemotherapies are the mainstay of treatment for AGC. Since continuous 5-FU infusion has shown promising results in the treatment of AGC in Phase II trials, combination therapies have been developed (9). Oral f luoropyrimidines are the best alternative to infusional 5-FU in three-drug regimens for AGC. Tegafur (UFT) is an oral f luoropyrimidine and its antitumor activity is known to generate plasma 5-FU levels that are similar to those of infusional 5-FU (10-12).

This pilot study was conducted to examine the safety and toxicity of combination chemotherapy consisting of epirubicin, cisplatin, and UFT regimen in chemo-naïve AGC outpatients.

Patients and methods

Patients

Forty-one AGC patients who admitted to Istanbul University Oncology Institute between September 2003 and December 2006 were included in this study. Patients with histologically or surgically proven metastatic or locally advanced inoperable gastric carcinoma were eligible. They were required to have a performance status (PS) level of (0) or (1) according to WHO criteria. There was no age limit. Informed consent was obtained from all patients and the study was approved by the Institutional Review Board. All patients were required to have a leukocyte count ≥4000/μL; platelet count ≥100,000/μL; hemoglobin ≥10.0 g/dL; aspartate transaminase (AST) and aminotransferase (ALT) below two times the upper normal limit; creatinine serum level ≤1.3 mg/dL; and total serum bilirubin <2 mg/dL. Exclusion criteria included patients who had received any type of previous adjuvant treatment and patients with other types of tumors, heart or lung failure, myocardial infarction, previous chemotherapy, brain metastasis, active infection, breast-feeding, or pregnancy.

Drug administration and dose adjustments

The following regimen was given to patients: cisplatin (60 mg/m²) IV 1-hour infusion with standard hydration on Day 1; epirubicin (50mg/m²) IV 30 minutes infusion on day 1; UFT (Tegafur/uracil; Bristol Myers Squibb, Spain) 300 mg/m² taken orally on days 1-21 (q 28-d); and leucovorin (Rescuvolin®, Netherlands) administered 90 mg/day orally on days 1-21 (q 28-d).

The total daily dose of UFT was divided into three doses given every 8 hours, beginning with an initial dose of 300 mg/m^2/day. UFT was supplied in the form of 100 mg capsules (100 mg tegafur and 225 mg uracil). Leucovorin was supplied as 15 mg oral tablets and the fixed total daily dose (90 mg) was divided into three doses. Treatment was repeated every 4 weeks until disease progression, patient refusal, intolerance to therapy, or unacceptable adverse reactions occurred.

ECU regimen dose reduction was planned in the event of severe hematological and/or non-hematological toxic events. Hematological tests were performed at baseline in all patients and they were repeated in asymptomatic patients before the beginning of each cycle. In patients with signs and symptoms of hematological toxicity, the tests were ordered at the onset of the symptoms and weekly thereafter until the condition resolved. The doses of UFT, epirubicin, and cisplatin were reduced 25% in subsequent cycles in the event of the following conditions: 1) Grade III-IV neutropenia or thrombocytopenia lasting for seven days or more, and 2) Grade IV non-hematological toxicity. In cases of insufficient hematological function (neutrophil count <1,500/μL and platelet count <100,000/μL) chemotherapy was delayed for as long as 14 days. If no recovery occurred at this point, treatment was discontinued. A maximum of 2 dose reductions were allowed per patient. Cisplatin doses were reduced 25% when the creatinine level was between 1.4 and 1.9 mg/dL. For a creatinine level between 2.0 and 2.2 mg/dL, a 50% dose reduction was allowed.

Study end points and evaluation of treatment

This was a single-center pilot study. The primary objective was to evaluate the safety and toxicity of the ECU regimen in AGC outpatients. The secondary objectives were to determine time to progression (TTP), overall survival (OS) rates, and response rates. Toxicity was graded and defined using NCI CTC Version 2. RECIST criteria were used to assess response to treatment. For the evaluation of response, the extent of measurable disease was assessed by computerized tomography before the first cycle and after every 2 cycles. Time to progression was defined as the duration from the initiation of the regimen to the date of documented disease progression or death by any cause. Overall survival was defined as the duration from initiation of chemotherapy to the date of death or last follow-up.

Table 1 Patient characteristics (n=41)

Characteristic	
Median age, y (range)	41 (26 -71)
Male/female ratio	31/10
W HO performance status	
0	19 (46.3%)
1	22 (53.7%)
No prior treatment	41 (100%)
Surgically diagnosed	7 (17.0%)
Primary metastatic	26 (63.4%)
Locally advanced	8 (19.5%)
Disease location	
Gastroesophageal	2 (4.9%)
Linitis plastica	7 (17.0%)
Corpus	15 (36.6%)
Antrum	17 (41.5%)
Site of measurable disease*	
Liver	15 (36.6%)
Liver and peritoneal K	3 (7.3%)
rukenberg tumor	2 (4.9%)
Locally advanced	8 (19.5%)
Abdominal lymph node	4 (9.7%)
Site of non-measurable disease	
Peritoneal disease	9 (22.0%)
Tumor grade	
Grade II	19 (46.3%)
Grade III	22 (53.7%)

Unlessother wise stated, data are presentedasn (%). *A measurable disease had to be dimensionally measurable.

Table 2 Treatment response

Definition of response	n=41
Complete response	3 (7.3%)
Partial response	15 (36.6%)
Stable disease	14 (34.1%)
Progressive disease	9 (22.0%)
Overall response	18 (43.9%)
Median time to progression (months)	5.2
Median sur vival (months)	12.3

Unless other wise stated, data are presented as n (%).

Statistical analysis

Kaplan-Meier analysis was used for TTP and overall survival analyses and the log-rank test was used for comparisons. Survivors were censored on the date they were last known to be alive.

Results

Patient characteristics

Patient characteristics are shown in *Table 1*. No patient was withdrawn from the study. Al l patients had PS0 or PS1. Two patients (4.9%) had gastroesophageal adenocarcinomas, 15 (36.6 %) had corpus tumors, and 17 (41.5%) had antral tumors. Twenty-two patients (53.7%) had histopathologically grade III tumors and 19 (46.3%) had grade II tumors. Eight patients (19.5%) had locally advanced tumors and the remaining had metastatic disease. Median age of patients was 54 (range: 26-71).

Response to chemotherapy

One-hundred fifty-nine courses of treatment were administered. The median delivered dose intensities of epirubicin, cisplatin, and oral UFT were 91.8%, 92.5%, and 91.2%, respectively. The median number of chemotherapy cycles was 4 (range: 1-6) and average duration of follow-up was 12.7 months (range: 2.9-49.5) (*Table 2*).

Three patients (7.3%) had complete response after 6 (n=2) or 4 cycles (n=1). Fifteen patients (36.6%) had partial response and 14 (34.1%) had stable disease. Nine patients (22%) showed progression. The overall response rate was 43.9% (complete response plus partial response) (95% CI; 28.5-60.3) (*Table 2*).

Twelve patients (29.2%) required dose modification only once during treatment and 2 patients (4.9%) required dose modification twice. Of the 2 patients with locally advanced disease who underwent surgery after 6 cycles of chemotherapy, 1 is still alive and the other died due to postoperative complications. Brain metastasis developed in one patient after 3 cycles of chemotherapy.

Toxicity

The main grade III-IV non-hematological toxicities encountered with the ECU regimen were nausea and vomiting (19.5%). Neutropenia was the main grade IIIIV hematological toxicity (12.1%; *Table 3*). Grade III-IV diarrhea occurred in 4 patients (9.8%). Reasons for dose

Table 3 Grade I-II to IV toxicity during ECU treatment (n=41)

	Grade		
	I-II, n (%)	III, n (%)	IV, n (%)
Non-hematological toxicity			
Nausea and vomiting	7 (17.0%)	7 (17.0%)	1 (2.4%)
Stomatitis/mucositis	4 (9.7%)	–	–
Diarrhea	6 (14.6%)	2 (4.9%)	2 (4.9%)
Anorexia	7 (17.0%)	1 (2.4%)	–
Fatigue	5 (12.1%)	–	–
Acute renal failure	–	–	1 (2.4%)
Thrombosis	–	2 (4.9%)	–
Hypopotassemia	–	1 (2.4%)	–
Gastric perforation	–	–	1 (2.4%)
Hematological tox icity			
Neutropenia	6 (14.6%)	4 (9.5%)	1 (2.4%)
Decreased hemoglobin levels	8 (19.4%)	2 (4.9%)	–
Leukopenia	7 (17.0%)	2 (4.9%)	1 (2.4%)

modifications were prolonged neutropenia, neutropenic fever, hypopotassemia, diarrhea, and anorexia.

The most serious grade IV adverse events included acute renal failure (2.4%) and gastric perforation (2.4%). A gastric perforation that occurred after 1 cycle of chemotherapy in a patient with locally advanced disease was repaired surgically and the patient continued treatment with 4 cycles of cisplatin and infusional 5-FU and survived for 23 months.

Acute renal failure developed in 1 female patient due to grade IV diarrhea, nausea, and vomiting after the fifth cycle. She did not seek medical help immediately, resulting in a delayed admission to hospital. She was subsequently treated with hemodialysis and recovered.

Grade III hypokalemia occurred in 1 patient (2.4%) without diarrhea, nausea, or vomiting. Deep vein and portal vein thrombosis developed in 2 other patients (4.9%) who were considered to have disease progression. There were no chemotherapy-related deaths. Eight patients (19.5%) discontinued chemotherapy due to intolerance after 1 to 5 cycles. Toxicity-related treatment delays were observed in 17 patients (41.5%).

Survival

Median time to progression was 5.2 months (95% CI: 0.53 -9.86) and median overall survival was 12.3 months (95% CI: 5.3-19.3) (*Figure 1*). One year survival was 68.4% for patients with grade II tumors (16.3 months; 95%CI: 10.6-21.9) and 27.3% for those with grade III tumors (7.3 months; 95% CI: 5.62-8.41), corresponding to a significant difference in survival rate (P=0.05) (*Figure 2*).

Discussion

Management of AGC has been evolving since the 1990's. Pyrhonen showed the advantage of chemotherapy compared to best supportive care (BSC) in AGC in a small sample size using bolus 5-FU (13). Findlay showed that the administration of epirubicin, cisplatin, and continuous infusion 5-FU (ECF) was associated with an objective tumor response rate of 71% (14). These encouraging results led to a randomized trial in which ECF was compared with FAMTX (fluorouracil-doxorubicin-methotrexate) (15). In that study, median survival of patients receiving ECF (8.9 months) was also better, compared to FAMTX (5.7 months). As a result, the benefits of infusional 5-FU in the treatment of AGC was definitively established for the first time in terms of clinical response and overall survival. Folates are known to prolong the retention of the 5-f luoro-2'-deoxyuridine 5'-monophosphate (FdUMP)-TS complex (16). Inhibition of TS by FdUMP is thought to be the primary mechanism for the action of 5-FU (17). A two-drug regimen consisting of cisplatin and 5-FU was shown to decrease TS mRNA levels in adenocarcinoma of the stomach, which explains the mechanism of action of combination therapies (18). Subsequent meta-analyses showed best results with three-drug regimens in AGC patients (6).

UFT is a combination (in a 1:4 M ratio) of tegafur, an oral prodrug of 5-FU that is metabolized to 5-FU primarily in the liver, and uracil, a natural substrate for the liver enzyme dihydropyrimidine dehydrogenase (DPD). Compound uracil serves as a competitive antagonist for DPD and enhances the concentration and half-life of 5-FU (11,12). UFT is administered alone or with folinic acid (leucovorin) tablets to increase the effect on thymidylate synthetase (TS).

Oral UFT monotherapy with leucovorin has shown overall response rates (ORRs) of 10.5-28% and median OS rates of 5.8-6.1 months (19,20), which is similar to those reported for 5-FU single-agent continuous infusion (11). ORRs with two-drug regimens (UFT and cisplatin, etoposide, or paclitaxel) were 35%-51% and average OS was 8.1-10.1 months in the treatment of AGC patients (21-23).

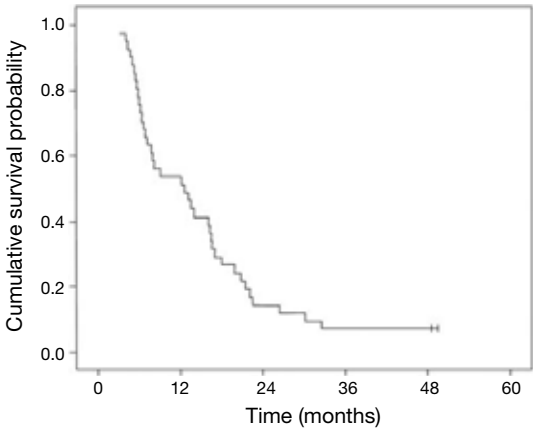

Figure 1 Kaplan-Meiercurve for the cumulative survival probability of all patients.

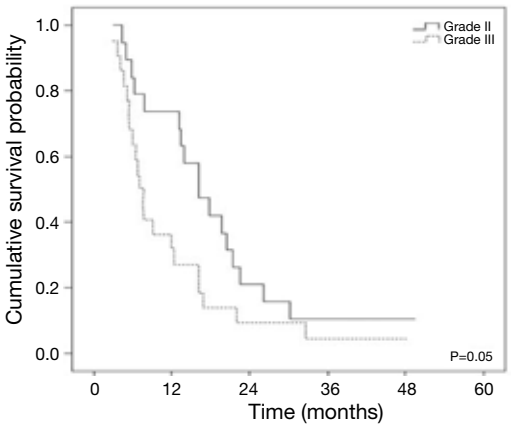

Figure 2 Kapla n-Meiercurves showing the significant survival difference between grade II and grade III tumors.

Finally, three-drug regimens with oral UFT have shown promising results in the treatment of AGC (24-28). Even complete remission of AGC has been reported using the suppository form of UFT (29). UFT is absorbed readily in the gastrointestinal system, which helps improve patient compliance and maintain constant plasma levels of 5-FU. In addition, catheter-related complications are avoided (30).

Although UFT and leucovorin doses have been studied for the last two decades, to date, an optimal administration schedule has not been established. The goal of adding leucovorin is to increase efficacy without additional toxicity. Newman (31) and Buroker *et al*. (32) showed no survival advantage of high-dose leucovorin but observed increased toxicity. On the other hand, in a randomized study of colon cancer patients, Köhne *et al*. found a benefit only in terms of better progression-free survival when leucovorin was added to 5-FU (33). However, this benefit was at the expense of increased toxicity. Pazdur *et al*. showed that UFT with leucovorin was equal to FUFA in colon cancer treatment, with less toxicity in favor of UFT (34). No studies have ever compared UFT versus UFT/LV treatment in gastric and colon cancers, but colon cancer studies usually provide guidance for approximate UFT doses. Fixed leucovorin doses between 25 mg/m² and 90 mg/m² have been given to patients, but it is primarily the UFT dose that accounts for the overall response rate and toxicity (22,27-30). Therefore, low doses of leucovorin might be recommended as opposed to not implementing UFT at all.

In this study, administration of the ECU regimen in AGC patients was associated with acceptable toxicity. The most serious toxicities observed were gastric perforation and acute renal failure. The patient with gastric perforation had locally advanced linitis plastica and lived for 23 months. This is a very rare complication, with only one case reported in the after a single cycle of UFT (35). Perforation may be attributed to impaired connective tissue repair induced by chemotherapy in the tumors (36) and/or it may be the result of chemosensivity. The other serious toxicity event was acute renal failure, which was directly related to delayed hospitalization for grade IV diarrhea, vomiting, and nausea. Previously, Woo reported a patient with grade IV diarrhea, vomiting, and nausea who required a 75% reduction in cisplatin dose (29), and Kim reported one case with grade IV diarrhea that received the same three-drug UFT regimen and required hospitalization (27).

In this study, grade III-IV mucositis was not observed, but grade III-IV diarrhea occurred in 4 patients (9.8%). If UFT doses as high as 480 mg/m^2 had been used as a single agent, more cases with grade III-IV mucositis and diarrhea might have been observed (29). In a study by Kim *et al*., grade III-IV mucositis was reported in 13% of patients receiving a UFT dose of 360 mg/m², while other studies reported mucositis in 6% of subjects receiving 300 mg/m² UFT in ECU regimens. The incidence of diarrhea was also higher in the former study (10.8% *vs*. <6%) (24-27).

The incidence of grade III-IV neutropenia (11.9%) was lower in this study compared to other studies with epirubicin, cisplatin, and UFT regimens (24-27,29). A 1-week drug-free interval after 3 weeks of UFT administration, the exclusion of patients with PS 2, and no UFT doses above 300 mg/m^2 may account for this low incidence (*Table 4*). Hand-foot syndrome, neurotoxicity, or cardiac problems were not observed in this study, which may be attributed to the uracil component of UFT, since it is

Table 4 Previous studies with epirubicin, cisplatin, UFT regimens

Study	UFT regimen	N	PS	PS 2 (%)	MC	OR	OS
K im *et al*.,1999 (24)	UFT: 360 mg/m^2 LV: 25 mg/day D1-21/q28	37	0,1,3	PS 3 (18.9%)	(4)	54%	10.0
Jeen *et al*., 2001 (25)	UFT: 300 mg/m^2 LV: 30 mg/day D1-21/q28	47	0-2	25%	(5)	57.5%	15.0
Woo *et al*., 2005 (26)	UFT: 300 mg/m^2 LV: 45 mg/m^2/day D1-21/q21	35	0-2	34%	(4)	40.6%	7.1
Idelevic *et al*., 2007 (27)	UFT: 300 mg/m^2 LV: 30 mg/m^2/day D1-22/q28	39	0-2	21%	(5)	38%	9.5
Saglam *et al*., 2010 (Present study)	UFT: 300 mg/m^2 LV: 90 mg/m^2/day D1-22/q28	41	0-1	–	(4)	43.9%	12.3

N, number of patients; PS, performance status; MC, median cycle of chemotherapy; OR, overall response; OS, overall survival in months; D, day; LV, leucovorin.

known to prevent skin exfoliation and cardiac events (37-40). Thrombosis occurred in 2 patients (4.9%). Thrombosis is an important toxicity event during the treatment of AGC; it occurs frequently at the initiation and during the course of chemotherapy, resulting in poor OS (41).

In addition to its acceptable toxicity profile and convenience of administration on an outpatient basis, the ECU regimen also appears to be promising in terms of efficacy. Overall median survival was 12.3 months compared to 8.2 months obtained in a previous study with the ECF regimen (epirubicin, cisplatin, infusional 5-f luorouracil) (14). Conversely, overall response rates varied between 25% and 71% in studies using the ECF regimen for AGC (14,42), whereas they varied between 38% and 54% in studies with the ECU regimen (including this study) (24,25). Therefore, the efficacy of ECU versus ECF needs to be studied in larger controlled trials.

One-year survival rates for Grade II and Grade III tumors were 68.4% and 27.3%, respectively (P=0.05). The proportion of patients with grade III tumors in this study is close to the general profile of Turkish patients with AGC (4). In future studies, the efficacy and safety of the ECU regimen should be studied in patients with different pathological grades. Another important factor affecting treatment outcome is the performance status of patients with AGC. It has a direct impact on survival, as shown in a meta-analysis by Yoshida in AGC (43) . The relationship between performance status and survival can be seen in *Table 4*.

Conclusion

This study has shown the feasibility of the ECU chemotherapy regimen, with manageable toxicity in an outpatient setting for patients with AGC. UFT could be considered as a substitute for infusional 5-FU and the ECU regimen might represent a treatment model for three-drug regimens for the management of AGC.

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Targeting angiogenesis in advanced gastric cancer: is this end of the road?

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Despite recent advances in the management of several solid tumour types, gastric cancer remains a challenging disease to treat. In 2008, gastric cancer accounted for almost one million new cases and over 738,000 deaths, making it the fourth most common malignancy and second most common cause of cancer-related death in the world (1). The majority of cases (713,000) occur in developing countries, predominantly in Eastern Asia, with a male:female ratio of approximately 2:1. In the Western world, most patients with gastric cancer have advanced inoperable disease at presentation which contrasts sharply with countries such as Japan where an established screening program permits frequent diagnosis of early-stage disease (2). The prognosis for advanced gastric cancer is particularly dismal, with a median survival of less than one year (3). There is no single global standard regimen for first line treatment and patients are often treated with a platinum and fluoropyrimidine-based doublet or triplet regimen. The UK multicentre REAL-2 study demonstrated that infusional 5-fluorouracil and cisplatin can be safely replaced by capecitabine and oxaliplatin respectively, thereby improving tolerability and patient convenience (3). However, there remains a significant unmet need for more effective treatment strategies and therapeutics targeted against crucial survival pathways within the cancer cells and tumour micro-environment.

Angiogenesis is the process by which new blood vessels arise from the pre-existing vascular bed, and is known to play an important role during embryogenesis and wound healing, as well as being well recognised as an important hallmark of cancer development (4). The possibility of targeting tumour angiogenesis as a therapeutic strategy was postulated almost 40 years ago, though the development of anti-angiogenic agents has only reached fruition with the past decade. Bevacizumab is a humanised recombinant monoclonal antibody against vascular endothelial growth factor A (VEGF-A) which is a major regulator of normal and pathological angiogenesis (5). Although the exact mechanism of action of bevacizumab is poorly understood, it is postulated that bevacizumab sensitises the endothelial cells to chemotherapy-induced apoptosis, leading to a normalization of tumour vasculature and improved chemotherapy and oxygen delivery (14). Bevacizumab and other targeted therapies directed against the angiogenesis pathway have now been shown to be of clinical benefit across many cancer types, including colorectal, breast, lung and ovarian cancers (6-9). In gastric cancer, initial studies demonstrated that increased VEGF-A expression was present in a proportion of tumours and correlated with poor prognosis due to a more aggressive tumour phenotype (10,11). Following this finding, early phase trials of bevacizumab in advanced gastric cancer demonstrated encouraging results (12), and prompted further evaluation in a large phase III study.

The randomised phase III Avastin in Gastric Cancer (AVAGAST) study was designed to evaluate the efficacy of bevacizumab in advanced gastric cancer (13). In this double-blind, placebo-controlled study, 774 patients with advanced gastric or gastro-esophageal cancer were treated with a cisplatin-capecitabine chemotherapy doublet and were randomised between the addition of bevacizumab or placebo. Cisplatin was given for six cycles, and capecitabine and bevacizumab were continued until disease progression or unacceptable toxicity. Addition of bevacizumab to chemotherapy resulted in a significant improvement in progression-free survival (PFS) (6.7 months versus 5.3 months; hazard ratio, 0.80; 95% CI, 0.68-0.93;

P=0.0037) and overall response rate (ORR) (46.0% versus 37.4%; P=0.0315) but was not associated with significant improvements in overall survival (OS) and the study therefore failed to meet its primary end-point (12.1 months versus 10.1 months; hazard ratio, 0.87; 95% CI, 0.73-1.03; P=0.1002). Safety data revealed comparable toxicity profiles between the two arms, with no increase in chemotherapy related toxicity from the addition of bevacizumab.

The AVAGAST study is the largest study of bevacizumab in advanced gastric cancer. Disappointingly, the trial was negative however these data do raise several important questions about the use of anti-angiogenic agents in gastric cancer: Why there was no OS benefit demonstrated? Is bevacizumab the right drug for targeting angiogenesis? Are there definable subsets of patients who do derive meaningful survival benefit from use of bevacizumab? Is a 1.5 months PFS benefit of sufficient importance to justify further evaluation of bevacizumab in gastric cancer? Will other anti-angiogenic therapies be similarly ineffective?

Although a benefit has been demonstrated from use of bevacizumab in other tumour types, recent data suggest that the approach of targeting only the VEGF-A ligand with bevacizumab, is vulnerable to subversion via activation of the other ligands in the angiogenesis pathway (14), and it is therefore possible that a more multi-targeted approach may be needed to effectively target angiogenesis in gastric cancer and other tumour types. This may partly explain the discrepancy between the pre-clinical and the clinical studies of bevacizumab in gastric cancer and in other cancer types, many of which also demonstrate improved RR and PFS without OS benefit. Indeed, alternative anti-angiogenic strategies with agents targeting the VEGF receptor and other components of the angiogenesis pathway are currently undergoing evaluation in clinical trials. Pre-clinical studies have also raised concerns regarding disease rebound after stopping anti-angiogenic agents, although this phenomenon has not been reported in clinical studies, and it is unlikely that this was responsible for the lack of benefit in overall survival in the AVAGAST study.

In the AVAGAST study, there was no survival benefit in the intention-to-treat population however a pre-planned subgroup analysis demonstrated a significant OS benefit with the addition of bevacizumab in the pan-American subgroup, with no benefit being found in patients from the Asian subcontinent. This is most likely due to inherent global differences in disease biology and host or tumour-related genetic factors, as well as differences in clinical practice such as use of second-line chemotherapy. Taken together, these factors probably explain the regional difference in outcomes, reaffirming that gastric cancer trials data are not readily applicable worldwide and that 'East versus West' does matter in gastric cancer.

Although there were demonstrated improvements in the secondary end point of RR and PFS from the addition of bevacizumab, given the negative OS result in the ITT analysis, the use of bevacizumab in advanced gastric cancer cannot be justified currently. However, these data do confirm some activity for bevacizumab in advanced gastric cancer. The improved response rate may be of particular importance in the setting of operable gastric cancer where a higher response rate to preoperative chemotherapy may potentially facilitate a greater rate of R0 resection and hence lead to long-term survival benefit. The ongoing phase III UK MRC ST03 study is evaluating the benefit of adding bevacizumab to perioperative chemotherapy in operable gastro-oesophageal cancer (15).

Given the above data which provide some evidence of activity of bevacizumab in an unselected population, it remains distinctly possible that a subgroup of patients may derive more significant benefit than can be detected in a trial such as AVAGAST. Indeed, there are now ample data with other targeted agents which suggest efficacy in only a subgroup of patients with specific tumour characetesitics (16,17). Extensive research is currently ongoing to identify patients who will benefit from bevacizumab, though at present, there are no established predictive biomarkers for either bevacizumab or other anti-angiogenic drugs. Nevertheless, the established benefits of anti-angiogenic therapies in other cancer types, plus the improvements in RR and PFS in the AVAGAST trial, provide sufficient support for further evaluation in this setting, and these results should certainly not be considered as the end of the road for anti-angiogenic agents in gastric cancer. Indeed, it is imperative that we undertake focussed research in this area, including current and future trials of anti-angiogenic agents, in order to answer many of the outstanding questions surrounding this therapeutic strategy. This will be a difficult task with many potential pitfalls and challenges, but these are precisely the challenges which scientists and oncologists of today must overcome if we are to achieve personalized therapy for our patients and improve outcomes from this aggressive disease.

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Costs of trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or gastroesophageal junction cancer: does one "Analysis" fit all?

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Abstract: New cancer treatments are posing a significant financial burden on health-care systems worldwide. Cost effectiveness analyses of novel cancer treatments have received increased attention in oncology and are being used to make reimbursement decisions. In this article, we review a recently published economic evaluation of adding Trastuzumab to chemotherapy for HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer in China. The study suggests that the addition of trastuzumab to conventional chemotherapy might not be cost-effective based on incremental cost-effectiveness ratios of $251,667.10/QALY gained. Although highlighting an opportunity for efficient investment in cancer care, we believe that the results of this analysis are not generalizable to other health care system. While the incremental cost-effectiveness is likely to remain quite large in any context, it is known that cost-effectiveness is heavily dependent on a ceiling ratio and a decision maker's willingness to pay for a unit of quality of life gained.

Keywords: Cost effectiveness analysis; trastuzumab; gastric cancer; QALY. ToGA trial

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While increased survival is needed for patients with Gastric cancer, new treatments are posing a significant economic burden on health care systems worldwide. The Trastuzumab for Gastric Cancer (ToGA) study (1) reported a statistically significant overall survival benefit of 11 weeks for trastuzumab plus chemotherapy compared with chemotherapy alone for first-line treatment of advanced gastric and gastroesophageal cancer. However, Bin Wu *et al*. (2) suggested in an economic evaluation in a Chinese population that the addition of trastuzumab to conventional chemotherapy might not be cost effective in patients with HER-2 positive advanced Gastric and GE junction cancer. In their analysis, they concluded that poor overall survival time has the largest impact on cost.

Trastuzumab has been approved for HER-2 positive breast cancer for several years in the adjuvant and metastatic setting. Several cost-effectiveness analyses have been performed to assess the clinical and economic implication of adding trastuzumab to the treatment of breast cancer. In a US based analysis published in 2007, the projected additional lifetime cost of adjuvant trastuzumab per quality-adjusted life year (QALY) gained was $26,417 (3). Discounted incremental lifetime cost was $44,923, and projected life expectancy was 3 years longer for patients who received trastuzumab. The projected cost of adding trastuzumab to chemotherapy during a 20 year horizon was $34,201 per QALY gained.

Similar results were reported in an Australian analysis where adjuvant trastuzumab for early breast cancer was found to be cost effective when given over either 52 or

9 weeks (4). Another Italian/American analysis (5) concluded that adjuvant trastuzumab increases life expectancy by 1.54 (1.18 discounted) QALYs, and trastuzumab achieves its clinical benefit at a cost of 14,861 Euros and 18,970 dollars per QALY gained. The incremental cost effectiveness was higher than 50,000 Euros/QALY (or 60,000 dollars/QALY) at time horizons shorter than 7.8 years and for patients older than 76 years or with a 10-year risk of relapse lower than 15%. In a different analysis from the United Kingdom (6), the cost effectiveness of adjuvant trastuzumab was thought to be uncertain and dependent on assumptions regarding its clinical effect. Uncertainty around cost effectiveness was mostly related to the length of treatment and late toxicities.

Similar analyses have been reported in metastatic breast cancer (MBC); in a French analysis published in 2009 (7), the cost of adding trastuzumab to the treatment was 3 times higher (€39,608 *vs*. €12,795). The cost per additional life-year gained was estimated to be €27,492/year of life. The study concluded that despite the high price, trastuzumab is cost-effective in MBC patients to the extent that its incremental cost per life-year saved remains lower than the per capita gross domestic product, a commonly used threshold. Another analysis from France showed similar results where the mean overall cost was 33,271 euro per patient treated with trastuzumab versus 11,191 euro per patient treat it without it. The additional cost was 15,370 euros per QALYS gained (8).

This study we are reviewing here investigated the cost-effectiveness of adding trastuzumab to chemotherapy for patients with HER-2 positive advanced gastric or gastro-esophageal junction cancer in China (2). The time horizon for this analysis was 5 years. Relative to chemotherapy alone, the addition of trastuzumab increased cost and effectiveness by $56,004 and 0.18 QALYs, respectively, resulting in an ICER of $251,667/QALY gained. The study concluded that, for the Chinese health care system, adding trastuzumab was not cost-effective in this population. The methods of the study were appropriate. However, there is a risk of bias due to the key variables coming from an open label study. On the other hand, gastric cancer is a heterogeneous disease and it has been suggested that outcomes in an Asian population are better than in other populations. In the ToGA trial, only 50% of the patients were from Asia, making it difficult to generalize the results to other populations. This is especially true since the utility value for the control group was taken from a Chinese study. This study assumed that the additional trastuzumab had no impact on quality of life beyond the impact of the underlying chemotherapy regimen. Consideration of this impact would only make trastuzumab even less cost-effective than in the baseline analysis.

Generalizing this data to other countries with different health care systems, costs and utilization patterns requires further investigation. The authors reported a number of limitations, including not considering other chemotherapy regimens for the treatment of gastric cancer, which was not feasible since such trials have not yet been reported. The major limitation of this model is the lack of long-term survival data. Some factors were omitted entirely, such as HER-2 testing cost and non-treatment related supportive care cost including nutrition, pain management, doctor visits, etc. The latter costs may be quite significant after disease progression and changing to second line treatment.

An important subgroup, not examined in the study by Wu *et al*., are patients with high HER-2 expression. Patients in the ToGA trials with high HER-2 expression on immunohistochemistry (IHC 3+) had a better overall outcome, and a Korean and Japanese sub-group population of the ToGA trial were analyzed based on their IHC staining (9). In this base-case analysis, the incremental cost-effectiveness ratio was JPY 6.1 million (€55,000) per QALY gained and JPY 4.3 million (€39,000) per life-year gained concluding that trastuzumab treatment for the IHC 3+ population is cost effective.

The results of the analysis must be considered within the context of the study, including the population and time horizon. The impact of other adverse event and supportive care cost were not captured because of the small number of patients who were alive at the time of the analysis. Patients and caregiver's time cost and out-of-pocket expenses were not included as well. In order to increase the value derived from adding trastuzumab similar to breast cancer, the survival benefit must be significantly greater. The results of this analysis are clearly distinct from the breast cancer literature where trastuzumab has been demonstrated to be cost-effective and been approved for years in the metastatic and adjuvant setting. While the improvement in survival in the ToGA trial was statistically significant, it was very small.

The cost-effectiveness analysis by Wu *et al*. in the Chinese population is not generalizable to non-Asian populations with different health care systems. While the incremental cost-effectiveness is likely to remain quite large, many developed countries have shown a willingness to accept much higher thresholds of cost-effectiveness in oncology.

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Pharmacoeconomic studies of targeted agents in gastric cancer: ready for prime time?

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Gastric or gastroesophageal junction (GEJ) cancer represents a major health public issue. This disease is the second leading cause of cancer related death among men and the fourth among women (1). In China, the well known decline of incidence was less dramatic than other countries; in fact, an increase has been observed in the oldest and the youngest age subgroup, and a less remarkable decline has been observed among women than in men (2). Of note is that the age of onset of developing gastric cancer in Chinese population is younger than that in the West. The high mortality rate from gastric cancer is a result of the high incidence of metastatic disease, the aggressive clinical course and lack of effective systemic therapies. The frustrating lack of significant advancements in the treatment of advanced gastric cancer remains one of medical oncology's biggest disappointments. This has resulted in regulators, investigators, and practicing oncologists gradually lowering their standards/expectations with regard to interpreting clinical trials. Moreover, with the exception of trastuzumab, the combination of target agents with standard chemotherapy has failed to produce any added benefit to patients with advanced gastric cancer.

HER2 overexpression can be determined by immunohistochemistry (IHC) using a monoclonal antibody or by the detection of HER2 gene amplification through fluorescent *in situ* hybridization (FISH). Increased expression of HER2 has been detected in 13-23% of patients with gastric cancer. In Asians, most gastric tumors arise distally to the GEJ. Large, unselected Asian population series show lower HER2 positivity rates (ranging from 6% to 15%) than those from Western countries (ranging from 10% to 23%) (3). Because of its observed overexpression and/or amplification in a significant percentage of gastric cancers and its association with poor prognosis, the human epidermal growth factor receptor 2 (HER-2) signalling cascade has been treated with targeted agents in recent trials.

Trastuzumab (Herceptin), a humanized monoclonal antibody directed against the extracellular domain of HER2, was approved by the US Food and Drug Administration (FDA), and by the European authorities, for treatment of metastatic breast cancer (MBC) overexpressing HER-2, as detected either by immunohistochemistry (IHC) or by fluorescence in situ hybridization (FISH). Based on the phase III, randomized, ToGA trial, trastuzumab in combination with standard cisplatin and fluoropyrimidine (either 5-fluorouracil or capecitabine) received FDA approval as first-line treatment for advanced gastric or gastroesophageal junction cancer. The addition of trastuzumab to chemotherapy improved median overall survival from 11.1 months (95% CI, 12-16 months) in the control arm to 13.8 months (95% CI, 10-13 months) in those assigned to chemotherapy alone (hazard ratio 0.74; 95% CI, 0.60-0.91; P=0.0046) (4). One relevant problem with the ToGA study is that the economic impact of the incremental survival benefit is still unknown. Indeed, there is a growing consensus world-wide that cost-effectiveness considerations should be taken into account when making private or public health insurance decisions for coverage of innovative and costly medical procedures. Medical decision makers need information on the economic value of the new treatment for medical resource optimisation.

In gastric cancer, tumor heterogeneity of the HER2 genotype, which can lead to discrepancies in the results

from IHC and FISH testing, is more prominent than what was experienced in breast cancer (5). Incomplete basolateral membrane HER2 IHC staining is also more common in gastric cancer, due to the higher frequency of glandular formations that occur in gastric tissue. According to FDA, a patient with an IHC score of 3+ and/or positive FISH (with any IHC result) could be treated with a trastuzumab-based regimen. In fact, HER2 testing in the ToGA trial required both IHC and FISH and only one positive test was needed to indicate eligibility for HER2-targeted therapy (IHC 3+ or FISH+). Of the randomized patients included in the ToGA trial, 25% (146/584) of the population could have been missed using the current FDA approved breast cancer HER2 testing algorithm if only one HER2 test was used (i.e. IHC 0/FISH+, IHC 1+/FISH+, IHC 3+/FISH-). However, the National Comprehensive Cancer Network (NCCN) guidelines panel recommended that less than 3+ overexpression of HER2 by IHC should be additionally examined by FISH or other *in situ* hybridization methods.

In this issue of Translational Gastrointestinal Oncology, Wu and Colleagues provided a pharmacoeconomic assessment of the use of trastuzumab in the Chinese patients population with advanced gastric cancer. In this analysis, the direct costs were estimated from the perspective of Chinese health care system. Secondly, the Markov model simulated the natural progression of advanced gastric and closely matched the reported PFS curve and mortality. The Authors demonstrate that the incremental cost-effectiveness of trastuzumab is dramatically unsatisfactory, i.e. quality-adjusted life-years (QALYs) was far less than 1 (0.18) and the incremental cost-effectiveness ratio (ICER) was $ 251,667,10/QALY gain.

It is very important to highlight that a discount plan for trastuzumab would certainly decrease the ICER of the combination of trastuzumab with chemotherapy in gastric cancer. However, some remarks should be addressed. The exploratory retrospective analysis of the ToGA trial revealed that treatment with trastuzumab in combination with chemotherapy improved in a statistically and clinically meaningful manner the median OS in patients with IHC2+/FISH+ and IHC3+ gastric or gastroesophageal junction adenocarcinoma. Thus, the European board, EMEA, approved trastuzumab for the treatment of metastasized adenocarcinomas of the stomach and immunohistochemical testing is the primary method of choice to determine HER2 status in gastric cancer, while FISH is restricted to those cases that have equivocal (IHC2+) HER2 expression. Specifically, in the post-hoc identified subgroups with IHC2+/FISH+ and IHC3+, median OS increased from 11.8 months for the chemotherapy treatment arm to the encouraging 16.0 months for the chemotherapy with trastuzumab arm (hazard ratio 0.65; 95% CI, 0.51-0.83). Conversely, in patients with gastric tumors with low HER2 expression (0/1+) and FISH+, the addition of trastuzumab to chemotherapy was not associated with an evident benefit (hazard ratio 1.07; 95% CI, 0.70-1.62). There was evidence of a significant interaction test (P=0.036) between treatment and the high HER2 expression versus low HER2 expression groups. The hazard ratio of OS for patients with IHC 2+/FISH+ was 0.75 (95% CI, 0.51-1.11). In the pre-planned subgroup analysis of patients with IHC3+/FISH+, the median OS reached 17.9 months with trastuzumab-based chemotherapy and the hazard ratio was 0.58 (95% CI, 0.41-0.81). Thus, the administration of trastuzumab in patients with HER2 3+ gastric cancer could be cost-effective. This evidence was previously demonstrated by the pharmacoeconomic evaluation of the U.K. Authority (NICE) (6) and by a subgroup analysis of Japanese and Korean patients enrolled in the ToGA trial (7).

In our opinion, one of the most important ways to improve the value of trastuzumab in gastric cancer is to further develop the validation of biomarkers to improve the selection of patients benefiting from treatment. Active research is ongoing to improve the knowledge of molecular biology of gastric cancer and to identify reliable prognostic and predictive factors that may improve the cost-effectiveness of targeted agents.

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A case report of trastuzumab dose in gastric cancer

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Introduction: Trastuzumab (Herceptin®, F. Hoffman-La Roche) is now approved for the treatment of metastatic HER2-positive gastric cancer based on the improved survival observed on the phase III Trastuzumab for Gastric Adenocarcinoma (ToGA) study. Standard dosing of trastuzumab is currently extrapolated from breast cancer data: a 3-week schedule (8 mg/kg load, 6 mg/kg q 3 weeks) or a weekly schedule (4 mg/kg load, 2 mg/kg q week).

Case study: Our case study examines an HER2-positive metastatic gastric cancer patient that required a higher than currently recommended standard dose of trastuzumab to achieve treatment response.

Discussion: Several mechanisms may explain these findings and include higher clearance of trastuzumab, higher tumor burden, and pharmacologic resistance in metastatic gastric cancer versus breast cancer. The question of trastuzumab dosing in gastric cancer is currently being evaluated in a phase III clinical trial.

Keywords: Trastuzumab; metastatic gastric cancer; pharmacokinetics

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Introduction

Trastuzumab (Herceptin®, F. Hoffman-La Roche) is approved for the treatment of metastatic HER2-positive gastric cancer. The Trastuzumab for Gastric Adenocarcinoma (ToGA) study was a randomized Phase III clinical trial evaluating chemotherapy with and without trastuzumab in patients with HER2-positive gastric cancer, as defined as FISH positive (HER2:CEP17 >2.0) or IHC 3+ (using Hofmann scoring criteria (1). Following a loading dose, patients randomized to the trastuzumab arm received trastuzumab 2 mg/kg/wk as was established as standard treatment in breast cancer (2). Patients randomly assigned to receive trastuzumab with chemotherapy had significantly improved survival and clinical outcome (hazard ratio 0.74, 95% CI, 0.60-0.91, P=0.0046) (3). Based on this positive study, trastuzumab with cisplatinum/5-FU-based chemotherapy is now standard of care for HER2-positive gastric cancer.

Here, we describe a patient with HER2-positive metastatic gastric adenocarcinoma who had progressed on the standard dose of trastuzumab, but then responded to a higher dose.

Case report

A 68-year-old man with metastatic gastric cancer to the mediastinum and cervical lymph nodes was initially diagnosed in September 2010 when he presented with supraclavicular adenopathy. Excisional biopsy (9/17/10) revealed poorly-differentiated metastatic adenocarcinoma. The tumor was positive for CK7, CK20, p53, and negative for CDX2, TTF-1, EGFR/kRAS, ALK, and PSA. He had widespread metastatic disease including metastases to lymph nodes in the neck, bilateral hila, mediastinum, and retroperitoneum, as well as multiple sites within the lumbar spine.

Upper endoscopy (10/19/2010) revealed distal esophageal thickening and biopsy of confirmed adenocarcinoma, positive for HER2 (FISH 3.0, IHC 2+) (DAKO). He began chemotherapy for metastatic HER2-positive gastroesophageal junction adenocarcinoma on 11/9/2010,

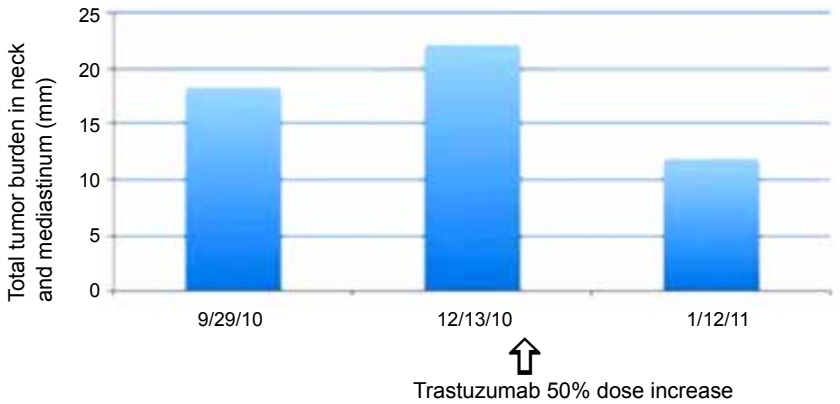

Figure 1 Clinical response with Trastuzumab dose increase. While initially effective, patient eventually progressed on standard Herceptin dosing (4 mg q 2 weeks) with innumerable cervical lymph nodes. Dose increase by 50% (6 mg q 2 weeks) of Trastuzumab led to marked response and resolution of paratracheal lymph nodes.

receiving FOLFOX and trastuzumab (6 mg/kg load), followed by FOLFOX and trastuzumab 4 mg/kg every two weeks. However, after 3 cycles, on 12/13/10, the patient presented with increasing supraclavicular and neck adenopathy causing positional dyspnea. CT neck confirmed progressive lymphadenopathy involving every level of the neck. The trastuzumab dose was increased by 50% (6 mg every two weeks), and the FOLFOX chemotherapy remained unchanged. The patient quickly demonstrated clinical response with improvement in neck adenopathy and in resting dyspnea with a change in trastuzumab dose alone. CT CAP (1/21/11) demonstrated response with interval decrease in mediastinal, retrocrural, abdominal and upper retroperitoneal adenopathy. *Figure 1* describes the cumulative tumor burden of his neck and upper chest adenopathy over time. The patient remained on therapy with FOLFOX and trastuzumab 6 mg/kg every 2 weeks with subsequent imaging demonstrating continued response to therapy (2/14/11, 4/14/11). The patient had progressive disease by June 2011, and died of advanced gastric cancer in August 2011.

Discussion

We present a case of HER2-positive metastatic gastric cancer that required a higher than standard dose of trastuzumab to achieve a response to therapy. Standard breast cancer dosing of trastuzumab on a 3-week schedule is 8 mg/kg load followed by 6 mg/kg q 3 weeks, or on a weekly schedule (4 mg/kg load, 2 mg/kg q week) (1). Our patient was treated with FOLFOX chemotherapy every two weeks, and thus received an appropriate proportional trastuzumab dose (6 mg/kg load, 4 mg/kg q 2 weeks). The patient progressed very quickly following initiation of therapy (after 3 treatments), and subsequently responded immediately following an increase in trastuzumab dose to 6 mg/kg q 2 weeks (i.e., 50% dose increase in maintenance). This response was noted without a change in the FOLFOX cytotoxic therapy, suggesting that the initial administered dose of trastuzumab was insufficient for treatment response; more specifically, the patient required a higher dose of trastuzumab to achieve a response to therapy.

The observation that our patient responded to a higher dose of trastuzumab than routinely administered suggests that some patients with HER2-positive gastric cancer may be underdosed. It is suggested that gastric cancer patients may have a higher renal clearance of trastuzumab than patients with HER2-positive breast cancer. Bruno and colleagues (4) determined the steady state pharmacokinetics of trastuzumab in patients with metastatic breast cancer. On the weekly trastuzumab schedule, trastuzumab clearance is 0.231 L/day (for a median body weight of 68 kg) with a corresponding elimination half-life of approximately 3 weeks. On the every 3-week schedule in metastatic breast cancer, the trastuzumab pharmacokinetics is very similar (1). In contrast, the pharmacokinetic profile of trastuzumab reported from the ToGA study in patients with metastatic gastric cancer demonstrate a higher clearance is 0.378 L/day (~70% higher), with a corresponding elimination half-life of approximately only 2 weeks (Roche, Inc 2011) (*Table 1*) (5). This suggests that the current "standard" dosing of trastuzumab in metastatic gastric cancer may be grossly underdosed by nearly 50%,

Table 1 Pharmacokinetics of trastuzumab (Herceptin) in breast cancer *vs.* metastatic gastric cancer

Dose	Breast cancer		Metastatic gastric cancer
	4 mg/kg (load) 2 mg/kg q week*	8 mg/kg (load) 6 mg/kg q 3 weeks (1)	8 mg/kg (load) 6 mg/kg q 3 weeks*
Renal clearance (for a body weight of 68 kg, L/d)	0.231	0.235	0.378
Volume of distribution (L)	2.79		3.91
Elimination half-life (days)	21	19	14

*Roche, Inc 2011 (5).

and that higher trastuzumab doses may be necessary in some patients for maximum efficacy.

In breast cancer, it has been shown that patients with four or more metastatic sites of disease have faster clearance, independent of HER-2 extracellular domain levels (4). Trastuzumab elimination appears to depend on serum levels of circulating HER-2 extracellular domains, which can be cleaved from the surfaces of cancer cells by matrix metalloproteinase. While the relationship between circulating HER2neu extracellular domains (shed antigen) and tumor burden is unknown, it is reasonable to expect higher HER2 levels to be associated with higher tumor burden. This implies that patients with high HER-2 extracellular domain levels tend to have a shorter trastuzumab half-life and lower minimum concentrations (6). Together, these data suggest that many patients with gastric cancer with a high disease burden may be associated with a higher clearance of trastuzumab due to increased levels of shed Her-2 antigen. Consistent with this argument, our patient had a high disease burden with his primary tumor unresected, and with multiple metastases to bone and widespread adenopathy involving bilateral neck, mediastinum, and retroperitoneum.

Primary or acquired resistance to trastuzumab presents another possibility of compromised therapeutic efficacy. Resistance to trastuzumab will invariably develop in patients with advanced cancers treated with trastuzumab-containing regimens. Indeed, the rate of primary resistance to single-agent trastuzumab in HER2-overexpressing metastatic breast carcinomas is 66-88% (7-9). Proposed mechanisms of resistance in breast cancer include activation of multiple downstream signaling pathways (such as P13K/AKT pathway) (10), disruption of the interaction between the therapeutic agent and the target protein (11), and loss of the binding site on truncated HER2 receptors (12,13). There are currently no data regarding resistance mechanisms to trastuzumab in gastric cancer and no currently available *in vitro* tests available that effectively predict trastuzumab resistance in gastric cancer (14).

This case highlights that a higher dosing of trastuzumab may be necessary to compensate for increased renal clearance of the drug in metastatic gastric adenocarcinoma. Currently, trastuzumab's elimination pathways are not clearly defined and the clinical relevance of trastuzumab's kinetic variability is unknown. This is the subject of an ongoing international phase III study examining standard dosing versus high dosing trastuzumab + chemotherapy in metastatic HER2-positive gastric cancer (HELOISE Study) (NCT01450696 on www.clinicaltrials.gov). Although provocative, best practice suggests that we continue with standard dosing of trastuzumab until the results of the HELOISE study are available.

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Long-term survival in an advanced gastric cancer patient treated with cetuximab in association with FOLFIRI: a case report

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Abstract: In December 2004, a 52-year-old woman with metastatic gastric cancer was enrolled in the phase II clinical trial FOLCETUX, receiving cetuximab at an initial dose of 400 mg/m² i.v. followed by weekly doses of 250 mg/m², irinotecan 180 mg/m² i.v. on day 1, LFA 100 mg/m² i.v. followed by 5-FU 400 mg/m² i.v. bolus and 600 mg/m² i.v. 22-h continuous infusion on days 1 and 2 every two weeks, to a total of 17 cycles. CT and PET-CT performed after six weeks treatment failed to show any residual disease, with complete radiological response in accord to RECIST criteria and complete metabolic response. A total of 24 maintenance administrations with cetuximab alone (250 mg/m² weekly) were performed, as foreseen by the protocol in responders. In November 2012 a clinical, radiological (CT) and metabolic (PET-CT) patient examination proved negative for recurrent disease, signifying 95 months' progression free survival.

Keywords: Gastric cancer; cetuximab; FOLCETUX; FOLFIRI

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Introduction

Treatment of advanced gastric cancer, traditionally with double or triple cytotoxic chemotherapy regimens, involves an advantage in overall survival of about 7-11 months compared to best supportive care (1). Though some data have emerged from a recent meta-analysis (2), there is currently no standard of treatment in the gastric cancer first-line setting. Again, at the time we were deciding how to treat our patient one was unable to use trastuzumab in metastatic gastric or gastroesophageal junction (GEJ) cancer HER2 positive, resulting later in a significant benefit in combination with cisplatin and 5-FU or capecitabine *vs.* chemotherapy alone (3).

Starting from gene expression tumor profiling, and given the presence of epidermal growth factor (EGF) in 25-30% of gastric cancer as well as the positive experience obtained in the metastatic colorectal cancer (mCRC) setting (4), we were prompted to investigate anti-EGFR therapy in gastric and GEJ cancer. Epidermal growth factor receptor (EGFR) is over expressed in 18-81% of gastric cancer, representing an unfavorable prognostic marker in multivariate data, typically associated with older age, more aggressive histology, higher stage disease and shorter survival. Tumors exhibiting EGF and EGFR simultaneously show a greater degree of local invasion and lymph node metastasis.

Case report

A 52-year old woman with recurrent epigastric pain and significant weight loss underwent esophagogastroduodenoscopy which revealed a large ulcerated lesion in the gastric antrum-body. Pre-operative radiological investigations did not show any metastatic disease. In November 2003, the patient underwent total gastrectomy with omentectomy and D2 lymphadenectomy, mechanical end-to-side anastomosis of the jejunal loop excluded by Roux. The antral region proved to have a macroscopic ulcerative vegetating lesion of about 6 cm infiltrating the wall and extending to the sierosa and adipose perigastric tissue. Histological examination gave

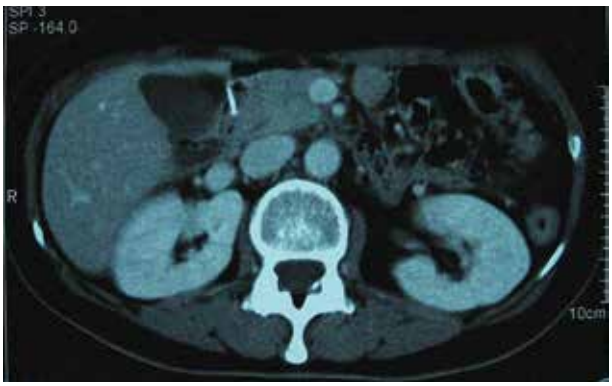

Figure 1 CT baseline.

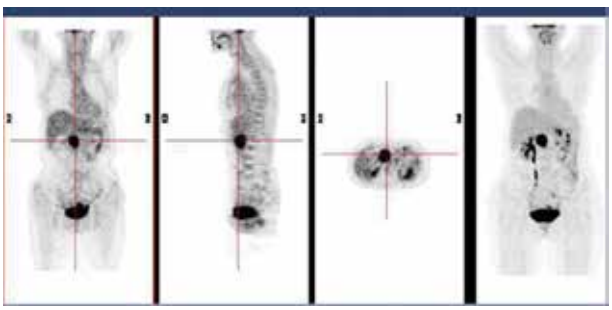

Figure 2 PET-CT baseline.

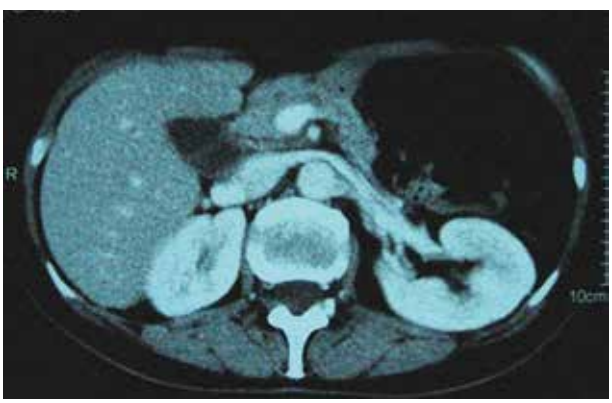

Figure 3 CT after six weeks of FOLFIRI/cetuximab: complete response.

evidence of intestinal adenocarcinoma, poorly differentiated and with focal areas of mucoid (pT3N3M0-Stage IIIA, G3; p53 100%, Ki67 52%, EGFR overexpressed).

From December 2003 to May 2004 adjuvant chemotherapy with a modified PELF regimen was performed to a total of six cycles.

In December 2004 during a clinical follow-up, CT and ^{18}F-FDG-PET-CT showed a retroperitoneal lymph node relapse in the form of a homogeneous solid mass sited at the pancreatic uncinate process, the maximum diameter being 5 cm (*Figure 1*), with SUV_{max} =18 at PET-CT (*Figure 2*). As a candidate for first-line chemotherapy treatment, she was enrolled in the phase II clinical trial FOLCETUX, receiving cetuximab at an initial dose of 400 mg/m² i.v. followed by weekly doses of 250 mg/m², irinotecan 180 mg/m² i.v. on day 1, LFA 100 mg/m² i.v. followed by 5-FU 400 mg/m² i.v. bolus and 600 mg/m² i.v. 22-h continuous infusion on days 1 and 2 every two weeks, to a total of 17 cycles. CT and PET-CT performed after six weeks treatment failed to show any residual disease, with complete radiological (*Figure 3*) response in accord to RECIST criteria and complete metabolic response (*Figure 4*). A total of 24 maintenance administrations with cetuximab alone (250 mg/m² weekly) were performed, as foreseen by the protocol in responders. A grade 3 skin rash was observed during treatment.

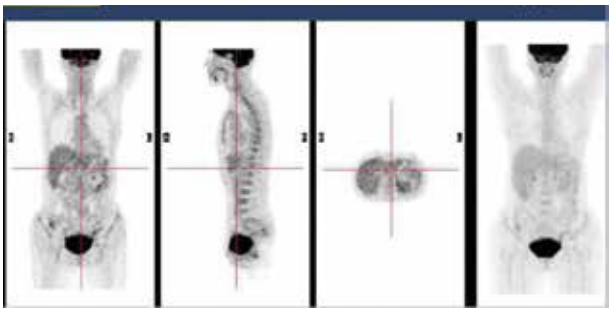

Figure 4 PET-CT after six weeks of FOLFIRI/cetuximab: complete metabolic response.

In November 2005 elevated serum transaminases (AST =289 U/L; ALT =321 U/L) and subsequent diagnosis of HCV infection led to suspension of the cetuximab maintenance. The total body CT and PET-CT imaging continued to show no residual metabolic disease at the end of treatment.

In December 2007, since clinical and radiological response continued to be complete, treatment with interferon and ribavirin was started, and discontinued in January 2009.

In November 2012 a clinical, radiological (CT) and metabolic (PET-CT) patient examination proved negative for recurrent disease, signifying 95 months' progression free survival.

Discussion

Cetuximab, the partially humanized murine anti-EGFR

Table 1 Phase II study on first-line chemotherapy plus cetuximab in advanced gastric cancer

Author	No. of patients	Chemotherapy regimens	ORR (%)	PFS (months)	OS (months)
Pinto *et al*. 2007	38	Cetuximab + FOLFIRI	44	8	16
Woell *et al*. 2008	51	Cetuximab + oxaliplatin/irinotecan	63	6.2	9.5
Pinto *et al*. 2009	48	Cetuximab + cisplatin/docetaxel	41.2	5	9
Han *et al*. 2009	40	Cetuximab + mFOLFOX6	50	5.5	9.9
Kanzler *et al*. 2009	49	Cetuximab + FUFIRI	42	8.5	16.6
Yeh *et al*. 2009	35	Cetuximab + 5FU/LV/cisplatin	69	11	14.5
Zhang *et al*. 2009	49	Cetuximab + cisplatin/capecitabine	48	5.2	NS
Lordick *et al*. 2010	52	Cetuximab + FUFOX	65	7.6	9.5
Enzinger *et al*. 2010	245	Cetuximab + ECF/IC/FOLFOX	58/38/51	5.6/5/5.7	10.0/8.6/10.0
Moehler *et al*. 2011	49	Cetuximab + FOLFIRI	46	9	16.5
Kim *et al*. 2011	44	Cetuximab + XELOX	52.3	6.5	9.8

monoclonal antibody, has been the most examined anti-EGFR therapy in gastric cancer. It has low activity as a single agent (5), but the trend is different when it is added to single or double chemotherapy regimens. Eleven non-randomized first line phase II studies (6-16) have evaluated the activity and safety of cetuximab combined with different chemotherapy regimens, showing a response rate ranging from 38-69%, time to progression from 5.0 to 11 months and median overall survival between 8.6 and 16.6 months (*Table 1*).

As to what is the best chemotherapy regimen combination including cetuximab, there are no answers based on statistical significance, though the clinical results indicate substantial benefit when using irinotecan.

Tolerance of treatment and quality of life are of considerable importance in patients with advanced gastric cancer because most of them are symptomatic at baseline. Irinotecan monotherapy is active in gastric cancer patients with a phase II trial response rate of about 14-23%. This drug is more active when administered with 5-FU/folinic acid, and in two phase II trials achieves an overall response rate of 21-40% as well as median overall survival times of 6.4-11.3 months (17,18). In a large phase III study conducted by Dank *et al*., irinotecan plus 5-FU regimen showed a time-to-progression trend that was superior to cisplatin plus 5-FU: 5.0 versus 4.2 months, similar overall response rate (31.8% versus 25.8%) and median overall survival time (9.0 versus 8.7 months), but a better safety and toxicity profile.

In the FOLCETUX study the addition of cetuximab to the FOLFIRI regimen resulted in a median survival time of 16.6 months, longer time to progression and also an acceptable level of safety and a shorter time-to-response (six weeks) (6). These promising results prompted the German group to conduct a biomarker-oriented phase II study using the same combination but with a different administration schedule. Over a period of one year, a total of 49 patients enrolled achieved an overall response rate of about 46%; The disease control rate was 79%, median PFS and OS were 9.0 and 16.5 months, comparable with previously reported findings. The paper published by Moehler *et al*., as expected contained a pre-planned analysis of biomarkers involved in treatment outcomes using anti-EGFR targeted agents. The final data confirmed most of the analysis later carried out by us (19): the frequency of KRAS, BRAF and PIK3CA activating mutations found was very low. Unlike mCRC, where KRAS tumor mutation frequency is approximately 40%, and hence a negative prognostic and predictive factor of response to treatment with cetuximab, in gastric cancer KRAS mutation status seems to be an unsuitable predictive marker of cetuximab efficacy.

High hopes were placed in the EXPAND study presented at ESMO 2012, a large open-label, randomized, controlled phase III trial of cetuximab in combination with capecitabine and cisplatin in patients with advanced gastric cancer (20).

The results of the study failed to show benefit from the addition of cetuximab. The study protocol was terminated early due to the low progression-free survival observed. Between June 2008 and December 2010, 904 patients from 25 countries were enrolled and randomized, 455 patients received capecitabine, cisplatin and cetuximab while 449 received only cisplatin and capecitabine. Patient outcomes

were similar between treatment groups, in that the primary and secondary endpoints were not met, progression-free survival was 4.4 compared to 5.6 months and overall survival was 9.4 compared to 10.7 months (respectively in the cetuximab-combination and control groups). The overall response rate was respectively 29% and 30%. Although toxicity grade 3/4 events and serious adverse reactions were reported more in the cetuximab-containing arm, the negative results of this process cannot only be explained by the increase in toxicity rates. Perhaps excessive enthusiasm deriving from the results obtained in small phase II trials inflated the importance of a randomized multicenter investigation into this, the best chemotherapy association previously tested.

The advantage of biological material stored in 97% of patients and currently under study is that EXPAND was a large study in a metastatic setting, performed in a homogeneous patient population, where the clinical database is of high quality, permitting translational research and establishing future subgroups of different types of gastric cancer based on gene expression profiling.

We must not forget that antibody drugs trigger intracellular cascades that can be augmented by chemotherapy association, for which reason perhaps the same holds for trastuzumab in combination with cisplatin and 5-FU or capecitabine does not apply to cetuximab, which is more effective for enhancing tumor shrinkage when combined with irinotecan, as has emerged in wild type KRAS mCRC.

When investigating the role of prognostic and predictive markers in an aggressive and disabling disease such as advanced gastric cancer, it is mandatory to define the patient setting clarifying who can obtain the most clinical benefit from the various biological and chemotherapy combination therapies.

Acknowledgements

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Genetics and molecular pathology of gastric malignancy: Development of targeted therapies in the era of personalized medicine

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Abstract: Gastric malignancy constitutes a major cause of cancer deaths worldwide. Despite recent advances in surgical techniques combined with neoadjuvant chemotherapy and radiotherapy approaches, patients with advanced disease still have poor outcomes. An emerging understanding of the molecular pathways that characterize cell growth, cell cycle, apoptosis, angiogenesis, invasion and metastasis has provided novel targets in gastric cancer therapy. In this review, recent advances in the understanding of molecular tumorigenesis for common gastric malignancies are discussed. We also briefly review the current targeted therapies in the treatment of gastric malignancies. Practical insights are highlighted including HER2 testing and target therapy in gastric adenocarcinoma, morphologic features and molecular signatures of imatinib-resistance GISTs, and recent investigations aimed at tumor-specific therapy for neuroendocrine tumors.

Keywords: Gastric malignancy; genetics and molecular pathology; targeted therapy

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Introduction

Personalized medicine is a medical model proposing the customization of healthcare, with decisions and practices being tailored to the individual patient by use of genetic or other information. Under the present paradigm personalized medicine offers a glimpse at the future of medicine. As a result, a new issue arises: The best for some or for all? Will this new model of medicine be an instrument for the few or the many? Molecular pathology, an initially expensive yet powerful tool in the post-genomic medical armatorium, lies at the crux of this issue. It offers physicians the ability to customize therapy for the individual patient based on his or her unique molecular pathological process. Defining the unique subsets of patients that can gain benefit from specific and expensive therapuetic agents is critical in both providing high quality care and cost-effective medicine. Globally, gastric cancer is the second most common cause of cancer-related death, with the majority of the health burden borne by economically less-developed countries (1). Here we review the prospects from genetics and beyond in regard to targeted molecular therapies for three common gastric malignancies.

Molecular pathology of gastric adenocarcinoma

Gastric cancer is the second most common cause of cancer death worldwide (2). The incidence of gastric adenocarcinoma has been declining for decades; however its prognosis remains poor (3). Epidemiological studies have shown that environmental factors such as Helicobacter pylori, diet, and smoking play a significant role in gastric carcinogenesis (4). However, host genetics are thought to contribute as well. For example, although H. pylori infection is known to be associated with an increased risk of gastric cancer, the risk is much higher in

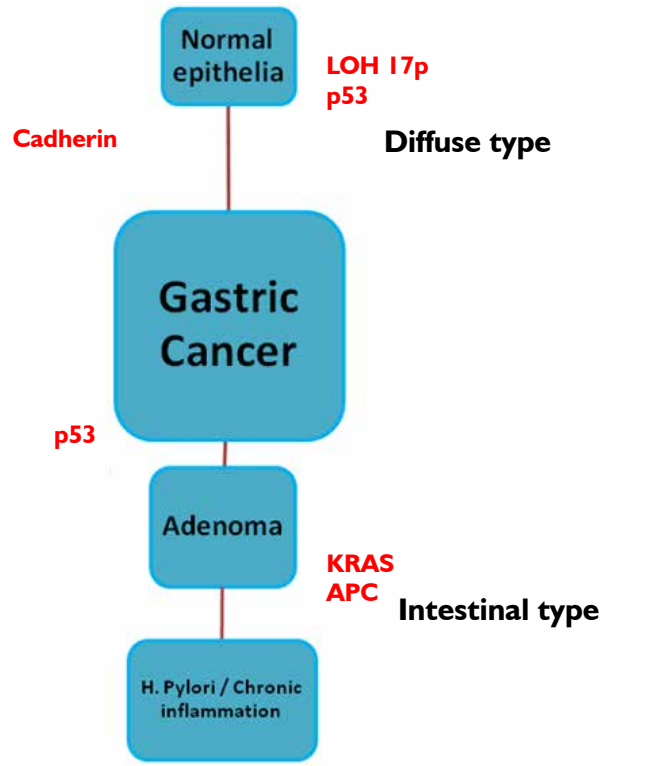

Figure 1 Genetics and pathogenesis of gastric adenocarcinoma.

subgroups of infected patients who have atrophic gastritis and extensive intestinal metaplasia, suggesting that host genetics influence how often precancerous lesions appear in H. pylori-infected individuals (5).

There are two distinct types of gastric adenocarcinoma, intestinal (well-differentiated) and diffuse (undifferentiated), which have distinct morphologic appearance, epidemiology, pathogenesis, and genetic profiles (6,7). A molecular basis for this difference is now apparent (6). The morphologic differences are attributable to intercellular adhesion molecules, which are well preserved in intestinal-type tumors and defective in diffuse carcinomas.

The main carcinogenic event in diffuse carcinomas is loss of expression of E-cadherin, a key cell surface protein for establishing intercellular connections and maintaining the organization of epithelial tissues. Biallelic inactivation of the gene encoding E-cadherin, CDH1, can occur through germline or somatic mutation, allelic imbalance events (e.g., loss of heterozygosity), or epigenetic silencing of gene transcription through aberrant methylation of the CDH1 promoter. Approximately 10-15% of gastric cancers are familial. Hereditary diffuse gastric cancer, a highly penetrant autosomal dominant condition, is caused by germline mutations in the epithelial cadherin gene and is characterized by an increased risk for diffuse gastric cancer and lobular breast cancer (2). Approximately one third of families have inactivating mutations in the epithelial cadherin gene (2). Other cancer syndromes also display an increased risk in gastric cancer, such as, hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), Peutz-Jegher's syndrome and BRAC2 mutation carriers (*Figure 1*) (2).

HER2 gene amplification and overexpression has been well recognized as a strong driver of carcinogenesis, especially in breast cancer. Increasing evidence has shown that HER2 amplification is also involved in a substantial number of gastric cancers, up to 34% (1). Moreover, treatment with tratuzumab increased survival benefits in patients with cancers that had high HER2-expression (8). HER2 testing in gastric cancer differs from HER2 testing in breast cancer (1). Gastric cancer more often display heterogeneous incomplete focal membrane staining. Histological differences between gastric and breast cancers necessitate modifications to the HER2 scoring system for gastric cancer. Gastric cancer-specific HER2 testing protocols have been developed and standardized. Immunohistochemistry is the initial testing methodology followed by fluorescence in-situ hybridization or silver in-situ hybridization in immunohistochemically 2+ equivocal cases. Using the scoring criteria for HER2 established in breast cancer on gastric cancer cases may underscore tumors by as much as 50% compared with the cases scored in the trastuzumab for gastric cancer trial; thus, preventing eligible patients access to effective therapy (9). Biopsies are the preferred specimen for optimal results. The scoring criteria for HER2 immunohistochemical testing in gastric cancer are summarized (*Table 1*, *Figures 2,3*).

HER2 testing in gastric carcinoma opens a new promising therapeutic option for patients. The progress in molecular pathology enables understanding the biology of gastric and GEJ cancer and in discovering possible novel molecular therapy targets. These therapeutic strategies include epidermal growth factor receptor inhibitors, antiangiogenic agents, cell cycle inhibitors, apoptosis promoters, and matrix metalloproteinases inhibitors. The agents targeting the human epidermal growth factor receptor HER 2 and epidermal growth factor receptor 1 (EGFR1), vascular endothelial growth factor (VEGF), MET and regulators of cell cycle are being integrated into therapeutic studies with the goal of improving therapeutic options for this disease (10).

Table 1 HER2 grading criteria by immunohistochemistry (1)

IHC score	Description
0	No staining or membrane staining in <10% of invasive tumor cells
1+	Faint/barely perceptible membrane staining in ≥10% of invasive tumor cells; cells are only stained in part of their membranes
2+	Weak to moderate complete or basolateral membrane staining in ≥10% of invasive tumor cells
3+	Moderate to strong complete or basolateral membrane staining in ≥10% of invasive tumor cells. Tumor cell cluster with strong complete, basolateral, or lateral membrane reactivity irrespective of percentage of invasive tumor cells stained

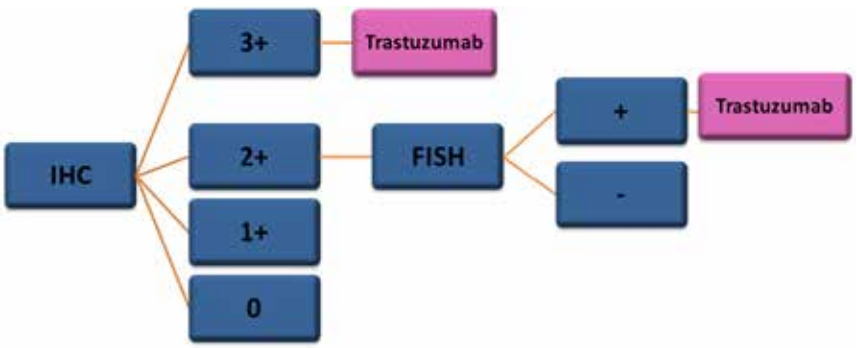

Figure 2 HER2 testing algorithm in GC/GEJ cancer; cut off for FISH = HER2:CEP17 ratio ≥2.

Molecular pathology of gastrointestinal stromal tumors

Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors of the gastrointestinal tract, accounting for 80% of gastrointestinal mesenchymal tumors (10). However, they are rare with respect to all GI malignancies, as they constitute only 1-3% (10). At presentation, nearly half of malignant GISTs are metastatic, however less than a third of GISTs are classified as malignant (10).

Prior to 1998, GISTs were diagnostically problematic, being mistaken for smooth muscle tumors such as leiomyoblastomas, leiomyomas and leiomyosarcomas (11). Electron microscopy studies in the 1970s and immunohistochemical studies in the late 1980s revealed that these tumors were in fact not derived from smooth muscle (11).

Rather, these studies pointed to the interstitial cells of Cajal as the cell of origin of GISTs. The interstitial cells of Cajal are the pacemaker cells of the gastrointestinal track. They regulate intestinal motility and peristalsis and are found in-between the autonomic nervous system and the muscular wall of the GI tract (11). These cells have immunophenotypic and ultrastructural features of smooth muscle and neuronal cells similar to GISTs (11). Like GISTs they stain positive by IHC for CD34, CD117, and DOG1 (*Figure 4*).

In 1998 Hirota and colleagues published a sentinel paper showing that most GISTs harbored mutations in the c-kit gene which results in ligand-independent activation of KIT protein (12). They also showed that GISTs usually express the KIT protein, using an immunohistochemistry stain c-kit or CD117, providing pathologists with a critical diagnostic test (12). This sentinel discovery changed the paradigm of GISTs pathogenesis, diagnosis, and treatment. Further studies showed that a subset of GISTs contain mutations in another tyrosine kinase receptor gene called platelet-derived growth factor receptor (PDGFRA).

Regardless of site of involvement, most GISTs express the CD34 antigen (70-80%) and the CD117 antigen (72-94%). A relatively new immunohistochemistry marker, DOG1, which was discovered using gene expression profiling (13), is highly specific for GISTs. Negativity for both DOG1 and KIT has been observed in only 2.6% of GISTs of the gastrointestinal tract (13).

The term GIST is now generally used to specify a mesenchymal tumor of the gastrointestinal tract that contains either a *KIT* or *PDGFRA* driver mutation and

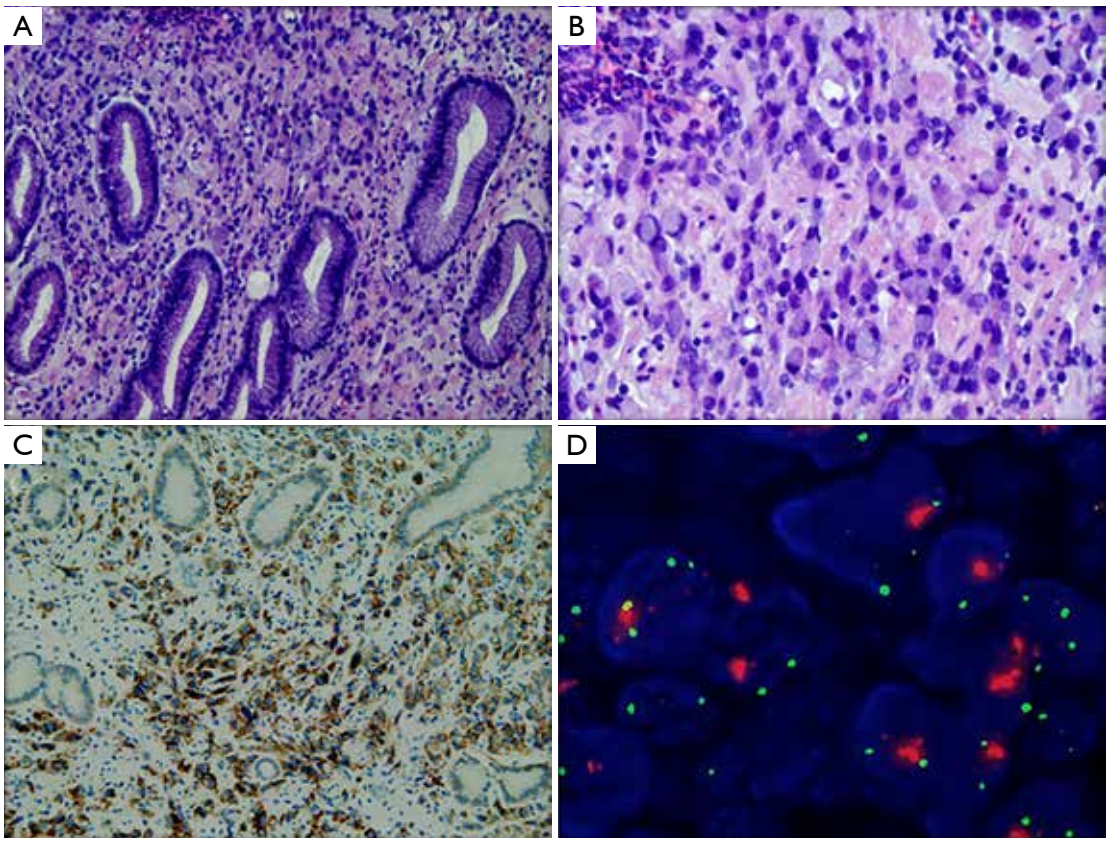

Figure 3 H&E stained section of a poorly differentiated gastric adenocarcinoma. (A) At low power, the tumor cells show invasive growth pattern; (B) at high power, tumor cells shows feature of signet ring cells; (C) immunohistochemical stain of HER-2 in tumor cells (3+); (D) FISH study of HER2 demonstrates amplification (red signals: HER2, green signals: CEP17).

displays a characteristic histology which includes spindle, epithelioid, and rarely pleomorphic cells (14).

KIT is a transmembrane tyrosine kinase receptor that plays an important role in the maturation of hematopoetic cells, melanocytes, and interstitial cells of Cajal (11). The binding of *stem cell factor* to the extracellular domain of the receptor results in autophosphorylation of several tyrosine residues and activation. Once activated KIT phosphorylates other proteins and transcription factors leading to activation of signal transduction cascades, such as the Ras/MAP kinase pathway (15). These activated pathways ultimately lead to several cellular modifications including changes in cell adhesion, migration, and differentiation.

KIT mutations are seen in 85% to 95% of GISTs, almost always resulting in ligand-independent activation (11). The mutations tend to cluster in 4 exons: exon 9 (extracellular domain), exon 11 (intracellular juxtamembrane domain), exon 13 (split kinase domain), and exon 17 (kinase activation loop) (11). Exon 11 mutations are the most common, representing 60% to 70% of the cases. Exon 9 mutations are present in 10% of cases and are associated with small-bowel location and a more aggressive clinical behavior. Exon 13 and 17 mutations are rare, each representing approximately 1% of GIST cases (11) (*Figure 5*).

Thus far *KIT* and *PDGFRA* mutations are thought to be mutually exclusive (11). Approximately 5% to 10% of GISTs harbor PDGFRA mutations involving exons 12, 14, and 18 (11). Akin to *KIT* mutations, *PDGFRA* mutations result in ligand-independent activation (11). Almost all *PDGFRA*-mutant GISTs have an epithelioid morphology and are found in the stomach. CD117 expression in *PDGFRA*-mutant tumors is often weak and focal or entirely negative (11). Approximately 5% of GISTs do not harbor either KIT or PDGFRA mutations and yet, can still be positive for CD117 by immunohistochemistry (11). These are known as "wild-type" GISTs.

Most GISTs are sporadic, however, small percentages

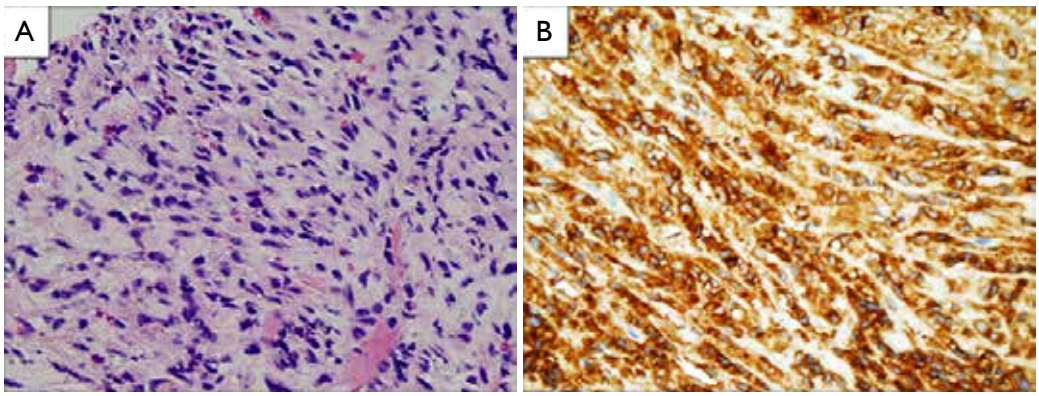

Figure 4 A. H&E stained section of gastric spindle cell GIST; B. By immunohistochemistry, the tumor cells are diffusely positive for CD117 with cytoplasmic and perinuclear staining (original magnification, 40×).

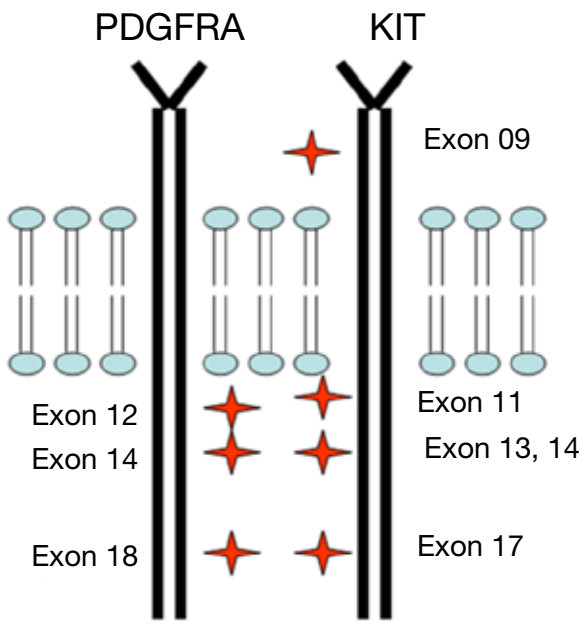

Figure 5 Schematic representation of KIT and platelet-derived growth factor receptor alpha (PDGFRA) molecules and the common KIT and PDGFA mutations in GIST. The mutation on the Kit gene at exon 11 is by far the most common cause of GIST.

(less than 5%) do occur in the rare GIST associated tumor syndromes: neurofibromatosis type 1 (NF1), Carney triad, and familial GIST syndrome (14). From the Armed Forces Institute of Pathology (AFIP) series, 6% of duodenal GISTs belong to patients with NF1 (14). Although NF1 patients can have GISTs elsewhere, the great majority occur in the small bowel in this population. The tumors are frequently multiple, small, and indolent with a low mitotic activity. However, NF1 patients can go on to develop malignant GISTs, which can be confused with malignant schwannomas if immunohistochemical studies are not carried out. Interestingly, GISTs in NF1 patients likely have a different pathogenic pathway, since they rarely if ever have the *c-kit* and PDGFRA mutations as seen in sporadic GISTs (16) (*Table 2*).

The Carney triad includes gastric GIST, paraganglioma, and pulmonary chondroma. These GISTs are usually epithelioid. They often occur in children and have a strong female predominance (85%) and the majority are indolent, even in the setting of metastatic disease (14).

Rare cases of familial GIST syndrome have been reported (14). Usually, they show autosomal dominant transmission of activating *KIT* or *PDGFRA* mutations. Patients with germline KIT or PDGFRA mutations have shown Cajal cell hyperplasia and progression to discrete GISTs (17). Tumors are typically multiple with biological behavior that varies from indolent to malignant. These individuals also develop cutaneous hyperpigmentation and mastocytosis (18). A study using PCR for clonality analysis showed that diffuse Cajal cell proliferations seen in these patients are polyclonal, whereas the GIST tumors are monoclonal (18). This suggests that additional genetic alterations are required before clonal expansion and malignant transformation can occur (14).

The therapeutic drug of choice for unresectable, metastatic, or recurrent GISTs is imatinib, a competitive antagonist of the ATP binding site of tyrosine kinases such as KIT, platelet growth factor receptors alpha and beta, ABL, and ABL-related gene product. It causes interruption of the downstream signaling process that leads to cellular proliferation. Ten to twenty percent of

Table 2 The incidence mutations of KIT and PDGFA in GIST		
cKit 85%	exon 11	common
	exon 9	aggressive
	exon 13	rare
	exon 14	rare
PDGRA 15%	exon 12	
	exon 14	
	exon 18	
Wild Type 5%		

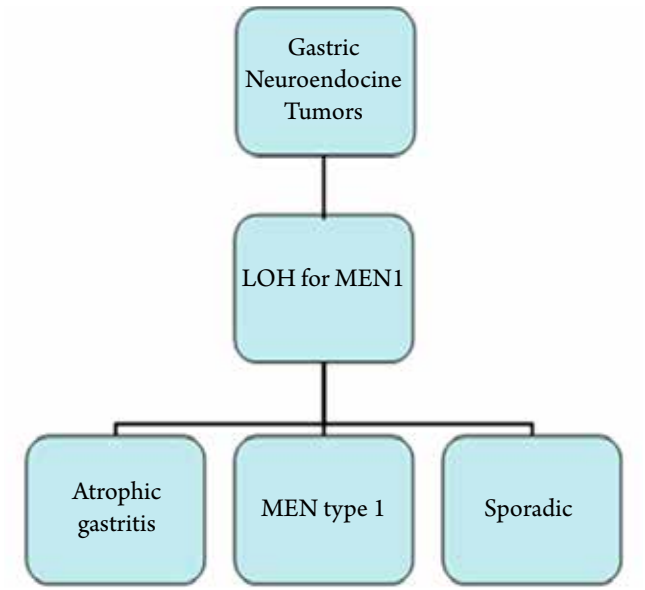

Figure 6 Molecular pathogenesis and classification of gastric neuroendocrine tumors.

GISTs exhibit resistance to imatinib (10). This resistance has been associated with selection of mutations that in some cases interrupt the binding site of imatinib (19). Patients with the Kit exon 9 mutations often require a higher dose of imatinib, often double the starting dose recommended for exon 11 mutants (10). Resistance is also thought to result from secondary mutations in the KIT and/or PDGFRA kinase domain. Several other inhibitors are being developed for resistant tumors. Surgery however, remains the only curative treatment for GISTs.

Molecular pathology of gastric neuroendocrine tumors

Gastric neuroendocrine tumors are being diagnosed with higher and higher frequency than previously reported (20). Some have ascribed this to more frequent endoscopies and more accurate diagnosis with immunohistochemistry markers (21). Gastric endocrine tumors make up to 20% of all gastroentero-pancreatic neuroendocrine tumors and 1% of gastric neoplasms (22). Gastric neuroendocrine tumors are thought to be local endodermally derived cells and not neural crest derived based on studies of chick-quail chimeras (23,24). Gastric carcinoids have often been classified in a tripartite system as follows: tumors associated with chronic atrophic gastritis; tumors associated with MEN type 1, and Zollinger-Ellison syndrome; and sporadic tumors (25).

There are many classifications of the neuroendocrine tumors. An older classification scheme, divided these tumors into foregut (stomach and first part of the duodenum), midgut (small intestine: second portion of duodenum, jejunum, ileum, appendix and ascending colon) and hindgut (transverse and descending colon and rectum) (26). Molecular studies actually show that NETs of foregut, midgut, and hindgut display different genetically distinct abnormalities (27).

Foregut NETs (stomach and duodenum) show frequent loss of heterozygosity (LOH) for the MEN1 gene and is currently thought to play an initial role in gastric neuorendocrine tumor genesis in both familial and sporadic cases (26). The protein product menin, a 610-amino acid protein, is predominately nuclear and involved in transcription regulation, genome stability and cell division (*Figure 6*) (28).

The WHO classification of endocrine tumors has divided NET into well differentiated endocrine tumors (benign or uncertain behavior), well differentiated endocrine carcinomas (low-grade malignant behavior) and poorly differentiated endocrine carcinoma (high-grade malignant behavior) (29). Studies have shown that malignant progression of NET is associated with complex allelotypes and chromosomal instability (30).

Interestingly, one study showed that 8 of 11 diffuse gastric cancer cases with signet ring cells express one or more neuroendocrine markers, a finding previously thought to be rare, showing that the greater proportion of signet ring cancer cells express specific general neuroendocrine markers, indicating a neuroendocrine origin (31). More extensive research into the genes involved in gastrointestinal NET tumorigenesis and the cellular roles of their protein products is still under investigation.

Surgery remains the primary method of cure in limited

disease (28). Multiple therapeutic options are available for metastatic disease including, surgery, ablation, and chemotherapy. However, cure is less likely and the therapeutic goal changes to extending survival, relieving symptoms, and improving quality of life. Approximately 80% of gastric NETs express somatostatin receptors, which can be targeted by octreotide and other somatostatin analogues (32). Although somatostatin analogues perform well with regards to symptom relief, their anti-neoplastic activity is thought to be minimal (28). A recent small study in patients with gastric neuroendocrine carcinoma reported promising results using the combination cisplatin and irinotecan (33).

Several receptors such as EGF, PDGF, IGF-1, and VEGF and downstream kinases like mTOR are known to be up-regulated in gastric and pancreatic NETs providing potential targets for personalized therapy (28). Clinical trials are already underway; unfortunately, most of these are in pancreatic NETs, which are known to have a different biology. Based on phase III evidence, mTOR inhibitor (Everolimus) has been approved by FDA for patients with metastatic pancreatic neuroendocrine tumors. More studies will be needed to know if the same results can be expected in gastric NETs.

Conclusions

The more we understand the different molecular pathways of tumorigenesis and progression to metastatic disease, the more accurate and effective we will become in tailoring targeted therapies. In the scope of new targeted cancer therapy approaches, molecular tests and new technologies that can analyze many genes simultaneously with high quality and cost-effectiveness are required to identify patients who will benefit from these therapies. The role of molecular pathology will only increase as clinicians and patients demand more novel diagnostic and prognostic information from the pathologist, which will ultimately allow for more personalized and effective therapy.

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Molecular therapy for gastric cancer

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Abstract: Several agents that target specific molecules have been investigated for the treatment of gastric cancer in many preclinical and clinical studies. Anti-HER2 antibody, when combined with classical cytotoxic agents, has been shown to confer a significant survival benefit in patients with HER2-positive gastric cancer. This is the only targeted drug that has been shown to be successful for the treatment of gastric cancer. We need to determine specific targets for regulating gastric cancer cells by translational research, develop precise diagnostic procedures for personalized medicine, and identify candidate drugs for gastric cancer.

Keywords: Gastric cancer; molecular therapy; anti-HER2 antibody; HER2-positive gastric cancer

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Introduction

Gastric cancer can be divided into two types: differentiated, which is intestinal type in Lauren's classification, and undifferentiated, which is diffuse type in Lauren's classification histologically (1,2). The pathological findings can generally be divided into two metastatic patterns: peritoneal dissemination and hematogenous spread to the liver or lungs. Many types of genetic or epigenetic alterations cause these diverse phenotypes of gastric cancer (3-9). Overexpression of human epidermal growth factor receptor (EGFR, HER1), HER2, and HER3 is commonly observed by immunohistochemistry (IHC). On the other hand, gene mutations in members of the HER family are rare in gastric cancer (*Figure 1*). In addition, gene mutations are not commonly observed for downstream signal-transducing molecules under membrane receptors. The frequency of KRAS mutations of codon 12 or 13 was 5%, that of PIK3CA mutations in exon 9 was 5%, and that of NRAS mutations of codon 12 or 13 was in 2% in primary gastric cancer.

HER family

HER2

The HER2 gene is amplified or its product is overexpressed in 10% to 22% of gastric cancers, and is associated with enhanced cell proliferation and survival (5). Patients who highly overexpressed HER2 by IHC accounted for 10% of gastric cancers (3). HER2 is not the worse prognostic factor in gastric cancer, as opposed to breast cancer. A recent global randomized trial (ToGA) showed that trastuzumab, a humanized anti-HER2 monoclonal antibody, was effective against HER2-positive gastric cancer (5). IHC3+ and/or FISH-positive, which was defined as a HER2:EP17 ratio of 2 or more, was considered to be "HER2-positive" in the ToGA trial. In that study, the IHC3+ rate was 11.0%, and the FISH-positive rate was 23.1%. Trastuzumab exerts its anticancer effects by inducing antibody-dependent cytotoxicity that inhibits HER2-mediated signaling, and by preventing cleavage of the extracellular domain of HER2. In ToGA, patients with HER2-positive gastric cancer were randomized to receive 5-fluorouracil or capecitabine and cisplatin with trastuzumab every 3 weeks for 6 cycles, or chemotherapy alone. Tumor specimens from 3,807 patients were centrally tested to determine the HER2 status: 22.1% were HER2-positive. The median survival time (MST) was significantly improved with trastuzumab plus chemotherapy compared to chemotherapy alone (13.5 *vs.* 11.1 months, respectively) (P=0.0048; HR 0.74, 95% CI, 0.60, 0.91). RR was 47.3% in the trastuzumab plus chemotherapy arm and

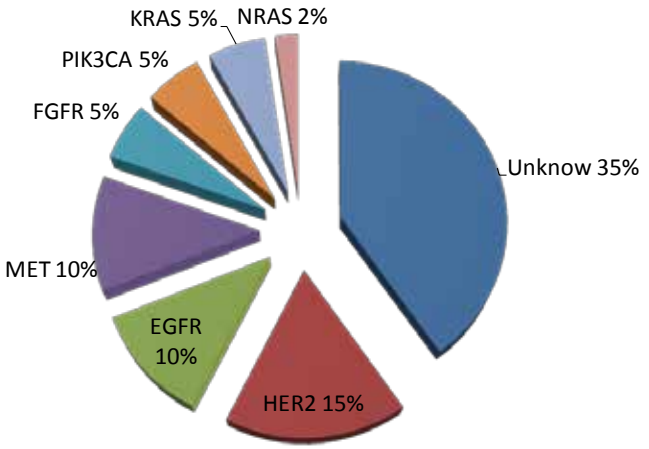

Figure 1 Estimated proportion of possible molecular targets in gastric cancer.

34.5% with chemotherapy alone (P=0.0017). The safety profiles in the two groups were similar, and there were no unexpected adverse events in the trastuzumab arm. There was no difference in symptomatic congestive heart failure between the two arms. Decreases in asymptomatic left ventricular ejection fraction were reported in 4.6% of patients in the trastuzumab combined arm and in 1.1% of those in the chemotherapy arm.

Lapatinib is a tyrosine kinase inhibitor (TKI) against HER2 and EGFR. A phase II study (10,11) evaluated first-line lapatinib monotherapy in 47 patients and reported modest activity. Only 3 patients (7%) had a confirmed partial response (PR) and 2 (5%) had an unconfirmed PR. Nine patients (20%) had stable disease (SD). The median time to treatment failure (TTF) was 2 months and MST was 5 months. Another trial reported no partial response in 21 evaluable patients who had been treated with multiple prior therapies (11). In this study, gastroesophageal cancer patients were selected for EGFR-positivity using IHC and/or for HER2-positivity by FISH. Two patients had durable stable disease with 1,000 mg lapatinib, which lasted for 37 and 16 weeks. Multivariate proportional hazards modeling of IHC biomarkers revealed that higher levels of TGF-α were associated with a shorter TTP (P<0.05). Two phase III studies are currently underway for the development of second-line and first-line therapies (12,13). TYTAN is a randomized phase III study that is comparing paclitaxel with or without lapatinib as a second-line therapy in patients with HER2 FISH-amplified gastric cancer. The primary endpoint is overall survival and 260 patients will be enrolled (12). The LOGiC trial is comparing capecitabine and oxaliplatin with or without lapatinib as a first-line therapy in patients with advanced gastric cancer with HER2 amplification by FISH. The primary endpoint is overall survival (13). The results will be reported in the near future.

T-DM1, which is a three-part immunoconjugate consisting of trastuzumab, a stable linker, and the potent maytansine derivative DM-1 combines the antitumor activity of trastuzumab with the ability to deliver a microtubule-disrupting cytotoxic agent specifically to antigen-expressing tumor cells. In the phase III study EMILIA, T-DM1 was shown to be effective for advanced HER2-positive breast cancer (14). Pertuzumab inhibits the dimerization of HER2, and suppresses multiple HER signaling pathways, which leads to a more comprehensive blockade of HER2-drivensignaling (15). In the phase III study CLEOPATRA, pertuzumab plus trastuzumab and docetaxel combination therapy conferred a survival benefit compared with trastuzumab and docetaxel for HER2-positive breast cancer (16). These two drugs may also be promising for the treatment of HER2-positive gastric cancer.

EGFR

The overexpression of EGFR occurs in 58-86% of gastric adenocarcinomas (3,17-19). Patients that highly overexpressed EGFR by IHC accounted for 24% of gastric cancers. The prognostic value of EGFR is controversial. A phase II study for gastric cancer was carried out using gefitinib, a TKI of the EGFR, but the expected therapeutic outcome was not achieved (17,18). The response rate was 0% and 18% of the patients showed stable disease (17). In another phase II trial with erlotinib, the response rate was only 9% in patients who had esophago-gastric junctional cancer (18).

Monotherapy with cetuximab, a chimeric anti-EGFR monoclonal antibody, did not induce a response in gastric cancer patients (19). In phase II studies, cetuximab plus first-line fluoropyrimidine with irinotecan or platinum compounds has shown promising activity (20,21). The results of a randomized controlled phase III study of capecitabine and cisplatin (XP) with or without cetuximab in gastric and gastroesophageal junction cancer have recently been reported (22). Nine hundred four patients were randomized to 3-week cycles of twice-daily (days 1-15) capecitabine at a dose of 1,000 mg/m^2 and iv cisplatin 80 mg/m^2 on day 1 every 3 weeks, and weekly cetuximab 400 mg/m^2 followed by 250 mg/m^2/week, or chemotherapy alone. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, best overall response, and

safety. The median PFS was 4.4 months (95% CI, 4.2-5.5 months) in the cetuximab arm and 5.6 (5.1-5.7) in the XP arm (HR 1.091, 95% CI, 0.920-1.292; P=0.3158). The MST was 9.4 months (95% CI, 8.3-10.6 months) in the cetuximab arm and 10.7 (9.4-11.3) in the XP arm (HR 1.004, 95% CI, 0.866-1.165; P=0.9547). The RR was 30% with cetuximab and 29% with chemotherapy. XP plus cetuximab showed no benefit compared to XP alone in the first-line treatment of advanced gastric cancer.

The REAL-3 trial evaluated the addition of panitumumab, a fully human anti-EGFR monoclonal antibody, to epirubicin, oxaliplatin and capecitabine (EOC) in advanced esophagogastric cancer (23). Five hundred fifty-three patients were randomised to receive EOC, epirubicin 50 mg/m^2, oxaliplatin 130 mg/m^2, and capecitabine 1,250 mg/m^2/day, or mEOC, epirubicin 50 mg/m^2, oxaliplatin 100 mg/m^2, capecitabine 1,000 mg/m^2/day, and panitumumab 9 mg/kg. The primary endpoint was overall survival. The secondary endpoints were PFS, RR, and safety. The MST was 11.3 months with EOC compared to 8.8 months with mEOC plus panitumumab (HR 1.37, 95% CI, 1.07-1.76; P=0.013). The median PFS was 7.4 and 6.0 months, respectively (HR 1.22, 95% CI, 0.98-1.52; P=0.068), with the RR was 42% and 46%. Multivariate analysis demonstrated that *KRAS* mutation (HR 2.1: 95% CI, 1.10-4.05, P=0.025) and *PIK3CA* mutation (HR 3.2: 95% CI, 1.01-10.40, P=0.048) each had negative prognostic value. These results suggest that an EGFR-targeted agent alone is not effective in all patients with gastric cancer.

Nimotuzumab is a humanized monoclonal IgG_1 antibody against human EGFR. In a randomized phase II trial, patients received nimotuzumab plus irinotecan or irinotecan alone as a second-line therapy (24). The primary endpoint was PFS. Median PFS was 73 and 85 days, respectively (HR 0.860, 95% CI, 0.516-1.435; P=0.5668). The MST was 250.5 and 232 days in the nimotuzumab and irinotecan monotherapy groups, respectively (HR 0.994, 95% CI, 0.618-1.599; P=0.9778). The RR was 18.4% and 10.3%, respectively. A subset analysis of EGFR 2+ or 3+ patients by IHC revealed a median PFS of 118.5 and 59.0 days in the nimotuzumab and irinotecan monotherapy groups, respectively. On the other hand, a shorter median PFS was observed in EGFR 0 or 1+ patients (58.5 and 87.5 days). Nimotuzumab might show some activity in EGFR 2+, 3+ patients.

HER3

HER3 is a key dimerization partner for of the HER family that activates oncogenic signaling pathways to lead to cell survival and proliferation (25,26). Acquired resistance to anti-EGFR inhibitors may result from the activation of HER3 and/or HER2, which share overlapping signaling pathways. U3-1287 is a fully human anti-HER3 monoclonal antibody that has been shown to exhibit anticancer activity in preclinical models. In a Japanese phase I trial, it was shown to be tolerable up to 20 mg/kg. No DLTs were observed. U3-1287-related adverse events included an increase in ALT in 3 patients, and increases in thrombocytopenia, diarrhea, stomatitis, cheilitis, rash, and AST in 2 patients each (26).

c-MET/HGF

The *MET* proto-oncogene encodes the receptor (MET) of hepatocyte growth factor (HGF), and its amplification is observed only in advanced cancer; i.e., 19% in well-differentiated adenocarcinoma but as high as 39% in scirrhous gastric cancer (27-29). The activation of *MET* suppresses apoptosis and promotes tumor cell survival, gene transcription, angiogenesis, cellular proliferation, migration, mitosis, and differentiation. In gastric cancer, the activation of *MET* has reportedly been attributed to gene amplification (4-6). The results of a phase II study of foretinib, which inhibits several kinases including c-MET, VEGFR-2, PDGFR, RON, KIT, and TIE2, in poorly differentiated gastric cancer have been reported (30). The primary endpoint was RR. *MET* amplification, as determined by FISH of archival tissue, was defined as at least three copies of 7q31 including both a high level of gene amplification and a low level of aneuploidy of chromosome 7. Three of 64 (4.7%) patients showed high-level *MET* gene amplification. One of these three highly amplified *MET* showed SD, and the other two showed progressive disease. *MET* gene amplification is not observed solely in the poorly differentiated type. The RR was 0% with foretinib on a schedule of 5 days on/9 days off. Plasma levels of shed MET and VEGF-A tended to increase during the treatment periods compared with the drug holidays, and may reflect biological changes following foretinib (31). Tivantinib is a selective, non-ATP competitive, MET inhibitor (32). No objective response was observed, and the SD rate was 36.7% in a phase II study with tivantinib monotherapy against previously treated gastric cancer. The median PFS was only 43 (95% CI, 29-92) days. No obvious relationship was seen between outcomes and *MET* gene amplification, c-MET or HGF expression in tumor and serum. Four patients with *MET* gene amplification showed SD and PD (n=2 each).

The histologic type in one of the four amplified patients was poorly to moderately differentiated adenocarcinoma, and the others were moderately differentiated adenocarcinoma.

Rilotumumab (AMG 102) is a fully human IgG2 monoclonal antibody to HGF. A placebo-controlled randomized phase 2 study of epirubicin, cisplatin, and capecitabine (ECX) with or without rilotumumab in gastric and esophago-gastric junctional cancer showed promising results (33). Chemo-naïve patients were randomized 1:1:1 to receive ECX (50 mg/m^2 iv day 1, 60 mg/m^2 iv day 1, 625 mg/m^2 bid orally days 1-21, respectively) plus rilotumumab 15 mg/kg (Arm A), rilotumumab 7.5 mg/kg (Arm B), or placebo (Arm C) iv on day 1 every 3 weeks. MET protein was measured in archival tumor samples by IHC. Overall survival and PFS were evaluated. The MST was 10.6 months (95% CI, 9.5-12.0 months) in Arms A+B compared to 8.9 months (95% CI, 5.7-10.6 months) in Arm C (HR 0.70, 95% CI, 0.45-1.09). The median PFS was 5.7 and 4.2 months, respectively (HR 0.60, 95% CI, 0.39-0.91). The MST in MET-positive patients by immunohistochemistry was 11.5 months (n=27; 95% CI, 9.2-12.1 months) in Arms A+B compared to 5.7 months (n=11, 95% CI, 4.5-10.4) in Arm C (HR 0.34, 95% CI, 0.15-0.78). The median PFS was 6.9 and 4.4 months, respectively (HR 0.44, 95% CI, 0.20-0.96). A planned phase III study will test the efficacy of rilotumumab plus ECX in MET-positive gastric cancer. MetMAb is a monoclonal monovalent antibody to MET (34). A 48-year-old woman with advanced gastric cancer was treated with MetMAb at a dose of 20 mg/kg as part of a phase I study and experienced CR after 3 months from the beginning of MetMAb, which lasted approximately 2 years. She then progressed with new lesions in her peritoneum. The histology was poorly differentiated adenocarcinoma with signet ring cell components. An analysis of the *MET* copy number of primary gastric tumors revealed high polysomy and MET protein expression by IHC.

Patients with an increase in the *MET* copy number of 5< accounted for 10% (21/216), and showed a significantly worse prognosis with a multivariate hazard ratio of 2.91 for overall survival (28). In another report, 10 of 489 (2%) patients harbored *MET* amplification. The highest frequency of MET positivity was observed in esophago-gastric junctional tumors (3%, 3/97). Two of 4 four patients with *MET*-amplified tumors who were treated with crizotinib showed tumor shrinkage of 30% and 16%, and PFS of 3.7 and 3.5 months, respectively (29). Few patients with gastric cancer show *MET* amplification, and the efficacy of TKI of MET was quite limited. The preliminary effects of antibodies to MET or HGF have been reported in *MET*-amplified gastric cancer.

VEGFR/VEGF

Tumor angiogenesis through vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) signaling is involved in the progression of gastric cancer (35-37). VEGF-R2 is a potent regulator of vascular endothelial cells and has been directly linked to tumor angiogenesis and blood vessel-dependent metastasis. On the other hand, VEGF-R1 may contribute to pathological vascularization directly by stimulating endothelial cell function and indirectly by mediating the recruitment of bone marrow progenitor cells. Several studies have found that the expression of VEGF ligands and subtypes is correlated with the prognosis in gastric cancer (36,37) and the expression of soluble VEGF-R1 also predicts the prognosis (38). Hirashima *et al*. analyzed VEGF-R expression levels in primary tumors from 86 patients with advanced gastric cancer, and reported that the expression of VEGF-R1, 2 and 3 in stromal vessels in primary gastric tumors significantly predicted poor survival (35).

Multi-targeted TKIs like sunitinib were generally ineffective against gastric cancer in a phase II study in gastric cancer. The RR was 2.6% (2/78) in a phase II study of sunitinib monotherapy as second-line treatment (39). Twenty-five of 78 patients (32.1%) had SD, and 4 (5.1%) experienced SD that lasted more than 24 weeks. The median PFS was 2.3 months. In another German phase II trial with sunitinib monotherapy for chemo-refractory patients, the response rate was 3.9%, with a median PFS of 1.28 months (40). Tumor VEGF-C expression, which combines VEGFR-2 and 3, compared with no expression, was associated with a significantly shorter median PFS (1.23 *vs*. 2.86 months; P=0.019), however, there was no difference in the tumor control rate (P=0.142) (40). Sunitinib had an antiproliferative effect in gastric cancer cell lines with high PDGFRA expression (41).

Cediranib and sorafenib are also multi-target TKIs. Both agents were combined with cisplatin plus S-1 or capecitabine, which is a standard first-line treatment for gastric cancer (42,43). The most common adverse events were neutropenia, anorexia, nausea, fatigue, diarrhea, and hand-foot syndrome. The results of these combination studies were not so promising compared with chemotherapy alone with contiguous non-hematologic toxicities in a first-line setting.

AVAGAST and AVATAR were randomized placebo-controlled trials that were designed to evaluate the efficacy of adding bevacizumab to capecitabine or fluorouracil plus cisplatin in first-line treatment against advanced gastric cancer (44,45). The primary endpoint was overall survival, and 774 patients were enrolled. The MST was 12.1 months with bevacizumab plus fluoropyrimidine and cisplatin (FP) and 10.1 months with placebo plus FP (HR 0.87, 95% CI, 0.73-1.03; P=0.1002). The median PFS (6.7 *vs.* 5.3 months, HR 0.80, 95% CI, 0.68-0.93; P=0.0037) and RR (46.0% *vs.* 37.4%, P=0.0315) were both significantly improved with bevacizumab versus placebo. Although AVAGAST did not reach its primary endpoint, some anti-angiogenic activity was suggested with the addition of bevacizumab to chemotherapy, which was associated with significant increases in PFS and RR in the first-line treatment of advanced gastric cancer. Low tumor neuropilin-1 expression was associated with shorter overall survival in placebo-treated patients (46). The addition of BV seems to produce a survival benefit; patients with low tumor neuropilin-1 expression had OS treatment hazard ratio values that were better than those in patients with high neuropilin-1 expression.

Ramucirumab is a fully human IgG1 antibody to VEGFR2. A randomized phase III study of ramucirumab plus paclitaxel versus paclitaxel monotherapy as second-line treatment is ongoing (47).

FGFR

Fibroblast growth factor receptor (FGFR) 2 gene amplification in gastric cancer cell lines confers hypersensitivity to FGFR inhibitors. A copy number assay and FISH analysis revealed that 5% (7/152) of gastric cancers harbored *FGFR2* amplification; histologically, five patients had diffuse type and two had intestinal type (48). The amplification of *FGFR1*, *3* and *4* was not detected. A FISH analysis showed that six of the seven tumors were highly amplified, while the remaining tumor had a relatively low grade of amplification. Patients with *FGFR2* amplification tended to exhibit a shorter overall survival period. *FGFR2* gene amplification is almost entirely mutually exclusive with *HER2* and *MET* gene amplification. Cediranib exerted potent antitumor activity against gastric cancer xenografts overexpressing FGFR2. AZD4547 is a pan-FGFR TKI that is under clinical development (49).

IGFR

Insulin-like growth factor type 1 receptor (IGF-1R) is a cell membrane receptor that is activated by its ligands, IGF-1 and IGF-2 (50). IGF-1R participates in cell proliferation, differentiation, and the prevention of apoptosis. Since IGF-1R is also involved in malignant transformation the development of IGF-1R-directed cancer therapy has been initiated. IGF-1R is frequently overexpressed in human cancers, and the association between IGF-1R expression and outcomes has been assessed for breast cancer and other solid tumors. Patients who highly overexpressed IGF-1R by IHC accounted for 29% (25/87) of gastric cancers: 40% (16/40) of intestinal type and 19% (9/47) of diffuse type (3). About 30 agents that target the IGF-IR have been investigated, including the anti-IGF-IR antibodies IMC-A12, AMG-479, AVE1642, BIIB022, CP-751871, MK0646, and Sch717454, and the small-molecule inhibitors OSI-906 and XL228 (50).

mTOR

Everolimus is an oral inhibitor of the mammalian target of rapamycin serine-threonine kinase. A downstream component of the PI3K-AKT signaling pathway is deregulated in gastric cancer cells and everolimus has shown anti-cancer effects in both *in vitro* and *in vivo* models of gastric cancer (51). No objective responses were observed in phase II of everolimus monotherapy for previously treated patients with gastric cancer. The PD rate was 45% (24/53) and the median PFS was 83 days (95% CI, 50-91 days) (52). Everolimus did not show a significant survival benefit compared with best supportive care (BSC) in previously treated patients with advanced gastric cancer in a subsequent phase III trial. The MST was 5.39 months with everolimus and 4.34 months with BSC (HR 0.90, 95% CI, 0.75-1.08; P=0.1244) (53).

Conclusions

The outcomes of future clinical trials in gastric cancer should improve with advances in diagnostic technology to help us identify the right agents for specific targets.

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Palliative radiation therapy for primary gastric melanoma

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Introduction: Primary gastric melanoma is an exceedingly rare cause of upper gastrointestinal bleeding (GI bleeding). Prior reports of primary gastric melanoma have mostly been treated with surgery with utilization of radiation therapy being unreported. Radiation therapy has been used to palliate bleeding of other cancers including lung, bladder, cervix, and more recently primary gastric cancers.

Case presentation: This case documents an 87-year-old male who presented with fatigue and melena, and was found to have severe anemia. Endoscopy with biopsy revealed an isolated focus of melanoma. After discharge, he presented two days later and was found to have continued bleeding. Because he was deemed a poor surgical candidate he elected to undergo palliative radiation therapy for bleeding control.

Discussion: The diagnosis of primary verses metastatic melanoma is a topic of debate. Case reports of patients with no known extra-gastric primary have undergone surgical treatment with varying outcomes. Patients with metastatic gastric melanoma have relied on chemotherapy and radiation in addition to surgery, with radiation being used in the palliative setting. The use of radiation to control bleeding in other cancers including primary gastric adenocarcinoma has been previously studied. This case documents the utilization of radiation therapy in bleeding due to primary gastric melanoma.

Conclusions: Radiation therapy can provide adequate bleeding palliation in patients with primary gastric melanoma.

Keywords: Palliation; radiation therapy; gastric melanoma

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Introduction

Malignant melanoma is known to metastasize to visceral organs with the gastrointestinal tract (GI tract) being one of the more common sites (1). Less common, however, is primary malignant melanoma of the GI tract. Gastric melanoma can often present with vague symptoms; however, a more alarming presentation is that of an upper gastrointestinal bleeding (GI bleeding) (2,3). Case reports of primary gastric melanoma, presenting with upper GI bleeding or otherwise, have demonstrated surgery as the primary method of treatment (2-9), while the utility of radiation in the management of primary gastric melanoma has been unreported. Radiation therapy has been known to palliate bleeding of cancers of the lung, bladder and cervix (10-13), and more recently palliation of bleeding to primary gastric adenocarcinoma has been studied (14-17). The role of radiation therapy in patients with bleeding secondary to primary gastric melanoma has not yet been defined. We report a case of gastric melanoma with no identifiable cutaneous primary, treated with palliative radiation therapy for control of bleeding.

Case presentation

An 87-year-old Hispanic male presented at an outside institution with a one month history of fatigue, 10-pound weight loss, and melena. He was found to have severe anemia (Hgb 6.7) requiring transfusion. Initial CT of the abdomen and pelvis showed a possible gastric mass. Esophagogastroduodenoscopy (EGD) was performed revealing an 8 cm pedunculated mass at the greater

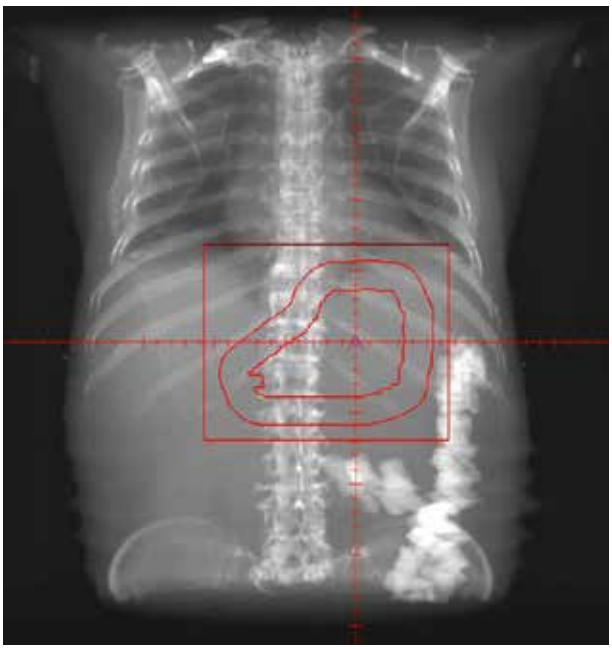

Figure 1 Beam's eye view of the gastric melanoma target on AP X-ray.

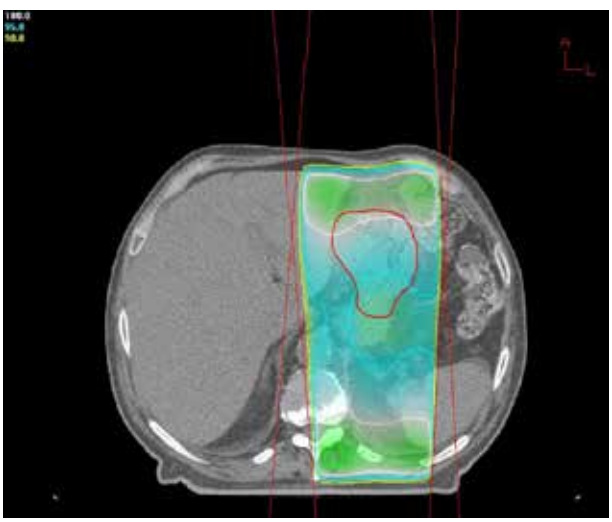

Figure 2 Axial image of AP and PA X-ray beams treating the gastric melanoma.

curvature of the stomach, partly black, partly green, partly white. Endoscopic ultrasound showed an isohypoechoic heterogenous mass with visible stalk. Biopsies were taken and showed extensive, ulcerated, poorly-differentiated spindle and epithelioid cell tumor with immunohistochemistry positive for S100 and Melan-A, negative for CD117, AE1/AE3, CDX2, and BRAF mutation negative. The diagnosis of gastric malignant melanoma was made and the patient was scheduled to be seen by a surgical oncologist.

Two days after discharge from the outside facility, he presented to our institution with worsening fatigue and melena, his hemoglobin on presentation was 7.8. His bleeding was controlled and he underwent at PET/CT scan, dermatologic physical exam and ophthalmologic exam to evaluate for a primary melanoma. Dermatologic and ophthalmologic exam did not reveal a primary, PET/CT was only positive for a gastric mass with an SUV of 17. He was diagnosed with T4N0M0 Stage IIB primary gastric melanoma.

Due to the patient's age and functional status, he was deemed unresectable and was offered palliative radiotherapy to control bleeding and anemia. He received a dose of 16 Gy to the stomach in four fractions. Following this treatment he remained hemodynamically stable for four months; at that time he presented to the emergency department with worsening fatigue, complete blood count revealed a hemoglobin of 7.0 and patient underwent further transfusion. He was offered a second course of palliative radiotherapy during which he received an additional 9 Gy to the stomach in three fractions (*Figures 1,2*). At the time of this writing he has tolerated his second course of therapy without complication.

Discussion

This case documents upper GI bleeding as a clinical presentation for primary gastric melanoma, a presentation that has been documented previously (2,3); other unique presentations of primary gastric melanoma include a non-healing ulcer with benign mucosa on initial biopsy (4), and progressive axilla swelling (18). Literature review of other cases of primary gastric melanoma and metastatic gastric melanoma reveals that the presentation is often vague with nonspecific symptoms of anorexia, dysphagia, nausea, vomiting, epigastric pain, fatigue, and weight loss (5-7,9,19,20). The vague symptoms and nonspecific resentation of gastric melanoma can lead to a delay in diagnosis.

There is still significant controversy surrounding even the diagnosis of primary malignant melanoma of the GI tract. Arguments in support of the idea that GI melanomas are metastatic lesions even in the absence of a primary are based on the natural history of melanoma. The fact that the GI tract is the most common site of metastases of cutaneous melanoma (21) and that the stomach epithelium is devoid of melanocytes is the foundational argument supporting

the assertion that all gastric melanoma is metastatic (4,8). Additionally, several cases of spontaneous regression of a primary cutaneous melanoma with subsequent visceral and nodal metastases have been reported (22,23). An autopsy study on small bowel melanoma concluded that even in the absence of a known primary, small bowel melanoma most likely represents metastatic disease (24). Alternative explanations that argue for the development of primary GI melanomas include the migration of neural crest cells through the omphalomesenteric canal (an explanation that is applicable to melanoma of the ileum only) (25), and the neoplastic transformation of APUD cells (amine precursor uptake and decarboxylation cells) in noncutaneous sites (26,27).

The lack of clarity of GI melanoma pathogenesis has led to the development of criteria for diagnosing a primary GI malignant melanoma. These include: no concurrent or prior excision of melanoma or atypical melanotic lesion from the skin, lack of involvement of other organs, lack of in situ change in overlying or adjacent GI epithelium, and 12 month disease-free survival after diagnosis (28).

Management of primary gastric melanoma is primarily surgical. A review of nine cases of gastric melanoma in which no known extra-gastric primary was identified reveals that eight of the nine cases were treated with surgery. Three of the cases were treated with partial gastrectomy and splenectomy (2,4,6), two cases were treated with partial gastrectomy alone (5,8), one with total gastrectomy (7), one with gastrectomy, pancreatectomy, splenectomy, and transverse colectomy (9), and one stated to be "palliative resection" (3). Only one case was treated with adjuvant therapy and that patient received 12 months of adjuvant interferon (4). The primary gastric melanoma case that was not treated surgically was treated with dacarbazine and cisplatin-based chemo due to peripancreatic and axillary nodal metastases (18).

Those with no identifiable primary lesion had variable outcomes. In the case treated with partial gastrectomy and splenectomy followed by 12 months of adjuvant interferon, the patient showed no evidence of disease on EGD two years post-operative (4). Another case treated with partial gastrectomy and splenectomy showed a similar outcome with the patient being disease free at 16 months post-op (6), and one case reported patient survival with no evidence of disease at five years post-total gastrectomy (7). Of the surgical cases with poorer outcomes, one patient with comorbid dermatomyositis died due to post-operative complications following a partial gastrectomy (5), one patient succumbed to metastases 12 months following a distal gastrectomy (8), and another patient died 11 months post-operative following a gastrectomy, pancreatectomy, splenectomy, and transverse colectomy for a locally invasive gastric melanoma (9). Two cases were lost to follow up (2,3).

In contrast to the surgery-based management of gastric melanoma with no known primary, chemotherapy and radiation therapy play a larger role gastric melanoma with a known extra-gastric primary. One case of metastatic gastric melanoma was treated with a wedge resection of the cardia, but the patient ultimately underwent palliative whole brain radiation for recurrent metastases (29). In another case the patient received neoadjuvant temozolomide chemotherapy followed by a wedge resection of the stomach (29). Three other cases of metastatic gastric melanoma were managed with chemotherapy alone, one reported controlled disease after one course of dacarbazine, nimustine, and cisplatin (30), and two other reports did not state which chemotherapy agents were used (19,31).

Radiation therapy has been used to control bleeding in a variety of cancers. Studies have shown radiation therapy to be beneficial in controlling hemoptysis in lung cancer, hematuria in bladder cancer, and vaginal bleeding in cervical cancer (10-13), more recently studies on radiation therapy to treat gastric bleeding have been reported. One retrospective study demonstrated a 54% response to bleeding in patients with locally advanced or recurrent gastric cancer who were treated with radiation therapy alone (17). Another retrospective study demonstrated a 70% response to bleeding in patients who received radiation therapy with or without concurrent chemotherapy (16).

Subsequent studies have focused on the effects of radiation dose in symptomatic palliation. A 2009 retrospective study showed that patients with bleeding from primary gastric cancer who received a dose of greater than or equal to 40 Gy in 16 fractions have statistically significant improvement in control of bleeding compared to those who received less than 40 Gy in 16 fractions (15). Most recently a study on patients who received 30 Gy in 10 fractions showed a 73% hemostasis rate. Additionally this study demonstrated that those treated with chemotherapy and radiation had a significant longer time to rebleeding when compared to those who received radiation therapy alone (14).

The case presented marks the first use of standalone radiation therapy as a palliative therapy for persistent upper GI bleeding secondary to primary gastric melanoma. In the case presented, palliative radiation therapy of 16 Gy in four fractions provided four months of symptomatic relief. In addition, the patient tolerated a second course of therapy of

9 Gy in three fractions for his rebleeding and is currently asymptomatic.

In conclusion, malignant melanoma of the stomach with no identifiable extra-gastric primary is a rare occurrence with surgery being the current mainstay of therapy. In symptomatic patients who are poor surgical candidates, palliative radiation therapy can provide symptomatic relief and improve quality of life.

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Research on microRNAs leads to new frontiers of clinical and translational relevance for gastric cancer management

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Abstract: Over the past few years several studies correlated the aberrant profile of small non-coding RNAs (microRNAs) with the occurrence of a number of human malignancies, including gastric cancer. Extensive evidence showed that microRNAs play an important role in the regulation of gene expression binding the 3'UTR of the mRNA target. Moreover, microRNAs are involved in the execution of important biological processes ranging from cell growth and cell cycle to apoptosis, cell migration, cellular senescence and chemoresistance. On the same extent, microRNAs' profiling of cancerous tissues represents a new frontier for the identification of novel molecular biomarkers useful for the early neoplastic detection, the clinical monitoring and the prognosis assessment. In this article we highlighted and commented on the original findings recently provided by Tang and colleagues on the miR-200b and miR-200c involvement in gastric tumorigenesis. The expression of these two tumor suppressor microRNAs impacts on the DNA methylation process and restores the expression of important oncosoppressors genes previously silenced. These findings disclose new features of miRNAs' involvement in gastric tumorigenesis and provide evidences of their role as prognostic and diagnostic biomarkers. This also prospects the potential use of demethylating agents for new clinical and therapeutic strategies.

Keywords: miRNA, gastric cancer, methylation, chemoresistance

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The microRNAs (miRNAs) are a new field of ongoing cancer research, motivating the enthusiasms of scientists from all over the world. It is our opinion that the recent paper by Tang *et al*., published by the journal *Clinical Cancer Research* represents an excellent evidence of this paradigm (1). miRNAs are small non-coding RNAs controlling gene expression that were initially discovered in 1993 in the nematode Caenorhabditis elegans (2).

Since then, the miRNAs were the objective of an increasing number of investigations; the first evidence of their involvement in human cancers was provided in 2002 with the studies conducted by Croce *et al*., on the chronic lymphocytic leukemia (3). Henceforward, several authors investigated the miRNAs expression through microarray or PCR analyses in different cancerous tissues and cell lines. Indeed, over the last few years, the assessment of miRNAs has been characterized by the definition of their profile and their targets in serum and different normal and cancerous tissues.

In this field, Volinia and colleagues conducted a large genomic analysis investigating several gastrointestinal (GI) cancers (including stomach, pancreas and colon cancers) and documented the miRNAs' profiling as cancer-specific. According to their results, GI cancers seemed to have a distinct miRNA's signature comparing with non-GI cancers as e.g., lung or breast neoplasms (4).

In addition, the miRNAs' signatures have been documented as tissue-specific as they could identify the specific cancer tissue from where they originated, and thus specifically classify those GI cancers derived e.g., from the stomach versus liver,

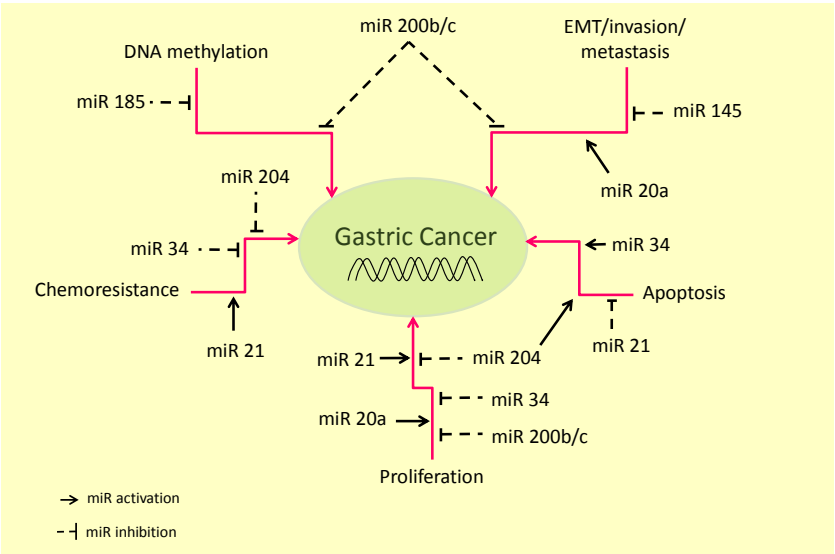

Figure 1 Schematic representation of principal pathways and selective miRs implicated in gastric cancer transformation. The figure shows principal pathways involved in gastric cancer development and selective microRNAs that promote or inhibit protein target implicated in DNA methylation, EMT/invasion/metastasis, apoptosis, proliferation and chemoresistance. miR, microRNA; EMT, epithelial-to-mesenchymal transition.

esophagus, colon or pancreas (5). Furthermore, the aberrant miRNAs' expression profile has been documented as correlated with the occurrence, the development, and the prognosis of GI cancers (4).

The study of miRNAs, however, usually involves the assessment of their molecular targets that are implicated in many important biological processes ranging from cell growth, to cell cycle, apoptosis, cell migration, senescence and chemoresistance (*Figure 1*). As miRNAs have multiple targets, their function in tumorigenesis could be either correlated to the regulation of a few or a number of specific targets and thus, specific pathways associated to cancer development (6).

Target-prediction algorithms can be used to identify the mRNA targets on the basis of (I) the complementarity between the mature miRNA's sequence and the target; (II) the binding energy of the complex miRNA-target duplex; (III) the evolutionary conservation of the target site sequences and position in aligned UTRs of homologous genes (7).

However, this process has to be experimentally validated in order to eliminate the false positives, since the number of predicted sites is usually very large (6).

Intriguingly, also the identification of miRNAs' targets involved in cancer and contributing to the malignant transformation could characterize different pathways that control miRNAs' aberrant expression.

Nevertheless, if miRNA targets are crucial for the expression of the malignant phenotype and the cancer cells depend on target disregulation for proliferation and survival, we could expect that the use of miRNAs or anti-miRNAs molecules will lead to tumour regression (6).

In fact, as over the last few years we observed a shift from conventional chemotherapy to targeted therapies, we could speculate that miRNAs and anti-miRNAs will contribute in a short future to the development of advanced tailored therapies (6).

On the basis of this solid background, it seems clear that the characterization of miRNAs' signature in the neoplastic tissues and in the serum samples of cancer patients might lead to new frontiers of high translational impact. This includes the early neoplastic detection, the clinical monitoring, the management of the prognosis, and possibly the development of new gene-based therapies or agents able to overcome the chemoresistance.

The identification of miRNAs' signature associated with gastric cancer is nowadays a field of ongoing and intense research.

Gastric cancer is the 4th most common cancer worldwide (8), with more than 70% of cases occurring in the developing countries. Gastric carcinogenesis is a multistep process that involves many environmental and genetic factors, including the infection by Helicobacter pylori, as well as other genetic,

dietary, chronic gastric inflammation-causing factors.

Recently, aberrant miRNAs' expression has been associated with gastric carcinogenesis (9); indeed, several authors investigated the aberrant miRNA's profiling (over-expression *vs*. down-regulation) in different types of gastric tumors and at different stages (*Figure 1*).

We recently profiled the expression of 851 human miRNAs in gastric tumours tissues and their matched peri-tumoural samples. This led to the identification of miRNA-204 as statistically and significantly down-regulated in cancerous tissues. According to our results, the down-regulation of miRNA204 was associated with the T stage of disease, since patients presenting a T1 stage displayed a lower down-regulation comparing to those with more advanced stage. On the basis of this background miRNA-204 might be used as a molecular biomarker for gastric cancer staging. The combination of the hysto-pathological (TNM) and molecular features (including e.g., miRNA204, Bcl-2, p53 status, ErbB2, c-myc) might strongly contribute to an accurate molecular profiling of gastric tumours (10).

As mentioned before, several mechanisms contribute to miRNAs' aberrant expression during carcinogenesis, including genetic mutations, epigenetic silencing and a deregulated transcriptional activity.

It has been observed that several miRNAs could constitute a cluster of 2-7 genes controlled by the same regulatory sequences and whose expression might be highly similar (11); these different miRNAs could be considered altogether and investigated also as a family of interrelated non-coding RNAs.

One of the most investigated miRNA families is that of the miRNA200 which comprises five members (miRNA200a, miRNA200b, miRNA200c, miRNA141, and miRNA429) clustered and expressed as two separate polycistronic pre-miRNA transcripts; precisely the miRNA200b-200a-429 cluster is located at 1p36 and miRNA200c-141 cluster at chromosomal location 12p13.

Previous evidence has shown that the miRNA200 family is an important regulator of the epithelial-to-mesenchymal transition (EMT) system; the EMT has been described as a part of the embryonic development, but it has been also documented during the carcinogenesis process, when cancer cells shift from a differentiated to a more invasive and undifferentiated shape.

After EMT induction, cells loose the epithelial feature, acquire the flattened/mesenchymal characteristics (including vimentin filaments) and an invasive phenotype (by the expression of proteases which allow migration) and thus displaying all those crucial steps towards the metastatization process (12).

Because of their influence on the EMT process, the miRNA200 family has been recognized with a tumor suppressive role in a wide range of cancers, including breast (13), colorectal (14) pancreatic (14) and endometrial carcinomas (15); to date, however, its role in gastric cancer remains undefined.

The study presented from Tang and colleagues on "*Clinical Cancer Research*" analyzed the level of expression of miRNA200b and miRNA200c in 126 gastric cancer tissues and in adjacent normal gastric mucosae, as well as in eight gastric epithelial cell lines and in non-malignant gastric cells GES-1; authors detected that the expression of these miRNAs inversely correlated with the depth of invasion, the stage of the disease, and the presence of nodal metastases in gastric cancer patients; moreover the over-expression of either miRNA200b and miRNA200c markedly attenuated cell proliferation, migration ability and invasion of MGC-803 and AGS gastric cancer cells lines (1) (*Figure 1*). Furthermore, the down-regulation of miRNA200b and miRNA200c resulted as an independent predictor of worse overall and disease free survival for gastric cancer patients (1).

Notably, the serum concentration of miRNA200c has been documented as an epithelial-specific clinical biomarker useful for gastric cancer diagnosis and an independent prognostic marker for progression and survival of gastric cancer patients (16).

To understand the suppressive role of miRNA200b and miRNA200c in gastric cancer growth and invasion, Tang and colleagues used the TaregtScan and Miranda algorithms for putative mRNA targets. They identified that the DNA methyltransferases (DNMTs) DNMT3A and DNMT3B were predicted to be targets for miRNA200b and miRNA200c by both algorithms. DNA methyltransferases are enzymes involved in DNA methylation that cooperate in establishing and maintaining CpG-island methylation patterns; thereby playing a major role in the regulation of gene expression.

DNA methylation is a well-studied epigenetic phenomena, it plays a key role in X-chromosome inactivation, in the transcriptional silencing of foreign DNA elements and in the gene imprinting; moreover, it is essential for normal growth processes, for the maintenance of chromosomes conformation and function, as well as for the embryogenesis and fetal development.

Methylation of CpG dinucleotide occurs in human cells when a methyl group is covalently added into the carbon-5' of CpG dinucleotide leading to the formation of

5' methylcytosine (5-mC); an aberrant DNA methylation pattern has been correlated to aging and chronic inflammation and it is implicated with viral infections and cancer development (17).

The methylation process is mediated by at least three active DNMTs: DNMT1 preferentially acts on hemimethylated CpG dinucleotide and it is necessary for the maintenance of specific methylation patterns during DNA replication, while DNMT3A and DNMT3B contribute to the methylation of unmodified DNA (18).

Tang and colleagues demonstrated that the transfection of miRNA200b or miRNA200c into MGC-803 and AGS cells markedly reduced the level of DNMT3A and DNMT3B proteins.

Furthermore, although DNMT1 was not a predicted target of miRNA200 family, the transfection of miRNA200b or miRNA200c into MGC-803 and AGS cells also reduced the level of the DNMT1 protein. The latter is frequently over-expressed in gastric cancers (19).

Further experiments documented that the down-regulation of DNMT1 was a consequence of the reduced activity of SP1, a zinc finger transcription factor that directly binds to the promoter of DNMT1 up-regulating the transcription (1).

Sp1 binds GC-rich elements that are common regulatory elements found in the promoters of several genes. Its expression is increased in a number of cancer cells including in those of gastric, breast and pancreatic carcinomas and it has been inversely correlated with the survival of gastric cancer patients (20).

According to the Targetscan 6.2 algorithm, the 3'UTR of Sp1 contains one predicted binding site for mRNA200b and miRNA200c through which miRNAs could down-regulate the protein expression and inhibit the DNMT1 transactivation.

Indeed, the restoration of miRNA200b and miRNA200c levels in MGC-803 and AGS cell lines resulted in a global DNA hypo-methylation that occurred through the direct binding of DNMT3A and DNMT3B to 3'UTR and only partially to an indirect effect on the DNMT1 promoter (1) (*Figure 1*).

The silencing of tumor suppressor genes by aberrant hyper-methylation is one of the earliest molecular events associated with cellular transformation that could be considered a predictor of tumor progression.

Many studies are evaluating the application of gene methylation *status* as a specific marker for allowing cancer diagnosis in biopsy specimens and non-invasive body fluids, such as serum or gastric washes.

The high prevalence of gene methylation, such as DAPK, CDH1, GSTP1, p15, and p16, has been documented in the serum of gastric cancer patients possibly due to the release of nucleic acid by gastric cancer cells, and it has been significantly correlated with the gene methylation in gastric cancer tissues.

Serum RASSF1A methylation has been documented significantly higher in gastric cancer patients comparing to those evidenced in benign gastric disease. The methylation of p16 promoter has been frequently detected in tumor samples, but not in matched normal tissues; moreover, p16 methylation is an early molecular event in gastric carcinogenesis. Therefore, the detection of methylated genes in serum may be a useful biomarker for early detection of gastric cancer (21).

According to this background, the DNA methylation would be an excellent target for anti-cancer therapies. It was found that accompanying DNA demethylation is a dramatic reactivation of the silenced genes and inhibition of cancer cell proliferation, promotion of cell apoptosis, or sensitization of cells to other chemotherapeutic reagents.

Several small natural and synthetic molecules are able to contrast the DNA hyper-methylation through inhibition of DNA methyl-transferase (DNMTi). Indeed, de-methylating agents are drugs which inhibit the methylation process and restore the expression of the previously hyper-methylated and silenced genes.

Emerging interest in the use of DNMTi as a potential strategy for cancer treatment is constantly increasing. Several small natural and synthetic molecules are widely used for *in vitro* studies and in clinical trials for their potential anti-cancer activities (22,23).

Cytidine analogs such as 5-azacytidine (azacitidine) and 5-azadeoxycytidine (decitabine) are the most commonly used demethylating agents. Both these drugs have been approved in the treatment of myelodysplastic syndrome (MDS) by Food and Drug Administration (FDA) in United States.

It seems important to highlight, however, that DNMTi for chemotherapy is still at a very early stage of progression, but nevertheless it is a field of ongoing researches and investigations. Those progress made in epigenetic research will lead to a better understanding of the actions of DNMTi, which will promote the translation from “bench to the bedside”. An ideal epigenetic therapy should be able to distinguish aberrantly methylated genes from normally methylated genes.

One of the most important findings reported by Tang

Table 1 Representative publications on gastric cancer associated miRNAs and the relative clinical relevance. In the table are listed more recent study of microRNAs associated with gastric carcinogenesis and the relative clinical relevance

Author	Journal	Year	miRNA	Sample	N of patients	Clinical Relevance
Kim CH	*BMC Medical Genomics*	2011	let-7g, miRNA342, miRNA16, miRNA181, miRNA1, and miRNA34	Cancer tissues	8	Chemo-sensitivity
Sacconi A	*Cell Death Dis*	2012	miRNA204	Cancer tissues and cell lines	123	Correlation with survival; chemo-sensitivity (*in vitro* assays)
Wu H	*Cancer Chemother Pharmacol*	2013	miRNA34c-5p	Cancer tissues and cell lines	43	Chemo-sensitivity (*in vitro* assays)
Ziang Y	*FEBS Letters*	2013	miRNA106a	Cell lines	–	Multi-drug resistance
Yang SM	*Toxicology*	2013	miRNA21	Cell lines	–	Chemo-resistance
Tang H	*Clin Cancer Res*	2013	miRNA200b, miRNA200c	Cancer tissues and cell lines	126	Correlation with stage and survival; identification of possible therapeutic targets

miRNA, microRNA.

and colleagues was that over-expression of miRNA200b and miRNA200c not only reduced gastric cancer cell proliferation and invasion but also global DNA methylation restoring the expression of p16, E-cadherin and RASSF1A (1).

Indeed, it is our opinion that the investigation of miRNAs also in gastric cancer tissues is moving forward to the identification of new frontiers of clinical use (*Table 1*): the ultimate comprehension of the tumorigenesis and of the network of genetic alterations involved in tumor's development would contribute to tailor more personalized cancer treatments.

Indeed as stated by a recent comprehensive review by Iorio (24) the potential of miRNAs' expression to correlate with the response to different therapies needs to be further investigated and validated by *in vivo* studies aiming to the definition of chemosensitivity or conversely to drug resistance. However, since the vast majority of the literature in this field reports preclinical studies, this area of investigation still represents an open question for future research. This process can be speed pursuing interdisciplinary cooperation between basic, translational and clinical scientists.

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Clinical and molecular aspects of miR-200 family in gastric cancer

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Gastric cancer, like all tumors, is a complex disease in which many predisposing and triggering factors, both environmental and genetic, are summed and combined until the development of the malignancy. Among the genetic causes and modifiers of the clinical course of gastric cancer, microRNAs (miRNAs) as wide-spectrum post-transcriptional regulators, play a central role. Their special characteristics, i.e., their tissue-, and even cell-type-, specificity, their stability in different biological fluids, and their deregulation during tumorigenesis, make to miRNAs the focus of a huge amount of studies searching for their application as potential biomarkers and therapeutic targets in cancer.

Tang and co-workers (1) published last year an interesting paper in which they analyze the expression of two miRNAs from miR-200 family, miR-200b and miR-200c, as putative prognostic biomarkers in gastric cancer. In addition, the authors provide novel data and insights into the function of these miRNAs and their contribution to the gastric cancer development and progression. These data include the establishment of DNMT3A and DNMT3B as direct targets for miR-200b and miR-200c. Moreover, the authors demonstrate that DNMT1 is also indirectly regulated by miR-200b and miR-200c through the control of expression of the transcriptional factor SP1. DNMT3A, DNMT3B and DNMT1 are DNA-methyltransferases which catalyze the methylation of CpG islands contributing thus to the epigenetic silencing of gene expression. The importance of these findings lies in the central role that the malfunction of epigenetic regulation plays in cancer, and specifically in gastric cancer, in which there is a generalized hypermethylation along the entire genome. Therefore, we can hypothesize that the downregulation of miR-200b and miR-200c may be part of the molecular mechanism involved in the aberrant hypermethylation found in the majority of gastric cancers. So, when miR-200b and miR-200c are overexpressed in gastric cancer cells, as determined by the authors, it is generated a decrease in the global DNA methylation: miR-200b and miR-200c directly repress the expression of DNMT3A and DNMT3B and indirectly inhibit the expression of DNMT1 repressing the activator, SP1. As consequence of this global decrease in DNA methylation, it is triggered the restoration of expression of many genes, including those involved in the control of tumor progression (tumor suppressors), such as E-cadherin, p16 and RASSF1A. This has important implications for tumor behavior, both to clinical and biological levels. First, the overexpression of miR-200b and miR-200c reduces the proliferative and invasive capability of gastric cancer cells in vitro. And second, in the majority of gastric cancer tissues analyzed by the authors, miR-200b and miR-200c are underexpressed regarding paired non-tumor adjacent samples. These interesting findings add a novel piece to the functional puzzle already depicted in literature about the role of miR-200 miRNA family in cancer. The miR-200 miRNA family is well known to be a key determinant of epithelial phenotype of cancer cells through the regulation of E-cadherin transcriptional repressors, ZEB1 and ZEB2 (2-4). Additionally, ZEB1 is able to reciprocally repress the expression of miR-200 miRNA family members, miR-200c and miR-141 (5) thus constituting a double negative feedback regulatory loop. This highly unstable system depends on small changes in the levels of miR-200 miRNA family members and ZEB transcriptional factors to induce switches between the epithelial and mesenchymal cell states. This epithelial-to-mesenchymal plasticity (EMP; term that embraces the phenomena of epithelial-to-mesenchymal transition, EMT, and the mesenchymal-to-epithelial transition, MET)

is key to understand many of invasive and proliferative characteristics of tumors. The system is so sensitive to micro-environmental cues that any molecular disturbance affecting the delicate balance between its members is able to drive changes in cell phenotype. In this sense, it is paradigmatic the effect that TGF-beta signaling displays on this system for the establishment and maintenance of mesenchymal phenotype (6). TGF-beta signaling not only is able to activate the sustained ZEB expression with the consequent miR-200 repression, but also can reinforce and stabilize this inhibition by hypermethylation of the miR-200 loci upon prolonged exposure to the signal. This last data is in accordance with the fact that, as demonstrated by Tang and co-workers (1), miR-200b and miR-200c are regulators of several DNMTs, and with the hypomethylation seen in liver metastasis from colorectal cancer overexpressing miR-200c and miR-141 (7). Furthermore, since TGF-beta cytokines are proven targets for miR-200 family members, the inhibition of miR-200 expression enhances the TGF-beta production and contributes to the maintenance of an autocrine/paracrine signaling and its effects, i.e., the stabilization of mesenchymal state. However, given the structure of the miR-200/ZEB/TGF-beta axis, the interruption in the inductive signal (in this case, TGF-beta) causes re-expression of miRNAs from miR-200 family and reversion to an epithelial phenotype. Thus, different cancer cells in different moments may display different phenotypic states depending on the signal affecting cells in such moments. And, in fact, inside of tumors and metastases, many molecular cues coming from microenvironment (stromal cells, immune cells, endothelial cells, etc.) interact with cancer cells to modulate their appearance and behavior. This, in combination with the elevated genetic heterogeneity existing among cells within tumors and metastases, makes that such cells can display a highly variable phenotype through the expression of different genes and miRNAs. And more importantly, cells with distinct phenotypes are not randomly distributed within tumors but they occupy a specific location in function of their capabilities, like a living organism that evolves and wants its own survival. In this way, it has been demonstrated in colorrectal cancer that cells in the invasive front of tumor undergo complete EMT, associated with loss of miR-200 family members and E-cadherin expression, and increase in ZEB1 levels (8). This contrasts with the elevated expression of miR-200 in the tumor core (8) where tumor cells display epithelial characteristics necessary for their intense proliferation (7). The mesenchymal phenotype of cells at the invasive front of tumor enables them to destroy and migrate through the basement epithelial membrane reaching other local and/or distant tissues. However, once tumor cells reach a secondary location, they become epithelial again by using the mechanism of MET, which allows their expansion and colonization. This phenotypic reversion has been seen in colorectal tumors where distant liver and regional lymph node metastasis and proximal vascular tumor deposits show elevated levels of different miRNAs from miR-200 family (7,8). In line with this, it has been demonstrated in vitro that the overexpression of miR-200 is a distinctive feature of breast cancer cell lines with elevated metastatic potential (9,10). This phenotypic duality may explain the discordance found in the expression of miR-200 and other miRNAs between primary lesions and metastases in different studies, perhaps due to the analysis of primary tumors with different preponderant pathological and phenotypic characteristics (9,11). Also, while in primary gastric tumors, low levels of miR-200b and miR-200c have been found regarding healthy tissue (1), in patients' blood, high levels of miR-200c were found regarding healthy controls (12), indicating poor prognostic. Beyond their role regulating the TGF-beta/ZEB/E-cadherin axis, the miRNAs from miR-200 family play other functions, many of them yet undiscovered, in consonance with the nature of miRNAs as multi-target regulatory tools. And these functions, when deregulated, have important implications both in the proliferation and dissemination of tumors. For example, studies in vitro demonstrated that the expression of Sec23a, a protein involved in the secretory pathway, is controlled by miR-200 (9), and that the upregulation of miR-200 is able to elicit deep changes in the secretome of cancer cells with potential effects on the metastatic process (9,13). Also, it has been recently demonstrated the role of miR-200 inhibiting angiogenesis (14), which might explain the attraction of blood vessels toward the invasive front of tumors where miR-200 is downregulated.

In the clinical setting, Tang and co-workers (1) demonstrated that the downregulation of miR-200b and miR-200c in primary gastric tissues is able to predict shorter survival. The prognostic significance of miR-200a and miR-200b downregulation in primary gastric tumors was also confirmed in a recent article in which these miRNAs were found to form part of a mesenchymal miRNA signature associated with poor outcome (15). In addition to their role in prognostic assessment, miRNAs from miR-200 family may also be related to resistance to systemic therapy in gastric cancer. Thus, in a recent paper, it has been shown that three

miRNAs from miR-200 family (miR-141, miR-200a and miR-200b) are only expressed in 10-hydroxycamptothecin-sensitive gastric cancer cell lines (16). The fact that gastric cancer cells expressing miR-200 may be more sensitive to chemotherapy could have a direct impact on the measure of outcomes: since only those patients over-expressing miR-200 are more sensitive to treatment, only these patients show better survival. And more importantly, this opens the door to the use of miRNAs from miR-200 family as hypothetical predictive biomarkers. The findings of Tang and co-workers (1) also could point to a potential therapeutic solution for gastric cancer patients with downregulation of miR-200 and poor response to treatment. Given that these patients show an overall increase in DNA methylation, a treatment option to explore could be the administration of any demethylating agent in combination with standard therapy. This therapeutic approach perhaps could restore the expression of key tumor suppressors (17), including miR-200 family, thus minimizing the invasive capacity of gastric cancer cells and increasing their sensitivity to conventional chemotherapy.

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Translational Research

ADAM and EMMPRIN: a promising couple for more prognostic precision in patients with gastric cancer

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Gastric cancer is still a highly problematic tumor entity. Even in early stages, individual clinical prognosis can be rather poor, and limited response to neo-adjuvant and adjuvant therapeutics still remains to be a considerable problem. For these and other instances, powerful molecular markers able to more precisely predict the individual risk for tumor recurrence and metastasis for the individual, as well as the probability to respond to certain types of therapeutics are still desperately needed.

Already more than a decade ago, different research groups including our own have implicated tumor-associated proteases and especially the urokinase-type plasminogen activator (u-PA) system as promising candidates for the development of independent prognostic markers in gastric cancer (1-4), and since then, more and more highly interesting proteinases, their molecular actions and interactions and their potential for diagnostic and therapeutic purposes have been defined. EMMPRIN (Extracellular Matrix Metalloproteinase Inducer) has been shown to be highly expressed especially by tumor cells, but also in the stroma (5) in several cancer entities, and has been demonstrated to support several aspects of tumor progression and metastasis by, for example, promoting the degradation of extracellular matrix components, at least in part by inducing matrix metalloproteinases and also the uPA-system (6-10). Recent reports suggest that a significant increase of EMMPRIN-expression in tumor cells might at least in part be due to epidermal growth factor receptor-related signaling (11), and interestingly, ADAM17, a member of the A Disintegrin and Metalloproteinase (ADAM)-family, has been shown to regulate activity of epidermal growth factor receptor, at least in part due to its ability to regulate cleavage and activity of cell membrane-anchored receptor ligands.

Based on this background, in the recent issue of Annals of Surgery (11), SHOU and colleagues conducted a highly interesting retrospective study at 436 out of 1,200 consecutive gastric cancer patients who underwent gastrectomy between 1998 and 2004. At resected gastric cancer - and corresponding normal tissue samples established on tissue microarrays, they immunohistochemically investigated the expression of ADAM17 and EMMPRIN and their association with clinical prognostic parameters. A high expression of ADAM17 was found in around 36% of resected tumor tissue specimens in contrast to corresponding normal tissues, whereas a similarly high percentage of around 37% of the tumors revealed a high expression of EMMPRIN. There was a highly significant correlation between the expression of ADAM17 and EMMPRIN in the gastric cancer tissues investigated ($P<0.01$). A high expression of ADAM17 as well as of EMMPRIN was significantly associated with advanced tumor stages, especially invasion of lymph nodes and distant metastasis. Also, a high expression of ADAM17 and also EMMPRIN was significantly associated with poorer overall survival. Both ADAM17 and also EMMPRIN revealed to be independent prognostic parameters in a multivariate Cox proportional hazard analysis which considered all relevant clinical prognostic parameters known for gastric cancer to date.

An especially important result from my point of view is that stage II gastric cancer patients with low ADAM17 expression showed significantly longer mean survival than stage I patients with high expression of ADAM17. This result could become of special importance since this suggests that ADAM17, after appropriate future validation, could become a biomarker that can discriminate patients with early stage gastric cancer that, from a biological point of view, are high at risk for later tumor recurrence or progression in contrast to patients with biologically more uncritical early disease. On the other hand, stage II patients with low ADAM17 expression might be treated less aggressively than the ones with high expression. If validated in further studies, this should have clinical consequences in terms of, e.g., changing clinical follow-up protocols for such patients and/or considering more individualized therapeutic concepts in addition to curative tumor surgery, e.g., within adjuvant therapy protocols. Another interesting aspect which is discussed by the authors in their article is that ADAM17 has been suggested to be able to predict certain therapeutic outcomes. For example, as the authors mention, ADAM17 might be able to indicate patients with a high probability of resistance to therapeutic regimen directed either against EGFR or c-erbB2. This has been indicated in studies at other tumor entities such as specifically breast cancer. However, since it is known that a considerable percentage of gastric cancers express immunhistochemically easily detectable c-erbB2 (12-17), ADAM17 might also become an important biomarker to predict patients able to respond to HER2-directed therapies in gastric cancer. Suchlike speculations are based on recent studies suggesting that, for example, ADAM-inhibitors are able to inhibit the process of activation of erbB-ligands, leading to an inhibition of gefitinib-resistant HER3 signaling and enhancing the ability of compounds such as gefitinib to inhibit EGFR-initiated signaling (18). Furthermore, since, in their present paper, SHOU *et al.* found significant correlations between the expression of ADAM17 and EMMPRIN and since it has been described that two EGFR-ligands have been reported to induce EMMPRIN expression (19), the authors speculate that their data on 436 gastric cancer patients support the hypothesis that ADAM17 might enhance expression of EMMPRIN via an activation of expression of the epidermal growth factor receptor.

Certainly, as the authors also rightfully acknowledge, the present study by SHOU *et al.* which is retrospective needs to be further and independently confirmed by large prospective clinical studies, not only confirming the independent prognostic relevance of ADAM17 and EMMPRIN expression in gastric cancer and deeper exploring their ability to predict therapy response, but also contributing to a higher level of international standardization of ADAM17 and EMMPRIN measurement and the clinically relevant definition of ADAM17 and/or EMMPRIN positivity. Nevertheless, besides previously defined tumor-associated proteinase systems such as the u-PAR/PAI1-system, ADAM17 and also EMMPRIN might be promising and prognostically relevant molecular markers for the initiation of further studies. The study also supports attempts to proceed with the development of targeted therapies against ADAM17 and/or EMMPRIN in the search for novel tools to combat gastric cancer.

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Translational Research

Evaluation of JWA and XRCC1 expressions in gastric cancer

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Abstract: Recently surgery in combination with chemotherapy, and radiation therapy largely improved the clinical outcomes in comprehensive treatment of gastric cancer. However the overall survival rate of gastric cancer patients is still poor in terms of the stages of the disease. In order to achieve a more satisfactory prognosis, proper individual treatment plans should be developed due to the new guidance tools. In this respect, previously proposed actual biomarkers cannot provide expected benefit. Supporting evidences suggested that potential prognostic properties of JWA and DNA repair enzyme X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) seem promising. Since endogenous and exogenous factors may induce DNA damage and subsequent gastric cancer development, assessment of JWA and XRCC1 expression status may be favorable. For the validation of the guidance of JWA and XRCC1 expression in all cases randomly, further investigations are necessary in a large series of gastric cancer patients. Because of the ethical considerations, actual standard methods should be used in addition to the JWA and XRCC1 evaluation in gastric cancer cases. Consequently screening for gastric cancer is still cost-effective in countries with high risk as well as moderate risk populations.

Keywords: Gastric cancer; chemotherapy; JWA; X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1)

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Gastric carcinoma is the fourth most common cancer worldwide (1) and the second in Asia while more than half of the world's gastric cancer cases appear in Eastern Asia (2). In the West, the gold standard for diagnosing cancer is to detect depth of tumor invasion into the gastric wall, whereas in Far East, it is more important to detect cellular atypia or structural atypia, regardless of invasion (3). Accepted by all, the classical independent prognostic factors influence the five-year survival rate are serosal invasion, extragastric lymph node metastasis, liver metastasis, stage of disease, resection margin, and operative curability in gastric cancer patients (4). Last ten years treatment modalities for gastric cancer have been changed on a large scale. Curative endoscopic submucosal dissection provides the five-year overall survival rate of 97.1% for early gastric cancer (5). Among these, approximately 22.4% developed lymph node metastasis, which is associated with a poor five-year survival rate of only 72.7% (6). Unfortunately, the rate of early gastric cancer detection varies by country, and recently, the best early gastric cancer/advanced gastric cancer ratio is 2.9 (7). Furthermore, after endoscopic resection of early gastric cancer, overall, the rate of residual/recurrent tumor is 33.3% (8). Still overall survival rates in patients with early gastric cancer were 94% and 90% at five and ten years, respectively (9). Thus screening for gastric cancer is cost-effective in countries with high incidence. Even in populations with moderate frequency risk stratification may increase the cost-effectiveness of screening (2). As it can mostly be diagnosed at an advanced stage, the overall survival rate is 20-40% (10). Actually in patients with stage I-III gastric cancer, no improvement in long term survival could yet be seen (11). For localized gastric cancer, the treatment strategies alter country by country.

While in western countries, preoperative chemotherapy or adjuvant chemo-radiation is favored, D2 gastrectomy followed by adjuvant chemotherapy is a routine approach in Asia (12). Gastric Cancer Working Group reported that R0 resection with D2 lymph node dissection has produced the best survival data and also post-operative adjuvant chemotherapy including S-1 (tegafur, 5-chloro-2, 4-dihydropyrimidine, and potassium oxonate) is recommended after surgery. Adjuvant chemotherapy for gastric cancer, fluorouracils plus platinum is the most widely accepted first-line regimens, whereas taxanes or irinotecan are mostly used in second- and third-line settings (2). Indeed the outcome of gastric cancer is extremely complex and varies with the stage of disease as well as in patients with similar pathological features. Even in early stages, although appropriate surgery and adjuvant chemotherapy, prognosis may be poor. It is evident that in order to arrange proper individual treatment plan, we need new guidance tools.

In this respect, literature survey suggests that combinations of carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and CA72-4 are the most effective ways for staging before surgery or chemotherapy. However, the positive rates are 21.1% for CEA, 27.8% for CA19-9, and 30.0% for CA72-4 (13). It was shown that positive expression of the breast and ovarian cancer susceptibility gene 1 (BRCA1) exists with the significantly prolonged overall survival in stage II-III gastric cancer patients. Although response to platinum-based adjuvant chemotherapy is a good prognostic factor, the BRCA1-negative patients benefit more from platinum-based adjuvant chemotherapy (14). Patients with BRCA1 expression have a better prognosis in gastric cancer, contrarily, patients without BRCA1 expression can benefit from platinum-based adjuvant chemotherapy. Because of this dilemma BRCA1 expression in gastric cancer is open to debate.

Conversely, an apparent concordance was defined considering the potential prognostic properties of JWA and X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) with the low expression rate in resectable gastric cancer patients. Low expression of JWA and XRCC1 are also significantly associated with gastric cancer and unfavorable TNM stage. This result is in accordance with the positive predictive effect of low expression of JWA and XRCC1 on survival in adjuvant platinum-based-chemotherapy received patients. However in the series of cases of Wang *et al.* it was not mentioned whether the rate of R0 resection and D2 dissection were performed (15). It is argued that JWA and XRCC1 low-expression provides an advantage in terms of both progression of gastric cancer with unfavorable TNM stage and response to platinum-based-chemotherapy with favorable survival.

Prolonged and excessive generation of reactive oxygen and nitrogen species are assumed to contribute to the development of carcinogenesis by inducing oxidative DNA damage when combined with low DNA repair capacity (16). XRCC1 is one of the prominent base excision repair (BER) enzymes and plays an essential role in the removal of endogenous and exogenous DNA damage (16-18). Capella *et al.* and Ratnasinghe *et al.* found relationship between Arg allele of XRCC1 at codon 399 and gastric cancer (19,20), while Huang *et al.* in Polish people and Duarte *et al.* in a Brazillian population could not demonstrate the similar findings (21,22). However in our previous study, we have found that the individuals carrying homozygous Gln allele have increased risk of gastric cancer 2.540 folds (23). Contrarily, in Far East populations, no association between XRCC1 Arg399Gln polymorphism and gastric cancer has been shown (24,25). Wang *et al.* did not investigate the gastric cancer patients for the presence of XRCC1 polymorphisms. On the other hand, mechanistic studies have demonstrated that JWA regulates XRCC1 expression at both the transcriptional and post-translational levels (26) and JWA displays a key role in protecting cells from oxidative stress induced-DNA damage via increased levels of XRCC1 (27). It seems reasonable to pay attention to status of JWA and XRCC1 expression in addition to classical methods during the evaluation of gastric cancer patients. However the contribution JWA and XRCC1 instability to the life expectancy should be checked in TNM stage-matched gastric cancer groups following surgery plus chemotherapy.

Taken together all these data, individual genetic susceptibility and alteration in serum markers are not determined precisely at prognostic level in gastric cancer patients, yet. Therefore further investigations are necessary due to the complexity of personal cancer progress and to select the most beneficial surgical intervention and chemotherapeutic regimens.

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Translational Research

Re: Clinical significance of SOD2 and GSTP1 gene polymorphisms in Chinese patients with gastric cancer by Xu *et al*.

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The article of Xu *et al*. (1) describes the investigation of SOD2 and GSTP1 gene polymorphisms association with gastric cancer incidence, prognosis and progression in patients from a Chinese population. The authors report that there were strong associations between the SOD2 rs4880 and GSTP1 rs1695 genotypes with lymph node metastasis, tumor size, progression, and tumor aggressiveness. Of perhaps even greater interest, SOD2 rs4880 CT and CC genotypes were correlated significantly with shorter overall survival. The authors did not investigate and other polymorphisms i.e. SOD2 T5482C that have be found to be closely associated with an increased susceptibility to the development and differentiation of gastric cancer different populations like Korean (2). Since, polymorphisms of GSTP1 have also been associated with platinum-based chemotherapy efficacy in different cancers (3,4), including gastric cancer (5), revealing their clinical potential as a biomarker to predict platinum-related chemosensitivity, it would be interesting to further evaluate the functional role of these polymorphisms. Nonetheless, the paper is very interesting in that it indicates that the genetic background of the tumor or/and patient, rather than just the characteristics of the cancer, may play a role in the biological progression of the tumor. Stepwise progression of human cancer has been clinically well recognized. SOD2 has been considered as one of the most important antioxidant enzymes that regulate the cellular redox state in normal and tumorigenic conditions. Studies suggested that alteration in SOD2 level may influence the metastatic potential of tumor cells via activating mitogen-activated protein kinases (MAPK), and regulating the expression of matrix metalloproteinase (MMP) gene family members (including MMP-1 and MMP-9) (6). However, the role of SOD2 in carcinogenesis has been widely studied but remains ambiguous (7). Regarding the GSTP1, several GST isoenzymes have been shown to modulate cell signaling pathways that control cell proliferation and cell death (apoptosis) (8). A variety of human cancers, including of breast, colon, kidney, lung, and ovarian, usually express high levels of GSTP1 compared with the surrounding tissues. Consequently, GSTP1 expression has been considered to be a marker for cancer development. High expression levels have been associated not only with disease progression but also with drug resistance in patients undergoing chemotherapy.

A challenge issue of cancer investigators has been the identification of specific markers of cancer progression. Most studies have focused on the identification of genetic characteristics of tumor cells that could be used to predict their risk of progression, metastasis and/or outcome. Such prognostic markers could then be used clinically to define individualized treatment for patients. Some of these markers may predict the response of a cancer to a particular treatment. Recently gene expression, as well as gene single nucleotide polymorphisms (SNPs) array analysis has identified numerous gene expression patterns or SNPs that are promising prognostic or markers but have yet to find their way into general clinical acceptance. All of these are based on “molecular signatures” from the cancer cells.

The article by Xu *et al*. (1), as well as the work of others, point up some interesting findings concerning the potential for the tumor and/or host genetic background to contribute to the progression of the cancer. These types of findings need to be expanded to further evaluate genetic background influences on the metastasis of gastrointestinal cancers or

other malignancies.

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The usefulness of CDH1 methylation as a gastric cancer peritoneal metastasis biomarker

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Gastric cancer (GC) remains one of the most prevalent malignant diseases worldwide, being considered the second leading cause of global cancer deaths, affecting close to one million people per year (1). Although some recent advances in molecular biology, surgery, chemotherapy, and radiotherapy have been made, the poor prognosis and high mortality rate continue to make gastric cancer an attractive target of active clinical and basic scientific research (2).

Due to GC heterogeneity, some classifications have been proposed over the years, based on histopathology, clinical aspects, and endoscopic characteristics (3-5). However, the most widely used is the one proposed by Laurén (4), which classifies GC into intestinal and diffuse types, according to structural characteristics of the tumors. Some studies point out differences in the clinicopathological characteristics between these two types, indicating that they are a result of distinct molecular pathways (6).

The etiology of GC is considered multifactorial as many inherited and environmental factors, like diet, lifestyle, genetic and socioeconomic factors, play a role in its carcinogenesis. However, it is clear that the major etiologic risk factor for GC is *Helicobacter pylori* (*H. pylori*), which is responsible for more than 80% of cases (7).

A number of studies provide evidences that both genetic and epigenetic alterations play critical roles in GC. Although the role of genetic alterations has long been recognized, in the last decade epigenetic modifications have also been considered as an important factor in GC pathway (7). Accumulating evidence indicates that aberrant promoter methylation is one of the most common molecular alterations in GC, being considered as a sensitive and very promising biomarker in early diagnosis of tumors (8).

A number of tumor-suppressor and tumor-related genes, including *APC*, *CDH1*, *MHL1*, *CDKN2A*, *CDKN2B* and *RUNX3* are commonly methylated in GC (6), suggesting the potential clinical value of DNA methylation as a marker for risk prediction and prognosis (9). Among those, *CDH1* deserves special attention as is widely reported as silenced in GC, mainly of the diffuse type, especially by promoter methylation (10-12).

CDH1, a suppressor gene located on chromosome 16q22.1 and member of the APC pathway, codifies for the E-cadherin protein and belongs to a family of cell surface glycoproteins that mediates the cell-cell adhesion playing an important role in the maintenance of the tissue architecture (13,14). The inactivation of E-cadherin results in a decreased cell adhesion, an increased cell motility and abnormal polarity, which favors the infiltrative ability and promotes tumor metastasis (8,15,16).

Various degrees of methylation in the *CDH1* promoter CpG islands and the consequent loss of E-cadherin expression were reported in GC (8,17), including the Hereditary Diffuse Gastric Cancer (HDGC) as 25-40% of the cases are caused by heterozygous silence of E-cadherin (12,18).

The main consequence of *CDH1* inactivation is the loss of cell-cell adhesion which is correlated with an infiltrative

and metastatic ability in GC (12,19). *CDH1* inactivation is so strongly correlated with GC prognosis and survival that patients with E-cadherin-positive gastric cancers showed statistically significant prolonged 3- and 5-year survival rates, compared to patients with E-cadherin-negative tumors (20).

Frequently, GC is diagnosed in advanced stage where the surgical resection is the only option for treatment (21). Considering this information and the high level of metastasis, including in the peritoneum, the identification of biomarkers for early detection and/or presence of GC metastasis is a very important task for its prevention and treatment (22).

Peritoneal metastasis is an important event in the GC prognosis as it may be responsible for resistance to various chemotherapeutic drugs and causes ascites and intestinal obstruction. This type of metastasis has a difficult identification as it may occurs in cases with negative cytological examination (23,24). The methylation pattern of several genes was evaluated in peritoneal washes in order to identify possible biomarkers of abdomen metastasis. The methylation observed in the peritoneum fluid (PF) was successful in the detection of occult neoplastic cells on the peritoneum, and that its use along with a cytological examination might increase the positive detection of cancer cells in PF (24).

Recently, Yu *et al.* (25) published an important paper in this subject, reporting that alterations in the methylation pattern of *CDH1* in preoperative peritoneal washes were significant correlated with abdomen metastasis and poor prognosis, suggesting that this marker could be used for the diagnosis of tumor invasion, metastasis and progression of GC.

In conclusion, even with few studies focusing the search for peritoneal metastasis biomarkers which can be predictive of poor prognosis, we can speculate that studies in this field are extremely important as they have great utility for the medical community and consequently for the patients' survival.

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Fatal attraction: tumor recruitment of myeloid-derived suppressor cells is mediated by IL-17-producing CD8$^+$ T cells

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Abstract: The interaction between tumor tissue and the host immune system is critical to tumor development. These interactions are regulated through a variety of immune cells and cytokines. IL-17 is a proinflammatory cytokine produced by Th17 and Tc17 cells that affects the development of cancer. However, the role of IL-17 in influencing tumor growth or in enhancing anti-tumor immunity is somewhat controversial. Zhuang *et al*. (Gastroenterology 2012, 143:951) elucidated that the IL-17 produced by Tc17 cells plays an important role in the pathogenesis of gastric cancer. Based on the findings of Zhuang *et al*. and other studies in the literature, we propose a model involving complex interactions between Tc17 cells, regulatory T cells, monocytes, tumor cells, myeloid-derived suppressor cells, and cytotoxic T lymphocytes within the tumor microenvironment.

Keywords: IL-17; myeloid-derived suppressor cells; regulatory T cells; Tc17

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The tumor microenvironment comprises immune cells, tumor cells, stromal cells, and the extracellular matrix. This microenvironment is the key location for neoplastic progression, nurturing the proliferation, survival, and migration of tumor cells. Although a relationship between inflammation and cancer has been appreciated for several decades, researchers have not elucidated a complete picture for the complex networks in the tumor microenvironment. Recently, in an article in the journal *Gastroenterology* (1), Zhuang *et al*. provided compelling evidence that IL-17-producing CD8$^+$ T cells play an important role in the pathogenesis of gastric cancer. They proposed a model of cross-talk between the host immune system and tumor cells leading to IL-17-producing CD8$^+$ T cell development and myeloid-derived suppressor cell-mediated immunosuppression.

IL-17-producing CD8$^+$ T cells were first characterized by Liu *et al*. (2) as a distinct subset of CD8$^+$ T cells that are fundamentally different from canonical cytotoxic T lymphocytes (Tc). Because of their low levels of cytotoxicity, the IL-17-producing CD8$^+$ T cell subset was initially designated as T noncytotoxic 17 (Tnc17) (2). Several independent research groups have also reported that IL-17-producing CD8$^+$ T cells have negative or low cytolytic activity and markers (3-5). To maintain a comparative convention with cytotoxic T lymphocytes, Tc1 or Tc2, these IL-17-producing CD8$^+$ T cells are now termed Tc17 cells. Tc1 cells are well known to primarily secrete IFN-γ and kill their tumor targets by either perforin- or Fas-mediated mechanisms, whereas Tc2 cells secrete IL-4, IL-5, IL-6, and IL-10 and kill their tumor targets predominantly through the perforin pathway (6). In contrast, Tc17 cells secrete IL-17 and have fewer cytotoxic effector functions due to diminished levels of the T-box transcription factor Eomesodermin, IFN-γ, and the cytolytic molecule granzyme B (4).

Tc17 cells have been detected in a variety of tumors (1,4,7-13), autoimmune diseases (14-16), and infections (3,17). Such cells are believed to be involved in enhancing protection against viral infection (3,17) and antitumor immunity (10,11). Direct evidence from a study using

adoptive transfer to identify the role of Tc17 cells in a B16 melanoma model demonstrated that Tc17 cells exhibit antitumor immunity and reduce tumor growth (11,12). However, an increasing body of work also indicates that Tc17 cells accumulate with disease progression (7-10) or promote tumor progression due to the low expression of perforin, granzyme B, and IFN-γ (4,7).

Cytokines in the tumor microenvironment play a crucial role in tumor growth and survival. TGF-β, IL-6, and prostaglandin E2 levels have been shown to be elevated in the malignant effusions of cancer patients (18). TGF-β and IL-6 appear to be essential for the induction of IL-17-producing T cells (2,19). In addition, prostaglandin E2 has been shown to induce IL-23 production (20,21), and IL-23 is important for IL-17-producing T cell survival and expansion (19). A tumor microenvironment with these cytokines will favor the differentiation of IL-17-producing T cells. Notably, Zhuang *et al*. demonstrated that a set of key cytokines (IL-6, IL-1β, and IL-23) derived from tumor-associated monocytes plays an essential role in the induction of Tc17 cells (1). Consistent with the findings of Kuang *et al*. (8), tumor-activated monocytes also have been shown to secrete IL-6, IL-1β, and IL-23 to trigger the expansion of Tc17 cells in hepatocellular carcinoma (HCC). Altogether, these results suggest that cytokines present in the microenvironments of a variety of tumors encourage the development of IL-17-producing T cells.

Zhuang *et al*. found IL-17-producing $CD8^+$ T cells to be enriched at tumor sites in gastric cancer patients (1). A comprehensive analysis indicated that the percentage of IL-17-producing $CD8^+$ T cells increased significantly as the gastric cancer progressed, and this percentage was associated with overall survival time. In addition, these intratumoral IL-17-producing $CD8^+$ T cells expressed less IFN-γ, IL-4, IL-10, and IL-9. These results suggest that the IL-17-producing $CD8^+$ T subset in gastric cancer is neither the Tc1 nor the Tc2 subset and can be categorized as the Tc17 subset. Further characterization of Tc17 cells revealed that they express minimal amounts of perforin, granzyme B, FoxP3, or programmed death 1 receptor. These characteristics imply that the main role of Tc17 cells is likely to be the secretion of IL-17 rather than the direct execution of effector functions such as cytotoxicity or immunosuppression.

If Tc17 cells do not have a direct effector function, what is the role of the IL-17 secreted by Tc17 cells? The most important finding in the Zhuang *et al*. (1) study is the identification of a downstream mechanism for IL-17. In particular, IL-17 stimulates tumor cells to secrete CXCL12, which may recruit myeloid-derived suppressor cells to the tumor microenvironment and promote tumor progression in gastric cancer. In fact, the role of IL-17 in cancer development is still paradoxical (22). However, the study by Zhuang *et al*. strongly supports the view that the interaction of monocytes and tumor cells creates a favorable environment for Tc17 development (1); the IL-17 secreted by Tc17 then attracts myeloid-derived suppressor cells to foster immune privilege in gastric cancer. When the cytotoxic $CD8^+$ T cell is no longer a killer cell but a traitor, the consequence is tumor growth.

Regulatory T cells play a significant role in suppressing anti-tumor immunity, and their interaction with Tc17 cannot be ignored. Tsai *et al*. demonstrated that the presence of regulatory T cells and the consumption of IL-2 maintains or promotes Tc17 cell differentiation (13). These results suggest a beneficial effect of regulatory T cells for Tc17. What is the possibility that Tc17 are 'inflammatory' regulatory cells? Kryczek *et al*. identified a population of IL-17+ regulatory T cells that express both IL-17 and FoxP3 in ulcerative colitis and colon cancer carcinoma (23). They suggested that this cell population plays a role in chronic inflammatory environments. Zhuang *et al*. (1) also examined whether such intratumoral Tc17 cells expressed the conventional markers of regulatory T cells and observed these Tc17 cells to lack markers including perforin, granzyme B, programmed death 1 receptor, and FoxP3. These results indicate that the main role of these cells is likely to be the production of IL-17 rather than a direct effector function.

Taking these results together and synthesizing the recent findings from several research groups, we propose a model of a cancer immunoediting mechanism involving Tc17 cells, regulatory T cells, tumor cells, monocytes, myeloid-derived suppressor cells, cytotoxic T lymphocytes and their associated cytokines, and other mediators (*Figure 1*). Dead or dying tumor cells activate monocytes and create a unique microenvironment containing TGF-β, IL-6, and IL-1β, which induces naive $CD8^+$ T cells to differentiate into Tc17 cells. Prostaglandin E2 and IL-23 thereby contribute to the survival and expansion of such Tc17 cells. Regulatory T cells, which consume IL-2, maintain the presence of the Tc17 cells. The IL-17 secreted by these Tc17 cells (Th17 may also contribute to the production of IL-17) stimulates tumor cells to release CXCL12. Consequently, CXCR4-bearing myeloid-derived suppressor cells migrate to the tumors. The recruited myeloid-derived suppressor

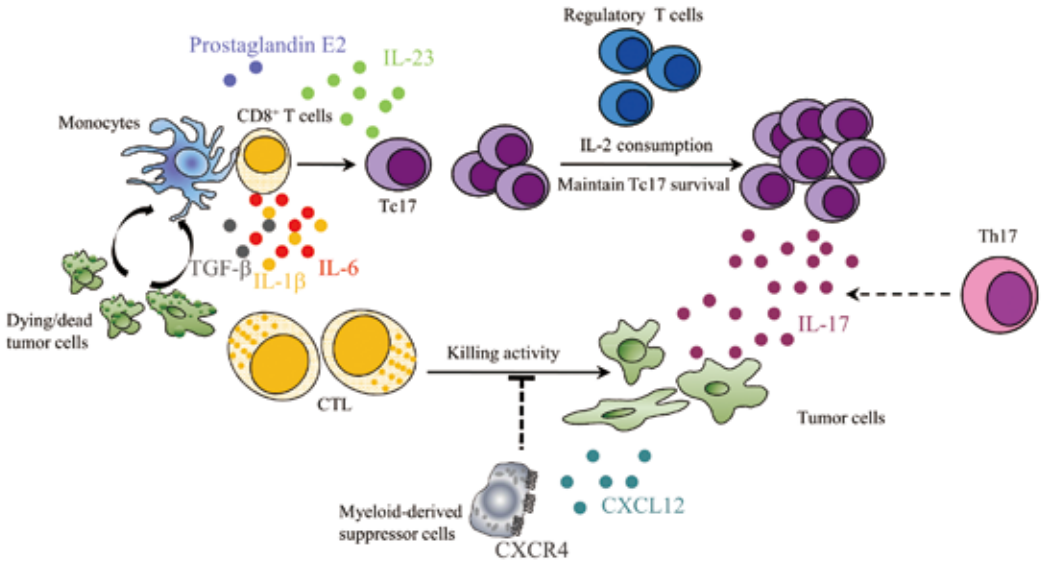

Figure 1 A proposed cancer immunoediting mechanism mediated via Tc17. Dead or dying tumor cells activate monocytes and create a unique microenvironment containing TGF-β, IL-6, and IL-1β, which induces naive $CD8^+$ T cells to differentiate into Tc17 cells. Prostaglandin E2 and IL-23 thereby contribute to the survival and expansion of such Tc17 cells. Regulatory T cells, which consume IL-2, maintain the presence of the Tc17 cells. IL-17, which is secreted by these Tc17 cells (Th17 may also contribute to the production of IL-17), stimulates tumor cells to release CXCL12. Consequently, CXCR4-bearing myeloid-derived suppressor cells migrate to the tumors. The recruited myeloid-derived suppressor cells exert their immunosuppressive function and inhibit cytotoxic T lymphocyte killing activity

cells exert their immunosuppressive function and inhibit cytotoxic T lymphocyte killing activity. As a consequence, tumor growth progresses unimpeded.

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Optimal lymphadenectomy for gastric cancer: is there a magic number?

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Xu and colleagues propose the ambitious tasks of evaluating in gastric cancer patients "the long-term effect of number of examined lymph nodes on the prognosis of patients," and exploring "the optimal number of lymph nodes for accurate staging in patients with node-negative gastric cancer after D2 dissection" (1). These two distinctly different goals require very dissimilar analytic strategies. To our surprise, they report one number, not two: 16. The question persists—"Is there a magic number of resected lymph nodes that ensures an optimal lymphadenectomy for gastric cancer?"

How was the analysis done?

The authors use the process of evident differences ("best cutoff") in survival to identify patient groups based on number of lymph nodes resected. Simply, each group had a range of survival that fell within the confidence limits (*Figure 1*). This produced 4 groups (1 to 6 nodes resected, 7 to 10, 11 to 15, and ≥16) that did not include an identical range of lymph nodes resected and ignored the quasi-continuous nature of this ordinal variable. The composition of these groups was very different. Patients with ≥16 lymph nodes resected were younger, had more distal gastric cancers, and more T1 and T2 cancers. The authors correctly comment that these factors "influenced the number of nodes resected," but did not perform any adjustments, thus ignoring these differences and relying solely on univariable analysis.

The outcome was disease-specific mortality, a ratio with the numerator being number of deaths attributed to the disease during a specific time interval, and the denominator the size of the population at the midpoint of the interval (2). We are not given details of how the authors actually calculated this outcome. Five-year gastric cancer-specific survival was 66%, 70%, 79%, and 91% for groups 1 to 4, respectively. The authors chose to test the effect of number of nodes resected, dichotomized as <16 and ≥16, on gastric cancer-specific survival in a stepwise univariable fashion with increasing T classification. Survival was similar for the two groups for T1 cancers, but different for T2, T3, and T4 cancers. Although the authors attribute these results to number of lymph nodes resected, these differences may also be explained by difference in group composition. The analysis was not constructed or conducted to identify an exact number; it can only address the unequally dichotomized groups, one with a range of 0 to 15 lymph nodes and the other with an unlimited range of ≥16.

The population studied included only patients free of regional lymph node metastases; this exclusion makes the authors' second goal of accurate staging unattainable.

What is known?

Recent papers using study groups of variable size and composition and multiple analytic techniques have tried to determine the number of resected lymph nodes that predicts improved survival in patients undergoing gastrectomy for cancer. Huang and colleagues studied 211 node-negative gastric cancer patients and found that to improve survival, ≥15 nodes should be resected for pT1 and pT2 patients and ≥20 nodes for pT3 and pT4 patients (3). Smith and colleagues used SEER data and found a near linear trend between

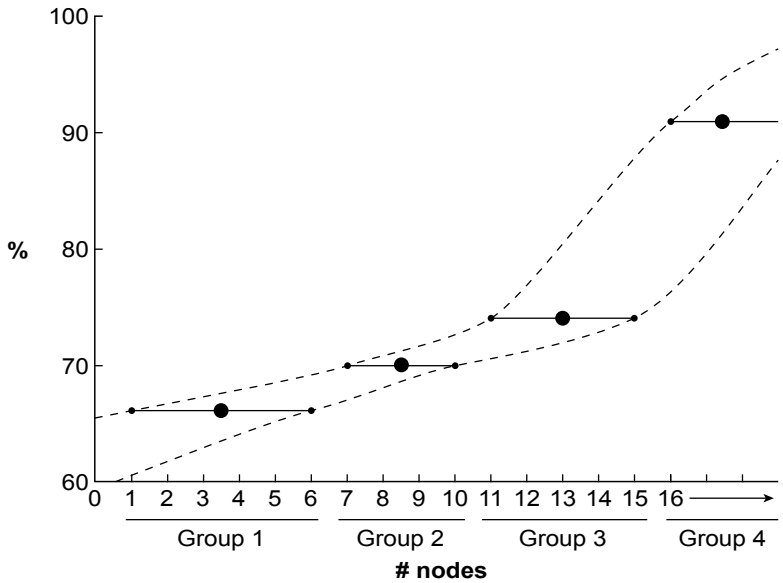

Figure 1 Identification of study groups: The process evaluated evident differences in survival (5-year, *y* axis) relative to number of lymph nodes resected (*x* axis). By "evident differences," we have depicted that the upper confidence limit of 5-year survival at a lower number of nodes touches the lower confidence limit of a higher number of nodes. Successive ranges of 5-year survival (horizontal lines) that fell within the confidence limits (dotted lines) produced 4 groups. Note that we do not know exactly what was done by the authors, but most methods to produce groupings rely on techniques approximating this

superior survival and number of lymph nodes examined (4). A cut-point analysis revealed the greatest survival difference at 10 lymph nodes examined, but survival improved up to 40 lymph nodes examined. Giuliani and colleagues reported no deaths in node-negative patients with ≥23 lymph nodes resected (5), and Volpe and colleagues reported improved survival in patients undergoing a D2 resection with ≥15 lymph nodes resected (6). None of these articles addresses the number of lymph nodes that need to be resected to produce accurate staging.

The esophageal cancer experience has addressed the authors' two goals. The number of lymph nodes resected that maximizes overall survival was related to T classification: 10 lymph nodes for pT1, 20 for pT2, and ≥30 for pT3 (7). The number of lymph nodes resected for accurate staging that adequately predicts positive lymph node classification (pN+) is a range that depends on the degree of certainty required. Although the sensitivity of classifying pN+ continued to improve up to 100 nodes examined, maximum increase of sensitivity occurred from 0 to 6 nodes, and over 90% sensitivity was reached at 12 (8). For esophageal cancer, the magic number—the number that maximizes overall survival—is the larger of these two. However, this is not a single number, but one that is dependent on T classification.

What should be done?

It is evident that a single number does not define optimal lymphadenectomy for gastric cancer. Xu and colleagues in their stated purposes outline the dual duties of the surgeon during lymphadenectomy for cancer. A sufficient number of lymph nodes must be excised to accurately stage cancer and to maximize survival. We predict that for gastric cancer, similar to esophageal cancer, it is likely the number of lymph nodes that maximizes overall survival. However, this will not be a single number but will vary depending on other cancer characteristics.

The surgeon should remove as many regional lymph nodes as is safely possible. More is better. There is no magic number.

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Translational Research

Survival of metastatic gastric cancer: significance of age, sex and race/ethnicity

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Background: Despite the success of modern chemotherapy in the treatment of large bowel cancers, patients with metastatic gastric cancer continue to have a dismal outcome. Identifying predictive and prognostic markers is an important step to improving current treatment approaches and extending survival.

Methods: Extracting data from the US NCI's Surveillance, Epidemiology, and End Results (SEER) registries, we compared overall survival for patients with metastatic gastric cancer by gender, age, and ethnicity using Cox proportional hazards models. 13,840 patients (≥18 years) were identified from 1988-2004. Males and females were categorized by age grouping and ethnicity.

Results: 19% of Hispanic patients were diagnosed <45 years of age as compared to 5.5% of Caucasians. Caucasian patients and men were more likely to be diagnosed with tumors in the gastric cardia (P<0.001). In our survival analysis, we found that women had a lower risk of dying as compared to men (P<0.001). Overall survival diminished with age (P<0.001). The median overall survival was 6 months in patients of ≤44 years old as compared to 3 months in patients 75 years and older. Gender differences in overall survival significantly varied by race and tumor grade/differentiation (P for interaction =0.003 and 0.005, respectively).

Conclusion: This is the largest study of metastatic gastric cancer patients from the SEER registry to show that age, gender, and tumor location are significant independent prognostic factors for overall survival in patients with metastatic gastric cancer.

Keywords: Gastric cancer, gender, age, ethnicity, survival

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Introduction

Although its incidence and mortality has declined over the last half-century, gastric cancer remains the fourth most common cancer and the second most frequent cause of cancer death in the world (1,2). The American Cancer Society estimates that in 2008, there were 21,500 new cases of gastric cancer and 10,880 deaths in the United States (3). As gastric cancer incidence declines, the frequency of prox imal gastric and gastroesophageal junctional adenocarcinomas continues to rise and has become a significant clinical challenge (4,5). There is substantial geographic variation in the incidence and mortality of gastric cancer, with the highest rates in East Asia and the lowest in North America (2). H. pylori infection, dietary factors, and smoking patterns may contribute to these disparities (6-9).

The survival rates for gastric cancer are among the

worst of any solid tumor. Despite the success of modern chemotherapy in the treatment of large bowel cancers, the 5-year survival of patients with advanced gastric cancer is 3.1% (1,4). The role of surgery is also limited as only 23% of stage IV gastric cancer patients receiving a palliative gastrectomy are alive one year after surgery (4). Progress was recently made as treating Her-2-Neu (H2N) overexpressing gastric cancers with Traztuzumab was found to significantly improve survival (10). Identifying additional predictive and prognostic markers is an important step to improving current treatment approaches and extending survival.

Two distinct histologic types of gastric cancer, the "intestinal type" and "diffuse type", have been described (11). The diffuse type of gastric cancer is undifferentiated and characterized by the loss of E-cadherin expression; an adhesion protein that helps maintains cellular organization (12). The well differentiated intestinal type is sporadic and highly associated with environmental exposures, especially H. pylori infection (13). There are also biologic differences between these subtypes of gastric cancer that may guide treatment approaches. H2N is over expressed more often in the intestinal *vs.* the diffuse type, 30% *vs.* 6% in one study (14). The Beta-catenin/Wnt signaling pathway is also recognized to play a large role in the molecular carcinogenesis of the intestinal type cancer (15).

Despite the genetic heterogeneity of gastric cancer, several biological determinants of risk and prognosis have been identified. Genetic polymorphisms of cytokines released with "oxidative stress" such as IL-Iβ, IL-10, and TNF-A have been associated with increased gastric cancer risk (16-18). Over expression of the oncogenes, tie-1, CMET and AKT have been found to confer a poor prognosis in both subtypes (19-21). Tumor expression of the isoenzyme COX-2 is an independent prognostic factor for gastric cancer survival (22). This benefit may be mediated by a reduction in lymphangiogenesis, another correlate of prognosis (22,23). Recently Her-2/Neu over expression, an important predictive and prognostic factor in breast cancer has been independently associated with a poor prognosis in gastric cancer (24,25).

The prognostic significance of age, gender, and ethnicity in metastatic gastric cancer is unclear. The prevailing belief that young patients with gastric cancer have a more aggressive disease has been recently called into question (26,27). Several prospective and population studies since 1996 have consistently shown that age is not a prognostic factor for survival, despite the higher prevalence of "diffuse type" cancer which typically has a worse outcome (28,29). However, according to a recent population-based study of gastric cancer, a significant impact of age on survival was found in patients with stage IV disease (30).

As compared to women, men are twice as likely to develop and die from gastric cancer, in the US (1). Although this may represent varying environmental exposures between genders, studies demonstrate that menstrual factors such as age of menopause and years of fertility are associated with gastric cancer incidence (31). Interestingly, woman may be more likely to have a "diffuse type histology" (32).

There are also significant ethnic and racial differences in gastric cancer incidence and survival. Asian patients consistently have increased survival rates compared to their western counterparts (33). Ethnic Asians living in the US share this benefit which suggests that these differences are not likely treatment related (34). Other racial differences in the US are notable as the incidence and mortality is 50% higher in African Americans than Caucasians (35).

Our study sought to evaluate the clinical correlates of survival in metastatic gastric cancer. Specifically we examined the inf luence of age, gender, ethnicity on survival. We also explored the interactions between patient characteristics and tumor histology, grade, size, and location (cardia vs non-cardia).

Patients and methods

Data source

Adult patients with metastatic gastric cancer were identified from the SEER registry 1988-2004 database, which collects information on all new cases of cancer from 17 populationbased registries covering approximately 26% of the US population.

Study population

The disease was defined by the following International Classification of Diseases for Oncology (ICD-O-2) codes: C16.0-C16.9. We identified patients (n=15,360) who had metastatic disease defined by SEER Extent of Disease code: 85. We restricted eligibility to adults (aged 18 years or older) who were diagnosed with metastatic gastric cancer (MGC) in 1988 and later (n=15,348); because the record of extent of disease was not available for accurate staging prior to 1988. We excluded cases (less than 10% of adult patients with metastatic gastric cancer) who were diagnosed at death certificate or autopsy, no follow-up records (survival time code of 0 months),

as well as lacking documentation on race/ethnicity. A total of 13,840 MGC patients of 18 years and older were included in the final sample for the current analysis.

Variable definitions

Information on age at diagnosis, sex, race, and ethnicity, marital status, treatment type, primary site, tumor grade and differentiation, histology, tumor size, and lymph node involvement, and overall survival were coded and available in SEER database. The primary endpoint in this study was overall survival that was defined as the months lapsing from diagnosis to death. For the patients who were still alive at last follow-up, overall survival was censored at the date of last follow-up or December 31, 2004, whichever came first.

Age
We chose the cut points for age groups based on the previous studies (18-44, 45-54, 55-64, 65-74, and 75 and older).

Ethnicity
Patients were divided into five ethnic groups, "Caucasian" (Race/Ethnicity code, 1), "African American" (Race/Ethnicity code, 2), "Asian" (Race/Ethnicity code, 4-97), "Hispanic" (Spanish/Hispanic Origin code, 1-8), and Native American (Race/Ethnicity code, 3).

Primary site
According to the latest guidelines for gastric cancer classificationa, the stomach is anatomically delineated into the upper, middle, and lower thirds by dividing the lesser and greater curvatures at two equidistant points and joining these points. The sites were defined by the following codes from ICD-O-2: Cardia, (C16.0), Body (C16.1-2, C16.5-6), Lower (C16.3-4), and Overlapping lesion of stomach (C16.8). For the ones that are not specified, they were categorized together as Stomach, NOS (C16.9).

Marital status
Subjects were categorized into "Not married" (including never married, separated, divorced, widowed, and unknowns) and "Married" (including common law).

Treatment type
SEER variables, RX Summ-radiation and RX summ-surg prim site were used to define treatment types: "Surgery" for patients who had surgery (local tumor destruction and excision, and gastrectomy) and/no radiation, "Radiation therapy only" for patients who only had radiation therapy, "Untreated" for patients who did not have surgery nor radiation therapy, and "Unknown". Information on chemotherapy was not available in SEER.

Grade
Grade was defined by the following ICD-O-2 codes; well/moderately differentiated (Code 1-2), poorly differentiated/undifferentiated (Code 3-4), and others (Code 5-9).

Histological type
Histological types were defined by the following ICD-O-3 codes: 8140- for adenocarcinoma, 8490 for Signet ring cell carcinoma, and the rest of the types were categorized as 'Others'.

The size of the primary tumor and the presence of lymph node involvement were not of interest in the current analysis. Our cohort consisted entirely of patients with metastatic disease.

Statistical analysis

Subjects were grouped by age to 18-44, 45-54, 55-64, 65-74, and 75 and older. We stratified them by sex, race, marital status, treatment type, grade, histological type, and primary site. Descriptive statistics were calculated for categorical variables using frequencies and proportions. Sex, race, tumor grade, marital status, primary site, histological type, and treatment type were independent variables. Differences among age groups in each subgroup were evaluated using the chi-square test.

We constructed Cox proportional hazards models to examine the association between age and survival in men and female separately. We compared survival across age groups adjusting for potential confounders including geographic region and year of diagnosis. By conducting this ana lysis separately by gender, we were able to determine pattern differences between genders. The Cox proportional hazards model included year of diagnosis and participating SEER registry site as stratification variables. Marital status, treatment, primary site, histology, tumor grade and differentiation, size of primary tumor, and lymph node involvement were used as covariates. Hazard Ratios (HRs) and 95% confidence intervals were generated, with hazard ratios less than 1.0 indicating survival benefit (or reduced mortality). Pairwise interactions (age and sex, age and race, and sex and race) were checked using stratified models and

were tested by comparing corresponding likelihood ratio statistics between the baseline and nested Cox proportional hazards models that included the multiplicative product terms (36). Departure of the proportional hazard assumption of Cox models will be examined graphically such as log-log survival curves or smoothed plots of weighted Schoenfeld residuals (37) and by including a time-dependent component individually for each predictor.

All analyses were conducted using P<0.05 as the significance level and statistical analyses were performed with the use of SAS software (version 9.1; SAS Institute, Cary, NC).

Results

Patient baseline characteristics

The final cohort for analysis consisted of 13,840 patients, 8710 men (63%), and 5130 women (37%). Their age distribution is as follows: 1,207 (9%) aged 18–44; 1,698 (12%) aged 45–54; 2,701 (20%) aged 55–64; 3,901 (28%) aged 65–74; and 4,333 (31%) aged 75 years and older. The median age was 68 years (range: 18–104). 60% of the MGC cohort were White, 13% African American, 13% Asian, 14 % Hispanic, and 1% Native American. Tumor characteristics and treatment received are shown in *Table 1*.

Age and ethnicity in MGC

5.5% of Whites with MGC were between 18-44 years of ages as compared to 10% of African Americans, 11% of Asians, and 19% of Hispanic patients. 36% of White gastric cancer patients were diagnosed over 75 years of age; 29% of Asian, 27% of AA, and 20% of Hispanic.

Tumor location: cardia vs. non-cardia

The incidence of cardia and non-cardia tumors varied significantly depending on gender and ethnic background. 30% of men and 14% of women had gastric ca arising from the cardia. The incidence of cardia cancers also varied significantly across ethnicities. 32% of Whites had cardia primaries, 13% of AA's, 11% of Asians, and 14% of Hispanics.

Survival analysis

The median overall survival (OS) in patients with MGC was only 4 months. The prognostic significance of several clinical and tumor characteristics were limited as the median OS varied little when stratified by sex, race, tumor site, grade/ differentiation, and histology (*Table 1*).

However, age, use of local treatment, tumor differentiation, and tumor site were found to have a clinically significant effect. The youngest group of patients had an improved OS when compared to their older counterparts (*Table 1*), as the median OS for patients 44 years or younger was 6 months compared to 3 months in patients 75 years or older. Survival was significantly worse in every successive age decile. Patients who had received any treatment had significantly improved survival. Gastrectomy or local surgery had a median OS of 8 months compared to a median OS of 3 months in patients who were not treated with surgery or radiation [HR =0.600 (0.561, 0.643)] (*Table 1*). Similarly, patients receiving radiation treatment had a survival benefit [HR =0.802 (0.746, 0.862)].

Tumor characteristics had a significant impact on survival. As expected, patients with poorly differentiated tumors had a worse survival than those with moderately or well differentiated tumors [HR 1.19, P<0.001 (1.139, 1.250)]. We also found that tumors located in the gastric cardia conferred a survival benefit when compared to nonproximal tumors [HR=0.945, P<0.001 (0.904, 0.989)].

In multivariate analysis, sex, age, treatment, and tumor characteristics were significantly associated with overall survival. Females had lower risk of dying compared to males (HR=0.916, 95%CI: 0.881–0.952) and mortality increased with age at diagnosis (P<0.001, *Table 1*). There was no significant difference in OS across race/ethnicity groups (P=0.16, *Table 1*).

Sex, race, grade/differentiation and MGC

The effect of sex on OS was signif icantly varied by race and tumor differentiation in patients with MGC (Pfor interaction =0.003 and 0.005, respectively, *Table 2*). White and African American woman had significantly lower risk of dying compared to their male counterparts. In Asian, Hispanic, and Native American populations, men and women had equivalent survival (*Table 2*) Women also had a significantly lower risk of dying compared to males in patients whose tumors were poorly differentiated or undifferentiated or had unknown tumor grade (*Table 2*).

Discussion

This cohort of metastatic gastric cancer patients from the

Table 1 Overall survival of patients with metastatic gastric cancer by demographic and clinicopathologic characteristics and treatment, SEER data 1988-2004

Characteristics	N	Median OS (95% CI), months	Hazard R atio (95% CI)*	P value*
Sex				<0.001
Male	8710	4 (4, 4)	1 (Reference)	
Female	5130	4 (4, 4)	0.916 (0.881, 0.952)	
Age, years				<0.001
18-44	1207	6 (5, 6)	0.806 (0.748, 0.868)	
45-54	1698	5 (5, 6)	0.920 (0.862, 0.981)	
55-64	2701	5 (4, 5)	1 (Reference)	
65-74	3901	4 (4, 4)	1.119 (1.062, 1.179)	
≥75	4333	3 (3, 3)	1.395 (1.325, 1.470)	
Race				0.16
White	8281	4 (4, 4)	1 (Reference)	
African American	1781	4 (3, 4)	1.040 (0.982, 1.102)	
Asian	1770	4 (4, 5)	0.966 (0.905, 1.031)	
Hispanic	1880	4 (4, 5)	1.024 (0.965, 1.087)	
Native American	128	3 (2, 4)	1.222 (0.959, 1.556)	
Site				0.003
Cardia	3383	5 (4, 5)	0.969 (0.919, 1.021)	
Body	3402	4 (4, 4)	1 (Reference)	
Lower	2417	4 (4, 4)	0.996 (0.942, 1.053)	
Overlapping lesion of stomach	1635	4 (4, 4)	1.086 (1.020, 1.157)	
NOS	3003	3 (3, 4)	1.048 (0.994, 1.105)	
Treatment				<0.001
Surgery	1573	8 (7, 8)	0.600 (0.561, 0.643)	
Radiation alone	1779	5 (5, 5)	0.802 (0.746, 0.862)	
Untreated	4774	3 (3, 3)	1 (Reference)	
Unknown	5714	4 (3, 4)	0.922 (0.843, 1.009)	
Grade/differentiation				<0.001
Well/moderately differentiated	2874	5 (4, 5)	1 (Reference)	
Poorly differentiated or undifferentiated	7917	4 (4, 4)	1.193 (1.139, 1.250)	
Unknown	3049	4 (3, 4)	1.040 (0.982, 1.101)	
Histolog y				<.001
Adenocarcinoma	8041	4 (4, 4)	1 (Reference)	
Signet ring cell carcinoma	2485	4 (4, 4)	0.985 (0.936, 1.037)	
Other	3314	4 (4, 4)	0.883 (0.843, 0.925)	

*, Based on Cox proportional hazards model included all variables in the table, tumor size, lymph node involvement, and marital status.

Table 2 Overall survival of patients with gastric cancer by sex, SEER data 1988-2004

	Males			Females			(95% CI)†
	N	MS (95%, CI), ms	Hazard ratio (95% CI)*	N	MS (95%, CI), ms	Hazard ratio (95% CI)*	
Race							
White	5373	4 (4, 4)	1 (Reference)	2908	4 (3, 4)	1 (Reference)	0.907 (0.862, 0.956)
African American	1129	3 (3, 4)	1.082 (1.006, 1.165)	652	4 (4, 5)	0.977 (0.884, 1.079)	0.818 (0.729, 0.918)
Asian	1039	4 (4, 5)	0.892 (0.819, 0.972)	731	4 (4, 5)	1.077 (0.968, 1.199)	1.027 (0.918, 1.150)
Hispanic	1095	4 (4, 4)	1.031 (0.955, 1.114)	785	5 (4, 5)	1.052 (0.953, 1.161)	0.925 (0.827, 1.034)
Native American	74	3 (2, 4)	1.036 (0.749, 1.433)	54	3 (2, 5)	1.304 (0.866, 1.963)	1.016 (0.536, 1.927)
P value for interaction*	0.003						
Grade/differentiation							
Well/moderately differentiated	1990	5 (4, 5)	1 (Reference)	884	4 (4, 4)	1 (Reference)	1.009 (0.917, 1.112)
Poorly differentiated or undifferentiated	4965	4 (4, 4)	1.231 (1.162, 1.303)	2952	4 (4, 4)	1.130 (1.037, 1.231)	0.913 (0.867, 0.961)
Unknown	1755	4 (3, 4)	1.105 (1.028, 1.187)	1294	4 (3, 4)	0.956 (0.864, 1.057)	0.870 (0.797, 0.950)
P value for interaction*	0.005						

*, Based on Coxproportional hazards model in males and females, separately, adjusted for age, marital status, site of primary tumor, treatment, histolog y, grade, tumor size, and lymph node involvement. †, Hazard ratios compared overall sur vival in females to males (reference group) across race or grade/differentiation based on Cox model adjusted for age, marital status, site of primary tumor, treatment, histolog y, grade, tumor size, and lymph node involvement.

SEER database represents a wide cross-section of patients with variable socioeconomic and ethnic backgrounds. Our analysis also included a robust variety of pathology and is likely a more generalizable representation than can be found in clinical trials or case series.

As expected, we found tumor characteristics such as grade, differentiation, and histology were associated with survival in advanced gastric cancer. Notably, there was a survival advantage attributable to gastric cardia lesions when compared to non-cardia lesions. This sur vival advantage persisted after controlling for the increased prevalence of cardia lesions in Caucasians and men.

Survival differences between cardia and non-cardia lesions may reflect differences in pathogenesis and tumor biology. H. pylori infection is recognized as a unique risk factor for non-cardia lesions while gastroesophageal reflux disease plays a role in the development of proximal lesions (38,39). Interestingly, there is growing evidence that H2N expression is variably expressed in proximal and distal gastric cancer lesions (40). The proto-oncogene Her-2/neu (H2N) is located on chromosome 17q21 and encodes a transmembrane tyrosine kinase growth factor receptor featuring substantial homology with the EGFR (41,42). Over-expression of the H2N protein has been identified in from 10 to 34% of breast cancers and is associated with a poor prognosis (43). Over-expression of H2N has been reported in gastric and gastro-esophageal tumors (24). Additionally, there are studies describing H2N as a poor prognostic factor in gastric cancer (40). Further studies are needed to investigate its role in the development of proximal and distal gastric lesions.

In addition to tumor characteristics, patient features, such as age and sex, also had significant prognostic impact. Ethnicity—often described in gastric cancer literature as having a prominent prognostic role—had no effect on survival. We could not confirm previous reports that Asian and Hispanic patients with gastric cancer have an improved outcome. We did find that a higher percentage of Hispanic patients present at a younger age. 36% of our Hispanic patients presented at ages less than 54 yo *vs.* 16% of white patients. These findings are consistent with a single institution study, which found that Hispanics present at a younger age when compared to other ethnicities (44).

After adjusting for sex, race, marital status , treatment type, primary site, histology, the year of diagnosis and SEER site, we found significant increased cancerspecific mortality among men and older age groups. The survival

for our youngest age group was 2 fold higher than the oldest age group. Our findings do not confirm previous reports that younger patients with metastatic gastric cancer have poorer survival. Outside of treatment with surgery, young age was the best prognostic marker. We could not address the role of systemic chemotherapy on overall survival in the current study due to lack of information in SEER. This likely ref lects the higher rate of treatment we found in the younger patients and unlikely represents differences in tumor biology or kinetics.

Consistent with previous reports, we found that women with MGC lived longer than men. We did not find any association between gender disparities and age. Women of every age group, pre-and postmenopausal, had an equivalent survival advantage. When examined more closely, we found that this difference was limited to African American and White patients. There were no gender differences in the Hispanic and Asian patients. These differences were not attributable to the presence of cardia or non-cardia lesions. Although there have been no reports of variable expression of H2N by gender, there are gender differences in expression of estrogen receptor (ER) and ER messenger RNA in gastric cancer (45). A possible explanation for the survival advantages in women may be found in a recent study addressing the interactions between the estrogen receptor and her- 2neu receptor pathways in breast cancer development and treatment response. Hurtado and colleagues found her-2-neu up regulation following the silencing of PAX-2 in cell lines treated with tamoxifen, which suggests that tamoxifen-estrogen receptor and estradiol-estrogen receptor complexes inhibits transcription of Her-2-Neu via Pax-2 (46).

Despite the clinical and genetic variability of advanced gastric cancer, we were able to identify clinical correlates for improved outcomes, which included gender and age. We did not find an association between ethnicity and survival. This is thought provoking as there are clear differences in the age of presentation and the prevalence of cardiac tumors. Hispanic patients were twice as likely to develop gastric cancer at <45 years old than Caucasians. Conversely Caucasians were twice as likely to develop gastric cardia lesions *vs.* non-proximal cancers. Further research into biological basis for these differences is warranted.

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Translational Research

Gastric cancer—a clinicopathological study in a tertiary care centre of North-eastern India

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Background: The incidence of gastric cancer varies in different parts of the world and among various ethnic groups. It remains the fifth most common cancer among males and seventh most common cancer among females in India.

Materials and methods: We conducted a retrospective study using the data base of 158 patients of primary gastric cancer diagnosed in the Department of Surgery at Regional Cancer Centre, RIMS, Manipur, India from July 2009 to June 2013.

Results: Our study revealed a male to female ratio of 2.16:1, distribution of age varied from 28 to 91 years. Majority of the men were in the age group of more than 60 years (45.37%) and majority of females were of 51-60 years (44%). Nearly 7.6% patients had a positive family history. Dietary history of intake salted, fermented fish was present in 67.7% of patients, whereas history of consumption of smoked meat was found in 77.8% of patients. Only 27.8% of patients in our study had history of regular consumption of fresh fruits. About 35.4% of the patients had poor drinking water source. Nearly, 67.6% of males and 44% of females had smoking history. Combined consumption of alcohol and smoking was present in 33.5% of patients. Vague abdominal discomfort was the most common presenting symptom in 61.4% of patients. The most common site of gastric cancer in our study was antrum (50.6%) followed by cardia (17.1%). The most common histological type was adenocarcinoma (95.6%). Most of our patients presented in locally advanced stage (62.7%).

Conclusions: Our analysis suggests that poor dietary habits such as smoked mead, dried fish and excessive use of tobacco are associated with high occurrence of gastric cancer in this part of the India. Increasing the awareness regarding the aetiology and varied clinical presentation among general population and health providers is needed for prevention and early detection.

Keywords: Gastric cancer; North-eastern India; dried fish; smoked meat

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Introduction

Cancer is a biggest burden of modern society. This is the second most common disease after cardiovascular disorders for maximum deaths in the world (1). Carcinoma of the stomach is a second leading cause of cancer death worldwide. The incidence of gastric cancer varies in different parts of the world and among various ethnic groups. It remains the fifth most common cancer among males and seventh most common cancer among females in India (2). However, the overall incidence of gastric cancer in India is less compared to the worldwide incidence and India falls under the low incidence region category for gastric cancer. Incidence of gastric cancer varies widely among the various regions within India due diverse culture and related food habits. Reports from the National Cancer Registry Programme (NCRP) 2010, suggested that the mean age-adjusted rate (AAR) of gastric cancer among urban registries in India varied from 3.0 to 13.2, with the highest rate being

recorded in Chennai registry (3-5). However, the prevalence was found to be much higher in the north eastern region of India. Currently, the north eastern state of Mizoram occupies the first position among Indian states and fifth position globally with AAR of 46.3 to 70.2 (6).

The prevalence of gastric cancer is also high in the state of Manipur. Based on our Hospital Based Cancer Registry (HBCR) 2012 gastric cancer is the second most common cancer among males comprising 6.1% of all the cancers and represents 2% in females. The aetiology of gastric cancer is multi-factorial and various dietary and environmental factors have been attributed. Diet is believed to play a major role in the development of gastric cancer. It is very well known that salt rich, smoked or poorly preserved foods, nitrates, nitrites have been associated with an increase in gastric cancer. Conversely, diets high in raw vegetables, fresh fruits (containing vitamin C, antioxidants) are associated with decreased risk (7-9). Helicobacter pylori infection is associated with an approximately two-fold increased risk of developing gastric cancer (10-12). Pylori H have been categorized as a "Group-1 human carcinogen" by the International Agency for Research on Cancer (13). The role of tobacco in the occurrence of gastric cancers cannot be undermined (6).

The state of Manipur, located in the north eastern region of India bordering Myanmar, has different customs, food habits, life-style, diverse ethnic groups, and the pattern of tobacco use as compared to the rest of the country. Majority of the people here consume dried salted fish, fermented, smoked and pickled meat and the use of tobacco is also widely prevalent. We undertook this study to analyse the demographic pattern, clinical presentations, pathological characteristics and stage at presentation of stomach cancer at Regional Cancer centre, Regional Institute of Medical Sciences (RIMS), situated in Imphal, Manipur state, is the biggest referral centre for the neighbouring North eastern states in India and bordering Myanmar.

Materials and methods

We conducted a retrospective study using the data base of 158 patients of primary gastric cancer diagnosed in the Department of Surgery at Regional Cancer Centre, RIMS, Manipur, India from July 2009 to June 2013. All these patients were diagnosed on clinical, radiological and endoscopic examination. The diagnosis was confirmed pathologically after the histopathological examination of either the resected specimen or the endoscopic biopsy specimen. All the patients with a confirmed gastric carcinoma were included in the study. The cases with primary gastric lymphoma, gastro intestinal stromal tumours (GIST) and gastric melanoma were excluded. Restaging was performed according to AJCC staging system (7^{th} edition) based on the available clinical and radiological findings. The compiled data included demographic data, medical history of chronic gastritis, peptic ulcer disease, family history of gastric cancer, dietary habits (intake of fermented, smoked meat, red meat), drinking water source, smoking habits, consumption of alcohol, chief presenting complaints, histological grade, TNM staging and the site of metastasis.

Descriptive statistics were used for analysing the data using SPSS version 20 and results were presented in percentage and simple frequency.

Results

This study included 158 patients with male to female ratio of 2.16:1, distribution of age varied from 28 to 91 years old. Majority of the men were in the age group of more than 60 years old (45.37%), followed by 51-60-year age group (31.4%) whereas majority of females were of 51-60-year-old category (44%), followed by more than 60-year-old group (36%). All in all, 93.5% males and 96% of females were more than 50 years old. Out of 158 patients in this study, 7.6% patients had a positive family history. Dietary history of intake salted, fermented fish was present in 67.7% of patients, whereas history of consumption of smoked meat was found in 77.8% of patients. Only 27.8% of patients in our study had history of regular consumption of fresh fruits. About 35.4% of the patients had poor drinking water source. Nearly, 67.6% of males and 44% of females had smoking history. Male to female ratio of smoking was 3.3:1. History of alcohol consumption was present in 55.5% of male and 10% of female cases. Combined consumption of alcohol and smoking was present in 33.5% of patients. Vague abdominal discomfort was the most common presenting symptom in 61.4% of patients followed by weight loss (59.5%), nausea (39.9%), early satiety and poor appetite (34.8%), vomiting (20.9%), dysphagia (18.4%) and melaena (15.8%) (*Figure 1*). About 25.3% of patients presented with abdominal lump, 55.5% of patients with tumour at cardia had history of dyphagia, 62.3% of patients with tumour in antro-pyloric region had history of weight loss, and 84.2% of patients had multiple presenting symptoms (*Table 1*). Pallor was noted in 48.7% of patients

at presentation, 53/108 males (49.07%) and 24/50 females (48%). Most common site of gastric cancer in our study was antrum (50.6%) followed by cardia (17.1%), body (13.9%), pylorus (13.3%) and fundus (2.5%). The most common site of tumour in both males and females was antrum, 57.4% and 36% respectively. The second most common site was cardia (17.6%) in males and body of the stomach (22%) in females. The most common histological type was adenocarcinoma (95.6%) followed by squamous cell carcinoma (3.2%). About 44.3% of the tumours were poorly differentiated, 35.8% moderately differentiated and 19.6% well differentiated (*Table 2*). Majority of the patients were of T3 stage (53.2%) at presentation followed by T2 (23.4%), T4 (15.8%) and T1 (7.6%). Likewise, N2 nodal staging was leading with 35.4% followed by N0 (27.8%), N1 (20.3%) and N3 (16.5%). Overall 37.3% of patients had distant metastasis at the time of presentation. Liver was the most common site of metastasis found in 17.1% patients followed by left supraclavicular lymph node (7.6%), peritoneal meatastais (7%) and multiple metastases (5.1%). Majority of the patients in our study were found to have locoregional disease at presentation (62.7%); of these early gastric cancers was found in 7.6% patients (*Figure 2*).

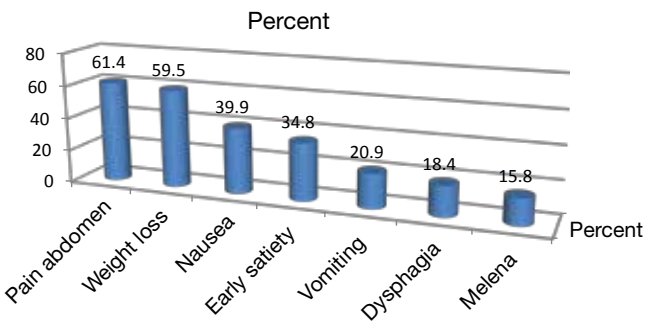

Figure 1 Common symptoms in gastric cancer patients.

Discussion

There is worldwide variation regarding the incidence and patterns of gastric cancer. Countries of Southeast Asia, Japan, South Korea and China have noted a high incidence of gastric cancer (14,15). The overall incidence of gastric cancer in India is less compared to rest of the world (4-6). However, certain regions of India have recorded a high incidence, especially the north eastern states like Mizoram (6). In North-East region very high incidence of all sites of cancers in general and tobacco related cancers in particular have been reported. Pattern of tobacco use is noted to be different in North-East region. The genetic susceptibility of cancer due to ethnic variation related to polymorphism and mutation in autosomal recessive genes has been suspected. Certain dietary and tobacco related carcinogens are known to act as co-factors to bring out genetic changes (16). A high incidence of gastric cancer has also been reported in the state of Manipur, where it constitutes the second most common malignancy among males. There is lack of clinic-pathological information about gastric cancer from Manipur.

In our study, the peak incidence of gastric cancer was in age group older than 60 years old (42.4%). Also male predominance was noted with male to female ratio of 2.16:1, which are comparable with other studies (17-21). Presumably, this male preponderance could be attributed to the high incidence of smoking (67.6%) found among the males, with male to female smoking ratio of 3.3:1 in our study. About 7.6% of patients in our study had a positive family history which was similar to another study (17).

Table 1 Symptoms with respect to location of tumour

Symptoms	Cardia	Fundus	Body	Antrum	Pylorus	Nos	Total [%]
Weight loss	16	3	10	50	13	2	94 [59.5]
Pain abdomen	9	3	14	55	12	4	97 [61.4]
Nausea	10	3	9	32	7	2	63 [39.9]
Vomiting	6	1	4	17	4	1	33 [20.9]
Early satiety	7	2	7	33	6	0	55 [34.8]
Dysphagia	15	1	2	9	2	0	29 [18.4]
Melena	3	2	5	11	4	0	25 [15.8]
Anemia	13	3	10	39	10	2	77 [48.7]
Mass abdomen	4	2	5	22	6	1	40 [25.3]

Table 2 Demographic and Clinico-pathologic characteristics of patients with gastric cancer

Variable	Subgroup	N [%]
Age at diagnosis [years] [n=158]	<40	9 [5.7]
	41-50	26 [16.5]
	51-60	56 [35.4]
	>60	67 [42.4]
Sex	Male	108 [68.4]
	Female	50 [31.6]
Family history	Present	12 [7.6]
Dietary history	Dried, fermented fish	107 [67.7]
	Fresh fruits	44 [27.8]
	Smoking	95 [60.12]
	Alcohol	65 [41.13]
Tumour site	Antrum	80 [50.6]
	Cardia	27 [17.1]
	Pylorus	21 [13.3]
	Body	22 [13.9]
	Others	8 [5]
T stage	T1	12 [7.6]
	T2	37 [23.4]
	T3	84 [53.2]
	T4	25 [15.8]
N stage	N0	44 [27.8]
	N1	32 [20.3]
	N2	56 [35.4]
	N3	26 [16.5]
M stage	M0	99 [62.7]
	M1	59 [37.3]
Tumour grade*	Well differentiated	31 [19.6]
	Moderately	55 [34.8]
	Poory	70 [44.3]
Tumour stage	Early gastric cancer	12 [7.6]
	Advanced Gastric cancer	87 [55.1]
	Systemic disease	59 [37.3]

*, tumour grade information not available for two cases.

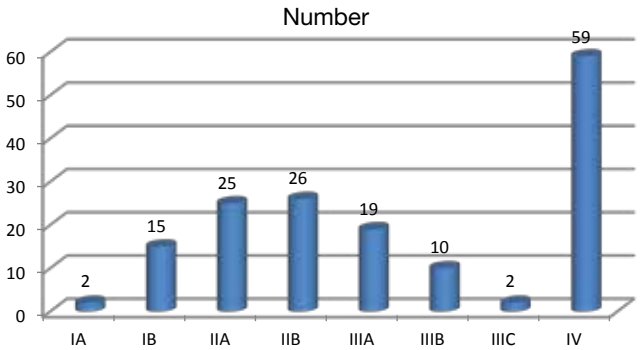

Figure 2 Frequency of overall staging.

However, many other studies have reported a positive family history of 17% of patients (22). Our low estimate of family history could have been because of poor reporting by patient attendees. An overwhelming majority of patients (77.8%) in our study had a history of consumption of smoked meat, and 67.7% of patients had history of consumption of dried, fermented fish. Whereas, only 27.8% of the patients had a history of regular consumption of fresh fruits. Consumption of dried fish has found to increase the risk of gastric cancer (23). It is also well known that high consumption of smoked meat and decreased consumption of fresh fruits increases the risk of gastric cancer (8,9). The most common presenting symptoms in our study abdominal pain (61.4%) and weight loss (59.5%), which were similar to other studies (17,24). Our findings revealed that most common site of tumour was antrum (57.45%) followed by cardia (17.1%) which are consistent with many other studies (25-28). However, increased incidence of tumour occurrence in gastro-esophageal junction has been noted in many western studies (27).

Considering the histological type, majority (95.6%) were found to be adenocarcinoma consistent with other studies (17,29). Majority of the tumours (44.3%) in our study were poorly differentiated, similar to other studies (17,30). Studies have shown that elder patients were more likely to have well or moderately differentiated tumours and young patients were more likely to have poorly-differentiated tumours [Nakamura *et al.*, (31)]. Similarly in our study six out of nine patients with <40 years old of age had poorly differentiated tumours. Early gastric cancer was present in 7.6% cases and majority (62.7%) had locally advanced gastric cancers at the time of presentation in our study. This figure is less compared 9-17% seen in western countries and far less compared to the prevalence of Japan where mass screening programmes for gastric cancer are in place (32). This highlights the need for aggressive endoscopy and biopsy for minimally symptomatic patients to improve the survival.

There is evidence to implicate chronic Pylori H infection as a major risk factor for the development of intestinal type of gastric cancer (9,11,12). However, we had no information regarding the infection status of patients in our study.

Conclusions

Our analysis suggests that poor dietary habits such as smoked meat, dried fish and excessive use of tobacco are associated with high occurrence of gastric cancer in this part of the India. Symptoms of weight loss and abdominal pain in elderly population should alert the healthcare providers about the possibility of gastric cancer. Increasing the awareness regarding the aetiology and varied clinical presentation among general population and health providers is needed for prevention and early detection. High risk subset may be undertaken for screening the disease.

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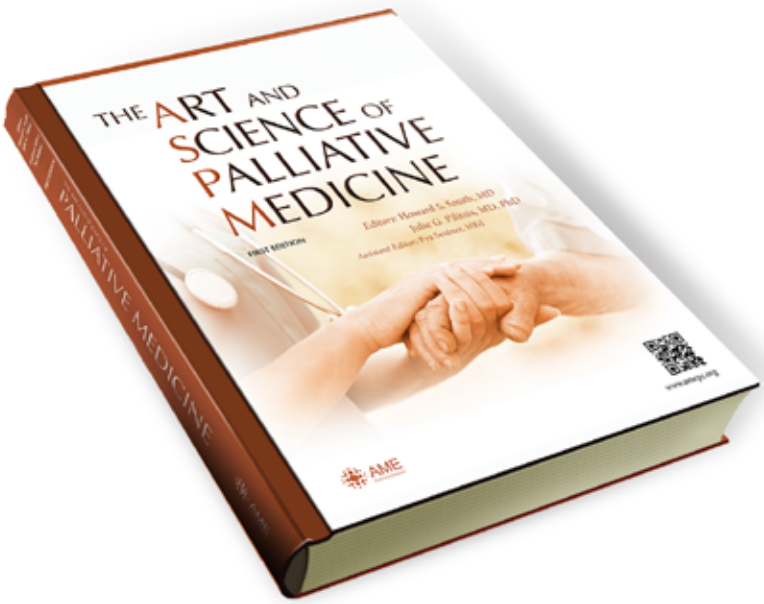

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