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Achalasia and Other Esophageal Motility Disorders

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Abstract Achalasia, diffuse esophageal spasm, nutcracker esophagus, and the hypertensive lower esophageal sphincter are considered primary esophageal motility disorder. These disorders are characterized by esophageal dysmotility that is responsible for the symptoms. While there is today a reasonable consensus about the pathophysiology, the diagnosis, and the treatment of achalasia, this has not occurred for the other disorders. A careful evaluation is therefore necessary before an operation is considered.

Keywords Primary esophageal motility disorders · Esophageal achalasia · Diffuse esophageal spasm · Nutcracker esophagus · Hypertensive lower esophageal sphincter · Esophageal manometry · Minimally invasive surgery

Achalasia, diffuse esophageal spasm (DES), nutcracker esophagus (NE), and the hypertensive lower esophageal sphincter (HTN-LES) are considered primary esophageal motility disorders (PEMD), as they occur in the absence of an identifiable cause such as gastroesophageal reflux disease (GERD).[1] These disorders present with a specific manometric pattern, and the dysmotility is considered responsible for the symptoms. While a reasonable consensus has developed for the pathophysiology, the diagnosis, and the treatment of achalasia, this has not occurred for the other disorders. The goal of this study is to review the clinical presentation, the diagnosis, and the role of minimally invasive surgery in their treatment.

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Esophageal Achalasia

Evaluation

In a study of 145 patients with untreated achalasia, dysphagia was the most common symptom as it was present in 94% of patients. Regurgitation was present in 76% of patients, heartburn in 52%, and chest pain in 41%.[2] At the time of referral, 65 patients (45%) were taking acid reducing medications on the assumption that GERD was the cause of their symptoms.[2] This study shows that symptoms are less sensitive and specific for the diagnosis of GERD than commonly thought. Patients with achalasia experience heartburn because of stasis and fermentation of food in the esophagus rather than real reflux.[3]

Endoscopy is usually the first test that is performed to rule out the presence of esophagitis or a mechanical obstruction secondary to a peptic stricture or cancer. It is important to remember that the presentation and the manometric picture of achalasia can be caused by a malignancy (secondary achalasia or pseudoachalasia), mostly at the level of the gastroesophageal junction.[4] Patients with secondary achalasia are usually older, have experienced symptoms for a shorter time, and have had a greater weight loss as compared with patients with primary achalasia. When an underlying malignancy is suspected, an endoscopic ultrasound or a CT scan with fine cuts of the

gastroesophageal junction is recommended. Barium swallow shows in most cases distal esophageal tapering, and it is important to assess the diameter and the axis of the esophagus (straight versus sigmoid).

Esophageal manometry is the gold standard for the diagnosis of achalasia. Lack of peristalsis and absent or incomplete relaxation of the lower esophageal sphincter (LES) in response to swallowing are the key criteria for the diagnosis. Contrary to common belief, the LES is hypertensive in less than half of patients.[2] Recently, a new classification of esophageal achalasia has been proposed based on high resolution manometry (HRM).[5] Using HRM, Pandolfino and colleagues identified three achalasia subtypes: type I, classic, with minimal esophageal pressurization; type II, achalasia with esophageal compression; and type III, achalasia with spasm. According to their results, type II is associated to the best therapeutic response (91% with dilatation and 100% with Heller myotomy). On the other hand, a favorable response to therapy was present in only 56% of type I and 29% of type III patients.[5] The importance of the manometric pattern as predictor of treatment success has also been demonstrated by others.[6] Further studies are necessary to confirm these results.

Ambulatory pH monitoring is important in untreated patients when the diagnosis is not clear (achalasia versus GERD) and in patients who still have dysphagia after endoscopic dilatation to see if abnormal reflux is present.[2] Rather than relying on the reflux score only, it is important to examine the tracings to distinguish between true and false reflux.[3]

Treatment

The first minimally invasive myotomy for achalasia was performed in the USA in January of 1991.[7] While the initial experience was based on a left thoracoscopic approach, the technique eventually evolved into a laparoscopic myotomy with a partial fundoplication. The high success rate of this operation[8–12] has brought a shift in practice, as surgery has gradually become the preferred treatment modality for most gastroenterologists and other referring physicians.[13, 14] This remarkable change has followed documentation that a laparoscopic myotomy outperforms balloon dilatation and intra-sphincteric botulinum toxin injection.[15–18]

The technique of a laparoscopic Heller myotomy and Dor fundoplication is described elsewhere.[19] The myotomy is usually 7 to 8 cm in length and extends for 2.0–2.5 cm onto the gastric wall. After the myotomy is completed, the muscle edges are gently separated to expose the mucosa for about 40% of the circumference. The Dor is a 180° anterior fundoplication which covers the exposed mucosa. Alternatively, a posterior partial fundoplication can be used.[20]

Some areas in the treatment of achalasia are still controversial, and often there is not enough evidence to clearly support one approach versus another.

- Thoracoscopic versus laparoscopic approach

  Even though the thoracoscopic approach gave very good relief of dysphagia, some shortcomings became soon apparent: cumbersome intraoperative management (double lumen endotracheal tube, left lateral decubitus, one lung ventilation), limited exposure of the gastroesophageal junction, postoperative discomfort, and a high rate of postoperative reflux (around 60%). These problems were mostly eliminated by the laparoscopic approach (simpler anesthesia in the supine position, better exposure of the gastroesophageal junction, possibility to perform a fundoplication).[13]
- Length of the myotomy

  When the thoracoscopic approach was used, the myotomy extended onto the gastric wall for 5 mm only.[7] With the laparoscopic approach, a longer myotomy can be easily performed avoiding the risk of persistent dysphagia, and a fundoplication added. Intraoperative endoscopy to locate the squamo-columnar junction is useful until enough experience is gained. Most surgeons today extend the myotomy onto the gastric wall for 1.5 to 2.5 cm, as it has been suggested that a longer myotomy is associated to better relief of dysphagia.[21]
- Difficulty of the myotomy

  Be aware of patients that are sent for surgery after failed endoscopic therapy (pneumatic dilatation and intra-sphincteric botulinum toxin injection). In some patients, particularly after treatment with botulinum toxin, a fibrotic reaction may occur at the level of the gastroesophageal junction with obliteration of the anatomic planes.[22–24] In these patients, the myotomy is more difficult, a perforation more frequent, and the relief of dysphagia less predictable.
- Fundoplication after laparoscopic Heller myotomy

  Gastroesophageal reflux into the aperistaltic esophagus can occur after a myotomy and may cause a stricture, Barrett's esophagus, and even adenocarcinoma.[25] Because a myotomy alone is associated to reflux in 40% to 60% of patients,[13, 26] a fundoplication must be added. In a prospective and randomized trial of myotomy alone or myotomy plus Dor fundoplication, Richards and colleagues showed that postoperative reflux was present in 48% of patients after myotomy alone but in only 9% of patients when a Dor fundoplication was added.[26] Even though it has been shown that a Nissen fundoplication is the best operation for GERD,[27] this procedure creates too much resistance at the level of the gastroesophageal junction in achalasia patients who have no peristalsis.[28, 29] In a prospective

and randomized trial of Dor fundoplication versus Nissen fundoplication after Heller myotomy, Rebecchi and colleagues showed that at a 5-year follow-up 15% of patients after myotomy and Nissen fundoplication had dysphagia as compared to only 2.8% after myotomy and Dor fundoplication.[29]

A partial fundoplication, either anterior or posterior, is therefore the procedure of choice in conjunction to a Heller myotomy for achalasia. To date, there has been no direct comparison between these two procedures in terms of reflux control. While a posterior fundoplication might determine better control of reflux and keep the edges of the myotomy open, an anterior fundoplication offers the advantage of a more limited dissection and of covering the exposed mucosa.[30]

- Procedure of choice in patients with sigmoid esophagus

  In the past, it was thought that patients with a dilated and sigmoid esophagus should undergo an esophagectomy for the fear that a myotomy would not improve the esophageal emptying with persistence of dysphagia.[25] An esophagectomy, however, is associated to considerable morbidity even in the hands of experienced esophageal surgeons. For instance, Devaney and colleagues reported a 10% rate of anastomotic leak, 5% rate of hoarseness, and 2% rate of bleeding, chylothorax, and death among 93 patients who had an esophagectomy for achalasia. In addition, 46% of patients had dysphagia requiring dilatation of the anastomosis.[25] Most surgeons today feel that a Heller myotomy should be the primary treatment for achalasia, regardless of the size and shape of the esophagus, and that an esophagectomy should be reserved as last resort for patients whose dysphagia is not amenable to other treatment.[31–33] For instance, Sweet and colleagues analyzed the outcome of a Heller myotomy among 113 achalasia patients who were divided in four groups based on the size and shape of the esophagus. A logistic regression model was created to examine factors associated with fair/poor outcome. Neither the size of the esophagus, age, sex, and preoperative LES pressure affected outcome. The only factor associated to a poor outcome was the preoperative treatment with botulinum toxin.[33]
- Persistent and recurrent dysphagia after Heller myotomy

  While persistent dysphagia is usually due to a technical problem (wrong diagnosis, short myotomy, wrong configuration of the fundoplication), recurrent dysphagia after a symptom-free interval can be secondary to a variety of factors such as formation of scar tissue at the end of the myotomy and gastroesophageal reflux with a peptic stricture.[34] A careful evaluation must be performed, including a careful history, review of the operative report, barium swallow, endoscopy, esophageal manometry, and ambulatory pH monitoring.[35] After the workup is completed and a possible cause identified, dilatation or a second operation are the options to be considered to improve the swallowing status.[33, 36–38] A dilatation should be tried first as it is effective in most patients.[33, 38] A second myotomy should be the second step,[36, 37] while an esophagectomy should be the last resort when all the other therapeutic modalities have been exhausted.

Other Primary Esophageal Motility Disorders

DES, NE, and the HTN-LES are the other primary esophageal motility disorders. Overall these disorders have not been studied extensively as achalasia, and they are still poorly understood.[39]

Evaluation

Most patients with DES and HTN-LES present with dysphagia. On the other hand, chest pain is the most common complaint of patients with NE.[40] For this reason, the majority of NE patients are referred to a gastroenterologist or a surgeon after a proper workup has excluded the presence of cardiac pathology.

Due to the intermittent nature of DES, a barium swallow shows a "corkscrew" esophagus in about 30% of patients. This test can be normal in patients with NE or similar to achalasia in patients with HTN-LES.[40]

An endoscopy is usually done in patients with dysphagia. Esophageal manometry shows the following findings:[1]

- DES: the LES can be similar to achalasia or normal. Esophageal peristalsis is characterized by simultaneous contractions following more than 20% but less than 100% of wet swallows.
- NE: the LES can be similar to achalasia or normal. Esophageal peristalsis is characterized by peristaltic waves in the distal esophagus of high amplitude (>180 mmHg) and prolonged duration (>6 s).

HTN-LES: LES pressure above 45 mmHg. Peristalsis is usually normal.

Ambulatory pH monitoring is of key importance in patients with a manometric picture of DES or NE. If GERD is present, these motility patterns should be considered secondary rather than primary, and therapy should be directed towards the correction of the abnormal reflux.[41]

Treatment

Selected patients with DES who have not responded to medical therapy should be considered surgical candidates.

The surgical treatment of DES is similar to that of achalasia (myotomy and partial fundoplication). The myotomy is usually extended more proximally than in patients with achalasia. The operation, performed either by an open or a laparoscopic approach, gives very good results.[40, 42, 43] For instance, Patti and colleagues reported the results of minimally invasive surgery in 34 patients with DES.[40] Dysphagia was relieved in 80% of patients after thoracoscopic myotomy and in 86% of patients after laparoscopic myotomy. Chest pain was relieved in 75% and 80% of patients, respectively. Regurgitation was also significantly improved.[40]

In patients with NE and chest pain, the results of surgery are disappointing. Patti and colleagues reported improvement of chest pain in only six of 12 patients with NE.[40] Dysphagia was instead improved in 80% of patients. Currently, these Authors propose a myotomy only in patients whose main symptom is dysphagia, or when associated pathology such as an epiphrenic diverticulum is present. The treatment of HTN-LES is similar to that of achalasia.

Epiphrenic Diverticulum

Epiphrenic diverticulum is a pulsion diverticulum, usually located in the distal 10 cm of the esophagus. It is due to herniation of the mucosa and submucosa through the muscle layers of the esophageal wall

Most patients complain of dysphagia, and respiratory symptoms are often present due to aspiration. A barium swallow is of key importance as it shows the position of the diverticulum (more frequently on the right side), the width of the diverticular neck, and its distance from the gastroesophageal junction. Endoscopy is important to rule out a neoplastic process and for proper placement of a manometry catheter.

Most authors today feel that an epiphrenic diverticulum is always caused by an underlying esophageal motility disorder.[44–47] While conventional manometry demonstrates a motility disorder in about 70% of patients, ambulatory manometry allows determination of the underlying problem in all patients.[44] These findings support the rationale for performing a myotomy in all patients with an epiphrenic diverticulum, regardless of the findings of conventional stationary manometry. Therefore, the operation of choice is resection of the diverticulum, esophageal myotomy, and partial fundoplication. Traditionally, the operation was performed through a left thoracotomy.[46] The development of minimally invasive surgery has brought a drastic change, as today most of these diverticula are resected through a laparoscopic approach.[45, 47]

Conclusions

The evaluation and treatment of PEMD has evolved during the last 20 years. Patient's evaluation is of key importance to clearly define the motility abnormality. Minimally invasive surgery has brought a shift in the treatment algorithm, as a laparoscopic Heller myotomy with partial fundoplication is today the procedure of choice for most patients with PEMD.

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REVIEW ARTICLE

Barrett's Esophagus: A Review of the Literature

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Abstract Barrett's esophagus (BE) is the premalignant lesion of esophageal adenocarcinoma (EAC) defined as specialized intestinal metaplasia of the tubular esophagus that results from chronic gastroesophageal reflux. Which patients are at risk of having BE and which are at further risk of developing EAC has yet to be fully established. Many aspects of the management of BE have changed considerably in the past 5 years alone. The aim of this review is to define the critical elements necessary to effectively manage individuals with BE. The general prevalence of BE is estimated at 1.6–3% and follows a demographic distribution similar to EAC. Both short-segment (<3 cm) and long-segment (≥3 cm) BE confer a significant risk for EAC that is increased by the development of dysplasia. The treatment for flat high-grade dysplasia is endoscopic radiofrequency ablation therapy. The benefits of ablation for non-dysplastic BE and BE with low-grade dysplasia have yet to be validated. By understanding the intricacies of the development, screening, surveillance, and treatment of BE, new insights will be gained into the prevention and early detection of EAC that may ultimately lead to a reduction in morbidity and mortality in this patient population.

Keywords Barrett's esophagus · Specialized intestinal metaplasia · Esophageal adenocarcinoma · Gastroesophageal reflux · Endoscopic therapy · Radiofrequency ablation

Introduction

Barrett's esophagus (BE) is the link between one of the most common gastrointestinal diseases, gastroesophageal reflux disease (GERD) and the most rapidly increasing cancer of the GI tract. The clinical importance of Barrett's esophagus is that it is a premalignant lesion for esophageal adenocarcinoma (EAC). The incidence of esophageal adenocarcinoma is rising at a staggering pace in the Western world, a 600% increase in 25 years.[1] Which patients are at risk of BE and which of those are at further risk of developing EAC has yet to be fully established. The objective of this article is to review the current body of knowledge of BE including the many components of disease management that have changed considerably in the last few years alone. By understanding the intricacies of the development, screening, surveillance, and treatment of BE new insights might be gained into the prevention and early detection of EAC.

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Definition

Barrett's esophagus (BE) was first described by Norman Barrett in 1950 as gastric epithelium lining the lower part of the anatomical esophagus.[2] The historical belief was that the presence of columnar epithelium for the last 2–3 cm of the distal esophagus was a normal finding. Thus, pathologic Barrett's esophagus was initially described as a columnar-lined esophagus (CLE) for greater than 3 cm proximal to the gastroesophageal junction (GEJ).[3]

The current definition, widely accepted in North America, is the endoscopic appearance of a columnar epithelium in the tubular esophagus and a biopsy demonstrating specialized intestinal metaplasia (SIM) on histological examination (Fig. 1).[4] SIM is itself characterized by the presence of goblet cells and is considered the hallmark lesion of Barrett's esophagus because it is known to predispose to the development of dysplasia and, therefore, adenocarcinoma

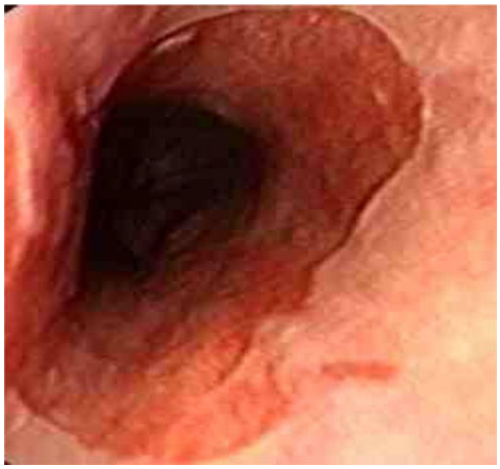

Fig. 1 Barrett's esophagus

regardless of the location in the esophagus. Barrett's esophagus is subdivided into long segment BE (≥3 cm) and short segment BE (<3 cm). Although this is an arbitrary distinction stemming from the origins of Barrett's esophagus, it has important clinical relevance.

Epidemiology

The true prevalence of Barrett's esophagus is not well known as many patients with BE are asymptomatic and because endoscopy is necessary to make the diagnosis. In the general population, the prevalence of BE is estimated to be between 1.6% and 6.8% (see Table 1). In one of the first papers to look at Barrett's prevalence, BE was found in seven of 733 unselected autopsy specimens.[5] This study was limited by the definition of BE which did not include SIM <3 cm from the gastroesophageal junction. This prevalence (0.34%) is comparable to current estimates for long segment BE. More recently, a random sampling of 1,000 people from a total population of 21,610 completed a gastroesophageal reflux disease (GERD) symptom survey and underwent esophagogastroduodenoscopy (EGD). Total prevalence of BE was 1.6%, 2.3% in patients with GERD symptoms, and 1.2% in patients without symptoms.[6] In a retrospective review of 5,019 EGD reports, the corresponding total population prevalence of BE was 1.7% (4.39% in symptomatic patients and 1.46% in asymptomatic patients).[7] If these estimates are correct, a BE prevalence of 1.6% of the US population over the age of 25 translates to >3 million individuals with Barrett's esophagus.

The demographic distribution of BE differs by gender, race, and age in a similar fashion to esophageal adenocarcinoma (EAC). When prevalence is estimated in older, non-Hispanic, Caucasian males, it is found to be between 8% and 25%. In a large community-based observational study, 4,205 patients were followed for 9 years. The annual incidence of BE was highest in non-Hispanic, white males (39/100,000 patient years) and higher in men than women (31 vs. 17/100,000 patient years, respectively) corroborating results of similar studies. This study also found an increase in frequency of the diagnosis of BE in parallel with a diagnosis of EAC suggesting that cancer risk is related to underlying BE rather than from differing risks of progression among demographic groups.

Table 1 Prevalence of Barrett's esophagus

Author	Type of study	Number of patients	Prevalence of BE	Limitations
Rex et al.[84]	Prospective observational study	961	6.8% (8.3% in pts with GERD and 5.6% in pts without GERD)	Bias towards older patients
Cameron et al.[5]	Prospective observational study (autopsy)	226	0.34%	Did not include BE <3 cm
Corely et al.[85]	Observational study	4,205	0.13%	Based on coding for BE dx (not pathology); adjusted for increase in use of endoscopy
Fan et al.[7]	Retrospective review	4,500	1.7% (4.39% in patients with GERD and 1.46% in those without)	
Gerson et al.[86]	Prospective observational study	110	25%	Performed in an at risk population (mean age 61, 73% Caucasian, 92% male)
Abrams et al.[87]	Retrospective cross-sectional study	2,100	4.4%	On initial endoscopy
Ronkainen et al.[6]	Prospective observational study	1,000	1.6% (2.3% in patients with GERD and 1.2% in those without)	
Zagari et al.[88]	Prospective cohort study	1,033	1.3% (1.5% in patients with GERD and 1.0% in those without)	
Westhoff et al.[89]	Prospective cohort study	378	13.2% in patients with GERD	Only in symptomatic patients. Bias towards older patients (median age 56) and male (94%)
Veldhuyzen van Zenten et al.[90]	Prospective cohort study	1,040	2.4% (4% in patients with GERD)	On initial endoscopy of patients with dyspepsia

Etiology

Risk Factors

Barrett's esophagus is associated with the presence of chronic gastrointestinal reflux disease. It is also associated with more frequent symptoms of GERD, the presence of typical GERD symptoms, and reflux episodes lasting longer than 5 min.[8] Further evidence of the relationship of GERD with columnar metaplasia comes from esophagectomy patients where columnar metaplasia may develop proximal to the gastric conduit in an area of the esophagus where there was previously normal squamous epithelium.[9]

Other notable associations with BE are high social status,[10] central obesity,[11] and smoking.[12] Anatomic and physiologic findings that confer an increased risk of BE include hiatal hernia greater than 4 cm, a defective lower esophageal sphincter, defective lower esophageal contraction, and the presence of bile reflux.

Protective Factors

As a precancerous state, Barrett's esophagus demonstrates increasing cyclooxygenase 2 (COX-2) expression with higher degrees of dysplasia.[13] Inhibition of COX-2 expression may be of value in the prevention of progression from SIM to cancer. A systematic review of nine observational studies evaluating NSAIDs and/or aspirin use and the incidence of esophageal cancer (both adenocarcinoma and squamous cell carcinoma) demonstrated a 33% reduction in the relative risk (OR 0.67) in patients using aspirin and/or NSAIDs. An ongoing prospective trial comparing the chemoprevention effects of esomeprazole with and without aspirin in patients with BE is expected to be completed in 2011.[14]

The role of *Helicobacter pylori* in the development of Barrett's adenocarcinoma has also been studied. An inverse association exists between *H. pylori* infection and the presence of BE with high-grade dysplasia (HGD) and EAC.[15] The mechanism of the protective properties of *H. pylori* infection in this setting remains unclear, but may be related to the relative achlorhydria of the patient infected with *H. pylori*, leading to a less injurious refluxate, should GERD be present.

Barrett's Esophagus and Risk of Esophageal Adenocarcinoma

A diagnosis of BE confers a 30–60-fold increase in risk for EAC. Estimates of the annual risk of progression to HGD or EAC are between 0.5% and 1.3%,[16,17] and only a minority of patients with BE go on to develop EAC.[18] Current evidence supporting the role of BE in the development of EAC when it is not seen at the initial endoscopy is the uncovering of BE following neoadjuvant chemotherapy and its presence in the esophagectomy specimen when BE was not appreciated on pre operative endoscopy.[19]

The risk of progression to malignancy appears to increase significantly with increasing lengths of BE,[20,21] although there is conflicting evidence in the literature.[22] One explanation for the observations of similar risk of progression regardless of length of BE is the likelihood of identifying SIM increases with increasing proximity to the squamo-columnar junction making the length of BE less relevant.[23] Both short-segment and long-segment BE are biologically identical and have significant if not equivalent malignant potential.

Pathology and Pathophysiology

The esophagus is normally lined with stratified squamous epithelium. In order for adenocarcinoma to develop in the esophagus, the squamous epithelium must transition to columnar epithelium and subsequently become dysplastic. This metaplasia–dysplasia–carcinoma sequence is attributed to the repeated injury of the esophagus by gastroesophageal reflux. The presence of any amount of columnar epithelium in the tubular esophagus is histological evidence of GERD. BE is characterized by the presence of one or more of three types of epithelium: cardiac type (presence of mucous secreting columnar cells, chief and parietal cells), junctional, or oxynto-cardiac type (presence of mucous-secreting columnar cells without chief and parietal cells), and specialized intestinal metaplasia type (presence of intestinal goblet cells).[24] The significance of the presence of the different kinds of columnar epithelium in the CLE is still a focus of controversy.

It is suggested that cardiac type mucosa is the initial inflammatory change resulting from GERD and a precursor of both junctional type and intestinal metaplasia.[23] Some believe cardiac type CLE has an equivalent risk of malignant transformation as SIM because of the frequent inability to find goblet cells within columnar epithelium surrounding neoplasms at the GEJ.[25] Also, there are no significant differences in the DNA properties of columnar epithelium with and without SIM, although, both have significant differences compared to control gastric biopsies suggesting that columnar epithelium may have a similar neoplastic potential as SIM.[26] In contrast to the known risk of malignancy from SIM,[27] the inherent risk of cardiac epithelium to progress to adenocarcinoma remains unclear.

Dysplasia in Barrett's Esophagus

BE is classified histologically as having no dysplasia, low-grade dysplasia (LGD), high-grade dysplasia or being

indefinite for dysplasia.[28] The presence of LGD is a marker of increased risk for the development of HGD and adenocarcinoma, but the annual incidence of HGD or EAC in patients with LGD varies widely from 1–13.4%.[17,29–31] In a retrospective, multicenter pathological review a 13.4% incidence of HGD/EAC per patient year was found in patients with a confirmed baseline diagnosis of LGD in contrast to an incidence of 0.49% per patient year in patients with baseline diagnosis of non-dysplastic BE. The latent period of transition to HGD/EAC is significantly shorter for patients with LGD (median of 2.75 years) than for patients without LGD (median of 9.88 years).[32] Although the risk of progression from LGD to HGD/EAC is clear, many patients with baseline LGD have no evidence of dysplasia on follow-up endoscopy,[17,18,31] possibly as a result of regression on therapy or interobserver variability.

Among pathologists, there are frequent disagreements in the grading of dysplasia and, to a lesser extent, the identification of intramucosal carcinoma. This is an important confounding bias in the literature which can in part explain the heterogeneity of results.[28,33] Low-grade dysplasia has interobserver variation as high as 50% whereas high-grade dysplasia is more frequently agreed upon. Otherwise known as carcinoma in situ, HGD does not involve the mucosa deep to the basement membrane. When cancer is found deep to the basement membrane, in the lamina propria (or touching, but not through the muscularis mucosae), this is termed intramucosal carcinoma (IMC) and is regarded as stage T1a by the American Joint Committee on Cancer staging.[34] Carcinoma penetrating the muscularis mucosae, into the submucosa is classified as T1b, and may have associated lymph node metastases in about 20–25% of patients at this stage.[35]

Diagnosis

The first step to a reliable diagnosis of BE is clear identification of the gastroesophageal junction. The GEJ is best defined as the proximal margin of gastric folds observed in a minimally distended esophagus (Fig. 2). Once the GEJ is identified, the length and circumferential extent of CLE, as well as the maximum length of the tongues of Barrett's can be determined.[36]

The identification of SIM requires biopsy and is subject to sampling bias. Therefore, multiple systematic biopsies are necessary for the accurate diagnosis of BE. The number of biopsies necessary has not been established, but eight is the minimum number suggested.[37] A commonly used protocol consists of four quadrant biopsies every 1 cm of CLE. Additional sampling of any visibly suspicious mucosa improves the accuracy of identifying SIM and dysplasia.[38]

New technologies have been developed for improved targeting of suspicious areas in a field of BE. These include high-resolution white light endoscopy,[39] chromoendoscopy,[40] narrow band imaging[41], and tri-modal endoscopy[42] which are beyond the scope of this review but may be useful as adjuncts to the endoscopic detection of dysplastic Barrett's.

Screening

At present there is no evidence that screening for BE decreases the incidence or mortality of EAC. In 2008, the American Gastroenterological Association Institute eliminated their guideline recommending screening for patients with chronic GERD symptoms.[4] If one were to target a group for screening, the most likely candidate group would be non-Hispanic, Caucasian males over 50 years of age with chronic GERD symptoms. In this group, some experts suggests at least one time in a life endoscopy at about 50 years of age. Unfortunately, some of these recommendations are based on decision analysis models rather than large-scale population-based screening studies.[43]

Of patients with esophageal adenocarcinoma and cardia adenocarcinoma, only 61% and 38%, respectively, recalled having a history of GERD symptoms for more than 5 years. When GERD symptoms at any time are taken into account,

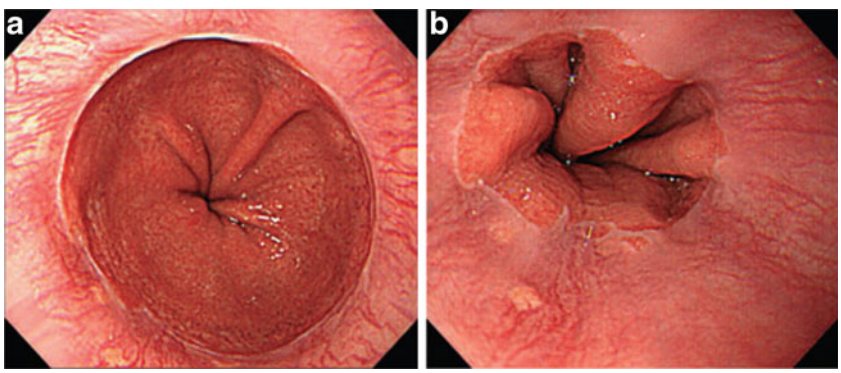

Fig. 2 Endoscopic view of the normal gastroesophageal junction in the same patient demostrating that the position of the proximal margin of the gastric fold can easily change with degree of air insufflation. **a** Standard view with air inflation. **b** Same view with excessive air deflated[91]

80% of patients with esophageal adenocarcinoma and 66% of those with cardia adenocarcinoma are identified as candidates for screening. This data is subject to recall bias, but it is clear that limiting screening to patients with GERD symptoms will overlook a significant proportion of patients who will develop cancer.[44]

A more difficult task is the identification of BE in asymptomatic patients. For this group there is no recommended strategy. Office-based unsedated small caliber endoscopy has emerged as a possible screening tool that reduces screening costs by 25%.[45] A randomized trial that compared small caliber endoscopy with conventional endoscopy found the prevalence of BE with these techniques to be similar.[46]

Surveillance

The current recommendations for surveillance are:

- Patients with BE and no dysplasia: perform two endoscopies with biopsy within a year, and then endoscopy every 3 years.
- Patients with BE and low-grade dysplasia: perform repeat endoscopy with biopsy within 6 months and yearly thereafter until no dysplasia is found in two consecutive endoscopies.
- Patients with BE and high-grade dysplasia: perform endoscopy with biopsy every 3 months or the patient should undergo ablation of the HGD or esophagectomy, usually with a transhiatal approach.[4]

The finding of dysplasia needs to be confirmed by a second expert pathologist in order to minimize the effects of interobserver variability. Ideally, the patient should be on antireflux medication to allow for better visualization of the epithelium during endoscopic examination and to minimize inflammatory changes in biopsy specimens that may mask BE and make dysplasia difficult to diagnose.[4]

Prospective trials have shown benefit with surveillance programs. Patients diagnosed with HGD and early stages EAC have improved 5-year survival rates following esophagectomy. Also, there are cost–benefit advantages of surveillance over patients outside of the surveillance program.[47–49] The benefits of surveillance programs are not a universal finding, however, and many studies have called their utility into question.[16,43]

Once a diagnosis of HGD has been confirmed the benefits of continued surveillance include avoiding the over treatment (especially with esophagectomy) of patients who do not progress to EAC. The major risk of surveillance of high-grade dysplasia is that undetected invasive cancer might metastasize to lymph nodes during surveillance. Up to 80% of individuals under surveillance will eventually develop cancer.[50] Patients with HGD found at various levels of the esophagus and patients with visible lesions of the mucosa are at an even higher risk of harboring concurrent EAC.[51] Up to 45% of surgical specimens from patients preoperatively diagnosed with HGD will have EAC on pathologic review.[50,52] This risk of incidental adenocarcinoma persists in patients who undergo extensive pre-surgical biopsies. Histological characteristics that reflect a higher rate of synchronous carcinoma include a cribiform pattern of growth, dilated tubules, ulceration, polymorphonuclear leukocytes within the area of dysplasia and invasion of squamous epithelium. When two or more of these features are present the risk of concurrent EAC is 85%.[53]

Treatment of BE

The primary goal for the management of Barrett's esophagus is eradication of gastroesophageal reflux. Secondary goals include regression or eradication of SIM with the expected benefit of reducing the number of patients who go on to develop dysplasia and subsequent EAC. Current practice guidelines suggest the surrogate endpoint for normalization of intraesophageal pH should be the control of reflux symptoms.[4]

There are two problems with a recommendation that uses symptoms to guide therapy. The first is the onset of Barrett's esophagus may be insidious and without associated reflux symptoms, most likely as a consequence of decreased sensitivity of the metaplastic intestinal mucosa to acid and bile. Based on modest evidence there is consensus that an asymptomatic patient diagnosed with incidental Barrett's esophagus should be treated with proton pump inhibitors (PPIs).[54] The second concern is that acid suppression may not be complete at the point symptoms are suppressed.[55] In this setting, although the patient is asymptomatic and on acid suppressive therapy, there continues to be ongoing reflux and epithelial damage. Furthermore, even high-dose proton pump inhibitor therapy cannot assure normalization of intraesophageal pH.[56]

Medical Management of Non-dysplastic Barrett's Esophagus

The appropriate treatment for BE is guided by the extent of intestinal metaplasia and degree of dysplasia (if present). In patients with BE and no evidence of dysplasia, treatment begins with pharmacological acid suppression therapy with PPIs in conjunction with dietary and lifestyle modifications.[57] Patients who continue to have reflux symptoms on high-dose PPI therapy should be considered for antireflux surgery. Response of BE to PPI therapy may be related to the extent of disease at the initiation of medical therapy. Multiple studies have shown that regression of SIM is more likely in

short-segment BE than long-segment BE after long-term antireflux therapy.[58] In a double-blind randomized control trial comparing the amount of BE regression in patients on histamine receptor blocker (H2) with those on PPI therapy, a decrease in surface area of 8% was seen in the PPI group and no significant change was seen in the H2 group.[59] Also, in two retrospective observational trials, a decrease in rate of progression from non-dysplastic BE to HGD/EAC was found with PPI use.[54,60]

Based on current evidence, PPIs are to be prescribed in a dose escalating fashion until symptoms of GERD are controlled. It is unlikely that medical suppression of acid reflux alone is sufficient to promote eradication of BE and prevent progression to adenocarcinoma. However, the risk of EAC in patients with GERD not taking PPIs is two to four times higher than the risk of EAC in patients who are on acid suppression therapy.[60,61]

Surgical Treatment of BE

Antireflux surgery (ARS) is indicated for the 10–40% patients who have incomplete symptom control or develop early recurrence of symptoms on escalating doses of PPIs or in patients with an intolerance or unwillingness to maintain long-term medical therapy. The most common persistent symptoms in refractory GERD are heartburn and regurgitation. Characteristics associated with unsuccessful medical management of GERD include incompetent lower esophageal sphincter, hiatal hernia, poor distal esophageal motility, and lack of symptoms to guide adequate medical therapy. These subsets of patients should be considered candidates for ARS. Fifty percent of patients with symptoms controlled on PPIs and up to 70% of patients who do not respond to PPI therapy have evidence of biliary reflux.[62] ARS serves to reduce both acid and bile reflux, a benefit not matched by medical therapy. Patients with documented reflux disease and a history of improvement of symptoms with medical therapy have excellent outcomes from ARS.

The most common antireflux operation performed today is a laparoscopic 360° fundoplication (Nissen). This operation has proved to be a safe and durable procedure especially in nonobese, young-to-middle-aged adults with objective evidence of pathologic reflux and no significant comorbid conditions. In a retrospective review of 312 consecutive patients following laparoscopic Nissen fundoplication, 92% reported improvement in symptoms and 70% did not use antireflux medications at a median follow-up of 11 years.[63] Only 8% of patients in this series underwent redo fundoplication.

Medical vs. Surgical Treatment of BE

In a prospective trial comparing PPI therapy with laparoscopic ARS in chronic GERD patients with and without BE, no difference was seen at 3 years in reflux symptoms or quality of life between the two groups; however, pH suppression was more complete following laparoscopic ARS than with PPI therapy.[64] A randomized control trial comparing medical treatment with antireflux surgery found that patients in the surgical arm benefitted from a higher cure rate of esophagitis, a small but significant regression of BE and a decreased incidence of dysplasia on subsequent endoscopies.[65] In a more recent case–control study, 63.2% of patients on high-dose PPIs had regression of LGD whereas 93.8% of surgical patients were found to have regression of dysplasia at 12 months.[66] Surgery also appears to offer a cost–benefit advantage over lifelong medical therapy, especially in patients less than 45 years old.[67]

In a recent systematic review, it appeared that ARS was superior to PPIs at preventing cancer; however, when only prospective studies were considered, a benefit for surgery at EAC prevention could not be confirmed.[68] Additionally, when cancer occurs in a BE patient following ARS, it is more likely that the antireflux barrier of the fundoplication has failed.[69] As such, continued surveillance following ARS in patients with BE is essential.

Management of BE with LGD

Patients with low-grade dysplasia have an annual risk of developing EAC that is 2–5.5 times greater than patients with non-dysplastic BE.[18,32,70] Because of this increase in risk, current guidelines recommend yearly endoscopic surveillance in patients with BE and LGD.[4] Shortcomings of the surveillance-only approach include poor compliance, cost ineffectiveness, and the concern that even early EAC has a poor prognosis.[71] In addition, it is difficult to predict which patients will progress to HGD/EAC and in what time frame, a problem that is compounded by the possibilities of understaging from inadequate sampling and interobserver variability of the histological specimen.[72]

Because surveillance strategies are not designed to prevent cancer, it is not surprising that randomized trials comparing endoscopic ablation of dysplastic BE to surveillance with biopsy show a significant decrease in rate of progression to EAC in groups undergoing ablation.[73] A review analyzing the natural history of LGD reported an annual incidence of EAC of 1.7% without ablation compared to 0.6% in patients following ablation of LGD. This represents an estimated relative risk reduction of 75%.[74] Early studies investigating the benefits of ablation for treatment of ND BE and BE with LGD have demonstrated a potential improvement in quality-adjusted life years as well as a cost–benefit with ablative therapy.[71,75]

Management of BE with HGD

In contrast to non-dysplastic BE and BE with LGD, there is uniform consensus that high-grade dysplasia warrants

intervention after pathologic confirmation of the diagnosis.[4] This recommendation stems primarily from the concern of understaging due to sampling error as every missed diagnosis of cancer in this setting may lead to a preventable death.[50] Once HGD is diagnosed, there is a risk of lymph node involvement similar to that of IMC (1–1.3%).[76,77]

The possibilities of underlying cancer and lymph node involvement made esophagectomy the historical standard of care for management HGD. It offers the most definitive opportunity for cure because all premalignant epithelium is removed, but it is not without significant morbidity and mortality even in patients undergoing esophagectomy for HGD.[78] Recently, esophagectomy has been supplanted as the treatment of choice for HGD by radiofrequency ablation of flat Barrett's segments combined with endoscopic mucosal resection (EMR) of nodules in a field of Barrett's when indicated as nodules may represent IMC or early invasive cancer. This is an important distinction that cannot be made without tissue sampling, which is why ablation of nodules is NOT recommended.[79]

Endoscopic Therapeutic Interventions

Endoscopic interventions can be subdivided into mucosal ablative therapy and endoscopic mucosal resection. Ablative therapies destroy the metaplastic epithelium allowing replacement with neo-squamous epithelium. The modalities that have been used for this purpose include multipolar electrocoagulation, photodynamic therapy, cryotherapy, laser therapy, and argon plasma coagulation all of which have been replaced by radiofrequency ablation.

In radiofrequency ablation (RFA), a high-power short burst of energy is applied to the columnar epithelium via direct contact. A dose of 10–12 Js/cm^2 removes all epithelium without damage to underlying submucosa.[80] With this technique there is a lower incidence of treatment-related stricture and improved rates of ablation of dysplasia and BE. A multicenter sham-controlled trial found eradication of dysplasia in 90.5% in the RFA group compared to 22.7% in the control group and complete eradication of SIM in 77.4% and 2.3%, respectively. Disease progression to EAC was also lower in the treatment group (3.6%) compared to the control group (19%). Buried intestinal metaplasia was more common in patients prior to therapy (25.2%) than following therapy (5.1%). Complications were greater in the treatment group and included 6% with treatment-related esophageal stricture formation.[73]

A limitation of all ablative therapies is the lack of surgical specimen. With endoscopic mucosal resection, this limitation is overcome. It is utilized most frequently to excise discrete superficial mucosal lesions. The specimen retrieved can provide histologic assessment of both radial and deep margins (down to the muscularis propria) and is more accurate than endoscopic ultrasonography at differentiating between mucosal and submucosal involvement.[81] Due to the frequent multi-focality of carcinoma within dysplastic BE, a concomitant ablative procedure of BE is required to assure complete eradication of disease. Because of concern for a high stricture rate, EMR specimens should generally be limited to less than 5 cm in diameter and used primarily for resection of nodules associated with BE rather than for complete Barrett's eradication. When mucosal lesions are present and represent early disease, EMR is successful in obtaining an initial complete (R0) resection in 28% and in 74.5% of patients after repeat resection.[79]

There are no prospective trials comparing outcomes of endoscopic therapy (resection and/or ablation) with surgical therapy (esophagectomy) for BE with HGD, although a number of retrospective trials have been conducted.[50,82,83] Put together, these experiences did not demonstrate a survival difference for either surgery or ablation with or without resection, although early mortality was higher in the surgical group. There was significant treatment failure observed in the endotherapy groups as 6–20% of patients developed new or metachronous cancer. There were no EAC recurrences in any post-surgical patient in any study.

Conclusion

A great deal of progress has been made in the understanding and treatment of Barrett's esophagus over the last half century. A strong relationship has been established between the presence of goblet cells (specialized intestinal metaplasia) and the transformation to adenocarcinoma. It is clear that antireflux surgery has a role in the prevention of BE progression by improved control of gastroduodenal reflux, but the superiority of ARS to medical management in achieving cancer prevention remains controversial, because of the rarity of cancer and the occasional failure of ARS to maintain an effective antireflux barrier. The development of endoscopic therapeutic interventions that safely and effectively treat high-grade dysplasia and early stages of esophageal adenocarcinoma already play a pivotal role in decreasing the morbidity associated with this disease. The use of endoscopic therapies in early stages of BE in combination with antireflux surgery may prove to be a successful preventive strategy. With the continued integration of knowledge and expertise from different fields of medicine, it will be possible to decrease the incidence of EAC and achieve accurate, early detection of cancer, thereby improving both survival and quality of life in patients with Barrett's esophagus.

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Update on Staging and Surgical Treatment Options for Esophageal Cancer

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Abstract
Introduction Esophageal cancer remains a challenging clinical problem, with overall long-term survivorship consistently at a level of approximately 30%. The incidence of esophageal cancer is increasing worldwide, with the most dramatic increase being seen with respect to esophageal adenocarcinoma.
Discussion Pretreatment staging accuracy has improved with the utilization of CT and PET scans, as well as endoscopic ultrasound and endoscopic mucosal resection. In an increasing percentage of patients, endoscopic techniques are being utilized in selected patients for the treatment of high-grade dysplasia in Barrett's and intramucosal cancer. Surgery remains the treatment of choice in all appropriate patients with invasive and locoregional esophageal cancer, although multimodality therapy is now used in most patients with stage II or stage III disease.
Conclusion Outcomes for esophagectomy have been dominated by concerns regarding high mortality and morbidity; however, mortality rates associated with esophageal resection have dramatically decreased, especially in high-volume specialty centers. This manuscript highlights some of the evolutionary issues associated with staging and endoscopic and surgical treatments of Barrett's and esophageal cancer.

Keywords Esophageal cancer · Esophagectomy · Complications · Endoscopic therapy · Quality of life

Pretreatment Staging

Initial presentation of esophageal adenocarcinoma is most often associated with dysphagia and, as a result, the most common initial investigations typically involve either a barium contrast study or, more commonly, an upper endoscopy. Endoscopic examination will provide a visual impression of the presence of Barrett's, location and extent of stricture or tumor, and extent of gastric involvement.

Confirmation of cancer should initiate a series of investigations to complete a clinical TNM staging which has recently been changed in the American Joint Committee on Cancer (AJCC) Seventh Edition. Tumor or "T" characteristics are best assessed with endoscopic ultrasound. Accuracy of endoscopic ultrasound increases with increasing depth of invasion.[1] Endoscopic ultrasound has less overall accuracy in T1 disease,[2] and overall accuracy of endoscopic ultrasound assessment decreases dramatically after neoadjuvant therapy.[3] Endoscopic ultrasound assessment can also be limited when dense malignant strictures prohibit a complete assessment.

CT scan is generally not accurate for early T stage but can provide important information regarding locoregional invasion (T4). Aortic invasion is suggested when tumor contacts over 90% of the circumference of the vessel. Concerns for tracheal invasion should be addressed with bronchoscopy with or without endobronchial ultrasound. MRI can sometimes provide additional information when critical T4 disease is suspected.

Nodal or "N" status is best assessed by a combination of contrast CT, [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scans, and endoscopic ultrasound. CT scan provides lymph node evaluation strictly on size criteria. The FDG-PET scan provides additional information, but peritumoral nodes are often difficult or impossible to assess due to their close proximity to the primary tumor. PET scan is more important for identifying nonregional adenopathy; however, positive findings in good surgical candidates should be confirmed histologically whenever feasible. Endoscopic ultrasound provides the best modality for assessing locore-

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gional nodes (sensitivity, 85%; specificity, 97%), especially when fine-needle biopsy of suspicious nodes is feasible.[1]

Most common locations for metastatic "M" disease from esophageal adenocarcinoma involve the liver, lung, and bone. CT scanning can often demonstrate macrometastasis, but the addition of FGD PET scan can increase the yield of identifying occult metastases by as much as 20%.[4]

Management of Early-Stage Disease

High-Grade Dysplasia in Barrett's Esophagus and Intramucosal Cancer (T1a)

It is currently estimated that 10% of patients with chronic reflux have Barrett's esophagus. A recent study utilizing a computer simulation disease model of esophageal adenocarcinoma within the Surveillance, Epidemiology and End Results (SEER) database suggests that the incidence of Barrett's in the general population may be as high as 5.6%.[5] In cases of patients with high-grade dysplasia, up to 30% will develop esophageal adenocarcinoma within 5 years.

Surgical resection has historically been the standard treatment for high-grade dysplasia, with recent series demonstrating that resection can be done in high-volume centers with minimal operative mortality. Table 1 demonstrates that five major surgical series since 2006 have reported zero mortality. One of the most compelling points favoring resection over endoscopic therapy was the incidence of discovering undiagnosed intramucosal or invasive cancer (incidence typically ranging 15–45%; Table 1) following resection in patients with high-grade dysplasia. Due to improved techniques for screening, most importantly including high-resolution endoscopy and endoscopic mucosal resection, the current rate of missing invasive cancer at the time of endoscopic assessment should now be 5% or less.[6]

Table 1 Outcomes associated with surgical resection for high-grade dysplasia and intramucosal cancer

		N	Morbidity (%)	Mortality (%)	Incidence of occult cancer (%)	5-Year survival
Headrick et al.[86]	2002	54		1.8	35	96%
Fernando et al.[89]	2002	28	54	4	39	
Tseng et al.[90]	2003	60	29	1.7	30	
Reed et al.[91]	2005	49	N/A	2	37	
Sujendran et al.[92]	2005	17	29	0	65	
Moraca and Low[87]	2006	36	44	0	39%	100%
Chang et al.[85]	2006	38	29	0	N/A	97%
Rice[93]	2006	111	N/A	0	45	
Williams et al.[94]	2007	38	37	0	29%	

Endoscopic options for treating high-grade dysplasia and intramucosal cancer have significantly expanded over the last 20 years. Initially, options included argon beam coagulation, laser, and photodynamic therapy. More recently, endoscopic mucosal resection, radiofrequency ablation, cryotherapy, and free-hand mucosal resection have been increasingly applied. There have been numerous recent publications demonstrating the safety and efficacy of radiofrequency ablation for the treatment of high-grade dysplasia and intramucosal cancer.[7] The best designed study was reported by Shaheen et al., who studied 127 patients in a multi-center sham-controlled trial. They reported eradication of high-grade dysplasia in 81% of patients, and the treatment group demonstrated less progression of dysplasia and less progression to cancer.[7]

There have been several published comparisons of endoscopic therapy versus esophagectomy at high-volume multidisciplinary centers. Most important is the finding that patients in both treatment groups did well, and long-term survival appears to be equivalent.[8,9] This impression is supported in a recent meta-analysis, although identifying which endoscopic technique is superior is not possible at the present time.[10]

Endoscopic therapy is not appropriate for all patients, and some will fail treatment and require resection. In high-grade dysplasia and T1a cancer, a vagal-sparing esophagectomy can provide an alternative to standard resection. Vagal-sparing esophagectomy involves removing the esophagus from the mediastinum with a stripping device that leaves the vagal nerves and the lymph nodes in place. In appropriate candidates, vagal-sparing esophageal resection has demonstrated advantages over standard approaches including maintaining meal size, gastric emptying, and BMI.[11] An outcome comparison between vagal-sparing esophagectomy and transhiatal esophagectomy demonstrated shorter length of stay and less complications as well as less weight loss, dumping, and diarrhea associated with vagal preservation.[12] The technique of vagal sparing or "inversion" has also been applied using a minimally invasive approach.

It should be acknowledged that long-term follow-up is not generally available for endoscopic techniques, especially radiofrequency ablation, which is the most popular current approach. All these patients require long-term endoscopic follow-up, and each patient should be carefully assessed histologically (preferably with endoscopic mucosal resection) prior to deciding on a definitive treatment approach.

T1b (Submucosal) and T2 Cancer

Unlike intramucosal cancer (T1a), where metastasis to lymph nodes is uncommon, invasive cancer, which penetrates into the

Table 2 Outcomes from surgical series of resection of patients with T1 esophageal cancer: incidence of lymph node metastasis

	Ancona et al. 2008[13]	Pennathur et al. 2009[15]	Sepesi et al. 2010[16]	Leers et al. 2010[14]
T1 tumors	98	100	54	126
Adenocarcinoma	64%	91%	100%	100%
Squamous cell	36%	9%		
R0 resection	97%	99%		
Lymph node metastases				
T1a	*N*=27, 0%	*N*=27, 7%	*N*=25, 0%	*N*=75, 1.3%
T1b	N=71, 28%	N=73, 27%	N=29, 21–50%	N=51, 22%
SM1[a]	8.3%		21%	
SM2[a]	49%		36%	
SM3[a]			50%	
5-Year survival				
Overall	56.7%	62%		
T1a	77.7%	73%		
T1b	53.3%	60%		

[a] Designates individual "submucosal" layer

submucosa, has a high risk of lymph node involvement. Table 2 demonstrates that the incidence of spread to lymph nodes in four surgical series in patients with adenocarcinoma and submucosal extension (T1b) ranges between 21% and 50%.[13–16] A clinical series reported by Manner et al. demonstrated that endoscopic therapy could be used to treat "low-risk" submucosal tumors that were staged and managed predominately with endoscopic mucosal resection[17]. Low risk was described as pathologic determination of tumor extension into only the most superficial submucosal layer (SM1), low-grade tumor differentiation (G1–2), and no evidence of lymphovascular invasion. At mean follow-up of 5 years, there were no tumor-related deaths. However, Leers found nodal metastases in 16.5% of these "low risk" patients and Sepsesi and colleagues demonstrated lymph node metastasis in 21% of patients with T1b disease limited to the SM1 layer, indicating that a significant component of even "low-risk" patients will have the potential for lymph node involvement.[13–16] In addition, accurate pathologic determination of the depth of submucosal invasion is not always possible.

Endoscopic ultrasound is currently the most commonly used staging modality assigning "T" stage. However, a meta-analysis of papers comparing endoscopic ultrasound and surgical or endoscopic mucosal resection staging demonstrated that endoscopic ultrasound predicted accurate depth of tumor invasion in only 56% of patients.[2] Therefore, especially if endoscopic treatment is contemplated, staging should include endoscopic mucosal resection, and any indication of submucosal invasion should lead to recommendation for surgical resection in appropriate candidates.

A review of the outcomes in clinical T2N0M0 patients demonstrated that the current approaches to clinical staging resulted in accurate pathologic stage in only 13% of cases. Of the patients inaccurately staged, 63% were overstaged and 37% were understaged. Subsequent recommendations for treatment of cT2N0M0 patients involved proceeding directly to surgery as this would currently be considered a definitive treatment in patients who are accurately staged or overstaged. Patients who are discovered to be understaged can be considered for adjuvant therapy.[18]

Multimodality Therapy for Locoregional Esophageal Cancer

There is an ongoing debate as to the best methodology for treating patients presenting with extensive locoregional disease, i.e., T3N0–3, T2N1–3. Primary surgery remains an option in these patients, although significant survival advantage has been demonstrated in patients having pronounced responses to neoadjuvant therapy or demonstrating pathologic complete responses. There have been geographic variations in the approach to multimodality therapy, with most centers in North America predominantly favoring neoadjuvant chemoradiation, whereas in the United Kingdom, neoadjuvant chemotherapy is more commonly utilized.

The MRC trial from the United Kingdom randomized over 800 patients between surgery alone and chemotherapy followed by surgery and demonstrated a significant survival advantage and no identification of increased surgical complications in the chemotherapy group.[19] These results have been reanalyzed at a median of 6 years' follow-up, and the survival advantage has been maintained.[20] A recent meta-analysis did demonstrate a survival advantage of neoadjuvant chemotherapy and surgery compared to surgery alone but not to the same extent as was seen with neoadjuvant chemoradiotherapy.[21]

A meta-analysis of the results of neoadjuvant chemoradiotherapy plus surgery versus surgery alone demonstrates a

survival advantage for trimodality therapy. A general review of the literature assessing the risks and benefits of neoadjuvant chemoradiotherapy summarized collective results as demonstrating a R0 resection rate of 88.4% and an overall pathologic complete response rate of 25.8%. Mortality rates associated with neoadjuvant chemoradiotherapy alone were reported as 2.3% compared to a mortality rate of 5.2% with trimodality.[22]

There has been some concern that neoadjuvant chemoradiotherapy will increase morbidity especially associated with respiratory complications and mortality associated with surgical resection. However, other studies have shown no difference in morbidity, mortality, or length of stay in patients receiving neoadjuvant chemoradiotherapy.[23,24] There is also evidence showing that carefully selected older patients can safely undergo trimodality therapy.

A recent randomized trial (the CROSS Study) compared 363 patients receiving surgery alone versus preoperative radiotherapy and chemotherapy with paclitaxel and carboplatin followed by surgery. The trimodality group demonstrated a higher R0 resection rate, and significantly improved overall survivorship. Perioperative mortality rates between the two groups were virtually identical.[25]

Institutional assessments and meta-analysis comparing outcomes of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy have demonstrated improved pathologic complete response rates and overall survival with neoadjuvant chemoradiotherapy and surgery.[21,26,27] With pathologic complete response rates reaching levels ranging between 25% and 40%,[22] this has led to the suggestion that definitive chemoradiotherapy is sufficient treatment especially in patients with early-stage disease.

There is also increasing evidence for a differential response rate following chemoradiotherapy in patients with squamous cell carcinoma versus adenocarcinoma.[28,29] With respect to prognosis, a pathologic response appears to be of more importance in squamous cell cancer. However, in adenocarcinoma, the absence of nodal metastasis seems to be of greater prognostic importance.[30,31] Recent analysis of national databases and single-institution outcomes have shown comparable outcomes in assessments of surgery alone versus definitive chemoradiotherapy in patients with squamous cell carcinoma.[32,33] This finding also raises the question as to whether patients with squamous cell carcinoma can be treated with definitive chemoradiotherapy and undergo resection for persistent or recurrent disease. At the present time, however, there is no definitive methodology for identifying patients with complete pathologic response other than proceeding on with surgical resection. A recent retrospective review of 123 patients with squamous cell carcinoma who received neoadjuvant chemoradiotherapy showed that 50% of patients had negative endoscopic biopsies for cancer. However, 64% of patients with negative biopsies and no visible evidence of tumor were found to have residual cancer at the time of resection.[34] Biopsy results are clearly inaccurate, and post-neoadjuvant PET scans are currently being assessed as an alternative for identifying patients with complete pathologic responses.

Surgical Treatment of Invasive Esophageal Cancer

Factors Affecting Mortality Associated with Esophagectomy

Surgery has been, and remains, the gold standard approach for treating esophageal cancer. Esophagectomy has historically earned a reputation for high morbidity and mortality. An oft-quoted review of outcomes of major cancer operations from the SEER database showed that mortality rates in the USA between 1994 and 1999 in low-volume centers was 18.9% and that in high-volume centers was 8.1%.[35] A review of over 57,000 esophagectomies from the National In-Patient Sample demonstrated that US mortality rates improved from 12.1% in 1998 to 7% in 2006.[36] Table 3 shows mortality rates from high-volume centers highlighting that rates of under 5% can be achieved and will be increasingly expected.

There are indications that outcomes, specifically mortality, are linked to issues such as subspecialty training and cancer center designation. However, the greatest influence on mortality appears to be related to the volume of resections performed by an individual surgeon or institution,[35,37] with the high volume performed by the surgeon likely being most important. The designation of high volume has not been standardized ranging between >6 to >50 resections, with a recent review suggesting that >15 was likely the most meaningful target to indicate "high volume."[38] The importance of this issue has been highlighted by the Leapfrog group (http://www.leapfroggroup.org/) that monitors quality outcomes for consumers and purchasers of health care and targets >13 resections per year as an appropriate target number for institutional resections. The issue cannot be simplified to just the number of resections as some centers

Table 3 Current mortality outcomes of esophagectomy at high-volume centers

		Operation	*N*	Mortality
Portale	2006	Open	263	4.5%
Orringer	2007	Open	2,007	3.0%
Low	2007	Open	340	0.3%
Smithers	2007	Open	114	2.6%
van Heijl	2010	Open	940	3.3%
Luketich	2003	MIE	222	1.4%
Palanivelu	2006	MIE	130	1.5%

doing lower number of resections have published good outcomes. High-volume centers are more likely to have expertise not only in surgical services but also in thoracic anesthesia, ICU care, and interventional radiology and gastroenterology. They are also more likely to work with oncologic nurse coordinators, utilize multidisciplinary tumor boards, and have established databases for monitoring outcomes.

Operative Options

Surgeons have historically invested significant effort to convince each other of the relative merits of one surgical approach to esophageal resection over another. In fact, no one technical operation is appropriate in all patients, and centers offering a diversified approach to resection depending on physiologic factors and tumor characteristics in each patient are most likely to provide the best outcomes.

Initial randomized trials comparing outcomes between open transhiatal and transthoracic operations suggest that transhiatal operations have a higher instance of anastomotic complications and vocal cord paralysis. Transthoracic procedures demonstrated more pulmonary and wound complications as well as greater operative blood loss, longer length of hospital stay, and higher perioperative mortality. However, no difference in 5-year survival has been observed between the two approaches. The most recent randomized trial done by Hulscher and colleagues,[39] in which 220 patients with esophageal and esophagogastric junction adenocarcinoma were randomized between transhiatal and transthoracic resections, demonstrated that complications and costs of treatment were higher in the transthoracic group, although no difference was noted in mortality. A trend towards improved 5-year survival in the transthoracic group did not reach statistical significance,[40] but when a subanalysis was done, taking into account tumor location (esophageal versus esophagogastric junction tumors), a survival advantage of 14% was noted in esophageal tumors with the transthoracic approach. This led to the recommendation for a transthoracic operation in cases of esophageal tumors, with the transhiatal operations being more appropriate for cancers involving the esophagogastric junction.[41]

The application of minimally invasive approaches to esophageal resection has increased dramatically over the last 20 years. Due to a perception that minimally invasive operations can decrease morbidity and mortality, a wide variety of purely minimally invasive and hybrid procedures have been introduced. Assessments, including international surveys, as well as the United Kingdom National Oesophago-Gastric Cancer Audit indicate that currently between 14% and 31% of resections globally utilize minimally invasive techniques.[42,43]

There have been many uncontrolled retrospective comparisons between open and minimally invasive operations. Table 4 summarizes the major outcome parameters indicating that minimally invasive operations typically take longer but are associated with less blood loss. There is less convincing information to suggest that minimally invasive approaches may be associated with less respiratory complications and shorter length of hospital stay. In the absence of randomized comparisons, the strongest statement supporting the potential for minimally invasive procedures is the fact that, unlike other minimally invasive operations, the introduction and learning curve have been initiated without significant differences noted in overall complications or mortality compared to open procedures. Equally important is the indication in published reports from single institutions that minimally

Table 4 Assessing contemporary outcome measures of minimally invasive versus open esophagectomy

	Op times	Blood loss	Nodes removed	Length of stay	Complications			Mortality
					All	Resp	Leak	
Nguyen 2000	MIE	MIE	ND	MIE		ND	ND	ND
Braghetto 2006					MIE		ND	ND
Smithers 2007	Open	MIE	ND	MIE		ND	ND	ND
Hamouda 2009	ND			NE		ND	ND	ND
Parameswaran 2009	Open	ND		Open	ND	MIE	ND	ND
Zingg 2009	Open	MIE		ND	ND	ND	ND	ND
Safranek 2010	Open		ND	ND		ND	Open	ND
Gao 2010	Open	MIE	ND	MIE	ND	ND	ND	ND
Pham 2010	Open	MIE		ND	ND	ND	ND	ND
Schoppman 2010	ND	MIE	ND	MIE	MIE	MIE[b]		ND[a]

ND no difference noted in outcome, *MIE* minimally invasive esophagectomy

invasive resections produce lymph node yields comparable to open procedures (see Table 4). This highlights that appropriate cancer principles have been maintained associated with the introduction of minimally invasive procedures. It is likely that additional well-designed prospective or randomized studies will provide additional information regarding the potential advantages of minimally invasive procedures.

Technical Issues Associated with Esophageal Resection for Cancer

1. Location of the Anastomosis.

   Assessment of two of the three randomized trials suggests that cervical anastomoses are associated with more anastomotic leaks and recurrent nerve palsies, but thoracic anastomoses have closer margins or higher incidence of R1 resections. These issues were not confirmed in the third randomized comparison, but all three agreed that there was no significant difference in operative mortality or overall survivorship.[44–46] A more recent prospective nonrandomized comparison also showed no difference in postoperative quality of life. At the present time, no significant advantage can be determined between the thoracic and cervical anastomosis.
2. Stapled or Handsewn Anastomosis.

   There remains a significant degree of personal preference and opinion regarding the most appropriate anastomotic method. A meta-analysis of randomized controlled trials in 2001 showed a trend toward shorter operative times but higher mortality associated with a stapled anastomosis.[47] A more recent randomized assessment of handsewn versus stapled chest anastomoses showed no difference in mortality, although stapled anastomoses had higher stricture rates.[48]

   There are three nonrandomized, single-institution studies comparing the two anastomotic techniques in solely cervical,[49] solely thoracic,[48] and mixed locations.[50] Techniques differed in that one series utilized a circular stapler technique[49] whereas the others utilized a linear stapling approach.[48,50] Leak rate was similar in two studies[48,49] but significantly favored stapled anastomoses in the series performing both neck and chest anastomoses.[50] Handsewn anastomoses demonstrated a significantly higher requirement for dilation in all three reviews.

   Results of both handsewn and stapled anastomoses are acceptable. Although randomized and single-institution studies are not consistent, postop stricture rates are likely more common in handsewn anastomoses. Linear stapled anastomosis may be more trouble-free than the circular stapled anastomosis.
3. Type of Esophageal Conduit.

   The decision regarding conduit reconstruction is often dictated by tumor location and previous surgical procedures. Pedicled Roux-en-Y jejunal reconstructions are typically reserved for instances when stomach or colon is unavailable and are limited with extent to proximal extension, although careful mobilization can potentially allow anastomosis above the inferior pulmonary vein. Free jejunal interpositions can be utilized wherever suitable blood supply for microvascular anastomoses can be identified but are most commonly used in conjunction with laryngeal resections.

   Stomach and colon are the most commonly used post-resection conduits. Stomach is most commonly used worldwide. The stomach has a reliable blood supply and is easily adaptable. In addition, mobilization can be accomplished in conjunction with standard lymph node dissection, and reconstruction is accomplished with a single anastomosis. Recognized drawbacks include the loss of gastric reservoir, lack of peristalsis in the conduit, increased risk of acid reflux (with the attendant risk of redevelopment of Barrett's), and the reality that a significant portion of the stomach, often including the tip of the conduit, undergoes radiation when neoadjuvant chemoradiation is used.

   Colonic reconstruction has the potential advantages of providing a peristaltic conduit, preserving the gastric reservoir and, overall, has a lower incidence of leaks and post-resectional esophageal reflux. Drawbacks include a much longer, more complex operation with three anastomoses, a less predictable blood supply, and an increased risk of internal hernias, and a tendency for even well-constructed colonic interpositions to become tortuous and dilated over time.

   The decision regarding the most suitable conduit will most often be based on type and location of the tumor, availability of conduit options, and personal experience of the surgical team. Reports from two large resectional series of patients with benign disease (and therefore long-term follow-up) showed that an experienced surgical team utilizing all three options, when appropriate, can produce excellent perioperative results, including mortality rates of under 5% and acceptable postoperative functional outcomes.[51,52]
4. Pyloric Drainage Procedure Following Reconstruction with Gastric Conduit.

   This is another area where there is no general agreement among surgeons. A meta-analysis of randomized controlled trials in 2002 comparing outcomes in patients who did and did not have pyloric drainage indicated a nonsignificant benefit of pyloric drainage with respect to gastric emptying, ability to eat, and postoperative nutrition. There did not appear to be any

demonstrable advantage with respect to late complications such as dumping or bile reflux in patients who did not have pyloric drainage.[53] Studies within this meta-analysis also indicated that there was no significant increase in complications associated with the pyloric procedure.[54]

Published results seem to suggest an advantage with respect to early symptoms of delayed gastric emptying with the utilization of a pyloric drainage procedure. More recent reports have suggested that botulinum toxin can be utilized either routinely intraoperatively or selectively postoperatively to decrease the incidence of delayed gastric drainage or to treat it postoperatively should it occur.[55]

5. Extent of Lymphadenectomy

A recent review of the evidence-based literature suggests that there is no documented superiority of a three-field over a two-field lymphadenectomy.[56] However, several studies analyzing results from the SEER database and multi-institution international databases suggest that the number of lymph nodes removed at surgery is directly related to overall survivorship.[57–59] There is no general agreement regarding the "minimum" number of nodes that should be removed at the time of resection, with current suggestions ranging from 18 to 30.[57–59] A review of the cohort of patients analyzed to develop the new AJCC Seventh Edition Staging System produced guidelines for the target number of lymph nodes that optimally should be removed according to "T" stage.[60] This publication suggested that 0 nodes were required for Tis disease, 10–12 for T1, 15–22 for T2, and 31–42 for T3/T4.

This has led to suggestions that operative approach and extent of lymph node dissection can be varied according to clinical stage. The practical difficulty associated with this approach is that clinical stage, particularly T status, often changes following surgical resection. Even patients with T1b disease will have a significant risk for lymph node metastasis (Table 2), which is often not appreciated prior to surgical resection. As a result, surgeons should aim to accomplish at least a complete and standardized two-field lymph node node dissection in all patients presenting with invasive cancer.

Complications Associated with Esophagectomy

Historically, mortality has dominated the analysis of outcomes with respect to esophageal resection for cancer. Previously in this review, we have demonstrated that, especially in high-volume centers, mortality rates have significantly decreased (Table 3), allowing a shift of concentration to the impact that complications have on outcomes. There are clear indications that complications significantly affect perioperative mortality, length of stay, and costs. There is less agreement whether complications affect postoperative quality of life and survival.[13,61,62] In a review of the Society of Thoracic Surgeons database between 2002 and 2007, major complications were defined as anastomotic leak, reintubation, ventilation >48 h, pneumonia, and reoperation for postoperative bleeding occurring in 24% of patients.[63] Complications in general are more prevalent in low-volume versus high-volume centers.[64,65] There is currently no generally accepted system for categorizing major complications associated with esophageal resection, which makes comparisons between surgeons and health systems difficult. As a result, reported complication rates for esophagectomy have ranged widely between 25% and 60%.

Anastomotic Leak and Conduit Necrosis

Anastomotic leak remains one of the most serious postoperative complications associated with esophagectomy. Generally speaking, leaks are more common when reconstruction is done with stomach versus colon, and are more commonly seen in neck versus thoracic anastomoses. Leaks within the chest have been considered potentially more clinically significant, although modern approaches to leak management appear to have decreased the level of risk.[66] The incidence of esophageal anastomotic leaks ranges between 3.5% and 21%, with a significant difference in the incidence of mortality within major series ranging from 0% to 35%.[67] The incidence of leaks does not seem to be directly related to the utilization of induction therapy.

Anastomotic leaks are often suspected clinically, but are most often diagnosed with water-soluble ± barium contrast studies. Anastomotic leaks have been reported between day 1 and 30, but are most commonly seen between day 4 and 8. There is no general agreement whether contrast studies should be routinely done following esophageal resection, with some surgeons utilizing them only when there is clinical suspicion for a leak. Contrast studies should be done initially with water-soluble medium. If normal, this should be followed by thin barium and, if these studies are normal and clinical suspicion remains high, by a CT scan of the neck and chest. Upper endoscopy is increasingly being used as an initial or a secondary assessment for anastomotic leak and conduit necrosis. In experienced hands, endoscopy can be done safely, and there is evolving evidence that a significant component of anastomotic leaks can be handled either conservatively or with endoscopically placed stents.[68] The incidence of strictures following anastomotic leaks appears to be decreased when temporary stents are utilized as definitive

treatment. Stent placement must be accompanied by appropriate interventional radiological or surgical drainage of contaminated spaces, and the stent is typically removed 2–10 weeks following placement.

It is critical to distinguish between a localized anastomotic defect and partial or complete conduit necrosis. Nonsurgical treatment is not appropriate in the latter, and this is another reason why early endoscopic assessment is often a valuable and appropriate investigational tool. The incidence of conduit necrosis in large series ranges from 0.5% to 2.6%.[69,70] The identification of major conduit failure necessitates surgical revision, usually involving proximal diversion, resection of the involved conduit, and delayed reconstruction, which is often done retrosternally.

Efforts to decrease the incidence of anastomotic and conduit necrosis have led to the assessment of ischemic preconditioning of the gastric conduit several weeks before resection and reconstruction. At the present time, there is no definitive evidence that the time and moderate risk entailed with this procedure result in measurable improvement in leak rate or improved conduit viability.

Chyle Leak

The incidence of postoperative, clinically significant chyle leak is currently estimated at between 2% and 3.5%, with higher incidences noted following transthoracic versus transhiatal operations.[71] Typical presentation involves high postoperative chest tube output, which is initially clear. Diagnosis is often made at the time of initiating enteric feeding when the volume increases and character of the drainage changes from clear to milky white.

Specific assessments of the pleural fluid can be done, and when triglyceride levels of >100 mg/dL are identified, this is considered diagnostic.[72] High chylous output can be associated with thoracic duct transection or a leaking major tributary. Most surgeons would recommend an initial nonsurgical response, which involves discontinuing enteric feeding and starting TPN. Subsequent treatment will be guided by the volume of output, the level of immediate response to nonsurgical therapy, and the nutritional status of the patient. Extended period of high-volume lymphatic output is to be avoided because it contributes to malnutrition in patients who may already be nutritionally compromised.

If chest tube drainage is >2 L/day and there is not a marked response to conservative therapy, early surgical intervention is recommended. If there is a significant drop in output associated with conservative therapy, which continues over ensuing days, a nonsurgical approach is appropriate; however, if output continues to be over a liter a day for five consecutive days, surgical intervention is recommended.[71,73]

While lymphangiography has fallen out of favor as a diagnostic tool, thoracic duct cannulization and embolization have seen some application in thoracic duct leaks associated with thoracic trauma and head and neck surgery.[74,75] However, intervention for persistent chyle leak is typically surgical. A high-fat-content liquid such as cream is typically given down a nasogastric or jejunostomy tube, and exploration can be through the original incision if a transthoracic resection has been carried out or through an open thoracotomy or with a thoracoscopic approach if the original resection was done transhiatally or with minimally invasive techniques. The leak is often fairly straightforward to visualize due to the output of whitish liquid, and it can be treated with either clips or fibrin glue or other pulmonary sealants. If no specific leak can be identified, the main thoracic duct should be ligated, which is best performed by encircling and ligating the entire contents of the space anterior to the spine and between the descending aorta and the azygos vein, just above the esophageal hiatus.

Respiratory Complications

Postoperative pulmonary complications following esophagectomy classically include pneumonia (either primary or associated with aspiration), prolonged air leak, clinically significant pneumothorax or pleural effusion, respiratory failure requiring reintubation, prolonged intubation, and pulmonary embolism. Respiratory complications have been identified as a major contributor to postoperative length of stay, treatment costs, and mortality.[76–78] Pulmonary complications have been indicated in 50% to 65% of mortalities in certain series.[76,79] Neoadjuvant therapy, particularly chemoradiation, has been implicated as a factor for increasing the incidence of pulmonary complications. However, a specific assessment of this issue has not demonstrated an association between induction therapy and the incidence of pulmonary morbidity.[76,80] Transhiatal and minimally invasive resectional approaches have been advocated due to the perception that respiratory complications are more common with resections done through a transthoracic approach. Recent studies have not confirmed that minimally invasive approaches definitively decrease respiratory complications (see Table 4) or that thoracotomy is a significant factor with respect to postoperative respiratory morbidity.[81] A specific review of pulmonary complications done by Law and colleagues, examined 421 patients with squamous cell carcinoma of the esophagus, of which 83% of them underwent transthoracic resection. Major pulmonary complications occurred in 16% and were responsible for 55% of the in-hospital mortalities (in-hospital mortality of 4.8%). Logistic regression analysis identified age, operative duration, and proximal tumor location as risks associated with pulmonary

complications but not neoadjuvant chemoradiation or operative approach.[78]

Specific issues, which have been demonstrated to decrease the incidence of postoperative pulmonary complications, include meticulous neck dissection to avoid recurrent laryngeal nerve injury,[82] minimizing perioperative blood loss,[78] minimizing perioperative fluid administration,[83] and appropriate utilization of regional anesthetic techniques, specifically epidurals, for postoperative pain control and early mobilization.[82,84]

Quality of Life Following Esophagectomy for Cancer

There have been three assessments of post-esophagectomy quality of life in series of patients undergoing resection for high-grade dysplasia utilizing a general assessment tool, specifically the Medical Outcomes Study 36-Item Short-Form Health Survey. Surgical mortality in all three series was <2%. In addition, findings were similar in that they demonstrated that quality of life following resection was at least equivalent to the general population.[85–87]

A recent review in 2010 utilized more specific assessment tools (QLQ-C30 and the QLQ-OES18) to assess pre- and postoperative quality of life in a consecutive series of patients undergoing minimally invasive esophageal resection. This study demonstrated that quality of life decreased postoperatively but improved at 3 months and had returned to baseline 6 months postoperatively.[88]

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An Evidence-Based Review of the Surgical Treatment of Gastric Adenocarcinoma

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Abstract The management of gastric adenocarcinoma continues to evolve. Chemotherapy is being increasingly used in both the neoadjuvant and adjuvant setting. Surgical resection of the stomach and regional lymph nodes remains the mainstay of potentially curative therapy, but significant regional differences persist in the surgical management. This review provides an update on the current literature regarding the preoperative evaluation and staging, extent of gastric resection, extent of lymph node resection, and adjuvant therapy for patients with gastric adenocarcinoma.

Keywords Gastric cancer · Surgery · Gastrectomy · Lymphadenectomy

Introduction

Gastric cancer is now the second leading cause of cancer death worldwide with about 866,000 deaths each year.[1] The incidence of gastric cancer varies tremendously throughout the world, with the highest incidence occurring in South Korea at 66.5–72.5 per 100,000 males and 19.5–30.4 per 100,000 females.[2] Other countries with a high incidence of gastric cancer are located in Eastern Asia, the Andean regions of South America, and Eastern Europe. The incidence of gastric cancer in the USA has been steadily declining and is currently only one tenth that of South Korea. The estimated number of new gastric cancer cases in the USA in 2010 was 21,000, and the estimated number of deaths was 10,570.[3] The decline in incidence of gastric cancer is due to a decrease in tumors of the stomach body and antrum. For unclear reasons, the incidence of proximal and esophagogastric junction tumors has been increasing since the 1980s.[4] Overall, males are affected twice as frequently as females, and the average age of presentation is between 60 and 70.

Gastric adenocarcinoma accounts for about 95% of gastric cancer cases. Risk factors for gastric adenocarcinoma include *Helicobacter pylori* infection, diets high in smoked or salty foods, pernicious anemia, prior gastric surgery, chronic atrophic gastritis, and intestinal metaplasia.[5] Cancer syndromes which increase the risk of gastric cancer include hereditary nonpolyposis colon cancer (HNPCC), Li–Fraumeni syndrome, Peutz–Jeghers syndrome, and hereditary diffuse gastric cancer (HDGC).[6]

Gastric adenocarcinoma arises in the inner mucosal lining of the stomach in the epithelial cell layer. As tumors grow deeper into the wall of the stomach (i.e., submucosa and muscularis propria), they can spread via lymphatics to regional lymph nodes and hematogenously to distant sites, most commonly to the liver.[5] For T1b tumors (invading the submucosa), lymph node metastases are found in about 20% of patients.[7] For T2 tumors (invading the muscularis propria), the lymph node metastasis rates increases to over 50%. Tumors that penetrate the subserosa (T3) or serosa (T4a) of the stomach can progress to invade adjacent structures such as the pancreas, spleen, and colon (T4b) or disseminate via the peritoneal cavity leading to carcinomatosis.

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Gastric adenocarcinoma is often asymptomatic in its early stages and in later stages causes weight loss, epigastric pain or discomfort, gastrointestinal bleeding, vomiting, and/or anorexia.[5] In Japan and South Korea, high awareness and common endoscopic screening for gastric cancer has led to the proportion of patients presenting with early gastric cancer (i.e., T1 tumors) to reach about 50%.[8,9] Unfortunately, in most other countries including the USA, gastric cancer is found most frequently in advanced stages.

Pathology

Several systems have been developed to classify gastric adenocarcinomas by macroscopic or histologic appearance. The most widely used histologic classification is the Lauren classification. In 1965, Lauren described two distinct histological subtypes of gastric adenocarcinomas: intestinal and diffuse.[10] The intestinal type exhibits components of glandular, solid, or intestinal architecture as well as tubular structures. The diffuse type demonstrates single cells or poorly cohesive cells infiltrating the gastric wall, and progressive disease can ultimately lead to linitus plastica. The two Lauren subtypes of gastric adenocarcinoma have distinct clinical profiles.[11] The intestinal type is more common and arises often from precancerous areas such as chronic atrophic gastritis or intestinal metaplasia. The intestinal type is more common in men and older patients, and is associated with environmental exposures such as *H. pylori* infection. The diffuse type does not typically arise from precancerous areas, is slightly more common in women and in younger patients, and more associated with familial occurrence, thus suggesting a more genetic etiology. The incidence of the intestinal type has been declining, while the incidence of the diffuse type has remained either stable or increased.[4]

Signet ring cells are neoplastic cells which contain a large amount of mucin, which pushes the nucleus to the periphery. There is a general perception that the presence of these cells is a poor prognostic factor. However, signet ring cells can be found in early T1 tumors and may be associated with *improved* survival compared to T1 tumors without signet ring cells.[12] Furthermore, for non-T1 tumors, the presence of signet ring cells may not be an independent prognostic factor when patients are stratified by stage.[13]

Linitis plastica historically has referred to involvement of the *entire* stomach by diffuse type gastric cancer creating a "leather bottle stomach." Linitis plastica of the entire stomach generally carries a very poor prognosis. These patients almost always have either clinically apparent or occult metastatic disease, and so, surgical resection is generally avoided in these patients.[14] The term linitus plastica is now sometimes used to describe diffuse type gastric cancer that is *not involving the entire stomach*, and for these tumors, surgical resection and chemotherapy may lead to cure.[15]

Preoperative Evaluation

The preoperative evaluation of patients with gastric adenocarcinoma involves establishing the diagnosis, assessment of local disease, rule out of distant disease, and assessment of the patient's general medical condition. All patients should have an upper endoscopy, and information should be obtained as to the location, size, and degree of infiltration of the tumor. Endoscopic biopsies of the tumor should be reviewed by an experienced pathologist. *H. pylori* infection should be tested for and treated if present. For proximal gastric tumors, the surgeon needs to reliably know the distance of the tumor from the esophagogastric junction. Sometimes, a repeat endoscopy by the surgeon is needed if findings from prior endoscopies are unclear. If endoscopic ultrasound (EUS) is available, this modality can give additional information regarding T and N stage. In a meta-analysis of 22 studies involving 1,896 gastric cancer patients, EUS had sensitivities for T1–T4 tumors of 88.1%, 82.3%, 89.7%, and 99.2%, respectively, and sensitivities for N1 and N2 disease of 58.2% and 64.9%, respectively,[16] but this modality is highly user-dependent. An abdominal computed tomography (CT) scan should be performed to identify possible regional and distant nodal disease, local extension of tumor to adjacent organs, liver metastases, and peritoneal metastases. The role of chest CT to rule out lung metastases or mediastinal nodal disease is controversial since the yield is low in the absence of intra-abdominal metastases. Positron emission tomography (PET) or PET/CT scans are not generally routinely obtained for staging given the low yield,[17] but PET scans may be useful in the assessment of response of tumors to neoadjuvant treatment.[18]

Small volume peritoneal carcinomatosis can be missed on abdominal CT scans, and so, diagnostic laparoscopy can be performed. Furthermore, patients without overt peritoneal carcinomatosis may have microscopic free peritoneal tumor cells when peritoneal washings are performed. In one study from Memorial Sloan-Kettering Cancer Center, radiologically occult metastatic disease was identified by laparoscopy in 25% of patients who were determined by EUS to have T3–4 or N+ disease and in 4% of patient who were determined by EUS to have T1–2 and N0 disease.[19] The survival of patients without peritoneal carcinomatosis but with free peritoneal tumor cells in peritoneal washings may be similar to those with overt peritoneal carcinomatosis, although the use of better chemotherapeutics has called this into question.[20] Thus, diagnostic laparoscopy with

peritoneal washings should likely be performed as an independent procedure prior to planned surgical resection. If neoadjuvant chemotherapy is administered, diagnostic laparoscopy with peritoneal washings should likely be performed prior to the initiation of neoadjuvant chemotherapy.[21]

Staging

The American Joint Committee on Cancer (AJCC) changed T and N definitions and the overall staging classifications of gastric cancer in the seventh edition of the AJCC Cancer Staging Manual published in 2010. A comparison of the sixth and seventh editions of the AJCC staging for gastric cancer is shown in Table 1.[22,23]

Gastric Resection for Distal or Mid-Gastric Tumors

For tumors in the distal or middle stomach, there have been several studies comparing distal or subtotal gastrectomy to total gastrectomy. In the French cooperative trial of 169 patients with antrum tumors, 93 underwent total gastrectomy, and 76 underwent subtotal gastrectomy.[24] There was no significant difference in perioperative mortality and no difference in 5-year survival (48%). In the Italian Gastrointestinal Study group multicenter, randomized trial of 618 patients with tumors of the distal half of stomach, there was also no difference in 5-year survival between patients that received subtotal or total gastrectomy (65% vs. 62%).[25] Morbidity and mortality data were not reported. Thus, for patients with distal or mid-body gastric tumors, distal or subtotal gastrectomy is adequate, and total gastrectomy does not improve survival.

There are few good studies on the optimal reconstruction after distal or subtotal gastrectomy. In Japan and Korea, the preferred type of reconstruction is generally a Billroth I reconstruction, while most US surgeons prefer a Billroth II reconstruction. Roux-en-Y reconstruction results in less bile reflux into the stomach but can result in a Roux stasis syndrome. Ishikawa et al. randomized 50 patients after distal gastrectomy for cancer to Billroth I or Roux-en-Y

Table 1 Sixth and seventh editions of the AJCC staging system for gastric adenocarcinoma

Sixth edition AJCC staging system		Seventh edition AJCC staging system	
Tis	Carcinoma in situ	Tis	Carcinoma in situ
T1	Invades lamina propria (T1a) or submucosa (T1b)	T1	Invades lamina propria (T1a) or submucosa (T1b)
T2	Invades muscularis propria or subserosa	T2[a]	Invades muscularis propria[a]
T3	Invades serosa	T3[a]	Invades subserosa[a]
T4	Invades adjacent organs	T4a[a]	Invades serosa[a]
		T4b[a]	Invades adjacent organs[a]
TX	Primary tumor cannot be assessed	TX	Primary tumor cannot be assessed
N0	No lymph node metastasis	N0	No lymph node metastasis
N1	Metastasis in 1–6 regional lymph nodes	N1[a]	Metastasis in 1–2 regional lymph nodes[a]
N2	Metastasis in 7–15 regional lymph nodes	N2[a]	Metastasis in 3–6 regional lymph nodes[a]
N3	Metastasis in more than 15 regional lymph nodes	N3a[a]	Metastasis in 7–15 regional lymph nodes[a]
		N3b[a]	Metastasis in more than 15 regional lymph nodes[a]
NX	Regional lymph node(s) cannot be assessed	NX	Regional lymph node(s) cannot be assessed
M0	No distant metastasis	M0	No distant metastasis
M1	Distant metastasis	M1	Distant metastasis
Stage 0	Tis, N0	Stage 0	Tis, N0
Stage IA	T1, N0	Stage IA	T1, N0
Stage IB	T1, N1; T2, N0	Stage IB	T1, N1; T2, N0
Stage II	T1, N2; T2, N1, T3, N0	Stage IIA	T1, N2; T2, N1; T3, N0
		Stage IIB	T1, N3; T2, N2; T3N1; T4aN0
Stage IIIA	T2, N2; T3, N1; T4, N0	Stage IIIA	T2, N3; T3, N2; T4a, N1
Stage IIIB	T3, N2	Stage IIIB	T3, N3; T4a, N2, T4b, N0–1
		Stage IIIC	T4aN3; T4b, N2–3
Stage IV	T4, N1–3; TI–3, N3; any T, any N, M1	Stage IV	Any T, any N, M1

Adapted from references[22,23]

[a] Changes in T and N definitions between sixth and seventh editions

reconstruction.[26] Five of 24 patients in the Roux group developed gastrojejunal stasis in the early postoperative period, and this group had a longer mean hospital stay, but the Billroth I group had a higher incidence of bile reflux gastritis at 6 months after surgery (62% vs. 30%). In another study, 30 patients were randomized to Billroth I or II reconstruction and 15 patients to Roux-en-Y reconstruction. Patients with Roux-en-Y reconstructions had less gastroesophageal reflux and faster and more complete gastric emptying but no improvement in Gastrointestinal Quality of Life Index.[27]

Gastric Resection for Proximal Gastric Tumors

For proximal gastric cancers, there have been few high quality studies examining the extent of gastric resection for proximal gastric tumors, and thus, the extent of gastric resection is largely governed by the preference of the surgeon. In one nonrandomized Norwegian study of 763 patients, complication and mortality rates were *higher* for patients who underwent proximal gastrectomy (52% and 16%) compared to total gastrectomy (38% and 8%).[28] In another large study from Korea, An et al. examined a total of 423 patients with early proximal gastric cancers who underwent surgical resection. Eighty-nine patients had a proximal gastrectomy, and 334 patients had a total gastrectomy. Complications were markedly higher in the proximal gastrectomy group (61.8% vs. 12.6%), with major differences found in the rate of anastomotic stenosis (6.9% vs. 1.8%) and reflux esophagitis (38.2% vs. 29.2%).[29] Some groups, however, continue to advocate proximal gastrectomies for proximal gastric cancers.[30,31] In terms of the surgical incision required to remove a proximal gastric cancer, a laparotomy incision is usually sufficient. The National Cancer Center (NCC) group in Tokyo, Japan, randomized 167 patients with proximal gastric tumors to total gastrectomy and D2 lymphadenectomy via a laparotomy or via a left thoraco-abdominal incision.[32] There were higher morbidity and mortality in the left thoraco-abdominal incision group, but no difference in survival.

Reconstruction after total gastrectomy is general performed with a Roux-en-Y esophagojejunostomy with or without a jejunal pouch. Lehnert et al. reviewed 14 small, randomized trials each having 20–70 patients. The pouch added minimal operative time and did not increase morbidity. Food intake was somewhat improved in the early months, but this advantage decreased with time. Only two of 12 trials found a difference in postoperative weight, and only two of nine trials found an improvement in quality of life. More recently, Fein et al. randomized 138 patients and found no differences in operative morbidity or mortality, and short- and long-term weight losses were similar in both groups.[33] However, quality of life was found to be improved in the third to fifth years after surgery.

Lymphadenectomy

Nodal Station and Lymphadenectomy Definitions

The extent of lymphadenectomy has been a persistent area of controversy in the treatment of gastric adenocarcinoma. Prior to discussion of lymph node dissections for gastric adenocarcinoma, one must define the terms to be used. The lymph node stations surrounding the stomach have been precisely defined by the Japanese Research Society for Gastric Cancer (JRSGC)[34] (Fig. 1 and Table 2). The JRSGC defines four levels of lymph node stations from N1 through N4. *The designation of N1–N4 nodes varies according to the site of the primary tumor* (*i.e.*, *upper*, *middle*, *or lower third of stomach*). The D level of lymphadenectomy (formerly known as the R level of lymphadenectomy) is based on the JRSGC definitions of lymph node station level.[35] A D1 lymphadenectomy is defined as removal of all N1 level nodes, and a D2 dissection is defined as removal of all N1 and N2 level nodes. Table 3 shows the lymph node stations which should be removed for a D1 and D2 lymphadenectomy (based on the location of the primary tumor) as recommended by the Japanese Gastric Cancer Association.[36]

Location of Metastatic Lymph Nodes

There are many excellent studies on the location of metastatic lymph nodes from gastric cancer based on tumor location and other tumor and patient factors. For decades, centers in Japan and South Korea have performed gastrectomies with extensive lymphadenectomies, and then ex vivo dissected out and labeled the nodal stations. Pathologists then examine each nodal station separately and document which nodal station contains nodes with metastatic disease. Using a large database of patients treated with D2 or greater lymphadenectomy, Maruyama et al. at the NCC calculated the risk of the lymph node metastases in each lymph node station by location of primary tumor (Table 4).[37] In 1989, the NCC database of 3,843 cases was used to create the Maruyama computer program.[38] This program estimates the risk of lymph node metastasis for each lymph node station based on the input of eight variables: sex, age, endoscopic or Bormann's classification, depth of invasion, maximal diameter, location (upper, middle, or lower third position (lesser or greater curvature, anterior or posterior wall, or circumferential), and WHO histological classification. The Maruyama computer program was later expanded to include 4,302 cases (WinE-

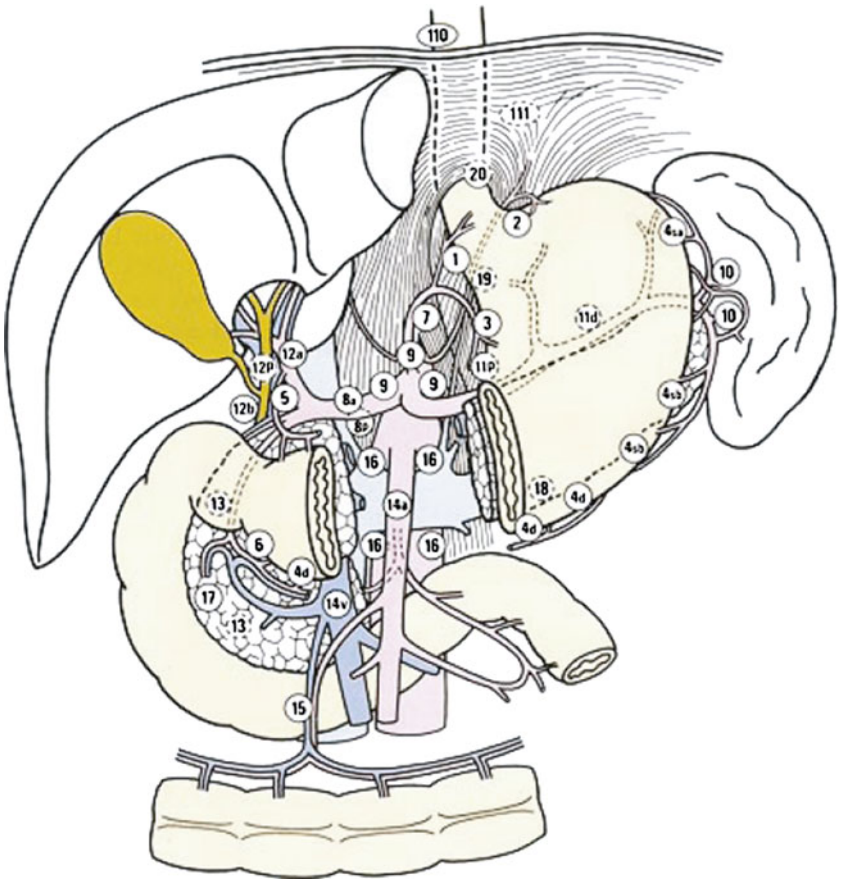

Fig. 1 Locations of lymph node stations. Adapted from reference[36]

stimate 2.5).[39] By matching input variables to this large database of patients, the program gives a percent likelihood of disease in each of the 16 lymph node stations defined by the JRSGC. Similar studies have been published from gastric cancer centers in South Korea.[40]

The studies from Japan and South Korea on the location of metastatic lymph nodes can be applied to Western patients. The applicability of the Maruyama computer program was analyzed in 222 patients treated at the Technical University in Munich, Germany, and the accuracy for lymph node stations 1–6, 7–12, and 13–16 were 82%, 89%, and 96%, respectively.[41] Guadagni et al. subsequently analyzed 282 Italian patients with gastric cancer who underwent at least a D2 lymphadenectomy and found the Maruyama program to be 83% accurate for stations 1–6, 82% for stations 7–12, and 72% for stations 13–16.[42]

Potential Benefits of More Extensive Lymphadenectomy

Lymphadenectomy for cancer can serve three *potential* purposes: staging of disease, prevention of loco-regional recurrence, and improvement in overall survival. There is little doubt that more extensive lymphadenectomies for gastric adenocarcinoma lead to better staging of disease. The 2010 seventh edition of American Joint Committee on Cancer (AJCC) Staging Manual for gastric adenocarcinoma recommends that at least 16 lymph nodes be examined for correct assessment of the N category.[23] Despite this, one analysis of the Surveillance, Epidemiology, and End Results (SEER) database found that only 29% of 10,807 resected gastric cancer patients had 15 or more lymph nodes examined.[43] It is difficult to be confident that a gastric cancer is truly node negative when fewer than ten lymph nodes are examined,[44,45] and N1 tumors can be upstaged to N2 or even N3 tumors as more lymph nodes are harvested.[45,46] Furthermore, it is impossible to be categorized as N3b if less than 16 lymph nodes are harvested. Thus, many patients are understaged following surgical resection of their gastric cancers due to inadequate lymph node sampling. Furthermore, significant variability in the extent of lymphadenectomy and number of lymph nodes examined pathologically leads to difficulty in comparing the outcomes of patients from different regions based on stage of disease as well as stage migration.

There is some evidence that more extensive lymphadenectomies result in lower rates of loco-regional recurrence. Loco-regional recurrence after potentially curative surgery for gastric adenocarcinoma can be quite high. In a 1982 series from the University of Minnesota, 107 patients with

Table 2 Regional lymph nodes of the stomach

Number	Description
1	Right pericardial
2	Left pericardial
3	Lesser curvature
4	Greater curvature
sa	Along short gastric vessels
sb	Along left gastroepiploic vessels
d	Along right gastroepiploic vessels
5	Suprapyloric
6	Infrapyloric
7	Along left gastric artery
8	Along common hepatic artery
a	Anterosuperior
p	Posterior group
9	Around celiac artery
10	Splenic hilum
11	Along splenic artery
p	Along proximal splenic artery
d	Along distal splenic artery
12	Hepatoduodenal ligament
a	Along hepatic artery
b	Along bile duct
p	Along portal vein
13	Posterior surface of pancreatic head
14	Along superior mesenteric vessels
v	Along superior mesenteric vein
a	Along superior mesenteric artery
15	Along middle colic vessels
16	
a1	Aortic hiatus
a2	Abdominal aorta (from upper margin of celiac trunk to lower margin left renal vein)
b1	Abdominal aorta (from lower margin left renal vein to upper margin inferior mesenteric artery)
b2	Abdominal aorta (from upper margin inferior mesenteric artery to aortic bifurcation)
17	On anterior surface of pancreatic head
18	Along inferior margin of pancreas
19	Infradiaphragmatic
20	In esophageal hiatus of diaphragm
110	Paraesophageal in lower thorax
111	Supradiaphragmatic
112	Posterior mediastinal

Adapted from reference[34]

Table 3 Extent of lymphadenectomy

Location	D1 dissection	D2 dissection
LMU	1–6	7, 8a, 9, 10, 11p, 11d, 12a 14v
LD/L	3, 4d, 5, 6	1, 7, 8a, 9, 11p, 12a, 14v
LM, M, ML	1, 3, 4sb, 4d, 5, 6	7, 8a, 9, 11p, 12a
MU, UM	1–6	7, 8a, 9, 10, 11p, 11d, 12a
U	1, 2, 3, 4sa, 4sb	4d, 7, 8a, 9, 10, 11p, 11d

When the tumor involves only one of the three portions of the stomach, this is expressed by U, M, or L. If the lesions involves more than one of the three portions of the stomach, this is expressed by listing the primarily involved portion first followed by the less involved portion(s). Adapted from reference[36]

L lower, *M* middle, *U* upper, *D* duodenum

gastric adenocarcinoma underwent second look laparotomy, and 80% had a recurrence.[47] Of these recurrences, 88% were loco-regional, 54% were peritoneal, and 29% were distant. More recently, in the US Intergroup 0116 trial, 177 of 275 patients (64%) in the surgery only group developed recurrent disease.[48] In terms of the site of first relapse, 29% had local recurrence, 72% had regional recurrence, and only 18% had distant recurrence. Rates of loco-regional recurrence are generally lower in reports from both Western and Asian institutions that perform more extensive lymphadenectomies. In a series of 367 patients with recurrent gastric adenocarcinoma from Memorial Sloan-Kettering Cancer Center over 15 years, 81% of patients had a D2 or greater lymphadenectomy, and the median number of lymph nodes removed was 22.[49] Of patients that recurred, loco-regional recurrence was the initial and only site of recurrence in 26% of patients and was a component of initial recurrence in 54% of patients. Yoo et al. examined 508 patients who developed recurrent disease after curative gastrectomy at Yonsei University in South Korea. Nineteen percent of patients had loco-regional recurrence only as the first site of recurrence, and 32.5% of patients had loco-regional recurrence combined with peritoneal or distant recurrence as the initial site of recurrent disease. In the Japanese prospective randomized trial of adjuvant S-1 chemotherapy, 188 (35.5%) of 530 patients treated with surgery suffered a recurrence.[50] The site of first recurrence in these 188 patients was local in 7.9% and in lymph nodes in 24.5%.

The effect of more extensive lymphadenectomies on overall survival for gastric cancer is still quite controversial. The majority of gastric surgeons in Korea and Japan believe that D2 or greater lymphadenectomies improve overall survival and refuse to perform a prospective, randomized trial of D1 versus D2 lymphadenectomy. Sasako et al. determined the 5-year survival of patients with positive lymph nodes in each of the nodal stations, and many D2 node stations, when positive for metastasis, have a significant percentage of patients surviving 5 years.[51] For example, a lower third tumor had a 23.4% incidence of station 7 metastases. When station 7 nodes were positive and resected as part of a D2 lymphadenectomy, 5-year survival was 34.9%.

Table 4 Frequency of lymph node metastasis based on location of primary tumor

Lymph node basin	Upper third (% with mets)	Middle third (% with mets)	Lower third (% with mets)
Pericardia (stations 1 and 2)	22	9	4
Lesser of greater curve (stations 3 and 4)	25	36	37
Right gastric artery/suprapyloric (station 5)	2	3	12
Infrapyloric (station 6)	3	15	49
Left gastric artery (station 7)	19	22	23
Common hepatic artery (station 8)	7	11	25
Celiac axis (stations 9)	13	8	13
Splenic artery/hilum (stations 10 and 11)	11	3	2
Hepatoduodenal (station 12)	1	2	8
Other	0–5	0–5	0–5

Adapted from reference[37]

There are several *retrospective* studies demonstrating that more extensive lymphadenectomies are correlated with improved survival. A study of 4,789 patients at Seoul National University Hospital found that for patients with stage IIIB disease, those who had more than 35 lymph nodes examined had better survival than those who had less than 20 nodes examined.[52] The German Gastric Carcinoma Study Group found in an analysis of 1,654 patients that those patients who underwent a radical lymphadenectomy (>25 lymph nodes) had a significantly improved survival rate compared to patients who had a standard lymph node dissection for stage II or stage IIIA tumors. [53] Karpeh et al. found in a study of 1,038 patients at the Memorial Sloan-Kettering Cancer Center that median survival for N1, N2, and N3 disease increased significantly when 15 or more lymph nodes were examined.[54] Undoubtedly, these retrospective studies suffer from the confounding issue of stage migration. Dissecting out additional lymph nodes will result in patients often being upstaged, which makes future comparisons regarding therapeutic benefit invalid.

Two large prospective randomized trials in Western countries have failed to identify a survival advantage for D2 over D1 lymphadenectomy.[55,56] However, these two trials had fairly high morbidity (43–46%) and mortality rates (10–13%) for D2 lymphadenectomy. In these trials, the distal pancreas and spleen were often resected during dissection of station 10 and 11 nodes, which significantly increased morbidity. Of note in the Dutch trial, if patients with hospital mortality are excluded, patient with N2 disease had significant survival advantage when treated with a D2 lymphadenectomy.[57] Several studies have now demonstrated that D2 lymphadenectomies can be performed without the need for distal pancreatectomy[58] or splenectomy.[59,60] Furthermore, a recent randomized trial in Taiwan demonstrated an overall survival advantage of more extensive lymphadenectomy over D1 lymphadenectomy, with overall 5-year survival being 59.5% compared to 53.6%, respectively (p=0.041).[61] However, the applicability of this trial to Western patients has been called into question.[62] Degiuli et al. in Italy have demonstrated that Western surgeons, following extensive training, can perform D2 lymphadenectomies on Western patients with low morbidity and almost no mortality,[63,64] and survival results from a prospective randomized trial of D1 versus D2 lymphadenectomy from this group are pending.[65]

Splenectomy, Distal Pancreatectomy, and D2+ Lymphadenectomies

Tumors of the upper and middle stomach are known to metastasize to the splenic artery (station 11) and splenic hilar (station 10) lymph nodes, and historically, distal pancreatectomy and splenectomy were routinely performed to clear these nodal stations.[51] Pancreatic fistula rates were high, thus significantly increasing the morbidity of the D2 lymphadenectomy procedure. Maruyama described a pancreas-preserving D2 lymphadenectomy that resected the spleen and splenic artery along with the station 10 and 11 lymph nodes.[58] A retrospective study from Japan of nearly 400 patients found that there was no improved survival benefit in patients undergoing total gastrectomy combined with distal pancreatectomy and splenectomy compared to patients undergoing total gastrectomy with splenectomy only.[66] Distal pancreatectomy is now generally considered to be unwarranted in the routine performance of a D2 lymphadenectomy unless there is direct extension of tumor.

While most expert gastric cancer surgeons no longer resect the distal pancreas as part of a D2 lymphadenectomy unless there is direct tumor extension, the resection of the spleen continues to be controversial. Two prospective randomized trials of total gastrectomy and lymphadenec-

tomy with or without splenectomy for proximal gastric cancers have been performed in Chile and South Korea.[67,68] Both studies found no improvement in overall survival, and the Chilean study found a significant increase in infectious complications in the splenectomy group. However, the number of patients in these studies was 187–207, and thus, the power of these studies to determine a modest improvement in survival for splenectomy is limited. A multicenter randomized trial to evaluate the role of splenectomy for proximal gastric cancers is currently underway in Japan.[69]

Taking lymph node stations beyond those incorporated in a D2 lymphadenectomy (D2+ lymphadenectomy) likely does not improve survival given disease at such distant nodal stations is unlikely to be cured by surgical therapy alone. Based on data from the National Cancer Center in Japan, the station 13 lymph nodes posterior to the head of the pancreas are rarely involved, and their involvement predicts a 5-year survival close to 0%.[51] Adding dissection of station 16 para-aortic nodes to a D2 lymphadenectomy was studied in a multicenter, prospective randomized trial in Japan. In this study, 523 patients were randomized to D2 lymphadenectomy or D2 lymphadenectomy plus additional para-aortic lymph node dissection (D2+).[70] Surgical morbidity was slightly higher in the D2+ group (28.1% versus 24.5%), but mortality was only 0.8% in both groups. The 5-year overall survival was 69–70% in both groups.[71] Thus, performing lymphadenectomies beyond a D2 lymphadenectomy is not warranted.

Regional Differences in Lymphadenectomy for Gastric Adenocarcinoma

Gastric cancer centers in Japan and South Korea often see a very high volume of gastric cancer cases. For example, two thirds of all gastric cancer surgeries in South Korea are performed at 16 high-volume institutions which perform over 200 gastric cancer surgeries per year. Thus, gastric cancer surgeons at high-volume institutions in Japan and South Korea gain tremendous experience in the surgical management of gastric cancer. The minimum lymphadenectomy performed by surgeons in Japan and Korea for gastric adenocarcinoma for T2 or greater tumors is generally a D2 lymphadenectomy. Despite performing extensive lymphadenectomies, the morbidity and mortality rates are quite low. For example, Seoul National University Hospital, which performs almost 1,000 gastric cancer operations per year, recently reported a morbidity rate of 18% and mortality rate of 0.5%.[72] Japanese patients with gastric cancer are also frequently treated at high-volume institutions with low complication rates. In a prospective, randomized trial from 24 Japanese institutions of D2 versus extended para-aortic lymphadenectomy, the morbidity rate was 20.9–28.1%, and the mortality rate was 0.8%.[70]

Unlike in South Korea and Japan, the majority of gastric cancer surgeries in the USA (and other low-incidence countries) are performed at non-referral centers, and thus, a "high-volume" institution in the USA has been reported in some studies to be centers with only 15–20 or more cases per year.[73,74] Birkmeyer et al. reviewed a database of Medicare patients and found that hospitals that performed more than 20 gastrectomies per year had significantly decreased mortality, yet over 80% of patients were operated on at centers that performed 20 or less gastrectomies per year.[73] Given most US general surgeons see few gastric cancer patients, these surgeons likely err on the side of more limited lymphadenectomies in order to avoid excess morbidity and mortality. In the Intergroup 0116 trial where patients were randomized after gastric cancer surgery to no further therapy or chemoradiation, more than 50% of patients enrolled received a less than a D1 lymphadenectomy.[48]

Despite the performance of less extensive lymphadenectomies in the USA, surgical morbidity and mortality rates for gastric adenocarcinoma are generally much higher in the USA than in South Korea and Japan. A recent analysis of the Nationwide Inpatient Sample from 1998 to 2003 of over 50,000 patents with gastric cancer found the overall mortality following gastric surgery was 6%.[75] Single institutions series have reported morbidity rates following gastrectomy of up to 40%.[76] Certain factors in Japanese and Korean patients such as less advanced gastric cancer and less comorbidities (e.g., cardiovascular disease and obesity) allow for lower morbidity and mortality rates, but likely, the surgical expertise and improved perioperative care that comes with higher volume play a significant role. Thus, in order for surgeons in low-incidence countries to consider performing more extensive lymphadenectomies with low morbidity and mortality, volume at referral centers needs to be increased, and some additional surgical training is likely needed. The learning curve for training general surgeons to perform a D2 lymphadenectomy has been estimated to be at least 23 cases.[77]

Laparoscopic Surgery

The application of the laparoscopic techniques to gastrointestinal malignancies has been curbed by concerns about adequacy of resection, increased risk of peritoneal and port site recurrences, and adequacy of training. Despite these concerns, laparoscopic colectomy has been successfully shown to be a safe, feasible alternative to open colectomy with similar oncologic outcomes, decreased postoperative pain, and diminished length of hospital stay.[78] The first laparoscopically assisted gastrectomy for gastric cancer was reported in 1994 by Kitano et al.[79] Since then, in the East,

laparoscopic gastrectomy has mainly been applied to the management of early gastric cancer (T1/T2, N0 tumors). There have been six prospective, randomized trials comparing laparoscopic versus open distal gastrectomy for gastric adenocarcinoma.[80–85] Four of these trials had less than 60 patients, while two trials had 164 and 340 patients, respectively. A recent meta-analysis of these six trials found that in the short term, there was an increase in the operating room time (81.8 min), decrease in estimated blood loss (115.6 mL), decrease in morbidity (odds ratio, 0.48), and similarly low rates of mortality.[86] This study also showed a decrease in the number of lymph nodes harvested in the laparoscopic group (4.79 nodes).

Similar to laparoscopic colectomy, there will likely be short-term benefits to laparoscopic gastrectomy in terms of blood loss, morbidity, postoperative pain, and/or length of stay, but the impact on survival is not definitively known. Only one of the randomized trials addressed long-term outcomes, with no significant difference noted in overall survival and disease-free survival between groups, but this trial had only 59 patients.[81] Several large, retrospective series have found long-term survival to be similar to historical controls.[87,88] The long-term oncological outcomes of laparoscopic gastrectomy are currently being examined in ongoing randomized clinical trials.

All but one of the six randomized controlled trials of laparoscopic versus open gastrectomy focused on early gastric cancer (T1/T2, N0). The sole trial with broader parameters (T1–T4, N0–N2) was from an Italian group.[81] In the East, the initial use of laparoscopic gastrectomy was limited to early gastric cancer. This limitation has not held fast for the advent of laparoscopic gastrectomy in the West, likely because most gastric cancer in the West presents with more advanced disease. There have been several small studies demonstrating the feasibility of laparoscopic gastrectomy in the West,[89,90] but the data on oncologic outcomes is not yet robust. Given the previously stated issues related to the quality of open gastrectomy and lymphadenectomy in the USA and other low-incidence countries, the use of laparoscopic gastrectomy should likely be limited to the few centers in low-incidence countries that see a relatively large number of gastric cancers.

Neoadjuvant and Adjuvant Therapy

The risk of loco-regional and distant recurrence is highly significant for all ≥T2 or node-positive gastric cancers even with surgical resection, thus providing rationale for the delivery of neoadjuvant and adjuvant therapies. The Intergroup 0116 trial was the first prospective, randomized trial to demonstrate a survival benefit of chemoradiation over surgery alone.[48] Three-year overall survival was increased from 41% to 50% with chemoradiation (p= 0.005). In this trial, 54% of patients received less than a D1 lymphadenectomy, only 10% of patients received a D2 lymphadenectomy, and the chemoradiation appeared to primarily reduce logo-regional recurrence. Thus, some have argued that chemoradiation likely improved survival by making up for inadequate surgery.[91] Of note, an observational study from Samsung Medical Center (Seoul, Korea) of 990 patients who underwent surgical resection along with D2 lymphadenectomy found that median survival was significantly increased in the 544 patients that received chemoradiation compared to the 446 patients who received no adjuvant therapy.[92]

Two prospective randomized trials, one from Europe and one from Japan, have shown survival benefits for neoadjuvant or adjuvant chemotherapy without radiation therapy.[50,93] The European Organisation for Research and Treatment of Cancer (EORTC) MAGIC trial randomized patients to three cycles of epirubicin, cisplatin, and 5-FU (ECF) chemotherapy before and after surgery or surgery alone and found 5-year overall survival of 36% in the chemotherapy plus surgery group and 23% in the surgery-alone group (p=0.009). Sakuramoto et al. randomized Japanese patients to surgery plus S-1, a 5-FU pro-drug combined with an agent that lowers bowel toxicity and an agent that prevents 5-FU degradation, or surgery alone and found that 3-year overall survival was 80% in the S-1 plus surgery group and 70% in the surgery-alone group (p= 0.002). The majority of patients in the EORTC MAGIC trial received at least a D1 lymphadenectomy, and the majority of patients in the Japanese trial received a D2 lymphadenectomy, supporting the notion that chemotherapy alone can improve survival in gastric cancer patients. The CRITICS multicenter trial is currently comparing MAGIC-style perioperative chemotherapy to preoperative chemotherapy followed by postoperative chemoradiation.

Follow-up

The utility of intensive follow-up of patients with gastric cancer following surgical resection is controversial, and there are significant differences in the recommendations of various groups. The European Society for Medical Oncology (ESMO) clinical recommendations for the follow-up of gastric cancer state “there is no evidence that regular intensive follow-up improves patient outcomes, [and] symptom-driven visits are recommended for most cases.”[94] However, many patients are uncomfortable with minimal or no follow-up. The National Comprehensive Cancer Network practice guidelines for gastric cancer recommend a history and physical examination every 3–6 months for 1–3 years, every 6 months for 3–5 years, and then annually.

CBC, chemistry profile, tumor markers (CEA and CA19-9), radiologic imaging, and endoscopy are recommended as clinically indicated.[95] Ultimately, the decision regarding the intensiveness of follow-up is left to the treating physician after discussion with the patient.

Summary

This article reviews the current literature on the workup and surgical management of patients with gastric adenocarcinoma. Useful diagnostic studies include upper endoscopy, endoscopic ultrasound, abdomen and pelvis CT scan, and diagnostic laparoscopy with peritoneal washings. The extent of gastric resection is governed by the location of the tumor. For mid and distal tumors, distal or subtotal gastrectomy can be performed, while for proximal tumors, total gastrectomy is generally performed. The extent of lymphadenectomy is also governed by the location of the tumor, but controversy exists as to whether a D1, D1+, or D2 lymphadenectomy is optimal. Two large randomized studies from Western countries comparing D1 and D2 lymphadenectomy demonstrate that there is no survival benefit for a D2 lymphadenectomy when performed with high morbidity and mortality. Experienced surgeons in high-incidence countries such as Japan and South Korea generally perform D2 lymphadenectomies for gastric adenocarcinoma, and do so with low morbidity and almost no mortality. Overall survival results are pending from an Italian prospective randomized trial of D1 versus D2 lymphadenectomy in which the D2 group had low morbidity and no mortality. Laparoscopic gastrectomy is feasible for experienced surgeons and associated with some short-term benefits, but the long-term outcomes need to be better characterized.

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PANCREAS CLUB MEETING PROCEEDINGS

Summary of the 44th Annual Pancreas Club Meeting Proceedings

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Abstract
Introduction The 44th meeting of the Pancreas Club was held on May 1 and 2, 2010 in New Orleans.
Discussion The program consisted of 42 oral presentations (Table 1) and 61 abstracts chosen for poster presentation. Ten posters each day were chosen for presentation as part of the professor rounds portion of the formal poster viewing program. Summaries of the oral presentations are provided.

Keywords Pancreas Club · Pancreatitis · Pancreatic cancer

Session I: Neoadjuvant vs. Adjuvant Therapy and Other Controversies in Clinical and Basic Sciences

The first paper in this session, (1) "Downstaging Chemotherapy (DCTX) May Alter the Classic CT/MRI Signs of Vascular Involvement in Patients with Pancreaticobiliary Cancers. This Should Influence Patient Selection for Surgery" was presented by Donahue et al. from UCLA. These investigators focused on the preoperative clinical and radiographic factors that predict resectability after DCTX and the efficacy of this treatment strategy. They reviewed a retrospective case series of 41 patients with locally advanced pancreaticobiliary cancers who underwent reoperation after completing a course of DCTX. Locally advanced staging included arterial or venous invasion by the tumor or involvement of the transverse mesocolon. Criteria for exploration after DCTX were: (1) CT/MRI evidence of tumor shrinkage or change in signs of vascular involvement, (2) carbohydrate antigen (CA) 19–9 decreases, and (3) good functional status. At operation, they were able to resect 34 of 41 patients who showed significant post-DCTX decreases in CA 19–9 levels, 32 of whom had pancreatic cancer. The CT/MRI scan was only 72% sensitive and 57% specific for detecting vascular involvement after DCTX. Radiographic decrease in tumor size did not predict resectability. Median follow-up of all survivors was 31 months. The median disease-specific survival of the 32 patients with pancreatic cancer who underwent resection was 52 months, and nine of these survived longer than 5 years, yielding a 28% 5-year survival rate. In summary, indications for resection of initially unresectable pancreatic cancers which respond to DCTX should include lack of disease progression, good functional status, and decrease in CA 19–9 (Table 1).

Chun et al. from the Fox Chase Cancer Center in Philadelphia presented their paper entitled (2) "Significance of Pathologic Response to Preoperative Therapy in Pancreatic Cancer" in which they documented their experience with 108 patients who were treated with gemcitabine or 5-fluorouracil-based chemoradiation prior to pancreatectomy for pancreatic cancer. They defined responses as minor (50% fibrosis relative to residual neoplastic cells), partial (50–94% fibrosis), and major (95–100% fibrosis). These responses were observed in 17%, 64%, and 19%, respectively, of the described study group. Tumor-free resection margins (R0) were observed in 67% of the minor responders, 52% in the partial category, and 86% in those with a major pathologic response to chemoradiation. Furthermore, positive lymph nodes were recovered in 22%, 35%, and 0% of the minor, partial, and major responders, respectively. Median tumor sizes in resected

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Table 1 Summary of 44th Annual Pancreas Club Program

Paper #	Title	Primary institution
Session I: Neoadjuvant vs. Adjuvant Therapy and Other Controversies—Clinical and Basic Science		
1	Downstaging Chemotherapy (DCTX) May Alter the Classic CT/MRI Signs of Vascular Involvement in Patients with Pancreaticobiliary Cancers. This Should Influence Patient Selection for Surgery	UCLA
2	Significance of Pathologic Response to Preoperative Therapy in Pancreatic Cancer	Fox Chase Cancer Center
3	Efficacy of Adjuvant Versus Neoadjuvant Therapy for Resectable Pancreatic Adenocarcinoma: A Decision Analysis	Brigham and Women's Hospital
4	CT Staging System for Pancreatic Cancer	Virginia Mason Medical Center
5	Does Neoadjuvant Therapy Improve Survival in Patients with Resectable Pancreatic Cancer?	Duke University
6	Molecular Mechanisms Underlying the Synergistic Interaction of the Novel Anticancer Drug Ukrain with Gemcitabine in Preclinical Models of Pancreatic Cancer	University of Pisa
7	Patterns and Predictors of Failure After Curative Resections of Pancreatic Endocrine Carcinoma	University of Verona
Session II: Technologies—Clinical and Basic Science		
8	Preliminary Data on Survival After Radiofrequency Ablation of Stage III Pancreatic Cancer: A Wind of Change?	University of Verona
9	Feasibility and Safety of Robotic Pancreatectomies: Analysis of Twenty-Nine Consecutive Operations	University of Pisa
10	Robot-Assisted Major Pancreatic Resections: A Retrospective Analysis of 30 Consecutive Patients	University of Pittsburgh
11	Perioperative Outcomes for Open Distal Pancreatectomy: Current Benchmarks for Comparison?	University of South Florida
12	A Novel Explant Culture System for the In Vitro Study of Murine Pancreatic Intraepithelial Neoplasia (PanIN)	Johns Hopkins University
13	Preoperative CT Measurement of Pancreatic Steatosis and Visceral Fat; Prognostic Markers for Dissemination and Lethality of Pancreatic Adenocarcinoma	University of South Florida
Session III: Cancer Translational Studies: Basic Science		
14	A Translational Clinical Study of a Pancreatic Cancer Vaccine as Neoadjuvant Treatment and Its Effect on the Tumor Microenvironment	Johns Hopkins University
15	Clinical Implications of the Status of Major Four Genes in Pancreatic Cancer Analyses of Mutations and Expression of The KRAS, TP53, P16, and SMAD4 Genes in Autopsy Cases	Johns Hopkins University
16	MicroRNA-21 from Bench to Bedside and Back: A Potential Marker of Clinical Outcome and a Target to Overcome Resistance to Gemcitabine in Pancreatic Cancer	University of Pisa
17	Overexpression of Epidermal Growth Factor Receptor (EGFR) Detected by Antibody Binding EGFR Internal Domain Predicts Poor Survival in Pancreatic Ductal Adenocarcinoma	Thomas Jefferson University
18	HUR Status Is a Powerful Clinical Marker for Resected Pancreatic Ductal Adenocarcinoma Patients and Can Bind to VEGF and HIF-1 alpha mRNA	Thomas Jefferson University
19	DPC4 Status Is Correlated with Tubular Morphology of Invasive Carcinoma Associated with Intraductal Papillary Mucinous Neoplasm of the Pancreas, but Not with Lymph Node Status	Johns Hopkins University
20	Repression of E-Cadherin by the Polycomb Group Protein EZH2 in Pancreatic Cancer	Thomas Jefferson University
21	Intraductal Mucinous Papillary Neoplasms: Genetic Characterization of Lesion Progression	William Beaumont Hospital
22	Loss of Heterozygosity (LOH) Status of D9S105 Marker Is Associated with Down-regulation of Kruppel-Like Factor 4 (KLF4) Expression in Pancreatic Ductal Adenocarcinoma and PanINs	University of Pisa
Session IV: Outcomes		
23	Preoperative Factors Predict Morbidity After Pancreaticoduodenectomy: Creation of a NSQIP Nomogram	University of Wisconsin
24	Pancreatectomy Risk Calculator: An ACS-NSQIP Resource	Indiana University
25	Brain Natriuretic Peptide (BNP) and Postoperative Fluid Balance in the Management of Patients Undergoing Pancreatectomy	MD Anderson Cancer Center
26	Differences in Methylation of Cell-Free Circulating DNA in Patients with Pancreatic Cancer and Chronic Pancreatitis	Rush University
27	The Burden of Infection for Elective Pancreatic Resections	Beth Israel Deaconess Medical Center
28	Support for a Postresection Prognostic Score for Pancreatic Endocrine Tumors	Loyola University

Table 1 (continued)

Paper #	Title	Primary institution
Session V: Cancer—Basic Science		
29	Adipocytes in the Tumor Microenvironment Promote Dissemination of Human Pancreatic Cancer	Indiana University
30	Low Dose Metronomic Gemcitabine Has High Antimetastatic Efficacy in an Orthotopic Mouse Model of Pancreatic Cancer	University of California San Diego
31	Tumor Suppressor, ANP32A, Disrupts HUR'S Regulation of Deoxycytidine Kinase in Pancreatic Cancer: Implications for Gemcitabine Therapy	Thomas Jefferson University
32	Induction of Monocyte Chemoattractant Protein-1 by Nicotine in Pancreatic Ductal Adenocarcinoma Cells: Role of Osteopontin	Thomas Jefferson University
33	A Molecular Link Between Epithelial Mesenchymal Transition and Cancer Stem Cell Properties in Pancreatic Cancer	University of Freiburg
34	Adipocytes Promote Pancreatic Cancer Proliferation via a Hepatocyte Growth Factor-Mediated Mechanism	Indiana University
35	Deregulation of the RB/E2F Pathway and P16 Expression in Pancreatic Adenocarcinoma	University of South Florida
36	A Novel Murine Model for the Study of Metastatic Pancreatic Adenocarcinoma	Johns Hopkins University
37	Blood Pressure Lowering Medications Disrupt Fatty Acid Metabolism in Pancreatic Cancer	Thomas Jefferson University
How I Do It Session: Adjuvant Therapy for Resected Pancreatic Cancer—Is There a Role for Radiation Therapy? Douglas Evans, MD and John Neoptolemos, MD		
Session VI: Pancreatitis		
38	Randomized Trial Comparing EUS and Surgery for Pancreatic Pseudocyst Drainage	University of Alabama Birmingham
39	Does Increasing Insurance Improve Outcomes for US Pancreatic Cancer Patients?	University of Massachusetts
40	Auto-islet Transplantation for Chronic Pancreatitis in Diabetic Patients: Why Bother?	Medical University of South Carolina
41	Abdominal Compartment Syndrome: An Early Lethal Complication of Acute Pancreatitis	University of Pittsburgh
42	Live Animal Molecular Imaging of Protease Activity in Acute Pancreatitis	University of California San Francisco

specimens were 3.5, 2.5, and 0.3 cm in minor, partial, and major responders, respectively. Median survival rates were 10 months in those with a minor response, 14 months in partial responders, and 51 months in major responders. They concluded that a major pathologic response is seen in a minority of patients subjected to preoperative chemoradiation therapy, but prolonged postoperative survival was identified in this small treatment responder subgroup. Fewer minor and more partial responses were seen in gemcitabine-based therapy as compared to 5-FU-based regimens, suggesting a tendency of superiority of the gemcitabine-based treatments.

The next paper, (3) "Efficacy of Adjuvant Versus Neoadjuvant Therapy for Resectable Pancreatic Adenocarcinoma. A Decision Analysis" by Ito et al. from the Brigham and Women's Hospital in Boston, compared two management strategies for simulated cohorts of patients with potentially resectable pancreatic adenocarcinoma. These authors observed problems with comparing the efficacy of chemotherapy or chemoradiation either preceding or directly following surgical resective procedures. The issues included both patient selection bias and so-called lead time bias in calculation of posttreatment survival. Furthermore, they noted that standardization of definitions is important in evaluating comparative studies from multiple institutions. Their study proposed to select appropriate patient cohorts from available literature as a consistent means of comparison. They described the use of the Markov transition model which follows and documents the course of patient survival following treatment. In selecting the comparative groups, they excluded retrospective reviews, trials including patients with borderline resectable or locally advanced cancer and trials of non-5-FU or gemcitabine-based therapy such as immunotherapy. Consequently, their patients included those with potentially resectable cancer derived from reports published from 1997 to 2009. These data sources included ten papers concerning use of neoadjuvant therapy and nine papers describing adjuvant therapy regimens. In the standard strategy, patients underwent surgical resection followed by adjuvant systemic chemotherapy (CT), chemoradiation (CRT), or both as tolerated. In the neoadjuvant strategy, patients were treated with 3 months of CT, CRT, or both and then underwent surgical resection. Two primary comparative outcomes were median overall survival (OS) and a factor termed as QoLE based on a quality of life utility factor ranging from 0 for death and with 1 representing perfect health. The QoLE represented expected survival duration incorporating these

utility factors. Those treated by means of postsurgery adjuvant therapy achieved a 20-month overall survival and a QoLE duration of 20 months. Neoadjuvant therapy administered preoperatively likewise resulted in OS of 27 months and a QoLE of 26 months. Their study suggested that neoadjuvant therapy-based management improves outcomes of patients with potentially resectable pancreatic cancer.

(4) "CT Staging System for Pancreatic Cancer" by Clark et al. from the Virginia Mason Medical Center in Seattle reported their efforts to accurately stage cases with locally extending disease including unresectable and borderline lesions based on high-quality CT imaging. They studied these scans in 220 patients with stage T3 or T4 pancreatic head cancer. Tumors with anterior capsule extension were classified as T3 lesions while T4 lesions represented those with major mesenteric vessel abutment. The configuration of the study involved inclusion of patients with locally advanced, biopsy proven pancreatic cancer without evidence of metastases and in whom no pancreatic resection was to be performed. The pancreas protocol CT was subjected to blinded review by a radiologist independent of this retrospective, single-center study. Included in the CT reviews were documentation of tumor size, presence of ascites or indeterminate liver lesions, and presence of mesenteric vessel involvement. The staging was completed by means of diagnostic laparoscopy and peritoneal lavage. These findings were correlated with survival. They concluded that while high-quality CT imaging can detect aggressive tumor behavior, it was not able to discern a survival difference for T3 vs T4 disease. Using the log-rank test, they documented significantly shorter survival times for patients with venous involvement compared to those without venous abutment. The presence of positive cytology produced significantly lower survival. The use of staging laparoscopy to detect occult liver metastases was only useful in stratifying survival in patients without mesenteric venous involvement. In this group, those who were found to have liver metastases survived 7 months, while those without metastases survived a mean of 17 months.

Papalezova et al. from Duke University presented their paper, (5) "Does Neoadjuvant Therapy Improve Survival in Patients with Resectable Pancreatic Cancer" relating their comparison of a preoperative neoadjuvant group compared to standard surgical "intent to resect" therapy. They reported on 92 patients who went directly to surgical treatment (SURGERY) and 144 patients who received preoperative neoadjuvant chemoradiation (NEOCRT). While the groups were similar in both age and tumor size, the NEOCRT group was more likely to have venous abutment and tended to have more comorbidities. In the NEOCRT group, 53% underwent resection, 20% had metastatic disease, and 11% were unresectable. In the SURGERY group, 73% underwent resection, 18% had metastatic disease, and 9% had locally unresectable disease. The NEOCRT group had an overall smaller tumor size and a lower incidence of positive lymph nodes. Median overall survival in the NEOCRT group was 27 months while in the SURGERY group it was 17 months. The NEOCRT group had a survival duration similar to the SURGERY group, suggesting that NEOCRT allowed for better patient selection.

(6) "Molecular Mechanisms Underlying the Synergistic Interaction of the Novel Anticancer Drug Ukrain with Gemcitabine in Preclinical Models of Pancreatic Cancer" was presented by Funel et al. from Pisa, Italy. They attempted to elucidate the mechanism by which the anti-neoplastic efficacy of gemcitabine could be enhanced by means of a second agent known as ukrain. This drug had been shown by previous reports to extend median survival in patients with unresectable cancer treated by gemcitabine and ukrain compared to gemcitabine alone (10.4 vs 5.2 months, respectively, $p=0.001$). The specific aim of the present study was to evaluate the modulation of expression of two pivotal genes (hENT1 and dCK) involved in gemcitabine activity. Using in vitro techniques, they treated both cultured pancreatic cancer cell lines and primary cell cultures from specimens obtained by surgical resection of human pancreatic tumors with ukrain at IC 50 concentration levels for 48 h. They found that ukrain produced a mean increase of 2.8-fold in expression of hENT1 mRNA in all of the cell culture lines compared to control cells. In half of the cell lines, ukrain positively affected mRNA expression of dCK as well. They proposed that a ukrain–gemcitabine combination therapy might be suitable for experimental clinical testing in patients with pancreatic cancer.

The last paper of this session was entitled (7) "Patterns and Predictors of Failure after Curative Resections of Pancreatic Endocrine Carcinoma" by Falconi et al. from Verona, Italy. The intent of this study was to document prognostic factors for pancreatic endocrine carcinoma (PEC) following surgical resection as well as the value of the lymph node ratio (LNR) in the surgical specimen in addition to patterns of recurrence after curative surgical removal of the PEC. Sixty-seven patients with a median age of 56 years were evaluated, and the resulting data were subjected to univariate and multivariate analysis. The median overall survival and median disease specific (DSS) were 125 and 76 months, respectively. Recurrent disease primarily in the liver was identified in 44.6% of the group, and the 2- and 5-year DSS were 69.8% and 52.1%, respectively. In the surgical specimens, 33% of the patients had negative lymph nodes. In the 67% of patients with positive nodes, the LNR was <0.20 in 50 patients, and the

remaining 17 patients had LNR >0.20. In patients in whom recurrence was observed as compared to those with no recurrence, the frequency of microvascular (76.8% vs 23.2%, $p=0.002$) and peripancreatic fat invasion (54.3% vs 35.7%, $p=0.0007$) was documented. The median value of Ki67, a genetic marker, for those with recurrence compared to no recurrence was 8% vs 3%, respectively, $p=0.003$. The LNR >0.20 and Ki67 5% values were found on multivariate analysis to be significant predictors of recurrence ($p<0.002$).

Session II: Technologies—Clinical and Basic Science

The first of these papers by Frigerio et al. from Verona, Italy was (8) "Preliminary Data on Survival After Radiofrequency Ablation of Stage III Pancreatic Cancer: A Wind of Change"? The purpose of this study was to evaluate survival after radiofrequency ablation (RFA) for non-resectable pancreatic cancer. They reported on 56 patients with locally advanced stage III pancreatic cancers who had been treated with RFA. The male-to-female ratio was equal, and the median age of the group was 61 years. The tumor was located in the head of the gland in 59% and in the body or tail in 41%. The mean diameter of the tumor was 37 mm. The procedure was performed as an "up front" therapy prior to defined treatment such as a surgical procedure. In this group, 76% of the patients received additional treatment following RFA. Mortality related to the procedure was reported as 2%, and early progression of the tumor within 3 months following RFA was 10%. Chemoradiation therapy was given to 24% of the group prior to RFA. Palliative surgery of any form was provided to 61% of the group. The 1- and 2-year overall survivals were 67% and 52%, respectively, for those treated with RFA compared to 45% and 23%, respectively, for those in the study who did not receive RFA. The authors reported a median survival of 20 months. In all, 34 of the 56 patients had recurrence of disease and 20 of them eventually died of the disease. The authors summarized by indicating their conclusion that RFA provided a positive impact on survival and that timing of its administration seemed not to modify the results. Discussants following the presentation expressed concern about duodenal and portal vein damage. The authors responded that they were continuing to assess the incidence of these complications.

The next paper, (9) "Feasibility and Safety of Robotic Pancreatectomies: Analysis of Twenty-Nine Consecutive Operations" by Chiaro et al. from Pisa, Italy was one of two papers concerning use of robotic surgery in treatment of pancreatic tumors. These authors reported their results on nine male and 20 female patients who underwent ten pancreatoduodenectomies, three central pancreatectomies, 13 distal pancreatectomies, two tumor enucleations, and one total pancreatectomy. The pathologic diagnosis included a variety of cystadenomas, neuroendocrine tumors, ductal adenocarcinoma, duodenal cancer, and one patient with chronic pancreatitis. There were no deaths, but 14 patients developed postoperative complications, primarily pancreatic fistulas, and one patient required reoperation for postoperative bleeding. Mean postoperative stay was 14.1 days. Four patients required perioperative transfusions. Their experience seemed to demonstrate the feasibility of robotic surgery for pancreatic disease with acceptable operative risk. The authors presented an extensive video of one of their procedures illustrating technical aspects of their robotic operations. They discussed the considerable learning curve involved even for surgeons with significant experience. The approximate duration for a robotic pancreaticoduodenectomy was stated at 8 h. They also commented on the pancreatic leak rate. Most of the leaks were grade A fistulas. They also mentioned that many of their patients had a soft pancreas, a known risk factor for postoperative pancreatic fistula.

The next paper by Zureikat et al. from the University of Pittsburgh, entitled (10) "Robot-Assisted Major Pancreatic Resections: A Retrospective Analysis of 30 Consecutive Patients", was the first of the afternoon short presentations. Their retrospective review of the procedures performed for pancreatic neoplasms and one case of chronic pancreatitis revealed the necessity for conversion to open pancreaticoduodenectomy in only seven cases. Unsuspected venous involvement and failure to progress were the two reasons for conversion. The mean operative time was 590 min with a median blood loss of 500 cc. They were able to achieve a tumor-free pancreatic transection margin 85% of the time using the robotic technique. Median lymph node harvest was 16 and median length of stay (LOS) was reported as 10 days. The incidence of pancreatic fistula was 23%, only 8% being grade C. There was one late death on postoperative day 87 resulting from multiple factors. This paper also was followed by discussion concerning the necessity of prerequisite experience with minimally invasive techniques before undertaking routine use of robotic surgery for treatment of pancreatic disease. The learning curve seems especially important in regard to being able to achieve tumor-free margins by use of this method.

The next short presentation by Tseng et al. from the University of South Florida was entitled (11) "Perioperative Outcomes for Open Distal Pancreatectomy: Current Benchmarks for Comparison?" They examined the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) for 2005 to 2007 to describe 30-day morbidity and mortality, operative time, transfusion requirement, and hospital LOS for patients undergoing open distal pancreatectomy (ODP). They

identified a study cohort of 868 patients. Univariate and multivariate analysis were performed to identify factors associated with complications and death in patients undergoing ODP. Any complication, severe complication, and mortality rates were 27.2%, 11.6%, and 1%, respectively. Mean operative time was 206 min; 18.1% patients required intraoperative red blood cell transfusion (median 2 U), and median LOS was 6 days. Predictors of complications were renal insufficiency, hypoalbuminemia, and worsening ASA classification. Malignant diagnosis was not associated with increased likelihood of morbidity or mortality. Discussants noted that while this study was an attempt to produce a gold standard for results of ODP using a large bulk of available data, there remains insufficient information in some areas. Protocols for coders may not allow for collection of all morbidities. For instance, the data base provided no information regarding postoperative pancreatic fistulas, incidence of splenectomy, method of pancreatic stump closure, pancreas and tumor characteristics, incidence of postoperative new onset diabetes, or information regarding surgeon or hospital operative volume for ODP. The authors concluded by stating that the reported data could be used as benchmark values to which patients undergoing laparoscopic distal pancreatectomy could be compared.

(12) "A Novel Explant Culture System for the In Vitro Study of Murine Pancreatic Intraepithelial Neoplasia (PanIN)" was presented by Karhadkar et al. from the Johns Hopkins Hospital. They described an in vitro technique which allows for the long-term maintenance of intact pancreatic sections. The purpose of this effort was to allow study of the local microenvironment and complex interaction between stromal and parenchymal cells present during tumor initiation. They explored the process known as pancreatic intraepithelial neoplasia which is the result of a histological and genetic progression to pancreatic cancer. Adult mouse pancreata were isolated and sectioned to a thickness of 200 μm. These microslices were maintained in culture for up to 4 weeks. Metabolic activity was verified with methyl methane thiosulfonate. By means of immunostaining, they were able to demonstrate intact pancreatic architecture exhibiting separate ductal, acinar, and endocrine compartments following specific biological stimulation. They documented that treatment of the microslices with cerulean induced proliferation in ductal and acinar compartments. They demonstrated that in vitro KRAS activation in cultured explants causes dose-dependent acinar cell proliferation and hedgehog pathway induction, a precursor to the cellular changes of pancreatic cancer. This represents an innovative in vitro model allowing for study of development, regeneration, and neoplasia in transgenic mouse pancreatic microslices. Discussion centered on factors lacking in this model including the effects of extra-pancreatic cellular ingress of stem cells, contributions of the immune system, and the development of neovascularization in the neoplastic process.

The last paper of the afternoon by Mathur et al. from the University of South Florida was (13) "Preoperative CT Measurement of Pancreatic Steatosis and Visceral Fat: Prognostic Markers for Dissemination and Lethality of Pancreatic Adenocarcinoma." The aim of this study was to determine the utility of preoperative CT measurements of pancreatic steatosis and visceral fat as prognostic indicators for patients with pancreatic adenocarcinoma. Their interest in these findings results from previous observations that increased visceral fat increases the risk of developing pancreatic cancer, while pancreatic steatosis promotes lymphatic metastases and a subsequent decrease of survival duration following pancreaticoduodenectomy. In 42 patients with pancreatic cancer, high-resolution CT scans were reviewed by two investigators blinded to clinical details of these patients. In addition to visceral and pancreatic fat measurement, the pathology slides of the cancer were postoperatively reviewed for tumor differentiation and invasion. Lymphatic metastases were present in 57% of patients. In these cancer patients, increased pancreatic and liver steatosis as well as increased visceral fat including perirenal adiposity were associated with lymphatic metastases and decreased duration of survival for those patients with lymphatic metastases (7 vs 16 months, $p<0.01$). They concluded that CT measurements of visceral fat predict the dissemination and lethality of pancreatic cancer.

Session III: Cancer Translational Studies—Basic Science

The first of the Sunday sessions addressed the issue of cancer translational studies. Edil et al. from the Johns Hopkins Hospital presented their paper entitled (14) "A Translational Clinical Study of a Pancreatic Cancer Vaccine as Neoadjuvant Treatment and Its Effect on the Tumor Microenvironment." In this interim study, they investigated the immunologic response to vaccination with an irradiated granulocyte–macrophage colony-stimulating factor (GM-CSF) secreting allogenic pancreatic tumor vaccine prior to pancreaticoduodenectomy with or without cyclophosphamide. The GM-CSF promotes recruitment and maturation of dendritic cells which aid in the activation of tumor specific T cells. This chemotherapeutic agent is thought to enhance the anti-tumor response of the vaccine by depleting immunosuppressive regulatory T cells. Prior to operation, patients were randomized to one of three groups: group A—vaccine alone, group B—vaccine with IV cyclophosphamide, and group C—vaccine with oral metronomic cyclophosphamide. Immunochemistry was used to investigate immune cells infiltrating resected tumors. Following

the preoperative treatment protocol, the patients underwent pancreaticoduodenectomy 2 weeks later. When compared to age- and sex-matched unvaccinated controls, the amount of intratumoral lymphoid aggregates (LAs) appeared to be increased, but the differences were not significant. The LAs were inversely correlated with regulatory T cells (FoxP3 Tregs) which expressed an immunosuppressive function. Intratumoral LAs have more proliferative activity, as measured by Ki67, than peritumoral LAs and may function in the generation of anti-tumor adaptive immune responses. However, immune tolerance remains an obstacle to effective immunotherapy. Consequently, the B7-H1 cells observed in the germinal centers may represent a mechanism of suppression of the anti-tumor response by the patient and might possibly represent a target for blockade in future vaccine trials.

Yachida et al. from Johns Hopkins presented their report entitled (15) "Clinical Implications of the Status of Major Four Genes in Pancreatic Cancer." The goal of this study was to compare the status of four genes (KRAS, p16, TP53, and SMAD4/DPC4) to clinicopathological features at autopsy in pancreatic cancers. Rapid autopsies were performed on 91 patients who had died of documented pancreatic cancer. Twenty-six of these patients had undergone pancreatic operations, and in two of these patients, no evidence of residual cancer was observed. Frozen samples were sequenced for KRAS2 and TP53. Paraffin-embedded samples were immunostained for p16 and SMAD4. The clinicopathologic features, including survival and metastatic burden, were determined and compared to the status of these four genes. Activating mutations in the KRAS2 gene were identified in 92% of the cancers. Inactivating mutations in the TP53 gene were identified in 67%. Loss of SMAD4 and p16 immunolabeling was identified in 58% and 90% of the primary tumors, respectively. Kaplan–Meier survival analysis in the 91 patients showed that the tumor size at the time of diagnosis and the status of SMAD4 gene were significantly associated with shorter survival. Genetic alteration of all four genes in the same carcinoma was highly correlated with extensive metastatic burden. The authors commented that perhaps analysis of SMAD4 could provide prognostic information and patterns of failure, especially in patients with surgically resected pancreatic cancer.

(16) "MicroRNA from Bench to Bedside and Back: A Potential Marker of Clinical Outcome and a Target to Overcome Resistance to Gemcitabine in Pancreatic Cancer" was presented by Giovannetti et al. from Pisa, Italy. MicroRNAs (miR-21) are small noncoding RNAs with important functions in development, cell differentiation, and apoptosis. Recently, miR-21 was reported to be overexpressed in pancreatic duct adenocarcinoma (PDAC) and contribute to tumor invasion and resistance to gemcitabine. Consequently, miR-21 might serve as a biomarker for maximizing the therapeutic efficacy and minimizing useless treatment in pancreatic cancer patients. The aim of this study was to evaluate whether miR-21 expression was associated with the OS of PDAC patients treated with gemcitabine. Expression of miR-21 was evaluated in neoplastic pancreatic cells and metastatic tissues. The role of miR-21 on the pharmacological effects of gemcitabine was studied in cells transfected with a specific miR-21 precursor. Inhibitors of pathways affected by activation of miR-21 and gemcitabine activity were used to test whether modulation of these pathways would prevent induced resistance to the pro-apoptotic effects of gemcitabine. In conclusion, the authors demonstrated a negative correlation between miR-21 overexpression and clinical outcome in PDAC patients treated with gemcitabine. Discussion following the presentation included an inquiry regarding the mechanism for regulation of miR-21. The authors responded that they intended to include this issue in future studies.

Next, Kline et al. from Thomas Jefferson University in Philadelphia presented their paper, (17) "Overexpression of Epidermal Growth Factor Receptor (EGFR) Detected by Antibody Binding EGFR Internal Domain Predicts Poor Survival in Pancreatic Ductal Adenocarcinoma." They observed that monoclonal antibodies and small molecule inhibitors targeting EGFR have been approved by the Food and Drug Administration in combination with gemcitabine for treatment of pancreatic ductal adenocarcinoma (PDA). The aim of this study was to evaluate expression of EGFR in PDA using a novel antibody binding the intracellular domain of EGFR. Eighteen cases of PDA from patients with long (>3 years) and 19 cases with short (<1 year) survival were included in this study. Immunohistochemical semiquantitative assessment of EGFR protein expression was based on the fraction of stained cells with assigned scores of 1+ to 3+, where 3+ was considered to represent EGFR overexpression. In addition, gene expression profiling was performed on stromal PDA tissue from six patients with long and seven patients with short survival. For those study cases, expression of epidermal growth factor (EGF) in tumor stroma was correlated with EGFR expression in tumor epithelium. Statistical analysis was performed using Fisher's exact test. There was a statistically significant correlation between EGFR expression and shorter survival ($p=0.0081$). However, two of two patients with EGFR overexpression and long survival had low EGF gene expression in tumor-associated stroma; conversely, all profiled cases with short survival had high EGF gene expression in the tumor stroma. They concluded that evaluation of both EGFR and EGF may select patients who best respond to targeted therapies with EGFR inhibitors.

(18) "HuR Status Is a Powerful Clinical Marker for Resected Pancreatic Ductal Adenocarcinoma Patients and Can Bind to VEGF and HIF-1 alpha MRNA" was presented by Richards et al. from Thomas Jefferson University. Two previously proposed prognostic markers, COX-2 and vascular endothelial growth factor (VEGF), are regulated by HuR, an mRNA binding protein that has been demonstrated to be a promising predictive marker of gemcitabine response. This study evaluated this protein as a marker for PDA and explored the association of HuR with the oncogene mRNA target genes, hypoxia inducible factor-1 (HIF-1) and VEGF. A tissue microarray of 53 PDA specimens from patients who had undergone a potentially curative resection was analyzed. HuR, COX-2, and VEGF status were compared and correlated with clinical data. Roughly 50% of patients had elevated cytoplasmic HuR expression (HuR+). These patients had worse prognostic pathologic features such as positive lymph nodes (75%) and advanced pathologic stage (94%) compared to HuR patients. Cytoplasmic HuR status correlated with staging better than VEGF or COX-2 expression alone. HuR cellular positivity with VEGF+ status yielded 100% lymph node positivity. Conversely, HuR status was a robust positive predictive marker for overall survival in patients treated with gemcitabine, producing a median survival of greater than 40 months in the HuR+ population (p=0.0049). They concluded that HuR status is a robust predictor of outcome for patients with resected PDA and may be useful in individualizing treatment.

Naito et al. from the Johns Hopkins Hospital presented their paper entitled (19) "DPC4 Status is Correlated with Tubular Morphology of Invasive Carcinoma Associated with Intraductal Papillary Mucinous Neoplasm of the Pancreas, but Not with Lymph Node Status." Two distinct types of invasive carcinoma commonly occur in association with IPMN, the tubular type which resembles standard pancreatic ductal adenocarcinoma and the colloid type which is characterized by extensive stromal pools of extracellular mucin. The goal of this study was to compare the clinicopathologic features and genetic status of DPC4 with adenocarcinomas associated with IPMN. Immunohistochemical analysis for DPC4 was performed on paraffin sections of each of 55 patients who had undergone pancreatic resections for IPMN. These results were correlated with the clinicopathologic features of each patient. The mean age and male gender for the group were 68.1 years and 47%, respectively. The mean IPMN size was 4.3 cm. and for infiltrating carcinomas it was 3 cm. Lymph node metastases were observed in 73% of those with tubular type carcinomas and 50% of those with colloid type tumors. Tumors of the tubular type tended to be larger than colloid tumors. Loss of DPC4 was more frequent among tubular vs colloid carcinomas. Analysis of the tubular carcinomas revealed that 63% with positive lymph nodes had DPC4 loss, while none of the colloid carcinomas with positive lymph nodes had DPC4 loss. The authors suggested different biological mechanisms for lymph node metastases in these two types of IPMN derived carcinomas.

The next paper by Kline et al. from Thomas Jefferson University was entitled (20) "Repression of E-Cadherin by the Polycomb Group Protein EZH2 in Pancreatic Cancer." In this study, the authors correlated the overexpression of histone methyltransferase (EZH2) with the silencing of E-cadherin, resulting in tumor aggressiveness. Furthermore, previous in vitro studies showed the EZH2 depletion sensitizes pancreatic cancer cells to gemcitabine. The authors reported additional data on this relationship and evaluated the response of gemcitabine to EZH2 expression. They applied specific stains to human pancreatic cancer tissue specimens for both EZH2 and E-cadherin. They studied 43 specimens of PDA, 14 IPMNs, and 5 chronic pancreatitis (CP) specimens. They reported that high EZH2 expression in PDA was significantly associated with decreased E-cadherin expression. There was a trend for longer survival (35 vs 15 months) in gemcitabine-treated patients with low compared to high EZH2 expression. High EZH2 expression was detected in IPMNs with moderate to severe dysplasia, but not in patients with CP.

(21) "Intraductal Papillary Mucinous Neoplasms: Genetic Characterization of Lesion Progress" was presented by Jury et al. from William Beaumont Hospital in Detroit. The authors investigated the changes in gene expression that occur in IPMNs during their progression from low- to high-grade dysplasia and then on to invasive carcinoma. Serial sections were cut from IPMN tissue obtained from surgical specimens. The authors' description of their technique stated that extracted RNA was analyzed for integrity and hybridized to Affymetrix Human Exon 1.0 ST arrays using proprietary procedures. Gene expression data were normalized and filtered using GCOS software and analyzed using Expression Console software and statistical analysis. While they did identify 96 genes which were differentially expressed with dysplastic IPMN, they reported 62 genes which demonstrated greater than two-fold changes in expression when comparing low- and moderate-grade areas with high-grade and invasive areas. A total of 41 genes were upregulated and 21 were downregulated. Many of the overexpressed genes lead to production of enzymes with the capacity to break down connective tissue, potentially allowing tumor invasion. They postulated that development of the ability to recognize genes associated with the progression of tumor dysplasia to invasion would result in a more refined capability to define appropriate and timely surgical intervention.

The final paper of this morning session, (22) "Loss of Heterozygosity (LOH) Status of D9S105 Marker is Associated with Down-regulation of Kruppel-Like Factor 4 (KLF4) Expression in Pancreatic Ductal Adenocarcinoma and PanINs", was presented by Funel et al. from Pisa, Italy. Homozygous deletion of 9q31–32 has been associated with KLF4 suppression, placing this gene as a putative tumor suppressor gene in several cancers. This study was aimed at evaluating the association between loss of 9q31–32 region and gene expression of KLF4 and to evaluate the role of this gene in PDAC. The authors investigated LOH in the 9q region and expression of KFL4 gene in PDAC, PanINs, normal ducts, and primary cell culture of PDAC. They used four microsatellite markers (D9S127, D9S53, D9S105, and D9S106) flanking KLF4 locus to test the LOH, both in PDAC and PanINs. In 47% of PDAC and 83% of PanIN lesions, there was a loss of the D9S105 marker. Lack of KLF4 expression was found to be significantly associated with (1) genomic deletion of flanking KLF4 in PDAC ($p=0.018$) and in PanINs ($p<0.01$), (2) LOH of D9S105 marker ($p=0.014$), and (3) presence of low-grade PDAC-associated PanIN ($p=0.021$). They concluded that the KLF4 gene can switch its role between tumor suppressor gene and oncogene depending on the biological context of PDAC, as illustrated by the known ability of ectopic Kras gene mutation to promote KLF4 as an oncogene in vitro.

Session IV: Outcomes

(23) "Preoperative Factors Predict Morbidity After Pancreaticoduodenectomy: Creation of a NSQIP Nomogram" was presented by Greenblatt and colleagues from the University of Wisconsin. These authors analyzed NSQIP data for patients undergoing pancreatoduodenectomy between 2005 and 2008 ($n=4,438$). They determined that contemporary *serious* morbidity among these patients was 27.5% and mortality was 2.7%. Using univariate and multivariate statistical analysis, they determined that age> 80, presence of congestive heart failure, albumin <2.0, and BMI>30 kg/m^2 were predictors of mortality. Using these data, they created a nomogram to predict morbidity and mortality (which they have posted on their department's web page). They found that their nomogram using preoperative data was more accurate in predicting mortality than morbidity and concluded that this would be a useful tool in preoperative patient discussions.

The next paper of this session was presented by Parikh and colleagues from Indiana University, entitled (24) "Pancreatectomy Risk Calculator: An ACS-NSQIP Resource." These authors analyzed the same NSQIP data set as the previous authors but included patients undergoing proximal, distal, total pancreatectomy, or enucleation (total $n=7,571$). They identified ten easily accessible preoperative parameters—age>74, male gender, BMI> 40, preoperative sepsis, dependent status, ASA classification>II, coronary disease, dyspnea on moderate exertion, presence of bleeding disorder, and proximal/total pancreatectomy—that were incorporated into a risk model for morbidity and mortality. This model will be on line soon as an ACS-NSQIP resource and should assist clinicians in preoperative decision making and counseling patients considered for pancreatic resection.

Berri et al. from MD Anderson Cancer Center presented the next paper: (25) "Brain Natriuretic Peptide (BNP) and Postoperative Fluid Balance in Patients Undergoing Pancreatectomy." These investigators collected serum BNP measurements to guide fluid resuscitation in 44 patients undergoing pancreatic resection. They observed two phases of decline in BNP as postoperative time progressed; BNP values correlated strongly with fluid balance over the first three postoperative days. Patients with cardiac dysfunction were less likely to follow the anticipated pattern of BNP change. They concluded that serum BNP may be used to monitor and guide fluid management after pancreatectomy.

(26) "Differences in Methylation of Cell-Free Circulating DNA in Patients with Pancreatic Cancer and Chronic Pancreatitis" was presented by Levenson from Rush University in Chicago. Pancreatic cancer develops with significantly increased frequency in the setting of chronic pancreatitis; however, no accurate method of detection currently exists. These authors compared methylation of gene promoters in cell-free plasma DNA from healthy patients, patients with chronic pancreatitis, and patients with pancreatic cancer ($n=30$ in each group). Using a 56 gene position array (MethDet56), they found that 12 gene promoters were differentially methylated in chronic pancreatitis vs control, 4 were differentially methylated in pancreatic cancer vs control, and 14 were differentially methylated in chronic pancreatitis vs pancreatic cancer. This proof-of-principle study highlights the potential power of promoter methylation analysis in developing biomarkers. However, the authors appropriately concluded that MethDet56 was unlikely to be clinically applicable. They are currently pursuing a 1,256 gene platform.

The next paper (27) "The Burden of Infection for Elective Pancreatic Resections" was presented by Kent and colleagues from the Beth Israel Deaconess Medical Center in Boston. These authors analyzed 550 patients undergoing pancreatic resection at their center over an 8-year period, focusing on infectious complications. Thirty-one percent of their patients suffered some infectious complication, one third of which were serious infections as classified by Clavien (classes 3–5). Patients with infectious complications had a longer length of hospital

stay, required more blood transfusions, used more ICU resources, and were readmitted more frequently than patients without infection (34% vs 12%). Not surprisingly, cost analysis showed an increasing cost differential commensurate with severity of infection. The authors will use these comprehensive data in guiding process evaluation and infection control initiatives in their center.

The final paper of this session, (28) "Support for a Postresection Prognostic Score for Pancreatic Endocrine Tumors," was presented by Hurtuk from Loyola University of Chicago. This short talk described the authors experience with 34 patients undergoing resection for pancreatic neuroendocrine tumor at their institution between 1996 and 2004. They used data from their patients to calculate a prognostic score based on a previously described prognostic score (Bilimoira et al., Ann Surg 2008;247:480) which used patient age, presence of metastases, and grade of tumor. The patients treated at Loyola had similar outcomes as were predicted, validating the prognostic score with single institutional data. The authors concluded that the score is a useful tool to dictate follow-up surveillance and treatment.

Session V: Cancer—Basic Science

The first paper of this session (29) "Adipocytes in the Tumor Microenvironment Promote Dissemination of Human Pancreatic Cancer" was presented by White and colleagues from Indiana University. These authors evaluated 20 lymph node negative and 20 lymph node positive patients with resected pancreatic cancer; these patients were matched for clinical features including age, BMI, gender, medical comorbidity, tumor size, neural invasion, and resection status (R0 vs R1). Histologic analysis showed that tumors from node positive patients contained nearly twice as much adipocyte volume as tumors from node negative patients. The authors concluded that adipocytes in the tumor microenvironment may promote the dissemination and lethality of pancreatic cancer.

The next paper (30) "Low Dose Metronomic Gemcitabine Has High Antimetastatic Efficacy in an Orthotopic Mouse Model of Pancreatic Cancer" was presented by Cao and colleagues from University of California at San Diego. Their study was designed to test the efficacy of low-dose (1 mg/kg) gemcitabine administered daily compared to standard dose gemcitabine (150 mg/kg) administered twice weekly. Both regimens were administered with and without the tyrosine kinase inhibitor sunitinib. The authors found that in their murine model, the combination of metronomic gemcitabine and sunitinib was well tolerated, improved survival, suppressed ascites, and inhibited metastatic progression of pancreatic cancer. Their future directions will include combining metronomic low-dose gemcitabine with other antiangiogenic or antistromal agents.

(31) "Tumor Suppressor, ANP32A, Disrupts HUR's Regulation of Deoxycytidine Kinase in Pancreatic Cancer: Implications for Gemcitabine Therapy" was presented by Witkiewicz on behalf of her colleagues from Thomas Jefferson University. These investigators studied ANP32A, a novel tumor suppressor (an "anti-survival" mechanism) by overexpressing this protein in human pancreatic cancer cells in culture. They found that ANP3A overexpression caused growth inhibition when compared to control cells. Follow-up experiments showed nuclear to cytoplasmic transport of ANP32A upon exposure to stressors including gemcitabine. Cells overexpressing ANP32A were resistant to gemcitabine; when ANP32A was silenced by siRNA, increased sensitivity to gemcitabine was observed. In human specimens, low nuclear expression of ANP32A correlated with high-grade tumors and the presence of lymphatic metastasis. The authors concluded that ANP32A is at least partially responsible for gemcitabine resistance and that ANP32A may be a new target for chemotherapeutic agents.

The next paper, (32) "Introduction of Monocyte Chemoattractant Protein-1 by Nicotine in Pancreatic Ductal Adenocarcinoma Cells: Role of Osteopontin" was presented by Lazar et al. from Thomas Jefferson University. This paper presents an extension of the authors work on osteopontin (OPN), a protein that regulates inflammation and metastasis. The current study evaluated the role of nicotine, the chemokine MCP-1, and osteopontin on pancreatic cancer cells in vitro. The authors found that nicotine treatment upregulated expression of MCP-1 mRNA and protein secretion in pancreatic cancer cells and that blockade of OPN by antibody or siRNA abolished this upregulation. MCP-1 and OPN co-localized in pancreatic cancers stained immunohistochemically, and MCP-1 was found in over 60% of invasive human pancreatic cancers. The authors concluded that smoking may induce pancreatic cancer inflammation through an MCP-1-mediated mechanism. Their future work will focus on further elucidating these mechanisms.

Paper (33) "A Molecular Link Between Epithelial–Mesenchymal Transition and Cancer Stem Cell Properties in Pancreatic Cancer" was presented by Wellner from Freiburg Germany. These authors investigated the role of the transcriptional repressor ZEB-1 in epithelial–mesenchymal transition (EMT) in pancreatic cancer. A series of elegant experiments were presented, demonstrating that ZEB-1 mediates EMT in human pancreatic cancer and that this is accompanied by the acquisition of cancer stem cell properties. Further experiments elaborated the potential molecular mechanism: repression of stemness-inhibiting microRNA. The authors conclude that ZEB-1-mediated

EMT increases in vivo tumor dissemination and is associated with acquisition of cancer stem cell traits in vivo and in vitro. These data support the hypothesis of migrating cancer stem cells.

The next paper (34) "Adipocytes Promote Pancreatic Cancer Proliferation via a Hepatocyte Growth Factor-Mediated Mechanism" was presented by Ziegler and her colleagues from Indiana University. These studies were designed to follow up the authors' in vivo observations that obesity (increased adiposity) promotes pancreatic cancer growth in mice. These authors studied the effect of exposing murine pancreatic cancer cells to supernatant from murine adipocytes in vitro. They found that adipocyte conditioned media enhanced proliferation of pancreatic cancer cells and that this enhanced proliferation was caused in part by adipocyte-secreted hepatocyte growth factor (HGF). They concluded that adipocytes promote pancreatic cancer growth in part via an HGF-mediated mechanism.

Hernandez from the University of South Florida presented the next paper (35) "Deregulation of the RB/E2F Pathway and P16 Expression in Pancreatic Adenocarcinoma." This study was undertaken to evaluate the influence of the RB/E2F pathway in pancreatic cancer. The investigators found homozygous deletion of RB/E2F exons in seven of ten cell lines, suggesting deregulation of this pathway by loss of p16. They then performed immunohistochemical staining of 26 pancreatic cancer specimens, finding p16 absent in 25 of 26. Interestingly, p16 was absent in 10 of 12 associated PanIN lesions in the same specimens. Taken together, these data suggest that dysregulation of the RB/E2F pathway by p16 deletion is common in pancreatic adenocarcinoma. They plan further work to focus on downstream mediators of this signaling pathway.

The next paper was (36) "A Novel Murine Model for the Study of Metastatic Pancreatic Adenocarcinoma," presented by Olino and colleagues from the Johns Hopkins Hospital. These investigators described a novel, reproducible model of pancreatic cancer liver metastasis. The model was created by injecting pancreatic cancer cells into the spleen of immunocompetent mice, followed by hemisplenectomy. Liver metastases developed in nearly 100% of treated animals. A very intriguing application of the model was the ability to co-inject other cells, such as mesenchymal stem cells (which facilitated tumor formation). The authors postulate that their model will be useful in studying interactions between pancreatic cancer cells and components of the tumor microenvironment such as stromal cells or infiltrating lymphocytes.

The final paper of this session, (37) "Blood Pressure Lowering Medications Disrupt Fatty Acid Metabolism in Pancreatic Cancer," was presented by Sivarajah from Thomas Jefferson University. This study investigated the molecular basis of angiotensin II (AngII) in pancreatic cancer development, specifically the role of fatty acid synthase (FAS). A logical series of in vitro experiments using pancreatic cancer cell lines showed that AngII upregulated FAS mRNA and protein. This upregulation was attenuated by blockade of AngII receptors 1 and 2 and appears to be regulated by extracellular signal-regulated kinase and AKT kinases. The transcription factor sterol regulatory element-binding protein 1 is essential for FAS transcription, and this effect was blunted by treatment with losartin. In vivo experiments in nude mice showed that losartin treatment significantly decreased expression of FAS, as well as the size of pancreatic cancer xenografts. Furthermore, human pancreatic cancer tissue expressed FAS by mRNA and immunohistochemical analysis, and FAS levels correlated with tumor stage and invasion status. These data provide insight into a novel mechanism affecting pancreatic cancer development and suggest that AngII blockade may be a viable treatment option for patients with pancreatic cancer.

How I Do It Session: Adjuvant Therapy for Pancreatic Cancer—Is There a Role for Radiation Therapy?

The How I Do It session took the form of a debate, with Dr. John Neoptolemos of the University of Liverpool taking the "pro" stance and Dr. Doug Evans of the Medical College of Wisconsin taking the opposing stance. A spirited discussion ensued. Drs. Evans' and Neoptolemos' presentations are available in video format on the Pancreas Club website http://pancreasclub.com/video.htm.

Session VI: Pancreatitis

The first paper of the pancreatitis session (38) "Randomized Trial Comparing EUS and Surgery for Pancreatic Pseudocyst Drainage" was presented by Christein from the University of Alabama at Birmingham. In this study, 36 patients with pancreatic pseudocysts >6 cm in size were prospectively randomized to treatment by endoscopic ultrasound (EUS) directed or surgical cyst-gastrostomy. The primary endpoint was cyst recurrence by 18 months; secondary endpoints were pain, QoL, and length of hospital stay. Both groups achieved similar technical success (100% each) and treatment success (94% vs 100%—treatment success defined as symptom relief without need for repeat intervention). Not surprisingly, short-term length of stay and cost were higher in the surgical group. Short-term quality of life indices were lower in the surgical group; QoL was equivalent at 3 months time. The authors concluded that EUS guided cyst-gastrostomy may be the preferred approach in patients evaluated by a multidisci-

plinary team. They highlight the need for appropriate patient selection (only 1/3 of screened patients were included in this study).

The next paper (39) "Does Increasing Insurance Improve Outcome for US Pancreatic Cancer Patients?" was presented by Smith and colleagues from the University of Massachusetts. These investigators utilized data from the US Census Bureau and the National Cancer Institute state cancer profiles to evaluate the rates of pancreatic cancer mortality relative to insurance coverage. They discovered that in states with the highest rate of uninsurance, pancreatic cancer was most lethal. This surprising finding highlights the need for further investigation to examine whether this association holds true at the community level and to identify specific barriers to cancer care.

Theruvath et al. from the Medical University of South Carolina presented the next paper: (40) "Auto-islet Transplantation for Chronic Pancreatitis in Diabetic Patients: Why Bother?" These investigators reviewed their results performing pancreatectomy with auto-islet transplantation in 26 patients, focusing on the outcomes of six patients who required insulin to control diabetes preoperatively. The islet cell yield in these patients was 546 IEQ/kg (compared to 2,298 IEQ/kg in non-diabetic patients). At a mean follow-up of 8 months, five of six patients actually had decreased insulin requirements (mean of 21 to 15 U daily; one was insulin-free). These patients also experienced significant weight loss (71 to 65 kg), nutritional improvement (median albumin 2.4 to 3.4 g/dL), and nearly 50% decrease in opiate usage (morphine equivalents 145 to 76). All of these patients demonstrated hypoglycemic awareness. The authors speculate that the surprising finding of decreased insulin requirement may be due to weight loss, better dietary compliance due to programmatic intervention, or decreased adrenergic glucose release due to better pain control. They concluded that islet cell transplant in patients requiring preoperative insulin is safe (patients do demonstrate hypoglycemic awareness) and that evaluation of a larger experience will be necessary to better understand the true benefits of islet cell transplant in this population.

(41) "Abdominal Compartment Syndrome: An Early, Lethal Complication of Necrotizing Pancreatitis" was presented by Boone from the University of Pittsburgh. These authors reviewed 12 patients with necrotizing pancreatitis who were subjected to laparotomy for abdominal compartment syndrome (ACS—defined as intra-abdominal pressure greater than 20 mmHg with new organ dysfunction). Ninety-nine other patients at their institution underwent debridement over the 10-year time period of their study. The median APACHE score for patients developing ACS was 25, and the median time from onset of pancreatitis to laparotomy was 4.5 days. Abdominal decompression decreased abdominal (bladder) pressure, peak airway pressure, and APACHE scores and increased urine output and the PaO_2/FiO_2 ratio. Fifty percent of patients undergoing laparotomy for ACS died. The only identifiable difference between survivors and those who died was increased age (48 vs 65 years old). The authors concluded that ACS may be an early complication in patients with necrotizing pancreatitis and that decompressive laparotomy may provide physiologic benefit.

The final paper of this year's program was presented by Lyo from the University of California at San Francisco and entitled (42) "Live Animal Imaging of Protease Activity in Acute Pancreatitis." These authors sought to determine the feasibility of detecting protease activity using activity-based probes (ABP), novel, fluorophore bound small molecules that permit accurate detection of activated enzymes. A second goal was to characterize proteases in chronic pancreatitis patients. The pancreata from mice with cerulean-induced pancreatitis and pancreatic juice from chronic pancreatitis patients were imaged with a variety of advanced microscopy techniques, including traditional and fiberoptic confocal microscopy as well as two-photon fluorescence excited microscopy. Spectacular static and real-time in vivo images were presented demonstrating increased protease activity in the pancreas specimens of cerulean-treated mice compared to control animals. Two-photon microscopy allowed visualization of tissue architecture, with superimposed fluorescent cathepsin activity. The potential for in vivo imaging at subcellular levels is powerful. Use of these ABP with traditional confocal microscopy demonstrated cathepsin activity at the basolateral position of acinar cells and co-localized with macrophages. Finally, the authors were able to demonstrate serine protease and cathepsin activity in the pancreatic juice of chronic pancreatitis patients. These unique new molecules in combination with cutting edge imaging provide a powerful tool with which to better our understanding of the molecular pathogenesis of pancreatitis; in addition, the potential for translational study in humans undergoing endoscopic retrograde cholangiopancreatography is clear.

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2010 SSAT POSTER PRESENTATION

Choledochoduodenostomy: Is It Really So Bad?

William McIver Leppard · Thomas Michael Shary · David B. Adams · Katherine A. Morgan

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Abstract
Background Choledochoduodenostomy (CDD) has been shunned by some surgeons for the management of the benign distal common bile duct stricture due to the potential complication of "sump syndrome." The feared sump syndrome is theorized to occur from bile stasis and reflux of duodenal contents into the terminal common bile duct with bacterial overgrowth, resulting in cholangitis or hepatic abscess. The true incidence and resultant morbidity of sump syndrome, however, are not well defined.
Methods With the approval of the Institutional Review Board, a retrospective chart review of all patients undergoing choledochoduodenostomy for benign disease at a single institution between 1994 and 2008 was undertaken. Data were collected with particular attention to operative indications, perioperative course, and long-term results. Long-term outcomes were assessed through clinical reports at outpatient follow-up, emergency room visits, and hospital readmissions.
Results Seventy-nine patients underwent side-to-side CDD for benign diseases over the 15-year period [51 (65%) men; mean age, 52 years (standard deviation (SD), 12)]. Indications for surgery included chronic pancreatitis (80%), choledocholithiasis (11%), and cholangitis (4%). Patients presented with abdominal pain (80%), nausea/vomiting (30%), and jaundice 13%. Sixty-one patients (77%) underwent an additional procedure at the time of their CDD, including lateral pancreaticojejunostomy (26%). There was no perioperative mortality. Postoperative complications occurred in 15 (19%) patients, including intraabdominal abscess (26%), wound infection (20%), and biliary leakage (13%). The mean hospital stay was 9.7 days (SD, 6.9). The mean follow-up was 6.2 years (SD, 4.2). There was no occurrence of cholangitis. Two patients (2.5%) developed hepatic abscess, which was managed by antibiotics and image-guided percutaneous drainage.
Conclusions CDD is a safe and effective method of decompressing the distal common bile duct in benign pancreatobiliary disease. Long-term results are acceptable, with sump syndrome being a rare occurrence.

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Keywords Choledochoduodenostomy · Chronic pancreatitis

Introduction

In a room dimly lit by overhanging gas lanterns, with the fresh smell of sawdust lying around the operating table, the surgical amphitheater was crowded with enthusiastic students and colleagues as Bernhard Riedel began his operation. The patient was a middle-aged woman who had survived a cholecystectomy on July 23, 1888. The patient was still jaundiced in December of that year, and Riedel was concerned that a residual stone was retained in the bile duct. Reidel removed several stones and carried out a side-to-side anastomosis between the bile duct and duodenum. The enthusiasm surrounding this operation, the first

choledochoduodenostomy, was short lived. The patient died 9 h later. At the autopsy, an anastomotic leakage was found.[1]

Choledochoduodenostomy (CDD) has been described in the literature since the nineteenth century. CDD is undertaken for many indications, including failure of clearance of distal common bile duct stones during common duct exploration, multiple large or primary common bile duct stones, benign biliary stricture, and malignant neoplasms.[2,3] CDD has been shunned, however, by some surgeons for the management of benign distal common bile duct strictures due to the potential complication of "sump syndrome." The feared sump syndrome is theorized to occur from bile stasis and reflux of duodenal contents into the terminal common bile duct with bacterial overgrowth, resulting in cholangitis or hepatic abscess. Many favor a choledochojejunostomy, utilizing a Roux-en-Y limb, to avoid this pathophysiology. The true incidence and resultant morbidity of sump syndrome, however, are not well defined and has not been well examined in the modern era.

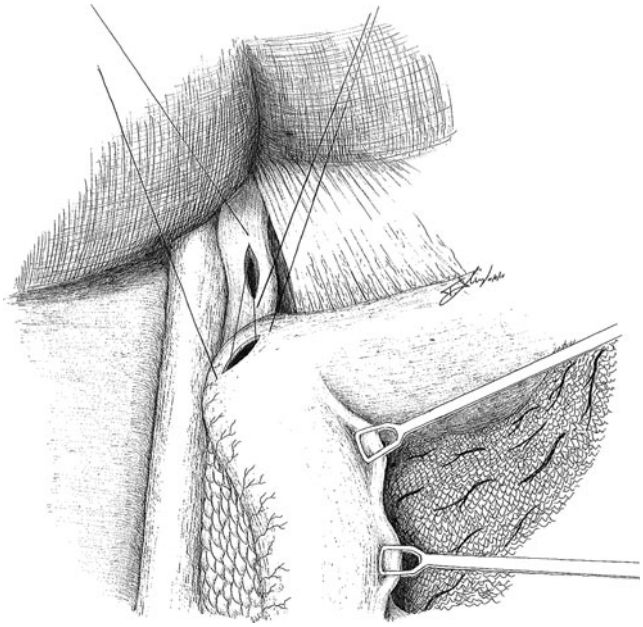

Fig. 1 A generous Kocher maneuver allows for maximal possible duodenal mobilization, where longitudinal incisions are performed with a side-to-side interrupted anastomosis. The anastomosis is a single layer with fine absorbable monofilament suture, at least 2 cm in length

Methods

With the approval of the Institutional Review Board, a retrospective chart review of all patients undergoing choledochoduodenostomy for benign disease at the Medical University of South Carolina between 1994 and 2008 was undertaken. Two surgeons performed all cases in the designated time period. The surgical technique employed was a side-to-side CDD with longitudinal incisions on the distal common bile duct and duodenum. A key portion of the surgery is maximal possible duodenal mobilization with a generous Kocher maneuver. Longitudinal incisions with a straightforward side-to-side interrupted anastomosis so the duodenum is least distorted. The anastomosis is a single layer with fine absorbable monofilament suture and approximately 2 cm (Fig. 1). Data were collected with particular attention to the operative indications and perioperative course, including symptoms, complications, hospital length of stay, and mortality. Long-term outcomes were assessed through clinical reports at outpatient follow-up, emergency room visits, and hospital readmissions.

Results

Seventy-nine patients underwent side-to-side CDD for benign diseases over the 15-year period [51 (65%) men; mean age, 52 years (standard deviation (SD), 12)]. Indications for surgery included chronic pancreatitis (80%), choledocholithiasis (11%), and cholangitis (4%; Table 1). Patients presented with abdominal pain (80%), nausea/vomiting (30%), and jaundice (13%; Table 2). Sixty-one patients (77%) underwent an additional procedure at the time of their CDD, most commonly lateral pancreaticojejunostomy (26%). There was no perioperative mortality. Postoperative complications occurred in 15 (19%) patients, including intraabdominal abscess (26%), wound infection (20%), and biliary leakage (13%) (Table 3). The mean hospital stay was 9.7 days (SD, 6.9). The mean follow-up was 6.2 years (SD, 4.2). There was no occurrence of cholangitis. Two patients (2.5%) developed hepatic abscess.

The first patient to develop a hepatic abscess underwent a CDD secondary to debilitating pain from chronic pancreatitis with distal biliary stricture and pancreatolithiasis. In addition to CDD, the patient underwent a lateral pancreaticojejunostomy, cholecystectomy, and feeding tube jejunostomy at the time of the CDD. The patient did not have any apparent postoperative complications. Just over 1 year after surgery, the patient presented to an outside hospital complaining of abdominal pain. A computed tomography scan (CT) revealed a right hepatic lobe abscess, which was successfully percutaneously drained in interventional radiology. Two weeks later, a follow-up CT showed a continued abscess. An endoscopic retrograde cholangiogram was performed, revealing a patent CDD. However, the anastomosis was small, and it was dilated to 10 mm, and a temporary biliary stent was placed. The patient did not have recurrence of his symptoms.

Table 1 Indications for surgery

Underlying disease	*N* (%)
Pancreatitis	63 (80%)
Choledocholithiasis	9 (11%)
Recurrent cholangitis	3 (4%)
CBD injury	2 (3%)
Mirizzi syndrome	1 (1%)
Sclerosing cholangitis	1 (1%)

N=79 in all groups

The other patient with hepatic abscess similarly underwent a CDD secondary to pain from chronic pancreatitis and distal biliary obstruction. The patient also underwent a lateral pancreaticojejunostomy procedure at the same time. The postoperative course was uneventful. Three months postoperatively, however, the patient developed new abdominal pain, and a CT showed a right hepatic lobe abscess. It resolved with percutaneous drainage, and no further intervention was undertaken.

Discussion

In 1928, Florcken reported 100 cases of CDD with excellent results. He stressed the importance of a large anastomosis to prevent cholangitis,[2] proposing the "more the barium [to pass up through the anastomosis] the better" in postoperative contrasted studies.[3] R.L. Sanders from Memphis, Tennessee presented his series of 25 patients who underwent CDD at the 57th Annual meeting of the Southern Surgical Association in 1945. He noted the effectiveness of CDD in relieving a distal obstruction in both benign and malignant disease.[4] Franklen and colleagues reported the successful performance of laparoscopic CDD in 1991 for a benign common bile duct obstruction.[5] But is CDD a surgery of historic interest only?

Table 2 Patient symptoms

Symptoms	*N* (%)
Abdominal pain	63 (80%)
Nausea/vomiting	24 (30%)
Jaundice	10 (13%)
Pruritus	4 (5%)
Fever	4 (5%)
Weight loss	4 (5%)
Diarrhea	2 (3%)
Bleeding	1 (1%)
Fatigue	1 (1%)

N=79 in all groups

Table 3 Postoperative complications

Complication	*N* (%)
Abscess	4 (26%)
Wound infection	3 (20%)
UTI	2 (13%)
Biliary leakage	2 (13%)
ECF	2 (13%)
Esophageal bleeding	1 (6%)
Seizure	1 (6%)
SB fistula	1 (6%)
Anastomotic bleeding	1 (6%)
Anastomotic leakage	1 (6%)
Anastomotic ulcer	1 (6%)
Splenic bleeding	1 (6%)
Gastroperesis	1 (6%)

N=15 patients

Postoperative morbidity after CDD is acceptable, reported as ranging from 9.8% to 28%,[2,6,7] consistent with the 17% in this study. The most commonly reported complications are wound infection and biliary leakage, similar to this series, with intraabdominal abscess (26%), wound infection (20%), and biliary leakage (13%).

The concern surrounding CDD lies in the long-term complication of sump syndrome. Sump syndrome is due to reflux of intestinal contents in the biliary tree. It is manifested clinically by infection associated with elevated liver enzymes and is most objectively defined as cholangitis or hepatic abscess. Inadequate stomal size and unfavorable anastomotic configuration resulting in poor biliary drainage are proposed factors lending to sump syndrome.[8] The prevalence of sump syndrome is reported between 0% and 9.6% in prior studies[9–11] and 2.5% in this modern study. Thus, it is a relatively rare occurrence.

Limiting the definition of sump syndrome to cholangitis and hepatic abscess may underreport the occurrence of enterobiliary reflux and any potential subclinical untoward biliary or hepatic pathology. Interestingly, to address these concerns, Mendes De Almeida and colleagues evaluated 35 patients after CDD with endoscopy and did not find inflammatory changes within the biliary tree in long-term follow-up.[6] Evidence for subclinical negative effects is therefore lacking.

The primary treatment of sump syndrome due to stomal stricture is endoscopic balloon cholangioplasty. Caroli-Bosc and colleagues described their experience with 30 patients with sump syndrome managed endoscopically. Presentation was a median of 5 years post surgery. At endoscopy, all patients had food debris (60%), biliary calculi (33%), or both (7%) in the biliary tree. All patients in this series underwent successful endoscopic management.[12] Sump

syndrome, then, is often amenable to minimally invasive, nonoperative interventions.

In an attempt to avoid the dreaded sump syndrome, many surgeons choose to undertake a Roux-en-Y choledochojejunostomy in the management of benign biliary disease. This surgery, however, is arguably more complex and time-consuming. It requires circumferential dissection of the common bile duct, which may be treacherous in the setting of chronic pancreatitis, the indication for surgery in 80% of patients in this study. It also requires an additional small bowel anastomosis, with potential for leakage or internal hernia. Finally, it has potential for Roux limb-associated motility abnormalities, which can also lend to enterobiliary reflux. Postoperative morbidity after choledochojejunostomy for benign disease ranges from 20% to 33% and overall mortality from 0% to 2%.[13–15] Thus, evidence does not suggest that choledochojejunostomy is less morbid than CDD.

Conclusions

CDD is a safe and effective method of decompressing the distal common bile duct in benign pancreatobiliary disease. Long-term results are acceptable, with sump syndrome being a rare occurrence. CDD should remain a valuable option in the armamentarium of the modern biliary surgeon.

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2010 SSAT POSTER PRESENTATION

Micro-laparoscopic Cholecystectomy: An Alternative to Single-Port Surgery

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Abstract
Introduction Recent advances in minimally invasive surgery aimed at diminishing incision size have led to the development of single-port surgery (SPS). SPS has an increased level of complexity and requires a higher level of surgical skill compared to traditional laparoscopy. We explored micro-laparoscopy as an alternative to routine laparoscopic cholecystectomy.
Methods The study is a retrospective review of consecutive elective laparoscopic cholecystectomies performed by a single surgeon at a community teaching hospital over 24 months. All surgeries were performed using a 5-mm trocar for the umbilical port and 3-mm trocars for other ports in standard configuration.
Results Seventy-nine cholecystectomies were performed by micro-laparoscopy during the 24-month period. Three cases required upgrade in trocar size for technical reasons, resulting in a completion rate of 96%. Intraoperative cholangiography was performed in 70 cases (89%). There were no conversions to open surgery. There were no intra- or postoperative complications, and all patients were discharged on the day of surgery.
Conclusion Micro-laparoscopic cholecystectomy is safe, feasible, and represents an alternative to other minimally invasive techniques. Future developments in surgical technology will allow the use of even smaller instruments, diminishing the surgical "footprint" even further and contributing to better cosmesis and decreased postoperative pain in cholecystectomy patients.

Keywords Micro-laparoscopic · Cholecystectomy · Single port

Introduction

Conventional four-port laparoscopic cholecystectomy (LC) utilizing one 10-mm umbilical port and three 5-mm ports is currently the gold standard for the treatment of symptomatic gallstone disease. However, micro-laparoscopic cholecystectomy (MC) and single-port surgery (SPS) were developed in an attempt to further decrease postoperative pain and improve cosmesis. MC employs smaller instruments in contrast to LC and has been associated with potentially decreased postoperative pain and improved cosmetic outcome, pulmonary function, and overall patient satisfaction in elective cases of cholecystectomy.[1–5] SPS confers the same cosmetic advantage as MC, but is associated with the need to learn a new surgical technique and use of modified instruments.[6] We therefore conducted a retrospective study to examine the feasibility and safety of MC in our hospital.

Materials and Methods

A retrospective chart review was conducted of consecutive elective cases of micro-laparoscopic cholecystectomies performed by a single surgeon (KAZ) over a 24-month period. Variables included patient age, gender, body mass

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index, indication for surgery, upgrade requirement, and complications.

Surgical Technique

One 5-mm port was inserted above the umbilicus, and three 3-mm ports (Ethicon Endosurgery, Cincinnati, OH) were inserted in the subxiphoid, right anterior and midclavicular axillary lines subcostally, according to standard configuration (Fig. 1). A 5-mm, 30° laparoscope (Karl Storz Endoscopy City) was then introduced into the umbilical port for adequate visualization of the gallbladder. Sufficient retraction and dissection of the cystic duct and artery were performed using 3-mm graspers and dissectors (Karl Storz Endoscopy City), creating a critical view of safety (Fig. 2). Intraoperative cholangiography (IOC) was performed when technically feasible. A negative IOC was defined as fluoroscopic imaging of the common bile duct, cystic duct, common, right and left hepatic ducts without filling defect. Upon completion of cholangiography, surgical clips were placed with an ethicon endosurgery ligamax (Ethicon Endosurgery, Cincinnati, OH) introduced through the 5-mm umbilical port while placing a 3-mm camera into the subxiphoid port. Monopolar electrocautery (Megadyne, Draper, UT, USA) was then used to remove the gallbladder from the liver bed and obtain adequate hemostasis. After removal from the liver bed, the gallbladder was placed in an Endocatch bag (Ethicon Endosurgery, Cincinnati, OH) and retrieved through the 5-mm incision under direct visualization of the 3-mm laparoscope (Karl Storz Endoscopy City). Gallbladder retrieval in many cases was facilitated by crushing and suctioning stone fragments within the specimen while extracting the Endocatch bag (Ethicon Endosurgery, Cincinnati, OH) through the 5-mm incision. In three (4%) cases of upgrade, the umbilical incision and fascial plane were minimally extended to facilitate removal of the gallbladder.

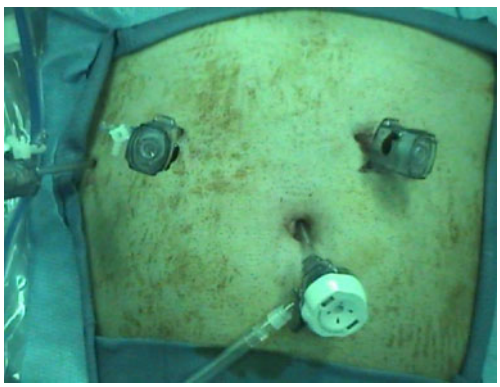

Fig. 1 The surgical technique involves insertion of one 5-mm port above the umbilicus and insertion of 3-mm ports in the subxiphoid, right anterior axillary and midclavicular line subcostally

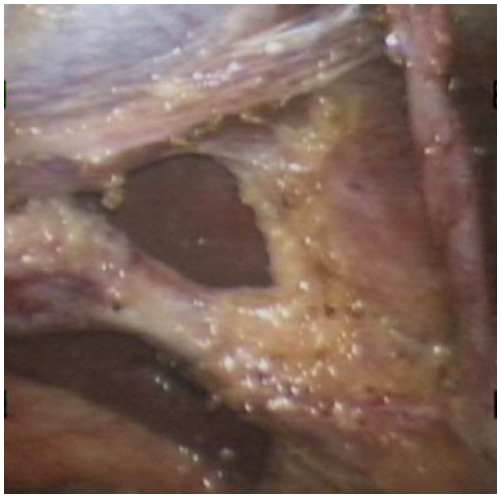

Fig. 2 Sufficient retraction and dissection of the cystic duct and artery were performed using 3-mm graspers and dissectors, creating a critical view of safety

Results

Elective micro-laparoscopic cholecystectomy was performed in 79 patients between October 2007 and November 2009. Demographics and indication for surgery are outlined in Tables 1 and 2, respectively. Fifty-four (68%) were female and 25 (32%) were male. The average age was 48 years old (range, 20–84). Average BMI was 29.7 (range, 19.2–46.4). Indications for cholecystectomy included biliary colic (89%), biliary dyskinesia (9%), and gallstone pancreatitis (3%). Seventy (89%) patients had routine IOC performed, which were all negative for choledocholithiasis. Three patients required upgrade to traditional 5-mm ports as a result of chronic gallbladder inflammation and wall thickening after repeated attempts to successfully grasp and retract the gallbladder using 3-mm instruments. In all three cases of upgrade, the indication for surgery was symptomatic cholelithiasis. Body mass indices for cases of upgrade were 28.1, 29.1, and 34.6, respectively. Upsizing the trocars was dictated by unanticipated pathology, including hydrops requiring decompression, an impacted stone in the infundibulum, and dense omental adhesions requiring extensive laparoscopic lysis. No patient required

Table 1 Patient demographics

Variable	(n=79)
Male	25 (32%)
Female	54 (68%)
Age	
Average (range)	48 (20–84)
Body mass index	
Average (range)	29.7 (19.2–46.4)

Table 2 Indications for surgery

Indication	(n=79)	%
Biliary colic	70	89
Biliary dyskinesia	7	9
Gallstone pancreatitis	2	3

conversion to an open procedure, and there were no intraoperative complications. In all cases of MC, patients were discharged the same operative day, and there were no cases of postoperative complication due to surgical technique within the established 2-week follow-up interval.

Discussion

Micro-laparoscopic cholecystectomy (MC) is a safe and technically feasible procedure for the treatment of gallstone disease and an alternative to single-port surgery (SPS). The procedure uses smaller adept instrumentation and represents a technological advancement of laparoscopic surgery and an improvement on the traditional laparoscopic method. Leggett and colleagues[7] successfully performed MC with only three laparoscopic ports and Unger et al[8] reported success of MC with port sizes as small as 2-mm. In a meta-analysis of MC versus LC, micro-laparoscopic cholecystectomy without IOC was successfully performed in a number of studies using a combination of three 3-mm ports with either 10-mm or 12-mm ports in study populations with variable exclusion criteria.[3] We successfully performed MC with routine IOC using one 5-mm and three 3-mm ports in 89% of consecutive elective cases of cholecystectomy, eliminating the likelihood of selection bias and demonstrating that IOC can be sufficiently performed as an adjuvant to the MC technique when deemed appropriate based on surgeon judgment or preference.

Furthermore, today's technology allows us to perform MC with unparalleled feasibility due to the advent of high-definition imaging, which permits the use of 3-mm laparoscopes and better 3-mm instrumentation in the majority of surgical candidates. In our study, a critical view of safety was achieved and maintained in 100% of cases, demonstrating that MC affords the surgeon the same superior quality of visualization as LC without compromising patient safety. MC in this form rivals SPS and must be considered as a simpler if not safer alternative.

Three cases in our study required upgrade to 5-mm port size for improved gallbladder retraction due to advanced gallbladder pathology, creating an upsizing rate of 4%. The complication rate in our study was negligible and comparable to other low rates reported in the literature.[1, 3–5, 7, 8] Body mass indices in our study ranged from 19.2 to 46.4 and was not a determinant factor in the feasibility of MC completion; however, other studies have found that MC operative times are progressively longer in patients with higher body weights.[8] Additionally, peritoneal adhesions, chronic inflammation, and gallbladder wall thickening have all been cited as obstacles to MC completion in various studies.[3] Despite these challenges, the results of our present study show that MC can be routinely performed in an elective setting with a low rate of upgrade to conventional laparoscopic port size.

In this study, subjective outcomes of postoperative pain and cosmesis regarding 5-mm versus 3-mm incision sites were not assessed. From a financial perspective, there was no cost difference associated with the use of 3-mm ports and other MC instruments compared to conventional instrumentation based on our accounting and cost allocation records. The MC technique in this study and the search for adequate instrumentation were developed and conducted over the course of several months. A learning curve was not conducted as a part of this case series. However, the MC technique follows the same principles as a LC, allowing the surgeon to gradually perform the same operative technique as a traditional laparoscopic cholecystectomy with the possibility of upsizing or adding additional trocars in technically difficult cases, where the continuation of MC would have a deleterious impact on the patient. The SPS technique, in contrary, is associated with loss of triangulation and decreased maneuverability, making the procedure technically demanding.[9] And while some may argue that SPS is a sensationally innovative procedure, it does not necessarily offer surgeons or patients a distinctive advantage over the gold standard in regard to cost, optimal pain control, and surgical feasibility.[9] Ultimately, MC remains a low-risk procedure with a negligible complication rate. The technique is feasible, efficacious, and associated with improved cosmesis and decreased postoperative pain, therefore making it advantageous to both surgeons and patients alike and a practicable alternative to SPS.

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2010 SSAT PLENARY PRESENTATION

The Duration of Symptoms Predicts the Presence of Malignancy in 210 Resected Cases of Pancreatic Intraductal Papillary Mucinous Neoplasms

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Abstract
Introduction Using Kaplan–Meier curves, a 2006 study illustrated a shorter time interval between development of symptoms and detection of malignant IPMN in the main pancreatic duct versus a side-branch duct location. Of 93 cases, only 62 were confirmed histologically. To support these interesting findings, we examined a larger cohort of cases where the diagnosis was confirmed histologically and asked if symptoms by themselves, as well as main duct location, were associated with malignant detection.
Methods Between 1989 and 2009, 210 IPMN cases meeting international criteria were resected and histologically examined. Actuarial rates of malignant detection over time were calculated from the first clinical symptom to malignant detection (resection). These rates of malignant detection over time were compared for main vs. side-branch duct location and symptomatic vs. asymptomatic cases.
Results The most common indications for resection were symptoms (88%) and main pancreatic duct location (65%). The actuarial malignant detection rates were significantly shorter for main duct location and also for symptomatic cases, regardless of duct location.
Conclusions Presence of symptoms followed by main pancreatic duct location had a significantly shorter elapsed time to malignant detection. The visual depiction of these actuarial rates highlights the importance of the clinical history. To determine malignant risk, the primary determinants for resection were either symptoms or main duct location (but not cyst size), confirming the 2006 study with a larger cohort of histologically confirmed cases.

Keywords Pancreas · Neoplasm · Surgery · Intraductal pancreatic neoplasm · Natural history

Introduction

A pancreatic intraductal papillary mucinous neoplasm (IPMN) has malignant potential as the disease process follows the adenoma–carcinoma sequence. IPMN lesions are commonly seen in clinical practice today as radiologists look for them and pathologists can classify them. As clinicians, we appreciate any description in estimating their time course toward malignancy (natural history) to assist us in making clinical decisions. These decisions are mainly in the following two scenarios—in consideration for when to resect and, in those that have been resected, how often to image the pancreatic remnant for development of new lesions. Recall that the primary goal of resection is to avoid malignancy. Can the time course to malignancy through observation of the natural history help us to decide when to resect?

Most articles on the subject indicate that the natural history is "unknown." However, as the literature expands, we have moved from the "unknown" stage to possessing a modest amount of knowledge about the natural history of

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IPMN. According to Shyr and colleagues, in 1996 there were only 104 cases of IPMN in the literature.[1] We recently reviewed the literature between 1993 and 2006 by analyzing 28 case series containing 2,547 resected cases and 7 additional case reports of 493 unresected cases.[2] The information gleaned from these studies suggests that side-branch duct (SBD) lesions will slowly enlarge in 10–15% of cases if followed for >3 years. Only a few of these SBD lesions were found to be malignant. In contrast, the majority of main pancreatic duct (MPD) lesions developed malignancy within 2 years. According to international guidelines,[3] MPD lesions should be resected in a timely fashion if the patient is a surgical candidate, but the guidelines for SBD lesions are not as dogmatic and rely on the presence of cyst size and symptoms. How important are symptoms?

Since most resected cases are symptomatic, an interesting method to estimate the natural history of IPMN was proposed by Levy and co-workers.[4] They measured the time interval between onset of symptoms that unmasked the presence of IPMN and when the amount of dysplasia was first detected (resection). The resection specimen provided an accurate assessment for the histological presence of malignancy and also the duct location for the disease (MPD versus SBD). They calculated the elapsed time between *clinical detection* (symptoms) and *pathological detection* of malignancy, if it occurred, after resection for MPD and SBD lesions. Note that "malignancy" meant either carcinoma-in-situ or invasive carcinoma. The Levy study's "occurrence rates" of malignancy visually compared, for the first time, the natural history of IPMN using Kaplan–Meier curves for MPD versus SBD lesions, i.e., the percent with malignancy over the elapsed time since the beginning of symptoms. They found that the elapsed time was slower and the percent with malignancy was statistically lower for SBD versus MPD disease ($p<0.001$). They estimated the detection of malignancy for SBD disease to be 9% at 2 years and 15% at 5 years after onset of symptoms. For MPD disease, the rate was estimated to be 58% at 2 years and 63% at 5 years after onset of symptoms.

This pictorial information is useful to understand IPMN and then make decisions; however, there are a number of caveats with the Levy study. First, the onset of symptoms is difficult to accurately measure if the presence of symptoms and the date of their onset was determined retrospectively. Second, 62/106 (58%) of their cases were histologically confirmed while the rest of the cases were "suspected." For the "suspected" cases, the histology was never known—this includes the true grading of dysplasia and the histologic confirmation of duct location (MPD vs. SBD). We designed the current trial to overcome these caveats.

The finding of increased frequency of malignancy with MPD lesions has been reported, but the estimated time course is new. An example is the study by Terris et al..[5] They found that the MPD location is more likely to be associated with malignancy than SBD lesions (57% versus 15%). The Kaplan–Meier curves by Levy and colleagues have provided a visual estimation of the risk for malignancy in a shorter period if the IPMN was in the MPD location. To affirm the Levy results of 62 histologically confirmed cases while compensating for the above caveats, we investigated 210 resected cases where the severity of dysplasia and duct location was histologically confirmed and not assumed. In addition, we assessed the date of onset of symptoms in a prospective manner—a variable that was measured and recorded preoperatively in every patient as part of a life-long assessment in each patient with IPMN. Finally, we looked at the importance of symptoms—whether detection by symptoms was associated with more or less chance of malignancy than incidental imaging (no symptoms). If the tumor was growing rapidly, then it might be expected to cause symptoms and qualify for resection earlier, thus shortening the interval. Caution should be observed when comparing symptomatic patients to those that have no symptoms, but the presence of symptoms represents a clinical reality that clinicians can observe and measure.

Patients and Methods

Patients and Pathological Classification

Between 1989 and 2009, 210 patients underwent pancreatic resection for IPMN by a single surgeon at Virginia Mason Medical Center, Seattle. Data were entered into a prospective IRB-approved database. All cases were reviewed independently by one of us (TM) and the database updated. All cases were histologically confirmed by one of ten staff pathologists that used collaborative opinions of their team. The details of histology were obtained by a review of the pathology reports. An IPMN was distinguished from a mucinous cystic neoplasm (MCN) by the former having connection to the pancreatic ductal system (based mainly on endoscopic retrograde cholangiopancreatography) and a lack of ovarian type stroma.[6] IPMN lesions were also distinguished from pancreatic intraepithelial neoplasia (PanIN) by the IPMN lesion being greater than 1 cm in size either grossly or radiographically.[7] We used the four categories of WHO classification for IPMN: adenoma, borderline, carcinoma-in-situ (CIS), and invasive carcinoma.[8,9] Adenoma and borderline lesions were considered as "benign" and CIS and invasive lesions were "malignant." The pathological diagnosis was based on the most severe epithelial dysplasia within the tumor as determined by the staff pathologist.

Definition of MPD and SBD Group

Using histopathologic examination of the surgical specimen, three ductal locations were described—MPD type, MPD+SBD type (mixed-type), and SBD type. The first two groups with the MPD involved were those that had histological proof of IPMN in the MPD.

Definition of Elapsed Time from Clinical Detection to Histologic Detection of Malignancy

Each patient had been interviewed and examined by the senior author and the presence of symptoms and the date of onset recorded in the medical record. The time when an IPMN was first detected clinically was either the time of first symptoms due to IPMN, or if asymptomatic, the first time the lesion was imaged. Symptoms attributable to IPMN were defined as pancreatitis-like symptoms (as determined at interview by the senior surgeon as recurrent upper abdominal pain, nausea, with or without mid-back pain), steatorrhea, jaundice, or weight loss (estimated to be >10% body weight). If a malignancy was detected in the IPMN lesion, then the time of malignancy was based on the first time it was diagnosed histologically (time of resection). The elapsed time from clinical detection (symptoms or imaging) to pathological detection of malignancy at the time of resection was then calculated in months.

Indication of Surgical Resection

There were three indications for resection based on international guidelines [3]—a symptomatic lesion, regardless of location in the ductal system; the IPMN was thought to involve the MPD even if asymptomatic; and those SBD lesions with "malignant risk" where an asymptomatic SBD type lesion was associated with at least one predictive criterion of malignancy. The latter indication included a SBD cyst >30 mm, any mural nodule in a SBD cyst by imaging, or if cytology suggested malignancy. An additional indication in the asymptomatic group was a strong family history of pancreatic cancer (two first kindred relatives) in the presence of any size IPMN.

Statistical Methods

Continuous data are presented as mean±standard deviation. The Mann–Whitney U test was used for all comparisons among continuous variables. Categorical variables were compared by using χ^2 test or Fisher's Exact test. The actuarial rate of malignant detection at the time of resection, if detected, was assessed using the Kaplan–Meier method. Then malignant detection was compared for presence or absence of symptoms and ductal location (MPD versus SBD) using the log–rank test. Another analysis was completed by excluding CIS and looking at the detection of just "invasive" IPMN. A $p<0.05$ was considered statistically significant.

Results

Preoperative Indications for Resection

Preoperative indications for resection included symptoms (88%) and/or what was felt to be MPD involvement preoperatively (65%). Surprisingly, in just 5% of the cases did the indication for resection depend other "malignant" risk criteria by international guidelines (Table 1).

Characteristics of 210 Patients

The tumors were located in the head (70%), body-tail (23%), or involved the entire pancreas, necessitating total pancreatectomy (7%). Patient characteristics of MPD, MPD+SBD, and SBD type are listed in Table 2. Significant differences were recognized in serum CA19-9 values of the MPD versus the SBD groups and the MPD+SBD versus SBD groups. Note the mean size of the SBD cyst was not different between MPD+SBD (29.6±15.8 mm) versus the SBD (23.2 ±12.4 mm, N.S.). The mean size of the cysts in SBD group was <3 cm because a large proportion of patients were symptomatic, and the indication for resection was not size but symptoms. Also, some of the asymptomatic SBD lesions <3 cm were resected for the other reasons listed in Table 1.

Table 1 Indication for resection in 210 cases with IPMN-like lesions by imaging

Preoperative indications included	*N*
Symptoms[a]	185 (88%)
MPD involvement	136 (65%)
Malignant risk by guidelines	11 (5%)
Cyst ≥30 mm only	6
Elevation of CA19-9	2
Familial history of pancreatic cancer[b]	2
Suspicious malignancy by cytology	1
Other	5 (2%)
Other disease of pancreas[c]	2
Before founding guidelines[d]	2
Different pre-diagnosis[e]	1

[a] Pancreatitis-like, steatorrhea, jaundice, or >10% weight loss

[b] Two first kindred relatives

[c] Neuroendocrine tumor and a duodenal gastrointestinal stromal tumor

[d] Side branch cyst <3 cm

[e] Mucinous cyst neoplasm that was an IPMN

Table 2 Comparison among MPD, MPD+SBD, and SBD type in clinic-pathologic findings

	Entire cohort (*N*=210)	MPD±SBD group (*N*=135)		SBD-only group (*N*=75)	*p*		
		MPD (*N*=44)	MPD+SBD (*N*=91)	SBD (*N*=75)	MPD vs. SBD	MPD vs. MPD+SBD	MPD+SBD vs. SBD
Demographics							
Mean age (year±SD)							
At first detection	65±11	66±10	65±10	63±12	NS	NS	NS
At diagnosis	66±11	67±11	67±11	64±12	NS	NS	NS
Gender (% male)	45%	43%	47%	41%	NS	NS	NS
History							
Acute pancreatitis[a]	31%	36%	33%	23%	NS	NS	NS
Diabetes	21%	24%	25%	16%	NS	NS	NS
Tumor marker							
Serum CA19-9	43±99	54±110	60±128	19±20	<0.05	NS	<0.05
Tumor location							
Head	70%	70%	68%	72%	NS	NS	NS
Body-tail	23%	16%	22%	28%	NS	NS	NS
Diffuse whole	7%	14%	10%	0%	<0.05	NS	<0.05
Radiography findings							
Mean size of dilated SBD (mm)	–	–	30±16	23±12	–	–	NS
SBD mural nodules[b]	–	–	11%	7%	–	–	NS
Histopathology							
Adenoma	36%	9%	31%	60%	<0.01	<0.05	<0.05
Borderline	25%	25%	26%	23%	NS	NS	NS
CIS	16%	20%	20%	8%	<0.05	NS	<0.05
Invasive	23%	45%	23%	9%	<0.01	<0.05	<0.05

[a] Documented by elevated serum amylase

[b] By imaging

Overall, the histopathology showed the following types of IPMN: adenoma (36%), borderline (25%), CIS (16%), or invasive (23%).The percent of invasive IPMN was significantly increased ($p<0.05$) if the MPD was involved, i.e., 45% (20/44) of the MPD-only group had invasive IPMN, 23% (21/91) of the MPD+SBD type, and 9% (7/75) of the SBD type.

Duration Between the Date of First Detection and the Date of Diagnosis

Table 3 outlines the incidence and type of symptoms in regards to IPMN ductal location. Most cases were not incidental discoveries by imaging alone but were symptomatic before imaging (88%, 185/210). Symptoms were noted in 77% of the SBD group which was a significantly lower symptom rate than the other two groups with MPD involvement (98% symptomatic in the MPD group and 92% in the MPD+SBD groups, both $p<0.001$ versus the SBD group). There was no difference in the rate of the specific symptoms listed in Table 3 between the ductal locations of IPMN.

Table 4 lists the elapsed time in the 25 cases with no symptoms between first imaging and resection. They required 16 to 17 months before a decision to resect was made, regardless of duct location. The decision to resect was made on international criteria for malignant risk in 11/25 cases (cyst size, mural nodules, etc.), and the other 14 decisions were based on MPD location. In the symptomatic group, the decision to resect was made statistically faster (16 months) if the MPD was involved versus if just the SBD was involved (25 months). Furthermore, the months with pancreatitis-like symptoms to resection in MPD group was significantly shorter (18 months) than SBD group (27 months).

Clinicopathologic Comparison: Symptomatic and Asymptomatic Patients

Table 5 lists a comparison within the SBD-only group for clinicopathologic findings—58 symptomatic versus 17

Table 3 Incidence of symptoms: comparison between main or side branch IPMN location

	Incidence (%)			*p*
	MPD (*N*=44)	MPD+SBD (*N*=91)	SBD (*N*=75)	
No symptoms (*N*=25)	2	8	23	<0.001[a]
Symptoms (*N*=185)	98	92	77	
Detail of first symptom				
Pancreatitis-like symptoms[b] (*N*=151)	71	76	68	NS
Steatorrhea (*N*=12)	7	7	4	NS
Jaundice (*N*=14)	11	7	4	NS
Weight loss[c] (*N*=7)	9	2	1	NS

MPD main pancreatic duct, *SBD* side branch duct

[a] Differences were recognized in MPD vs. SBD and MPD+SBD vs. SBD

[b] Pancreatitis-like symptoms were defined as upper abdominal pain, nausea, ±mid-back pain

[c] Weight loss=10% body weight

asymptomatic patients. There were no differences in demographics, CA19-9, and radiographic findings; however, cases with adenoma tended towards being asymptomatic (77%) versus symptomatic (55%). A comparison could not be made for the MPD group, as only 6% (8/135) of cases were asymptomatic, and only one of these had adenoma. Actuarial rate of malignant detection is between the first clinical detection of IPMN (symptoms or imaging) and pathological diagnosis of malignancy.

Symptoms Versus No Symptoms The Kaplan–Meier curves for "malignant" detection (CIS cases+invasive cases) over time from onset of symptoms (symptomatic IPMN, n=185) or detection by imaging (Asymptomatic IPMN, n=25) are shown in Fig. 1. There was a significant difference in the risk of malignancy for the symptomatic IPMN group versus asymptomatic group (p<0.02). In Fig. 2, the actuarial curves pictorially compare four subsets of cases: symptomatic MPD (*N*=127), asymptomatic MPD group (*N*=8), symptomatic SBD group (*N*=58), and asymptomatic SBD group (*N*=17). There was a significant difference for malignant detection rates over time between the SBD group—symptomatic SBD versus asymptomatic SBD (p<0.05), indicating that symptomatic SBD cases were at higher risk for malignant pathology since first detection of symptoms versus first detecting by imaging for the asymptomatic lesions.

We then excluded the CIS cases from the analysis in Fig. 3 and analyzed just the "invasive" IPMN cases by duct location, with or without symptoms. No significant differences of malignant risk rates over time were observed.

Ductal Location after Excluding Asymptomatic Cases

After excluding the asymptomatic cases (n=25), the actuarial rate of malignancy was higher for the MPD location to harbor a "malignant" diagnosis at 1, 2, and 5 years after the onset of symptoms (Fig. 4). A significant difference for malignant detection over time was observed for the MPD vs. MPD+SBD location (p<0.03), the MPD+SBD vs. SBD location (p<0.02), and for the MPD vs. SBD location (p<0.001), indicating that any MPD involvement in a symptomatic patient had a higher risk for malignancy in a shorter interval from onset of symptoms (CIS and/or invasive IPMN).

Then CIS cases were excluded and just "invasive" detection rates were compared by duct location (Fig. 5). The actuarial rate of "invasive" detection was higher for MPD lesions at 1, 2, and 5 years after the IPMN was first

Table 4 Duration of first clinical detection until pathological detection: comparison between main or side branch IPMN

	Months from 1st detection to resection			*p*
	MPD (*N*=44)	MPD+SBD (*N*=91)	SBD (*N*=75)	
No symptoms (*N*=25)[a]	1	17±46	16±15	NS
First symptom (*N*=185)	16±26	21±34	25±41	<0.05[b]
Detail of first symptom				
Pancreatitis-like symptoms (*N*=151)	18±27	22±39	27±43	<0.05[b]
Steatorrhea (*N*=12)	5±8	5±7	14±18	NS
Jaundice (*N*=14)	2±2	2±2	2±1	NS

[a] If no symptoms (n=25) then duration was based from time when first imaged

[b] Differences were recognized in MPD-only vs. SBD

Table 5 Comparison between symptomatic and asymptomatic groups in the rate of clinico-pathologic findings

	SBD group (N=75)		p
	Symptomatic (N=58)	Asymptomatic (N=17)	
Demographics			
Mean age (years)			
At first detection	61±12	68±8	NS
At diagnosis	63±12	70±8	NS
Gender (% male)	40%	47%	NS
Tumor marker			
Serum CA19-9	20±21	17±16	NS
Radiographic findings			
Size of cyst (mm)	23±13	22±8	NS
SBD mural nodules	9%	0%	NS
Histopathology			
Adenoma	55%	77%	<0.05
Borderline	22%	23%	NS
CIS	10%	0%	NS
Invasive	12%	0%	NS

SBD side branch duct

clinically detected by symptoms. A significant difference for invasive malignant detection over time was observed for the MPD vs. MPD+SBD location (p<0.05) and for the MPD vs. SBD location (p<0.001) indicating that any MPD involvement was at higher risk for malignancy in a shorter interval from onset of symptoms to have "invasive" cancer.

Discussion

In order to visualize the time course of malignant risk, a study must have the degree of dysplasia and the duct location documented histologically. Because we had the surgical specimen, all 210 resected cases had histologic assessment of dysplasia grading and duct location (MPD vs. SBD), exceeding the 62 histologically proven cases in the Levy study.[4] This means that the end point of malignant detection in our study, if it occurred, and its location in the ductal system was accurate. There was no speculation about

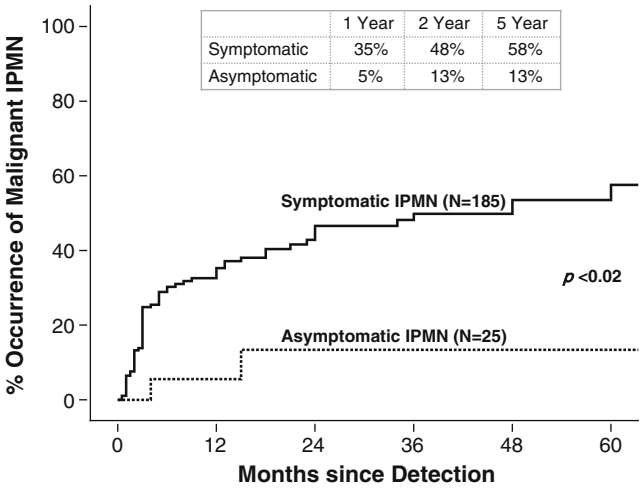

Fig. 1 The time course for degeneration into "malignant" IPMN for all cases, regardless of duct location, was compared for symptomatic versus asymptomatic cases of IPMN. The actuarial risk at 1, 2, and 5 years was 35%, 48%, and 58% (symptomatic group) and 5%, 13%, and 13% (asymptomatic group) provided a significant difference (p<0.02)

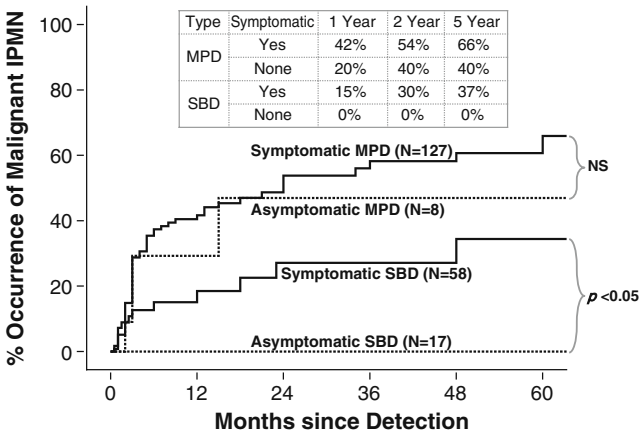

Fig. 2 The comparison of the time course for "malignant" (CIS or invasive IPMN) degeneration since the first detection (the first symptoms or the first imaging IPMN) among the patients with symptomatic MPD group (N=127) symptomatic MPD group (N=8) and symptomatic SBD group (N=58), and asymptomatic SBD group (N=17). The curves were calculated using Kaplan–Meier method from the first detection. The actuarial risk at 1, 2, and 5 years was 42%, 54%, and 66% (symptomatic MPD group), 20%, 40%, and 40% (asymptomatic MPD group), 15%, 30%, and 37% (symptomatic SBD group), and 0% (asymptomatic SBD group). There was a significant difference between the SBD curve—symptomatic SBD versus asymptomatic SBD group (p<0.05)

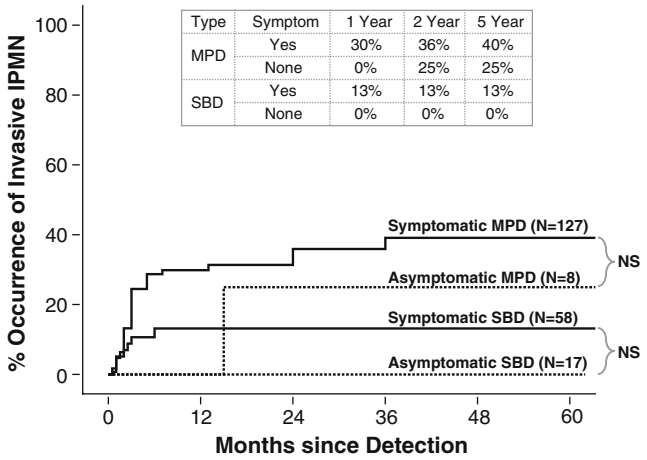

Fig. 3 The comparison of the time course for degeneration to "invasive" IPMN since the first detection (the first symptoms or the first imaging IPMN) among the patients with symptomatic MPD group (N=127), symptomatic MPD group (N=8), and symptomatic SBD group (N=58), and asymptomatic SBD group (N=17). The curves were calculated using Kaplan–Meier method from the first detection. The actuarial risk at 1, 2, and 5 years was 30%, 36%, and 40% (symptomatic MPD group), 0%, 25%, and 25% (asymptomatic MPD group), 13%, 13%, and 13% (symptomatic SBD group), and 0% (asymptomatic SBD group)

the presence of malignancy or whether it was in a MPD, mixed, or SBD-only duct location.

Another potential weakness in the Levy study was determining when the symptoms began. Each of our patients was seen by the same senior surgeon when they were questioned about the presence and the duration of symptoms. Otherwise, the onset of symptoms by reviewing

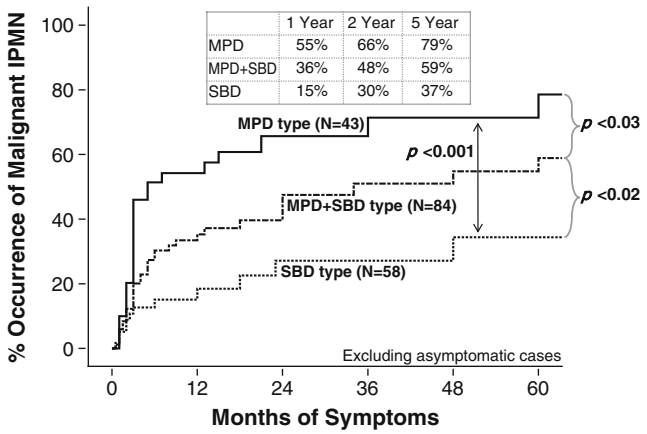

Fig. 4 After excluding the 25 asymptomatic cases, three actuarial curves depict the time course over time since development of symptoms to detection of "malignant" IPMN (CIS or invasive) in patients with MPD type (N=43), MPD+SBD type (N=84), and SBD type (N=58). The curves were calculated using Kaplan–Meier method from the first symptom. The actuarial risk of "malignant" IPMN at 1, 2, and 5 years was 55%, 66%, and 79% (MPD type), 36%, 48%, and 59% (MPD+SBD type), and 15%, 30%, and 37% (SBD type). A significant difference was observed for MPD+SBD vs. SBD (p<0.02) and MPD vs. SBD (p<0.001)

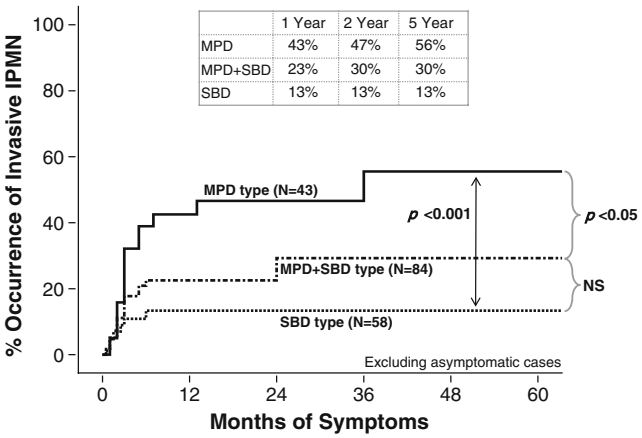

Fig. 5 The time course for "invasive" IPMN detection since the first symptom in patients with MPD type (N=43), MPD+SBD type (N=84), and SBD type (N=58). The curves were calculated using Kaplan–Meier method from the first symptom. The actuarial risk of "invasive" IPMN at 1, 2, and 5 years was 43%, 47%, and 56% (MPD type), 23%, 30%, and 30% (MPD+SBD type) and 13%, 13%, and 13% (SBD type). A significant difference was observed for MPD vs. MPD+SBD (p<0.05) and MPD vs. SBD (p<0.001)

a clinical history in retrospect would have been problematic. We did not find a difference in the incidence of the variety of types of symptoms associated with IPMN lesions between the more malignant MPD groups versus the SBD group (Table 3). In Table 4, we did observe that the duration of the more common pancreatitis-like symptoms before resection was shorter for the MPD-only group. "Pancreatitis-like symptoms" should be more rigidly defined and recorded in future studies, as well as the less frequent symptoms of steatorrhea or jaundice.

Table 4 also lists the elapsed time in the 25 cases with no symptoms between first imaging and resection. They required 16 to 17 months before a decision to resect was made, regardless of duct location. Recall that in 11 of these 25 cases, the decision to resect was made using the international criteria for malignant risk and 14 were made on MPD location. Therefore, in the cases without symptoms, the decision to resect was easier to make and might be an explanation why the resection decision was made earlier if imaging criteria were met. In the symptomatic group, the decision to resect was made statistically faster (16 months) if the MPD was involved versus if just the SBD was involved (25 months). Furthermore the months with pancreatitis-like symptoms to resection in MPD group was significantly shorter (18 months) than SBD group (27 months). It appears that the ultimate decision to resect was more difficult to reach based on symptoms alone if the SBD ducts were involved.

As in Table 2 and in the figures, the IPMN lesions located in the MPD location were more likely to be malignant (CIS or invasive) confirming other IPMN case series.[5,10] What is new is that the MPD lesions are more

likely to have an elevated serum CA19-9 level and a shorter duration from onset of symptoms to malignant detection at the time of resection. Since most cases were symptomatic (88%), it was also interesting to note that 98% of cases with MPD lesions had symptoms as compared to 77% of the SBD group ($p<0.001$).

These clues might help to explain how to interpret this study's observations regarding IPMN. The MPD location is more likely to be symptomatic and come to early detection and therefore early resection and early detection of malignancy. The symptoms may be due to MPD obstruction alone since they are strongly associated with pancreatitis-like symptoms of shorter duration. The symptoms caused by obstruction are also strongly related to malignancy as MPD lesions have a higher CA19-9 serum level (known to increase with ductal obstruction) and a lower incidence of adenoma (Table 5). Symptoms, MPD location, and earlier resection all suggest more rapid progression of the neoplastic process which is now visually depicted in the actuarial malignant risk curves.

Further support for increase risk of malignancy associated with symptoms comes from the cases without symptoms. These cases are generally incidental findings on imaging studies done for other reasons such as a workup for kidney stones. The inclusion of 25 asymptomatic IPMN lesions in this study that also have a surgical specimen has provided an interesting perspective. The amount of dysplasia and the ductal location were accurately designated. These 25 asymptomatic cases were followed expectantly and had met indications for resection based on international guidelines (Table 1). The international guidelines for resection include MPD location, symptoms, and cyst size if symptoms are not present. None of the resected asymptomatic SBD cases had progressed to malignancy, and this zero rate was markedly different than for resected symptomatic SBD cases. We can visualize the slow rate of progression in the asymptomatic groups in Figs. 1, 2, 3, albeit the starting point is not symptoms but rather the time of incidental detection. These curves provide more insight into the natural history of the IPMN spectrum. It appears that symptoms are very important to recognize and avoid malignancy —and this criteria of the international guidelines (symptoms) was more valuable to predict malignancy than cyst size. Schmidt and colleagues from Indiana University found a similar lack of value on cyst size but were not able to analyze for the importance of symptoms to detect malignancy because just 5 of their 150 resected cases (3%) did not have symptoms.[10] The latter study highlights the value of our study's 25 asymptomatic cases with histologically confirmed duct location and dysplasia grading that suggested a very slow progression to malignancy.

In the current study, the primary indication for resection was symptoms (88%) and then MPD location (65%). The strong association of MPD location with malignancy might place the presence of the even more common indication (symptoms) into the most important finding to decide on resection. For example we might not focus on invasive tests to determine MPD involvement if pancreatitis-like symptoms were present. The clinical history may be the most important factor to decide on resection. Recall that the incidence of any type of symptom was similar for any location (MPD, MPD+SBD, and SBD); however, the duration of the symptoms was very illustrative. The shortest elapsed time for onset of symptoms to first detection of malignancy for cases with MPD location was seen in the group with pancreatitis-like symptoms (18 months, Table 4).

How can these observations help us decide when resection is appropriate? As in Fig. 2, if any symptomatic lesion, including the hitherto “benign” SBD lesion, is on a faster time course to malignant detection versus an asymptomatic lesion, then the actuarial rate of malignant detection provides objective and easy to interpret information. Consider the 2-year occurrence rates for the various tumors based on duct location and presence of symptoms. A symptomatic MPD lesion has a 54% risk of malignant detection at 2 years after onset of symptoms. An asymptomatic SBD lesion, of which there were 17 in this series, had a zero malignant detection at 2 years. The symptomatic SBD lesion would be expected to have a time course to malignancy of 30% at 2 years after onset of symptoms comparable to an asymptomatic MPD lesion (40% at 2 years after first detected, Fig. 2). Serious consideration should be given to resection for any symptomatic lesion regardless of ductal location. Focusing on symptoms allowed clinical decision-making for resection in 88% of our 210 patients while allowing a de-emphasis on cyst size which was an indication for surgery in just 3% (6/210) of the cases in our series. None of the cyst size indications for resection yielded a malignant diagnosis. With a new emphasis on symptoms and their onset, this study has highlighted for us the need to more thoroughly define and focus the onset date in the clinical history allowing the health care system to de-emphasize expensive diagnostic tests.

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Discussion

DR. SHARON M. WEBER (Madison, WI): I want to start by thanking your group for this and many prior important studies evaluating pancreatic cystic neoplasms. What I take away from this presentation as the most important message is that one should resect symptomatic lesions. Interestingly, if you look back at the original Sendai criteria, they basically concluded the same thing. But I believe those recommendations were probably made based more on the fact that we could palliate symptoms, rather than because there was an increased cancer risk. As you much more eloquently point out, this increased risk of malignancy has not been well recognized until your very important paper.

The questions I have for you really center around this issue of symptoms——particularly to look more closely at the group that had symptoms. I was surprised at the high percentage of patients that were symptomatic. To put this in context, of all the patients that you evaluate for cystic neoplasms, what percentage did this represent? What was the denominator? From a national perspective, other authors have reported that only about 25% of all the cystic neoplasms we evaluate in the clinic are symptomatic. So that was a very high percentage to me, particularly for the side branch lesions.

And a second question, can you be more specific about how you define symptoms? For instance, a very common patient we might be referred would be someone who had some vague epigastric pain, then gets a CT scan where they are found to have a pancreatic cyst, but when they see us, are really doing fairly well, having no symptoms whatsoever. How would you classify that patient? Did that patient count as symptomatic?

Lastly, from a pathological perspective, IPMN has not been well recognized until the mid '90s or so, but yet you included patients who underwent resection dating back to 1989. Did your study include pathological re-review of the slides to assure that there was a homogeneous patient population?

Closing Discussant

DR. TOSHIYUKI MORIYA: The first symptom is—our data revealed 88% of the patient had symptoms. But this is not uncommon, I think, because Johns Hopkins data or another paper revealed 20% patients don't have any symptoms. Our data is not uncommon, I think.

The second question, I reviewed only clinical records. We have not standardized our manual before resection. That is a really weak point of our study.

I reviewed only the pathological report; it depends on our pathologists. Sorry, I don't know the pathological details.

DR. JENNIFER TSENG (Worcester, MA): The Kaplan–Meier curves are not truly Kaplan–Meiers, in the sense that they all start at 0, so you're assuming that the IPMNs are uniformly not malignant when they're diagnosed. And that if you took them to the OR, whether it was 17 months or plus or minus that, and had pathology return as malignant IPMN, suddenly they turned malignant at that exact time—when really you finally just had the gold standard pathology (and you were perhaps wrong assuming it was benign at time 0). I would argue that you are not perhaps actually looking at the time course to malignancy but the time course to resection. And then, at resection, it's either malignant or not. And I think your conclusions are still very valid, but perhaps a chi-square as to whether it's malignant or not, as opposed to a Kaplan–Meier type of presentation.

DR. WILLIAM TRAVERSO: The French study by Levy gave us the idea to do the study this way. They only had 66 patients that actually had histologically confirmed

malignancy for IPMN. So we wanted to see if what they found was supported by our 210 cases. And I had the same difficulty you did when I first read their paper.

But what the Kaplan–Meier curve measures is not the time course to malignancy but simply just what you said: the time course from the first time it was symptomatically detected to the time when they came to resection. And then at that time, the percentage of those cases that were malignant.

So over time, if 50% were malignant at the time of resection, it would suggest that they were on a faster time course to what the surgeon would know to predict whether they would have a malignancy, yes or no.

If the patients are not symptomatic, then we only know they're there because they are incidentally found at the time of some imaging study, like for kidney stones.

These patients have a much slower need for surgery. But when we did fortuitously operate on them for the other Sendai criteria, none of them had malignant disease. And so what the study brought out was if a person has symptoms, or the main pancreatic duct involvement, within 2 years of the detection of that entity, half of these patients, will have malignancy. But in the patients that have IPMN appearing on an just imaging study, those patients were not progressing and just had to be followed with caution. And the ones that we took out because they had exceeded the criteria from the Sendai group of greater than 3 cm, all of those were not malignant, which were a very small minority of the group.

The Indiana study that was published recently in Annals of Surgery shows that 93% of their cases were symptomatic. In ours, 88% were symptomatic. In this group of symptomatic people, you don't really need to do extra tests, don't need do EUS.

One just has to have a good clinical history to decide the chance for detecting malignancy at the time of the resection. And if the chance is over 50%, the doctor can show the patient the Kaplan–Meier curve, the patient can grasp this easily, and get behind the operation as a good thing to do.

DR. MICHAEL G. SARR (Rochester, MN): You are assuming that people with carcinoma-in-situ are going to go on and develop invasive disease. You call it cancer, as does the WHO. Is that an appropriate assumption?

DR. WILLIAM TRAVERSO: In the manuscript—we didn't present it here because we didn't have time—there's a second set of Kaplan–Meier curves for just invasive IPMN. And it established a similar trend.

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2010 SSAT POSTER PRESENTATION

Comparative Evaluation of Transpapillary Drainage with Nasopancreatic Drain and Stent in Patients with Large Pseudocysts Located Near Tail of Pancreas

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Abstract
Background Endoscopic transpapillary drainage is usually not advocated for large pseudocysts for fear of infection. We compared efficacy of transpapillary drainage with nasopancreatic drain (NPD) or stent alone in large pseudocysts (>6 cm) located near tail of pancreas.
Methods In a prospective study, a 5-Fr stent/NPD was placed across/near pancreatic duct disruption in 11 patients (nine chronic and two acute pancreatitis) with large pseudocysts located near tail of pancreas. The patients were followed up for resolution of pseudocyst, need for surgery, and complications.
Results Pseudocysts diameter ranged from 7 to 15 cm. An attempt to place NPD was made in five patients and a stent in six patients. In NPD group, deep cannulation could not be achieved in one patient; it was treated successfully with percutaneous drainage. In four patients with partial duct disruption, NPD was successfully placed bridging disruption and all had resolution within 6 weeks. In stent group, five had partial and one had complete duct disruption, who later recovered by placement of a stent. Of five patients with partial disruption, one recovered uneventfully at 6 weeks with stent bridging disruption. Other four patients (bridging stent in three) developed febrile illness and infection of pseudocyst. They required additional percutaneous drainage and antibiotics. There was no recurrence of pseudocysts over follow-up of 16.4 months.
Conclusion Endoscopic transpapillary drainage with NPD bridging disruption is associated with good outcome in patients with large pseudocysts at tail end of pancreas. However, there was increased frequency of infection when stent was used for drainage.

This work had been presented at DDW 2010, New Orleans, USA.

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Keywords Nasopancreatic drain · Stent · Pancreas · Pseudocyst · Chronic pancreatitis · Acute pancreatitis

Introduction

The treatment options for pancreatic pseudocysts include conservative (medical), radiologic (percutaneous), endoscopic, laparoscopic and surgical methods.[1–7] Endoscopic drainage (transmural, transpapillary placement of endoprostheses, or both) of single pancreatic pseudocyst is now a well established, minimally invasive, successful therapeutic modality.[2–6] Endoscopic transpapillary drainage is usually considered suitable for small communicating pancreatic pseudocysts and is not advocated for large (>6 cm) communicating pancreatic pseudocysts because of fear of infection.

However, we have earlier reported successful resolution of large as well as multiple pseudocysts by endoscopic transpapillary nasopancreatic drainage alone with minimal complications.[8] We have also reported successful resolution of pancreatic pseudocysts at atypical and distant locations by endoscopic transpapillary drainage using a nasopancreatic drain with minimal infective complications.[9–12] We believe that fewer infective complications occurred in our studies because of the usage of a nasopancreatic drain for transpapillary drainage. Our hypothesis is that if a stent gets blocked before the resolution of pseudocyst, it can cause infection. In contrast, a blocked nasopancreatic drain (NPD) can be opened by flushing and by aspiration, thus maintaining a constant drainage of the pancreatic juice till the resolution of the pseudocysts and decreasing the risk of infection. To confirm our hypothesis, we conducted this comparative prospective study comparing therapeutic efficacy of a transpapillary nasopancreatic drain with a stent in patients with large (>6 cm) pancreatic pseudocysts located at the tail end of pancreas.

Patients and Methods

From June 2006 to June 2009, all patients with symptomatic large (>6 cm) pseudocysts of pancreas located at tail region of pancreas were treated by an attempted endoscopic transpapillary NPD or stent placement. The patients were explained in detail about the pros and cons of a NPD or stent placement including the possibility of keeping a NPD in situ for a period of up to 8 weeks. Thereafter, a stent or NPD was placed as per the patients' choice. All the patients selected for the endoscopic therapy were symptomatic, had pseudocysts of the pancreas at tail end of pancreas as documented on computed tomography (CT) scan, and all had documented persistence of pseudocysts for 6 weeks or more. Patients with pancreatic mass, pregnancy, age less than 18 years, presence of chronic cardiac, renal or pulmonary failure, or patients not giving informed consent were excluded. In patients with acute pancreatitis, magnetic resonance imaging of the abdomen was done prior to endotherapy to exclude significant necrosis in the pancreatic fluid collection. The study was approved by the institutional ethics committee, and an informed consent was obtained from all the patients. In all the patients, endoscopic retrograde cholangiopancreatography (ERCP) demonstrated disruption of pancreatic duct and none of the patients had patulous papilla or mucin on suction at the papilla.

Intravenous ciprofloxacin was administered for antibiotic prophylaxis. ERCP was performed by standard technique using a TJF 145 or TJF 160 (Olympus Optical Co. Ltd., Tokyo, Japan) side-viewing duodenoscope under conscious sedation by intravenous midazolam and hyoscine butyl bromide was used to inhibit duodenal contractions. Initially, an attempt was made for contrast-free pancreatic duct cannulation and if that was not possible, minimal contrast was injected. Once cannulated, minimal contrast was injected to confirm pancreatic duct (PD) disruption, defined by free extravasation of contrast outside the pancreatic ductal system as seen on fluoroscopy. PD disruption was defined as complete when the main duct upstream to the disruption was not opacified and as partial when the main duct was visualized upstream from the site of disruption. After confirming the ductal disruption, a 5-Fr NPD or stent was placed across the papilla in to the PD by advancing it over a 0.025 or 0.035 in. hydrophilic guide wire (Jagwire; Microvasive Endoscopy, Boston Scientific Corp., Natick, MA). An attempt was made to place the NPD across the area of the disruption and if that was not possible, it was placed as close as possible to the disruption.

After the procedure, all the cases were admitted and kept under observation for 48 to 72 h and thereafter, the patients were discharged and followed up in the outpatient department till complete resolution of all the pseudocysts. At the time of the discharge, the patients were instructed to empty the bag containing secretions drained by NPD and record the daily drain output. The NPD was passed beneath the patients clothes and tied at the back of the ear, so as the patient can perform their daily activities and go to work also. They were advised to report if there was no drainage from the NPD in 24 h or the color of the output changed to bilious, indicating displacement of the NPD into the duodenum. When blockage was suspected (no output for 24 h), the NPD was initially aspirated and if that did not open the block, it was flushed with sterile saline and flow was established by suction using a disposable syringe. The patients were followed up every 2 weeks for (a) clinical re-evaluation and (b) abdominal ultrasound. CT abdomen

was repeated at the end when there was complete clinical recovery along with complete resolution of pseudocysts on the ultrasound of abdomen.

Therapeutic success was defined as symptomatic improvement with radiological resolution of the pseudocyst on CT scan. Therapeutic failure was defined as persistence of pseudocyst at 8 weeks after NPD placement or need for surgical intervention.

Results

Eleven patients with symptomatic large pseudocysts of pancreas located at the tail end (nine males, mean age: 41±9 years) were treated with attempted endoscopic transpapillary nasopancreatic or stent drainage. Nine patients had an underlying chronic pancreatitis and two patients had pseudocysts as sequelae of acute pancreatitis. Five patients had underlying alcohol-related chronic pancreatitis whereas four patients had idiopathic chronic pancreatitis. Out of two patients with acute pancreatitis, one had drug-induced pancreatitis and the other had idiopathic acute pancreatitis. All these patients had pseudocysts located at the tail end of the pancreas with size ranging from 7 to 15 cm (mean, 9.8±3.1 cm). All the patients had abdominal pain as their predominant symptom. ERP identified pancreatic duct disruption in all the 11 patients. It was partial in nine patients and complete in two patients. An attempt to place NPD was made in five patients and a stent in six patients as per the patient's preference. There was no significant difference in the size of the pseudocysts between the two groups.

In the NPD group (n=5), deep cannulation could not be achieved in one patient with complete disruption and he was treated successfully with antibiotics and percutaneous drainage. The other four patients had partial duct disruption. In these four patients, NPD (5-Fr) could be successfully placed bridging the disruption. The NPD got blocked in one patient at day 14 and was successfully opened by flushing. All these four patients had successful outcome with pseudocysts resolving within 4 to 8 weeks. No significant complications were noted in the NPD group.

On ERP in the stent group (n=6), five patients had partial and one patient had complete pancreatic duct disruption. In a patient with complete duct disruption, a non-bridging pancreatic duct stent (5-Fr) was placed. This patient had successful outcome with the pseudocyst resolving at 8 weeks. In five patients with partial duct disruption, a 5-Fr (n=3) or 7-Fr (n=2) stent could be successfully placed. The stent was bridging the disruption in four patients and non-bridging in one patient. One patient with a 5-Fr bridging pancreatic duct stent had successful outcome with pseudocyst resolving at 6 weeks. The other four patients (bridging stent in three) developed febrile illness and infection of the pseudocyst 3–10 days after insertion of the stent. They required additional percutaneous drainage and antibiotics for successful outcome (Figs. 1–5).

None of these patients had a recurrence of pseudocyst or required subsequent surgical intervention during the follow-up period of 16.4±11.4 months.

Discussion

Endoscopic transpapillary drainage is usually considered suitable for small communicating pancreatic pseudocysts and is not advocated for large (>6 cm) communicating pancreatic pseudocysts because of fear of infection of the large collections. The large pseudocysts are usually managed by transmural drainage or combination of transmural and transpapillary drainage.[13, 14] However, we have earlier reported successful resolution of large as well as multiple pseudocysts by endoscopic transpapillary nasopancreatic drainage alone with minimal complications.[8] We have also reported successful resolution of pancreatic pseudocysts at atypical and distant locations by endoscopic transpapillary drainage using a nasopancreatic drain with minimal infective complications.[9–12] But in all these studies, we used nasopancreatic drain for transpapillary drainage and in none of these patients pancreatic duct stent was used. There are no studies in the published literature that have compared the efficacy of transpapillary stent with nasopancreatic drainage. At our center, we have been preferring stent over NPD for pancreatic duct strictures, pancreas divisum, and single small pancreatic pseudocyst and use nasopancreatic drain for patients with complex clinical situations like communicating multiple pancreatic large pseudocysts, pancreatic ascites, and pleural effusions, where we feel that

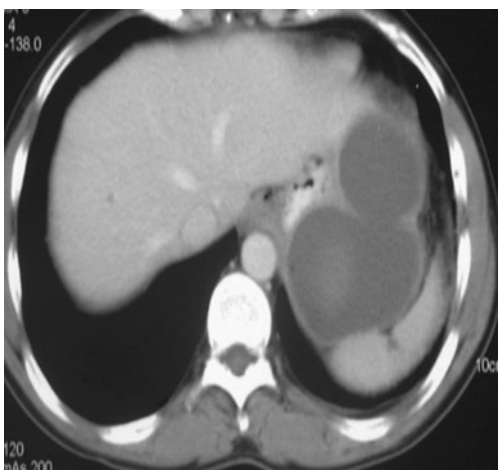

Fig. 1 Large pseudocyst at tail end of pancreas

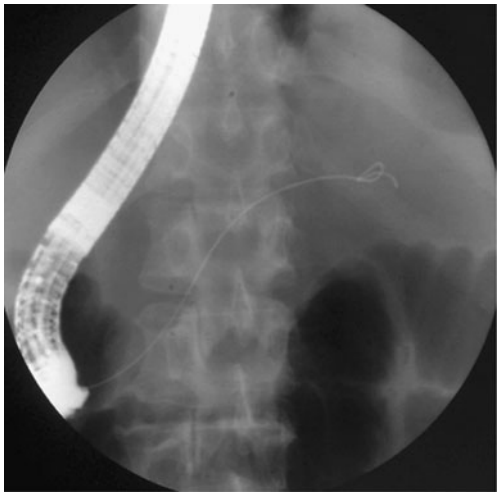

Fig. 2 ERCP: contrast-free cannulation of pancreatic duct done with a guide wire

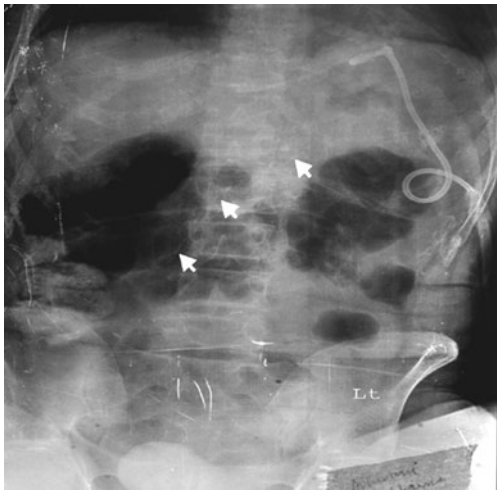

Fig. 4 Post stenting patient developed fever. A percutaneous drain was placed in the pseudocyst. Stent (*arrows*) is noted in the pancreatic duct

NPD gives us the following advantages: blocked NPD can be opened up with flushing and aspiration, and therefore, obviating the need of repeat ERCP and stent replacement as in case of a blocked stent; repeated pancreatograms can be obtained to demonstrate the healing of ductal disruption, without resorting to repeated ERCP; and after demonstrating healing of duct disruption after performing NPD gram, NPD can be removed without necessitating another endoscopy.

We believe that fewer infective complications occurred in our studies as well as in our routine practice because of the usage of a nasopancreatic drain for transpapillary drainage for large and multiple pseudocysts, pseudocysts at atypical locations, and large pseudocysts at tail end of pancreas. Our hypothesis is that if a stent get blocked before the resolution of pseudocyst, it can cause infection. In contrast, a blocked NPD can be opened by flushing and by aspiration, thus maintaining a constant drainage of the pancreatic juice till the resolution of the pseudocysts and decreasing the risk of infection. To test this hypothesis, we conducted this study of comparing stent with nasopancreatic drainage for large symptomatic pseudocysts of pancreas located at the tail region.

In the current study, all the four patients with NPD had successful outcome with no significant complications and these results were in accordance with our published results of successful outcome of complex pancreatic diseases with minimal complications with a transpapillary nasopancreatic drain only.[8–12] However, in the stent group, 4/6 (67%) patients developed infection of the pseudocyst post procedure and required additional percutaneous drainage and intravenous antibiotics for successful outcome. This was in spite of the fact that two patients in stent group had a 7-Fr stent whereas all the patients in the NPD group had a 5-Fr

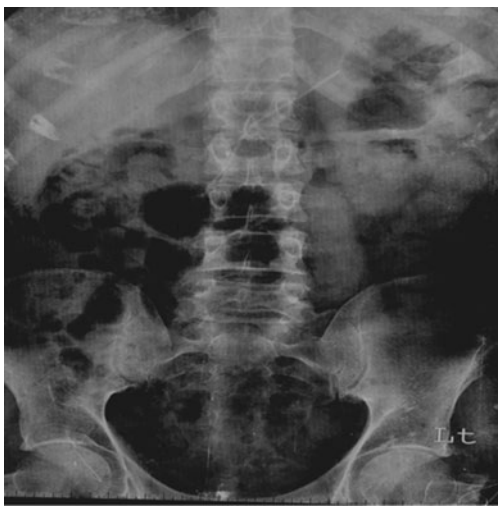

Fig. 3 Bridging 5-Fr stent placed across the disruption in pancreatic duct

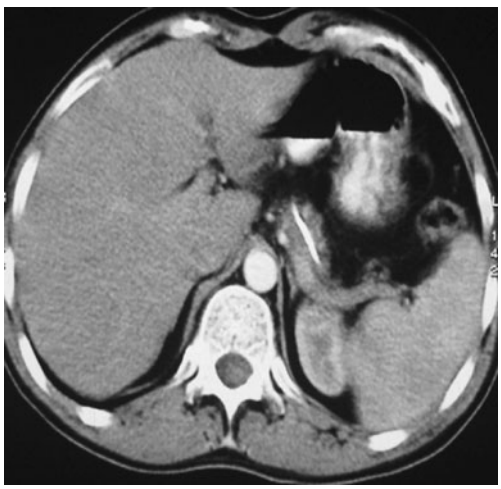

Fig. 5 CT at 6 weeks: resolution of pseudocyst. Pancreatic duct stent seen in situ

NPD. This is also in accordance with earlier published studies that have shown that transpapillary drainage with a stent is associated with increased risk of pancreatic pseudocyst infection especially in cases of large and distant pseudocysts.[6, 15, 16] The higher risk of infection of the pseudocyst with a stent in comparison to NPD could be because of the clogging of the stent before the resolution of the pseudocyst. The lower frequency of infection in the NPD group could be because of: even if NPD gets blocked, it can be detected without a need of endoscopy or any imaging and a blocked NPD can be opened by flushing and by aspiration, thus maintaining a constant drainage of the pancreatic juice till the resolution of the pseudocysts and decreasing the risk of infection.

The only concerns with placing a NPD are the discomfort to the patient and a risk of it being pulled out accidentally. However, all of our patients tolerated NPD well and in no patient did it become displaced. The small sample size and a non-randomized design are the limitations of the current study. However, large pancreatic pseudocysts at tail end are rare and therefore, we feel a sample size of 11 patients for this rare clinical problem has yielded important results which may be confirmed by large multi center studies. All the patients may not prefer NPD, and therefore, we did not conduct a randomized study but did a prospective comparative study where the choice of NPD or stent was left to the patient. Another interesting observation in this study was resolution of pseudocyst in one patient with complete disruption after placement of non-bridging pancreatic duct stent. In our earlier studies also, we have noted that some of the patients with complete disruption had also the resolution of the pseudocysts/fistulae after non-bridging transpapillary drainage although the results were not as spectacular as were noted in patients with partial disruption.[8, 9, 14, 17] Another large study by Varadarajulu et al. also reported successful resolution after transpapillary drainage in 26% (6/23) of patients with complete disruption.[18] The reason for resolution of pseudocysts in this situation is not clear, and further studies are needed.

In conclusion, endoscopic transpapillary drainage with a NPD bridging the disruption is associated with good outcome even in patients with large pseudocysts at the tail end of pancreas. However, there was increased frequency of infection when a stent was used for drainage.

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ORIGINAL ARTICLE

Management of Esophageal Perforation and Anastomotic Leak by Transluminal Drainage

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Abstract
Introduction The management of esophageal perforations and leaks remains a challenge. Although there are broad management principles, each situation may require a different surgical approach. The aim of this report was to describe the management of these esophageal crises by transluminal drainage via a transabdominal approach.
Methods Between 2005 and 2009, patients with anastomotic or gastric staple line leak (n=4) or esophageal perforation (n=2) underwent transabdominal surgery and transluminal drainage. This simple technique has, to the best of our knowledge, not been previously reported.
Results All six patients survived. The median intensive care unit and hospital stays were 12 days (range 0–32) and 63 days (range 32–99), respectively. At a median follow-up time of 25 months (range 15–60), five of the six patients remain alive and well. One patient with node positive esophageal carcinoma has died from relapsed disease.
Conclusions Transabdominal transluminal drainage should be added to the list of potential techniques that can be employed in management of esophageal leaks and perforations. It is a valuable adjunct to the armamentarium of the esophageal surgeon for dealing with these challenging situations.

Keywords Anastomosis · Surgical · Drainage · Esophageal perforation · Esophagectomy · Postoperative complications

Introduction

Esophageal perforations, iatrogenic, or postsurgical are associated with the rapid onset of severe peritoneal or mediastinal inflammation, the systemic inflammatory response syndrome, sepsis, and multiorgan dysfunction.[1,2] For spontaneous perforations, the mortality rate is in the order of 20% rising to 50% or greater with delayed treatment.[2–4] Postoperative perforation from anastomotic or staple line leakage following resection of esophagogastric cancer is also frequently fatal accounting for up to 40% of postoperative deaths.[5–7]

The broad objectives of management include appropriate drainage of mediastinal, pleural, or peritoneal infection, prevention of further contamination or leakage from the perforation, control of gastric reflux, restoration of gut integrity, and the establishment of nutritional support.[8] Both conservative,[9] endoscopic,[10–15] and operative management [1,4,16–24] strategies have been described to achieve these goals, each with their own advocates. Because of the relative rarity of these problems, there are no randomized controlled trials establishing the optimal management strategy. Reported operative approaches include primary esophageal repair with or without reinforcement,[4,16,17] T-drainage,[18,19] esophageal exclusion and diversion,[20,21] and resection.[1,22–24]

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Leaks at the level of the hiatus, such as after total gastrectomy, pose a distinct problem in that operative exposure can be difficult to achieve through thoracotomy. Furthermore, these patients will have undergone initial surgical access via laparotomy. Reoperation via a thoracotomy adds an additional body cavity incision. It is for the management of leaks at the level of the hiatus that transluminal drainage may be most appropriate.

This article reports transluminal drainage via laparotomy to treat esophageal leak or perforation. Although we are aware that this technique has been used previously in the UK, we are not aware of its application being formally reported.

Patients and Methods

Patients

During the time 2005–2010, six patients with esophageal perforation or leak were treated using the technique described below (Table 1). The study was approved by the Institutional Clinical Audit, Standards and Effectiveness Team. As this was a retrospective evaluation, patient consent was not required.

Surgical Technique

Boerhaave Syndrome

Under general anesthesia, an initial endoscopic examination of the upper gastrointestinal tract is made in order to assess the site of perforation/leakage and to ensure that conduit necrosis has not occurred. Upon confirmation of the leak, surgical access is provided by an upper midline laparotomy. The esophagus is mobilized from the phrenoesophageal ligament and crura to expose the mediastinum. Thorough saline lavage is performed prior to placement of a silicone drain into the mediastinum via the hiatus. The left pleura is incised and the pleural space opened so that it communicates with the mediastinum. This allows irrigation and suction lavage of the pleural space through the hiatus with a Poole sucker. The mediastinum is drained with a silicone drain, and the pleural cavity is drained separately, if this has not already been achieved preoperatively.

A 2-cm anterior gastrotomy is made in the mid-lower gastric corpus using diathermy and a 36 F silicone drain passed through the gastric lumen up into the esophagus. The gastrotomy is closed with two concentric purse string sutures using 2–0 PDS that is secured around the drain. The drain is brought through the anterior abdominal wall and secured to the skin using 0 silk. Intraoperative endoscopy is employed to confirm placement of the drain tip 5 cm cranial to the upper limit of the perforation.

After Total Gastrectomy or Esophagectomy

When this technique is utilized in patients after total gastrectomy, the transluminal drain is passed through the jejunum in an analogous fashion. After an esophagectomy, the transluminal drain is passed through an anterior gastrotomy in the antrum at the level of the hiatus.

Postoperative Management

A nasogastric tube is not required as the large lumen of the esophageal drain affords adequate control of saliva and gastric secretions. A feeding jejunostomy is placed in the proximal jejunum. Oral fluid or food intake is withheld until restoration of gastrointestinal continuity is indicated by absence of gastrointestinal content in the mediastinal and pleural drains, and the absence of a leak on a radiological contrast study. Broad-spectrum antibacterials are administered. Once the leak has sealed, the transluminal esophageal tube can be spigotted. It is removed 6 weeks after insertion, by the application of sustained gentle traction. Intravenous sedation or general anesthesia may be required.

Patients should be warned to expect discharge from the gastrocutaneous fistula similar to that seen following removal of a percutaneous endoscopic gastrostomy tube. Despite the fact that the stoma is relatively large, it is easily managed with a simple dressing and closes 1–2 weeks following drain removal.

Results

Table 1 summarizes the patient characteristics and outcome. The median intensive care unit and hospital stays were 12 days (range 0–32) and 63 days (range 32–99), respectively.

Discussion

The management of esophageal perforations and leaks remain a challenge because of the morbidity and mortality associated with these conditions. A recent UK-wide audit of over 3,600 esophagogastric resections performed during the years 2007–2009 identified anastomotic leak as being associated with odds ratios of 3.5 for mortality and 18.1 for reoperation. Median hospital stays in patients with leaks were 37 days after esophagectomy (interquartile range 25–55 days) and 43 days after gastrectomy (interquartile range 25–69 days).[25]

A number of different management techniques have been described that include “conservative management,” a

Table 1 Summary of characteristics for six patients

Patient	1	2	3	4	5	6
Gender	Male	Male	Female	Male	Male	Male
Age in years	74	73	54	65	53	46
Initial diagnosis	Adenocarcinoma of GEJ (Siewert 1)	Adenocarcinoma of GEJ (Siewert 3)	Squamous carcinoma of middle esophagus	Adenocarcinoma of GEJ (Siewert 3)	Ingested foreign body	Boerhaave syndrome
Treatment prior to perforation	Neoadjuvant chemotherapy + Ivor Lewis esophagogastrectomy	Ivor Lewis esophagogastrectomy	Ivor Lewis esophagogastrectomy	Total gastrectomy + splenectomy. Hunt–Lawrence pouch reconstruction	Rigid esophagoscopy and removal of foreign body (by otorhinolaryngology)	None
Pathological stage	ypT_3N_0	pT_2N_0	pT_2N_0	pT_2N_1	N/A	N/A
Site and cause of perforation	Anastomotic leak at level of azygos arch from stapled esophagogastric anastomosis (25 mm circular)	Anastomotic leak at level of azygos arch from handsewn esophagogastric anastomosis (3–0 nurolon)	Vertical gastric staple line leak at level of inferior pulmonary vein	Anastomotic leak in lower mediastinum from stapled esophagojejunal anastomosis (25 mm circular)	Iatrogenic esophageal perforation just above gastroesophageal junction	Spontaneous perforation just above gastroesophageal junction
Diagnostic modality for perforation	Enteric contents in chest drain. Leak on contrast study 2 days postop	CT	CT	CT showed collection 4 days postop. Leak on contrast study 7 days postop	CT	CT
Duration of ITU stay[a] (days)	32	27	0	7	5	18
Duration of ventilation[a]	27	21	0	3	0	17
Duration of hospital stay[a]	83	62	32	63	33	99
Duration of follow-up	60 months	29 months	26 months	Died—recurrence at 15 months	24 months	16 months

[a] After treatment for perforation commenced

number of operative techniques, and endoscopic stenting. Those numerous methods that have been employed are indicative that no single method is applicable to all patients.

The current technique was used at our institution by the Senior Surgeon (AWH) as this had been the method taught during his residency training in Scotland in the 1980s. It is indeed surprising that this has not been previously reported in the medical literature. The coauthors had favored alternative management strategies, notably T-drainage, but subsequently employed the described technique for dealing with leaks around the level of the hiatus. The current method minimizes leakage of saliva and gastric juice from the perforation site into the mediastinum or peritoneum. The method is complimentary to existing techniques, but we speculate that its value lies in dealing with leaks or perforations at the level of the hiatus, notably after total gastrectomy with disruption of 10–50% of the anastomotic circumference. In these situations, access to the hiatus may be better by laparotomy rather than by thoracotomy.

Proponents of endoscopic stenting would advocate a less radical approach.[10–15] However, stenting is not without morbidity. Recent series indicate median rates of 23% for stent migration (range 3–58%), 37% for unplanned endoscopic reintervention (range 13–59%), and the occurrence of intestinal obstruction in up to 16%, unless there is planned stent removal.[10–15] There is no doubt that endoscopic stenting has a role, but it may be best reserved for patients who do not have features of multiorgan dysfunction. Furthermore, as there is good evidence pointing to a better outcome with a reduced time interval between leak and reintervention, endoscopic therapy might delay definitive surgery, if that is ultimately required.

There are concerns that patients who have postoperative complications may have a poorer cancer-specific survival.[26,27] The four patients after surgical resection have survivals in the range 15–60 months, with one death in a patient with node-positive adenocarcinoma from relapsed disease at 15 months.

The length of hospitalization in our patients is longer than that reported from US centers.[28] A recent report from the University of Pittsburgh Medical Center of 30 patients with anastomotic leak after transhiatal esophagectomy noted a mean hospital stay of 18 days. However, 21 of these 30 patients had either grade 1 (nonclinical radiological leak) or grade 2 (disruption of <10% of anastomotic circumference) leaks.[28] The anastomotic leaks in our patients were grade 3 (disruption of 10–50% of anastomotic circumference). We do not routinely obtain postoperative contrast radiology, so we would not identify grade 1 leaks in our practice. Our length of hospital stay is comparable to that reported in the UK-wide audit (see above).[25]

The authors understand the limitation of patient numbers in this series but consider that the technique warrants further attention as an adjunct to existing therapies for treatment of esophageal perforation. The surgical approach described is complimentary rather than an alternative to other reported approaches, but nonetheless may be useful in the armamentarium of the esophageal surgeon.

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ORIGINAL ARTICLE

A Population-Based Analysis of Esophageal and Gastric Cardia Adenocarcinomas in Ontario, Canada: Incidence, Risk Factors, and Regional Variation

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Abstract
Introduction In Western countries, the incidence of esophageal adenocarcinoma (EA) and gastric cardia adenocarcinoma (GCA) is increasing. This population-based study describes the incidence of, associated patient risk factors for, and regional variation in EA/GCA in Ontario, Canada.
Methods All adults with a new diagnosis of EA or GCA between 1972 and 2005 in Ontario were identified. Adjusted annual incidence rates were calculated, and multivariate models were used to identify patient risk factors. Maps were created to explore regional variation.
Results Over the study period, 8,245 persons were diagnosed with EA/CGA; incidence increased from 1.01 to 3.9 per 100,000. Age (>65 vs. <50 years; rate ratio (RR), 3.4; 95% confidence interval (CI), 2.8–4.1) and comorbidity (highest vs. lowest, RR, 3.5; 95% CI, 2.9–4.2) were most strongly associated with the development of EA/GCA. We found considerable regional variation in the rates of EA/GCA (North West vs. Central region, RR, 6.5; 95% CI, 4.4–9.6). Maps suggested ethnicity may explain some regional variation, and that the current allocation of designated surgical treatment centers for EA/CGA may be suboptimal.
Conclusions The incidence of EA/GCA is rising dramatically in Ontario. Further investigation of observed regional variation is warranted, particularly for the allocation of cancer health resources.

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Keywords Esophagus · Gastric cardia · Adenocarcinoma · Population-based study

Background

Esophageal adenocarcinoma (EA) is a cancer of the upper gastrointestinal tract typically arising in the lower part of the esophagus. EA is thought to arise from Barrett's esophagus, a precancerous lesion in which the esophageal squamous epithelium is replaced by columnar epithelium and/or intestinal metaplasia. Gastric cardia adenocarcinoma (GCA) is commonly studied with EA due to its proximity to the esophagus, similar risk factors, and the difficulty in differentiating these two cancers.[1] Risk factors for EA/GCA include being male, having a history of gastroesophageal reflux disease (GERD), a higher body mass index, and being of Caucasian race.[2–4]

In many Western countries, the incidence of EA/GCA is rising dramatically; in fact, its rate of increase exceeds that of all other cancers.[5–8] In the United States during 1975 and 2000, the incidence of GCA doubled and the incidence of EA increased sixfold.[9] Currently, the United Kingdom has the highest incidence of EA/GCA in the world, with 7 cases per 100,000.[10,11] Worldwide, the prevalence of EA/GCA is projected to increase a further 140% between 2005 and 2025.[12]

Because EA/GCA is relatively uncommon and because of the recognized volume–outcome relationship for the surgical treatment of these cancers,[13] surgical services for EA/GCA and other thoracic surgeries are being centralized in Ontario. Eleven hospitals across the province that meet criteria specified in Cancer Care Ontario's *Thoracic Surgical Oncology Standards*[14] have been identified as designated surgical treatment centers.[15] According to this strategy, patients requiring thoracic and esophageal surgery should be referred from local health centers to a designated

Table 1 Codes used to define cases of esophageal adenocarcinoma and gastric cardia adenocarcinoma

Data elements	OCR
Esophageal adenocarcinoma (EA)	
ICD-9	150.X
ICD-O	8140–8141, 8143–8145, 8147, 8200–8201, 8255, 8260–8263, 8430, 8480–8481, 8560, 8562, 8570–8575
Malignant neoplasm of stomach–cardia (GCA)	
ICD-9	151.0
ICD-O	8140–8145, 8147, 8210–8211, 8214, 8220–8221, 8255, 8260–8263, 8310, 8480–8481, 8560, 8562, 8570–8576

International Classification of Diseases (ICD)-9 is used to code anatomic location while ICD-O is used for histology

Table 2 Characteristics of persons diagnosed with esophageal and gastric cardia adenocarcinomas in Ontario between 1993 and 2005 (n=4,881)

Characteristic	Number (%)
Age in years	
Less than 50	507 (10)
50–64	1,473 (30)
65 and older	2,901 (59)
Sex	
Female	826 (17)
Male	4,055 (83)
Income category	
Urban	
Low	779 (16)
2	837 (17)
3	861 (18)
4	788 (16)
High	750 (15)
Rural	845 (17)
Unknown	21
Comorbidity, no. of ADGs	
0	136 (3)
1–2	717 (15)
3–4	1,308 (27)
5–6	1,226 (25)
7+	1,494 (31)
Health region	
Erie St. Clair	281 (6)
South West	473 (10)
Waterloo Wellington	256 (5)
Hamilton Niagara Haldimand Brant	725 (15)
Central West	166 (3)
Mississauga Halton	282 (6)
Toronto Central	355 (7)
Central	421 (9)
Central East	542 (11)
South East	291 (6)
Champlain	472 (10)
North Simcoe Muskoka	202 (4)
North East	291 (6)
North West	120 (2)
Unknown	<5
Era	
1993–1998	1,969 (40)
1999–2005	2,912 (60)

ADG aggregated diagnosis group

surgical treatment center in an effort to ensure the highest quality care and to improve patient outcomes.

Canadian incidence trends for EA/GCA follow those in other Western countries. In Ontario, the incidence of GCA rose approximately 30% (from 2.5 to 3.3 per 100,000) during 1979–2002, while the incidence of EA rose 300% (from 0.8 to 2.5 per 100,000) over the same period.[2] Similar rates of increase have been documented in British Columbia.[16] While these studies showed that the incidence of EA/GCA is also on the rise in Canada, they did not report on patient factors associated with developing EA/GCA or examine geographic distribution.

In the current study, we present a population-based analysis of EA/GCA incidence in Ontario from 1972 to 2005 using the linked health administrative databases at Institute for Clinical Evaluative Sciences (ICES). Our aims were to report the incidence of EA/GCA in Ontario between 1972 and 2005, to identify patient factors associated with EA/GCA, and to describe regional variation in the incidence of EA/CGA.

Methods

The research ethics board at the Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada approved the study.

Data Sources

The study was conducted at ICES, which contains the health records for the roughly 13 million residents of Ontario. These records are held in administrative databases that are linked by an encrypted version of each resident's provincial health plan number.

For this study, we used the databases from the following programs: the Ontario Health Insurance Plan (OHIP), the Ontario Cancer Registry (OCR), the Registered Persons Database (RPDB), and the Canadian Institute for Health Information (CIHI). OHIP contains the records of all physician billings for inpatient and outpatient visits and procedures from January 1991. The OCR is a registry of all cancer cases and includes data on incidence and mortality in Ontario from 1964. The RPDB contains address information for all people registered for Ontario health insurance coverage. The CIHI Discharge Abstract Database contains clinical, demographic, and administrative data for hospital admissions and day surgeries in Canada from 1991.

Defining the Study Cohort

Using the OCR database, we identified all adults over the age 18 diagnosed with EA and GCA in Ontario from 1972 to 2005 using the International Classification of Diseases (ICD)-9 (site) and ICD-0 (histologic subtype) codes (Table 1). As EA and GCA are often hard to distinguish in the clinical setting, we analyzed them together as we felt that restricting the analysis to EA alone could lead to spurious findings of differences between regions or over time due to variation in coding practices rather than true differences in incidence. We excluded individuals with a record of a second cancer in OCR.

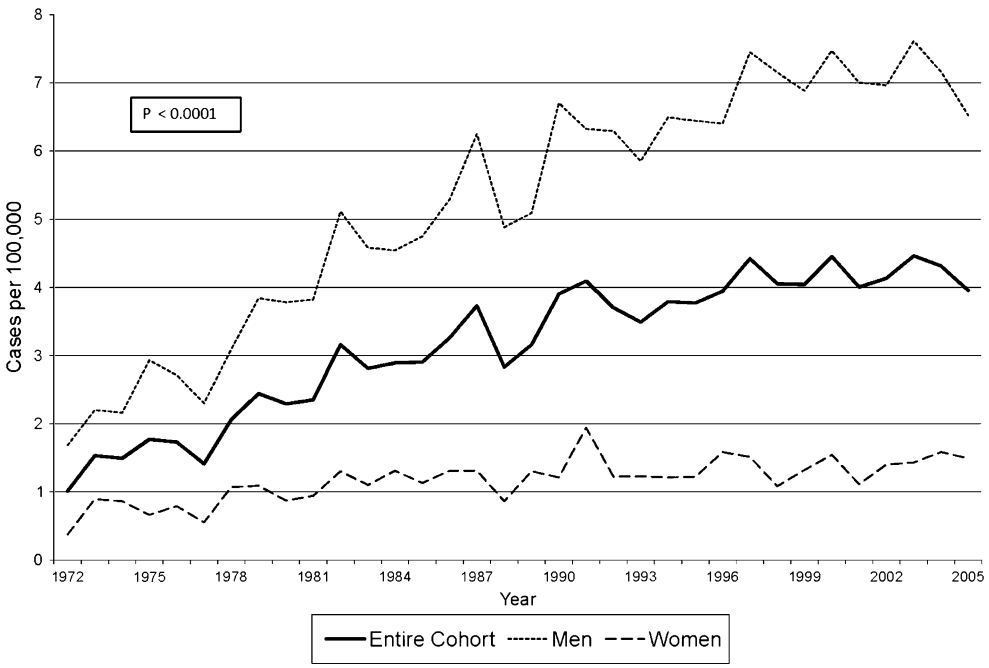

Fig. 1 Age-adjusted incidence of esophageal and gastric cardia adenocarcinomas in Ontario between 1972 and 2005 for the entire cohort (sex-adjusted), for men, and women

Table 3 Results of multivariate regression: risk factors for esophageal and gastric cardia adenocarcinomas in Ontario between 2003 and 2005

Characteristic	Relative rate (95% CI)	*P* value
Age in years		
Less than 50	1	N/A
50–64	2.6 (2.1, 3.1)	<0.0001
65 and older	3.4 (2.8, 4.1)	<0.0001
Sex		
Female	1	N/A
Male	1.8 (1.5, 2)	<0.0001
Income category		
Urban		
Low	1	N/A
2	0.9 (0.7, 1)	0.1112
3	0.9 (0.8, 1.1)	0.3434
4	0.8 (0.7, 1)	0.0582
High	0.8 (0.6, 1)	0.0138
Rural	0.5 (0.4, 0.7)	<0.0001
Comorbidity, no. of ADGs		
0–2	1	N/A
3–4	2 (1.7, 2.3)	<0.0001
5–6	3.1 (2.6, 3.7)	<0.0001
7 or more	3.5 (2.9, 4.2)	<0.0001
Health region		
Central	1	N/A
Erie St. Clair	2.3 (1.7, 3)	<0.0001
South West	2 (1.6, 2.7)	<0.0001
Waterloo Wellington	2.7 (2.1, 3.7)	<0.0001
Hamilton Niagara Haldimand Brant	1.3 (1, 1.6)	0.0362
Central West	1.9 (1.3, 2.7)	0.0005
Mississauga Halton	1.2 (0.9, 1.6)	0.1625
Toronto Central	1.1 (0.9, 1.5)	0.4047
Central East	1.3 (1, 1.6)	0.0616
South East	3.3 (2.4, 4.4)	<0.0001
Champlain	1.7 (1.4, 2.2)	<0.0001
North Simcoe Muskoka	3.5 (2.5, 4.8)	<0.0001
North East	2.9 (2.1, 3.9)	<0.0001
North West	6.5 (4.4, 9.6)	<0.0001
Year		
2003	1	N/A
2004	0.9 (0.8, 1.1)	0.3215
2005	0.9 (0.8, 1)	0.064

ADG aggregated diagnosis group, *N/A* not appropriate

Patient Factors Examined

We collected information on patient age, sex, median neighborhood income category, health region, and comorbidity at the date of diagnosis.

Median annual neighborhood household income at the level of enumeration area (ENA), obtained from Statistics Canada, was linked to patient postal code using the Postal Code Conversion File, a digital file linking Canada Postal Corporation postal codes with Canadian census information. This strategy has been used by others to impute socioeconomic status.[17,18] Subjects were classified into one of six income categories: five groups of equal size based on the median income of their ENA for those living in urban areas and a sixth group, consisting of those living in rural ENAs. We categorized rural ENAs separately from their urban counterparts as the use of median income of rural ENAs to represent the income of their residents is less accurate[19] as these ENAs tend to encompass larger geographic areas and consequently have wider variation in income than do urban ENAs.

Since April 2007, Ontario has been divided into 14 health regions for the purpose of health planning. These health regions are run by not-for-profit corporations that are responsible for managing the health service priorities of their designated health region, including the funding, planning, and integration of health services.[20] An ICES algorithm that maps each patient's Ontario Ministry of Health and Long-Term Care residence code was used to determine patient health region.

We determined patient comorbidity using the Johns Hopkins case-mix system, developed to measure the relationship of patient morbidity to health resource utilization,[21] which has been validated in the U.S.[22,23] and in Canada.[24,25] The Johns Hopkins case-mix system assigns patients to categories based on their inpatient and outpatient health care records over a specified period of time. For this study, we used Ontario inpatient (CIHI) and outpatient (OHIP) diagnosis codes from the year prior to the date of EA/GCA diagnosis to estimate case-mix. Specifically, we adjusted for comorbidity using aggregated diagnosis groups (ADGs), which are clinically meaningful groupings of diagnoses. Diagnoses within a given ADG are similar to each other in terms of disease severity and anticipated duration; we categorized comorbidity by the number of ADGs. We selected this comorbidity measure as it minimizes missing data when compared to another commonly used measure, the Deyo adaptation of the Charlson score,[26] which relies on inpatient diagnosis codes only.

Data Analysis

Age- and sex-adjusted annual incidence rates were calculated, standardized to the 2001 Ontario population. As EA and GCA are uncommon cancers, Statistics Canada annual population counts by age group and sex were used as denominators. Counts of the Ontario

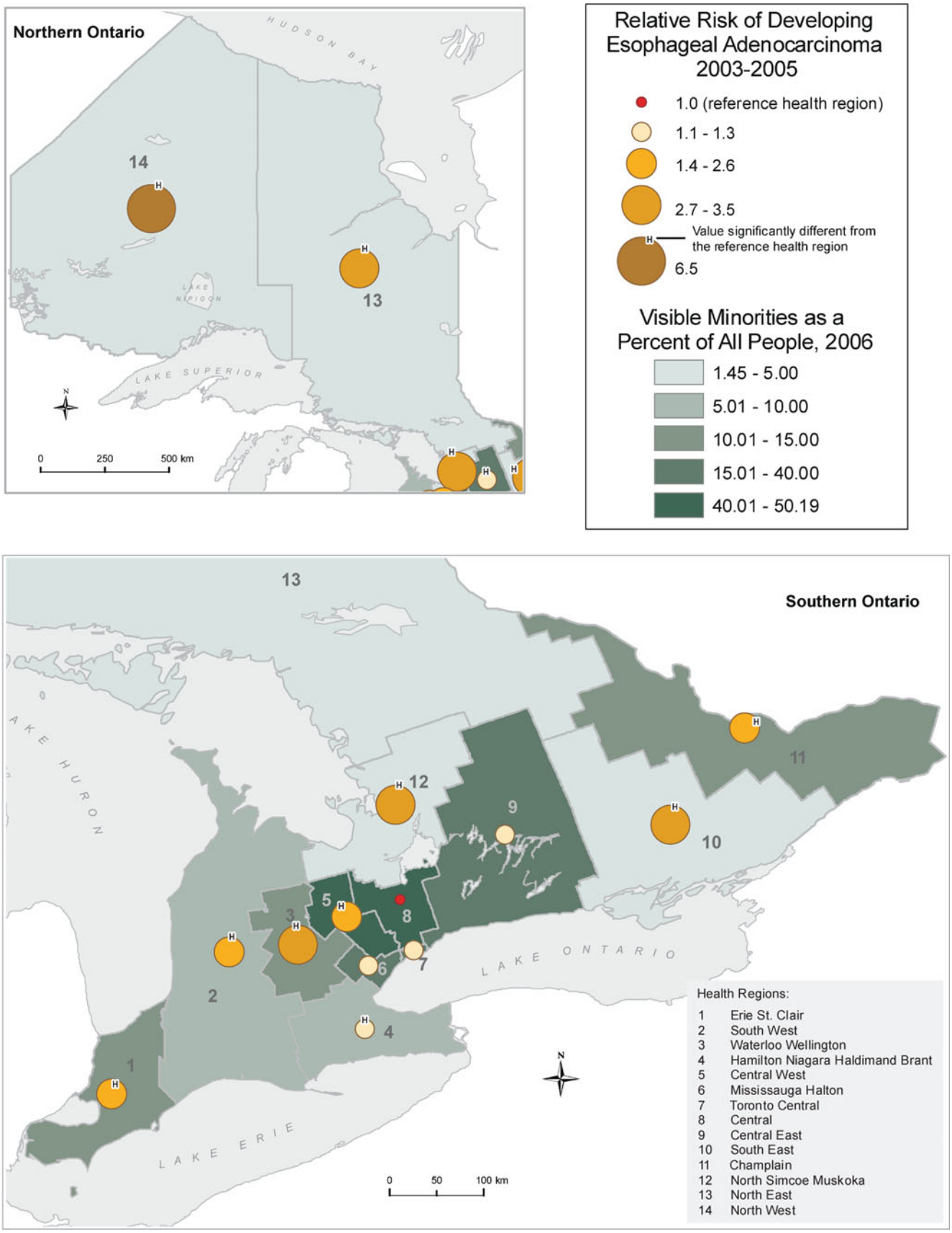

Fig. 2 Map of Ontario describing the relative risk of developing esophageal and gastric cardia adenocarcinomas relative to the proportion of visible minorities in each health region between 2003 and 2005

population are only available on an annual basis from 1972; therefore, these analyses were restricted to the period 1972–2005. Incidence rates were plotted over the study period for the entire cohort and by age and sex. Change in incidence over time was tested using Poisson regression.

Patient characteristics (age, sex, median neighborhood income category, health region, and comorbidity) are reported for the cohort. As the determination of patient characteristics required the use of the OHIP and CIHI databases, where reliable data are available only from 1992 onwards, these analyses were restricted to cases of EA/GCA diagnosed between 1993 and 2005, thereby allowing a year prior to EA/GCA diagnosis to collect comorbidity information.

We restricted the remaining analyses to 2003–2005 so that the results reflect the most recent time period. Patient factors (age, sex, income category, health region, comorbidity (classified as 0–2, 3–4, 5–6, or 7 or more ADGs), and year of diagnosis) associated with EA/GCA were evaluated using Poisson regression. We mapped the relative risk of EA/GCA and the proportion of visible minorities by health region as well as the number of cases of EA/GCA per health region and the location of designed surgical treatment centers. We used data from Statistics Canada to determine the proportion of visible minorities in each health region in 2006.

Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary NC). Statistical significance was defined as a p value<0.05.

Results

Demographic Characteristics

From 1972 to 2005, there were 8,245 persons diagnosed with EA/GCA; 4,881 were identified between 1993 and 2005. Among those diagnosed after 1993, 59% were 65 years of age or older and 83% were male. Patients were evenly distributed across income categories. The highest number of EA/GCA cases occurred in persons living in the Hamilton Niagara Haldimand Brant health region, while the lowest number occurred in those living in the North West health region (see Table 2).

Incidence

The incidence of EA/GCA increased significantly in the entire cohort, among men, and among women during 1972–2005 (see Fig. 1, $p<0.0001$ overall, for men and for women). In the entire cohort, the incidence of EA/GCA rose approximately fourfold over this time, from 1.01 per 100,000 in 1972 to 3.9 per 100,000 in 2005. The age- and sex-adjusted EA/GCA incidence for the entire period (1972–2005) for males, females, and the entire cohort were 5.6, 1.2, and 3.4 per 100,000, respectively.

Factors Associated with EA/GCA

In the multivariate analyses, older age, male sex, living in the lowest income urban neighborhood (compared to the highest income urban and to rural neighborhoods), and greater comorbidity were associated with EA/GCA. The strongest associations were for older age and greater comorbidity. Individuals aged 65 years and older were 3.4 times more likely to develop EA/GCA (95% confidence interval (CI), 2.8–4.1; $p<0.0001$) compared with individuals less than 50 years old, while persons with seven or more ADGs were 3.5 times more likely to develop EA/GCA compared with those with 0–2 ADGs (95% CI, 2.9–4.2; $p<0.0001$). There was a marked regional variation even after adjustment. Individuals living in the North West had a sixfold increased risk (rate ratio (RR), 6.5; 95% CI, 4.4–9.6; $p<0.0001$) of EA/GCA compared with those living in the Central health region (see Table 3).

In our exploratory analyses, we found that across health regions, the relative risk of developing EA/GCA was approximately inversely related to the proportion of visible minorities (see Fig. 2). In addition, the geographic distribution of designed surgical treatment centers did not align well with absolute number of cases of EA/GCA per health region. For example, in the four health regions comprising the greater Toronto area, there were 143 cases of EA/GCA in 2003–2005 and six designated surgical treatment centers, while in the four health regions to the west of Toronto, there were nearly twice as many cases (258), but half the number of treatment centers (see Fig. 3).

Discussion

The dramatic rise in the incidence of EA/GCA observed during 1972–2005 in Ontario is consistent with findings from other studies from Canada, the U.S, Europe, and Australia.[2,6–8,27] Although this cancer is the 19th most common cancer in Canada,[28] the magnitude of change in the incidence of EA/GCA indicates that it is an important emerging health problem. Similar to observations from other studies, age, male sex, and increased comorbidity were important risks factors for EA/GCA.[29] The latter finding is particularly relevant when considering treatment in EA/GCA patients as surgical intervention may not be a viable option for many of these patients due to their comorbidities.

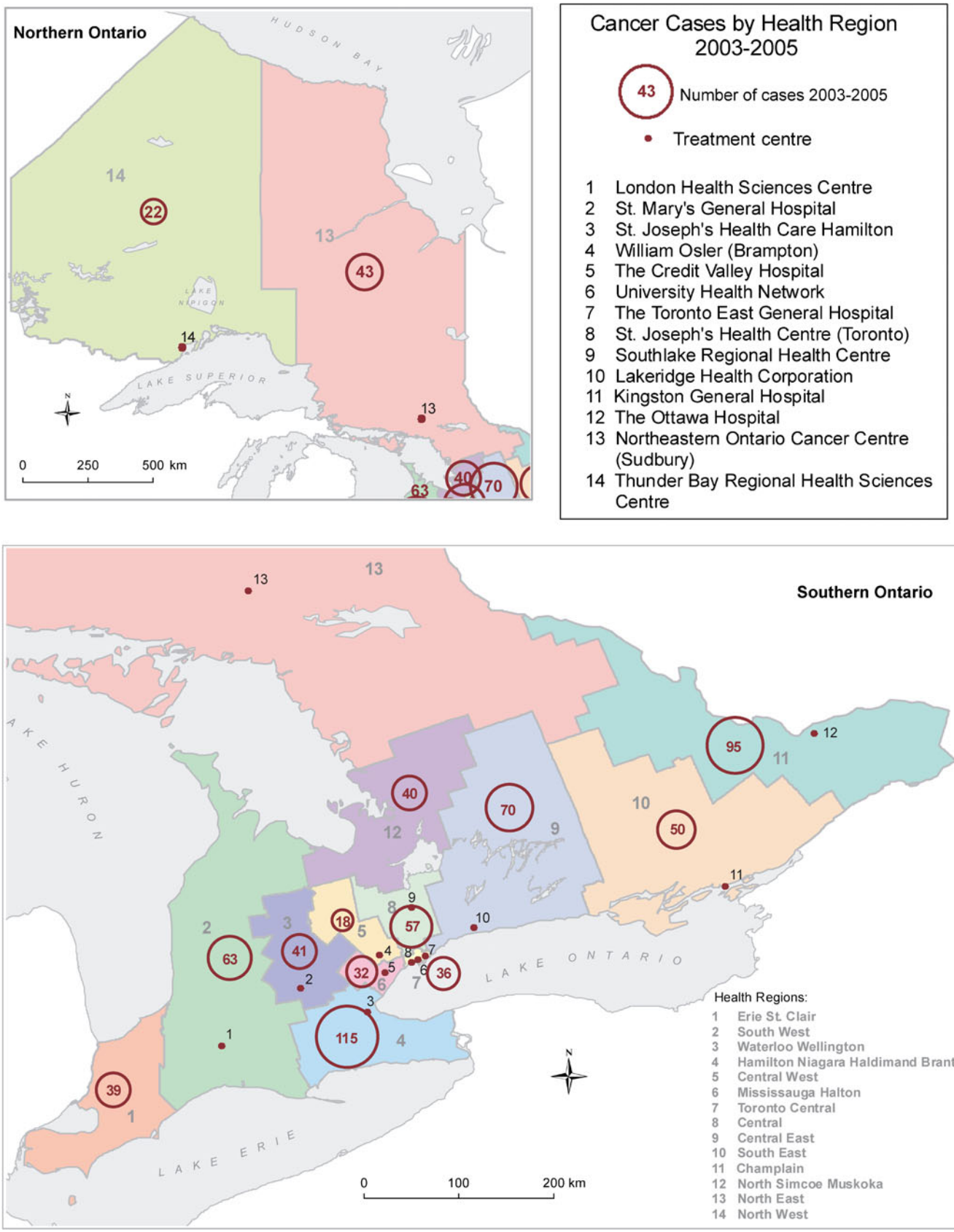

Fig. 3 The absolute number of cases of esophageal and gastric cardia adenocarcinomas and designated surgical treatment centers in Ontario by health region in Ontario between 2003 and 2005

Caucasian descent is recognized as a risk factor for EA/GCA,[2,30–32] but unfortunately, neither ethnicity nor race can be ascertained using the administrative data in Ontario. We found a substantial (sixfold) regional variation in EA/GCA incidence rates across health regions in Ontario; interestingly, incidence also appeared to be inversely related to the proportion of visible minorities living in each health region. Although this regional variation may be partly explained by the distribution of ethnicities across health regions, this explanation cannot entirely account for our observations. For example, persons who live in the North West health region have twice the risk of EA/GCA compared with those who live in the North East health region, yet the proportion of visible minorities is the same in the two health regions. Other factors, such as differences in rates of gastroesophageal reflux, environment exposures, lifestyle factors (smoking, alcohol consumption, etc.), and/or body mass index may also play a role. Future studies using formal geographic mapping/analytic techniques may be useful in elucidating more precisely the factors that underlie the considerable regional variation in the incidence of EA/GCA that we have observed.

Our study is particularly relevant in light of the recent initiative to centralize thoracic surgery procedures in Ontario.[14] As noted above, 11 institutions in Ontario have been identified as designated surgical treatment centers based on the annual number of thoracic surgeries, the number of surgeons with advanced training in thoracic surgery, affiliation with a Regional Cancer Program, and their physical and human resources.[14] Not surprisingly, designated surgical treatment centers are located in the most populous regions (e.g., the greater Toronto area); however, our study suggests that the distribution of these centers is not commensurate with the regional burden of EA/GCA. As a result, persons with EA/GCA living in relatively underserviced areas may be subject to important disparities in access to care (e.g., expertise, timeliness, and distance from a treatment center).

An important limitation of this study is that, due to the nature of administrative data, we were not able to reliably ascertain key clinical risk factors, such as body mass index or the diagnosis of GERD in our population. GERD is recognized as a very strong risk factor for EA/GCA,[3,33] and obesity, possibly because of its association with GERD, is also being increasingly recognized as an important risk factor. Clinical data such as height and weight that are used to calculate body mass index are not available in the administrative data. The Ontario administrative outpatient diagnosis codes are not specific enough to use to identify patients with GERD.

Conclusion

We report here that the incidence of EA/GCA has risen dramatically in Ontario between 1972 and 2005. We have also identified associated patient risk factors consistent with prior studies. The considerable regional variation in incidence that we observed is important from both epidemiologic and health planning perspectives and should be considered by policy makers as they allocate cancer health resources in the province.

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ORIGINAL ARTICLE

Alternating Treatment with S-1 Plus Low-Dose Cisplatin and S-1 Alone for Advanced Gastric Cancer

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Abstract
Background The aim of this study was to investigate the efficacy and safety of an alternating regimen of S-1 plus low-dose cisplatin and S-1 alone as adjuvant therapy in patients with advanced gastric cancer.
Patients and Methods The study group comprised 100 patients with stage IIIA, stage IIIB, or stage IV. Patients postoperatively received three 5-week cycles of chemotherapy. In the first cycle, S-1 (80 mg/m^2) was given daily for 3 weeks, followed by 2 weeks of rest, and low-dose cisplatin (10 mg) was given on days 1 to 5 and 8 to 12. In the second and third 5-week cycles, S-1 alone was given. The primary endpoints were median survival time, and survival at 1 and 3 years. Secondary endpoints were safety and overall response rates.
Results Median survival time was 18 months in stage IV and 32 months in stage IIIB. The rates of survival at 1 and 3 years were 68.7% and 30.6% in stage IV, 100% and 68.4% in stage IIIA, and 100% and 46.6% in stage IIIB, respectively. Adverse events of grade 3 or 4 occurred in 14% of the patients. The overall response rate of target lesions was 54%.
Conclusion Our regimen is effective and safe for adjuvant therapy in patients with curatively resected stage III gastric cancer.

Keywords Adjuvant chemotherapy · Gastric cancer · Low-dose cisplatin · S-1

Introduction

The outcomes of patients with unresectable or recurrent gastric cancer remain poor. Although various treatment regimens have been developed for the management of advanced gastric cancer, median survival is still less than 1 year.[1–9] In 2008, the S-1 plus cisplatin versus S-1 in RCT in the Treatment for Stomach Cancer (SPIRITS) trial reported that median survival time was significantly longer in patients with advanced gastric cancer who were assigned to S-1 plus cisplatin (13.0 months) than in those assigned to S-1 alone (11.0 months).[10] S-1 plus cisplatin is an effective regimen that is becoming a standard first-line treatment for patients with advanced gastric cancer in Japan. Both the Intergroup-0116 (INT-0116) study and the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial showed that adjuvant chemotherapy is effective for advanced gastric cancer.[11,12] However, which regimens are most effective remains controversial. In 2007, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial showed that the S-1 group had a higher rate of median survival time than the surgery-only group among patients with stage II or III gastric cancer who underwent gastrectomy with extended (D2) lymph node dissection.[13] S-1 has since become a standard drug for adjuvant therapy for this subgroup of patients in Japan.

S-1 (TS-1, Taiho Pharmaceutical) is an oral fluoropyrimidine anticancer drug designed to enhance the anticancer activity and reduce the gastrointestinal toxic effects of fluorouracil. S-1 consists of tegafur and two biochemical modulators: 5-chloro-2,4-dihydroxypyridine and potassium oxonate (molar ratio, 1:0.4:1).[14] Previous phase II studies of S-1 have reported overall response rates of 44% to 54% in patients with advanced gastric cancer.[15–17] Cisplatin

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enhances the therapeutic effect of S-1 in this indication. S-1 combined with low-dose cisplatin has also been reported to be effective with tolerable toxicity.[18,19]

We studied the efficacy and safety of an alternating regimen of S-1 plus low-dose cisplatin and S-1 alone as adjuvant therapy in patients with curatively resected, advanced (stage III) gastric cancer. The primary endpoints were median survival time and survival at 1 and 3 years. Secondary endpoints were safety and overall response rates.

Materials and Methods

Eligibility Criteria Eligible patients had to have (1) histologically or cytologically proved gastric cancer of stage IIIA with more than six positive lymph nodes, stage IIIB, or stage IV. In all stage III patients, standard gastrectomy of more than a D2 dissection was performed; (2) an Eastern Cooperative Oncology Group performance status of 2 or less; (3) an age of 20 years or older; (4) measurable tumor in patients who had unresectable or recurrent disease; (5) an expected survival of at least 3 months; (6) no previous treatment for any cancer; and (7) adequate organ function (leukocyte count >2,000/μl, platelet count >50,000/μl, transaminases <2.5 times the upper limit of normal, total bilirubin <2 times the upper limit of normal, and a serum creatinine level no greater than the upper limit of normal). The criteria of the Japanese Gastric Cancer Association were used to classify disease stage and assess resected specimens.[20] Written informed consent was obtained from all patients before enrollment in the study.

Procedures All patients postoperatively received an alternating regimen of S-1 plus low-dose cisplatin and S-1 alone. Each course of treatment consisted of three 5-week cycles. In the first cycle, oral S-1 (80 mg/m^2 in two divided doses) was given daily for the first 3 weeks, followed by 2 weeks of rest. Low-dose cisplatin (10 mg) was given on days 1 to 5 and 8 to 12 (total, 10 days). In the second and third 5-week cycles, patients received oral S-1 alone (80 mg/m^2 in two divided doses daily) for 3 weeks, followed by 2 weeks of rest. This 15-week course of treatment was repeated until unacceptable toxicity, withdrawal of consent by the patient, or the detection of progressive disease.

Statistical Analysis The primary endpoint was median survival time and survival at 1 and 3 years. Patients were assigned within 2 weeks after operation. Median survival time was defined as the period between the date of starting the first cycle of chemotherapy and the date of death, over which 50% of the patients are expected to be alive. Deaths from other diseases were considered events, and data on patients without an event were censored as of the date of the final evaluation. Secondary endpoints were safety and overall response rates. All patients with stage III disease were scheduled to be followed up for 5 years postoperatively. Hematologic tests were performed, and clinical symptoms were assessed every 5 weeks. Tumors were evaluated every 3 months by imaging studies (computed tomography, magnetic resonance imaging, chest radiography, and ultrasonography) and endoscopic examinations. The presence or absence of disease recurrence was determined by the same studies every 6 months. Response Evaluation Criteria in Solid Tumors (RECIST) was used to assess all images. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (NCI-CTC). The Kaplan–Meier method was used to plot survival curves, and the log-rank test was used to compare variables according to stage.

Results

Patient Characteristics Between April 2005 and March 2009, 107 patients were assigned to treatment with an alternating regimen of S-1 plus low-dose cisplatin and S-1 alone. Seven patients were ineligible. The reasons for ineligibility were operative mortality (two patients) and not meeting the protocol requirements (five patients). Therefore, 100 patients were evaluated. Twenty patients had stage IIIA disease with more than six positive lymph nodes, 22 had stage IIIB disease, and 58 had stage IV disease. Tables 1 and 2 show the clinical characteristics of the patients. The 58 patients with stage IV disease comprised 47 men and 11 women, with a median age of 66 years (range, 43–84 years), and the 42 patients with stage III disease comprised 33 men and nine women, with a median age of 64 years (range, 37–83 years). The median follow-up time was 20.1 months.

Survival of Patients with Stage IV Disease The survival curve for patients with stage IV disease is shown in Fig. 1. The median survival time of patients with stage IV disease was 18 months (95% confidence interval [CI], 4.6 to 31.4). The 1-year survival rate was 68.7% (95% CI, 62.2% to 75.2%), and the 3-year survival rate was 30.6% (95% CI, 22.9% to 38.3%). Forty-seven patients had unresectable gastric cancer, and their median survival time was 15 months (95% CI, 9.4% to 20.6%).

Survival of Patients with Stage III Disease The survival curve for patients with stage III disease is shown in Fig. 2. Median survival time in patients with stage IIIA disease

Table 1 Characteristics of patients with stage IV gastric cancer (n=58)

Characteristic	Number of patients (%)
Sex	
Male	47 (81)
Female	11 (19)
Age (years), median (range)	66 (43–84)
Tumor stage	
T3	24 (41)
T4	34 (59)
Metastasis site	
Lymph nodes	28 (48)
Liver	13 (22)
Peritoneal	15 (26)
Other	5 (9)
Curability	
R0	11 (19)
R1 and 2	47 (81)
Relapse	
Yes	7 (64)
No	4 (34)

was not reached, and the survival rate was 100% at 1 year and 68.4% (95% CI, 54.8% to 82.0%) at 3 years. Median survival time in patients with stage IIIB disease was 32 months (95% CI, 9.7 to 54.3), and the survival rate was 100% at 1 year and 46.6% at 3 years (95% CI, 29.5% to 63.7%).

Table 2 Characteristics of patients with stage III gastric cancer (n=42)

Characteristic	Number of patients (%)
Sex	
Male	33 (83)
Female	9 (17)
Age (years), median (range)	64 (37–83)
Cancer stage, Japanese classification	
Stage IIIA with more than six positive lymph nodes	20 (48)
Stage IIIB	22 (52)
Tumor stage	
T2	11 (26)
T3	28 (67)
T4	3 (7)
Nodal stage, Japanese classification	
N1	11 (26)
N2	31 (74)
Relapse	
Yes	24 (57)
No	18 (43)

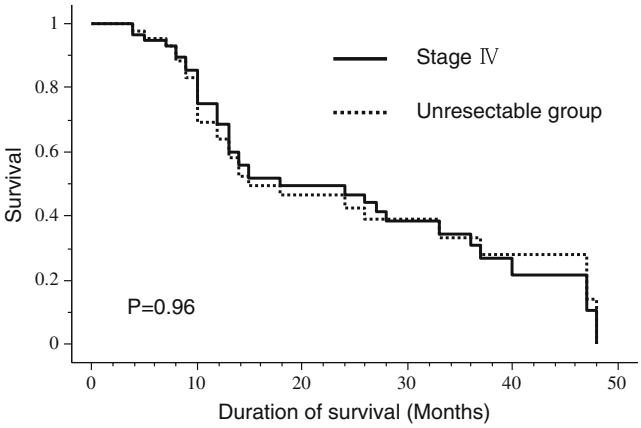

Fig. 1 Kaplan–Meier curves of overall survival of stage IV patients

Adverse Events The incidence of grade 3 or 4 adverse events was 14% for the study group as a whole. There were no treatment-related deaths. The most frequent adverse event of grade 3 or 4 was leukopenia (8%). Other common adverse events were thrombocytopenia (17%), anemia (22%), nausea (41%), vomiting (17%), and fatigue (13%). Most of these events were grade 1 or 2 (Table 3).

Site of Relapse A total of 31 patients had postoperative relapses (Table 4). Relapse occurred in 12 patients with stage IIIA disease who had more than six positive lymph nodes (relapse rate, 60%), 12 patients with stage IIIB disease (relapse rate, 54.5%), and 7 patients with stage IV disease after R0 operation (relapse rate, 63.6%). Peritoneal and lymph node relapses were significantly more common than hematogenous relapses (P<0.05).

Antitumor Efficacy Of the 54 patients who had measurable tumors, no patient had a complete response, and 29 had partial responses. As shown in Table 5, the response rate was 54% (95% CI, 40.0 to 67.3). The response rate according to the tumor site was 75% for primary lesions,

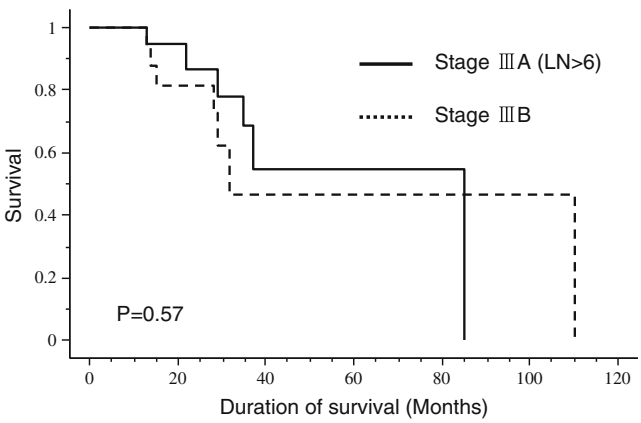

Fig. 2 Kaplan–Meier curves of overall survival of stage III patients

Table 3 Adverse events associated with S-1 plus low-dose cisplatin (n=100)

Event	Number of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukopenia	14	8	6	2	8
Anemia	17	5	3	0	3
Thrombocytopenia	12	5	2	0	2
Nausea	33	8	1	0	1
Vomiting	14	3	0	0	0
Diarrhea	7	4	0	0	0
Fatigue	11	2	0	0	0
Anorexia	5	2	0	0	0
Fever	5	2	0	0	0

Grades of adverse events were classified according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (NCI-CTC)

52% for lymph node metastases, 38% for hepatic metastases, and 40% for others.

Discussion

Previous phase III trials in patients with advanced gastric cancer reported that median survival time was 10.5 months with capecitabine plus cisplatin,[8] 9.2 months with docetaxel plus cisplatin plus fluorouracil,[7] and 11.2 months with capecitabine plus oxaliplatin plus epirubicin.[9] In the Japan Clinical Oncology Group (JCOG 9912) study, median survival time was 11.4 months with S-1 alone.[21] There was no significant difference between fluorouracil alone and S-1 alone, and irinotecan plus cisplatin was not better than fluorouracil alone. In 2008, the SPIRITS trial reported that median survival time was significantly longer in patients assigned to S-1 plus cisplatin (13.0 months) than in those assigned to S-1 alone (11.0 months).[10] This study was the first to show longer than 1-year median survival

Table 4 Sites of relapse

Site	Number of patients (%)			
	Stage IIIA (LN >6)	Stage IIIB	Stage IV after R0 operation	P value
Peritoneal	2	2	2	0.042
Lymph nodes	3	7	2	0.009
Hematogenous	7	3	3	
Total number of relapses (%)	12 (60)	12 (55)	7 (64)	

Peritoneal and lymph node relapses were significantly more common than hematogenous relapses

Table 5 Response of evaluable lesions to S-1 plus low-dose cisplatin therapy

Site of lesion	CR	PR	NC	PD	Response rate (%)
Overall	0	29	20	5	29 (54)
Primary lesion	0	9	2	1	9 (75)
Liver	0	3	4	1	3 (38)
Lymph nodes	0	15	11	3	15 (52)
Others	0	2	3	0	2 (40)

time. The incidence of adverse events was higher in the S-1 plus cisplatin group than in the S-1 alone group, but was lower than the incidences reported for capecitabine plus cisplatin,[8] docetaxel plus cisplatin plus fluorouracil,[7] and capecitabine plus oxaliplatin plus epirubicin.[9] These findings suggested that S-1 plus cisplatin therapy might be a standard first-line treatment for advanced gastric cancer in Japan.

Several clinical trials have shown that adjuvant chemotherapy is effective for the management of advanced gastric cancer, but conflicting results have also been obtained. Although the JCOG 8801 study demonstrated no benefit of adjuvant chemotherapy,[22] the INT-0116 study and the MAGIC trial showed that such therapy is effective.[11,12] The INT-0116 study reported the prolongation of median survival time and relapse-free survival in patients who received chemoradiotherapy after D0 or D1 surgery. The MAGIC trial showed that perioperative and postoperative therapy with epirubicin plus cisplatin and fluorouracil significantly prolonged median survival time and relapse-free survival, although most patients underwent D1 surgery. In 2005, a study performed in Japan by the National Surgical Adjuvant Study Group for Gastric Cancer (N-SAS-GC) reported that adjuvant therapy with uracil-tegafur (UFT) after D2 surgery was effective.[23] Moreover, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study has shown that S-1 alone is effective as adjuvant therapy in patients who undergo curative resection.[13] The most common adverse events of grade 3 or 4 as compared with surgery alone were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%). S-1 has thus been shown to be useful as adjuvant therapy after curative surgery in Japan.

As for S-1 plus cisplatin therapy, Koizumi et al. recommended that cisplatin 60 mg/m^2 should be given on day 8 of a 35-day cycle and obtained a response rate of 73.7% with this regimen.[18] Hyodo et al. administered cisplatin at a dose of 20 mg/m^2 on days 1 and 8 of a 21-day cycle and reported a response rate of 61.1%.[24] Iwase et al. gave cisplatin (70 mg/m^2) as a 24-h intravenous infusion on day 8 of a 28-day cycle to reduce the incidences of nausea and vomiting.[25] They obtained a response rate of 50%, and the incidence of grade 3 or 4 adverse events was 10%. Tsuji

et al. evaluated the efficacy of S-1 combined with low-dose cisplatin therapy (6 mg/m^2 2 days per week). The response rate was 78.1%, with no grade 3 or 4 nausea or vomiting.[26] The advantages of low-dose cisplatin were a reduced risk of toxicity-related renal failure, no need for hydration, and lower incidences of nausea and vomiting. As compared with high-dose regimens of cisplatin, low-dose cisplatin appears to be equally effective, with a lower risk of adverse events.

The Japanese Gastric Cancer Association classifies lymph node metastasis into four categories (N1, N2, N3, and M) based on the location of involved lymph nodes. In contrast, the nodal staging of the fifth edition of the UICC TNM classification is based on the number of metastatic lymph nodes. Chang et al. reported that the fifth edition of the UICC nodal staging was associated with more homogeneous survival for a given stage of disease than was the fourth edition, which was based on the site of metastasis.[27] The results of the present study suggest that patients with stage IIIA disease who have more than six positive lymph nodes have an increased risk of relapse, as compared with stage IIIA patients as a whole.

We evaluated the efficacy and safety of an alternating regimen of S-1 plus low-dose cisplatin and S-1 alone in 100 patients with advanced gastric cancer, including adjuvant therapy after curative surgery. In patients with stage IV disease, median survival time was 18 months. Forty-seven patients had unresectable gastric cancer, and their median survival time was 15 months. These results were similar to those of the SPIRITS trial. Moreover, in patients with stage III disease, survival rates at 1 and 3 years were 100% and 68.4% in patients with stage IIIA disease who had more than six positive lymph nodes and 100% and 46.6% in those with stage IIIB disease, respectively. Survival rates at 1 and 3 years according to the criteria of the Japanese Gastric Cancer Association were 85.8% and 66.1% in patients with stage IIIA disease and 72.6% and 30.9% in those with stage IIIB disease, respectively. Our results suggest that the effectiveness of an alternating regimen of S-1 plus low-dose cisplatin and S-1 alone is not inferior to that of conventional S-1 plus cisplatin in patients with unresectable or recurrent gastric cancer. To our knowledge, this is the first report to document the efficacy of S-1 plus cisplatin as adjuvant therapy for advanced gastric cancer.

We used a 15-week cycle consisting of alternating regimen of S-1 plus low-dose cisplatin and S-1 alone to reduce the incidence of adverse events and the duration of hospitalization. Most adverse events were grade 1 or 2. The incidence of grade 3 or 4 adverse events was less than 10%, and nausea (1%) and vomiting (0%) were especially uncommon. The incidence of severe toxic effects with our regimen was lower than that in previous studies of high-dose cisplatin.

Conclusion

In conclusion, we believe that an alternating regimen of S-1 plus low-dose cisplatin and S-1 alone is an effective adjuvant treatment for patients with curatively resected stage III gastric cancer.

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ORIGINAL ARTICLE

Small Bowel Adenocarcinoma in Crohn's Disease

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Abstract
Background An association between small bowel adenocarcinoma and Crohn's disease (CD) is well-established. We present our recent experience with this entity in order to further elucidate its clinicopathological features and update our series from 1991.
Methods A retrospective review was undertaken of all surgical patients with small bowel adenocarcinoma and CD seen at our institution between 1993 and 2009. Follow-up was assessed until time of death or by interview with survivors. Survival was calculated based on TNM (tumor extent, lymph node status, metastases staging) staging and comparing between our current and previous series.
Results Twenty-nine patients (ten females and 19 males) were identified and followed for a median of 2 years. The median age at onset of CD symptoms was 25, and the median age at cancer diagnosis was 55.4, for a mean interval of 25.3 years. Twenty-two cancers were ileal and five were jejunal. There were no cancers in excluded intestinal loops. Significant differences in 2-year survival were determined for: node-negative (79.3%, 95%CI 58.3–100%) versus node-positive cancers (49% %, 95%CI 20.0–78.0%), and for localized (92.3%, 95%CI 77.8–100%) versus metastatic disease (33.3%, 95%CI 6.6–60%). Overall 36-month survival was 69.3% (95%CI 51.5–87.1%) compared to 40% among those without excluded loops in our series from 1991. Sixteen patients had long periods of quiescent disease before diagnosis (7–45 years), and 16 required surgery for bowel obstruction that was refractory to medical management. Adequate information was not retrievable for three patients.
Conclusions A comparison to our previous series reveals similar clinical characteristics and a high rate of node-positive cancer at diagnosis. Our findings also confirm two important clinical indicators of malignancy: recrudescent symptoms after long periods of relative quiescence and small bowel obstruction that is refractory to medical therapy.

Keywords Crohn's disease · Small bowel adenocarcinoma

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Introduction

Small bowel adenocarcinoma is a well-described complication of Crohn's disease. An association between small bowel cancer and Crohn's disease was first reported by Ginzburg[1] in 1956 and has since been described in numerous case reports and reviews. A meta-analysis of eight population and hospital-based studies showed a relative risk of 33.2 compared to the general population.[2] Still, it is a relatively rare complication of Crohn's disease, with an estimated cumulative risk of only 2.2% after 25 years of regional ileitis.[3]

Small bowel adenocarcinoma remains a diagnostic challenge in Crohn's disease. Its presentation is both varied and non-specific. Signs include obstructive symptoms such as nausea, vomiting, and abdominal pain; constitutional manifes-

tations such as weight loss; or even acute complications like hemorrhage or perforation.[3,4] These symptoms are not easily distinguished from exacerbations of Crohn's disease. Often, preoperative investigation may reveal an intestinal mass, but a high-index of suspicion would be needed to suspect malignancy rather than the more common complications of Crohn's disease, such as abcesses and inflammatory masses.[4,5] This diagnostic difficulty contributes to the fact that nearly 30–35% of small adenocarcinomas diagnosed in patients with Crohn's Disease are stage IV by the time of diagnosis.[6,7]

In this study, we describe 29 patients with small bowel adenocarcinoma complicating Crohn's disease in order to further characterize the clinicopathologic features of this lethal entity and to update a previous series from our institution published in 1991.[5]

Material and Methods

A retrospective review was conducted of all patients identified with small bowel adenocarcinoma complicating Crohn's disease from January 1, 1993 to December 31, 2009. The terms "Crohn's," "carcinoma," and "adenocarcinoma" were used to search the GI Pathology database of Mount Sinai Hospital (PowerPath® system, Mount Sinai GI Pathology database). Inpatient and outpatient charts of all selected cases were then individually reviewed, and standardized clinical and pathologic information was tabulated. These data included medical and surgical history, treatment modalities and hospitalizations for Crohn's disease, clinical presentation and indications for surgical intervention, pathologic (TNM) staging of small bowel cancer, and postoperative chemotherapy. Patients who were included in the previous case series from this institution[5] were excluded, as were patients with small bowel cancers other than adenocarcinoma.

Long-term follow-up was conducted by telephone interview using a standardized questionnaire. Patients were followed until death or last date of follow-up. The study was approved by the Institutional Review Board of Mount Sinai School of Medicine (GCO no. 08-0436).

The Kaplan–Meier method was used to estimate survival curves for patients categorized by TNM. The log-rank test was used to calculate differences in survival among groups and to compare overall survival between patients from this series and those from the original 1991 series, which included 19 patients from 1960 to 1989.

Results

Twenty-nine patients were identified who met the inclusion criteria. Nineteen (65.5%) were male. Clinical characteristics of the patients are shown in Table 1. The median age at diagnosis of Crohn's disease was 25 (range 13–63). The median age at diagnosis of small bowl adenocarcinoma was 55.4, yielding a median interval for progression to cancer of 25.3 years. Median follow-up time after diagnosis of SBA was 2.1 years (range 0.6–14.9).

Indications for surgery, operative procedure, and TNM staging are shown in Table 2. Five patients had jejunal tumors, 22 had ileal tumors, and in two cases, the location of the primary tumor was not clear from pathology reports. There were no cancers in excluded intestinal loops. Cumulative survivals based on node and metastatic status are shown in Figs. 1 and 2. A comparison of overall survival between patients from this series and those from our 1991 series, including bypassed intestinal loops, is shown in Fig. 3.

Overall 36-month survival for our present series was 69.3% (95%CI 51.5–87.1%). While this survival finding

Table 1 Clinical characteristics of patients with small bowel adenocarcinoma complicating Crohn's disease

Patient	Sex	Age at CD diagnosis	Age at surgery	Progression to cancer (years)	Follow-up (years)	Outcome
1	F	21	49	28.9	1.2	Alive
2	M	21	54	33.4	3.5	Dead
3	M	19	55	36.4	6.9	Dead
4	M	27	78	51.3	1.4	Dead
5	F	48	73	25.0	10.7	Alive
6	F	33	61	28.3	0.9	Dead
7	M	25	59	34.2	2.1	Alive
8	F	26	45	19.0	0.5	Dead
9	M	17	40	23.5	14.2	Alive
10	M	16	35	19.6	2.1	Alive
11	M	14	22	8.1	0.8	Dead
12	M	46	81	35.3	3.0	Dead
13	M	25	53	28.2	1.9	Alive
14	F	16	61	45.9	0.8	Alive
15	F	42	58	16.2	14.9	Alive
16	F	21	46	25.3	5.9	Dead
17	M	16	49	33.4	0.7	Dead
18	M	Unk	68	68.9	1.7	Dead
19	M	45	59	14.1	0.6	Alive
20	M	16	41	25.2	9.6	Alive
21	F	49	51	2.7	0.7	Alive
22	M	42	70	28.0	8.8	Alive
23	F	63	68	5.1	12.2	Alive
24	M	21	38	17.0	2.9	Dead
25	M	22	72	50.6	0.9	Dead
26	M	34	49	15.4	3.3	Alive
27	F	49	69	20.4	1.5	Dead
28	M	13	45	32.1	2.7	Alive
29	M	59	59	0.8	1.1	Dead

Unk unknown

Table 2 Surgical indication, staging, and clinical indicators of progression to cancer in patients with small bowel adenocarcinoma complicating Crohn's disease

Patient	Indication for surgery	Procedure	Stage at diagnosis	T	N	M	Cancer-directed surgery	Long quiescent period	Obstruction refractory to MM
1	Obstruction	ICR	3	4	2	0		Yes	Yes
2	Obstruction	SBR	4	4	0	1		Yes	
3	Peritoneal Implants	Secondary ICR	2	3	0	0			
4	Obstruction	ICR	4	4	2	1			Yes
5	Obstruction	Secondary ICR	1	2	0	0			Yes
6	Obstruction	ICR	4	3	2	1		Yes	Yes
7	Obstruction	Secondary ICR	3	4	2	0	Yes	Yes	
8	Fistula, Abcess	SBR	4	3	X	1			
9	Obstruction	SBR	2	3	0	0			Yes
10	Obstruction	SBR	1	1	0	0		Yes	
11	Hemorrhage	SBR	4	3	2	1	Yes		
12	Obstruction	ICR	4	3	1	1			Yes
13	Obstruction	ICR	2	4	0	0		Yes	Yes
14	Obstruction	ICR, SBR	3	3	1	0		Yes	
15	Obstruction	ICR	2	3	0	0		Yes	Yes
16	Obstruction	ICR	2	3	0	0		Yes	
17	Obstruction	ICR	4	4	1	1			Yes
18	Obstruction	ICR	2	3	X	0	Yes		Yes
19	Obstruction	ICR	2	3	0	0		Yes	
20	Obstruction	ICR	3	4	2	X	Yes		Yes
21	Obstruction	ICR	1	1	0	0		Yes	
22	Unknown	Secondary ICR	1	1	0	0			
23	Fistula, Abcess	ICR, FR	2	3	0	0			
24	Obstruction	SBR	4	3	1	1		Yes	Yes
25	Obstruction	SBR	4	4	1	1		Yes	Yes
26	Obstruction	Secondary ICR	2	3	0	0		Yes	Yes
27	Obstruction	ICR	4	3	0	1		Yes	Yes
28	Obstruction	SBR	4	3	1	1		Yes	Yes
29	Obstruction	ICR	3	3	2	1			

MM Medical Management, *ICR* ileocolic resection, *SBR* small bowel resection, *FR* fistula repair

was significantly ($p=0.024$) different from our overall 1991 cohort, there was no significant difference ($p=0.146$) when bypassed intestinal loops were omitted from analysis of the earlier series (Fig. 4). Not unexpectedly, significant differences in a 2-year survival were observed for node-negative (79.3%, 95%CI 58.3–100%) versus node-positive cancers (49%, 95%CI 20.0–78.0%) and for localized (92.3%, 95% CI 77.8–100%) versus metastatic disease (33.3%, 95%CI 6.6–60%). However, we did not find an independent association between depth of tumor involvement (T stage) and survival.

Four of the 29 patients had cancer-directed surgeries for confirmed adenocarcinoma, while the remaining 25 were discovered only postoperatively. The most common indication for surgery was a worsening of obstructive symptoms, which was present in 24 patients (85.2%). Of these, 16 (55.2%) were hospitalized for complete small bowel obstruction which was refractory to medical management. Sixteen patients (55.2%) were also found to have a "quiescent period" of disease activity before a sudden recurrence of symptoms. Only three patients in this series did not have refractory obstruction or a period of quiescent disease before diagnosis of small bowel adenocarcinoma. In three other cases, this information was not retrievable through telephone interviews or chart review.

Discussion

These 29 patients represent one of the largest single-institution series of small bowel adenocarcinoma in Crohn's disease. In previously reported series, including our own,

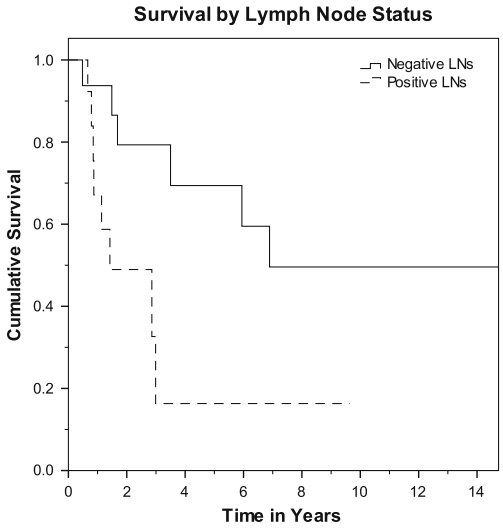

Fig. 1 Kaplan–Meier survival curve based on node-negative (AJCC stages 1and 2) versus node-positive (AJCC stages 3 and 4) small bowel adenocarcinoma in Crohn's disease

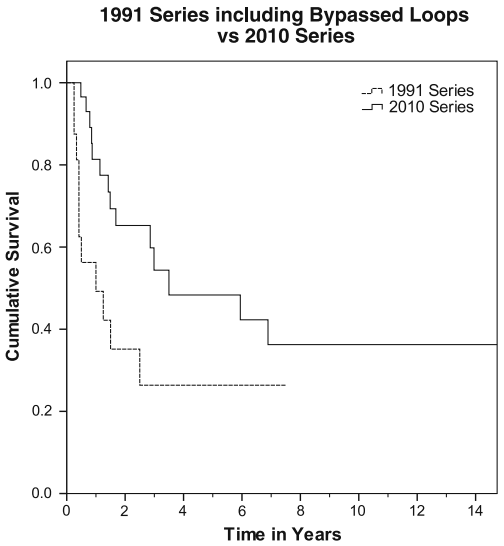

Fig. 3 Kaplan–Meier survival curve between our previous and current series including patients with bypassed intestinal loops from the 1991 series

small bowel adenocarcinoma complicating Crohn's disease had characteristic clinical features: distal location, younger age at time of diagnosis, and male predominance.[2,3,5,8] Seventy-five percent of cancers arose in the terminal ileum, a location that accounts for only 13% of tumors in sporadic small bowel adenocarcinoma.[9] Patients with Crohn's disease also develop small bowel adenocarcinoma at an average age of 48 versus 65 in the general population, with a male-to-female ratio approaching 3:1.[3,7,8,10]

The clinical characteristics of patients in this current series do not differ significantly from those previously reported, with respect to age of disease onset (55.4) and male-to-female ratio (2:1). Our present observations also confirm the poor prognosis associated with node-positive and metastatic cancers (Figs. 1 and 2).

Similarly, we found no significant difference in a 36-month survival between patients in this series and those from our 1991 series, when bypassed intestinal loops were excluded from the analysis. Survival rates for bowel adenocarcinoma complicating Crohn's disease have traditionally been lower compared to sporadic small bowel cancers, with a 2-year survival of as low as 9% in one series.[5,8,11,12] One reason for this difference is the presence of excluded intestinal loops in those patients who have

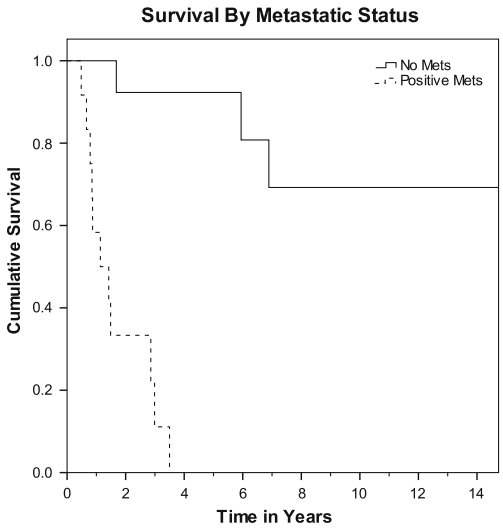

Fig. 2 Kaplan–Meier survival curve according to M stage based on AJCC, 7th ed.

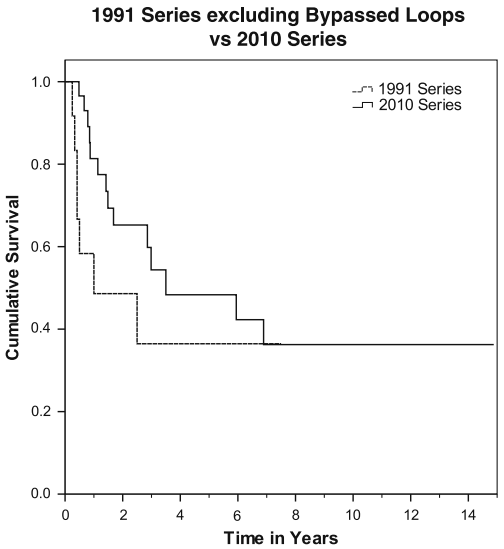

Fig. 4 Kaplan–Meier survival curve based on our previous and current series excluding patients with bypassed intestinal loops from the 1991 series

undergone diversionary surgery. As first reported by Greenstein and Janowitz,[12] and substantiated by multiple subsequent studies, cancers in bypassed intestinal loops show a trend towards shorter survival than cancers in-continuity.[8,13,14] As this surgical procedure has largely been abandoned, however, the difference in prognosis for small bowel cancer complicating CD and sporadic cancers may be diminishing.[8]

Indeed, the poor overall prognosis of small bowel adenocarcinoma may possibly be improving.[11] The primary treatment approach for these tumors is surgical, with radical resection portending an improved prognosis.[15] With metastatic disease or incomplete resections, there is a clear role for chemotherapy based on 5-FU or a platinum analog-based combination.[16,17] Average overall survival with metastatic disease has increased from 9–11 months to 17–20 months.[18]

Advances in imaging may also have contributed to this improvement. Traditional techniques could not provide adequate assessment of the small bowel mucosa. Both CT and small bowel follow-through may miss small tumors and in situ dysplasia. Endoscopy is limited by the length of the small bowel, and video capsule endoscopy presents challenges in the localization of lesions and visualization in the setting of a poor bowel preparation. Double-balloon endoscopy is the newest tool to be utilized and provides opportunity for both diagnosis and intervention with a high degree of success.[19]

Only a small minority of our patients (13.8%) were diagnosed with SBA preoperatively. Even worse, according to a large review by Dosset et al.[3] in 2006, a mere 3.1% of patients were diagnosed preoperatively. With nearly 38% of patients having metastatic disease and 55% node-positive by the time of diagnosis, these dismal figures suggest the need for a practical means of distinguishing cancer from an ordinary exacerbation of Crohn's disease.

With the exception of three cases, data concerning preoperative symptoms and hospital course were available for all of our patients via medical chart documentation or telephone interviews. Two clinical indicators of small bowel adenocarcinoma were identified in 24 patients: intestinal obstruction that was not relieved by medical management or a period of quiescent disease prior to the onset of severe symptoms meriting hospitalization. The near unanimity in patient reporting of one or both of these clinical scenarios suggests their importance as potential indicators of progression to small bowel adenocarcinoma.

The recognition of these clinical indicators of progression to cancer has the potential to achieve two goals: the diagnosis of small bowel adenocarcinoma at an earlier stage of disease and an increase in cancer-directed surgeries. In this study, many patients were hospitalized multiple times for refractory small bowel obstruction in the weeks and months leading up to surgery. This delay likely worsened the stage of their cancers at diagnosis.

Conclusion

In conclusion, small bowel adenocarcinoma complicating Crohn's disease continues to be difficult to diagnose. Given the lack of a significant improvement in prognosis for these patients since our last published series in 1991, further studies are needed to elucidate possible screening and treatment modalities for this disease. The identification of clinical indicators of progression to cancer is a first step in this process, as it may lead to earlier diagnosis and an increase in cancer-directed surgery.

Competing Interests The authors have no competing interests or financial affiliations to report.

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ORIGINAL ARTICLE

Doppler-Guided Hemorrhoidal Artery Ligation: The Experience of a Single Institution

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Abstract
Purpose This study aims to review the short-term recurrence and complications of Doppler-guided hemorrhoidal artery ligation (DG-HAL) with mucopexy.
Methods Approval was obtained for a retrospective chart review of patients who underwent DG-HAL from January 2007 to June 2009. A treatment failure was recorded if internal hemorrhoids were noted at follow up or symptoms persisted. All recurrences were assessed for predictive factors.
Results The procedures were performed by four surgeons. Ninety-six patients were included. The average age was 63.5 years (21–81 years). The mean follow up was 15 months (3–35 months). Of the patients, 93 (96.8%) reported bleeding pre-operatively. Mucopexy accompanied DG-HAL in 87 (90.6%). Postoperative complications occurred in nine (9%) patients. Residual hemorrhoids were evident in 20 (21%) patients, 13 of whom required further management for symptomatic disease, five with DG-HAL. Fifty percent (10/20) and 70% (9/13) of the recurrences necessitating further treatment transpired during the first 20 procedures of each surgeon. All 13 symptomatic recurrences demonstrated large, circumferential internal hemorrhoids.
Conclusions DG-HAL is a simple procedure with a low complication rate. Recurrences are more frequent during the learning curve. Patients with large, circumferential internal hemorrhoids should be counseled about a possible higher rate of recurrence. DG-HAL can be effectively repeated for recurrences.

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Keywords Hemorrhoids · Arterial ligation · Mucopexy · Recurrence · Circumferential

Introduction

"Hemorrhoids" is a ubiquitous complaint among Americans, indicating symptoms and signs as varied as rectal bleeding, perianal itching, anal pain, prolapse, a sensation of incomplete evacuation, and mucus discharge. After the age of 50 years, approximately 50% of individuals will experience symptoms attributable to hemorrhoidal disease.[1] The true prevalence of hemorrhoidal disease is difficult to gauge but is estimated to range from 4.4% to 36.4%.[2, 3] As many as 1 million Americans are afflicted each year.[1] The standard options to manage hemorrhoidal disease have long included office-based procedures such as sclerotherapy, rubber band ligation, and cryotherapy as well as surgical

hemorrhoidectomy. The emergence of new treatment alternatives for hemorrhoidal disease—infrared coagulation, stapled hemorrhoidopexy (PPH), and Doppler-guided hemorrhoidal artery ligation (DG-HAL)—reflects the demand for relatively painless and complication-free surgery as compared to the gold standard of excisional hemorrhoidectomy, while preserving its efficacy.

The Doppler-guided hemorrhoidal artery ligation, introduced in 1995 by Moreigna et al., presents another choice in the surgical armamentarium against hemorrhoidal disease. This method involves the suture ligation of the terminal branches of the superior rectal arteries as identified via a proctoscope equipped with a Doppler device.[4] The interruption of the arterial supply reduces the arteriovenous pressures within the anal cushions, leading to the diminution—"decongestion"—of the blood vessels and to the reconstitution of the fibromuscular scaffolding.[5, 6] In the initial study from Morinaga et al.,[4] the recurrence rate was 2.6% among 116 patients after a follow up of 5–12 months, with no complications recorded. To improve the incidence of recurrent hemorrhoidal prolapse, particularly for grade III and IV disease, the technique was further modified in 2002 to add the suture plication of the enlarged internal hemorrhoids within the anal canal, known as mucopexy, anopexy, or rectoanal repair.[5–8]

This retrospective review reports the short-term recurrence rates and complications of Doppler-guided hemorrhoidal artery ligation with and without mucopexy in a single institution.

Methods

IRB approval was obtained for a retrospective chart review of the electronic medical records of all patients who underwent hemorrhoidal artery ligation with and without mucopexy between January 2007 and June 2009 at the Cleveland Clinic Foundation, Cleveland, OH, USA. The electronic medical record was accessed for various data: patient demographics, preoperative symptoms and their duration, previous treatment of hemorrhoidal disease, and the extent of the internal hemorrhoidal disease. The indications for which the procedure was offered included rectal bleeding; anal pain, itching, or burning; internal hemorrhoidal prolapse; and/or failure of previous treatments. Grade IV internal hemorrhoids were not treated with this method. Among the operative data that was gathered was the date of surgery, the length of the procedure, the addition of a mucopexy, the inclusion of a concomitant procedure, and the performance of an anal block. The exact timing of the post-operative follow-up visits was at the discretion of the individual surgeon; such visits were generally arranged between 4 and 6 weeks after surgery. Additional office visits were scheduled as dictated by the patients' post-operative course. The post-operative follow-up period, complications, recurrences, and the method of management for the recurrences were recorded. The entire electronic medical record was also queried for recurrent hemorrhoidal symptoms following the procedure for which the patient sought treatment with other providers, including their primary care physician. A treatment failure was reported if recurrent or residual internal hemorrhoids of any size were noted on follow-up anoscopic examination or if the pretreatment symptoms persisted or recurred. All recurrences were further assessed for possible predictive factors.

Nominal variables were expressed as numbers and percentages. Parametric data was presented as means and non-parametric data as medians and ranges.

Procedure

The four surgeons performed the procedure in the same manner. In all cases, the procedures were done with the patient in the lithotomy position under general anesthesia. The patients were given pre-operative enemas in the absence of a concurrent colonoscopy. The four surgeons utilized the Doppler-guided hemorrhoidal artery ligation/rectoanal repair (DG HAL-RAR®) system (A.M.I. Agency for Medical Innovations, Natick, MA, USA). The disposable proctoscope, lubricated with ultrasound gel, is inserted into the anus, with the Doppler transducer (8.2 Mhz frequency) initially directed towards the posterior midline.[9] The proctoscope is rotated until a Doppler signal from a terminal branch of the superior rectal artery is obtained. The strength of the Doppler signal, as displayed on the instrument screen, indicates the depth of the artery; the terminal branches typically are found between 4.5 and 5.5 mm. A 2–0 absorbable suture—Vicryl (Ethicon, Somerville, NJ, USA) on a UR-6 needle—is then placed through the ligation window of the proctoscope, located proximal to the transducer, in a figure-of-eight fashion, approximately 2–3 cm proximal to the dentate line.[9, 10] The Doppler signal is lost once the suture is tied down, indicating successful ligation of the artery. The mucopexy involves placement of a running 2-0 absorbable suture—introduced to the depth of the mucosa and submucosa—from the proximal to distal aspect of the prolapsing internal hemorrhoid, avoiding the dentate line. Securing the suture in a cranial direction lifts and fixes the prolapsing tissue within the anus. A second revolution of the proctoscope is completed to ensure the loss of a Doppler signal.

Results

The procedures were performed by four colorectal surgeons who had been trained in the technique, with two surgeons

responsible for 66% of the surgeries. Ninety-six patients, 39 of whom were male, were included in the review. The average age was 63.5 years (range, 21–81 years). The mean length of follow-up was 15 months (range, 3–35 months).

Preoperatively, 93 (96.8%) patients complained of rectal bleeding. Additional preoperative symptoms involved internal hemorrhoidal prolapse (n=38), pain (n=21), itching (n=7), anemia (n=1), and thrombosis (n=1). The duration of these symptoms varied from 1 week to "many years," with 50% of the patients claiming to have experienced symptoms for more than 5 years. The pre-operative Goligher grade was not universally recorded; however, 40% of the patients had grade II to III internal hemorrhoids. Twenty-six patients underwent prior treatment for rectal bleeding: rubber band ligation (n=15), excisional hemorrhoidectomy (n=4), and PPH (n=3). Four patients had multiple prior interventions for management of their hemorrhoidal disease. All patients were offered a trial of fiber supplementation prior to surgery.

The total anesthesia time lasted from 45 to 150 min, with an average of 64 min. The total anesthesia time included concurrent procedures in 20 patients (21%): colonoscopy (n=5), anal canal biopsy (n=2), anal polypectomy (n=2), fissurectomy (n=1), Botox injection for anal fissure (n=1), and proctoscopy (n=1), with the most common being skin tag excision for the patients' cosmetic concerns (n=7). The number of ligations was not universally recorded but, where noted, ranged from seven to 13. In the majority of patients—87 (90.6%)—a mucopexy accompanied the hemorrhoidal artery ligation; mucopexy was performed if redundant hemorrhoidal tissue was identified. Sixteen patients, all of whom were operated upon in the early period of the study, did not receive an anal block for post-operative pain control.

Post-operative complications occurred in nine (9%) patients, among which were bleeding (n=3), anal pain (n=2), anal fissure (n=2), and urinary retention (n=2). A 58-year-old male with rectal bleeding resulting in symptomatic anemia underwent an excisional hemorrhoidectomy on post-operative day 7. Another patient with post-operative bleeding was treated with desmopressin acetate for her known von Willebrand's disease, while a third patient, with a suspected coagulopathy, had an operative ligation of a mucopexy site on post-operative day 11. One patient with post-operative pain—a 26-year-old female with anal pain, prolapse, and bleeding as her presenting complaints—was briefly hospitalized for intravenous narcotics. The other patient with self-limited, severe post-operative pain—a 42-year-old woman with pre-existing pain and bleeding—was noted to have a hematoma during the DG-HAL. A patient with a suspected acute fissure returned to the operating room for a two quadrant excisional hemorrhoidectomy, with the "fissure" determined to be a superficial mucosal tear that required only cauterization; the other patient with an actual fissure was managed conservatively with topical applications. The two instances of urinary retention resolved after placement of a foley catheter; both patients had unrecognized pre-operative urinary symptoms consistent with benign prostatic hypertrophy.

Recurrent or residual internal hemorrhoids were identified in 20 (21%) patients over the mean follow-up period of 15 months. An anoscopic examination at a post-operative visit revealed identifiable internal hemorrhoidal tissue, no matter the size, in these 20 patients. Seven of these 20 patients reported no symptoms consistent with internal hemorrhoidal disease and received no further treatment. In 13 (65%) of these 20 patients, the recurrent or residual internal hemorrhoids were symptomatic—with eight patients experiencing recurrent or persistent bleeding and five prolapse—requiring further intervention: office rubber band ligation (n=6), repeat hemorrhoidal artery ligation with mucopexy (n=5), and single quadrant excisional hemorrhoidectomy (n=2). These reinterventions were performed between 3 and 23 months post-operatively, with a mean of 10.9 months. Prolapse was one of the initial pre-operative presenting complaints in five (38.6%) of these 13 symptomatic patients. Three of the 13 patients who had a symptomatic recurrence that necessitated further treatment did not undergo a mucopexy; two of these three patients had a repeat DG-HAL with mucopexy while the third patient had rubber band ligation. After the redo DG-HAL/RAR, one of the five patients needed rubber band ligation of one small remaining internal hemorrhoid to rectify her symptoms. A second patient was managed with biofeedback for a pre-existing evacuation disorder following the redo DG-HAL/RAR, with resolution of her symptoms. By the time of their last follow-up visit, all 13 patients who had further therapy for their hemorrhoidal disease after DG-HAL were free of symptoms. The recurrence rate in those 87 patients who had a mucopexy was 11.5%. Fifty percent (10/20) of the recurrences and, in particular, 70% (9/13) of the recurrences leading to additional measures occurred during the first 20 procedures of each of the surgeons. Thirteen of the 20 recurrences (65%) developed in patients with internal hemorrhoids that had been described as large and circumferential in the operative note.

Discussion

Since its introduction in 1995, the Doppler-guided hemorrhoidal artery ligation has been pursued by physicians and patients alike as an alternative to more invasive techniques, with their attendant pain, prolonged recovery, and potential complications. Mucopexy is a more recent modification of the procedure, with few small series detailing their results.[5, 8] Like

rubber band ligation, this method interrupts the arterial blood supply to the internal hemorrhoids, albeit in a targeted manner. Ultimately, ligation of the artery produces a reduction in the bulk of the hemorrhoidal tissue while allowing for the reconstitution of the connective tissue scaffolding.[11] Akin to the stapled hemorrhoidopexy, a concomitant mucopexy restores the prolapsed tissue to its normal anatomic position, yet avoiding the possible severe complications of a circumferential mucosal resection. The mucopexy further creates a fibrotic reaction that fixes the mucosa to the rectal wall.[5]

Early studies of their vascular anatomy suggest that the anal cushions are supplied by an average of five terminal branches of the superior rectal artery.[12] The middle rectal artery, but generally not the inferior rectal artery, variably contributes to the hemorrhoidal arterial inflow.[1] With color Doppler ultrasound, Meintjes mapped the terminal branches to the right posterolateral, right midlateral, right anterolateral, left midlateral, and left posterolateral positions (1, 3, 5, 7, 9, and 11 o'clock in the lithotomy position).[13, 14] Previous reviews report that a median of six to nine sutures (range 4–16) are placed during the DG-HAL procedure to ligate these arterial branches.[5, 6, 8, 9] The authors in the current study did not universally state the number of ligations that were performed; when recorded, the ligations ranged from seven to 13.

Our early experience with the Doppler-guided hemorrhoidal artery ligation yielded an overall success rate of 86.4% after a mean follow up of 15 months. For those 87 procedures that included mucopexy, the success rate improved to 88.5%. Mucopexy extended the total anesthesia time as compared to hemorrhoidal artery ligation alone, as did the addition of a concurrent procedure; other series of Doppler-guided hemorrhoidal artery ligation without mucopexy recorded operative times of 5–50 min.[15] In 20 (21%) patients, recurrent or residual internal hemorrhoids were seen on anoscopic examination at a post-operative visit during the mean 15 months follow-up period; even the presence of small internal hemorrhoids was recorded, despite an absence of symptoms. Of these cases, 13 (65%) were symptomatic, requiring further treatment between 3 and 23 months after the initial surgery. Other studies of Doppler-guided hemorrhoidal artery ligation alone related success rates of 73.5–96% after follow-up intervals varying from 1.5 to 60 months.[8] During a 3-year study period, Faucheron and Gangner recorded a recurrence rate of 12% among 100 patients treated solely with hemorrhoidal artery ligation, presenting at a mean of 12.6 months following surgery.[6] Hemorrhoidal artery ligation, even without mucopexy, demonstrates success rates similar to the 69–97% associated with rubber band ligation.[16–18] Bayer et al. communicated a success rate of 79% for rubber band ligation in 2,697 patients with grade II and III internal hemorrhoids after approximately 1 year of follow up.[19] Repeat rubber band ligations—often in multiple sessions—are pursued in 17–86% of patients, in contrast to an operative procedure such as DG-HAL.[7, 19] There is no study that directly compares rubber band ligation to Doppler-guided hemorrhoidal artery ligation, in particular with an included mucopexy. The authors of this review offer Doppler-guided hemorrhoidal artery ligation with, as appropriate, mucopexy in patients who have failed rubber band ligation; cannot tolerate such an office procedure; or prefer an operative procedure.

In this review, five (38.5%) of the 13 symptomatic recurrences transpired among the 38 patients who initially complained of hemorrhoidal prolapse, for a success rate of 86.8%. The single patient with hemorrhoidal prolapse who did not undergo a mucopexy did not experience a recurrence. The cure rate for hemorrhoidal prolapse treated with HAL/RAR was thus 86.4%. For hemorrhoidal prolapse, the success rate from various studies of hemorrhoidal artery ligation alone was 75–97% over follow-up periods of 11–46 months.[6, 8] After a mean follow up of 46 months, Dal Monte et al.[5] noted a success rate of 92% among 119 patients with internal hemorrhoidal prolapse, with recurrences arising in five patients with grade III and 4 with grade IV internal hemorrhoids. With the incorporation of "anopexy" later in their experience with the procedure, Dal Monte et al.[5] recorded a nonsignificant but improved rate of success in patients with grade III and IV internal hemorrhoids as compared to arterial ligation alone. This review determined that advanced hemorrhoidal disease was correlated with a higher incidence of recurrence. In particular, all 13 patients who experienced a symptomatic recurrence had large and circumferential internal hemorrhoids seen intra-operatively, although the pre-operative Goligher grade was not documented. Despite the good outcomes in several limited reviews of hemorrhoidal artery ligation with mucopexy, those patients with more advanced hemorrhoidal disease should be apprised of a higher probability of recurrent prolapse following surgery. Still, for hemorrhoidal prolapse, the results of hemorrhoidal artery ligation persist over time. The meta-analysis from Giordano et al.[15] concluded that, as opposed to recurrent bleeding and anal pain, the incidence of recurrent hemorrhoidal prolapse did not significantly increase with longer follow up.

During the study period, eight patients presented with recurrent or persistent bleeding that required intervention, for a rate of 8.3%. A meta-analysis of hemorrhoidal artery ligation from Giordano et al.[15] identified a 9.7% incidence of recurrent bleeding 1 year after surgery. Yet, hemorrhoidal artery ligation leads to a marked decrease in the arterial supply to the hemorrhoidal arteriovenous plexus.[20] A significant reduction in blood flow has been detected as long as 6 months after DG-HAL.[16] The basis for recurrent

hemorrhoidal bleeding is a subject of speculation. Meintjes[14] posits that failure to properly ligate the submucosal branches of the superior rectal artery may produce this recurrent bleeding. He also notes that the middle or inferior rectal arteries—seen on color Doppler ultrasound—may provide blood flow to the internal hemorrhoidal tissue despite successful ligation of the terminal branches of the superior rectal artery.[14] Similarly, Jongen and Johannes[18] suggest that ligation of the terminal branches of the superior rectal artery may bring about an enlargement of smaller arteries, thus initiating a recurrence of the hemorrhoidal bleeding. Collateralization of the ligated branches themselves may also play a role in recurrent bleeding over time.[17] Based upon gross and microscopic cadaver studies and transperineal color Doppler ultrasonography, Aigner et al.[10] propose that, in addition to the submucosal branches, terminal transmural branches of the superior rectal artery supply the arteriovenous network of the internal hemorrhoids. These transmural branches—present dorsally and ventrally along the rectal wall in 54% and 34%, respectively, of the transperineal ultrasounds—travel outside the rectal wall, only entering the hemorrhoidal arteriovenous complex as far distal as the levator ani muscle.[10] Suture ligation of the submucosal branches at the more proximal location proscribed by the DG-HAL/RAR device does not address these more distal transmural contributions of the superior rectal artery, particularly those of the posterolateral rectal wall, possibly resulting in persistent or recurrent hemorrhoidal bleeding.[10] Yet, Bursics et al.[11] comment that, even with an excisional hemorrhoidectomy, not all of the terminal branches of the superior rectal artery are ligated, a maneuver which would result in the removal of an excessive amount of anoderm. While hemorrhoidal artery ligation alone may not transfix the more distal transmural branches when in their submucosal position, the multiple, more distal submucosal sutures included in a mucopexy possibly do obliterate these vessels.

This current study detailed a 9% rate of post-operative complications: bleeding (n=3), fissure (n=2), pain (n=2), and urinary retention (n=2). Other reviews report complication rates of up to 22%.[8] Faucheron et al.[6] record a 6% rate of complications among 100 patients treated with hemorrhoidal artery ligation after 3 years of follow up: fissure (n=4), pain (n=1), and dyschezia (n=1). Previous studies specified complications such as bleeding, submucosal hematoma, thrombosis, pain, submucosal fistula, abscess, fecal urgency, anal ulcer, proctitis, and anal fissure. No peri-operative deaths have been noted among the various studies, in contrast to the experience with pelvic sepsis and rubber band ligation. The complication rate attributed to hemorrhoidal artery ligation with mucopexy in the series from Dal Monte et al.[21]—6.4%—does not differ from that of hemorrhoidal artery ligation alone. In the initial review of hemorrhoidal artery ligation, Morinaga et al.[4] remarked upon their concerns regarding post-operative submucosal hematoma, tissue necrosis, or anal fissure—none of which were experienced by their patients—as a consequence of the procedure due to the diminished blood flow. Bursics et al.[11] submit that pain (and fissure) following DG-HAL originates from ischemia due to the multiple ligations. In one patient with severe post-operative pain in this current review, a hematoma was noted at the time of surgery. However, Dal Monte[16] did not perceive ischemic changes on anoscopic exams 1 month following the surgery. Theodoropoulos et al.[8] concluded that mucopexy results in significantly greater post-operative discomfort than ligation alone, likely due to the amount of tissue incorporated into the mucopexy or to an inadvertent incursion onto the dentate line. Both of the patients in this current review who complained of significant pain had mucopexy performed. Yet, Dal Monte did not relate a similar finding in those DG-HAL patients with mucopexy.[16] Acute post-operative hemorrhage possibly arises from a sudden elevated blood flow in terminal branches of the superior rectal artery that were incompletely ligated during the procedure.[22] Felice et al. disclosed one patient who required a transfusion of two units of packed red blood cells due to such hemorrhage.[22] One patient in this current review experienced symptomatic anemia due to post-operative bleeding. A meta-analysis from Gioradno et al.[15] described three patients, one with a coagulopathy, with significant post-operative bleeding. Two patients with post-operative bleeding in this current review similarly had a coagulopathy.

In this current review, 13 of the patients who experienced recurrence or persistence of their symptoms—all of whom had large and circumferential internal hemorrhoids—pursued an additional intervention, five with a repeat DG-HAL. Hemorrhoidal artery ligation was similarly repeated without any complication in 48 of the 308 patients in the series from Scheyer et al. This current review used rubber band ligation in six of the recurrent cases of hemorrhoidal disease, while only two patients needed a formal excisional hemorrhoidectomy. The operative reintervention rate was thus 7.2% in this series, comparable to the 9% reported by Wilkerson et al.[23] in 90 patients after 30 months of follow up. This finding indicates that HAL/RAR likely serves as an alternative between rubber band ligation and the more invasive excisional hemorrhoidectomy and stapled hemorrhoidopexy. Hemorrhoidal artery ligation minimizes the extent of a subsequent excisional procedure, in the event of a symptomatic recurrence. The two patients in this current review who had an excisional hemorrhoidectomy only required removal of a single quadrant. Of the 12 recurrences in the series from Conaghan and Farouk[7], four

patients underwent only single quadrant excisional hemorrhoidectomy with resolution of their symptoms.

Of note, 70% (9/13) of the recurrences that led to further treatment occurred during the first 20 procedures of each of the surgeons, suggesting that the learning curve is rapid. For the surgeon who performed the most procedures, six symptomatic recurrences arose among the 18 cases during the first 15 months of the study period while two transpired among the 26 patients operated upon during the second 15 months. Faucheron and Gangner indicated that the technique may be mastered after three to five procedures, fewer than for the stapled hemorrhoidopexy, while Wilkerson et al. proposed 10 procedures.[6, 23]

The study has various limitations. It is a retrospective review of the experience of four different surgeons. The follow up is relatively short, although comparable to that of previous retrospective reviews. The pre-operative Goligher grade of the internal hemorrhoids was not consistently reported. The post-operative pain scores were not available for these patients.

Conclusions

This study reviews our early experience with hemorrhoidal artery ligation and, in the majority of cases, mucopexy for the treatment of hemorrhoidal disease. It adds to the paucity of data on mucopexy within the literature on Doppler-guided hemorrhoidal artery ligation. HAL/RAR is a simple and safe procedure with a recurrence rate that decreases as the facility of the surgeon grows. The procedure is moreover associated with a low complication rate. Patients with large circumferential internal hemorrhoids should be counseled about a possible higher rate of recurrence that may warrant office or operative reintervention. HAL/RAR can be safely and effectively repeated for such recurrences. The extent of a subsequent excisional hemorrhoidectomy, if needed, is lessened by a preceding HAL/RAR. Longer follow up within large randomized trials is required to adequately gauge the efficacy of this technique.

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ORIGINAL ARTICLE

Antioxidant Treatment Attenuates Intestinal Mucosal Damage and Gut Barrier Dysfunction After Major Hepatectomy. Study in a Porcine Model

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Abstract

Background This study aims to evaluate whether injury of gut mucosa in a porcine model of post-hepatectomy liver dysfunction can be prevented using antioxidant treatment with desferrioxamine.

Methods Post-hepatectomy liver failure was induced in pigs combining major (70%) liver resection and ischemia/reperfusion injury. An ischemic period of 150 minutes, was followed by reperfusion for 24 h. Animals were randomly divided into a control group (n=6) and a desferrioxamine group (DFX, n=6). DFX animals were treated with continuous IV infusion of desferrioxamine 100 mg/kg. Intestinal mucosal injury (IMI), bacterial and endotoxin translocation (BT) were evaluated in all animals. Intestinal mucosa was also evaluated for oxidative markers.

Results DFX animals had significantly lower IMI score (3.3±1.2 vs. 1.8±0.9, p<0.05), decreased BT in the portal circulation at 0 and 12 h of reperfusion (p=0.007 and p=0.008, respectively), decreased portal endotoxin levels at 6 (p=0.006) and 24 h (p=0.004), decreased systemic endotoxin levels (p=0.01) at 24 h compared to controls. Also, 24 h post-reperfusion mucosal malondialdehyde and protein carbonyls were decreased in DFX animals compared to controls (4.1±1.2 vs. 2.5±1.2, p=0.05 and 0.5±0.1 vs. 0.4±0.1, p=0.04 respectively).

Conclusion Desferrioxamine seems to attenuate mucosal injury from post-hepatectomy liver dysfunction possibly through blockage of iron-catalyzed oxidative reactions.

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Keywords Bacterial translocation · Liver ischemia reperfusion injury · Gut barrier · Hepatectomy · Desferrioxamine

Abbreviations

ROS	Reactive oxygen species
RNS	Reactive nitrate species
CVP	Central venous pressure
MAP	Mean arterial pressure
PP	Portal pressure
MDA	Malondialdehyde
CFU	Colony forming units
IMI	Intestinal mucosa injury

Introduction

Post-hepatectomy septic complications seem to occur in up to 20% of the cases and can significantly increase morbidity and mortality.[1–3] Experimental and clinical studies suggest that the involved microorganisms may derive from the gut lumen, possibly due to the disruption of the gut barrier.[4]

Major liver resections can be complicated with postoperative liver dysfunction due to both inadequate remnant liver mass and ischemia/reperfusion injury, caused by intra-operative maneuvers for vascular control. Although such maneuvers are invaluable in preventing excessive blood loss, they result in the production of reactive oxygen and nitrogen species (ROS–RNS), which are responsible for induction of oxidative and nitrosative stress.[5,6] The resulting tissue injury is not limited only to the liver; spillage of cytokines and inflammatory mediators can promote remote injury.[7] Moreover, in the setting of liver failure, several factors that contribute to gut barrier function have been shown to be compromised.[4,8–11]

The aim of the present study was to evaluate the effect of desferrioxamine, as an antioxidant agent, on gut barrier function in an experimental model of major hepatectomy combined with ischemia/reperfusion injury of the liver remnant. Desferrioxamine has been used in the past as an iron chelating agent and has been shown to protect the liver from oxidative damage.[12–14] However, its effect on the attenuation of remote intestinal mucosal injury and gut barrier dysfunction in the setting of post-hepatectomy liver dysfunction has not been previously evaluated.

Methods

This protocol was approved by the Animal Research Committee of the University of Athens and the Committee of Bioethics of Aretaieion Hospital. Care and handling of the animals was in accordance with European guidelines for ethical animal research. Twelve female Landrace pigs weighing 30–35 kg were used. The animals were randomly divided in two groups: a desferrioxamine treatment group (DFX, $n=6$) and a control group ($n=6$). DFX animals received a constant intravenous infusion of desferrioxamine beginning at the time of initiation of hepatic ischemia until the end of the experiment.

Surgical Procedure

All surgical procedures were performed under sterile conditions. Immediately after endotracheal intubation, the right femoral artery was surgically catheterized using a 20G catheter for blood sampling and arterial pressure measurement. The right internal jugular vein was catheterized using a central vein catheter with polyurethane one-lumen sheath 6.5 Fr (Arrow International, Bernville Rd Reading, PA, USA).

Following laparotomy, a Folley catheter was inserted in the bladder through a cystotomy. Afterwards, a side-to-side porta-caval anastomosis was performed using continuous 5-0 prolene sutures, in order to prevent splanchnic congestion. During the creation of the anastomosis, care was taken not to interrupt blood flow through the vessels and the portal vein was side-clamped using a Satinsky clamp. After the anastomosis, the left hepatic artery was ligated and the hepatoduodenal ligament was clamped (Pringle maneuver). Afterwards, 70% hepatectomy was performed by resection of the median and left liver lobes. Blood loss was <100 ml in all animals. The liver remnant was kept ischemic for 150 min and then the porta-caval anastomosis was clamped and portal blood flow was redirected back to the liver remnant by unclamping the hepatoduodenal ligament (Fig. 1). A 20G catheter was then inserted in the portal vein through a side branch for portal pressure monitoring and portal blood sampling. The abdomen was closed, and the liver was reperfused for a 24-h period during which the animals were kept under mechanical ventilation and monitored. Mean arterial pressure (MAP) and portal pressure (PP) were recorded, and blood samples from the systemic and portal circulation were taken at the beginning of the reperfusion period and at 6, 12, and 24 h of reperfusion. At the end of the experiment, all animals were euthanized with intravenous infusion of thiopental 5 mg/kg and 2 g KCl, and the last 10 cm of the ileum were sampled for histological studies and measurement of malondialdehyde (MDA) and protein carbonyls content.

Desferrioxamine Administration Protocol

Desferrioxamine 100 mg/kg was administered continuously with I.V. starting at the time of occlusion of the hepato-

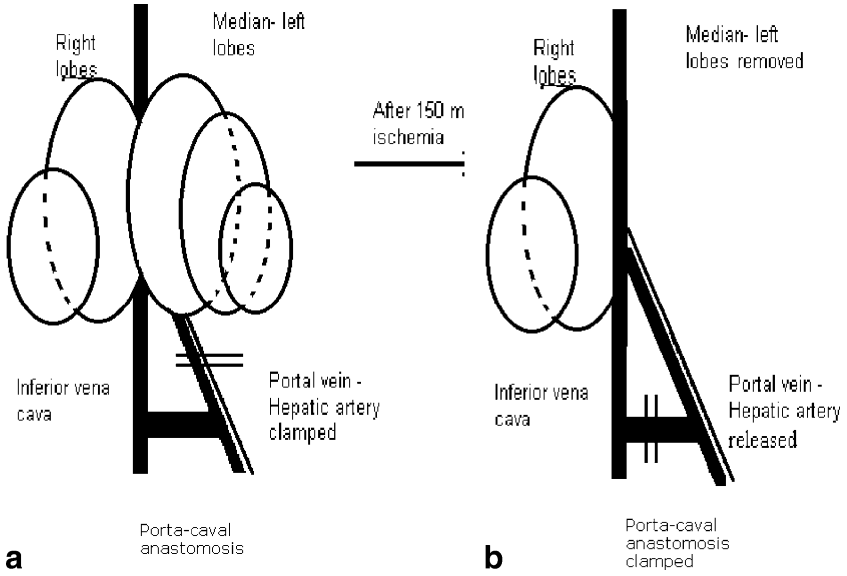

Fig. 1 **a** After the construction of the side-to-side porta-caval anastomosis, the hepatoduodenal ligament is clamped and a warm ischemic period of 150 min is initiated. **b** Left liver lobes have been removed (70% of liver mass). The porta-caval anastomosis is clamped and the hepatoduodenal ligament is released, redirecting portal blood flow to the intact right liver lobes

duodenal ligament (start of ischemia), until the end of the experiment. The total dose was divided in 66 mg/kg that were administered during the ischemic period until the sixth hour of reperfusion and 34 mg/kg that were administered after the sixth hour, until the end of the experiment. Animals in the control group received an equal volume of normal saline 0.9%.

Bacteriological Analysis Protocol

Quantitative bacteriological analysis of portal and systemic blood was performed using the Isolator pediatric tubes (Oxoid Limited, Hants, England) culture system. We used this system as it has been shown to yield an improved rate of isolation and culture of bacteria, as well as faster identification of septicemia in comparison with other bacterial culture analysis systems.[15,16] In detail, after blood sampling and under sterile conditions, 1 ml of blood was transferred to the isolator tubes which contained polypropylene glycol 8 mg/L, sodium polyanetholsulphonate 9.6 g/L, purified saponin 40 g/L and were kept in room temperature for 2 h. The blood samples were inoculated in blood agar plates (Bioprerare, Athens, Greece) and were incubated aerobically in 37°C for 24 h. Colonies were identified with conventional bacteriological methods. Enteric Gram-negative bacteria were identified by the API 20 System, Gram-positive bacteria by the API STAPH and API 20 Strep System (BioMerieux, Marcy-l' Etoile, France). The results are expressed as base-10 logarithm of colony forming units (CFU) cultured per milliliter of blood sampled.

Endotoxin Measurement

Endotoxin concentration was determined in systemic and portal blood with the limulus amebocyte lysate test, using the kinetic turbidimetric method (Pyrogent-5000 bulk kit, Longa Walkerville Inc, Walkersville, USA), as previously described.[17,18] The bacterial strain of standard endotoxin was *Escherichia coli* O55:B5. The range of the assay was 0.01–1 EU/ml. All samples were measured in duplicate and were subjected to spiked concentration measurements. Sample treatment for inhibition consisted of 1/100 dilution and heating at 75°C for 15 min.

MDA and Protein Carbonyl Content Determination

Tissue MDA and protein carbonyls are sensitive markers of oxidative injury.[19] Tissue was sampled at the end of the experiment and stored at −80°C until analysis. For the determination of tissue MDA, ileal mucosa was suspended in an ice-cold buffer containing 100 mM NaCl, 0.5 mM KCl, 3.1 mM CaCl2, 1 mM MgSO4, 0.55 mM KH_2PO_4, and 50 mM Tris–HCl pH 7.4. The final concentration of the tissue in the homogenization buffer was 10% *w/v*. The tissues were homogenized by sonication, and the resulting suspension was centrifuged at 500×*g* for 10 min. The pellets were discarded and the supernatants were centrifuged at 20,000×*g* for 20 min. The supernatant was discarded and the pellet (membrane fraction) was suspended in the aforementioned buffer to a final concentration of 10% *w/v*. The total protein of the membrane fraction was determined by the Bradford method,[20] and MDA content

was determined according to the method of Jentzsch et al.[21] using 100 μg of membrane protein. Protein carbonyls were measured using the colorimetric assay kit from Cayman Chemical (Ann Arbor, MI). Results are expressed as nanomole per milligram of tissue homogenate protein.

Intestinal Pathology Evaluation

The ileal biopsy specimens were immediately stored in 4% formaldehyde, embedded in paraffin, cut in 3–5 μm sections sagitally to the serosa, stained with hematoxylin–eosin (HE) and processed for microscopy analysis. Microscopic evaluation was performed by two independent expert pathologists who were unaware of the treatment groups. Intestinal mucosal injury score was based on the pathology scoring of Chiu et al. as briefly described in Table 1. This scoring system has been shown to be effective in evaluating injury to the gut mucosa.[22] The recorded score was the mean score of the two pathologists.

Statistical Analysis

Analysis of variance was used in order to determine statistical significance when the distribution was normal. When the distribution was not normal, when the data was ordinal, and when standard deviations differed significantly, the non-parametric Mann–Whitney test was used. Normality was tested using the Kolmogorov–Smirnov technique. All calculations were carried out using SPSS 15.0 for Windows. Colony forming units were expressed in logarithmic form. The level of statistical significance was set to $p<0.05$. Data are expressed as mean±SD.

Table 1 Intestinal mucosal injury score as proposed by Chiu et al.[24]

Grade	Microscopy findings
0	Mucosa with normal villi
1	Developing of the sub-epithelial Gruenhagen's space, usually at the villus apex, frequently associated with capillary congestion
2	Extension of the sub-epithelial space with moderate lifting of epithelial layer from the lamina propria
3	Massive epithelial lifting down the sides of the villi
4	Denuded villi with lamina propria and dilated capillaries exposed. Increased cellularity of lamina propria may be noted
5	Digestion and disintegration of lamina propria; hemorrhage and ulceration

Results

Intestinal Mucosa Injury Score

Intestinal mucosa was severely injured in the control group, while in animals treated with desferrioxamine, the injury was attenuated ($p<0.05$), as shown in Figs. 2 and 3.

Bacterial Translocation

Animals in the DFX group had fewer CFUs per milliliter in the portal circulation immediately after reperfusion and at 12 h post-reperfusion compared with controls ($p<0.01$), whereas no differences were noted either at 24 h or at any other timepoint in the systemic circulation (Fig. 4).

Serum Endotoxin Concentration

In DFX animals, endotoxin concentration was lower in the portal circulation 6 and 24 h after reperfusion ($p<0.01$) and in systemic circulation ($p<0.01$) at 24 h compared to controls (Fig. 5).

Portal Pressure

No significant differences regarding portal pressure measurements were observed between the groups throughout the experiment, despite a transient, non-significant increase immediately following reperfusion (Fig. 6).

Tissue MDA and Protein Carbonyls Content

Tissue oxidative injury was decreased in the DFX group. Tissue MDA and protein carbonyl concentration were both significantly decreased at 24 h after reperfusion ($p<0.05$) (Fig. 7).

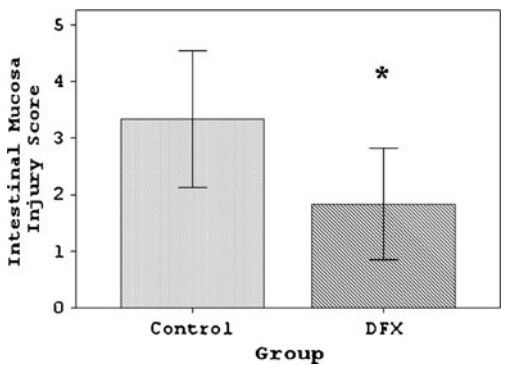

Fig. 2 Intestinal mucosa injury scores in control and DFX group. Animals in the control group showed increased mucosal injury after hepatectomy (*$p<0.05$)

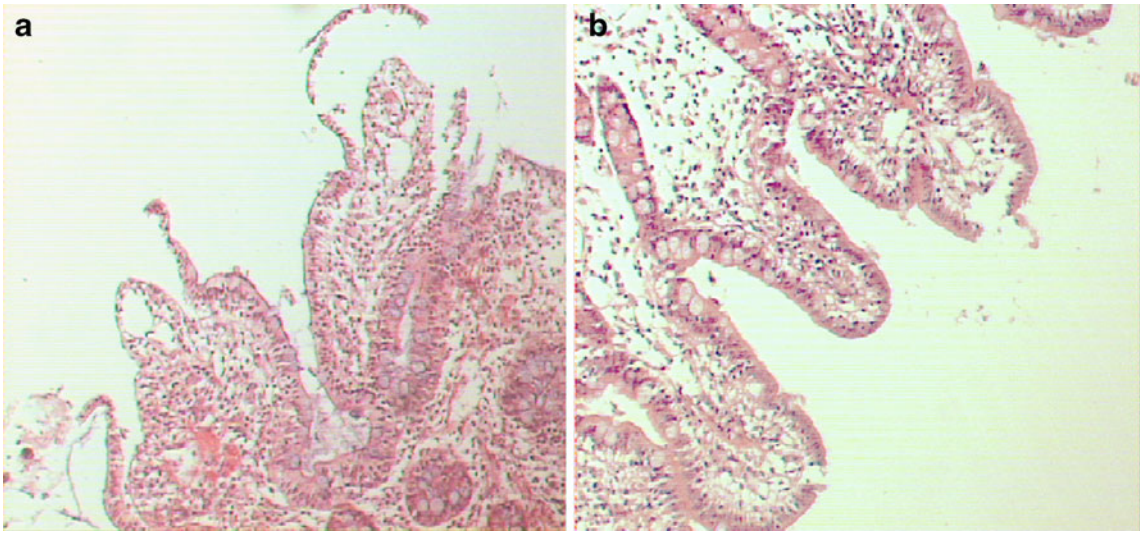

Fig. 3 **a** Intestinal mucosa from the distal ileum of animals of the control group 24 h after reperfusion. Massive epithelial lifting down the sides of the villi. Dilated capillaries exposed (grade 3 mucosal injury). (Hematoxylin–eosin stain, 100×). **b** Intestinal mucosa from the distal ileum of animals of the DFX group 24 h after reperfusion. Extension of the sub-epithelial Gruenhagen's space with moderate lifting of epithelial layer from the lamina propria (grade 2 mucosal injury). (Hematoxylin–Eosin stain, 100×)

Discussion

This study was carried out in order to evaluate the role of desferrioxamine in the preservation of intestinal mucosa integrity and attenuation of bacterial and endotoxin translocation following major hepatectomy. The animals developed postoperative liver dysfunction, due to massive liver resection combined with ischemia/reperfusion injury, as we have previously shown.[23] Our results show that desferrioxamine attenuates intestinal mucosal injury and bacterial translocation in this setting.

Septic complications that appear in postoperative patients who have undergone major hepatectomy and manifest liver dysfunction are thought to originate from the gut flora.[24] Normal mucosal barrier function prevents bacteria and their toxins from translocating in the circulation. In post-hepatectomy liver dysfunction, normal defensive mechanisms known as gut barrier and intestinal mucosal integrity are compromised.[25] In addition, in liver ischemia/reperfusion, ROS production may cause remote injury to the intestinal mucosa through the systemic circulation. During major hepatectomy, occlusion of the hepatoduodenal ligament

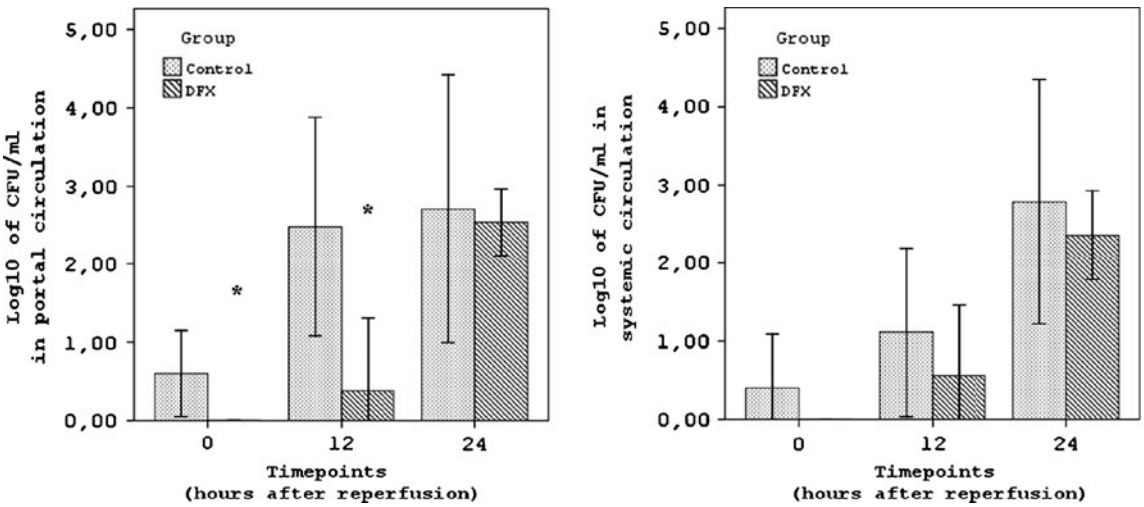

Fig. 4 Bacterial translocation in the portal and systemic circulation during the experiment. Desferrioxamine treatment attenuated bacterial translocation in the portal circulation immediately after ischemia and until 12 h after reperfusion. The effect faded at the 24 h timepoint. There was no statistical significant difference in the systemic circulation. The results are expressed as base-10 logarithm of colony forming units (CFU) cultured per milliliter of blood sampled (*$p<0.05$)

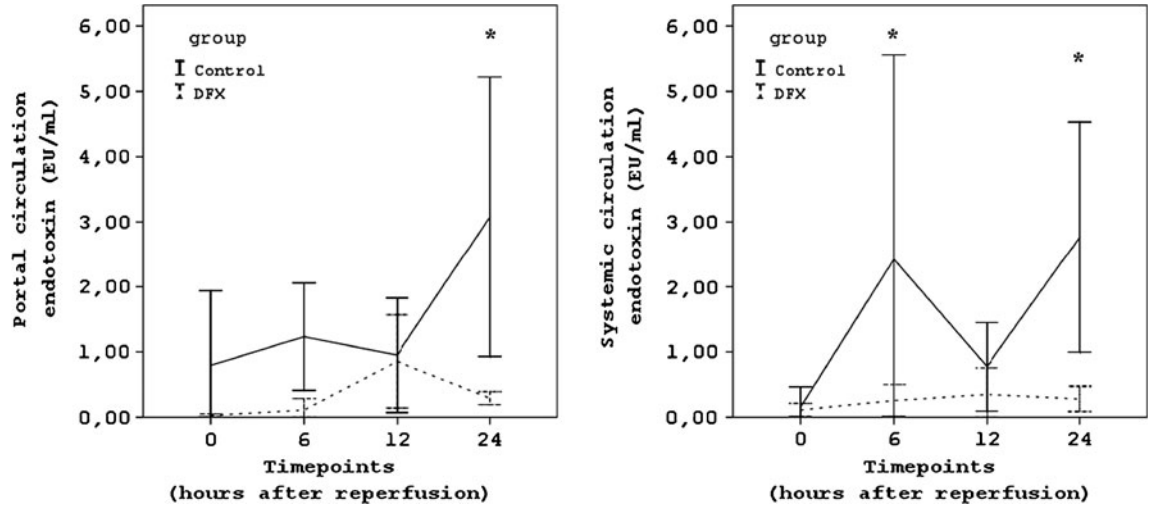

Fig. 5 Endotoxin concentration in portal and systemic circulation expressed as endotoxin units per milliliter of blood sampled. Endotoxin levels were decreased in desferrioxamine treated animals at 24 h of reperfusion both in systemic and portal circulation. The desferrioxamine had the same effect starting early in the postoperative period in the systemic circulation (6 h time point). (*$p<0.05$)

increases portal pressure, and as a result, can cause direct damage to the intestinal mucosa and gut barrier.[26] In our study, we constructed a porta-caval shunt prior to the Pringle maneuver in order to avoid congestive injury of the gut mucosa and assess remote gut mucosa oxidative injury derived from liver produced ROS.

Antioxidant therapy has already been used for the prevention of postoperative liver injury after major hepatectomy.[27] Desferrioxamine chelates iron and prevents the production of oxygen free radicals though the Fenton equation.[28] Desferrioxamine also induces the expression of hypoxia-inducible factor 1-alpha (HIF-1alpha) protection against hypoxic states.[29] Through these mechanisms, desferrioxamine has been shown to attenuate ischemic and oxidative injuries to the liver and other tissues.[30–32] We chose to use desferrioxamine as it blocks an alternate pathway (Fenton reaction) in the production of reactive oxygen species compared to other antioxidants such as N-acetyl cysteine. In addition, in previous experiments involving liver devascularization and liver ischemia/reperfusion injury

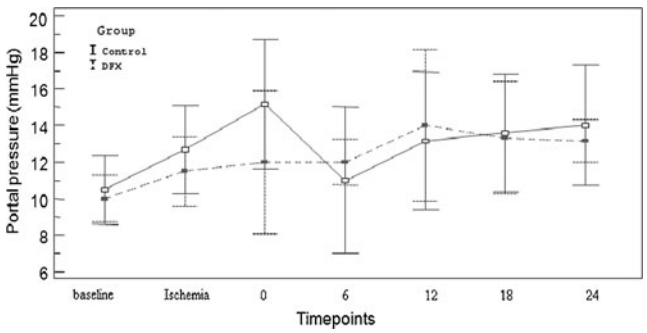

Fig. 6 Portal pressure (mmHg) during ischemia and in the reperfusion period. There are no differences between the two groups

combined with major hepatectomy, we have shown that desferrioxamine can protect not only the liver from oxidative injury[23] but also remote target organs.

Our data show that bacterial translocation and endotoxinemia in the portal and systemic circulation take place early after hepatectomy and reperfusion in the control group. Similar findings have been reported by Wang et al. in rodents after 70% hepatectomy[24] and Lemaire et al. in a large animal model of 50% hepatectomy combined with porta-caval shunt and ischemia–reperfusion injury.[33]

Desferrioxamine attenuated bacterial translocation and endotoxemia during reperfusion. Immediately after reperfusion and 12 h afterwards, bacterial translocation was found to be significantly lower in the portal circulation of the DFX group, compared with the control group. At the end of the experiment, there was no difference in translocating bacteria in the portal and systemic circulation of the DFX group. Endotoxin concentration revealed decreased values in portal circulation as early as 6 h after reperfusion in the DFX group compared with controls and significantly lower values in both portal and systemic circulation compared to controls at the end of the experiment. The decrease of endotoxin at the end of the experiment does not correlate to bacteremia, which was found not to have differences between groups at that time point. This could possibly be due to higher endotoxin clearance associated with improved liver function of DFX animals.

During bacteriological analysis, we used the isolator pediatric systems in order to quantify blood bacteremia in the portal and systemic circulation. The isolator systems contain blood purified saponin, which lyses erythrocytes and leukocytes in order to permit the culture of microorganisms that have already undergone phagocytosis. In

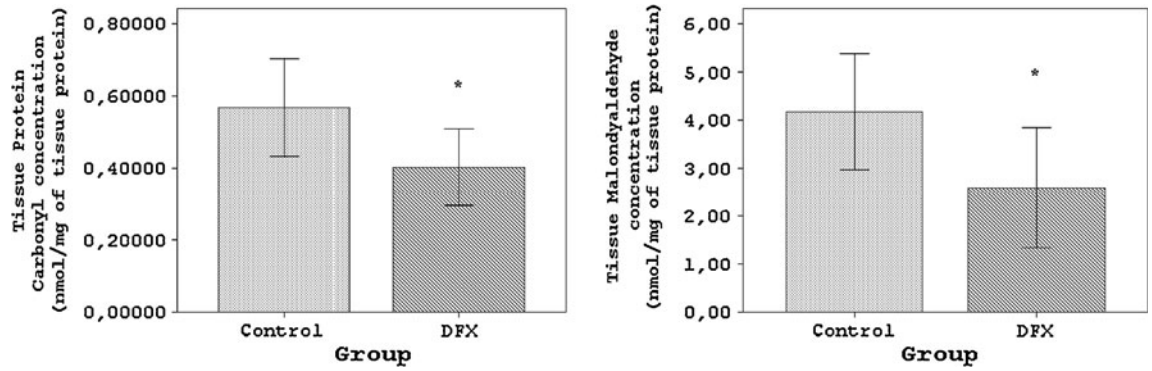

Fig. 7 Tissue protein carbonyl and malondyaldehyde concentration expressed in nanomole per milligram of intestinal mucosa protein 24 h after reperfusion. Both oxidative markers are decreased after desferrioxamine treatment (*$p<0.05$)

addition, they contain sodium polyanetholsulphonate, which is an anticoagulant neutralizing phagocytosis and the bactericidal properties of blood.[15,16] As a result, the bacteria cultured represent more accurately the amount of translocating bacteria without the effect of intravascular immune defense mechanisms.

The above findings also correlate with intestinal mucosal injury. Control animals developed moderate to severe mucosal damage, while DFX group only developed mild mucosal injury. Intestinal mucosal injury after major hepatectomy has been reported by Wang et al. and Xu et al. in rats as well,[25,34] correlating with endotoxemia and the degree of liver resection.

Decreased oxidative markers of the intestinal mucosa show that the decreased tissue injury noted in the DFX group is probably due to attenuation of oxidative stress induced by desferrioxamine. Okey et al. and Alexandris et al.[35,36] have also demonstrated similar results after antioxidant treatment. They proposed that protein oxidation of the tight junctions in the intestinal mucosa may be responsible for gut barrier dysfunction, resulting in increased intestinal permeability to bacteria and toxins.[36]

It has been shown that intestinal venous congestion can lead to gut barrier compromise.[26] In our study, there were no differences in portal pressure between the groups, and as a result, the difference noted in gut barrier function is not affected by this variable. More likely, the improvement in gut barrier function in the DFX group is attributable to the decrease of oxidative stress-derived mediators released from the liver due to ischemia/reperfusion injury.

According to our data, DFX-treated animals did not appear to develop bacterial and endotoxin translocation immediately after or in the early stages of reperfusion. However, this effect faded at the end of the experiment, as recorded by the increase in bacterial translocation in portal circulation. This may be due to the decrease in the desferrioxamine administered after 6 h of reperfusion. The dose of desferrioxamine varies amongst studies, ranging from 50 to 150 mg/kg. We chose to administer desferrioxamine in increased dosage during the early phase of the experiment, as recent studies have demonstrated that an earlier "pretreatment" seems to be necessary in order for intracellular levels to be adequate during the insult.[37] We have previously shown that the dosage scheme used in this study is capable of attenuating oxidative injury in the liver and the lung in a severe model of complete liver devascularization[30] as well as in the model used in this study.[23,38] Another possibility is that factors related to liver dysfunction other than oxidative mucosal injury, which could not be reversed by desferrioxamine administration, contribute to late mucosal failure.

Other limitations of our study include the brief monitoring period and the fact that other aspects of bacterial translocation, such as translocation to the lymphatics and translocation of anaerobes were not addressed. We chose not to sample mesenteric lymph nodes as this would require re-laparotomy during the experiment and maneuvers that could possibly further compromise gut barrier function. Anaerobes were not cultured because their role in bacterial translocation remains controversial, as they have been shown to translocate rarely, and in fact play a protective role against translocation of other intraluminal bacteria.[39–41] The difference found in endotoxemia in systemic circulation 6 h after reperfusion had a quite broad range, increasing the standard deviation, which in combination with the small sample size ($n=6$) should be taken into account in the interpretation of our results. Finally, it is not clear by our experiment whether desferrioxamine improved gut barrier function only due to its antioxidant properties, or whether its contribution to the reversal of postoperative liver dysfunction played a significant role as well.

In conclusion, our study suggests that desferrioxamine treatment in a porcine model of major hepatectomy combined with ischemia/reperfusion injury of the liver remnant may be associated with decreased intestinal mucosal injury and improvement of gut barrier function.

This concept needs to be further investigated using different dosage schemes and combinations of antioxidants in order to evaluate the protection of gut barrier function during major hepatectomy.

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ORIGINAL ARTICLE

Single-Centre Comparative Study of Laparoscopic Versus Open Right Hepatectomy

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Abstract
Background Expansion of laparoscopic major hepatectomy is still limited mainly due to the well-recognised technical difficulties compared to open surgery, and doubts regarding the oncological efficiency when major resections are required.
Methods Patients undergoing open right hepatectomy (ORH) were matched with patients undergoing laparoscopic right hepatectomy (LRH) and compared for perioperative outcomes.
Results Seventy patients were included: 36 patients underwent LRH and 34 ORH. Operative time was significantly longer for LRH (median, 300 min vs. 180 min for ORH; $p<0.0001$). Intensive care unit (median, 2 days for LRH vs. 4 days for ORH; $p<0.0001$) and postoperative length of stay (5 days for LRH vs. 9 days for ORH; $p<0.0001$) were significantly shorter for LRH. Four laparoscopic cases were converted to open surgery. No significant difference in postoperative complications and mortality was observed between LRH and ORH. Among patients with colorectal carcinoma liver metastases, R0 resection was obtained in 20/21 (95%) cases after LRH, and in 20/25 (80%) after ORH ($p=0.198$). Mid-term overall survival did not significantly differ between the laparoscopic and the open group.
Conclusions LRH can be a safe, effective, and oncologically efficient alternative to open resection in selected cases. Extensive experience in hepatic and laparoscopic surgery is required.

Keywords Right hepatectomy · Laparoscopy · Case–control study · Outcome · Survival

Introduction

Laparoscopic liver resection is progressively gaining popularity. For minor liver resections, the minimally invasive approach has been shown to be feasible, safe and efficient when appropriate criteria are applied to patient selection.[1–12] In contrast, expansion of laparoscopic major hepatectomy (e.g. right or left hepatectomy) is still limited. This is mainly due to: (1) the well-recognised technical difficulties compared to open surgery; (2) doubts regarding the oncological efficiency when major resections are required. Evidence available from a few case series supports the role of laparoscopic major hepatectomy as a safe and efficient procedure when performed in selected patients and in centres with extensive experience in hepatic and laparoscopic surgery.[10,13] However, encouraging results from comparative and prospective randomized studies are needed before promoting laparoscopic major hepatectomies on a large scale.

Dr. Mohammed Abu Hilal and Dr. Francesco Di Fabio equally contributed to the scientific content of this paper.

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Open right hepatectomy (ORH) is a well-standardized surgical procedure and represents an optimal group to compare with the laparoscopic counterpart for assessing limits and advantages of the minimally invasive approach for major hepatectomy. To date, one comparative study is available in the English literature, analysing short-term results in 22 patients undergoing laparoscopic right hepatectomy (LRH).[13] The authors concluded that laparoscopy improves surgical and postsurgical outcomes compared with ORH in selected patients, with similar operative time. More evidence is certainly needed, including assessment of oncological efficiency when the laparoscopic approach is adopted for patient with malignant disease.

The aim of this study was to compare short-term postoperative outcomes of LRH with ORH in a case–control study from a high-volume laparoscopic liver centre. In addition, we discussed the oncological validity of the laparoscopic approach in terms of tumour-free resection margins and mid-term overall survival in patients operated for colorectal carcinoma liver metastasis.

Patients and Methods

We compared patients undergoing LRH with matched patients undergoing ORH between 2006 and 2009 at Southampton University Hospitals NHS Trust. The 4-year period was chosen for this case-controlled study as LRH was started in our institution in 2006.

Patients requiring right hepatectomy in whom the procedure appeared possible via either open or laparoscopic surgery were identified by the hepatobiliary multidisciplinary team, including surgeons, pathologists, oncologists, gastroenterologists and radiologists in our centre.

Exclusion criteria for the comparison were: tumours near the hilum; tumours near the planned resection margin; very large fixed tumours; patients with cirrhosis Child-Pugh category B and C; patients who underwent non-anatomic resection or additional procedures.

Patients in the open-surgery group were matched according to sex, age and liver disease.

Patients undergoing laparoscopic resection were under the care of two surgeons (MAH and NWP). Most of the patients undergoing open resection (85%) were under the care of another surgeon (JNP). The remaining 15% of the open resections were performed by MAH or NWP. These 15% were not converted cases, but planned open resections. The three surgeons were all working in the same hospital and the two laparoscopic surgeons received their basic training in liver surgery at Southampton University Hospitals NHS Trust.

The variables considered for the comparison were: demographics, conversion rate, number of portal triad clamping, intra-operative blood loss (calculated by measuring the volume of blood in the suction bottles, after subtracting wash fluid, at the end of surgery with the addition of weighed swabs), patients requiring transfusion, operation time, rate of benign/malignant lesions, weight of the resected specimen, resection margins, high dependency unit/intensive care unit length of stay, postoperative length of stay, postoperative complications and mortality (within 30 days from surgery).

Complications were classified into specific hepatectomy related (e.g. hepatic failure, bile leak and bleeding) and general complications.

Overall survival analysis was limited to patients with colorectal carcinoma liver metastases. In this group, resections margins were classified into R0 (microscopically more than 1 mm from resection margin) and R1 (microscopically less than 1 mm from resection margin).

When performing LRH, a pure laparoscopic approach was attempted in all patients.[14] Standard nomenclature was used to describe the resection performed.[15] Our technique for LRH has previously been described in details elsewhere.[16]

Statistical Analysis

The analyses were performed using the statistical software Strata for Windows (Strata Corporation; College Station, TX, USA). Median values and range were considered for continuous variables as their values' distribution was skewed. The nonparametric Mann–Whitney *U* test was used to compare continuous variables. Chi-square or Fisher's exact test was applied for analysis of categorical variables. When conversion to open or laparoscopic-assisted surgery was required in the LRH group, patients were analysed in the laparoscopic group on an intention-to-treat basis. Survival analysis was limited to patients with colorectal carcinoma liver metastases, excluding patients who died within 30 days from surgery. Overall survival was analysed by the Kaplan–Meier method with log-rank comparison between groups. Survival was calculated from the date of surgery until the date of death or the time of manuscript preparation for those patients known to be alive. The level of statistical significance was set at $p<0.05$.

Results

During the study period 95 patients underwent right hepatectomy at Southampton University Hospitals NHS Trust. Laparoscopic resection was attempted in 36 patients (38%). From the 59 patients who underwent ORH, 34 were selected for matching with the laparoscopic group. The remaining 15 cases did not fit the inclusion criteria for comparison with the laparoscopic group. Indication for surgery is summarized in Table 1.

Table 1 Indication for surgery

Indication for surgery	LRH (n=36)	ORH (n=34)
Colorectal carcinoma metastases	21 (58%)	26 (76%)
HCC	4 (11%)	4 (12%)
Non-colorectal carcinoma metastases	5 (14%)	2 (6%)
Adenoma	3 (8%)	1 (3%)
Oriental cholangiopathy	1 (3%)	0
Uncertain preoperative diagnosis	2 (6%)	1 (3%)

A detailed comparison of demographic variables, surgical results and postoperative course is summarized in Table 2. Operative time was significantly longer for LRH (median 300 vs. 180 min for ORH; $p<0.0001$, Mann–Whitney U test). No significant improvement in operative time was observed in the laparoscopic group by comparing the first half of the cases with the second half ($p=0.656$, Mann–Whitney U test). Intensive care unit/high dependency unit length of stay (median, 2 days for LRH vs. 4 days for ORH; $p<0.0001$; Mann–Whitney U test) and postoperative length of stay (5 days for LRH vs. 9 days for ORH; $p<0.0001$; Mann–Whitney U test) were significantly shorter for LRH.

A total of four patients in the laparoscopic group required conversion to formal open surgery and four other patients required conversion to a laparoscopic-assisted surgery. This procedure involves a mini-laparotomy in the right upper quadrant to complete the procedure. Most of the conversions (six of eight) happened in the first half of the patients undergoing LRH. The causes for conversion to open procedure were: failure to locate tumour with intra-operative ultrasound in one case, failed hilar dissection in two cases, and difficulty manipulating a large necrotic tumour in one case. The causes of conversion to laparoscopic-assisted technique were: difficult control of

Table 2 Demographics, surgical results and postoperative course

Variables	LRH (n=36)	ORH (n=34)	p values
Demographics			
Female/male	18:18	16:18	0.806[b]
Age at operation in years (median (range))	64 (26–82)	63 (25–84)	0.431[a]
Surgical results			
Conversions			
Laparoscopic-assisted	4 (11%)	–	–
Open	4 (11%)		
Number of portal triad clamping	20 (56%)	13 (38%)	0.147[b]
Estimated blood loss in millilitres (median (range))	700 (75–3,000)	500 (50–5,200)	0.156[a]
Received transfusion	8 (22%)	7 (21%)	0.868[b]
Operation time in minutes (median (range))	300 (180–465)	180 (90–360)	<0.0001[a]
Benign/malignant lesions	7/29	2/32	0.152[c]
Weight of resected specimen in grammes (median (range))	668 (463–1,500)	625 (341–2,820)	0.782[a]
R0 resections[d]	20/21	20/25	0.198[c]
Postoperative course			
High dependency unit/Intensive care unit stay in days (median (range))	2 (0–8)	4 (2–48)	<0.0001[a]
Postoperative length of stay in days (median (range))	5 (3–20)	9 (4–48)	<0.0001[a]
Patients with postoperative complications	5 (14%)	5 (15%)	0.922[b]
Mortality	0	2 (6%)	0.232[c]

LRH laparoscopic right hepatectomy, *ORH* open right hepatectomy

[a] Mann–Whitney U test

[b] Chi-square test

[c] Fisher's exact test

[d] Colorectal carcinoma liver metastases only

bleeding in two cases, bile leak in one case, and closure of diaphragm in one case. Conversion was significantly associated with longer high dependency unit/intensive care unit stay (median, 2.5 for converted cases vs. 2 days for pure laparoscopic cases; $p=0.025$; Mann–Whitney U test), and longer postoperative stay (median, 9 for converted cases vs. 4 days for pure laparoscopic cases; $p=0.0003$; Mann–Whitney U test).

No significant difference in postoperative complications between the two groups was observed. Complications occurred in five patients undergoing LRH (14%) and in five patients undergoing ORH (15%). Two patients from the open group died in the postoperative period. Details on postoperative complications are shown in Table 3.

Surgical Margins and Mid-term Survival in Patients with Colorectal Carcinoma Liver Metastases

Twenty-one patients in the laparoscopic group and 25 in the open group were considered for surgical margins and survival analysis. R0 resection was obtained in 20/21 (95%) patients after laparoscopic surgery, and in 20/25 (80%) in the open group ($p=0.198$, Fisher's exact test). When considering R0 resections in patients with colorectal carcinoma liver metastases, a median tumour-free resection margin of 20 mm (2–50 mm) was achieved in LRH and 10 mm (2–60 mm) in ORH. To date, we have a median follow-up of 14 months (range, 6–51 months) for the laparoscopic group and median overall survival has not yet been reached. This compares with a median follow-up of 13 months (range, 7–50) and a median overall survival of 27 months in the open group. We recorded a 61% 2-year survival in the open group and 73% in the laparoscopic group ($p=0.283$, log-rank test) (Figure 1). There have been 12 deaths during follow-up (eight among ORH and four among LRH).

Discussion

Laparoscopic major hepatectomies are technically demanding and require great expertise in open liver surgery and minimally invasive techniques.[10,17] Several series have confirmed the advantages of the laparoscopic approach in minor liver resections in terms of less pain and analgesic drug consumption, shorter hospital stay, less transfusion requirements, faster recovery, less postoperative adhesion, reduction of abdominal wall damage and improved cosmetic results compared to open surgery.[1,6,9] However, it is unclear whether these benefits are maintained in laparoscopic major hepatectomy. Furthermore, the oncological validity of laparoscopic major liver resection for malignant diseases is still a matter of discussion.[18] Encouraging and solid results are needed before advocating this approach on a large scale.

In this observational case–control study, we compared two well-matched groups of patients undergoing open and laparoscopic right hepatectomy. We analysed both short-term results and oncological validity of both approaches showing that LRH can be a safe, effective,

Table 3 Description of postoperative complications and outcome

Complications	Indication/Histology	Outcome
Laparoscopic right hepatectomy		
Hepatectomy-related complications		
Splenic traction injury	NET metastasis	Laparoscopic splenectomy—healed
Bile leak	CRC metastasis	Healed
Hematoma	CRC metastasis	CT-guided drainage—healed
General complications		
Acute renal failure (and minor pneumothorax)	CRC metastasis	Hemofiltration—healed
Pneumonia	CRC metastasis	Healed
Open right hepatectomy		
Hepatectomy-related complications		
Liver failure	HCC and cirrhosis	Died
Intraperitoneal bleeding	CRC metastasis	Laparotomy—healed
Sub-hepatic collection	CRC metastasis	CT-guided drainage—healed
General complications		
Severe ARDS, upper GI bleed and sepsis	CRC metastasis	Died
Pneumonia	CRC metastasis	CPAP—healed

CRC colorectal carcinoma, *HCC* hepatocellular carcinoma, *NET* neuroendocrine tumour, *CPAP* continuous positive airway pressure

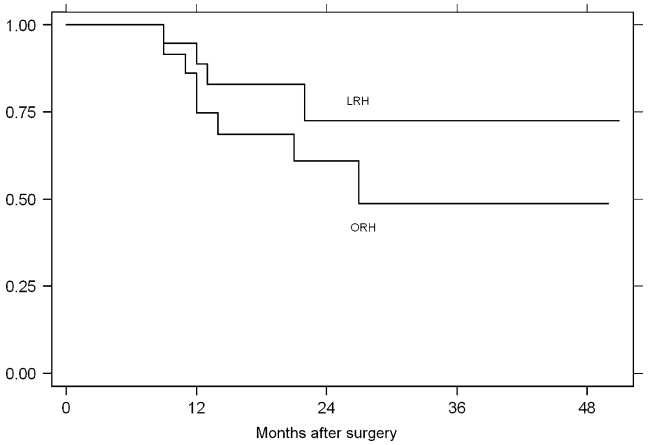

Fig. 1 Mid-term overall survival comparison (Kaplan–Meier method) between laparoscopic right hepatectomy (*LRH*) and open right hepatectomy (*ORH*) for colorectal carcinoma liver metastases (p= 0.283; log-rank test)

and oncologically efficient alternative to ORH in selected cases.

Operation time was longer in the laparoscopic group. This observation is confirmed by most previous series comparing laparoscopic vs. open minor liver resection.[19–21] Interestingly, the only available case–control study comparing laparoscopic and open right hepatectomy reports similar operation times in the two groups. The significantly shorter operation time we noticed in the open group remained constant throughout our whole laparoscopic experience. Therefore, it would not be significantly affected by the learning curve so far.

There is universal agreement that conversion should not be viewed as a complication of laparoscopic liver surgery, but as prudent care when continuation of the procedure is no longer safe for the patient.[14,17] However, the fact that most of the conversions (six of eight) occurred in the first half of the patients undergoing LRH is the positive result of improved skills, better management of the liver parenchyma, and standardization of laparoscopic instruments and techniques.

Despite all the available preventive measures, bleeding during liver resection was still a frequent occurrence in the laparoscopic group, although no significant difference with the open group was found. Bleeding can obscure views, making surgery difficult, and occasionally causing conversion to open procedure.[12] Bleeding during a LRH is initially controlled by application of pressure to the transection surface. This usually stops minor bleeding or oozing and permits the surgeon to gain time while a more definitive method, such as intracorporeal sutures, bipolar diathermy, or an appropriate clip is used for more serious bleeding.[12]

Our data clearly showed that laparoscopy drastically reduced intensive care and postoperative length of stay in patients requiring right hepatectomy, without any increase in postoperative morbidity and mortality. A median postoperative length of stay of 5 days (with a minimum of 3 days) after a right hepatectomy is a major achievement which contributes to lowering the cost of patients' hospitalization and favouring early return of patients to family and social life. Predictably, subgroup analysis in the laparoscopic group showed that conversion adversely affected intensive care unit and postoperative length of stay.

Analysis of postoperative complications did not revealed significant differences between the laparoscopic and the open group. The two fatalities reported in our series occurred in the open group and they potentially affected the median length of stay in the open group. Studies comparing laparoscopic with open surgery for minor liver resections have suggested that the frequency of postoperative complications is lower for laparoscopy than for open surgery.[7,20,22] This may be the result of the fact that challenging liver lesions in unfit patients are more commonly selected for an open approach. Our observation that operative time was significantly shorter in the open group may, however, reflect fair criteria adopted for group selection in the matching process.

Oncological validity of LRH was confirmed by showing favourably comparable free resection margins to the open group. Furthermore, no peritoneal or wound seeding was observed in this series. We showed that LRH for colorectal carcinoma liver metastases is associated on the mid-term with an overall survival similar to the open group. Our data are comparable with other series including minor and major liver resections, showing that the laparoscopic approach is associated with adequate medium-term survival. O'Rourke at al.[23] recorded a 75% 2-year survival rate after laparoscopic resections for colorectal carcinoma metastases, suggesting that the adequacy of resection does not suffer using the laparoscopic approach.

Conclusions

This case-controlled study showed that laparoscopy drastically reduced intensive care and postoperative length of stay after right hepatectomy. In addition, we observed that LRH can be an oncologically efficient alternative to open resection in selected cases treated by experienced laparoscopic liver surgeons. The main limitation of this study is the retrospective design. The ideal setting for the comparison between open and laparoscopic right hepatectomy would be within a large randomized controlled clinical trial, which is still lacking. Meanwhile, large observational studies are needed to provide relevant evidence useful in clinical practice.

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ORIGINAL ARTICLE

Reflux Esophagitis and Marginal Ulcer After Pancreaticoduodenectomy

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Abstract
Background Reflux esophagitis is a common complication following a distal gastrectomy. Increasingly, Roux-en-Y reconstruction has been used to prevent reflux esophagitis; however, marginal ulcer is a concern in patients with a Roux-en-Y reconstruction after distal gastrectomy. The effect of Roux-en-Y reconstruction on the development of reflux esophagitis and marginal ulcer after pancreaticoduodenectomy (PD) has not been studied.
Methods We retrospectively studied both reflux esophagitis and marginal ulcer after 371 PDs and analyzed the association with different methods of gastrointestinal reconstruction.
Results In a median follow-up time of 20 months, 40 (10.8%) of the 371 patients developed reflux esophagitis, 15 after 158 standard PD, and 25 after 213 pylorus-preserving pancreaticoduodenectomy (PPPD; P=0.62). Cox regression model showed Roux-en-Y reconstruction was significantly inversely related to occurrence of reflux esophagitis in 158 patients after standard PD (P=0.04) but not in 213 patients after PPPD (P=0.24). Thirty-five of 371 studied patients developed marginal ulcer, 15 after standard PD and 20 after PPPD (P=0.45). Multivariate analysis showed that Roux-en-Y reconstruction was the only significant predictor for marginal ulcer after PD (P=0.02).
Conclusions Our data support the use of Roux-en-Y reconstruction after standard PD but not after PPPD.

Keywords Pancreaticoduodenectomy · Anastomosis · Roux-en-Y · Marginal ulcer · Reflux esophagitis

Roux-en-Y reconstruction was associated with significantly less reflux esophagitis after standard pancreaticoduodenectomy (but not after pylorus-preserving pancreaticoduodenectomy), and was associated with a significantly greater incidence of marginal ulcer after both standard and pylorus-preserving pancreaticoduodenectomy.

Introduction

Pancreaticoduodenectomy (PD) is performed for the treatment of periampullary and pancreatic head neoplasms. With improvements in surgical technique, advancements in postoperative care, and performance of this operation in high-volume referral centers, PD has become much safer than it had been and is more widely used for patients with chronic pancreatitis or benign or low-grade malignant periampullary neoplasms.[1–3] Since more and more PDs are performed for patients with benign or low-grade malignant pancreatic disease, and because long-term survival is anticipated, late complications and quality of life after surgery become increasingly important.

Late complications after PD include marginal ulcer, reflux esophagitis, diabetes mellitus, and biliary stricture. Pylorus-preserving pancreaticoduodenectomy (PPPD) was initially performed to prevent marginal ulcer after PD in patients with chronic pancreatitis.[4] Recently, PPPD has been used increasingly because the preservation of the duodenal bulb results in better postoperative gastrointestinal function, with similar oncological outcome.[5] Although some studies have revealed a lower rate of marginal ulcer after PPPD than after standard PD,[4,6–8] others have reported opposite results.[9,10] In addition, several papers have reported that delayed gastric emptying (DGE) developed significantly more often after PPPD than after standard PD.[11–13] Some authors have reported the use of Roux-en-Y gastrointestinal reconstruction (R-Y) after PD to prevent

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DGE;[14,15] however, an R-Y reconstruction after PPPD has been reported to be associated with a high incidence of marginal ulcer.[16]

Reflux esophagitis is a common complication following distal gastrectomy. The combination of antrectomy and pylorectomy decreases gastrin secretion and allows unhindered retrograde flow of duodenal contents into the gastric remnant, which cannot accommodate the increased volume.[17] Reconstruction after a distal gastrectomy typically has been performed by using either the Billroth I (BI) or Billroth II (BII) operations. Recently, an R-Y reconstruction has been used increasingly to prevent duodenogastric reflux;[18,19] however, despite significantly reduced incidence of reflux esophagitis, marginal ulcer has developed significantly more frequently in patients with an R-Y reconstruction than in patients with conventional B-I or B-II reconstruction after distal gastrectomy.[18–20] Therefore, study of maneuvers to prevent postoperative reflux esophagitis should always take marginal ulcer into consideration.

To the best of our knowledge, reflux esophagitis has never been studied in conjunction with marginal ulcer after PD. In this report, we study both reflux esophagitis and marginal ulcer after PD and analyze the association of these postoperative complications with different methods of gastrointestinal reconstruction.

Patients and Methods

From 2001 to 2008, a total of 371 consecutive patients underwent PD in our hospital. The medical records of all of these patients were reviewed retrospectively. After PD, 20–30 cm of the proximal jejunum was pulled up retrocolically for pancreatic and biliary reconstruction, and then, an antecolic gastrojejunostomy or duodenojejunostomy was performed. Uncut Roux-en-Y digestive tract reconstruction was performed as described previously.[15] Briefly, in patients with Roux-en-Y digestive tract reconstruction, a section 45 cm from the stomach or duodenum, along the efferent limb, was raised to the afferent limb, creating a side-to-side jejunojejunostomy. A TA 30–3.5 stapler (Ethicon, Cornelia, GA, USA) was used to close the afferent limb just proximal to its entrance into the stomach or duodenum.[15]

Standard PD with hemigastrectomy was performed in 158 patients. The hemigastrectomy line was determined by selecting a point on the greater curvature where the left gastroepiploic artery most nearly approximated the greater curvature wall. The lesser curvature of the stomach was divided just distal to the third prominent vein on the lesser curvature. In the standard PD group, the gastrointestinal tract was reconstructed by the antecolic Roux-en-Y method in 110 patients and by antecolic gastrojejunostomy in 48 patients. PPPD included resection of the pancreatic head and the duodenum 3 cm distal to the pylorus. Neither the right gastric artery nor the right gastroepiploic artery was preserved. The type of PD (standard PD or pylorus preserving) and the type of management of the pancreatic stump (pancreaticojejunostomy or pancreaticogastrostomy) were determined according to the surgeons' preferences.

To evaluate the status of the esophagus and duodeno- or gastrojejunal anastomosis, upper gastrointestinal endoscope was performed 6 months after the operation. Periodic endoscope was performed at least once every 6 months. If patients developed symptoms suggesting of marginal ulcer or reflux esophagitis, endoscope was performed immediately. It is difficult to definitely differentiate Roux stasis syndromes from reflux esophagitis by symptoms because symptoms related to Roux stasis syndrome such as abdominal pain, nausea, or vomiting can also be noted in patients with reflux esophagitis. Therefore, endoscope was performed for all patients with these symptoms, and reflux esophagitis was diagnosed only after endoscopic confirmation. The location and size of any marginal ulcer, as well as the presence or absence of active bleeding, were also confirmed only by endoscope. Reflux esophagitis was diagnosed by endoscopic findings such as mucosal breakage, which was graded according to the Los Angeles classification.[21]

Statistical Analysis

All values are expressed as mean ± standard deviation unless otherwise specified. Statistical analysis was performed with SPSS 13.0 for Windows 98/NT (SPSS Inc., Chicago, IL, USA). Time-dependent analyses of factors related to occurrence of marginal ulcer or reflux esophagitis after pancreaticoduodenectomy were performed using Cox regression test and expressed as odds ratio (OR), 95% confidence interval (CI), and P value. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

PPPD was performed in 213 patients, and standard PD was performed in 158 patients. After PPPD, the gastrointestinal tract was reconstructed with uncut R-Y method in 157 patients and with antecolic duodenojejunostomy in 56 patients. After standard PD, the gastrointestinal tract was reconstructed with uncut R-Y method in 110 patients and with conventional antecolic gastrojejunostomy in 48 patients.

After a median follow-up of 20 months (range, 2–110 months), 35 patients (9.4%) developed marginal ulcer, 15 (9.5%) in the standard PD group and 20 (9.4%) in the PPPD group (P=0.97). Symptoms associated with 35 marginal ulcers after pancreaticoduodenectomy included epigastralgia in 19 patients, anemia in 8 patients, abdominal fullness in 5 patients, and asymptomatic but diagnosed by routine periodic follow-up endoscopic examination in 3 patients. Of the 35 patients with marginal ulcer, 34 responded well to proton pump inhibitor with both symptomatic and endoscopic improvements. However, one patient with marginal ulcer was initially treated with proton pump inhibitor for 6 months. He had ulcer perforation 1 month after discontinuation of proton pump inhibitor. Re-laparotomy and simple closure of the perforation were done. He was then treated by PPI and *Helicobacter pylori* eradication and remained well till last follow-up. Univariate analysis by Cox regression model showed patients' age, sex, peptic ulcer history, method of pancreatic reconstruction, pathology of chronic pancreatitis, or preservation of pylorus were not significantly related to occurrence of marginal ulcer after PD (Table 1), but R-Y reconstruction was significantly related to occurrence of marginal ulcer after pancreaticoduodenectomy (P=0.01, OR=40.76, 95% CI=2.01–828.58, Table 1). Multivariate Cox regression analysis also showed that R-Y reconstruction was the only statistically significant predictor of postoperative marginal ulcer independent of pylorus preservation, type of pancreatic reconstruction (pancreaticojejunostomy or pancreaticogastrostomy), presence of chronic pancreatitis (by histologic diagnosis), and peptic ulcer history (P=0.02, OR=15.04, 95% CI=2.02–112, Table 1).

After a median follow-up of 20 months (range, 2–110 months), 40 patients (10.8%) developed reflux esophagitis—15 (9.5%) in the standard PD group and 25 (11.7%) in the PPPD group. Symptoms associated with the 40 reflux esophagitis after PD included heartburn sensation in 16 patients, epigastralgia in 10 patients, acid regurgitation in 9 patients, and nausea in 5 patients. Of the 40 reflux esophagitis diagnosed after PD, 31 were grade A, 8 were grade B, and 1 was grade C. Of the 40 patients with reflux esophagitis after PD, 26 responded well to proton pump inhibitor, 11 responded well to protease inhibitor, and 3 had symptomatic improvement after both protease inhibitor and proton pump inhibitor. None of them needed surgery for complications or symptoms associated with reflux esophagitis. Both univariate and multivariate analyses by Cox regression model showed patients' age, sex, peptic ulcer history, method of pancreatic reconstruction, pathology of chronic pancreatitis, preservation of pylorus, or R-Y reconstruction was not significantly related to occurrence of reflux esophagitis after PD (Table 2). However, in the 158 patients in the standard PD group, reflux esophagitis developed significantly more frequently in patients status post conventional gastrojejunostomy (eight of 49 patients) than in patients with R-Y reconstruction (seven of 109 patients, P=0.042). In contrast, in the 213 patients in the PPPD group, reflux esophagitis did not develop significantly more frequently in patients with conventional gastrojejunostomy (nine of 56 patients) than in patients with R-Y reconstruction (16 of 157 patients, P=0.24). Cox regression analysis also showed R-Y reconstruction was significantly inversely related to occurrence of reflux esophagitis in 158 patients after standard PD (P=0.04, OR=0.47, 95% CI=0.24–0.94) but not in 213 patients after PPPD (P=0.243, OR=0.615, 95% CI=0.27–1.39).

Four patients had both reflux esophagitis and marginal ulcer after PD. The appearance of both complications was simultaneous in two patients and metachoronous in two patients. Marginal ulcer came first in both patients with metachronous complications 1 and 3 months before reflux esophagitis.

Discussion

Symptoms of reflux esophagitis have been reported to occur in about 30% of patients undergoing distal gastrectomy;[22,23] however, reflux esophagitis after standard PD has never been addressed. In a median follow-up time of

Table 1 Risk factors for the development of marginal ulcer after pancreaticoduodenectomy

All patients (N=371)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age, < 60 vs. ≧60	1.10 (0.57–2.14)	0.78	0.97 (0.50–1.90)	0.93
Gender, male vs. female	1.69 (0.83–3.45)	0.15	1.68 (0.80–3.55)	0.17
Peptic ulcer history	1.94 (0.84–4.43)	0.12	1.49 (0.62–3.58)	0.37
PD for chronic pancreatitis	0.60 (0.18–1.97)	0.40	0.59 (0.18–1.94)	0.38
Pancreatic reconstruction, PJ vs. PG	0.63 (0.29–1.36)	0.24	0.51 (0.22–1.19)	0.12
Pylorus preservation	1.30 (0.66–2.54)	0.45	1.05 (0.51–2.18)	0.90
Roux-en-Y gastrointestinal reconstruction	40.76 (2.01–828.58)	0.01	15.04 (2.02–112)	0.02

PD pancreaticoduodenectomy, *PJ* pancreaticojejunostomy, *PG* pancreaticogastrostomy

Table 2 Risk factors for the development of reflux esophagitis after pancreaticoduodenectomy

All patients (N=371)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age, < 60 vs. ≧60	1.52 (0.81–2.86)	0.19	1.39 (0.72–2.66)	0.33
Gender, male vs. female	0.75 (0.40–1.39)	0.36	0.77 (0.40–1.48)	0.43
Reflux esophagitis history	1.15 (0.16–8.42)	0.89	1.04 (0.14–8.03)	0.97
PD for chronic pancreatitis	0.67 (0.24–1.89)	0.45	0.62 (0.21–1.84)	0.39
Pancreatic reconstruction, PJ vs. PG	0.59 (0.29–1.19)	0.14	0.60 (0.29–1.26)	0.18
Pylorus preservation	0.85 (0.44–1.62)	0.62	0.78 (0.39–1.55)	0.47
Roux-en-Y gastrointestinal reconstruction	1.42 (0.70–2.89)	0.33	1.41 (0.69–2.88)	0.35

PD pancreaticoduodenectomy, *PJ* pancreaticojejunostomy, *PG* pancreaticogastrostomy

20 months, 40 of the 371 patients (10.8%) developed reflux esophagitis, and only one of them had gastroesophageal reflux disease preoperatively. To our surprise, reflux esophagitis developed not only after standard PD but also after PPPD (in 15 of 158 patients status post standard PD and in 25 of 213 patients status post PPPD, P=0.62). After standard PD, reflux esophagitis developed significantly more frequently in patients who underwent reconstruction with conventional antecolic gastrojejunostomy (seven of 40 patients) than in patients who underwent reconstruction with R-Y method (eight of 103 patients, P=0.04); however, there was no significant difference in the incidence of reflux esophagitis after PPPD between patients who underwent reconstruction with conventional antecolic duodenojejunostomy (nine of 47 patients) and with Roux-en-Y method (16 of 141 patients). Therefore, we conclude that R-Y reconstruction significantly reduces the incidence of gastroesophageal reflux disease (GERD) after standard PD but not after PPPD.

The pathology of reflux esophagitis is classified into three types: alkaline (caused mainly by reflux of pancreatic juice and bile), acidic (caused mainly by gastric hydrochloric acid), or mixed.[24] Reflux disease (GERD) following a distal gastrectomy and standard PD are caused by the combination of antrectomy and pylorectomy, which decreases gastrin secretion and allows unhindered retrograde flow of duodenal contents into the gastric remnant.[18] The severity of esophagitis after a distal gastrectomy varies depending on the extent of gastrectomy, the degree of dissection of vagus nerve, and the amount of refluxed bile and pancreatic juice;[18] however, in contrast to standard PD, the pylorus, antrum, and vagus nerve are all preserved in PPPD. Therefore, reflux esophagitis following a PPPD in patients without past history of GERD is most likely caused by disruption of reflux-preventing systems at the gastroesophageal junction, thereby allowing reflux of gastric acid into the esophagus. In the healthy individual, the stomach is fixed at junction of the esophagus and duodenum. After division of the right gastric artery, right gastroepiploic artery, and duodenal bulb, the stomach becomes mobile and tends to change position from a transverse to a vertical orientation, which may damage the reflux-preventing system and thereby promote reflux esophagitis. This may also account for the failure of R-Y reconstruction to prevent reflux esophagitis after PPPD.

Marginal ulcer is a concern in R-Y reconstruction after distal gastrectomy because there is less alkaline bile reflux into the stomach,[25] and the jejunum is vulnerable to acid.[26] As shown in other studies,[18–20] of the 371 studied patients, marginal ulcer developed significantly more frequently in patients who underwent reconstruction with the R-Y method than in patients who underwent reconstruction with conventional antecolic gastro- or duodenojejunostomy. Multivariate analysis also showed that R-Y reconstruction was the only significant predictor for marginal ulcer after PD independent of preservation of the pylorus, type of pancreatic reconstruction (pancreaticojejunostomy or pancreaticogastrostomy), history of peptic ulcer, or operation for chronic pancreatitis.

Typsin activity in the esophageal refluxate was reported to be associated with the development of reflux esophagitis after gastrectomy, and protease inhibitor has been used for conservative treatment of alkaline reflux esophagitis.[27–31] However, the protease inhibitor has also been reported to be ineffective in 35.7% of patients after 6 weeks of administration.[32]. In contrast to alkaline reflux esophagitis, for which medical control has a high failure rate, marginal ulcer can be controlled much more effectively with proton pump inhibitor and/or *H. pylori* eradication.[33–35] Untreated reflux esophagitis has been reported to have a greater effect on quality of life than do other conditions including angina pectoris, untreated hypertension, and duodenal ulcer.[36,37] This may account for the increasing use of Roux-en-Y reconstruction after a distal gastrectomy for gastric cancer.[18]

In conclusion, our study showed that R-Y reconstruction was associated with significantly less reflux esophagitis after standard PD (but not after PPPD) and was associated with a significantly greater incidence of marginal ulcer after both standard PD and PPPD. Our data support the use of R-Y reconstruction after standard PD but not after PPPD.

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ORIGINAL ARTICLE

Bypass Surgery Versus Intentionally Incomplete Resection in Palliation of Pancreatic Cancer: Is Resection the Lesser Evil?

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Abstract
Objective As technical expertise increases, the indication for pancreatic resection for advanced pancreatic cancer has been expanded over the last years. Recently, several groups reported their series of unintentionally incomplete tumor resections and reported a potential survival benefit for patients after incomplete resection when compared with palliative bypass surgery. We investigated in a retrospective analysis whether even tumor resection that was intended to be incomplete might provide a better outcome than conventional palliative procedures.
Methods Twenty-two patients with a locally non-resectable or disseminated adenocarcinoma of the pancreas underwent a palliative intentionally incomplete resection. Outcome after resection was compared with that of 46 patients matched for age, sex, and histopathological tumor type who underwent a palliative bypass operation.
Results Overall surgical morbidity was significantly higher in the resection group (59%) compared with the bypass group (33%, $p<0.05$), resulting in a higher relaparotomy rate and a significantly longer postoperative hospital stay ($p<0.001$). Surgery-related mortality was significantly higher in the resection group ($p<0.05$). Overall survival showed no statistically significant difference between the two groups.
Conclusions Because of the higher surgery-related morbidity and mortality and lack of survival benefit in cases of advanced adenocarcinoma of the pancreas, intentionally incomplete palliative resection is not advisable.

Keywords Palliation · Pancreas · Adenocarcinoma · Incomplete resection

Introduction

Palliative treatment strategies for locally advanced or metastasized pancreatic adenocarcinoma include a wide range of medical, surgical, and other interventions. However, randomized, prospective trials and meta-analysis show that none of the treatment strategies have been proven to provide any significant benefit for quality of life and survival.[1–4]

With increasing surgical technical expertise, as well as improved perioperative management, pancreatic surgery can be carried out safely, with mortality rates under 5% even for advanced pancreatic cancer.[5–10] Several authors have recently reported series of the so-called "palliative Whipple's procedure", including our group. Some describe a statistically significant survival benefit for those patients who received incomplete resections compared with those who received palliative bypass surgery.[11–15] However, this experience refers to so-called non-intentional palliative resections. This raises the question of whether, in patients with advanced pancreatic adenocarcinoma for which curative resection is not possible, even resection that is intended to be macroscopically incomplete (R2) might not only improve survival but also quality of life, playing a new role in palliation for such

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patients. It is clear that such an aggressive surgical approach could only be justified, if it improved survival and/or quality of life, and if the related morbidity and mortality did not exceed those of other non-resection palliative interventions. The current literature has no published data that address this controversial question. Here, we report our experience of intentional palliative major resection procedures of pancreatic cancer to clarify whether palliative bypass or palliative R2 resection is the "lesser evil" for pancreatic adenocarcinoma that cannot be curatively resected.

Materials and Methods

The ethical committee of the local chamber of physicians approved the systematic registration in an electronic prospective database of all patients with pancreatic adenocarcinoma, who were treated at the University Medical Center Hamburg-Eppendorf.

Identification of Tumors where Curative Resection Was Precluded

Diagnosis was based on histopathological examination, with tumors categorized according to the sixth edition of the tumor–node–metastasis classification of the International Union against Cancer. Preoperative staging examinations were based on abdominal ultrasonography and helical contrast computed tomography with arterial, pancreatic, and portal phases. Endoscopic retrograde cholangiopancreatography and endoscopic ultrasound were performed in some patients.

Curative resection was ruled out if these examinations showed invasion of the tumor into vital anatomical structures such as the mesenteric root, the superior mesenteric artery, or the celiac trunk, and/or if metastatic lesions were identified.

Selection of Patients for Palliative Intentional R2 Resection

Indications for this operation were done as individual decisions of each patient and surgeon after an extensive explanation of the high risks of such a surgical intervention (high morbidity and mortality, further dissemination of tumor cells). The criteria for this operation were advanced, curatively unresectable, or metastasized pancreatic adenocarcinoma, with significant tumor-associated symptoms such as pain or gastric outlet obstruction related to tumor size and a very strong preference for surgery on the part of the patient.

Selection of Control Patients Undergoing Bypass Surgery

To compare perioperative variables and long-term outcome between patients with intentional R2 resection and those who received a bypass procedure without resection, after their tumor was found intraoperatively to be curatively unresectable, the database was screened for all patients who had undergone bypass procedures for palliation. Among these, a control group (nested case–control study) of patients was selected that was matched according to age (±3 years), sex, and treatment or not with palliative chemotherapy. The latter criterion was included because, while most patients in the R2 resection group received palliative chemotherapy, some either did not consent or did not fulfill fitness criteria for palliative chemotherapy.

In-Hospital Parameters, Surgical Procedures, and Diagnostic Work-Up

The following parameters were prospectively assessed and entered into the database: preoperative stent placement, operative time, blood transfusion requirement, surgical procedure, overall hospital and intensive care unit (ICU) stay, site of R2 resection, and relaparotomy rate.

Depending on the tumor location, patients in the resection group underwent classical pancreaticoduodenectomy (c-PD), pylorus-preserving pancreaticoduodenectomy (pp-PD), distal splenopancreatectomy (d-SP), and subtotal pancreatectomy (st-P). In some cases, additional multivisceral resections were performed.

The bypass procedure was done using the method that is standard at our institution, of retrocolic, end-to-side biliojejunal anastomosis using a Roux-en-Y loop, followed by antecolic gastroenterostomy about 60 cm distal to the bilioenterostomy and an end-to-side enteroenterostomy for reconstruction of alimentary patency.

Regarding surgical morbidity, we documented any occurrence of pancreatic fistula and of postpancreatectomy hemorrhage, anastomotic insufficiency (pancreatico-, choledocho-, gastro-, and jejunojejunostomy), and sepsis or intra-abdominal abscess formation. For patients treated before 2005, we defined pancreatic fistula as drainage of >20 mL/24 h of fluid with amylase activity more than three times the serum amylase activity level, after the third postoperative day. In 2005 and later, the definition of the International Study Group for Pancreatic Fistula was adopted[16]. Perioperative mortality was defined as in-hospital mortality.

Follow-Up

The mean follow-up duration was 7 months (1 to 36 months). These evaluations included regularly scheduled physical examinations, imaging tests, and studies of tumor markers (carcinoembryonic antigen and CA 19–9).

Statistical Analysis

Associations between categorical variables were assessed using Fisher's exact test. Kaplan–Meier method was used to estimate the probability of an event. Death was the only event considered. When no events were recorded, the patients were censored at the last contact. Point and interval estimates of survival rates at 6, 12, and 24 months were calculated. For comparison purposes, log-rank tests and exact stratified log-rank tests were applied. The chi-squared test was applied for selection of the bypass control group matched for the previously mentioned criteria. Two-tailed p values that were less than 0.05 were considered to be significant. Statistical analysis was carried out using SPSS 17.0 for Windows (SPCC Inc. Chicago, IL, USA).

Results

Patient Characteristics

Between January 2000 and February 2009, 22 patients (median age, 66; range, 44–89 years) with a locally advanced pancreatic adenocarcinoma that was not curatively resectable were treated with an intentional palliative R2 resection (the "resection group"). Local unresectability was determined preoperatively by staging examinations and histopathologically confirmed during surgery. The criteria for matching mentioned above were applied to identify a control group comprising 46 patients (median age, 66; range, 43–92 years) who received a palliative bypass (the "bypass group").

There was no significant difference between the palliative resection and bypass groups regarding age (p=0.88); sex (p=0.57); clinical symptoms, such as pain (p=0.80), jaundice (p=0.18), or weight loss (p=0.13); pTNM classification (pT, p=0.48; pN, p=0.71 and pM, p=0.79 or tumor grading (p=0.85); location of unresectable lesion (p=0.53), or adjuvant treatment (p=0.44; Table 1).

Location of Curatively Unresectable Lesion

In the resection and bypass groups, curative resection was not possible mainly because of liver metastasis (resection group, n=7 vs. bypass group, n=19), and local unresectability due to invasion of vital anatomical structures such as

Table 1 Characteristics of patients with advanced pancreatic adenocarcinoma who underwent palliative R2 resection and of a control group matched for age, sex, and treatment with palliative chemotherapy who underwent bypass

	R2 resections (n=22)	Bypass (n=46)	p Value
Median age, years (range)	66 (44–89)	66 (43–92)	0.88
Sex			
Female, %	5 (23)	15 (33)	
Male, %	17 (77)	31 (67)	0.57
Symptoms[a]			
Pain, %	13 (59)	25 (54)	0.80
Jaundice, %	5 (23)	19 (41)	0.18
Weight loss, %	7 (32)	24 (52)	0.13
Tumor staging[b]			
T 2%	1 (4)	0 (0)	
T 3%	13 (60)	12 (52)	
T 4%	8 (36)	11 (48)	0.48
N 0%	5 (23)	5 (33)	
N 1%	17 (77)	10 (67)	0.71
M 0%	8 (36)	15 (64)	
M 1%	14 (64)	31 (67)	0.79
Grade 1%	1 (5)	2 (8)	
Grade 2%	12 (57)	15 (60)	
Grade 3%	8 (38)	8 (32)	0.85
R2 site			
Locoregional, %	9 (41)	11 (23)	
Liver, %	7 (32)	19 (41)	
Combined, %	6 (27)	16 (36)	0.36
Adjuvant treatment			
Yes, %	10 (45)	12 (59)	
No, %	12 (55)	19 (41)	0.44

[a] Multiple symptoms possible per patient

[b] TNM status was not completely evaluable in every patient in the bypass group

the mesenteric root, the superior mesenteric artery, and the celiac trunk (resection group, $n=9$ vs. bypass group, $n=11$) or combined local and distant unresectability (resection group, $n=6$ vs. bypass group, $n=16$, $p=0.53$).

Type of Operation

Different surgical approaches were used for those patients who received tumor resection. Depending on the location of the tumor, patients underwent classical c-PD ($n=14$), pp-PD ($n=3$), st-P ($n=4$), and d-SP ($n=1$). In eight cases, multivisceral resections of different extent were performed (Table 2). Four extended or subtotal gastrectomies, three partial resections of the colon, three resections of the mesocolon, three splenectomies, and three resections of other organs such as adrenal gland or parts of the diaphragm were additionally performed. In five cases, the multivisceral resection involved more than two different organs. Such extended procedures were restricted to patients in good preoperative, clinical condition (American Society of Anesthesiologists score, I–II).

On the other hand, the palliative surgery conducted for the bypass group ($n=46$) encompassed a standard approach to both biliary (hepaticojejunostomy) and gastric (gastrojejunostomy) bypass procedures.

Intraoperative Parameters, Morbidity, and Mortality

Because of the variety of surgical procedures used in the resection group, it was important to analyze the homogeneity of the group. There was no statistically significant difference between the group of patients who received a multivisceral resection and the group with conventional resections, with regard to operation time ($p=0.90$) or blood transfusions ($p=0.59$); pTNM-stage (pT, $p=0.74$; pN, $p=1.0$; pM, $p=1.0$) or tumor grade ($p=0.55$); overall morbidity ($p=1.0$); minor or major complications ($p=1.0$ for both); relaparotomy rate ($p=1.0$); duration of hospitalization ($p=0.097$); in-hospital mortality ($p=1.0$), and overall survival ($p=0.43$).

In contrast, the comparison between the resection group and the bypass group (Table 3), revealed a significantly longer operating time for the resection group (367 min) compared with the bypass group (237 min, $p<0.0001$). More importantly, the resection group showed a significantly higher blood loss and thus need for blood transfusion compared with the bypass group ($n=4$ vs. $n=0$, $p<0.0001$). Furthermore, compared with the bypass group, the palliative tumor resection group had a longer ICU stay (median, 1; range, 0–53 days vs. median, 1; range, 0–6 days; $p=0.05$) and a longer hospital stay (median, 16; range, 12–60 days, vs. median 11, range 1–51 days; $p<0.001$).

Overall surgical morbidity was significantly higher in the resection group (59%) compared with the bypass group (33%, $p=0.035$). The predominant complication was fistula in the resection group (pancreatic fistula $n=5$; chyle fistula $n=3$). Other postoperative complications included gastric outlet syndrome ($n=1$), portal vein thrombosis ($n=1$), pulmonary artery embolism ($n=1$), hemorrhage ($n=1$), pneumonia ($n=2$), and other septic complications ($n=2$; Table 3). Surgery-related morbidity led to a relaparotomy rate of 14% in the resection group and 4% in the bypass group ($p=0.319$). Reasons for relaparotomy were portal vein thrombosis, hemorrhage, and persistent pancreatic fistula in the resection group and hemorrhage and pancreatic fistula in the bypass group.

Table 2 Operative details and in-hospital events for 22 patients with advanced pancreatic adenocarcinoma who underwent palliative intended R2 resection

	R2 resections ($n=22$)	Bypass ($n=46$)	p Value
Median operation time (range)	367 (220–618)	237 (105–420)	0.00
Median units of blood (range)	4 (0–12)	0 (0–4)	0.00
Frequency of complications[a]			
Minor, %	9 (41)	11 (24)	0.17
Wound infection, %	0 (0)	3 (7)	0.55
Sepsis, %	5 (23)	1 (2)	0.01
Others, %	5 (27)	7 (15)	0.32
Major, %	8 (36)	7 (15)	0.05
Pancreatic fistula, %	5 (23)	1 (2)	0.01
Bile leakage, %	0 (0)	1 (2)	1.00
Hemorrhage, %	1 (5)	2 (4)	1.00
Others, %	3 (14)	3 (7)	0.38
Relaparotomy, %	3 (14)	2 (4)	0.32
Median ICU stay, days	1 (0–53)	1 (0–6)	0.05
Median hospital stay, days	16 (12–60)	11 (1–51)	0.00
In-hospital mortality, %	6 (27)	3 (7)	0.05

[a] Multiple complications possible per patient

Table 3 Summary of intraoperative characteristics and in-hospital events for patients who underwent palliative surgery for advanced pancreatic adenocarcinoma, including a study group who received an intended R2 resection and a control group, matched for age, sex, and treatment with palliative chemotherapy

Patient no.	Sex	Age	Surgical procedure	Multivisceral resection[a]	R2 resection site[b]	T	N	M	Grade	Tumor location	Complications	Perioperative mortality
1	M	63	c-PD	1, 3	2	3	1	0	3	Head		Yes
2	M	67	c-PD	0	1	3	0	1	2	Head	Chyle fistula	NO
3	M	56	c-PD	0	2	3	1	0	3	Head	Gastric outlet syndrome	NO
4	F	63	c-PD	0	2	4	1	1	2	Head		NO
5	M	64	c-PD	0	3	2	1	1	2	Head		NO
6	M	59	c-PD	0	2	3	1	0	2	PU	Pn, S, portal vein thrombosis	Yes
7	F	76	c-PD	2	2	4	1	1	3	Head	Chyle fistula	No
8	F	66	c-PD	0	2	4	1	0	2	Head	PF, Pn, S	Yes
9	M	60	st-P	1, 2	3	4	1	1	3	Head	Lung artery embolism	No
10	F	67	pp-pD	0	3	3	1	1	2	Head		No
11	M	83	c-PD	0	1	3	1	1	2	Head	PF, Pn, S	Yes
12	M	65	st-P	3, 4	1	3	1	1	3	Head		No
13	M	64	pp-PD	0	3	4	1	1	2	Head		No
14	M	57	c-PD	1, 4, 9	1	4	1	1	2	Tail	Pn, S	No
15	M	44	d-SP	9	3	3	1	1	2	Body		No
16	M	62	st-PD	3	2	3	0	0	2	Head	Hemorrhage, S	Yes
17	M	65	pp-PD	0	1	3	1	1	3	Head		No
18	M	89	pp-PD	0	2	4	1	0	2	PU	Chyle fistula	Yes
19	M	72	c-PD	0	1	3	0	1	3	Head		No
20	M	79	c-PD	0	1	4	1	1	3	Head	PF	No
21	M	80	c-PD	0	2	3	0	0	1	Head	PF	No
22	M	57	st-P	1, 2 ,4, 9	3	3	0	0	2	Body	PF	No

c-PD pancreatoduodenectomy, *pp-PD* pylorus-preserving pancreatoduodenectomy, *st-P* subtotal pancreatectomy, *d-SP* distal splenopancreatectomy, *PU* processus uncinatus, *PF* pancreatic fistula, *PN* pneumonia, *S* sepsis

[a] In multivisceral resection, *1* indicates extended or subtotal gastric resection, *2* partial resection of the mesecolon and colon, *3* resection of the mesecolon, *4* splenectomy, *9* other

[b] In R2 resection site, *1* indicates liver metastasis, *2* locally irresectable, *3* combined locally irresectable and distant metastasis

Survival Analysis

The overall in-hospital mortality was significantly higher in the resection group compared with the bypass group (six of 22 [27%] vs. three of 46 [7%]; $p=0.049$; Table 3).

The median overall survival after intentional R2 resection was 5.1 months (95%CI 0.8–9.5 months) and was similar to the 5.8 months observed in the bypass group (95%CI 4.1–7.4). Likewise, there was no significant difference between the palliative resection group and the bypass group in estimated overall 0.5-, 1-, and 2-year survival after palliative surgery (resection group 45%, 18%, and 5%, respectively vs. bypass group 47%, 18%, and 4%; $p=0.845$; Fig. 1). Sub-stratification of patients regarding metastasis status revealed no significant differences between the two study groups with metastasis (resection group, mean survival 7.0°months, 95%°CI 4.7–9.4°months and bypass group, 6.6°months, 95%°CI 5.0–8.3°months; $p=0.985$) or without metastasis (resection group, mean survival 7.3°months, 95%°CI 0–14.7°months; bypass group, 8.4°months, 95%°CI 4.0–13.7; $p=0.490$).

Discussion

Recently, several retrospective studies have addressed the question of whether an incomplete tumor resection provides a survival benefit compared with palliative bypass for patients with advanced pancreatic cancer.[11–14,17,18] These studies exclusively investigated unintended incomplete resection, occurring as a result of technical unresectability during surgery. Unfortunately, the reported results are not

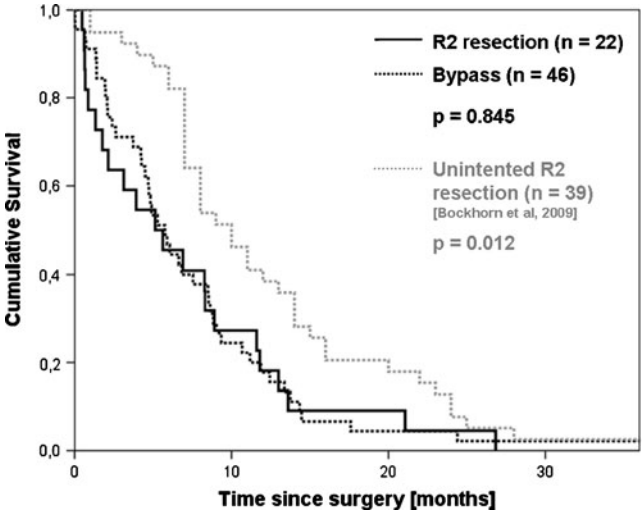

Fig. 1 Actuarial Kaplan–Meier survival analysis of patients who underwent intentional palliative R2 pancreatectomy compared with patients who received palliative bypass surgery (p=0.845, log-rank test). For ease of comparison, the estimated survival of patients who received an unintended R2 resection, as reported previously by Bockhorn and colleagues[12], is also shown (p=0.012)

uniform, and thus the advantages of either procedure remain unclear. None of the treatment options currently available today appear to offer substantially better palliation or, as the best scenario, a survival benefit. The recently published series by Köninger and colleagues show a significantly higher morbidity and mortality while lacking any survival benefit[17], but, in contrast, the majority of studies addressing the role of unintended R2 resections indicate improved survival for patients who received tumor resection. However, it has to be noted that pancreatic resection when compared with the bypass procedure was associated with an increased morbidity in most studies. The reason for the overall divergence in the results might be heterogeneous patient inclusion criteria. All but two studies also included patients with microscopically tumor invasion in the resection margins (R1) in the palliative resection group; this in turn clearly influences the results.

In a previously published study, we have reported a significant survival benefit for patients who received unintentional R2 resection compared with bypass procedures (11.5 months vs. 7.5 months, p=0.014).[12] As a logical extension of this analysis, in the current retrospective analysis, we wanted to address the question of whether resection, even in the setting of clearly visible, gross local tumor spread that would not allow for complete tumor resection or of already disseminated disease, would provide any benefit to patients. Over the last 10 years, 22 patients with a technically not completely resectable pancreatic adenocarcinoma were surgically treated with intentionally performed macroscopically incomplete resection of the tumor. These patients suffered from major tumor-associated symptoms such as pain or gastric outlet obstruction related to tumor size and a very strong preference for surgery on the part of the patient. Every indication was an individual decision of the patient and surgeon after an extensive discussion of the risks of an incomplete pancreatic tumor resection.

It is important to note that, in this study, we included patients with liver metastasis, the rationale being that bypass procedures are also performed in such patients as well as in those with local unresectable tumors. However, we additionally analyzed the overall survival of those patients without metastasis, which also revealed no significant difference between the resection and bypass group (p=0.490). The main reason for the apparently divergent finding of this sub-stratification and the previous study of the non-intentional macroscopic incomplete resections (where no metastatic diseases were implemented) is caused by the significantly smaller local extent but more central localization of the tumors inside the pancreatic head in the previous study.

Our analysis shows that not only overall morbidity but also the occurrence of severe complications was significantly higher in the resection group compared with the bypass group, and moreover, the higher morbidity resulted in significantly higher surgery-related mortality in the resection group. In addition, we were unable to define a subgroup of patients in this study for whom such aggressive surgical intervention might be of any benefit. Morbidity and mortality were not restricted to those patients who underwent multivisceral resection.

Nevertheless, some limitations of our current study need to be addressed. Bearing in mind the World Health Organization (WHO) definition of palliation, which emphasizes improvement in quality of life, it becomes clear that comprehensive evaluation of the benefit of such aggressive surgical strategies for managing pancreatic adenocarcinoma requires additional information, including the rehospitalization rate and a quality of life assessment. However, in our opinion, there is no need to address this question in further clinical trials. To experience quality of life, it is mandatory to survive the operation. Even if aggressive pancreatic resection in the context of disseminated disease would help to improve quality of life, this would be at the price of significantly higher surgery-related morbidity and mortality.

Conclusion

In summary, our data indicate that intentional R2 resection does not provide a life-prolonging alternative to the conventional palliative procedures. Even when those patients with perioperative mortality are excluded, there is still no advantage of the resection over the bypass

procedure (data not shown). While this result may appear trivial at first sight, since it is what would be expected intuitively, for the first time, we provide the clinical data and thus the evidence to support this stance.

Therefore, we firmly agree with and support the recent consensus position of Evans and colleagues[19] that palliative resection should not be routinely performed in the treatment of locally advanced and/or metastasized pancreatic adenocarcinoma.

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ORIGINAL ARTICLE

Patterns of Pancreatic Resection Differ Between Patients with Familial and Sporadic Pancreatic Cancer

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Abstract
Background Although the increased risk of developing pancreatic cancer (PC) in families with a strong history of the disease is well known, characteristics and outcomes of patients with familial PC is not described well.
Aims This study aims to evaluate outcomes following resection in patients with familial PC.
Methods We studied 208 patients who underwent resection of PC from 2000 to 2007 and had prospectively completed family history questionnaires for the Biospecimen Resource for Pancreas Research at our institution. We compared clinical characteristics and outcomes of familial and sporadic PC patients.
Results Familial (N=15) and sporadic PC patients (N=193) did not have significantly different demographics, pre-operative CA19-9, pre-operative weight loss, R0 status, or T-staging (all $p \geq 0.05$). Familial PC patients had lower pre-operative total serum bilirubin concentrations (p=0.03) and lesions outside of the pancreatic head more frequently (p=0.02) than sporadic PC patients. There was no difference in survival at 2 years between familial and sporadic PC patients (p=0.52).
Conclusions Familial PC patients appear to develop tumors outside of the pancreatic head more frequently than sporadic PC patients. This difference in tumor distribution may be due to a broader area of cancer susceptibility within the pancreas for familial PC patients.

Keywords Pancreatic cancer · Familial cancer syndrome · Familial pancreatic cancer

Background

The increased risk of developing pancreatic cancer (PC) in families with a strong history of the disease has been described increasingly since the late 1960s and early 1970s.[1–5] Since those initial reports, various studies have shown that 4–16% of patients who develop PC have a family history of PC.[6–8] These figures include patients with a variety of familial cancer syndromes such as hereditary non-polyposis colorectal cancer syndrome (Lynch II variant),[9] Peutz–Jegher syndrome (PJS),[10] hereditary breast–ovarian cancer syndrome (BRCA2),[11] familial atypical multiple mole melanoma syndrome,[12] and hereditary pancreatitis.[13] Despite the association between these cancer syndromes and PC, most patients with familial PC do not have an identifiable syndrome or known genetic change.[14]

Some patients with familial PC have features that could, in theory, affect outcomes. Specifically, familial PC patients with mutations in the Fanconi anemia/BRCA2 pathway are hypersensitive to a variety of chemotherapy agents,[15] patients with PJS may be predisposed to developing PC via intraductal papillary mucinous neoplasia (IPMN) and not pancreatic intraepithelial neoplasia (PanIN),[16] and patients with hereditary nonpolyposis colorectal cancer (HNPCC) have been shown to develop the medullary variant of pancreatic

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adenocarcinoma[17,18] which appears to be less lethal than typical PC.[19] Additionally, pancreatic specimens resected in familial PC patients can have multifocal precursor lesions producing a unique pattern of parenchymal atrophy and fibrosis which is not typically seen in sporadic PC.[14] Despite all of these unique associations, differences in clinical features and outcomes between familial PC and sporadic PC patients who undergo pancreatic resection is not described well.

Hypothesis/Study Aim

We hypothesized that familial PC patients and sporadic PC who undergo resection have different clinical features and survival. Our aim was to compare clinical features, pathology, and survival in familial PC patients to sporadic PC patients following pancreatic resection.

Methods

The Biospecimen Resource for Pancreas Research at our institution, supported by the Specialized Program of Research Excellence (SPORE) in Pancreatic Cancer (NCI P50CA102701), prospectively registered 326 patients who underwent resection of various pancreatic lesions from October 2000 to June 2007. Both the SPORE in pancreatic cancer and this study obtained full institutional review board approval at our institution prior to initiating the investigation. A final study sample was comprised of 234 patients who underwent resection of pancreatic ductal adenocarcinoma and had completed family history questionnaires in conjunction with registration into the Biospecimen Resource for Pancreas Research. Of these 234 patients, 208 had typical ductal adenocarcinoma and 26 had IPMN-invasive carcinoma. The group of 208 patients with typical ductal adenocarcinoma was the primary focus of this study (Fig. 1). We compared demographics, pre-operative clinical variables, surgical variables, staging, and outcomes of patients with familial PC (patients with one or more first-degree relative with PC) to patients with sporadic PC (patients who did not meet familial PC criteria).

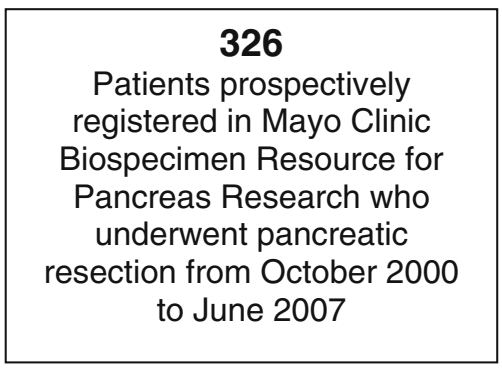

Fig. 1 Patient selection flowsheet

The clinical features of interest included age at resection (years), sex (male, female), body mass index (BMI; per admitting records), the symptoms of jaundice (per initial history), weight loss (per initial history), the use of adjuvant therapy (per oncology records), pre-operative serum total bilirubin concentration (mg/dL; within 30 days prior to operation), pre-operative serum CA 19-9 levels (U/L; within 30 days prior to operation), and lesion location per pre-operative imaging (head or uncinate, body and/or tail, head and body, or other by magnetic resonance imaging or computed tomography). The surgical features of interest included type of resection (pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy per operative reports), and resection margins (R0 versus R1 or R2 per operative and pathology reports). The pathologic features of interest obtained from the surgical pathologic report included tumor size (mm), tumor grade (1–4), tumor stage (T1, T2, T3, T4), lymph node stage (N0, N1).

Surgical margins were assessed initially by intra-operative frozen section analysis and then by routine permanent section. This approach allowed re-resection to achieve negative margins during the initial operation. Patients with resected PC were staged according to guidelines in the *American Joint Committee on Cancer—Cancer Staging Manual,* 6th edition. The surgical margins evaluated for pancreatoduodenectomy and total pancreatectomy specimens included the proximal common hepatic duct, pancreatic neck, margin at the uncinate process or the superior mesenteric artery, posterior, inferior, and superior (soft tissue) pancreatic margin, portal vein groove, and proximal duodenal margin if the patient was undergoing a pylorus-preserving resection. Margins evaluated for distal pancreatectomy specimens included the site of pancreatic transaction and radial pancreatic soft tissue.

Clinical, pathologic, and surgical features were compared between familial and sporadic PC patients using Wilcoxon rank sum, chi-square, and Fisher's exact tests. Overall survival and recurrence-free survival were estimated using the Kaplan–Meier method and compared between patient groups using log-rank tests. Statistical analyses were performed using the SAS software package (SAS Institute; Cary, NC, USA). All tests were two-sided and p values <0.05 were considered statistically significant.

Results

Clinical Features

Within the group of 208 patients who had typical ductal adenocarcinoma not associated with IPMN, there were 15

patients with familial PC and 193 patients with sporadic PC. These patients did not differ significantly in age, gender, pre-operative BMI or weight loss, pre-operative serum CA 19-9 level, and use of adjuvant therapy (all $p \geq 0.05$; Table 1). Familial PC patients had significantly lower pre-operative serum total bilirubin concentration and jaundice ($p=0.03$ each).

A total of 13 of 15 familial PC patients had only one first-degree relative with PC; two of these 13 patients had a strong family history of breast cancer (BRCA 2 status unknown), one was a member of an HNPCC kindred, and another was part of the third successive generation with PC. Of the two patients with more than one first-degree relative with PC, one had a parent and a sibling with PC, and one patient had two siblings with PC. The only patient with a documented cancer syndrome or genetic change was the single patient who was part of a known HNPCC kindred as described above.

Pathology

Margin status, nodal status, tumor grade, and tumor diameter did not differ significantly between familial and sporadic PC patients ($p>0.3$; Table 1). Familial and sporadic PC patients had a marginally different T stage distributions ($p=0.05$); T2 lesions were present in 40% of

Table 1 Clinical, surgical, and pathologic features between familial PC and sporadic PC patients with typical ductal adenocarcinoma only

	Sporadic PC ($N=193$)	Familial PC ($N=15$)	
Feature	Median (range)		*P* value
Age at resection (years)	64 (38–85)	69 (54–84)	0.11
BMI ($N=206$)	26.8 (16.5–41.3)	27.3 (22.8–35.0)	0.38
Bilirubin (mg/dL; $N=183$)	1.5 (0.2–32.4)	0.6 (0.3–12.4)	0.03
CA19-9 (U/L; $N=158$)	140 (0–335,300)	601 (17–2,860)	0.05
Tumor diameter (mm)	34 (6–95)	32 (20–55)	0.34
	N (%)		
Male sex	106 (55)	11 (73)	0.17
Jaundice ($N=201$)	114 (61)	4 (30)	0.03
Weight loss ($N=203$)	104 (55)	9 (64)	0.50
Lesion location on imaging ($N=207$)			
Head or uncinate	151 (79)	7 (47)	0.02
Body and/or tail	27 (14)	6 (40)	
Head and body	4 (2)	0	
No mass/NOS	10 (5)	2 (13)	
Type of resection			
Pancreatoduodenectomy	159 (82)	7 (47)	0.006
Distal pancreatectomy	29 (15)	7 (47)	
Total pancreatectomy	5 (3)	1 (7)	
Margins at Resection			
R0	156 (81)	11 (73)	0.59
R1	34 (18)	4 (27)	
R2	3 (2)	0	
Tumor grade ($N=207$)			
1	0	0	0.36
2	29 (15)	3 (20)	
3	132 (69)	8 (53)	
4	31 (16)	4 (27)	
Tumor stage			
T1	7 (4)	0	0.05
T2	48 (25)	6 (40)	
T3	158 (72)	8 (53)	
T4	0	1 (7)	
Nodal metastases ($N=207$)	112 (58)	7 (50)	0.56
Adjuvant treatment ($N=217$)	150 (84)	15 (87)	1.00

familial PC patients compared to only 26% of sporadic PC patients. When comparing frequencies of lesions that were T3 or higher, however, there was no difference between familial and sporadic PC patients (60% and 72% respectively; $p=0.38$). Familial PC patients had lesions requiring pancreatoduodenectomy in 47%, distal pancreatectomy in 47%, and total pancreatectomy in 7% compared to 82%, 11%, and 2%, respectively, in sporadic PC patients ($p=0.007$). There were no differences in overall or recurrence-free survival between familial PC and sporadic PC patients (all $p\geq0.5$; Figs. 2 and 3).

Inclusion of IPM-invasive Carcinoma Patients

There were no patients who met criteria for familial PC in the group of 26 patients with IPMN-invasive carcinoma. Inclusion of these 26 patients with the 193 patients who had sporadic and typical ductal adenocarcinoma, revealed no new associations with any of the variables studied (Table 2). Pre-operative total serum bilirubin concentration, jaundice, resection type, and lesion location on imaging remained significantly different between familial PC patients and this larger group of patients with sporadic ($p\leq0.03$).

Comparison of Resection Type and Tumor Location

The type of resection performed was compared to tumor location within the pancreas as depicted on preoperative imaging studies for all 234 patients assessed in this study. Pancreatic head and uncinate tumors were resected by pancreatoduodenectomy (PD) in 96% of patients. Body and/or tail lesions were resected by distal pancreatectomy in 92%. The location of the lesion on imaging was significantly associated with resection type ($p<0.0001$).

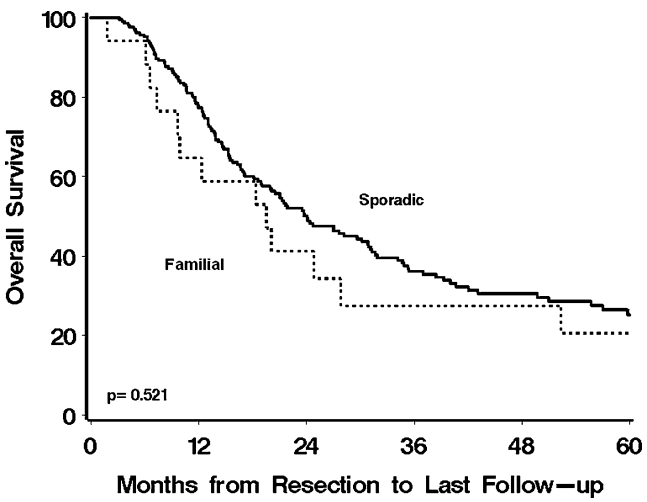

Fig. 2 Kaplan–Meier curve comparing overall survival following resection for familial PC patients compared sporadic PC patients

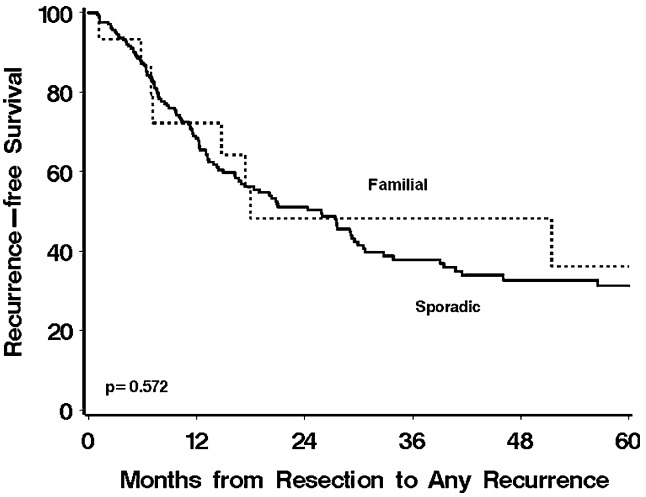

Fig. 3 Kaplan–Meier curve comparing recurrence-free survival following resection for familial PC patients compared to sporadic PC patients

Analysis of Patients who did not Complete Family History Questionnaires

Family history questionnaires were not completed by 73 (24%) patients who had been consented for participation into the Biospecimen Resource for Pancreas Research but, otherwise, would have met inclusion criteria for our study. Comparison of these 73 patients to the 234 patients who met final inclusion criteria revealed that patients who did not complete family history questionnaires had shorter overall survival ($p=0.003$) and a different distribution of resection types ($p=0.01$). Patients who completed family history questionnaires underwent PD in 80%, distal pancreatectomy in 18%, and total pancreatectomy in 3%; patients who did not complete family history questionnaires underwent PD in 85%, distal pancreatectomy in 7%, and total pancreatectomy in 8%. Lesion location on pre-operative imaging, however, was not different between patients with and without completed family history questionnaires ($p=0.09$). There was no significant difference between these groups for any of the remaining variables studied in Tables 1 and 2 ($p\geq0.06$).

Discussion

Our findings indicate that patients with familial PC required resections outside of the pancreatic head more frequently than sporadic PC patients. This difference correlates to a broader distribution of lesions within the pancreas on pre-operative imaging for patients with familial PC. Serum total bilirubin was significantly lower in familial PC patients likely reflecting the differences in lesion distribution. Serum CA 19-9 trended towards higher concentrations in

Table 2 Clinical, surgical, and pathologic features between familial PC and sporadic PC patients with typical ductal adenocarcinoma OR IPMN adenocarcinoma

	Sporadic PC (*N*=219)	Familial PC (*N*=15)	
Feature	Median (range)		*P* value
Age at resection (years)	66 (37–89)	71 (54–84)	0.15
BMI (*N*=231)	26.7 (16.5–44.5)	27.1 (22.8–35.0)	0.36
Bilirubin (mg/dL; *N*=205)	1.5 (0.2–32.4)	0.7 (0.3–12.4)	0.03
CA19-9 (U/L; *N*=175)	131 (0–335,300)	456 (17–2,860)	0.05
Tumor diameter (mm; *N*=232)	34 (6–95)	32 (20–55)	0.31
	N (%)		
Male sex	120 (55)	11 (73)	0.16
Jaundice (*N*=223)	126 (60)	4 (30)	0.04
Weight Loss (*N*=228)	114 (53)	9 (64)	0.41
Lesion location on imaging (*N*=233)			
Head or uncinate	172 (79)	7 (47)	0.02
Body and/or tail	31 (14)	6 (40)	
Head and body	4 (2)	0	
No mass/NOS	11 (5)	2 (13)	
Type of resection			
Pancreatoduodenectomy	182 (82)	7 (47)	0.007
Distal pancreatectomy	34 (16)	7 (47)	
Total pancreatectomy	5 (2)	1 (7)	
Margins at resection			
R0	179 (82)	11 (73)	0.43
R1	37 (17)	4 (27)	
R2	3 (1)	0	
Tumor grade (*N*= *233)*			
1	0	0	0.37
2	39 (18)	3 (20)	
3	147 (67)	8 (53)	
4	32 (15)	4 (27)	
Tumor stage			
T1	9 (4)	0	0.05
T2	56 (26)	6 (40)	
T3	154 (70)	8 (53)	
T4	0	1 (7)	
Nodal metastases (*N*=233)	124 (57)	7 (50)	0.63
Adjuvant treatment (*N*=217)	161 (80)	13 (87)	0.74

familial PC patients, albeit not significantly (p=0.05), which may reflect a difference in tumor characteristics and not just lesion distribution. Interestingly, despite these differences, overall and recurrence-free survival was similar between familial PC and sporadic PC patients.

There has been a wide variety of inclusion criteria in studies assessing the impact a family history has on the risk of developing PC.[20] We chose to study patients with one or more first-degree relative with PC which is in keeping with what the National Familial Pancreas Tumor Registry (NFPTR) at The Johns Hopkins Hospital considers familial PC: a parent–offspring pair or pair of siblings with pancreatic cancer in the kindred.[14] The risk of developing PC in first-degree relatives of patients with PC is about 6.5-fold greater than the background rate of 1:10,000 cases. When there are two relatives with PC, the risk of developing PC in first-degree relatives increases to 18-fold the background rate; with three affected relatives, the risk is increased to 57-fold.[21] These figures highlight not only the markedly increased risk of developing PC in first-degree relatives of patients with PC but the rationale behind the NFPTR definition of familial PC.

As discussed previously, patients with PJS appear to develop PC via IPMN as opposed to PanIN.[16] In order to isolate these two proposed pathways for PC development, we chose to analyze our cohort with and without IPMN

patients. There were no familial PC patients in the IPMN group. Conversely, of the 15 patients with familial PC, there were no patients diagnosed with PJS. In fact, only one patient was diagnosed with an inherited cancer syndrome out of the 15 patients with familial PC; this reflects the finding that a majority of familial PC patients do not have a documented cancer syndrome or genetic change.[14]

Despite differences in lesions distribution, we were unable to show a difference in survival between familial PC and sporadic PC patients. Since October 2000, 69% of patients who were seen at our institution for pancreatic lesions were consented for inclusion in our institution's Biospecimen Resource for Pancreas Research. Additionally, familial PC patients represented 7% of the study sample. Although our percentage of familial PC mirrors rates found in other studies,[6–8,20] both the overall recruitment rate (69%) and the percentage of familial PC patients in this study are potential limitations which may introduce selection bias and, by decreasing overall sample size, could affect our ability to detect a significant difference in survival and, perhaps, other variables studied. In order to detect a difference in survival of 50% versus 35% at 2 years between familial PC and sporadic PC patients (assuming 80% power and two-sided alpha of 0.05), we would need a sample size three times larger than in our current study. Given the use of prospectively collected family history questionnaires and our inclusion criteria, accruing a sample of this size would be difficult in a single institution.

The observed overall survival of familial PC patients may be affected by issues other than selection bias and sample size. It is plausible that familial PC patients seek medical care sooner than sporadic PC patients due to prior exposure and knowledge of the disease. Seeking earlier medical care could improve the overall survival of familial PC patients despite different tumor distribution.

Family history questionnaires were not completed by 73 (24%) patients who had been consented for participation into the Biospecimen Resource for Pancreas Research but, otherwise, would have met inclusion criteria for our study. In order to assess this possible selection bias, we compared these 73 patients to the 234 patients who met final inclusion criteria. Interestingly, these patient groups had different overall survival which limits the conclusions that can be inferred from our study particularly for survival. It is not clear why patients who did not complete family history questionnaires have lesser overall survival. It plausible but unsubstantiated that the burden of their disease may have affected their ability to complete all of the questionnaires associated with participation in the Biospecimen Resource for Pancreas Research. More importantly, it is unclear if this selection bias may have affected our ability to detect a difference between familial and sporadic PC patients for survival and even other variables investigated. A study assessing risk factors and outcomes in familial PC patients registered at the NFPTR, however, found no difference in survival as well between familial PC and sporadic PC patients.[22]

Although resection types performed were different between patients who did and did not complete family history questionnaires, lesion location on pre-operative imaging was similar. The difference found for resection types is driven largely by a slightly higher percentage of patients who underwent total pancreatectomy in the group of patients who did not complete family history questionnaires compared to those who did complete the family history questionnaires (8% vs. 3%). Interestingly, these groups had an equal absolute number of patients who underwent total pancreatectomy ($N=6$). Therefore, the difference in resection type between patients who did and did not complete family history questionnaires does not indicate that the differences found for lesion location between sporadic and familial PC patients is biased.

The role of family history in the occurrence of pancreatic cancer highlights the importance of further investigation of this role and the need for delineating screening programs for familial PC kindreds. Although a few patients in this study were recruited into multi-institutional studies investigating screening programs for patients with familial PC, the patients in our study were not part of any broad clinical screening program. Despite current screening programs under investigation at other institutions, there are no evidence-based standard of care recommendations for screening and interventions (other than genetic testing) in familial pancreatic cancer. Furthermore, there is no screening modality of choice since interpretation of findings, particularly with endoscopic ultrasound (EUS), is not clear. Therefore, EUS is not routinely offered at Mayo as a matter of course; however, it is made available to family members who request it.

In conclusion, familial PC patients who undergo resection appear to develop tumors outside of the pancreatic head more frequently than sporadic PC patients, as reflected by differences in the types of resections performed. As a result of these findings, we hypothesize that patients with familial PC may have a broader or at least different area of cancer *susceptibility* within the pancreas than patients with sporadic PC. These findings highlight the need for further pathological, genetic, and molecular studies of familial PC.

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ORIGINAL ARTICLE

Effect of Antecolic or Retrocolic Reconstruction of the Gastro/Duodenojejunostomy on Delayed Gastric Emptying After Pancreaticoduodenectomy: A Randomized Controlled Trial

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Abstract
Objective To study the effect of antecolic vs. retrocolic reconstruction on delayed gastric emptying (DGE) after pancreaticoduodenectomy (PD) and to analyze factors which may be associated with post-PD DGE.
Summary Background Data DGE is a troublesome complication occurring in 30–40% of patients undergoing PD leading to increased postoperative morbidity. Many factors have been implicated in the pathogenesis of DGE. Among the various methods employed to reduce the incidence, recent reports have suggested that an antecolic reconstruction of gastro/duodenojejunostomy may decrease the incidence of DGE.
Methods Between Sep 2006 and Nov 2008, 95 patients requiring PD (for both malignant and benign conditions) were eligible for the study. Of these, 72 patients finally underwent a PD and were randomized to either a retrocolic or antecolic reconstruction of the gastro/duodenojejunostomy. All patients underwent the standard Whipple's or a pylorus preserving pancreaticoduodenectomy (PPPD), and the randomization was stratified according to the type of PD done. DGE was assessed clinically using the Johns Hopkins criteria (Yeo et al. in Ann Surg 218: 229–37, 1993). In patients suspected to have DGE, mechanical causes were excluded by imaging and/or endoscopy. Occurrence of DGE was the primary endpoint, whereas duration of hospital stay and occurrence of intra-abdominal complications were the secondary end points.
Results The antecolic and retrocolic groups were comparable with regard to patient demographics, diagnosis, and other preoperative, intraoperative, and postoperative factors. Overall, DGE occurred in 21 patients (30.9%). There was no significant difference in the incidence of DGE in the antecolic vs. the retrocolic group (34.4% vs. 27.8%; $p=0.6$). On univariate analysis, older age, use of octreotide, and intra-abdominal complications were significantly associated with the occurrence of DGE; however, on a multivariate analysis, only age was found to be significant ($p=0.02$). The mean postoperative stay was longer among patients who developed DGE (21.9±9.3 days vs. 13±6.9 days; $p=0.0001$).
Conclusions Delayed gastric emptying is a cause of significant morbidity and prolongs the duration of hospitalization following pancreaticoduodenectomy. The incidence of DGE does not appear to be related to the method of reconstruction (antecolic or retrocolic). Older age may be a risk factor for its occurrence.

Keywords Pancreaticoduodenectomy · Gastric emptying · Gastrojejunostomy

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Introduction

Pancreaticoduodenectomy is the mainstay of treatment for patients with pancreatic or periampullary pathology. In the past, this procedure was associated with a

significant morbidity and mortality. With advances in surgical techniques and better perioperative management, the mortality rate has decreased; however, the morbidity rate still remains high.[1–5]

A major cause of early morbidity following pancreaticoduodenectomy (PD) is delayed gastric emptying (DGE). Although not a life-threatening complication, this condition results in significant morbidity by delaying oral alimentation, prolonging the hospital stay, and increasing the cost of hospitalization. Although DGE is strongly associated with intra-abdominal complication, the pathogenesis of DGE remains unclear in those without intra-abdominal complications.[6,7] The reported incidence of DGE in the literature ranges from 14% to 61%.[8] Various hypotheses have been proposed, but the exact cause of DGE remains unproven. Many studies have tried to identify factors other than intra-abdominal abscess but have not obtained consistent results.

Various technical and therapeutic measures have been advocated to decrease the incidence of DGE. These include pyloric dilation,[9] preservation of the left gastric vein,[10] preoperative use of erythromycin,[11], and cyclic enteral feeding.[12] A few recent studies have reported that the type of reconstruction of the duodenojejunostomy or gastrojejunostomy might have a bearing on the incidence of DGE.[13–15] The present randomized trial, therefore, aimed to evaluate the impact of the type of reconstruction of the duodenojejunostomy or gastrojejunostomy (viz., antecolic vs. retrocolic) on the incidence of delayed gastric emptying following PD.

Methods

This study was a prospective randomized controlled trial conducted between September 2006 and December 2008 in the Department of Gastrointestinal Surgery, at the All India Institute of Medical Sciences, New Delhi, India. The study was approved by the Institute's Ethics Committee and the study protocol conformed to the ethical guidelines of the "World Medical Association Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects." All patients less than 70 years with a good performance status (Eastern Cooperative Oncology Group scores 0, 1, and 2) [16] who underwent a classical Whipple's PD or a pylorus preserving PD (PPPD) for carcinoma (periampullary, duodenal, and pancreatic head), neuroendocrine tumors, or chronic pancreatitis were included. Informed consent was obtained from all the patients. Those who did not consent, those with metastatic and locally advanced disease, peptic ulcer disease, gastric outlet obstruction, tumor infiltration into the stomach, previous gastric surgery, and poorly controlled diabetes mellitus were excluded. We considered those patients to have poorly controlled diabetes who had a long standing history of diabetes with poor glycemic control (HbA1c>7.5%) or had systemic complications of diabetes.

Patient Evaluation

All the patients who fulfilled the inclusion criteria underwent a thorough clinical examination. The diagnosis and resectability was confirmed by ultrasound and dual phase contrast enhanced computed tomography (pancreas protocol) of the abdomen. A side-viewing endoscopy with biopsy was routinely done and augmented with an endoscopic ultrasound study whenever required. Magnetic resonance imaging including cholangiopancreatography, and endoscopic retrograde cholangiopancreatography (ERCP) were additionally done if required. Preoperative biliary drainage was done in patients with cholangitis, poor general condition, high grade jaundice (serum bilirubin more than 15 mg/dl), or an anticipated delay in surgery.

Sample Size and Randomization

Patients were randomized at surgery (after completion of resection) with computer-generated random numbers using a sealed envelope technique. The incidence of DGE as per our experience is about 30%. The study was designed to detect a 50% decrease in DGE in all patients randomly assigned to the antecolic group with 80% power at a 5% significance level requiring a sample size of 80 patients (40 in each group).

Operative Technique

All patients were explored through a roof-top incision. Obvious dissemination was excluded. After confirming the resectability, pancreaticoduodenectomy (classical Whipple's or PPPD) was performed. In general, PPPD was done for all periampullary tumors and small pancreatic head tumors (<2 cm) where a well-vascularized segment of proximal duodenum (at least 3 cm) was available for the anastomosis. When PPPD was not considered feasible in view of doubtful margins, antral involvement, large pancreatic head mass, presence of prepyloric lymph nodes, or compromised vascularity of the duodenum, a standard Whipple's procedure was done. The choice of procedure, however, was largely left to the discretion of the operating surgeon. The resected specimen included the gall bladder, distal common bile duct, pancreatic head, duodenum, and 10 cm of the proximal jejunum. The proximal duodenum (up to 3 cm distal to the pylorus) and the right gastric artery were preserved for a PPPD. Extended lymphadenectomy was not done.

Reconstruction

Bilio-pancreatic reconstruction was done using a loop of jejunum brought up through the transverse mesocolon to the right of the middle colic vessels. Pancreaticojejunostomy was done first using the "duct-to-mucosa" or the "invagination" technique. The choice was based on the pancreatic texture, diameter of the pancreatic duct, and the preference of the surgeon. The pancreaticojejunostomy (PJ) was stented at the surgeon's discretion with 5 or 6 French plastic feeding tube. The hepaticojejunostomy (HJ) was done using an interrupted single layer technique with 3-0 or 4-0 vicryl/PDS and stented with a T tube. Finally, the duodenojejunostomy or gastro-jejunostomy (in PPPD and Whipple's procedure, respectively) was constructed in two layers. For an *antecolic reconstruction*, the jejunal loop about 30 cm distal to the HJ, was brought up anterior to the transverse colon and anastomosed to the duodenum or stomach (Fig. 1a). For the *retrocolic reconstruction*, the jejunal loop was anastomosed to the duodenum or stomach through a separate mesocolic window on the left of the middle colic vessels (Fig. 1b). The reason for using a separate mesocolic window was to standardize both the procedures with respect to the distance of the gastro/duodenojejunostomy from the hepaticojejunostomy and the angulation of the jejunum, differing only in the manner in which the jejunum was brought up (retrocolic or antecolic). An abdominal tube drain (32F) was placed in the sub-hepatic region near the biliary and pancreatic anastomoses. All patients had a nasogastric (NG) tube inserted and a feeding jejunostomy was done in the efferent limb of the jejunum with a 12 French Malecot's catheter using the Weitzel technique.

Postoperative Care

All patients were given intravenous antibiotics (never erythromycin) and proton pump inhibitors in the immediate postoperative period. Nasogastric tube was left on continuous drainage. Octreotide (started intraoperatively; 100 μg SC 8hrly X 5–7 days) was used in patients with soft pancreas and small ducts. Epidural analgesia was discontinued by postoperative day 5. Intravenous opioid analgesia was avoided, and non-steroidal analgesics (diclofenac) were prescribed for postoperative pain relief.

The NG tube was removed if the output was less than 200 ml on two consecutive days. The day on which the NG tube was removed, the day on which clear liquids were started, and the day on which normal diet was resumed without feeding jejunostomy or parenteral supplementation was noted. Note was also made of any complications such as biliary leak (drainage of bilirubin rich fluid more than 50 ml/day), pancreatic leak (drainage of more than 50 ml/day of fluid with amylase >3 times serum amylase after postoperative day 3), postoperative hemorrhage, and intra-abdominal collection/abscess that could adversely affect DGE. The length of hospital stay was also recorded. Delayed gastric emptying was defined using the Johns Hopkins criteria [11] as the International Study Group of Pancreatic Surgery (ISGPS) definition [17] was published long after the commencement of this study. The ISGPS definition was also applied to the final data retrospectively at the time of analysis. In all patients suspected to have DGE, mechanical causes were excluded by imaging and/or endoscopy before ascribing it to DGE. The criteria used to define DGE were as follows: [11]

(1) Nasogastric tube left in place for 10 or more days, plus one of the following:
   (a) emesis after nasogastric tube removed
   (b) postoperative use of prokinetic agents after post-operative day 10
   (c) reinsertion of nasogastric tube
   (d) failure to progress with diet
   OR
2) Nasogastric tube in place fewer than 10 days plus two of (a) through (d).

The collected data was entered prospectively in Microsoft Excel 2000 and analyzed using SPSS 7.5 software. The results were tabulated for statistical analyses to identify significant differences between the two groups. Categorical variables were compared using chi-square test or Fisher's exact test. Continuous variables were analyzed using Student's t test or Mann–Whitney U test. A p value of <0.05 was considered significant.

Results

Between 1 September 2006 and 30 November 2008, 124 patients were assessed for inclusion in the study. The patients who met the inclusion criteria ($n=95$) were eligible. On exploration, 18 patients were excluded because of advanced/unresectable disease, and one patient was found to have cirrhosis, and the procedure was abandoned due to excessive bleeding during the initial dissection. In four patients, there was a change in treatment plan due to unexpected intraoperative finding such as ERCP-induced pancreatitis (one patient), tumor in the body of the pancreas (one patient), and chronic pancreatitis (two patients), and these were excluded. The remaining 72 patients were randomized after resection for an antecolic ($n=35$) or retrocolic ($n=37$) gastro-/duodenojejunostomy, stratified with respect to whether a Whipple's procedure or a PPPD was performed. Three patients died in the postoperative period in the antecolic group and one in the retrocolic group and were excluded from the final analysis. Therefore, 32

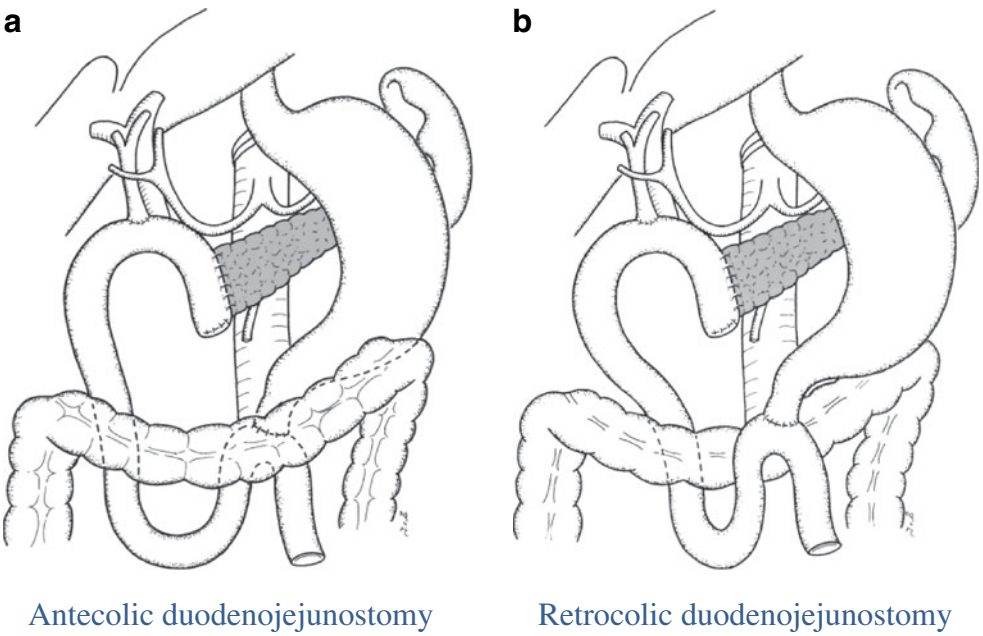


Fig. 1 **a**, **b** Schematic diagrams showing antecolic and retrocolic duodenojejunostomy following pancreatoduodenectomy (PPPD shown), respectively

patients (22 Whipple and 10 PPPD) were included in the antecolic group and 36 patients (22 Whipple and 14 PPPD) were included in the retrocolic group (Fig. 2).

Both groups were evenly matched with respect to the preoperative variables. The mean (SD) age of all the patients was 51.7 (11) years (range 16–75 years). Preoperative biliary drainage was done in 47 patients, out of whom 40 underwent endoscopic stenting, 4 underwent a cholecystojejunostomy, and 3 underwent a percutaneous transhepatic biliary drainage. An equal proportion of patients underwent biliary drainage in both the groups (p=0.8). In the antecolic group, 27 had a malignant etiology compared with 32 patients in the retrocolic group (p=0.6). The mean total leukocyte count, serum bilirubin, and serum albumin were also comparable (Table 1).

The number of patients undergoing Whipple's procedure or a PPPD were equally distributed in the two groups (p=0.5). The mean operative time, blood loss, and transfusion requirements were also similar. Extended resections (sleeve resection of the superior mesenteric vein/portal vein in two patients, sleeve resection of inferior vena cava in one patient, lateral pancreaticojejunostomy in one patient, and an extended cholecystectomy in one patient) were done in five patients, four (12.5%) in the antecolic groups, and one (2.8%) in the retrocolic groups (p=0.1). The type of pancreaticojejunostomy performed ("duct-to-mucosa" or "invagination" technique) was also similar in the two groups (p=0.6, Table 2).

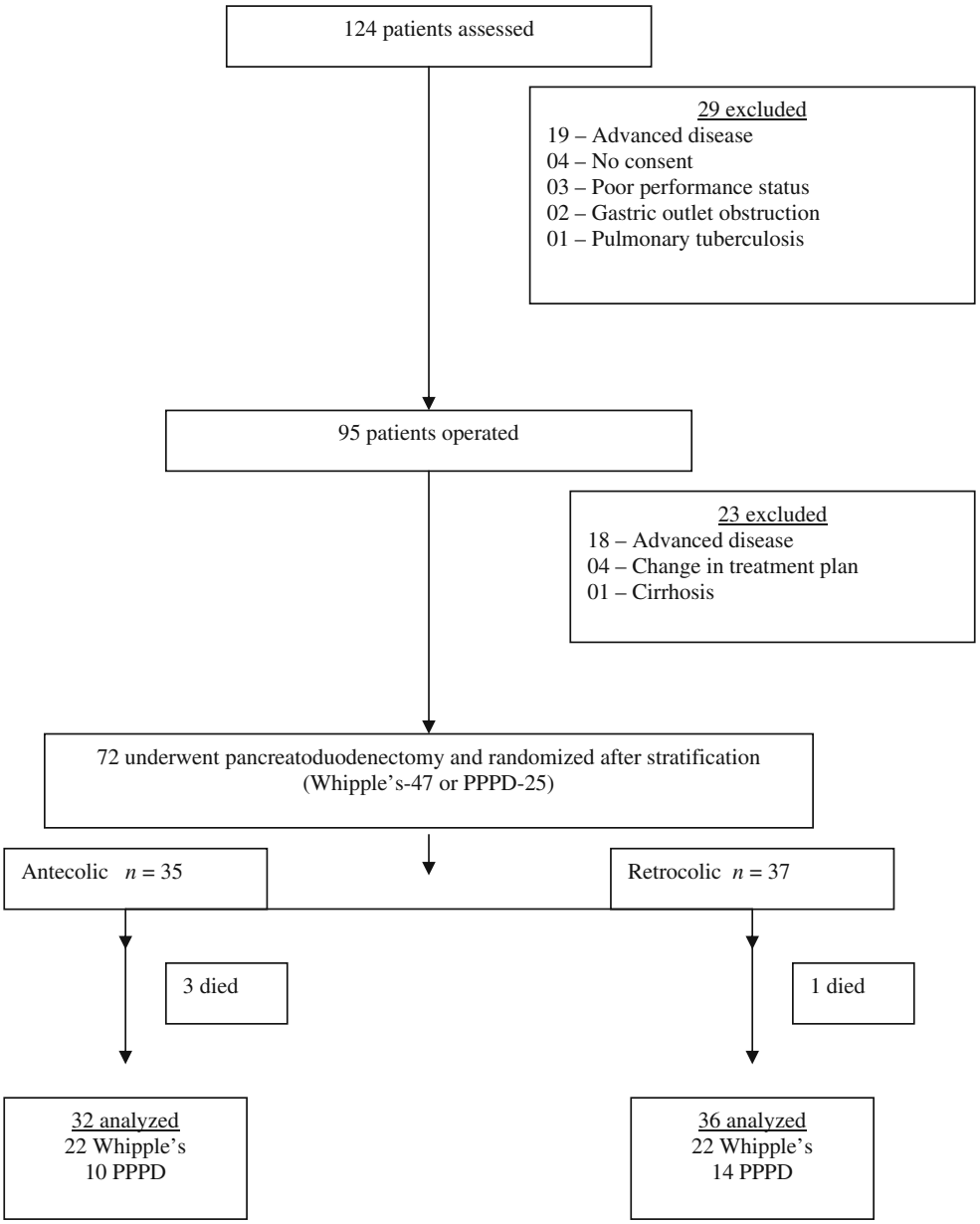
Postoperative cholangitis, bile leak, pancreatic leak, and hemorrhage occurred in 4.4%, 8.8%, 13.2%, and 2.9% of patients, respectively, with no significant difference between the two groups. Intra-abdominal abscess occurred in three (4.4%) patients requiring one time aspiration or percutaneous drainage. Four patients were re-explored in the retrocolic group. Two patients were re-explored for hemorrhage on day 7 and 13 and another two for intestinal obstruction on days 12 and 17, respectively. No patient in the antecolic group underwent re-exploration (p=0.05, Table 3).

Overall, the nasogastric tube was removed on postoperative day 4.6±1.7, liquid diet was started on postoperative day 6.4±2, and solid diet was started on postoperative day 9.3±4.5. Eighteen patients (26.4%) had vomiting after nasogastric tube removal, but nasogastric tube reinsertion was required in only eight patients (11.8%). Twenty-one (30.9%) patients required the use of prokinetics and in 16 (23.5%) patients, there was a failure to progress to normal diet by postoperative day 14. The overall incidence of clinical DGE in the entire group was 30.9% (21/68). DGE was seen in 11/32 (34.4%) in the antecolic group as compared to 10/36 (27.8%) in the retrocolic group (p=0.6). On applying the ISGPS definition, five patients had Grade A, nine had Grade B, and seven had Grade C DGE, and these were equally distributed in the antecolic and the retrocolic groups (p=0.6). Table 4 depicts the measures of DGE in the two groups. The mean postoperative hospital stay was longer among patients who developed DGE as compared to those who did not (21.9±9.3 vs. 13±6.9 days; p<0.0001)

Factors Associated with DGE

On univariate analysis, mean age (p=0.01), use of octreotide (p=0.008), and development of an intra-abdominal complication (p=0.005) were found to be significant risk factors for DGE (Table 5). There was no association of the sex

Fig. 2 Study profile



distribution, history of jaundice or cholangitis, preoperative biliary drainage, presence of malignancy, presence of diabetes, history of previous surgery, operative time, blood loss, and extended resections on the occurrence of DGE. On a multivariable analysis, however, only higher age [56.5± 8.9 years (DGE patients) vs. 49.6±11.3 years (no DGE patients)] was found to be significantly associated with occurrence of DGE (p=0.02).

Discussion

Delayed gastric emptying is a troublesome complication following pancreaticoduodenectomy and is seen in a significant proportion of patients leading to prolonged hospital stay, increased morbidity, and hospital costs.[8]

Many interventions have been tried in an attempt to reduce the high incidence of DGE. A retrospective study by Horstmann et al.[18] and a prospective by Hartel et al.[14] showed that antecolic reconstruction was better than retrocolic reconstruction in terms of DGE. Another randomized study by Tani et al. [15] also found a significant benefit in favor of antecolic reconstruction following PPPD. This randomized study was designed to test the hypothesis in all patients undergoing pancreaticoduodenectomy.

Prior abdominal surgery,[6,19] history of cholangitis,[20], and diabetes mellitus [21–23] have been described as possible risk factors for the development of DGE. Although some data

Table 1 Patient characteristics and preoperative variables in the two groups

Variable	Total (n=68)	Antecolic (n=32)	Retrocolic (n=36)	p value
Age (mean±SD)	51.7±11	52.8±11.6	50.8±10.6	0.5
Sex				0.9
Male, *n* (%)	49 (72.1)	23 (71.9)	26 (72.2)	
Female, *n* (%)	19 (27.9)	9 (28.1)	10 (27.8)	
Past surgery, *n* (%)	6 (8.8)	3 (9.4)	3 (8.3)	0.9
Diabetes, *n* (%)	14 (20.6)	7 (21.9)	7 (19.4)	0.8
Jaundice, *n* (%)	57 (83.8)	27 (84.4)	30 (83.3)	0.9
Cholangitis, *n* (%)	28 (41.2)	14 (43.8)	14 (38.9)	0.7
Preoperative biliary drainage, *n* (%)	47 (69.1)	22 (68.7)	25 (69.4)	0.8
Total leucocyte count (mean±SD)	9,979±4,676	10,281±5,170	9,711±4,245	0.6
S. bilirubin (mean±SD)	3.4±3.9	3±4.3	3.8±3.5	0.1
S. albumin (mean±SD)	3.8±0.6	3.8±0.6	3.8±0.5	0.8
Malignancy, *n* (%)	59 (86.8)	27 (84.4)	32 (88.9)	0.6

SD standard deviation, *n* refers to the number of patients, % refers to percentage

suggest that even modest degrees of hyperglycemia (≥144 mg/dL) retards gastric emptying,[21] it is not clear what level produces a clinically significant delay.[22] Since marked hyperglycemia significantly delays gastric emptying,[23] patients with *prolonged history* of uncontrolled diabetes were excluded from our study. Also in all patients with diabetes, strict glucose monitoring was done in the perioperative period. None of these factors, however, were found to be associated with the occurrence of DGE in the two groups in the present study.

Traditionally, PPPD has been thought to increase the incidence of DGE. However, adequately powered randomized controlled trials [24,25] and a recent meta-analysis [26] have not shown any increase in DGE after PPPD. Nevertheless, in this study to minimize bias, patients were randomized after stratification with respect to whether a Whipple's or a PPPD procedure was performed. However, no significant difference in the incidence of DGE was seen between the patients undergoing either a Whipple's procedure or a PPPD. In addition, the pancreatojejunostomy technique used ("invaginating" vs. "duct-to- mucosa") did not differ significantly in the two study groups (Table 2).

The difference in the incidence of individual complications across both groups was also not statistically significant. The only factor significantly different between the two groups was the higher incidence of re-exploration in the group with retrocolic reconstruction. Two were re-explored for post-pancreatectomy hemorrhage on days 7 and 13 after surgery, and two were re-explored for postoperative intestinal obstruction on days 12 and 17 after surgery. However, none of these patients who were re-explored had DGE after the first surgery (contrary to what one would expect), and hence, we concluded that this difference between the two groups was likely to be incidental with no bearing on the occurrence of DGE in this group.

Intra-abdominal complication (which has been reported to affect the incidence of DGE) was seen in 37.5% (12/32) in the antecolic group and 22.2% (8/36) in the retrocolic group (p=0.2). The pancreatic anastomotic leak rates which may influence the intra-abdominal complication rates were also not significantly different between the antecolic and retrocolic groups, the ISGPS Grade B/C pancreatic leaks being 3/32 vs. 4/36 (p=0.4) (Table 3). Similarly, the mean postoperative stay was not significantly different between

Table 2 Intraoperative variables in the two groups

Variable	Total (n=68)	Antecolic (n=32)	Retrocolic (n=36)	p value
Type of operation				0.5
Whipple, *n* (%)	44 (64.7)	22 (68.8)	22 (61.1)	
PPPD, *n* (%)	24 (35.3)	10 (31.3)	14 (38.9)	
Operative time (h) (mean)	6.1±1.3	6.1±1.1	6.2±1.5	0.8
Blood loss (ml) (mean)	962±469	1,007±426	920±509	0.2
Transfusion (units) (mean)	1.9±0.9	1.8±0.7	2.0±1.1	0.5
Extended resection, *n* (%)	5 (7.4)	4 (12.5)	1 (2.8)	0.1
PJ technique				0.6
Duct to mucosa	48 (70.6)	23 (71.9)	25 (69.4)	
Invagination	20 (29.4)	9 (28.1)	11 (30.6)	

n refers to the number of patients, % refers to percentage

Table 3 Postoperative factors and complications in the two groups

Variable	Total (n=68)	Antecolic (n=32)	Retrocolic (n=36)	p value
Octreotide, n (%)	13 (19.1)	5 (15.6)	8 (22.2)	0.5
Postoperative cholangitis, n (%)	3 (4.4)	1 (3.1)	2 (5.5)	0.7
Bile leak, n (%)	6 (8.8)	5 (15.6)	1 (2.8)	0.09
Pancreatic leak, n (%)[a]	9 (13.2)	3 (9.4)	6 (16.7)	0.4
Grade A	2	0	2	
Grade B	5	2	3	
Grade C	2	1	1	
Hemorrhage, n (%)	2 (2.9)	2 (6.2)	0 (0)	0.2
Intra-abdominal abscess, n (%)	3 (4.4)	3 (9.4)	0 (0)	0.4
Wound infection, n (%)	23 (33.8)	9 (28.1)	14 (38.9)	0.3
Re-exploration, n (%)	4 (5.9)	0 (0)	4 (11.1)	0.05

SD standard deviation, *n* refers to the number of patients, % refers to percentage

[a] According the definition by ISGPS

both the groups. Moreover, a comparison of the two study groups revealed no difference in the timing of nasogastric tube removal, and postoperative day on which liquid diet and solid diet were started. Also the proportion of patients who had emesis after nasogastric tube removal or who required nasogastric tube reinsertion or the use of prokinetics and who failed to progress with diet were not *significantly* different. Although in this study clinical DGE was defined by the Johns Hopkins criteria,[11] even when we applied the ISGPS criteria for DGE [17] retrospectively (Table 4), there was no significant difference between the two groups in the incidence of various grades of DGE. Overall in this study, 16 (16/68; 23.5%) patients of 21 (30.9%) who developed DGE had Grade B/C DGE by the ISGPS definition.

The incidence of DGE in this randomized study was not different when the two study groups were compared (antecolic group, 34% vs. retrocolic group, 28%; p=0.6). Although the desired sample size was not attained in the present study, we feel that this limitation does not weaken the impact of our conclusions as the observed incidence of DGE (the primary endpoint) was in fact higher in the "antecolic" arm.

These results are at variance with the published reports in the literature which have found a benefit of antecolic reconstruction in reducing the incidence of DGE. Horstmann et al. [17] were one of the first to suggest a benefit with this method. However, in their prospective series, there was no comparison group. The overall incidence of DGE (defined as NG decompression for >7 days or failure to progress to full regular diet by postoperative day 14) was 12.9%. Sugiyama et al.[13] documented an 8% (1/12) incidence of DGE (defined as NG decompression ≥10 days) following an antecolic reconstruction as compared to 72% (13/18) following a retrocolic reconstruction. Apart from a small sample size, this study was a retrospective one and a significantly higher number of patients in the retrocolic group (12/18) had a gastrostomy done as compared to the antecolic group (0/12)

Table 4 Measures of DGE in the two groups

Variable	Total (n=68)	Antecolic (n=32)	Retrocolic (n=36)	p value
NG removal (days) (mean±SD)	4.6±1.7	4.8±1.8	4.4±1.6	0.3
Emesis, n (%)	18 (26.4)	9 (28.1)	9 (25)	0.8
NG reinsertion, n (%)	8 (11.8)	2 (6.3)	6 (16.7)	0.2
Liquid diet (days) (mean±SD)	6.4 2	6.6±2	6.3±2	0.5
Solid diet (days) (mean±SD)	9.3 4.5	8.9±3.1	9.6±5.4	0.7
Prokinetics, n (%)	21 (30.9)	10 (31.3)	11 (30.6)	0.9
Failure to progress with diet (days), n (%)	16 (23.5)	7 (21.9)	9 (25)	0.8
Clinical DGE, n (%)[a]	21 (30.9)	11 (34.4)	10 (27.8)	0.6
Grade A	5	2	3	
Grade B	9	4	5	
Grade C	7	5	2	
Postoperative stay (days) (mean±SD)	15.8±8.8	16.3±8.4	15.3±9.2	0.6

SD standard deviation, *n* refers to the number of patients, % refers to percentage

[a] ISGPS definition for DGE applied retrospectively

Table 5 Factors influencing the development of DGE (univariate analysis)

Variable	Clinical DGE (n=21)	No clinical DGE (n=47)	p value
Age (mean±SD)	56.5±8.9	49.6±11.3	0.01
Sex			0.5
Male, n (%)	14 (66.7)	35 (74.5)	
Female, n (%)	7 (33.3)	12 (25.5)	
Past surgery, n (%)	3 (14.3)	3 (6.4)	0.3
Diabetes, n (%)	4 (19)	10 (21.3)	0.8
Jaundice, n (%)	18 (85.7)	39 (83)	0.8
Cholangitis, n (%)	12 (57.1)	16 (34)	0.07
Preoperative biliary drainage, n (%)	16 (76.2)	31 (66)	0.4
Malignancy, n (%)	20 (95.2)	39 (83)	0.1
Type of operation			0.4
Whipple, n (%)	12 (57.1)	32 (68.1)	
PPPD, n (%)	9 (42.9)	15 (31.9)	
Operative time (h) (mean±SD)	6.5±1.6	6±1.1	0.3
Blood loss (ml) (mean±SD)	525±800	937±428	0.7
Transfusion (units) (mean±SD)	1.3±2	1.8±0.8	0.4
Extended resection, n (%)	2 (9.5)	3 (6.4)	0.6
Octreotide, n (%)	8 (38.1)	5 (10.6)	0.008[a]
Intra-abdominal complication, n (%)	11 (52.4)	9 (19.1)	0.005[a]
Postoperative stay (days) (mean±SD)	21.9±9.3	13±6.9	0.0001[a]

[a] Not significant when tested by multivariate analysis

(p<0.001). These authors themselves state that gastrostomy done as a treatment of DGE may itself cause delayed emptying as it can disturb gastric motility. Hartel et al.[14] did a prospective study over two different time periods. They recruited 100 patients who had a retrocolic reconstruction in the earlier phase of their study and 100 patients who had an antecolic reconstruction in the later part of their study. They found the incidence of DGE (defined as NG decompression ≥10 days or failure to progress to normal diet by postoperative day 10) to be 5% in the antecolic group and 24% in the retrocolic group. Apart from the fact that this was not a randomized study, the two groups were not comparable with respect to a number of variables. More importantly, the antecolic group had a lower proportion of patients with blood loss >1,000 ml (17% vs. 41%) probably reflecting better surgical technique and experience with time. This factor may have been responsible for the lower incidence of DGE seen in the antecolic group in this study.

In the only randomized trial published, Tani et al.[15] found a 5% incidence of DGE (defined as NG≥10 days, need for reinsertion of NG tube, or failure to take normal diet by postoperative day 14) in the antecolic group and 50% in the retrocolic group. This study was underpowered. Though the authors started with a sample size of 58 patients in each arm, the study was terminated after an interim analysis with only 20 patients in each arm. Moreover, the incidence of DGE of 50% in the retrocolic group is unusually high compared to the recently quoted rates in various series in the literature. Lastly, though the incidence of individual complications were comparable between the two groups, a total of 12/20 patients in the retrocolic group had at least one postoperative complication as compared to 3/20 in the antecolic group. This discrepancy might also have influenced their results.

In this study, a number of factors were analyzed for a possible association with the development of DGE. We found that on *univariate* analysis, older age, use of octreotide, and the presence of intra-abdominal complications were all significantly associated with the occurrence of DGE in the entire study population. Although age as a risk factor for postoperative DGE has been described in literature, it remains controversial. Two studies investigating the effect of age on healthy volunteers gave contradictory results.[27,28] Some other studies analyzing risk factors for DGE after pancreaticoduodenectomy found no association with age [29–31], but in a recent prospective study, old age (>70 years) was found to be a risk factor for the development of DGE.[32] In our study, we found that the mean age of patients who had DGE was higher as compared to those patients who did not have DGE (56.5 years vs. 49.6 years; p=0.01).

The role of octreotide in DGE is controversial. Shan et al.[33], in a small study, found the use of intravenous somatostatin resulted in a marked delay in gastric emptying (p<0.01) after pancreaticoduodenectomy, but in another underpowered study of healthy non-operated volunteers, the subcutaneous infusion of the somatostatin analogue, octreotide accelerated gastric emptying.[34] In another recently published randomized trial,[35] prophylactic octreotide

after pancreatoduodenectomy had no influence on gastric emptying. In our study, the use of octreotide was higher in patients who developed DGE as compared to patients who did not develop DGE; however, it was not found to be significant on *multivariate* analysis.

Previous reports on influence of post-PD intra-abdominal complications on the development of DGE have been contradictory. In the study by Jimenez et al. [36], DGE was seen as an isolated event not related to any complication. Hartel et al.[14] also did not find surgical complication to be an etiological factor in the development of DGE. However, Henegouwen et al.[6] found a 65% incidence of DGE in patients with intra-abdominal complications ($p<0.0001$) after pancreaticoduodenectomy (PD). Similarly, in a prospective study, Park et al.[20] found a significantly high ($p<0.0001$) incidence of DGE in patients with postoperative intra-abdominal complications on multivariate analysis. Horstmann et al.[17] found an incidence of DGE of 1% when there were no postoperative complications which increased to 28% and 43% in the presence of moderate and severe complications, respectively ($p<0.0001$). Similar findings have been reported by others.[7,35,37] In the present study, however, intra-abdominal complication was not found to be a significant risk factor for the development of DGE on multivariate analysis.

We can therefore conclude that DGE is a common postoperative complication following PD occurring in 30.9% of the cases included in this study. Its occurrence was not affected by the type of procedure performed (classical Whipple's vs. PPPD) or the type of reconstruction of the gastro-/duodeno-jejunostomy (antecolic vs. retrocolic). Further, it was found that older age was significantly associated with a higher incidence of DGE following PD.

Conflict of Interest None.

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ORIGINAL ARTICLE

Immunonutrition with Long-Chain Fatty Acids Prevents Activation of Macrophages in the Gut Wall

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Abstract
Background Immune cells and inflammatory mediators are released from the gastrointestinal tract into the mesenteric lymph during sepsis causing distant organ dysfunction. Recently, it was demonstrated that macrophages in the gut wall are controlled by the vagus nerve, the so-called cholinergic anti-inflammatory pathway.
Aim This study aims to investigate whether an enteral diet with lipid prevents the activation of leukocytes in the gut wall.
Methods Mesenteric lymph was obtained from rats, receiving an enteral infusion of glucose or glucose+lipid before and after lipopolysaccharide (LPS) injection. Immune cells in mesenteric lymph were analyzed with fluorescence-activated cell sorting before and after LPS injection. Mesenteric lymph leukocytes from rats receiving enteral glucose with or without lipid were stimulated in vitro with LPS and tumor necrosis factor (TNF)α was measured in the supernatant.
Results The release of macrophages from the gut during sepsis was not significantly different in animals enterally treated with glucose or lipid. However, the release of TNFα from mesenteric lymph leukocytes after in vitro LPS stimulation was more than 3-fold higher in the glucose group compared to the lipid-treated group.
Conclusions During sepsis, activated macrophages are released from the gut into mesenteric lymph. However, an enteral diet with lipid is able to suppress the inflammatory cytokine release from mesenteric lymph leukocytes.

Friederike Eisner and Petra Jacob contributed equally to this manuscript.

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Introduction

Severe sepsis and septic shock are major healthcare problems, affecting millions of individuals around the world each year. In Germany, for example, sepsis is the third most common cause of death after cardial infarction and neoplasms.[1] The treatment of sepsis is difficult and needs an interdisciplinary approach. Early diagnosis is necessary to slow the progression of organ dysfunction and improve the patient outcome. According the Surviving Sepsis Campaign, early and aggressive hemodynamic therapy, early administration of broad-spectrum antimicrobial therapy, if possible within the first hour after the onset of sepsis, and surgical source control are the most promising therapeutic approaches.[2]

Multiple organ failure results from an increased release of pro-inflammatory mediators such as tumor necrosis factor (TNF)α, interleukin (IL)-1β, or IL6 of the host immune system elicited by components of the bacterial wall or by bacteria themselves. Overwhelming production of these pro-inflammatory cytokines evokes a systemic inflammatory reaction that leads to multiple organ dysfunction syndrome and death. Lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria, is one of the most common used endotoxins under experimental conditions. LPS can be administered intravenously or intraperitoneally (i.p.) and induces an inflammatory cascade similar to a gram-negative infection.[3] We have demonstrated that mediators released from the gastrointestinal tract into mesenteric lymph during LPS-induced sepsis cause septic pulmonary dysfunction.[4] Recent research has identified an immunomodulatory function of the vagus nerve whereby activation of vagal efferents results in regulation of cytokine production of macrophages in the gut wall. This immunomodulatory effect of the vagus nerve is called the "cholinergic anti-inflammatory pathway."[5] Stimulation of vagal efferents attenuates cytokine production of macrophages in the gut wall and improves survival in experimental sepsis.[6] Recently, we have shown that dietary fat can also activate the cholinergic anti-inflammatory pathway.[4] Lipid digestion (greater than C12) results in chylomicron formation, interaction of chylomicrons with endocrine cells and cholecystokinin (CCK) release of endocrine cells within the gut wall.[7] CCK is binding on CCK-1 receptors of vagal afferents and activates a vagovagal pathway relayed in the nucleus tractus solitarius which is both responsible for feedback inhibition of gastric motor function and for regulation of the immune response in the gastrointestinal tract.[4,8] Further, we have shown that a continuous enteral lipid application in the form of olive oil during sepsis has an immunomodulatory effect within the gut wall, since the cytokine output of the gastrointestinal tract into mesenteric lymph was significantly reduced in the lipid-treated animals compared to controls.[9] Additionally, septic pulmonary dysfunction caused by mesenteric lymph mediators was significantly ameliorated in rats receiving an enteral immunonutrition in form of olive oil.[9]

In the present study, we investigate the distinct cellular immune response of the gastrointestinal tract during sepsis with and without an enteral immunomodulatory diet in form of olive oil. This is achieved by fluorescence-activated cell sorting (FACS) analysis of immune cells released from the gastrointestinal tract into mesenteric lymph during sepsis. Further, we hypothesize that mesenteric lymph leukocytes collected during an enteral immunomodulatory diet in the form of olive oil are less susceptible for LPS to release inflammatory cytokines, since they are inactivated by the cholinergic anti-inflammatory pathway.

Material and Methods

Animals

Male Sprague-Dawley rats (200–250 g) were obtained from Charles River (Kieslegg, Germany). Animals were maintained on commercially available rat chow and were housed under controlled conditions of illumination (12:12-h light/dark cycle starting at 7:00 p.m.), humidity, and temperature (21°C) with free access to food and water. Before all surgical procedures, animals were not fed overnight but allowed water ad libitum. Institutional guidelines for the care and use of laboratory animals were followed throughout the study.

Mesenteric Lymph Collection

The method of mesenteric lymph duct cannulation was previously published by the authors.[4,9] In brief, animals were anesthetized using a combination of isoflurane (Abbott, Switzerland) and intraperitoneal ketamine/xylazine (100 and 5 mg/kg, respectively, Deltaselect, Germany and Bayer, Germany). A laparotomy was performed through a midline incision, the superior mesenteric lymph duct was identified using a microscope, and a polyvinyl tube was inserted into the lymph duct (Medical Grade, 0.50 mm ID, 0.80 mm OD, Dural Plastics, Australia). The tube was fixed in place with a drop of cyanoacrylate glue (Krazy Glue, Elmers Products Inc., Columbus, OH, USA) and externalized trough an incision in the right flank. A second catheter (Silastic, 1 mm ID, 2.15 mm OD) was placed into the duodenum through the fundus of the stomach, fixed with a

silk suture, and externalized through the left flank. To prevent catheters from dislocation, rats were placed in Bollman cages after surgery. A glucose-electrolyte solution (glucose 0.2 mol/L, NaCl 145 mmol/L, and KCl 4 mmol/L with or without 2% ClinOleic, a mixture of 80% olive oil and 20% soybean oil, Baxter, Germany) was infused continuously through the duodenal cannula at a rate of 3 mL/h. Rats were allowed to recover from surgery for 12 h while the mesenteric lymph was drained freely and rats were intestinally continuously infused as above mentioned. Thereafter, mesenteric lymph was collected from four different experimental groups.

In Vivo Experiments

In Vivo Glucose Group Rats were intestinally infused with a glucose solution, and mesenteric lymph was collected for 4 h before (control glucose lymph) and for 4 h after i.p. LPS injection (LPS, *Escherichia coli* serotype 0111:B1, Sigma, 5 mg/kg in 1 mL, sepsis glucose lymph). Lymph samples were used for FACS analysis to determine the cellular immune response from the gastrointestinal tract ($n=12$).

In Vivo Lipid Group Rats were intestinally infused with a glucose+lipid solution, and mesenteric lymph was collected for 4 h before (control lipid lymph) and for 4 h after i.p. LPS injection (LPS, *E. coli* serotype 0111:B1, Sigma, 5 mg/kg in 1 mL, sepsis lipid lymph). Lymph samples were used for FACS analysis to determine the cellular immune response from the gastrointestinal tract ($n=12$).

In Vitro Experiments

In Vitro Glucose Group Rats were intestinally infused with glucose solution, and mesenteric lymph was collected for 4 h (glucose lymph) for in vitro LPS stimulation experiments ($n=8$).

In Vitro Lipid Group Rats were intestinally infused with glucose+lipid solution, and mesenteric lymph was collected for 4 h (lipid lymph) for in vitro LPS stimulation experiments ($n=8$).

FACS Analysis of the Mesenteric Lymph Leukocytes

Cells were separated from the lymph by centrifugation (5 min, 400 g) and washed with phosphate buffered saline in 1% fetal calf serum; 0.5 μg monoclonal antibody/1×10^6 cells was incubated for 30 min at 4°C. One hundred thousand cells were analyzed by flow cytometry. The following antibodies were used for staining: fluorescein isothiocyanate (FITC) conjugated anti-rat CD11b/c (clone OX-42), FITC conjugated anti-rat CD3 (clone 1F4), biotinylated anti-rat CD8α (clone OX-8), phycoerythrin (PE) conjugated anti-rat CD11b/c (clone OX-42), PE conjugated anti-rat macrophage subset (clone HIS36), and allophycocyanin conjugated anti-rat CD4 (clone OX-35). Streptavidin–peridinin chlorophyll a protein was used to detect binding of biotinylated antibodies. All antibodies were purchased from Becton Dickinson (Heidelberg, Germany).

Blood Glucose Detection

Blood samples were taken for blood glucose detection before (basal) and 4 h after LPS injection, using the ACCU-Chek system (Roche, Germany). Animals were intestinally infused with a glucose-electrolyte solution (glucose 0.2 mol/L, NaCl 145 mmol/L, and KCl 4 mmol/L, $n=6$) or a lipid/glucose solution (glucose 0.2 mol/L, NaCl 145 mmol/L, and KCl 4 mmol/L, 2% vol ClinOleic, $n=6$).

In Vitro Stimulation of Leukocytes with LPS

Lymph samples were centrifuged at 400×*g* for 7 min at 4°C. Supernatant was discarded and the pellet was diluted in 1–2.5 mL RPMI medium (RPMI medium+GlutaMAX+penicillin 10,000 U/l+streptomycin 10,000 μg/mL; GIBCO, Germany). Cells were then counted using a Neubauer counting chamber and subsequently diluted in RPMI medium to a final concentration of 10^6 cells/225 μL. The aliquots were placed in duplicates into a 96-well plate, and LPS was added to a final concentration of 0 ng/mL, 10 ng/mL, 100 ng/mL, 1 μg/mL, and 10 μg/mL in each well (lipopolysaccharide, *E. coli* serotype 0111:B1, Sigma, Germany). After 22–24 h of incubation, supernatants were collected and stored immediately at −80°C until used for TNFα analysis. TNFα was determined by enzyme-linked immunosorbent assay (Quantikine kit for Rat TNFα/TNFSF1A, R&D-Systems, Minneapolis, MN, USA). Therefore, samples were defrosted, centrifuged at 1,000×*g* for 5 min at 4°C, and processed according to the manufacturer's instructions. All samples were measured and the mean of the duplicate samples was calculated and used as a single value for further statistical analysis.

Statistical Analysis

Data are presented as mean ± standard error of the mean. Differences between independent groups (in vitro experiments) were determined by unpaired Student's *t* test, and differences within a group (in vivo experiments) were determined by paired Student's *t* test using the software package of GraphPad Prism 3.02 (San Diego, CA, USA). A probability of $p<0.05$ was taken as significant.

Results

Effect of Sepsis on T Cell Release of the Gastrointestinal Tract

During abdominal sepsis, induced by bolus injection of LPS, the T cell release from the gastrointestinal tract into the mesenteric lymph was significantly increased by about 21% in the glucose treated rats (CD3+ cells/total cells in mesenteric lymph before and 4 h after LPS injection—59.3±3.4% vs. 72.0±5.0%, $p<0.05$) and by 10% in the lipid-treated rats (CD3+ cells in mesenteric lymph before and 4 h after LPS injection—64.0±3.3 vs. 70.7±3.0, $p<0.05$; Fig. 1a).

Subgroup analysis of the CD3+ cells for CD3+/CD4+ cells (T helper cells) and CD3+/CD8+ cells (cytotoxic T cells) revealed an increase of about 20% and 21%, respectively, in the glucose treated rats and about 13%

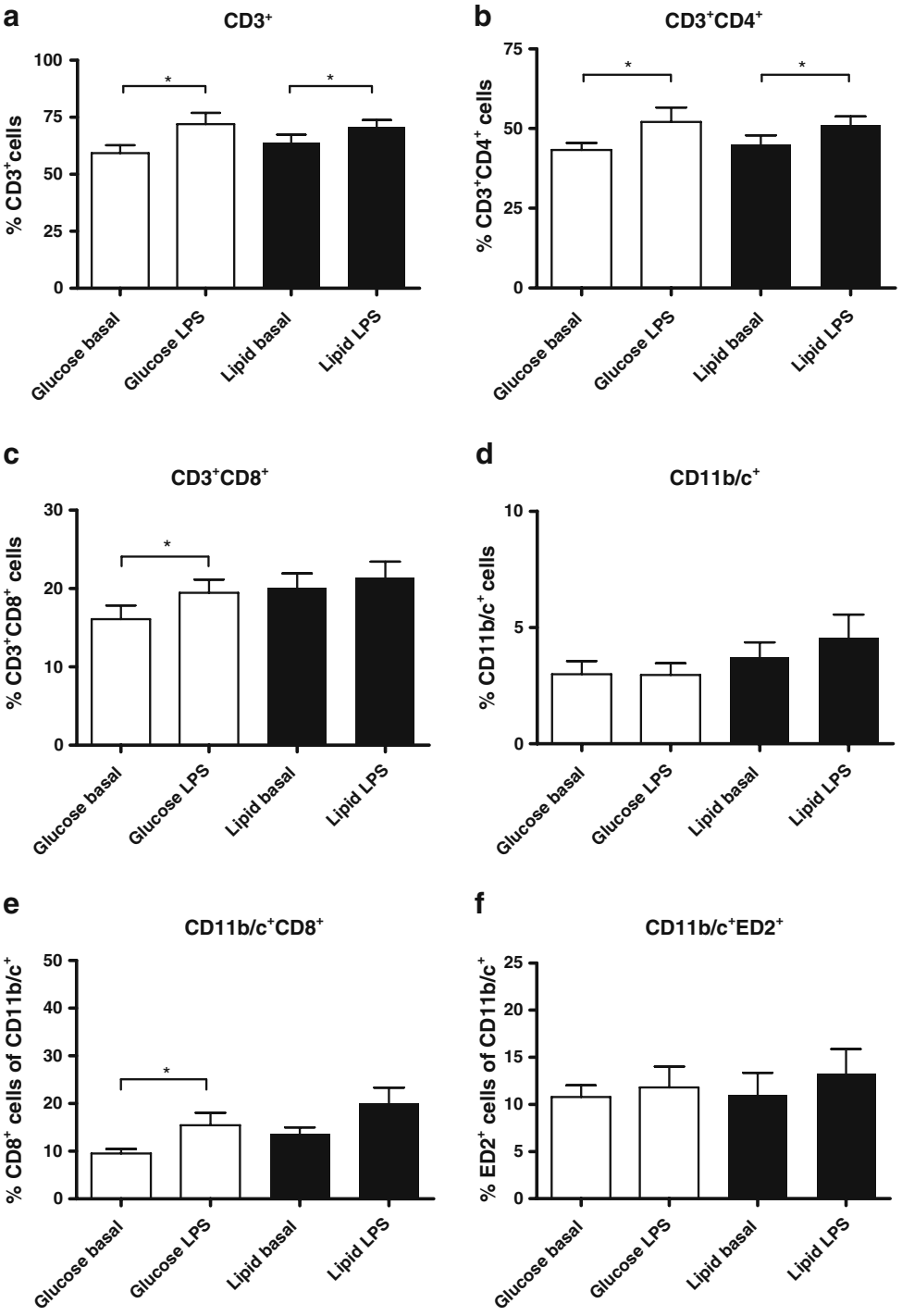

Fig. 1 The results of FACS analysis of immune cells released from the gastrointestinal tract into mesenteric lymph during basal conditions (before LPS administration) and during sepsis (after LPS administration) are shown for rats intestinally infused with glucose solution (*white bars*) and intestinally infused with glucose +lipid solution (*black bars*). The following cells were analyzed: **a** CD3+, **b** CD3+/CD4+, **c** CD3+/CD8+, **d** CD11b/c+, **e** CD11b/c+/CD8+, **f** CD11b/c+/ED2+; *$p<0.05$ vs. basal

and 6%, respectively, in the lipid-treated rats during sepsis (CD3+/CD4+ cells/total cells in mesenteric lymph before and 4 h after LPS injection; glucose 43.3±2.2% vs. 52.1±4.5%*; lipid 45.1±2.7% vs. 51.1±2.6%*; *$p<0.05$ vs. basal; CD3+/CD8+ cells/total cells in mesenteric lymph before and 4 h after LPS injection; glucose 16.1±1.8% vs. 19.5±1.7%*; lipid 20.1±1.8% vs. 21.4±2.0%; *$p<0.05$ vs. basal; Fig. 1b, c).

Dendritic Cells and Macrophage Release of the Gastrointestinal Tract During Sepsis

During abdominal sepsis, the release of CD11b/c+ cells (dendritic cells, granulocytes, and macrophages) from the gastrointestinal tract was not increased in the glucose treated rats and only increased by 1.2-fold in the lipid-treated rats during sepsis, not being statistically different (CD11b/c+ cells/total cells in mesenteric lymph before and 4 h after LPS injection; glucose 3.0±0.6% vs. 3.0±0.5%; lipid 3.7±0.6% vs. 4.5±1%; statistically not significant, Fig. 1d). The group of CD11b/c+ cells including dendritic cells, granulocytes, and macrophages was further analyzed for the CD11b/c+/CD8+ dendritic cell subset. About 10% to 14% of the CD11b/c+ cells were identified as CD11b/c+/CD8+ dendritic cells released during control conditions in rats intestinally infused with glucose and lipid, respectively. After sepsis induction with LPS, the percentage of CD11b/c+/CD8+ dendritic cells increased to about 16% and 20% in both glucose and lipid-treated animals with no statistical difference between the two groups (CD11b/c+/CD8+ cells in mesenteric lymph before and 4 h after LPS injection; glucose 9.5±0.9% vs. 15.5±2.6%*; lipid 13.6±1.4% vs. 20.1±3.3%; * $p<0.01$; Fig. 1e).

The CD11b/c+ were further analyzed for ED2-like antigen-positive cells, representing a major subset of the macrophages. The release of macrophages from the gastrointestinal tract during sepsis was interestingly neither affected by the source of intestinal treatment (glucose vs. lipid) nor by LPS application. The percentage of the ED2+ cells in mesenteric lymph was constantly by about 11% to 13% among the CD11b/c+ cell population including dendritic cells, granulocytes, and macrophages (CD11b/c+/ED2+ cells in mesenteric lymph before and 4 h after LPS injection; glucose 10.8±1.3% vs. 11.8±2.2%; lipid 11.0±2.4% vs. 13.2±2.6%; statistically not significant, Fig. 1f).

Effect of an Enteral Immunomodulation in Form of Olive Oil on Susceptibility of Leukocytes to LPS In Vitro

In vitro stimulation of leukocytes with LPS harvested from rats enterally infused with a glucose solution revealed a dose-dependent release of TNFα, reaching a maximal release of approximately 35 pg/mL TNFα at 100 ng and 10 μg LPS. In vitro stimulation of leukocytes harvested from rats enterally infused with a lipid+glucose solution revealed also a dose-dependent release of TNFα, reaching a maximum of 21±12 pg TNFα at 100 ng (Fig. 2b). The release of TNFα from mesenteric lymph leukocytes after LPS stimulation was more than 3-fold (1 and 10 μg) reduced when the rats were treated with lipid, indicating a reduced susceptibility of leukocytes to LPS in lipid-treated rats.

Effect of Sepsis on Blood Glucose Levels During Enteral Immunonutrition

Rats were intestinally infused with a glucose or a lipid/glucose solution before and after sepsis was induced. Serum glucose levels were not significantly different in the glucose, and the lipid/glucose group before or after sepsis was induced. However, the serum glucose was significantly reduced in both groups after sepsis was induced reaching the reference range (serum glucose levels

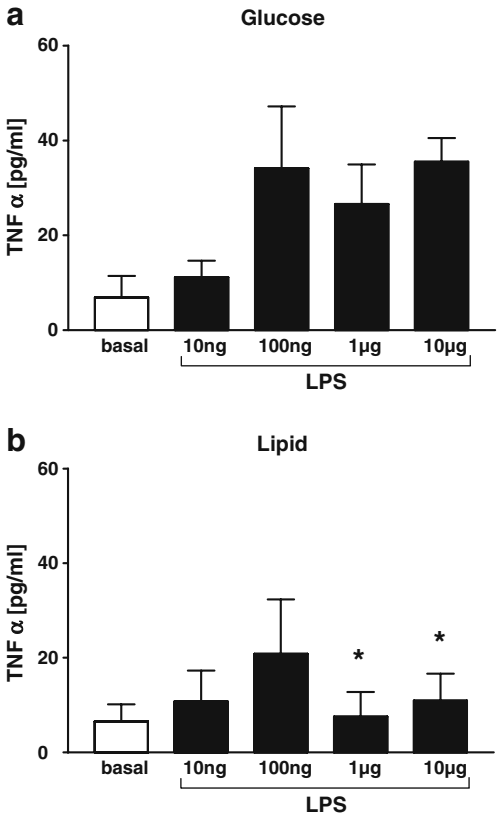

Fig. 2 The dose response of TNFα release from mesenteric lymph leukocytes basal (*white bars*) and after LPS (10 ng, 100 ng, 1 μg, 10 μg) stimulation (*black bars*) is expressed in figure **a** for mesenteric lymph harvested during intestinal glucose infusion and **b** for mesenteric lymph harvested during intestinal glucose+lipid infusion. The susceptibility of leukocytes for LPS is significantly reduced when the animals were intestinally infused with lipid; *$p<0.05$ vs. corresponding dose of intestinally glucose treated rats

(millimoles per liter): (1) glucose group, before sepsis was induced (basal)—9.9±1.4 and after sepsis was induced—6.75±0.6, $p<0.05$ vs. basal and (2) lipid/glucose group, before sepsis was induced (basal)—9.4±0.7 and after sepsis was induced—6.4±0.73, $p<0.05$ vs. basal).

Discussion

The present study investigates the release of immune cells from the gastrointestinal tract into mesenteric lymph under control and septic conditions. The basal release of T cells, dendritic cells, and macrophages from the gut during intestinal glucose or lipid infusion was statistically not different. During LPS-induced sepsis, there was a significant increase of CD3+ T cells in mesenteric lymph, independently whether the rats were intestinal infused with glucose or lipid. The vast majority of the CD3+ T cells were CD3+CD4+ T helper cells. The number of CD11bc+/CD8+ cells (dendritic cells, macrophages, and granulocytes) in mesenteric lymph was tendentially increased during sepsis. However, the release of ED2+ macrophages did not change in the mesenteric lymph during sepsis. Interestingly, we could demonstrate that the leukocytes in mesenteric lymph harvested from rats during intestinal lipid infusion were less susceptible to LPS than leukocytes harvested during control conditions. It is likely that lipid digestion is triggering the "cholinergic anti-inflammatory pathway," a vagovagal reflex pathway which controls the activation of immune cells in the gut wall.

There is some evidence that lipid in form of long-chain triglycerides can be beneficial during an acute insult to the gastrointestinal tract such as manipulation, ischemia, peritonitis, or sepsis.[10] Recently, Leite et al. demonstrated that mice fed with an enteral nutrition containing olive oil showed a longer survival during sepsis compared to the controls, assuming a reduced production of inflammatory mediators released from the gastrointestinal tract during sepsis.[11] The gastrointestinal tract is the largest lymphatic system in the body, releasing huge amounts of inflammatory mediators during sepsis.[12,13]. Via the thoracic duct, inflammatory mediators are drained from the gut into the systemic circulation, perfusing the lung as the first organ. In this context, several studies have shown that inflammatory mediators from the gastrointestinal tract are involved in mediating septic pulmonary dysfunction.[3,9] Recently, we have demonstrated that an immunonutrition with long-chain fatty acids reduces the release of gut-derived inflammatory mediators during sepsis and is improving septic pulmonary dysfunction.[4]

It is convincing that the vagus is mediating this immunoregulatory function, termed the "cholinergic anti-inflammatory pathway," which is triggered by intestinal lipid digestion.[5,6,14] The parasympathetic nervous system inhibits macrophage activation through the binding of acetylcholine to the alpha7 nicotinic acetylcholine receptor (α7 nAchR) located on macrophages.[14] Electrical stimulation of the vagus nerve decreased serum TNFα levels during sepsis, whereas surgical dissection of the vagus nerve enhanced systemic production of TNFα, accelerated the development of septic shock, and increased mortality.[6,15] Interestingly, administration of an enteral lipid application reduced circulating TNFα and IL-6 levels in rats subjected to hemorrhagic shock.[16] However, when these experiments were repeated in vagotomized animals, administration of an enteral lipid application no longer prevented the increase in TNFα or IL-6.[16]

TNFα is a primary mediator of inflammation and a potent inducer of other pro-inflammatory cytokines such as IL-6, eliciting considerable metabolic and hemodynamic changes such as end-organ dysfunction.[17] TNFα is synthesized mainly by macrophages and T cells. In the present study, we investigated the TNFα release from mesenteric lymph leukocytes upon the stimulation with LPS in vitro. Toll-like receptor 4 (TLR4), which recognizes LPS, leads to an activation of the nuclear factor-κB and to the synthesis of pro-inflammatory cytokines such as TNFα.[18] TLR4 is expressed on macrophages, CD4+, and CD8+ T cells.[19] Therefore, TNFα could be released in our in vitro experimental setup from both macrophages and T cells. So far, many reports exist about α7 nAchR and its role in suppressing the release of pro-inflammatory cytokines from macrophages.[20,21] but only few reports exist of α7 nAchR on T cells.[22] Regarding the release of immune cells from the gut during intestinal glucose or lipid infusion, there was no statistical difference of T cells, dendritic cells, and macrophages between the two groups. At this point, we are unable to detect precisely which cell population (T cells or macrophages) was releasing the TNFα after in vitro LPS stimulation. However, the results demonstrate clearly a significant reduced susceptibility of leukocytes to LPS, when the rats were intestinally treated with lipid in form of olive oil.

Conclusion

During sepsis, macrophages in the gut wall are activated releasing inflammatory mediators such as TNFα. However, an enteral immunomodulating diet with long-chain fatty acids in the form of olive oil is able to suppress TNFα release from gut-derived macrophages. This is likely mediated through vagovagal reflex pathway, termed the cholinergic anti-inflammatory pathway. An enteral immunomodulating diet in the form of olive oil might be a supportive therapeutic tool to prevent the release of disease-inducing cytokines into the circulation during sepsis.

Acknowledgments This work was supported by a grant from FORTÜNE 1843-0-0.

Conflict of Interest We do not have any conflict of interest.

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ORIGINAL ARTICLE

Local Peritoneal Irrigation with Intestinal Alkaline Phosphatase Is Protective Against Peritonitis in Mice

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Abstract
Background The brush-border enzyme intestinal alkaline phosphatase (IAP) functions as a gut mucosal defense factor and detoxifies different toll-like receptor ligands. This study aimed to determine the therapeutic effects of locally administered calf IAP (cIAP) in a cecal ligation and puncture (CLP) model of polymicrobial sepsis.
Methods C57BL/6 mice underwent CLP followed by intraperitoneal injection of cIAP or normal saline. Blood leukocyte counts, levels of cytokines and liver enzymes, and lung myeloperoxidase activity were determined. Peritoneal lavage fluid (PLF) was assayed for neutrophil infiltration and both aerobic and anaerobic bacterial counts.
Results After intraperitoneal injection, cIAP activity in PLF decreased 50% within 15 min with minimal activity evident at 4 h. Compared with irrigation with normal saline, cIAP irrigation increased the 7-day survival rate in mice undergoing CLP, with maximal effects seen at 25 units of cIAP (0% vs. 46% survival rate, respectively; $p<0.001$). cIAP treatment reduced lung inflammation, liver damage and levels of tumor necrosis factor alpha and interleukin-6.
Conclusions Peritoneal irrigation with cIAP significantly enhances survival in a mouse model of peritonitis, likely through reduction of local inflammation and remote organ damage. We suggest that intraperitoneal cIAP irrigation could be a novel therapy for intra-abdominal sepsis.

Keywords Sepsis · Cecal ligation and puncture · Intestinal alkaline phosphatase · Peritonitis

An abstract describing the data was presented at the SSAT Meeting, DDW Conference 2010, New Orleans, LA.

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Introduction

Intraperitoneal sepsis and sepsis-associated multiorgan failure remain to be major clinical challenges.[1] Intra-abdominal infections generate a peritoneal inflammatory response to gut-derived polymicrobial organisms from conditions such as complicated diverticulitis and appendicitis or from leakage after major abdominal surgery.[2]

The primary treatment strategy for peritonitis involves stabilization of possible organ dysfunction by routine supportive care, early systemic broad-spectrum antibiotics, isolation and control of contamination source, and finally restoration of a functional gastrointestinal tract, when possible. Peritoneal lavage may reduce the bacterial load, inhibit bacterial proliferation, and possibly minimize peritoneal adhesions.[3] Some believe that lavage is not always effective in flushing bacteria, as bacteria may adhere irreversibly to mesothelial cells.[3] Antibiotics may also be combined with lavage in order to further reduce bacterial survival. The use of antibiotics in lavage has varied widely

since their introduction in the late 1940s. Unlike with systemic antibiotics, there is a little clinical evidence regarding the effectiveness of adding an antibiotic to lavage solutions in improving morbidity and mortality.[3] The addition of antiseptics has been shown to produce toxic effects.[4] Intraperitoneal instillation of activated protein C,[5] lidocaine,[6] and taurolidine[7] has decreased mortality in a few experimental studies, but clinical trials are lacking.

Intestinal alkaline phosphatase (IAP) is a small intestinal brush-border enzyme that has been shown to dephosphorylate lipopolysaccharide (LPS) in vitro and in vivo under physiological conditions.[8–10] The toxic moiety of LPS, lipid A, contains two phosphate groups that are essential for its biological actions. Dephosphorylated LPS has been shown to be only a weak activator of macrophages and is much less toxic than diphosphoryl lipid A.[11] Poelstra et al. showed reduced inflammation in rats challenged with an intradermal injection of LPS that had first been exposed to IAP.[9] Moreover, they showed that oral administration of an IAP inhibitor increased the susceptibility of rats to *Escherichia coli*-mediated sepsis.[9] Bentala et al.[11] and Beumer et al.[12] also found that intravenous administration of IAP prevents death in mice exposed to lethal doses of LPS or Gram-negative bacteria.[11, 12]

The experimental rodent model of cecal ligation and puncture (CLP) has been used to mirror the clinical scenario of bowel perforation and mixed bacterial peritonitis.[13, 14] Although systemic (i.v.) injection of calf IAP (cIAP) did not reduce mortality in a CLP model[15] we hypothesized that injection of cIAP directly into the primary site of infection would attenuate the peritoneal inflammatory process and also prevent the systemic manifestations of peritonitis, perhaps resulting in enhanced survival.

In this report, we show that peritoneal irrigation with cIAP improves survival rate in a mouse model of peritonitis, and we suggest that irrigation with IAP could be a novel adjuvant therapy for intra-abdominal sepsis.

Materials and Methods

Animals

Specific-pathogen-free male C57BL/6 mice (8–10 weeks; Charles River Laboratory, Boston, MA) were housed in filter-top cages under standardized laboratory conditions and acclimatized for 24 h prior to all experiments. Mice were maintained in a temperature-controlled room (22°C to 24°C) with a 12-h light/12-h dark diurnal cycle with food and water ad libitum. All experiments were performed in accordance with the guidelines set forth by the Committee on Animals of Harvard Medical School (Boston, MA) and those prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Resources and the National Institutes of Health.

Determination of cIAP Activity in PLF

At 5, 10, 15, 30, 60, 120, 180, 240, and 300 min (n=3 for each time point) after intraperitoneal (i.p.) injection of 200 IU cIAP (New England Biolabs, Ipswich, MA) dissolved in 200-μL normal saline (NS), the activity of cIAP in peritoneal lavage fluid (PLF) was determined. Prior to aspiration of peritoneal fluid, animals were anesthetized (2% to 2.5% isoflurane; 1:1 O_2, air mixture) and 5 mL of saline was injected intraperitoneally. After abdominal massage, 1 mL of peritoneal fluid was aspirated.[15] To determine cIAP activity, spectrophotometric quantitation of the hydrolyzed product of *p*-nitrophenyl phosphate (*p*NPP), *p*-nitrophenol, was used and calculated as nanomoles of *p*NPP hydrolyzed per minute per microgram of protein. To confirm the specificity of the assay for cIAP activity, samples were also exposed to 10-mM phenylalanine, a known inhibitor of IAP, or 10-mM homoarginine, which has no effect on IAP activity but inhibits other isoforms of AP.[16]

Experimental Design

For survival analysis, 90 mice were randomly divided into six groups consisting of one sham group and five cecal ligation and puncture (CLP) groups (n=15 for each group). The five CLP groups were treated with i.p. injections of 200-μL NS (−cIAP group) or varying concentrations of cIAP (5, 10, 25, and 50 IU) dissolved in 200-μL NS (+cIAP group). Intraperitoneal cIAP or NS was given 15 min after CLP or sham laparotomy.[15] Survival rates were determined daily up to 7 days.

To compare the effects of systemic vs. local administration of cIAP on survival, 50 mice were randomly divided into five groups (n=10). The CLP groups received NS or 25 IU cIAP (maximal effective dose of the i.p. injection) intraperitoneally or intravenously through tail veins. Again, we evaluated the survival rates every day for 7 days.

To assess the effect of combination therapy with antibiotics, mice were divided into 5 groups, one sham and four CLP groups (n=10). For 7 days, CLP mice received twice daily intraperitoneal injections of NS, cIAP (25 IU), imipenem-cilastatin (500 μg, Merck & Co., Whitehouse Station, NJ), or a combination of cIAP and imipenem. Survival rates were determined daily for a week.[17, 18]

To investigate the inflammatory parameters and remote organ damage, four groups of mice (n=6) underwent either

CLP or sham operation and were treated with either cIAP or NS. All mice were killed 24 h after surgery for retrieval of blood, organs, and PLF. PLF was assessed for bacterial load, neutrophil count and cytokine levels. Right lungs were harvested for the assessment of myeloperoxidase activity, and blood samples were taken through cardiac puncture and sent to the MGH clinical lab to determine complete blood cell count (CBC), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities.

All of the experiments were single blinded: the researcher who did the procedures did know the type of treatment (NS, cIAP, or antibiotics) the animals received.

Cecal Ligation and Puncture

Mice were anesthetized with buprenorphine (Reckitt Benckiser Pharmaceutical, Parsippany, NJ) 0.05 to 0.1 mg/kg subcutaneously at 30 min preoperatively and inhalation of a mixture of N_2O/O_2 (1:1 (*v*/*v*); 1 to 2 L/min) and 2.0% to 2.5% isoflurane (Fort Dodge Animal Health, Fort Dodge, IA). During all operations, mice were kept on a heating pad at 37°C. After midline laparotomy, the cecum was mobilized, placed on a sterile wet pad (4×4 in., Tyco Healthcare Group LP., Mansfield, MA) and ligated with a 3-0 silk suture (Ethicon Inc., Somerville, NJ) between the ileocecal junction and its distal pole (75:25%, distance between the distal pole and the ligation: the distance from the ligation to the base of the cecum). A through and through perforation was made with an 18-gauge needle (Becton Dickinson and Company, Franklin Lakes, NJ).[19] The abdomen was closed in two layers with a running suture using 3-0 silk (Ethicon Inc.) for the abdominal fascia and metallic wound closure clips (Michel Roboz Surgical Instrument Co., Gaithersburg, Maryland) for the skin. Finally, 1 mL of normal saline was administered subcutaneously for fluid resuscitation. Sham-operated animals underwent identical laparotomy but did not undergo cecal ligation or puncture.

Peritoneal Lavage Fluid

For sample harvesting, all animals were re-anesthetized 24 h after CLP. The skin was cleaned with iodine, and peritoneal lavage was performed by intraperitoneal injection of 5-mL saline. After abdominal massage, as much fluid as possible was aspirated using a 26-gauge needle. Serial dilutions were cultured to determine the number of colony forming unit (CFU). One milliliter PLF was centrifuged (1,200×*g*; 10 min at 4°C), and the supernatant was stored at −80°C for cytokine assay. The pellet was re-suspended in 250-μL normal saline, and the total number of polymorphonuclear cells (PMN) was counted with a Z2 Coulter Particle Count and Size Analyzer (Beckman Coulter, Fullerton, CA; minimum diameter, 3.5 μm).

Bacterial Count in PLF

PLF was plated in serial log dilutions on blood agar plates (Becton Dickinson and Company, Franklin Lakes, NJ) and incubated at 37°C. CFU were counted after 24 h (aerobic conditions) or 48 h (anaerobic conditions). Quantitative cultures were expressed as average CFU/mL PLF±SEM.

Cytokine Assay

Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) from the peritoneal fluid were measured by mouse enzyme-linked immunosorbent assay (ELISA) kits (eBioscience Inc., San Diego, CA) following the manufacturer's instructions. Sham mice were used as control groups to determine basal cytokine levels.

Myeloperoxidase Assay

Myeloperoxidase (MPO) activity as a measure of neutrophil sequestration in lung was quantified as described previously.[19] Tissue samples were thawed, homogenized in 20-mM phosphate buffer (pH 7.4), and centrifuged (10,000×*g*, 10 min, 4°C), and the resulting pellet was re-suspended in 50-mM phosphate buffer (pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide (Sigma Chemical Co., St. Louis, MO). The suspension was subjected to four cycles of freezing and thawing and further disrupted by sonication (40 s) (Sonic Dismembrator Model 300, Fisher Scientific, Pittsburgh, PA). The sample was then centrifuged (10,000×*g*, 5 min, 4°C), and the supernatant was used for the MPO assay. The reaction mixture (300 μL) consisted of the supernatant containing 1.6-mM tetramethylbenzidine (Sigma Chemical Co.), 80-mM sodium phosphate buffer (pH 5.4), and 0.3-mM hydrogen peroxide. This mixture was incubated at 37°C for 10 min, the reaction was terminated with 50-μL 2-M H_2SO_4, and the absorbance was measured at 450 nm. Results were expressed as units per milligram (wet weight) of tissue.

Data Analysis

The Statistical Package for the Social Sciences (SPSS 17.0.1; SPSS, Inc., Chicago, Ill.) for Windows was used for data analysis. Mann–Whitney *U* tests were performed to determine the differences between two groups. Kaplan–Meier curves in combination with log rank tests were used for survival analysis. Significance was assumed when p values were <0.05.

Results

No significant differences were observed between the two sham-operated groups (treated with cIAP and saline) for any parameters (survival, transaminase, MPO, cytokines, CBC, peritoneal PMN count, and CFU). Results of these two groups have been combined into one group in survival analysis, marked sham.

cIAP Activity Is Rapidly Lost in PLF

To evaluate the activity of cIAP in PLF, samples were collected at 5, 10, 15, 30, 60, 120, 180, 240, and 300 min after i.p. injection of 200 IU cIAP. Fifteen minutes after i.p. injection, cIAP activity was nearly 50% of the maximal activity at zero time (Fig. 1). Sixty minutes after i.p. injection, cIAP activity dropped to 10% of maximal activity at zero time. While minimal cIAP activity was detected at 4 h, no cIAP activity was observed 5 h after injection into the peritoneal cavity.

Intraperitoneal Injection of cIAP Increased Survival Rates in CLP Mice

Kaplan–Meier survival curves (Fig. 2a) showed no mortality after sham operation (100% survival), while no mice in the CLP group that received NS survived after the third day ($p<0.001$). Most CLP mice died during the first 24 to 48 h after the procedure. Compared with the control CLP animals (-cIAP group) the survival rate was increased by cIAP with the most beneficial effects seen at the 25 U cIAP dosage (0% vs. 46%, respectively; $p<0.001$). The CLP mice treated with intravenous injection of 25 U cIAP had similar survival rate compared with the CLP mice that received either intravenous or intraperitonial NS (all animals died by day 3) (Fig. 2b).

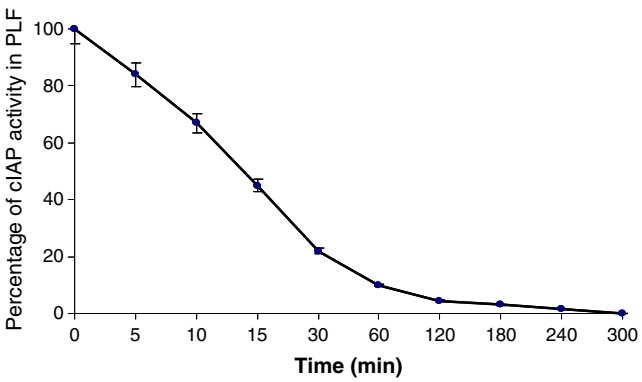

Fig. 1 Elimination curve of calf intestinal alkaline phosphatase (*cIAP*) from peritoneal lavage fluid (*PLF*). Each animal ($n=3$ per group) received 200 U (200 μL) i.p. of cIAP. After a specific time period, the animal received 5-mL normal saline i.p. to obtain PLF (the peritoneal cavity normally does not contain any fluid). One milliliter of PLF was aspirated, and cIAP activity was determined. Values are expressed as mean±SEM

The Antibiotic Imipenem Did Not Further Improve the Survival Rate of the CLP Mice Treated with cIAP

We next investigated whether the systemic (i.p.) use of the antibiotic imipenem combined with cIAP could further improve the survival rate of the CLP animals (see Fig. 2a). In comparison with the control CLP−cIAP (NS) mice, CLP mice treated with only imipenem had increased survival rate (0% vs. 40%, respectively; $p<0.001$) that equaled to the survival rate of the animals treated with only cIAP (Fig. 2c). Although on day 3 the mice receiving combination therapy (cIAP+imipenem) demonstrated better survival than those receiving imipenem alone, there was no survival difference at the end of day 7. It should be noted that we performed in vitro studies to ensure that cIAP has no direct effect on the antibiotic property of imipenem (data not shown).

Intraperitoneal Injection of cIAP Reduced Distant Organ Damage in CLP Mice

Hepatocellular damage was assessed by measuring AST and ALT plasma levels (Table 1). Twenty-four hours after CLP, plasma AST increased significantly (CLP−cIAP vs. sham−cIAP=647.0±30.2 vs. 132.5±2.5 U/mL; $p<0.001$). Treatment with cIAP resulted in lower levels of AST in CLP mice (CLP+cIAP vs. CLP−cIAP=451.8±18.3 vs. 647.0±30.2 U/mL; $p<0.05$). Similarly, in CLP mice that received NS, ALT levels were increased compared with sham-operated mice (CLP−cIAP vs. sham−cIAP=183.8± 19.9 vs. 38.5±0.5 U/mL; $p<0.001$). However, cIAP treatment did not significantly attenuate the ALT increase that occurred after CLP (CLP+cIAP vs. CLP−cIAP=159.4± 21.1 vs. 183.8±19.9 U/mL).

Remote inflammatory responses were assessed by measuring MPO activity in the lung. MPO is present in the granules of neutrophils and represents a measure of tissue inflammation. Increased MPO activity (Table 1) was demonstrated 24 h after CLP (CLP−cIAP vs. sham−cIAP= 99.0±4.0 vs. 36.0±6.0 U/g; $p<0.05$). cIAP-treated CLP mice showed less lung MPO activity compared with the NS-treated CLP mice (CLP+cIAP vs. CLP−cIAP=76.0± 4.0 vs. 99.0±4.0 U/g; $p<0.05$).

Intraperitoneal Injection of cIAP Reduced IL-6 and TNF-α Levels in PLF of CLP Mice

Figure 3a shows that 24 h after sham operation, animals had no IL-6 activity in PLF in the presence or absence of

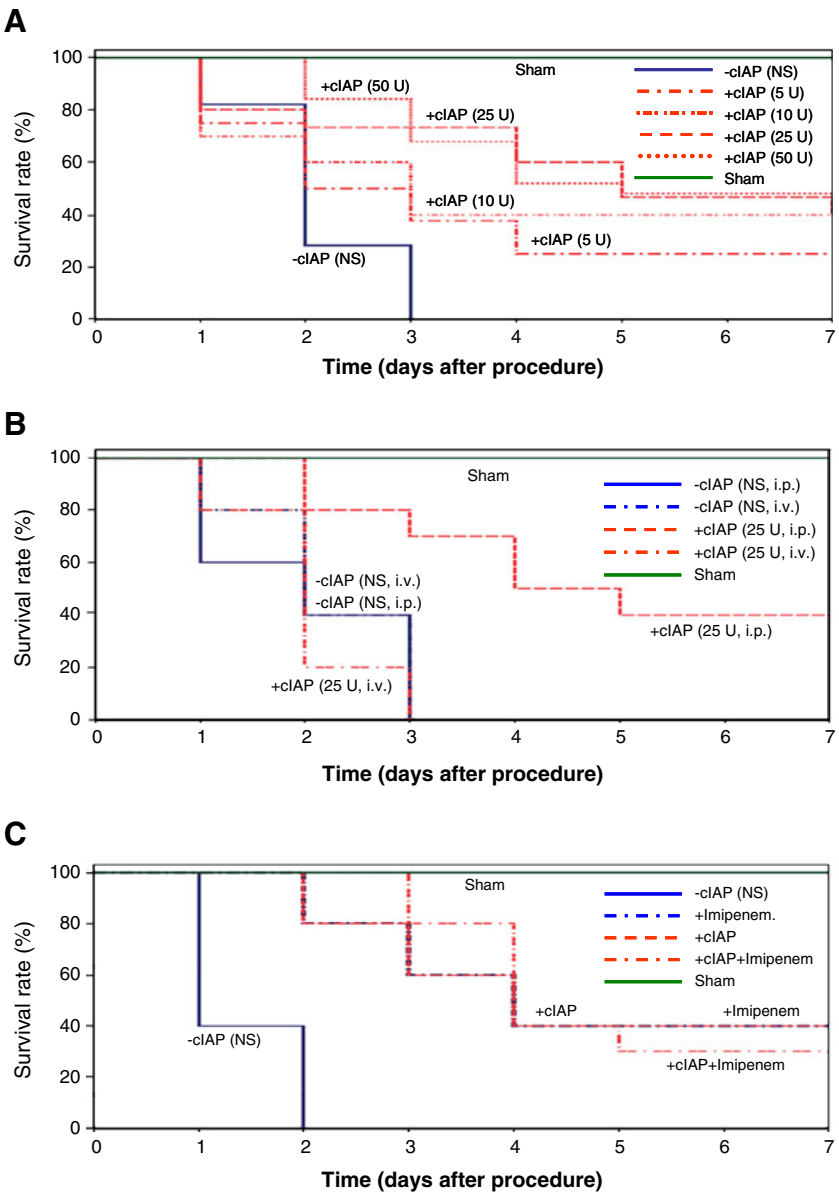

Fig. 2 **a** Dose–response effects of cIAP on the survival of mice undergoing cecal ligation and puncture (*CLP*). Each animal received a single i.p. injection of a specific amount of cIAP (5, 10, 25, or 50 U). cIAP was diluted in normal saline (*NS*; 0.9% sodium chloride). The control group received a single i.p. injection of NS. All animals received the same volume injection (200 μL). The animals were observed for 7 days. $n=15$ for each group. **b** Survival rate in CLP mice treated with a single i.p. injection of cIAP (25 U), single i.v. injection of cIAP (25 U), or NS. $n=10$ for each group. **c** Survival rate in CLP mice treated with NS, cIAP (25 U), imipenem (500 μg b.i.d.), or co-administration of cIAP and imipenem. $n=10$ for each group. Compared with the controls, the survival rate of animals treated with cIAP, imipenem, or cIAP+imipenem were significantly different ($p<0.05$)

Table 1 Effects of cIAP treatment on distal organ damage in CLP mice

Groups	AST (U/mL)	ALT (U/mL)	MPO activity (U/g)
Sham−cIAP (NS)	132.5±2.5	38.5±0.5	36.0±6.0
Sham+cIAP (25 U)	117±5.5	30.5±4.5	30.0±2.0
CLP−cIAP (NS)	647±30.2*	183.8±19.9***	99.0±4.0****
CLP+cIAP (25 U)	451.8±18.3**	159.4±21.1	76.0±4.0**

Cecal ligation and puncture (CLP) was performed and animals were treated with or without cIAP (25 U). Twenty-four hours after CLP, plasma levels of liver enzymes (AST and ALT) were determined. Remote inflammatory response in the lung was assessed by measuring myeloperoxidase (MPO) activity

*$p<0.001$ vs. sham−cIAP; **$p<0.05$ vs. CLP−cIAP; ***$p<0.001$ vs. sham−cIAP; ****$p<0.05$ vs. sham−cIAP

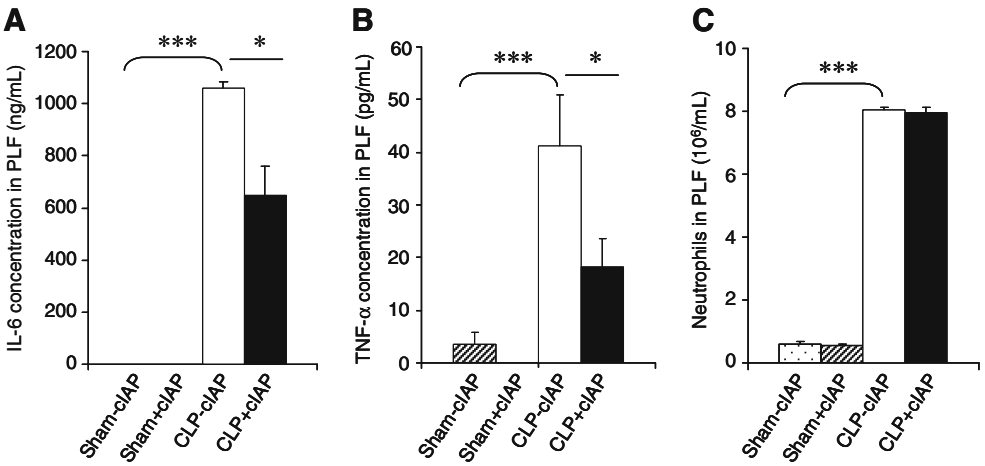

Fig. 3 Effects of cIAP treatment on local inflammatory response during peritonitis. Mice were subjected to peritonitis by CLP and were given cIAP (25 U) or normal saline (NS). Sham-treated mice received cIAP or NS. Pro-inflammatory cytokine levels were determined in the peritoneal lavage fluid (*PLF*) 24 h after CLP or sham operation. **a** Levels of IL-6, **b** levels of TNF-α, and **c** numbers of neutrophils. Values are expressed as mean±SEM. *$p<0.05$; ***$p<0.001$

cIAP. However, IL-6 concentration in PLF was dramatically elevated in the CLP−cIAP mice compared with the sham controls (CLP−cIAP vs. sham−cIAP=1,058.95±24.83 vs. 0 ng/mL; $p<0.001$). IL-6 levels were significantly reduced by cIAP treatment (CLP+cIAP vs. CLP−cIAP=646.63±114.36 vs. 1,058.9±24.8 ng/mL; $p<0.05$). Similarly, we observed minimal TNF-α activity in the PLF of sham-operated animals (Fig. 3b). TNF-α concentration in PLF was moderately elevated in the CLP−cIAP mice compared with the sham controls (CLP−cIAP vs. sham−cIAP=41.2±9.64 vs. 3.57±2.30 pg/mL; $p<0.001$). As expected, cIAP treatment also reduced the TNF-α levels (CLP+cIAP vs. CLP−cIAP=18.14±5.35 vs. 41.20±9.63 pg/mL; $p<0.05$).

We then determined the number of neutrophils in the PLF, and as expected, we observed a dramatic increase of neutrophils after CLP (CLP−cIAP vs. sham−cIAP=7.9E+6±1.1E+6 vs. 9.0E+5±0.1E+5 per mL, $p<0.001$) (Fig. 3c). cIAP treatment had no significant effects on neutrophil counts in the PLF of CLP mice.

To ascertain the effects of cIAP on the bacterial counts in PLF we plated serial dilutions of PLF on blood agar plates under aerobic and anaerobic conditions (see Materials and Methods). PLF of sham-operated animals had no bacteria, whereas, as expected, the numbers of both aerobic and anaerobic bacteria in PLF dramatically increased after CLP (Fig. 4). The number of aerobic bacteria in PLF was approximately 1.48E+11±9.20E+10 CFU/mL. Treatment with cIAP slightly reduced the number (8.33E+10±5.99E+10 CFU/mL); however, this difference was not statistically significant (Fig. 4a). Similarly, we observed a dramatic increase in anaerobic bacteria in the PLF (1.94E+13±1.11E+13 CFU/mL) (Fig. 4b). cIAP treatment slightly reduced the number of anaerobic bacteria (8.84E+12±5.29E+12 CFU/mL), but like the aerobes, this reduction in anaerobic bacteria was not statistically significant.

cIAP Treatment Decreased Blood Neutrophil Counts in CLP Mice

CLP mice showed significant reductions in blood leukocyte count (CLP−cIAP vs. sham−cIAP=4.6E+6±0.4E+6 vs. 15.6E+6±3.3E+6 per mL; $p<0.01$) (Fig. 5a). cIAP

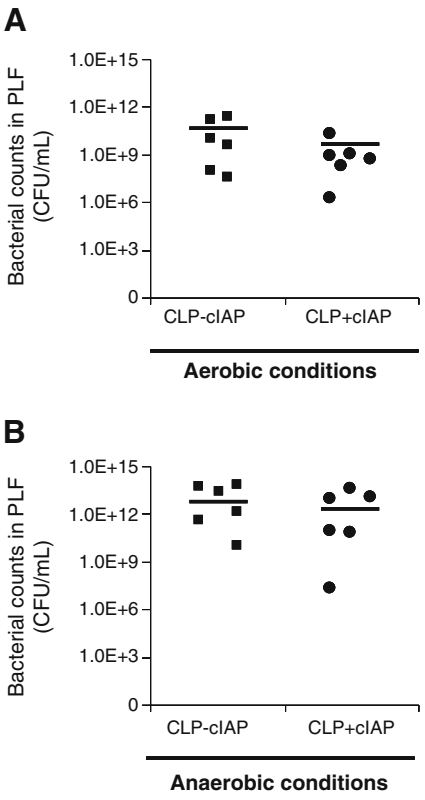

Fig. 4 Effects of cIAP treatment on peritoneal bacterial counts in mice with peritonitis. Peritoneal lavage fluid (*PLF*) samples from CLP or sham mice were plated in blood agar in **a** aerobic or **b** anaerobic conditions. Plates were incubated at 37°C overnight and CFU/mL of PLF was calculated

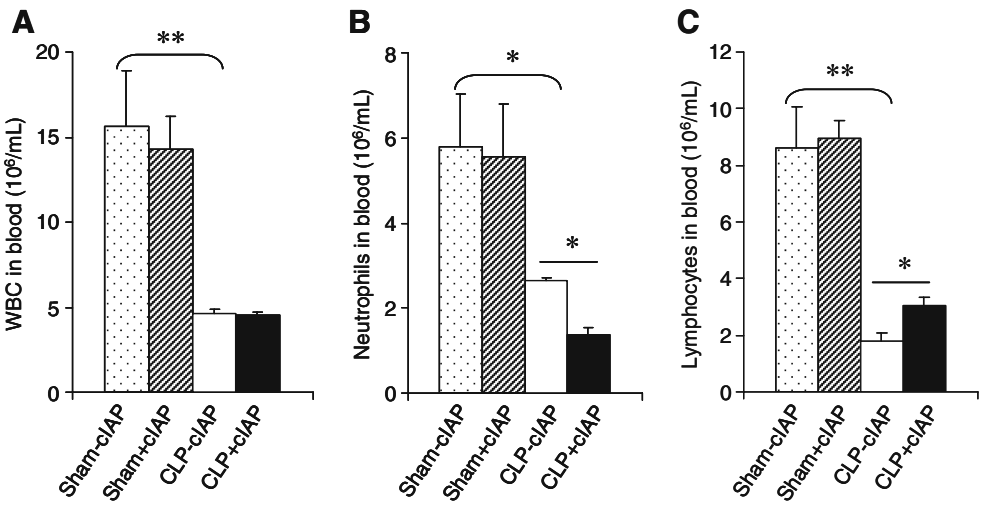

Fig. 5 Effects of cIAP treatment on systemic inflammatory responses to peritonitis. Mice were subjected to peritonitis by CLP and were given cIAP (25 U) or normal saline (NS). Sham-treated mice received cIAP or NS. Inflammatory cell counts per 1 mL blood were determined 24 h after CLP or sham operation. **a** WBC counts in blood. **b** Neutrophil counts in blood. **c** Lymphocyte counts in blood. Values are expressed as mean±SEM. *$p<0.05$; **$p<0.01$

treatment had no significant effect on the total number of leukocytes (Fig. 5a).

The neutrophil count was reduced in blood of the untreated CLP mice compared with the sham-operated mice (CLP−cIAP vs. sham−cIAP=2.6E+6±0.09E+6 vs. 5.8E+6±1.2E+6 per mL; $p<0.05$) (Fig. 5b). Although cIAP treatment did not affect overall counts of leukocytes (Fig. 5a), we observed that the relative neutrophil counts decreased significantly in the blood of cIAP-treated CLP mice (CLP+cIAP vs. CLP−cIAP=1.4E+6±0.2E+6 vs. 2.6E+6±0.08E+6 per mL; $p<0.05$) (Fig. 5b).

The lymphocyte count was also reduced in the untreated CLP mice compared with the sham-operated animals (CLP−cIAP vs. sham−cIAP=1.8E+6±0.3E+6 vs. 8.6E+6±1.5E+6 per mL; $p<0.01$) (Fig. 5c). As expected, cIAP-treated CLP mice had more lymphocytes compared with the untreated group (CLP+cIAP vs. CLP−cIAP=3.1E6±0.27E+6 vs. 1.8E+6±0.3E+6 per mL; $p<0.05$) (Fig. 5c).

Discussion

In this study, locally administered cIAP increased the survival rate in a mouse model of fecal peritonitis. Although cIAP showed no effects on neutrophil and bacterial counts in the peritoneal lavage fluid (Figs. 3c and 4, respectively), it decreased peritoneal IL-6 and TNF-α concentrations in CLP mice (Fig. 3a, b, respectively). cIAP treatment reduced the systemic inflammatory response and remote organ damage that occur after CLP, as evidenced by decreased PMN counts (Fig. 5b) and AST levels in blood as well as lung MPO activity (Table 1). These results clearly point to a beneficial effect of local cIAP treatment.

Previous studies have shown that the plasma elimination curve of cIAP consists of two phases: a fast initial phase and then a slow second phase.[12] The first phase eliminates most of the administered cIAP except a small portion that remains bound to the endothelial or liver cells. In the second phase, release of cIAP from these endothelial and liver cells into the bloodstream results in much slower plasma elimination. In our study, we also observed that cIAP injected into the peritoneum shows a similar pattern of elimination. The half life of intraperitoneal cIAP was about 15 min compared to 2 min in plasma. Moreover, serial measurement of cIAP activity in the peritoneal cavity demonstrated persistent activity for more than 4 h. We believe this slow second phase likely provides enough time for the cIAP enzyme to exert its beneficial effects.

Increased survival in mice was reported after LPS/*E. coli* injection in combination with placental alkaline phosphatase and bovine intestinal alkaline phosphatase (BIAP).[11, 12] However, in a study done by van Veen et al., systemic administration of 3–4 IU BIAP reduced the inflammatory response but had no significant effect on the survival of CLP mice.[13] We suggest, therefore, that the local application of IAP into the peritoneal cavity is more efficacious than systemic administration. This conclusion is supported by our experiment comparing the local vs. systemic treatments of the identical amounts of cIAP, in which the local peritoneal therapy showed a much greater therapeutic benefit (Fig. 2b).

Sepsis describes a complex clinical syndrome that results from a harmful or damaging host response to infection. Determining the structural components of bacteria that are responsible for initiating the septic process has been important not only in understanding the underlying mechanisms, but also in identifying potential therapeutic targets. In Gram-negative bacteria, LPS has a dominant role. The outer membrane of Gram-negative bacteria is constructed of a lipid bilayer, separated from the inner cytoplasmic membrane by peptidoglycan. The LPS molecule is embedded in the outer

membrane and the lipid A portion of the molecule serves to anchor LPS in the bacterial cell wall. There is no endotoxin in Gram-positive bacteria, but their cell walls do contain peptidoglycan and lipoteichoic acid.[20] Both peptidoglycan and lipoteichoic acid can bind to cell surface receptors and are pro-inflammatory, although they are much less active, on a weight-for-weight basis, than LPS. Several other bacterial components have been shown to have pro-inflammatory activity and are able to induce shock in experimental systems. These include cell wall structures such as flagellin[21] and curli[22], and unmethylated CpG sequences in naked bacterial DNA.[23] Receptors for some of these elements have been identified among the family of Toll-like proteins that are now known to be crucial in the cellular recognition of microbial structures.[24]

We have recently shown that IAP has multiple targets, inhibiting the pro-inflammatory response to CpG DNA and flagellin in vitro, in addition to LPS.[25] In an in vitro study, we also demonstrated that IAP, probably through dephosphorylation, is able to attenuate cytokine secretion by the target cells in response to pus from CLP mice. Although the role of CpG DNA and flagellin dephosphorylation in their interactions with toll-like receptors (TLR) have not yet been described, it has been shown that dephosphorylation of LPS by IAP alters the structure, leading to abolition of ligand-receptor binding.[26] We believe local peritoneal administration of cIAP may optimize the amount of enzyme that reaches the primary site of infection, helping to block the stimulation of the immune system by pro-inflammatory ligands before they reach systemic circulation. We believe cIAP could be a promising therapeutic agent for peritoneal lavage to reduce morbidity in patients with disease processes such as complicated diverticulitis, appendicitis, or bowel perforation from other causes.

Systemic antibiotics are a standard part of the treatment for all patients with intra-abdominal sepsis. Interestingly, we observed similar survival rates in the CLP mice that received a single injection of cIAP and the CLP group that received systemic imipenem twice a day for 7 days.

Increased AST and ALT plasma levels after CLP demonstrate significant hepatocellular damage. LPS released from bacteria as well as diminished blood flow to the liver are thought to cause this hepatocellular dysfunction.[27] Xu et al. showed increased sensitivity of the liver to LPS after inhibition of endogenous alkaline phosphatase synthesis and release.[28] It was suggested that high levels of alkaline phosphatase exert a protective effect against liver damage by neutralizing endotoxin. Although van Veen et al. did not observe any liver protection when cIAP was administered systemically as an early treatment after CLP, they showed that prophylactic administration of cIAP could reduce the harmful effects of LPS in the liver.[15] In the present study, we demonstrated that early local administration of cIAP after CLP reduced liver damage. In addition, MPO levels in the lung were also reduced by cIAP treatment, reflecting less pulmonary inflammation and damage. Mortality related to intra-abdominal sepsis is generally due to end organ damage and subsequent multiorgan failure.[29, 30] The protective role of locally administered cIAP against liver and lung damage likely resulted in the improved survival in this CLP model.

Cytokines are critical early mediators of sepsis, and activation of cytokines and other inflammatory mediators is induced by endotoxins, such as lipopolysaccharide (LPS).[31] Increasing concentrations of cytokines, especially at the primary site of inflammation, have been shown to correlate with the severity of sepsis and the tendency toward multiple organ failure.[32, 33] TNF-α is believed commonly to be an initiating factor in the pathogenesis of sepsis.[17] However, its role in sepsis is very complex. While TNF-α is the main mediator in the endotoxin model and while use of anti-TNF antibodies protects animals against this type of sepsis, its concentration is barely detectable in the CLP model, and blockade of TNF-α does not provide protection.[34] In this study, we evaluated the effect of cIAP on the peritoneal concentration of TNF-α at its peak, 24 h after CLP.[29, 35] Like in previous studies, we observed that the level of TNF-α in the CLP model is much lower than that generally seen in the endotoxin model. However, we observed that cIAP significantly reduced TNF-α concentration in the PLF, and we believe this reduction may play a part in improved survival rate of the CLP mice treated with cIAP (see Fig. 2).

Multiple studies have demonstrated that increased levels of IL-6 correlate with severity of sepsis.[32, 33] Moreover, clinical studies have shown that IL-6 is a good predictor of prognosis in septic patients,[36] its levels becoming elevated when patients become moribund.[37] We checked IL-6 levels 24 h after CLP due to the occurrence of organ injury and mortality soon after this time point. Interestingly, treatment with cIAP significantly reduced IL-6 levels in the peritoneal cavity, again correlating with improved survival.

During sepsis, there is an aggressive infiltration of neutrophils to the primary site of infection. The effects of cIAP treatment on neutrophil infiltration have varied in different models of inflammatory diseases. While intravenous administration of cIAP had no effect on neutrophil attraction to the peritoneal cavity of CLP mice,[15] oral administration of cIAP decreased the inflammatory cell influx to the intestinal wall of rats as well as mice with ulcerative colitis.[38, 39] Previous studies suggest a regulatory role for IL-6 in neutrophil migration to the primary site of infection.[40] Although local administration of cIAP reduced

IL-6 levels in the peritoneal cavity, it had no effect on neutrophil chemo-attraction to the abdominal cavity of CLP mice. This result is in agreement with previous studies showing that there is no clear-cut relationship between cytokines and neutrophil infiltration to the peritoneal cavity in this model of sepsis.[31] It seems that other factors may influence neutrophil migration to the site of inflammation in the CLP model.

There are marked alterations in WBC and differential counts in sepsis. Xiao et al. reported leukopenia that affected primarily the lymphocytes in the early phase of sepsis.[41] In our study, although cIAP treatment had no effect on leukopenia, it reduced neutrophil percentage and increased lymphocyte percentage in the blood. Similar changes were reported when Beumer et al. injected cIAP into animals that had received LPS.[12] Given the lack of difference in the number of neutrophils in the PLF of CLP mice treated with or without cIAP, it is unlikely that local neutrophils play a significant role in the enhanced survival of the cIAP-treated CLP mice.

Interestingly, we found that local administration of cIAP did not have any significant effect on bacterial counts of peritoneal lavage fluid in CLP mice. This is in consistent with previous studies by van Veen et al. who assessed the effects of systemic cIAP administration in a CLP model.[15] These results are consistent with IAP primarily working through an inhibition of the pro-inflammatory effects of bacterial products, rather than exerting a direct effect on the bacteria themselves.[25]

Conclusions

The results of this study show that direct administration of cIAP to the primary site of infection can increase survival and reduce local and systemic inflammatory responses as well as distant organ damage. Based upon our findings in this animal model, we believe that irrigation of the peritoneal cavity with cIAP may represent a novel adjunctive therapy in the surgical treatment of intra-abdominal sepsis resulting from conditions such as complicated diverticulitis, perforated appendicitis, or any intestinal perforation accompanied by generalized peritonitis.

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Competing interests The authors declare no conflicting financial interests.

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HOW I DO IT

Technical Aspects of Robotic-Assisted Pancreaticoduodenectomy (RAPD)

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Abstract Minimally invasive pancreaticoduodenctomy (MIPD) is a technically challenging procedure. Current laparoscopic equipment with its limited range of motion, poor surgeon ergonomics, and lack of 3D view has limited the addition of MIPD. The robotic platform is able to overcome these limitations, allowing the recreation of time-honored open surgical principles of this procedure through a minimally invasive approach. We present here the technical aspects of the University of Pittsburgh robotic-assisted pancreaticoduodenctomy.

Keywords Robotic · Laparoscopic · Minimally invasive · Pancreaticoduodenectomy · Whipple

Introduction

Laparoscopic surgery has evolved significantly since its introduction in the late 1980s. More advanced laparoscopic procedures are being performed at many centers; however, advanced GI procedures that require complicated resection and reconstruction, such as pancreaticoduodenectomy (PD), remain limited to a few centers. In fact, in the 14 years following the first description of laparoscopic pancreaticoduodenectomy by Gagner in 1994, only 146 laparoscopic PD were reported in the literature[1,2]. Recently, Palanivelu et al. presented 75 cases and Kendrick and Cusati reported 62 cases of totally laparoscopic PDs[3,4]. The slow adoption of laparoscopy to the pancreaticoduodenectomy is a result of the limitations inherent to the technology, namely, 2-dimensional imaging, limited range of instrument motion and poor surgeon ergonomics. In this situation, the surgical principles are altered to meet the limitations of the technology leading to reluctance on the part of many HPB surgeons.

Robotic-assisted minimally invasive surgery overcomes many of the shortcomings of laparoscopy with improved binocular 3-dimensional imaging, near 360-degree movement of surgical instruments, and improved surgeon comfort and precision. These technological innovations allow, for the first time, complex resections and anastomotic reconstructions to be performed with nearly identical principles to open surgery. We present here our technical description of a robotic-assisted minimally invasive pancreaticoduodenectomy (RAPD). This approach maintains maximal adherence to the traditional open surgical techniques with a minimally invasive approach.

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Technique

Patient Selection

We instituted a safety monitoring program to scrutinize outcomes of robotic pancreas surgery on a continuing basis. Robotic procedures are performed by a two-attending surgical team possessing a combination of advanced laparoscopic skills and extensive experience with open pancreatic surgery. Robotic-assisted pancreatic surgery is performed with the daVinci S Robotic Surgical System (Intuitive Surgical, Sunny Valley, CA, USA). The only absolute contraindication to attempted RAPD is obvious vascular involvement. Patients are not excluded based on BMI or co-morbidities.

Instruments/Conduct of Operation

Standard laparoscopic instruments are used for the initial mobilization of the pancreatic head. A combined laparoscopic/robotic approach by means of the daVinci® S robotic platform is utilized for the portal dissection and subsequent reconstruction. The procedure emphasizes teamwork between two experienced pancreatic surgeons and requires a four-handed technique for appropriate retraction and exposure of critical structures. Median operative time was 545 min.

Patient Position

The placement of the patient and equipment necessary for RAPD is illustrated in Fig. 1. The patient is placed on a split-leg table in the supine position. The patient's location on the table is determined by measuring the distance between the umbilicus and the head of the table to maintain the robotic camera arm within its "sweet spot."

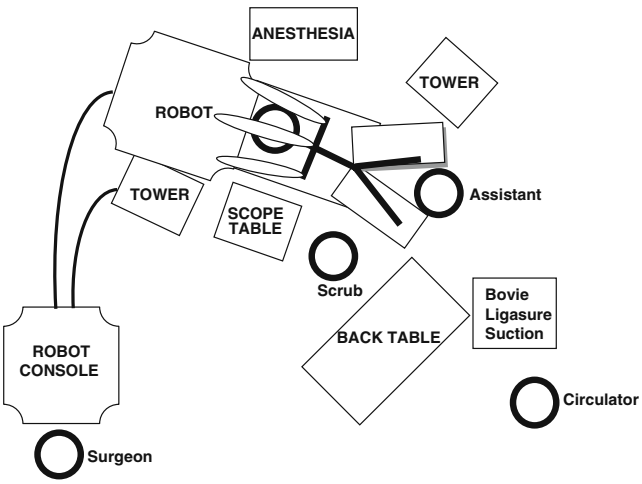

Fig. 1 Operating room set up

Invasive central and arterial lines are inserted, in addition to a nasogastric tube and a Foley catheter. The patient's arms are tucked and protected by foam padding. An upper body convective warming blanket is used to maintain normothermia.

Port Position

Port placement is illustrated in Fig. 2. The 5-mm optical separator is inserted in the left subcostal region to access the peritoneal cavity. Other ports are placed under direct vision. The 10-mm camera port is placed approximately 2–3 cm to the right of the umbilicus to improve visualization of the lateral border of the portal vein. The robotic 8-mm ports (R1 and R3) are placed approximately 2–3 cm cephalad to the camera port lateral to the mid-clavicular lines. R3 is placed in the midclavicular line in the right upper quadrant. The two assistant ports (A1 and A2) are placed approximately 4–5 cm caudad to the camera port along the mid-clavicular lines. A final 5-mm port is placed in the right anterior axillary line for the liver retractor (Fig. 3).

Step 1: Mobilization of the right colon, Kocherization, and mobilization of 3rd and 4th portions of the duodenum

The principle limitation of the current robotic platform is the inability to change the position of the table. Therefore, the first phase of the RAPD uses laparoscopic instruments to facilitate the mobilization of the right colon and dissection of the 3rd and 4th portions of the duodenum behind the mesenteric vessels. The hepatic flexure attachments of the right colon are divided down to the terminal ileum, and an exaggerated medial visceral rotation is performed to expose the superior mesenteric vein at the root of the small bowel mesentery. This is accomplished from the left side of the table using an atraumatic grasper and Ligasure® to reflect the colon inferiorly and medially by dividing the retroperitoneal attachments along the avascular plane. Next, an extended Kocher maneuver is performed mobilizing the transverse duodenum from the ligament of Trietz from the right side of the table beneath the mesenteric vessels. This maneuver allows the jejunum to be pulled into the right upper quadrant under the mesenteric vessels and transected with a 3.5-mm linear cutting stapler approximately 10 cm from the ligament of Trietz. The short duodenal perforating vessels are taken with the ligasure device or tied with 2–0 silk suture. The jejunum is marked 50–60 cm distally to signal the location of the future gastrojejunos-

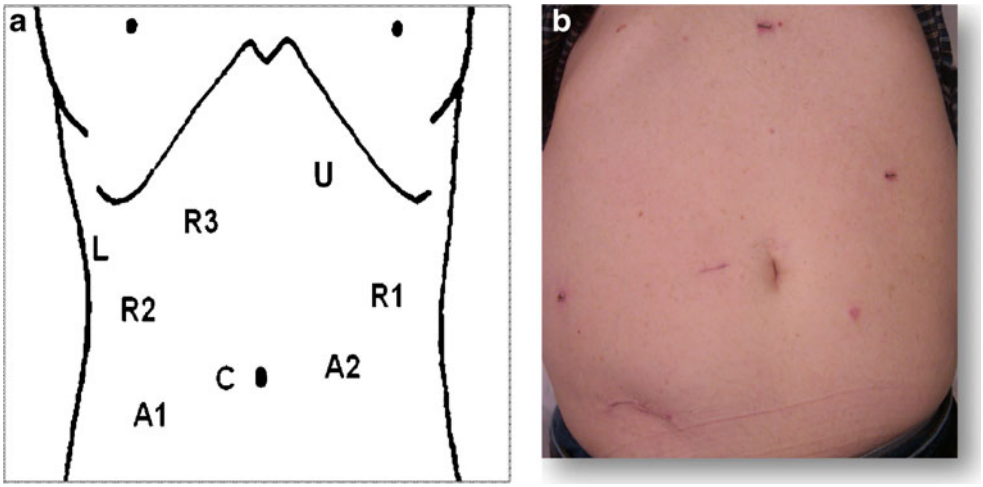

Fig. 2 **a** Port position for laparoscopic robotic-assisted Whipple. *R1–R3* robot arm ports, *C* camera port, *A1–A2* assistant ports, *L* liver retractor port, *U* utility access port. **b** Incisions at 6 weeks postoperative in patient undergoing RAPD

tomy. The jejunum is then passed back beneath the superior mesenteric vessels.

Step 2: Entrance into lesser sac and division of the stomach/duodenum

The gastrocolic omentum is then divided, and the posterior stomach is freed from the anterior surface of the pancreas. The distal stomach is identified and cleared of mesentery along its greater and lesser curves with the Ligasure®. The nasogastric tube is withdrawn, and the stomach is transected with a 4.8-mm linear cutting stapler. The proximal jejunum segment is then identified, pulled in front of the colon (antecolic), and sutured to the stomach in preparation for the gastrojejunostomy. An automated liver retractor is inserted through a 5-mm port in the far lateral right upper quadrant to expose the porta hepatis.

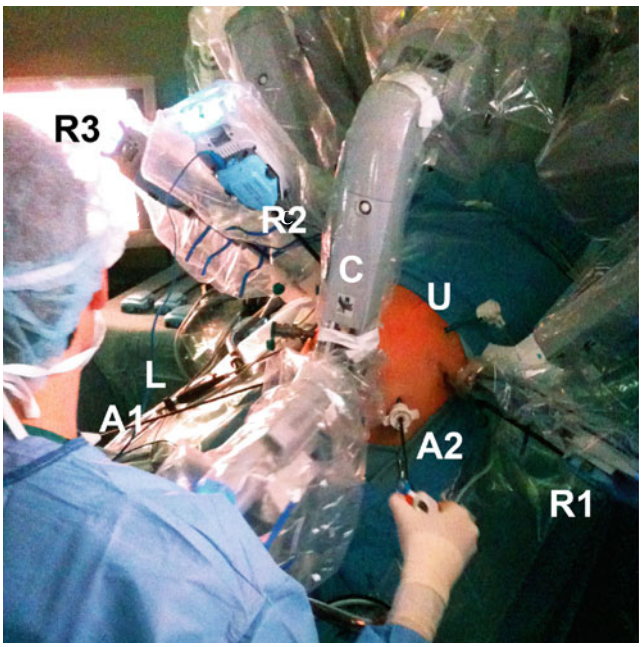

Fig. 3 Position of surgeon and docked robotic arms. *R1–R3* robot arm ports, *C* camera port, *A1–A2* assistant ports, *L* liver retractor port, *U* utility access port

Step 3: Docking the robot

The patient is positioned right-side up in steep reverse Trendelenberg position. The robot is docked directly over the head of the table. The robotic surgeon occupies the daVinci console and the laparoscopic surgeon stands or sits between the patient's leg to exchange instruments, pass needles, and manage the suction-irrigator, clip appliers, and Ligasure® as needed.

Step 4: Dissection of the porta-hepatis and division of the bile duct

Loose areolar tissue over the porta hepatis is identified and divided with robotic hook cautery to expose the superior border of the pancreas and the common hepatic artery (CHA). The CHA lymph node is mobilized and transected with the Ligasure® device and extracted for pathologic examination. The exposed CHA is followed into the porta hepatis to reveal the right gastric artery and gastroduodenal arteries (GDA). The right gastric artery is divided between clips. The GDA is cleared of surrounding tissue and elevated with a vessel loop. Laparoscopic B-D mode ultrasound is used to demonstrate continued pulsatile flow in the CHA with the GDA occluded. The GDA is then divided between 2–0 silk ties and a 4–0 prolene suture ligature, or with the vascular stapler, as necessary. The portal vein is then exposed to demonstrate the medial edge of the common bile duct. The common bile duct lymph nodes are cleared from the lateral border of the

common bile duct, taking care to identify aberrant right hepatic arterial anatomy. A vessel loop is passed behind the bile duct, and the duct is divided with robotic cautery scissors.

Step 5: Dissection of the superior mesenteric vein (SMV) and division of the neck of pancreas

The right gastroepiploic vein is followed to its origin to locate the SMV and the middle colic vein. These large tributary veins are either ligated and divided between 2–0 silk ties or stapled with a vascular load. The SMV is carefully freed from the inferior border and posterior neck of the pancreas to open the plane between the pancreatic neck and the SMV. The tunnel over the portal vein is completed with a laparoscopic articulated grasper, and a moistened umbilical tape is passed to facilitate division of the pancreatic neck. Then, 2–0 silk figure-of-eight sutures are placed on both sides of the inferior neck of the pancreas to control bleeding, and the pancreas is divided with the cautery hook. The bile duct and pancreatic margins are obtained and sent to pathology.

Step 6: Portal dissection and division of the retroperitoneal margin

The pancreas is mobilized from the lateral border of the SMV-PV working in a caudad to cephalad direction. Inferiorly, the first jejunal branch is identified and the small perforating branches from its genu to the uncinate process are divided with 3–0 silk or 4–0 prolene ligatures. The superior pancreaticoduodenal vein is typically divided between 3–0 silk ligatures reinforced with 5-mm clips. Tiny branches are divided with the Ligasure device. Once the SMV-PV is reflected medially, the SMA is identified posteriorly. Dissection proceeds along the plane of Leriche dividing the inferior and superior pancreaticoduodenal vessels between 2–0 silk ligatures, with 5 mm clips and Ligasure® being used for smaller perforators and the duodenal mesentery.

With the specimen completely free, the gallbladder is mobilized in an antegrade fashion, dividing the cystic artery and duct between clips. The specimens are placed in the right upper quadrant above the liver and extracted at the conclusion of the reconstruction.

Step 7: Reconstruction

The pancreticobiliary limb emerges behind the mesenteric vessels and is positioned in the right upper quadrant. A two-layer, end-to-side, duct-to-mucosa pancreaticojejunostomy is performed. The pancreatic duct sutures are placed first to facilitate visualization of the ductal mucosa (5–0 Vicryl). The sutures are clipped and reflected out of the way. Next, transpancreatic horizontal mattress sutures of 2–0 silk (modified Blumgart anastomosis) are passed to anchor the seromuscular layer of the jejunum to the pancreatic parenchyma. A small enterotomy is made using the robotic cautery shears, and an interrupted duct-to-mucosa anastamosis is completed. A pancreatic duct stent (5–7 French, 7 cm Zimmon® pancreatic stent, Cook Medical) is placed to assure duct patency. Most anastomoses require 5–6 interrupted sutures. If the pancreatic duct is difficult to identify, secretin (0.2 mcg/kg IV) is administered to stimulate pancreatic secretion. The anastomosis is completed with an anterior layer of 2–0 silk sutures. Approximately 10 cm downstream from the pancreaticojejunostomy, a singer-layer end-to-side hepaticojejunostomy is performed with 5–0 Vicryl in a running fashion for duct diameters >5 mm in diameter, or in interrupted fashion for ducts ≤5 mm. Stents are used selectively for tiny ducts. Finally, an antecolic stapled gastrojejunostomy is performed with a two-layered sutured closure of the common enterotomy at the location of the anchoring suture.

After assuring hemostasis and a correct needle count, two round 19-French surgical drains are placed, one anterior and posterior to the biliary and pancreatic anastomoses. The specimens are bagged and withdrawn to the right lower quadrant port site. The robot is undocked, and a McBurney's incision is used to extend the right lower quadrant port to exract the specimens. Ports greater than 5 mm in diameter are closed. The skin is closed with a monofilament subcuticular closure. Patients are awakened, extubated, and transferred to the surgical intensive care unit for overnight observation.

Discussion

The RAPD procedure incorporates all time-tested techniques of open pancreaticoduodenectomy into a truly minimally-invasive operation. The key technical similarities include: (1) transecting the pancreatic neck with electrocautery; (2) sharp dissection along the lateral wall of the portal vein with identification and individual ligation of venous tributaries; (3) retroperitoneal dissection in the adventitial plane of the SMA with ligation and control of arterial branches to maximize clearance of tumor at the surgical margin and prevent postpancreatec-

tomy hemorrhage; (4) interrupted, duct-to-mucosa pancreatojejunostomy in two layers under 30× magnification with the option to place a surgical stent; (5) running or interrupted hepaticojejunostomy depending on the caliber of the bile duct; and (6) two surgeon exposure and dissection. These similarities permit a direct comparison of perioperative and oncologic outcomes between the open and minimally-invasive procedures without potential confounding factors introduced by compromises in technique and instrumentation.

The most critical technical aspect of the procedure is the coordination and teamwork of the attending surgical team, consisting of two experienced pancreatic surgeons with advanced laparoscopic skills. Four-hand coordination is necessary to expose and resect tumors adjacent to the mesenteric vessels with safety and strict adherence to oncologic principles. The addition of magnified binocular vision and robotic-assisted dexterity allows for the exposure and suture control of brisk bleeding without resorting to crash laparotomy or reliance on clips that would not be used under corresponding circumstances during an open procedure.

An important technical consideration during advanced robotic surgery is the inability to reposition the patient after the system is docked. We have learned to mobilize the right colon, Kocherize the duodenum, and divide the ligament of Treitz laparoscopically to allow gravity to assist with exposure and retraction of the omentum, colon, and small bowel. The main advantage of the robot is the elimination of awkward angles for intracorporeal suturing and the added dexterity which approximates the capability of the surgeon under open conditions, albeit at the expense of added time to pass individual needles. Moreover, the robot-assited technique avoids the necessity of technical “short cuts” as compared to open pancreaticoduodenectomy.

Although robotic surgery extends the horizon of minimally-invasive pancreatic surgery significantly, there are significant limitations in current systems. There is a significant learning curve to the mechanical aspects of the procedure which is rapidly degraded if not routinely exercised. Operative times remain significantly longer,, and substituting visual clues for absent tactile feedback takes practice. Finally, sustaining the personal commitment of two experienced pancreatic surgeons cannot be overemphasized if safety is to be maintained. The authors recommend that surgeons wishing to initiate a robotic pancreatic surgery program should begin with cholecystectomy and distal pancreatectomy and gradually add technical complexity as experience and capability permit. Our institution has recently purchased the dual console daVinci. This allows the trainee to actively participate in portions of the case commensurate with their level of robotic experience. In addition, we have launched for our residents and fellows weekly robotic training including suturing and tying drills.

The first manuscript report describing robotic pancreaticoduodenectomy was published by Giulianotti et al in 2010[5]. The authors reported 134 patients who underwent robotic-assisted pancreatic surgery, of whom sixty underwent pancreaticoduodenectomy. The authors describe a five-port technique consisting of one camera port, three robotic ports, and one assistant port. The authors do not specify the extent of the operation performed laparoscopically or the role of the assistant after the robot is docked. The provision of a single port for the assistant diminishes the capacity for teamwork, which is a major technical asset during open surgery and a safety issue during rapid bleeding. The biggest technical difference between Giulianotti's technique and ours occurs during the reconstructive phase. In our technique all patients undergo a two-layer duct-to-mucosa pancreaticojejunostomy regardless of pancreatic duct size or parenchymal texture, a technical benefit of magnified vision and robotic precision. We have performed over 40 Robotic assisted pancreaticoduodenectomies using the described technique. In contrast, only 32% (19/60) of patients in Giulianotti’s series underwent pancreatic anastomosis, with the remaining 68% receiving pancreatic duct occlusion with biological glue. The comparative outcomes after two-layer anastomosis and planned duct occlusion in terms of pancreatic fistula formation, long-term endocrine function, and quality of life between these approaches have not been scrutinized.

Conclusion

Four-hand combined laparoscopic/robotic pancreaticoduodenectomy is safe and feasible when performed by two experienced pancreas surgeons with the requisite skill sets. The RAPD procedure does not compromise tested principles of open pancreaticoduodenectomy and is currently undergoing a formal safety evaluation to determine its comparative effectiveness.

Disclosures Dr. Chalikonda is a paid consultant for Intuitive Surgical and Covidein.

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REVIEW ARTICLE

Hand-Sewn Versus Stapled Oesophago-gastric Anastomosis: Systematic Review and Meta-analysis

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Abstract
Objective In this meta-analysis, data from relevant randomised controlled trials has been pooled together to gain a consensus in the comparison of outcome following hand-sewn versus stapled oesophago-gastric (OG) anastomoses.
Methods Medline, Embase, Cochrane, trial registries, conference proceedings and reference lists were searched for randomised controlled trials comparing hand-sewn and stapled OG anastomoses. Primary outcome measures were 30-day mortality, anastomotic leakage and stricture. Secondary outcomes were operative time, cardiac complications and pulmonary complications.
Results Nine randomised trials were included in this meta-analysis. There was no significant difference between the groups for 30-day mortality (pooled odds ratio=1.71; 95% CI=0.822 to 3.56; P=0.15) and anastomotic leakage (pooled odds ratio=1.06; 95% CI=0.62 to 1.80; P=0.83). There was a significantly increased rate of anastomotic stricture associated with stapled OG anastomosis (pooled odds ratio=1.76; 95% CI=1.09 to 2.86; P=0.02).
Discussion Meta-analysis of randomised controlled trials comparing hand-sewn with stapled OG anastomosis demonstrates that a stapled anastomosis is associated with a shorter operative time but with an increased rate of post-operative anastomotic stricture.

Keywords Sutured · Stapled · Anastomosis · Oesophageal · Gastric

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Introduction

Most techniques of surgical resection of oesophageal carcinoma involve removal of the diseased oesophageal portion, formation of a gastric conduit and creation of a gastro-oesophageal anastomosis. Oesophagectomy techniques are complex and associated with significant post-operative morbidity and mortality.[1] Anastomotic leakage is a significant cause of early post-operative morbidity that may lead to re-operation, prolonged hospital stay, psychological trauma and death. Anastomotic stricture can result in post-operative dysphagia, which may require additional invasive procedures with increased frequency of outpatient attendance and overall cost as well as nutritional compromise and reduction in quality of life.

With both of these complications being prevalent and serious following oesophagectomy, the method of anas-

tomosis has been the focus of much attention.[2,3] Oesophago-gastric anastomoses can be hand-sewn or stapled with a mechanical circular anastomotic stapling device. There has been much debate regarding the merits and negative aspects of stapled versus hand-sewn oesophago-gastric anastomoses.[4]

Through this pooled analysis of the available relevant randomised controlled trials, we aimed to gain a consensus in order to guide clinical practice regarding the most successful oesophago-gastric anastomotic technique.

Methods

A systematic literature search of Medline (1950–September 2010), Embase (1974–September 2010) and Cochrane Library (2010, Issue 2) databases was performed. The search terms 'esophagectomy', 'anastomosis', 'oesophagus', 'hand-sewn', 'stapled' and 'gastric' and MeSH headings 'anastomosis' (MeSH), 'hand-sewn' (MeSH), 'stapled' (MeSH) and 'esophagectomy' (MeSH) were used in combination with the Boolean operators AND or OR. The electronic search was supplemented by a hand search of published abstracts from the European Association for Endoscopic Surgery 2007–2010, the Clinical Robotic Surgery Association 2010, the Minimally Invasive Robotic Association 2005–2010, the Surgical Research Society, the Society of Academic and Research Surgery, and the Association of Surgeons of Great Britain and Ireland. Reference lists of all relevant studies were reviewed and the search included the Current Controlled Trials Register (http://www.controlled-trials.com).

Abstracts of the citations identified by the search were then scrutinised by two observers (SM and AK) in order to determine eligibility for inclusion in the meta-analysis. Studies were included if they met each of the following criteria: prospective controlled trial, separation into groups based on hand-sewn and sutured oesophago-gastric anastomosis. Exclusion criteria comprised trials with retrospective design, those without a control group undergoing hand-sewn anastomosis, or studies focusing on the paediatric population.

The primary outcome measures for the meta-analysis were 30-day mortality, anastomotic leakage and anastomotic strictures (developing within 6 months of operation requiring endoscopy). The secondary outcome measures for the meta-analysis were operative time, cardiac complications and pulmonary complications (a complication within the first month of the operation as a direct result of the initial operation). Data from eligible trials were entered into a computerised spreadsheet for analysis. The quality of each trial was assessed using the Jadad scoring system.[5] Statistical analysis was performed using Statsdirect 2.5.7 (Statsdirect Ltd, UK). The weighted mean difference was calculated for the effect size of stapled anastomoses on continuous variables such as operative time. Pooled odds ratios were calculated for the effect of stapled anastomoses on discrete variables such as 30-day mortality, anastomotic leakage, anastomotic strictures, and cardiac and pulmonary complications. Pooled outcome measures were determined using random-effects models as described by Der Simonian and Laird.[6] Heterogeneity amongst the trials was assessed by Cochran's Q statistic, a null hypothesis test in which $P < 0.05$ is taken to indicate the presence of significant heterogeneity. The Egger test was used to assess the funnel plot for significant asymmetry, indicating possible publication or other biases.

Results

After screening, nine randomised trials that met the inclusion criteria were identified[7–15] (QUORUM diagram). Patient demographic data and Jadad score for each trial is represented in Table 1.

Primary Outcome Measures

(a) 30-Day Mortality

Five trials reported the incidence of 30-day mortality following stapled versus hand-sewn anastomosis.[7,8,10,11,13] There was no significant difference in 30-day mortality following stapled versus hand-sewn oesophago-gastric anastomoses (Fig. 1) (pooled odds ratio=1.71; 95% CI=0.822 to 3.56; P=0.15). There was no evidence of statistical heterogeneity (Cochran's Q=2.81; P=0.42) or bias (Egger test=1.10; P=0.50; Table 2).

(b) Anastomotic Leakage

All nine trials reported the incidence of anastomotic leakage following surgery.[7–15] There was no significant difference in anastomotic leakage between the two groups (Fig. 2) (pooled odds ratio=1.06; 95% CI=0.62 to 1.80; P=0.83). There was no evidence of statistical heterogeneity (Cochran's Q=4.85; P=0.77) or bias (Egger test=0.03; P=0.97).

(c) Anastomotic Strictures

Eight studies reported the incidence of anastomotic stricture following surgery.[7–14] There was a significant increase in the incidence of anastomotic stricture following stapled anastomosis compared with hand-sewn anastomoses (Fig. 3) (pooled odds ratio=1.76; 95% CI=1.09 to 2.86; P=0.02). There was no evidence of statistical heterogeneity (Cochran's Q=9.40; P=0.23) or bias (Egger test=0.72; P=0.62).

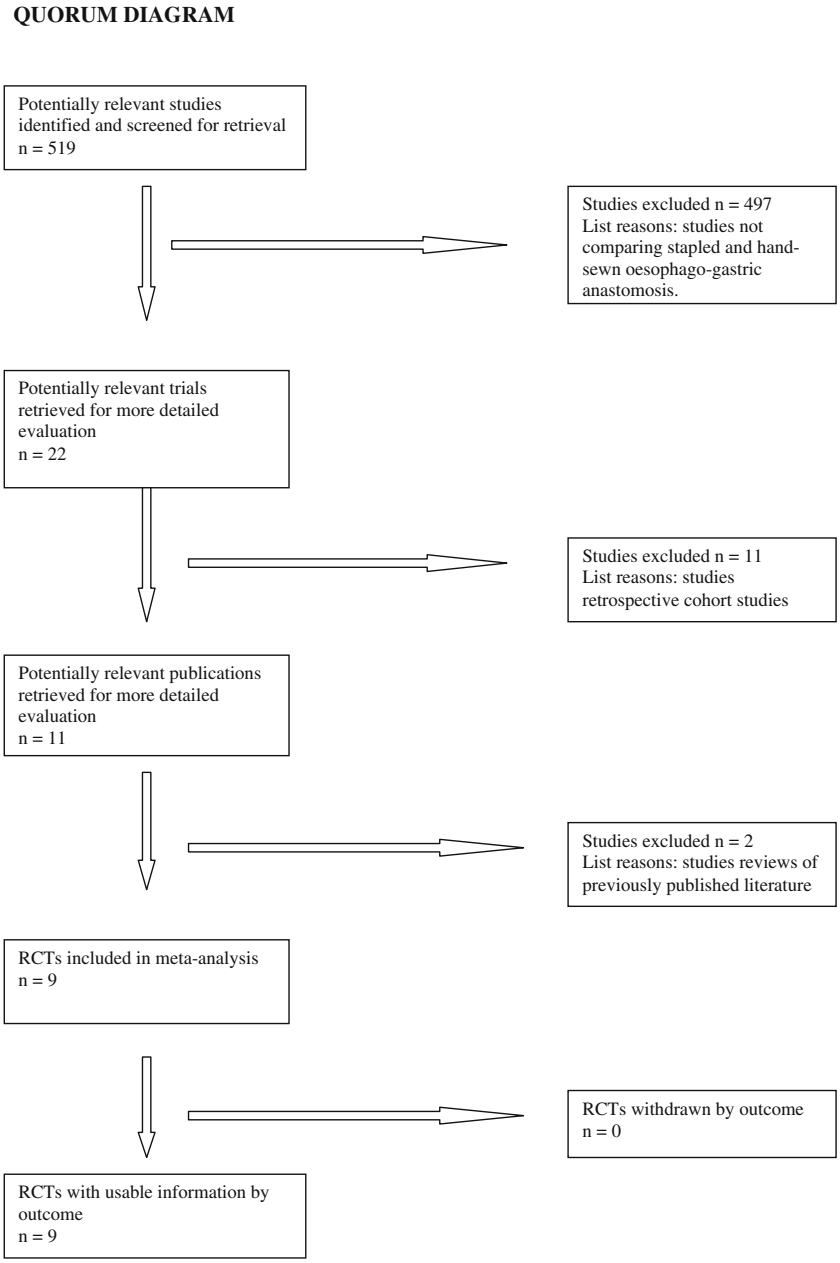

Table 1 Demographic data

Author	Patient no. (HS)	Patient no. (ST)	Age (HS)	Age (ST)	M/F ratio (HS)	M/F ratio (ST)	Jadad score
Law[7] (*n*=122)	61	61	64±1.2	63±1	54:7	53:8	2
Hsu[8] (*n*=64)	32	31	63±10	61±12	27:5	29:2	2
Laterza[9] (*n*=41)	21	20	50.9	51.9	4:17	3:17	3
Valverde[10] (*n*=152)	74	78	59±9	59±10	67:7	71:7	3
Luechakiettisak[11] (*n*=117)	59	58	63.6±2.2	62±2.2	50:9	48:10	2
Walther[12] (*n*=83)	41	42	68±2.3	66±2.6	28:13	29:13	3
Okuyama[13] (*n*=32)	18	14	64.3±2.1	63.6±1.6	16:2	13:1	2
Craig[14] (*n*=100)	50	50	–	–	–	–	2
George[15] (*n*=52)	25	27	63.7±15.8	65.3±14.5	–	–	2

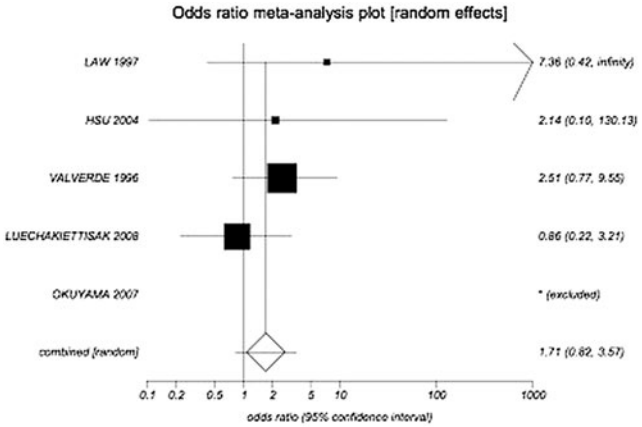

Fig. 1 Forrest plot for 30-day mortality

Secondary Outcome Measures

(a) Operative time

Six trials compared operative time between the two groups.[7,8,10–13] There was a significantly increased operative time with the hand-sewn anastomotic group (Fig. 4) (weighted mean difference=−1.56; 95% CI=−3.14 to 0.05; P=0.04). There was evidence of statistical heterogeneity (Cochran's Q=299.20; P< 0.0001), but no statistical evidence of bias (Egger test=−14.33; P=0.11; Table 3).

(b) Cardiac Complications

Eight trials compared the incidence of cardiac complications following surgery between the groups.[7–14] There was no significant difference in the incidence of cardiac complications between the groups (Fig. 5) (pooled odds ratio=1.02; 95% CI=0.68 to 1.54; P=0.92). There was no evidence of statistical heterogeneity (Cochran's Q=3.58; P=0.61) or bias (Egger test=−2.63; P=0.22).

(c) Pulmonary Complications

Seven trials compared the incidence of pulmonary complications between the groups.[7,8,10–14] There was no significant difference in the incidence of pulmonary complications between the groups (Fig. 6) (pooled odds ratio=1.31; 95% CI=0.88 to 1.93; P=0.18). There was no evidence of statistical heterogeneity (Cochran's Q=4.64; P=0.59) or bias (Egger test= 1.26; P=0.25).

Discussion

The aim of this meta-analysis was to compare clinical outcome following hand-sewn versus stapled oesophagogastric anastomosis. Following oesophagectomy, the reliability and consistency of this anastomosis is critically important for an uneventful post-operative course. A pooled analysis performed on this topic in 1998[16] demonstrated a similar incidence of anastomotic leak between the two groups; however, there was a greater propensity for stricture formation following stapled anastomosis. This analysis pooled together the results of studies that compared the two groups, although the authors did not attempt to produce a meta-analysis that could have helped produce a statistically sound argument on this topic. The first meta-analysis on this topic was performed in 2001.[17] The authors concluded that both methods give similar results for post-operative anastomotic leak and stricture; however, stapled anastomosis was associated with an increased mortality, but this was not elaborated upon further in this article. In this present meta-analysis, we have attempted to review the published randomised controlled trials on this topic to date in order to gain a pooled analysis and a consensus on the best anastomotic practice.

Table 2 Primary outcome measures

Author	30-Day mortality (HS)	30-Day mortality (ST)	Anastomotic leakage (HS)	Anastomotic leakage (ST)	Anastomotic stricture (HS)	Anastomotic stricture (ST)
Law[7]	0 (0%)	3 (4.9%)	1 (1.6%)	3 (4.9%)	5 (8.2%)	20 (32.8%)
Hsu[8]	1 (3.1%)	2 (6.5%)	7 (21.9%)	8 (25.8%)	4 (12.5%)	5 (16.1%)
Laterza[9]	2 (9.5%)	1 (5%)	1 (4.8%)	4 (20.0%)	2 (9.5%)	3 (15%)
Valverde[10]	5 (6.8%)	12 (15.4%)	12 (16.2%)	12 (15.4%)	8 (10.8%)	7 (9.0%)
Luechakiettisak[11]	7 (11.9%)	6 (10.3%)	4 (6.8%)	2 (3.4%)	10 (16.9%)	19 (32.8%)
Walther[12]	1 (2.4%)	1 (2.4%)	1 (2.4%)	0 (0%)	8 (19.5%)	12 (28.6%)
Okuyama[13]	0 (0%)	0 (0%)	3 (16.7%)	1 (7.1%)	0 (0%)	2 (14.3%)
Craig[14]	1 (2.0%)	4 (8.0%)	3 (6.0%)	4 (8.0%)	13 (26.0%)	13 (26.0%)
George[15]	–	–	1 (4.0%)	1 (3.7%)	–	–

HS hand-sewn anastomosis, *ST* stapled anastomosis

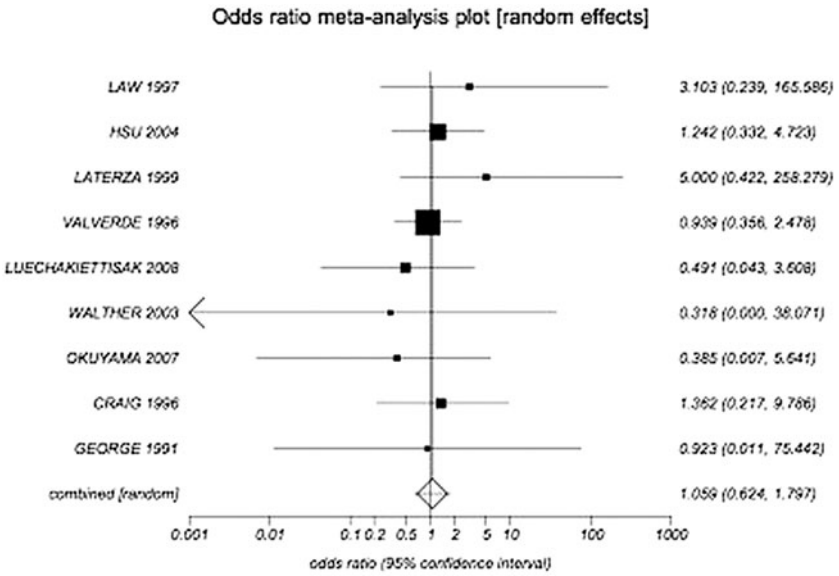

Fig. 2 Forrest plot for anastomotic leak

The primary outcome measures from our meta-analysis demonstrated that there was no significant difference between the two groups for 30-day mortality (pooled odds ratio=1.71; P=0.15) and anastomotic leak (pooled odds ratio=1.06; P=0.83). However, following stapled anastomosis there was a significantly increased incidence of anastomotic stricture compared with hand-sewn anastomosis (pooled odds ratio=1.76; P=0.02). For secondary outcome measures, the only difference identified between the two groups was an increased operative time in the hand-sewn anastomotic group (weighted mean difference=−1.56; P=0.04).

The success of an oesophageal anastomosis depends on attention to detail in optimising factors within the following two domains. First, in the preparation of the ends to be anastomosed, there must be appropriate mobilisation and dissection to ensure a tension-free anastomosis whilst also guaranteeing a healthy blood supply throughout the gastric pull-up and also at the divided oesophagus. The point chosen for resection must result in a disease-free margin, and the apposition between the oesophagus and gastric pull-up needs to be accurate with good size approximation and ideally with mucosal inversion. Second, there are a range of systemic

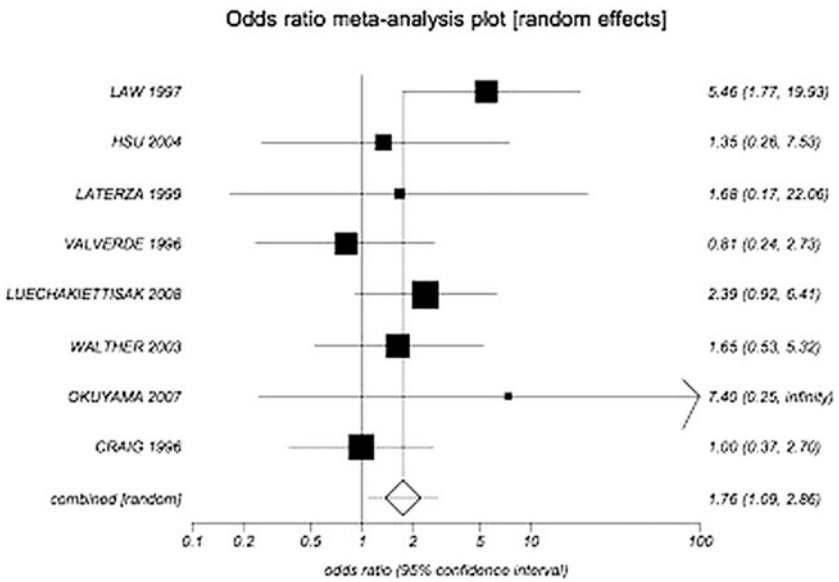

Fig. 3 Forrest plot for anastomotic stricture

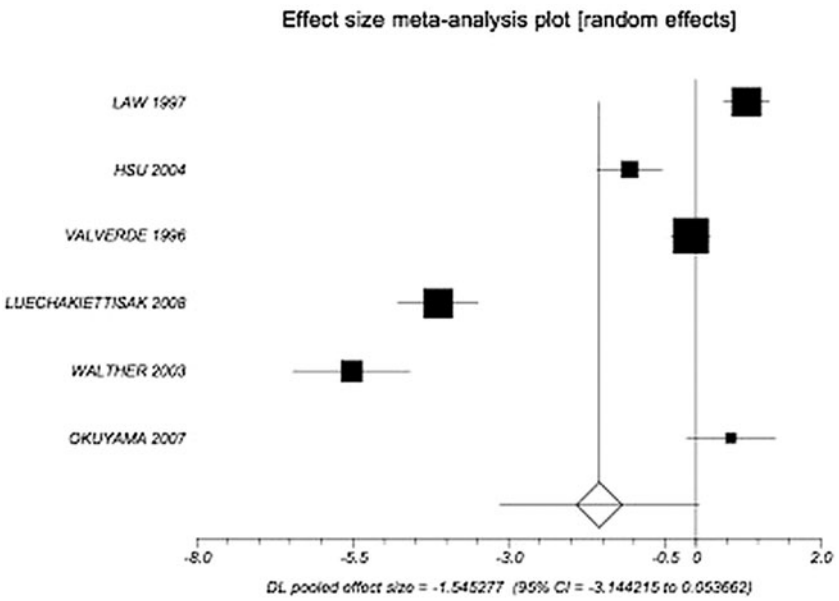

Fig. 4 Forrest plot for operative time

variables that can impact on the integrity and healing of an anastomosis, and good nutritional status and appropriate maintenance of fluid balance to support tissue perfusion and oxygenation are key amongst these. It is acknowledged that the influence of a large number of these confounding variables upon oesophago-gastric anastomotic outcome is difficult to quantify and their effect cannot always be reliably separated out. However, both hand-suturing and stapled techniques lend themselves to an attempt at standardisation, providing a basis for comparison.

Previous studies have demonstrated that a stapled anastomosis is associated with an increased rate of anastomotic stricture development in both colorectal[18] and gastrointestinal surgery.[19,20] A recent Cochrane review of ileocolic anastomoses showed that a stapled end-to-end ileocolic anastomosis is associated with fewer leaks than a hand-sewn anastomosis.[21] The meta-analysis presented here demonstrates that mechanical oesophago-gastric anastomosis can be performed in a safe manner with a similar leakage rate compared to hand-sewn anastomosis and with a shorter operative time. However, the rate of anastomotic stricture is greater with stapled anastomosis, which should serve as a cautionary note when using this technique. Two of the studies included in this meta-analysis have described an increased cost associated with stapled anastomoses, but there was insufficient data to allow formal meta-analysis of this outcome.[7,10]

Table 3 Secondary outcome measures

Author	Op time (HS) (min)	Op time (ST) (min)	Cardiac comps (HS)	Cardiac comps (ST)	Pulm comps (HS)	Pulm comps (ST)
Law[7]	214±4	217±3.4	13 (21.3%)	19 (31.1%)	6 (9.8%)	11 (18.0%)
Hsu[8]	524±77	447±64	9 (28.1%)	7 (22.6%)	9 (28.1%)	11 (35.5%)
Laterza[9]	–	–	–	–	–	–
Valverde[10]	401±130	390±120	10 (13.5%)	11 (14.1%)	37 (50.0%)	41 (52.6%)
Luechakiettisak[11]	218.1±4	203.7±2.8	10 (16.9%)	11 (19.0%)	8 (13.6%)	10 (17.2%)
Walther[12]	586±8.8	537±8.8	4 (9.8%)	4 (9.5%)	2 (4/9%)	4 (9.5%)
Okuyama[13]	547±95	593±57	0 (0%)	0 (0%)	2 (11.1%)	5 (35.7%)
Craig[14]	–	–	11 (22.0%)	6 (12.0%)	8 (16.0%)	5 (10.0%)
George[15]	207[a]	207[a]	–	–	–	–

HS hand-sewn anastomosis, *ST* stapled anastomosis, *Op time* operative time, *Cardiac comps* cardiac complications, *Pulm comps* pulmonary complications

[a] Result excluded from meta-analysis as no mean provided, preventing analysis

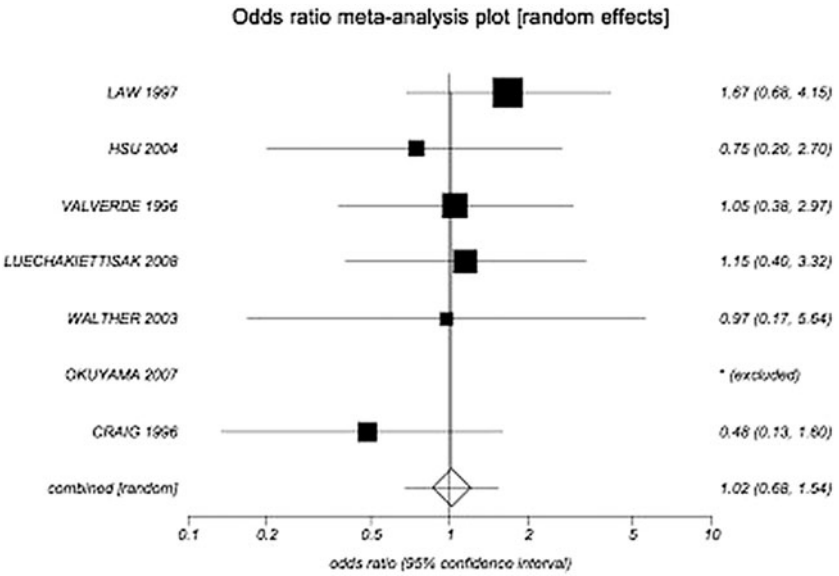

Fig. 5 Forrest plot for cardiac complications

Law et al.[7] have suggested possible theories as to why there is an increased formation of anastomotic stricture in the stapled group, and these include the lack of accurate mucosa-to-mucosa apposition. They also speculate that there might be necrosis of tissue in a limited area just beyond the staple line and where the tissues are compressed by the stapling device, and this may predispose to excessive fibrosis and stricture formation. They commented that retained mechanical sutures at the staple line might play a role in stimulating an intense fibrotic reaction resulting in anastomotic stricture formation. Hand-sewn anastomoses allow more accurate mucosa-to-mucosa apposition with less risk of tissue strangulation.

Anastomotic stricturing could also be the long-term result following an anastomotic leak that has healed with time. The fact that there was no statistical difference in the anastomotic leak rates between these techniques in the present meta-analysis, however, goes against this. The increased rate of stricture formation in the stapled group is more likely to be due to an independent factor specific for the mechanical anastomosis and not related to the healing of a previous anastomotic leak. Confounding variables in anastomotic

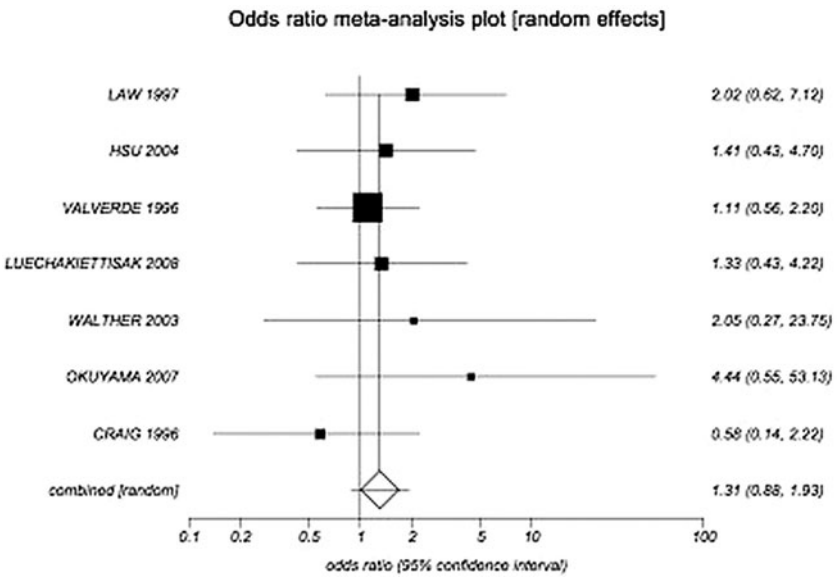

Fig. 6 Forrest plot for pulmonary complications

Table 4 Type of stapled anastomosis

Author	Type of stapler used for anastomosis	Size of stapler used for anastomosis
Law[7]	Circular EEA and ILS staplers	28–33 mm
Hsu[8]	ILS circular stapler	21 mm
Laterza[9]	Linear stapler	Two layers; 21 mm and 25 mm
Valverde[10]	ILS, EEA, PCEEA and DCEEA circular stapler	Not specified
Luechakiettisak[11]	ILS circular stapler	25 mm or 31 mm
Walther[12]	PCEEA circular stapler	25 mm, 28 mm or 31 mm
Okuyama[13]	PCEEA circular stapler	25 mm
Craig[14]	EEA stapler	Not specified
George[15]	EEA stapler	Not specified

ILS intraluminal stapler, *EEA* end-to-end anastomosis, *PCEEA* premium circular end-to-end anastomosis, *DCEEA* disposable circular end-to-end anastomosis

stricture following stapled anastomosis include the type and size of stapler used.[22,23] Table 4 describes the type and size of stapled anastomosis used in each trial. This illustrates the variability in stapling devices used in each trial that may have influenced the rate of post-operative anastomotic stricture in the stapled OG anastomotic group. However, unfortunately due to the small number of patients in each study, it was not possible for the effect of different stapling devices in anastomotic stricture formation.

Some studies have shown that cervical anastomoses have the added benefit of allowing more radical oesophageal resection. However, according to these papers, there is a higher rate of anastomotic leak and stricture formation in cervical anastomoses compared to intra-thoracic.[24,25] In the nine papers included in this analysis, there was variability in the site of oesophageal anastomosis. In some, all anastomoses were intra-thoracic and in some others all anastomoses were cervical irrespective of whether they were hand-sewn or stapled. In two studies[12,13], all hand-sewn anastomoses were cervical and all stapled anastomoses were intra-thoracic. Due to the small sample sizes used, it was not possible to analyse stapled and hand-sewn anastomosis based upon their location. Furthermore, Table 5 shows the use of pre- and post-operative chemoradiation in each study, but due to the small number of patients included in each study, it was not possible to stratify for the effect of chemo-radiation in anastomotic stricture formation.

Conclusion

This meta-analysis has shown that stapled oesophago-gastric anastomosis is associated with similar clinical outcomes and with a shorter operative time when compared with hand-sewn anastomosis. There is an increased rate of anastomotic stricturing with stapled anastomoses and this needs to be considered when selecting this technique.

Table 5 Site of oesophagectomy (cervical or intra-thoracic) and use of chemotherapy and radiotherapy

Author	Site of anastomosis	Chemo- or radiotherapy
Law[7]	Intra-thoracic (hand-sewn and stapled groups)	Post-operative radiation
Hsu[8]	Cervical (hand-sewn and stapled groups)	Pre-operative chemoradiation
Laterza[9]	Intra-thoracic (hand-sewn and stapled groups)	Pre-operative chemoradiation
Valverde[10]	Cervical or intra-thoracic anastomosis in hand-sewn and stapled groups	Pre-operative and post-operative chemoradiation
Luechakiettisak[11]	Intra-thoracic in hand-sewn and stapled groups	–
Walther[12]	Cervical (hand-sewn group) vs intra-thoracic (stapled group)	Pre-operative chemoradiation
Okuyama[13]	Cervical (hand-sewn group) vs intra-thoracic (stapled group)	Adjuvant chemotherapy
Craig[14]	Intra-thoracic in hand-sewn and stapled groups	–
George[15]	Intra-thoracic in hand-sewn and stapled groups	–

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Conflict of Interest None.

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CASE REPORT

Are Incisionless Fundoplication Procedures a Safer Alternative to the Laparoscopic Nissen for the Treatment of Chronic Gastroesophageal Reflux Disease?

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Introduction

Gastroesophageal reflux disease (GERD) is a complex disease that can be characterized by a broad spectrum of clinical symptoms. It is the most common upper gastrointestinal disorder in the western civilization with an increasing prevalence and incidence in the last two decades.[1] It has been estimated that 15–25% of adults experience gastroesophageal reflux symptoms at least weekly, and 5–12% suffer these symptoms on a daily basis.[2,3] The primary barrier to reflux is the esophagogastric junction which consists of the intrinsic lower esophageal sphincter (LES), extrinsic compression of the LES by the crus, intraabdominal position of the sphincter, integrity of phrenoesophageal ligament, and maintenance of the angle of His.[4] Although not completely understood, dysfunction or abnormalities in any of these components introduce the propensity for increased reflux. Due to complex etiology of GERD, the care and treatment ranges as wide as the spectrum of the disorder itself. Therapeutic modalities include lifestyle modification, medications, and ultimately surgical intervention. The initial and most conservative treatment of GERD is to advise lifestyle changes such as weight loss, avoiding foods that decrease LES pressure, avoiding lying down directly after eating, and raising the head of the bed while sleeping. Although there is definitive data that exist regarding the role of obesity and smoking in promoting GERD clinical manifestations, there is no evidence showing that dietary modifications improve symptoms.[5] Despite the insufficient evidence to support an association between dietary behavior and GERD, some dietary interventions continue to be recommended as first-line therapy.[6]

Although modern drug therapy is very effective in the long-term management of GERD, antireflux surgery seems to be more cost effective than medical therapy and safer regarding long-term effects of acid suppression and development of adenocarcinoma of the esophagus in patients with severe forms of the disease.[7] Since its conception in 1956, the Nissen fundoplication has been the surgical treatment of choice for GERD. As surgical techniques evolved into the laparoscopic era, the laparoscopic Nissen fundoplication has evolved into the gold standard in antireflux surgery with excellent control outcomes. Dallemagne et al. reported that 90% patients had symptom control 10 years after surgery, and less than 10% of patients had to resume medication again. Hence, the Nissen fundoplication procedure has been the "gold standard" unto which other procedures have been compared to.

As the surgical world continues to push towards less invasive techniques, endoscopic interventions have evolved in treating GERD. Currently, there exists several endoscopic options from suturing (i.e., Bard® EndoCinch™, the Wilson-Cook Endoscopic Suturing Device, the NDO Plicator™, and EsophyX®) to endoscopic injections or implantations(i.e., Enteryx®, the Gatekeeper™ Reflux Repair System, and Plexiglas®), all which bulk up the LES by injecting biopolymers into the muscularis layer of the esophagus.[8] Although these techniques are relatively new, there are groups that promote their cosmetic appeal and their effectiveness all without surgical necessity. As the treatment

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of GERD continues its endoscopic evolution, we must be critical of its feasibility, efficacy, and safety.

In this case review, we present two separate cases of esophageal perforation (EP) after endoscopic treatment of GERD with a Transoral Incisionless Fundoplication EsophyX® endoscopic procedure (EndoGastric Solutions®). This is an endoluminal, incisionless fundoplication device which deploys multiple full thickness serosa-to-serosa fasteners into the gastric wall to form an interrupted suture line at the base of the gastroesophageal junction. This procedure attempts to construct the antireflux valve and tighten the lower esophageal sphincter in order to reestablish a barrier to reflux and competency of the gastroesophageal junction.[9] Although these patients presented from outside institutions, we treated them according to our institution's established EP treatment algorithm (Fig. 1), which utilizes endoscopically placed retrievable covered metallic stents.

Case I

Our first case is a young healthy 38-year-old gentleman with a medical history significant for GERD and anterior left cervical vertebral fusion. He underwent an EsophyX® procedure for treatment of his chronic GERD. Per the operating surgeon and accompanying documentation, "difficulties" were encountered when withdrawing the device from the esophagus. Immediately following the procedure, the patient experienced dysphagia and upper chest, head, and neck pain with significant subcutaneous emphysema. A computed tomography of the chest was obtained at the referring institution showing mediastinal air tracking towards the neck (Fig. 2). Consequently, the patient was transferred to our facility within 12 h of his initial procedure. On endoscopy, a full thickness esophageal laceration was found 2 cm distal to the upper esophageal sphincter which extended 11 cm (Fig. 3). Given the location and his previous left anterior cervical vertebral fusion, we elected to endoscopically place a removable metallic covered stent (Fig. 4) as well as a gastrostomy tube. We confirmed that his esophageal perforation was sealed with an esophagram 24 h following stent placement. There was no need for thoracic drainage as there were no effusions noted on his radiographic exam following stent placement. He was discharged on hospital day 7 tolerating clear liquid diet. His stent was removed 3 weeks after placement, and a follow-up esophagogastroduodenoscopy (Fig. 5) and an esophagram revealed a healed esophageal perforation. At his follow-up visit, 4 weeks following his hospital discharge, he reported of no dysphagia and was able to tolerate a regular meal without any discomfort.

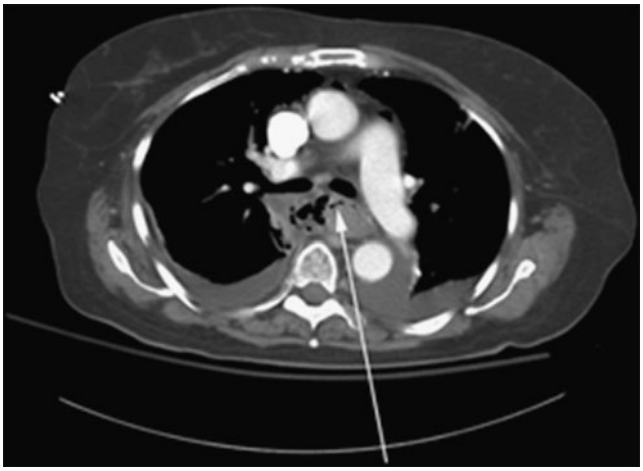

Fig. 2 Computed tomography of chest revealing mediastinal air

Case II

The second case is a 61-year-old female with medical history significant for chronic GERD, hypertension, hypo-

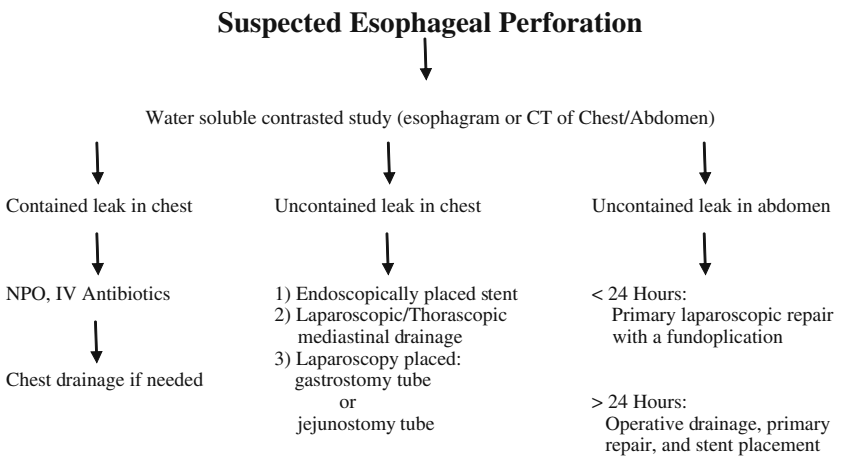

Fig. 1 Esophageal perforation treatment algorithm

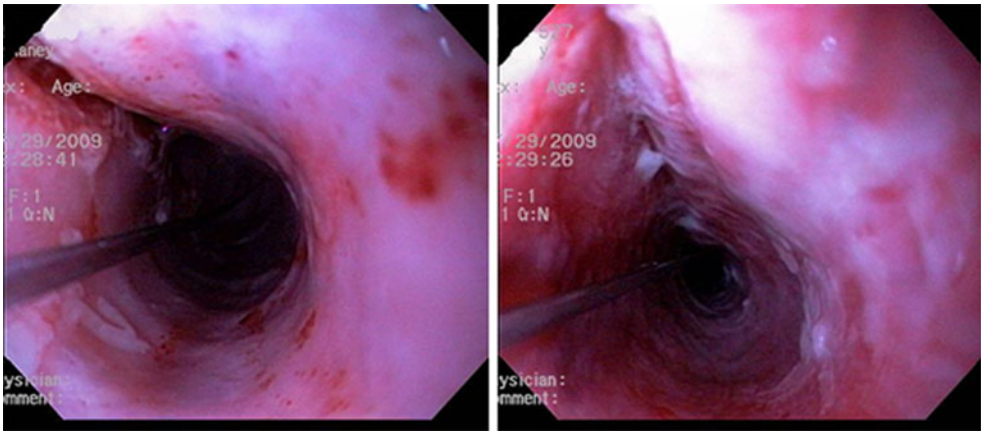

Fig. 3 Intra-operative EGD revealing the distal third of the full thickness laceration

thyroidism, and an unmeasured "small" hiatal hernia. She underwent an Esophyx® procedure that was complicated by an EP diagnosed 48 h following her initial "uncomplicated" procedure. She presented to the outside institution with abdominal pain and shortness of breath resulting in a computed tomography of the chest illustrating active extravasation of oral contrast. She was initially treated by the outside institution with a left thoracotomy and primary repair with buttressing. However, her postoperative course was complicated by a persistent leak requiring a repeat thoracotomy and wide drainage 2 days following her first thoracotomy. Unfortunately, she persisted to leak despite these efforts and was transferred to our tertiary care center for further treatment and care 2 weeks after the inciting endoscopic event.

An endoscopic covered metal stent was placed, and a laparoscopic feeding jejunostomy tube was performed for nutritional access. During our initial endoscopy we noted the perforation to be 3 cm in length and located 5 cm proximal to the gastroesophageal junction. Additionally, she was noted to have a hiatal hernia and two loose SerosaFuse® Fasteners (Fig. 6) suspended from within the esophageal wall at the level of esophageal perforation and inside the hiatal hernia.

Occlusion of the esophageal perforation with the stent was confirmed with an esophagogram 24 h post-stent deployment (Fig. 7). She was able to begin a clear liquid diet 24 h after her esophagogram confirmed no further extravasation of contrast. She was discharged 14 days after her transfer, and her stent was removed 4 weeks later. She is now without her feeding tube and complains of minimal dysphagia.

Discussion

The care and treatment of gastroesophageal reflux disease ranges from simple behavior modification and medication to surgical intervention. Most recently, endoscopic incisionless procedures have evolved as therapeutic modalities attempting to achieve effective control of reflux. More specifically, the EsophyX® is being marketed as a premier transoral incisionless fundoplication and has been studied as a procedure which achieves reflux control by creating a tight durable gastroesophageal valve while adhering to all the same principles of conventional reflux surgery. Although it has been reported that this incisionless procedure results in a 79% complete cure rate at 2 years follow-up, the

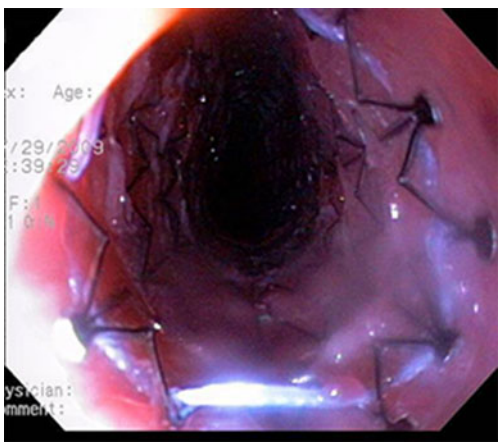

Fig. 4 Stent placement

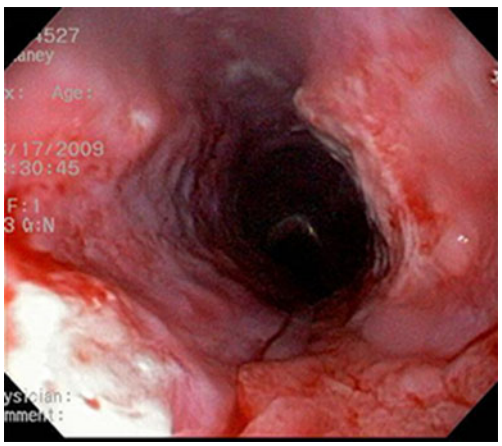

Fig. 5 Post-stent removal revealing healed esophageal laceration

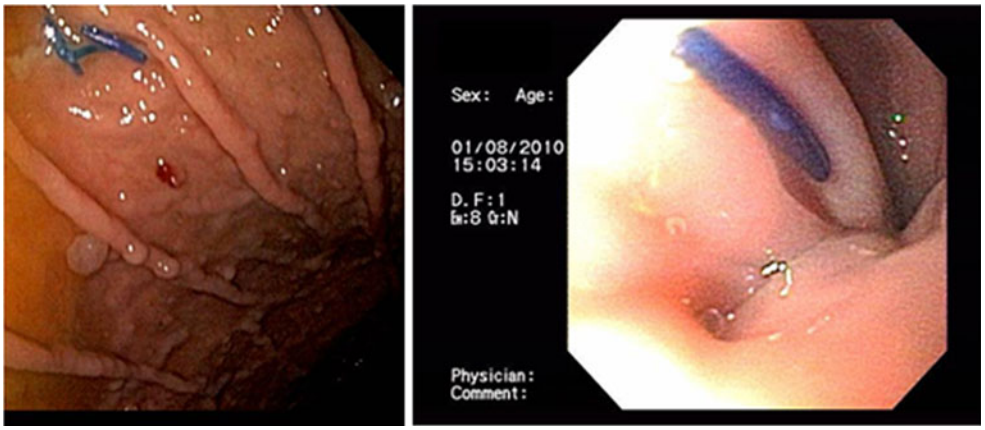

Fig. 6 EGD showing a hiatal hernia and two loose SerosaFuse® Fasteners

same authors indicated that at 2 years, no adverse events have been related to the transoral incisionless fundoplication with EsophyX®.[10,11] However, Cadière et al. demonstrated two esophageal perforations (2%) in a 12-month prospective study of the EsophyX® procedure performed in 86 patients.[10]

Our two separate case reports are not part of this initial experience but add a significant concern regarding adverse events with this type of procedure. As with any new procedure, a learning curve is expected with experience, volume, and time. However, both of these esophageal perforations were induced by two separate physicians who each have done more than 50 Transoral Incisionless Fundoplication EsophyX® procedures. Although, the argument can be made that from the quality of life surveys, it seems as though the EsophyX® procedure is effective, Repici et al. demonstrated a need for laparoscopic fundoplication in 20% of patients because of persistent symptoms.[11] This group also demonstrated an increase in acid exposure of the distal esophagus after the endoscopic procedure in 67% of subjects.

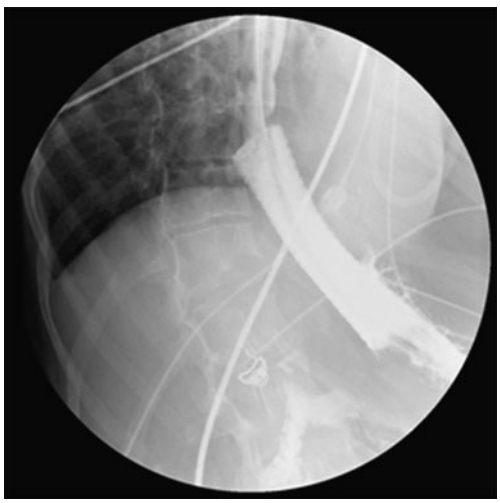

Fig. 7 Post-stent esophagogram confirming occlusion of the perforation

The EsophyX® device is FDA cleared for endoluminal full-thickness application for treatment of symptomatic chronic gastroesophageal reflux disease, narrowing of the GE junction and reducing hiatal hernias ≤2 cm in size. Considering that there is no objective, reliable, and/or reproducible way to accurately measure a hiatal hernia defect size, this loose definition can cause significant morbidity especially if this procedure is attempted in patients with hiatal hernias that are larger than 2 cm. Hence, we strongly propose that prior to any further treatments of "small" hiatal hernia defects, regardless of actual size, which cannot be measured with a significant degree of confidence or reproducibility, efforts need to be placed on this limiting step. Additionally, there are no published data as to why the hiatal hernia is limited to 2 cm nor why this is the size limit. Therefore, we believe that attempting this procedure in patients with hiatal hernia defects greater than 2 cm can result in similar adverse effects. It is unlikely that the SerosaFuse® Fasteners can repair this size defect without creating significant tension on the approximated tissues. This is why our second case presentation had two loose SerosaFuse® Fasteners (Fig. 6) suspended from within the esophageal wall at the level of esophageal perforation and inside the hiatal hernia suggesting that the tissues were pulled apart.

Although the management algorithm for esophageal perforations has evolved over the years, there is little debate about the gravity of esophageal perforations. Esophageal perforation, regardless of etiology, is associated with significant morbidity and as high as 20% mortality because of the perilous complications associated with the perforation.[12] However, outcomes have improved when the esophageal leak is sealed within 24 h of injury, leading to an 80–90% survival rate. If more than 24 h have elapsed since the intial insult, survival rate decreases to less than 50%.[13] Many groups, ourselves included, have been utilizing endoscopically placed covered metallic stents to treat these esophageal perforations in order to decrease the morbidity and mortality rates in significantly ill patients

who would otherwise not be surgical candidates or have failed primary surgical esophageal perforation repair. In fact, Freeman and colleagues have shown that endoluminal esophageal stent placement is an effective treatment for most spontaneous esophageal perforations resulting in rapid leak occlusion, reduction in length of stay and avoiding potential operative morbidities.[14]

The use of expandable esophageal stents in these unfortunate situations allows for earlier oral intake, decreased hospital stay, and less overall morbidity to patients. This theoretically results in reduced medical cost and patient convalescence. This treatment option offers severely ill patients presenting to our tertiary care center a good chance of survival even when initial primary repair has failed at the referring institution. Using this treatment algorithm (Fig. 1) allows us to be very consistent when caring for patients with esophageal perforations regardless of which type of physician is involved. This also enabled us to utilize the expertise of multiple medical services allowing for a multidisciplinary-care approach for these complex patients. Even though endoluminal esophageal stents are another endoscopic modality that can be criticized in the same manner as the EsophyX® procedure, this treatment modality is not used in an elective setting but rather used in dire situation as noted in our two patient presentations.

Laparoscopic Nissen fundoplication is often considered the gold standard surgical procedure for patients with GERD. It is frequently used as a comparison when validating other new alternative procedures. It is associated with a morbidity rate of 5.8% and a mortality rate of 0.03%.[15] More importantly, the increased frequency of the Nissen has led to a decrease in the complication rates, with recent studies showing less than a 1% rate of esophageal perforation.[16] A perforation during a Nissen fundoplication would most commonly occur in the distal esophagus, where it can be easily repaired and buttressed with the wrap. Comparatively, because the most common cause of EP is iatrogenic esophageal intubation, this endoscopic procedure inherently carries a higher rate of potential esophageal perforation. Additionally, the location of esophageal perforation with these devices can oftentimes be very difficult to manage due to its location and size. More specifically, as with our two patients, the esophageal perforations were both greater than 3 cm in length and located in the intrathoracic esophagus. This is an area that is not easily accessible, and the two separate surgeons performing the EsophyX® procedure did not feel comfortable enough to manage the perforation requiring transfer to a tertiary care center.

As the movement and excitement to less invasive surgical interventions continues to evolve, there must be check and balance systems to ensure that these procedures are feasible and reproducible by those that have been appropriately trained. We must evaluate these devices in a critical fashion in order to prevent unnecessary complications and ensure that those performing the procedure are able to care for patients even when they encounter complications as previously described. As we advance our technology and our understanding of intraluminal endoscopic therapies, the development of incisionless devices will continue to ignite a substantial amount of interest from consumers who are seeking less invasive therapies. Despite the proposed benefits of preventing port site complications, further decreasing discomfort associated with laparoscopic surgery and improving cosmesis, the safety of these incisionless endoluminal therapies need to be conclusively demonstrated in long-term clinical studies before this type of procedure is universally accepted as the treatment modality for patients with chronic gastroesophageal reflux disease and a hiatal hernia less than 2 cm.

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