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Transcervical Gastric Tube Drainage Facilitates Patient Mobility and Reduces the Risk of Pulmonary Complications After Esophagectomy

Matthew J. Schuchert · Brian L. Pettiford · Joshua P. Landreneau · Jonathon Waxman · Arman Kilic · Ricardo S. Santos · Michael S. Kent · Amgad El-Sherif · Ghulam Abbas · James D. Luketich · Rodney J. Landreneau

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Abstract
Background Standard nasogastric decompression following esophagectomy is associated with reduced patient comfort and mobility and impaired hypopharyngeal function—predisposing the patient to sinusitis, pharyngitis, and the risk of aspiration. In this study, we evaluate the results of the transcervical gastric tube drainage in the setting of esophagectomy.
Methods Transcervical gastric tube decompression was performed on 145 consecutive patients undergoing open esophagectomy between 2003 and 2007. Postoperative outcome variables include morbidity, mortality, esophagostomy duration, and length of stay.
Results There were 107 males and 38 females (median age=66; range=37–87). Perioperative mortality was 2.8%. Major complications included five anastomotic leaks (3.4%), ten pneumonias (6.9%), two myocardial infarctions (1.4%), and the need for reoperation in four patients (bleeding, dehiscence). Median duration of transcervical drainage was 8 days. No tubes were dislodged prematurely. There were no bleeding complications. Four patients developed cellulitis near the cervical gastric tube site and were treated successfully with antibiotics and/or tube removal.
Conclusions Transcervical gastric decompression can be performed safely with minimal complication risk. Inadvertent tube removal was not encountered in this series. The use of this technique may help to promote accelerated patient mobilization, greater patient comfort, and a durable means of gastric decompression.

Keywords Esophagectomy · Cervical esophagostomy · Gastric decompression · Anastomotic leak · Ischemia

Introduction

Gastric tube decompression is an important component of the early postoperative care following esophagectomy. Gastric distension in the immediate postoperative period

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M. J. Schuchert (✉) · B. L. Pettiford · J. P. Landreneau · J. Waxman · A. Kilic · R. S. Santos · M. S. Kent · A. El-Sherif · G. Abbas · R. J. Landreneau
Division of Thoracic and Foregut Surgery; Heart, Lung and Esophageal Surgery Institute, UPMC Health System, Shadyside Medical Building—Suite 715, 5200 Centre Avenue, Pittsburgh, PA 15232, USA
e-mail: schuchertmj@upmc.edu

R. J. Landreneau
e-mail: landreneaurj@upmc.edu

J. D. Luketich
Division of Thoracic and Foregut Surgery; Heart, Lung and Esophageal Surgery Institute, UPMC Health System, Presbyterian University Hospital, Suite C-800, 200 Lothrop St., Pittsburgh, PA 13213, USA
e-mail: luketichjd@upmc.edu

increases the aspiration risk and the potential for ischemia of the gastric tip, leading to esophagogastric anastomotic disruption and leak. Nasogastric tube decompression of the stomach tube remains the standard of care. However, patient comfort, pulmonary hygiene efforts, and early mobilization from bed are potentially compromised with this approach. Nasogastric decompression has been associated with impaired hypopharyngeal function and a predisposition to sinusitis and pharyngitis.[1,2]

Transcervical gastric tube drainage has been employed with good results in patients recovering from head and neck cancer operations[3,4] and those requiring prolonged enteral alimentation in lieu of gastrostomy or jejunostomy.[5] We report our experience with the use of transcervical gastric tube drainage as an alternative to nasogastric tube drainage following resection of the thoracic esophagus and gastroesophageal junction.

Materials and Methods

Patients

Approval for this study was provided by the Institutional Review Board of the University of Pittsburgh. We performed a retrospective review of 145 consecutive patients undergoing open esophagectomy with transcervical gastric tube drainage at the University of Pittsburgh from 2003 to 2007. There were 107 male and 38 female patients, with a median age of 66 years (range 37–87) (Table 1).

Table 1 Patient Demographics and Preoperative Data

	Open esophagectomy (n=145)
Median age (range)	66 (37–87)
Gender—M, F	107, 38
Approach	
THE	128
Ivor Lewis	11
Three-hole	6
Neoadjuvant therapy (%)	22 (15.2%)
Pathology	
Cancer	122
Barrett's/HGD	12
Achalasia/dysmotility	5
Perforation	3
Recalcitrant stricture	2
Caustic injury	1
Cancer cases (n=122)	
Adenocarcinoma	104
Squamous	13
Other	5
Cervical drain	
Esophagostomy	134
Pharyngostomy	11

THE Transhiatal esophagectomy, *HGD* high-grade dysplasia

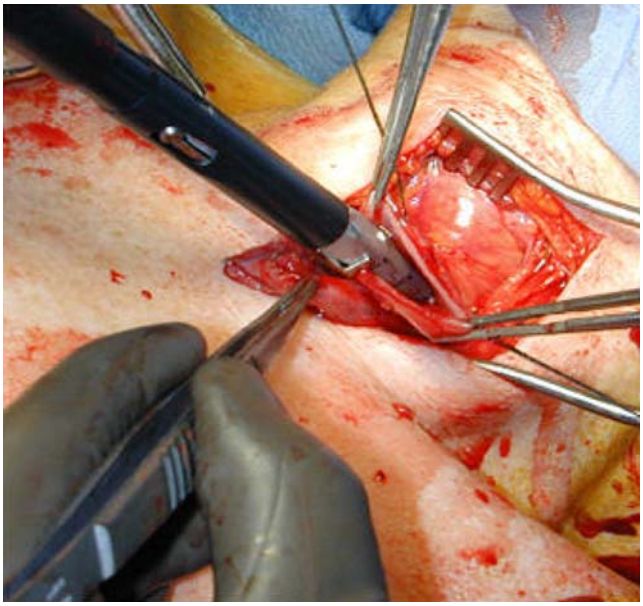


Figure 1 Total mechanical stapled anastomosis.

Operative Technique

Transhiatal esophagectomy (THE) was performed in 128 patients, as described previously.[6] A combined abdominal and thoracic exposure for esophagectomy (Ivor Lewis approach) was utilized in the 11 patients with mid-third esophageal cancers.[7] Six patients with higher thoracic esophageal cancers were approached with a three incisional, cervicothoracoabdominal (modified McKeown) exposure for esophagectomy.[8]

Transcervical gastric sump tube insertion was accomplished through a proximal cervical esophagostomy above the esophagogastric anastomosis in the 134 patients undergoing a transhiatal or modified McKeown approach to esophagectomy. The gastric sump tube was inserted into the proximal esophagus through a percutaneous pharyngostomy prior to thoracotomy among the 11 patients undergoing an Ivor Lewis esophagectomy. To create the cervical esophagostomy, a standard 16F Salem sump gastric tube was inserted through a separate 3-mm skin incision posterior to the cervicotomy incision and then through the sternal head of the sternocleidomastoid muscle anterior to the carotid sheath. A purse string created of 3-0 polyglycolic acid suture was made upon the proximal esophagus approximately 2 cm distal to the cricopharyngeus muscle. The posterolateral aspect of the cervical esophagogastric anastomosis is then created using the mechanical stapling device as previously described[6] (Fig. 1). Prior to

completion of the anterior aspect of the anastomosis, a right-angled forceps is introduced into the esophagus through the open anastomosis and directed toward the site of the purse string. Electrocautery is applied to the esophagus within the area of the purse string, and the tip of the right-angled forceps is positioned within this hole in the proximal esophagus made by the electrocautery. The tip of the sump drain is grasped by the forceps and delivered into the lumen of the esophagus and brought through the open esophagogastric anastomosis into the wound (Fig. 2). The sump drain is then inserted into the stomach through the open aspect of the cervical esophagogastric anastomosis. The anterior aspect of the anastomosis is then completed by firing a TA 60 stapling device across the approximated esophagogastric tissues (Fig. 3). A 10-mm Jackson–Pratt (JP) drain is then placed about the anastomosis through an additional cervical stab wound, and the neck incision is closed in a standard fashion. Figure 4 illustrates the location of the cervicogastric sump tube site and Jackson Pratt drainage site relative to the cervicotomy wound.

Among the patients undergoing an "Ivor Lewis" thoracoabdominal approach to esophagectomy, pharyngostomy tube drainage was utilized for gastric tube decompression.[9] After the completion of the abdominal aspect of the operation, the pharyngostomy site is established by inserting a large "kidney pedicle" clamp forceps through the mouth and pointing it to the lateral aspect of the pharynx just lateral and superior to the superior cornu of the thyroid cartilage and anterior to the carotid pulsation. The thin nature of the neck tissue in this location facilitates the percutaneous cut down and electrocautery establishment of communication with the tip of the forceps. The tip of the forceps is passed through the pharyngostomy site and then used to grasp the gastric sump tube. The sump is brought out through the mouth and then directed through the posterior pharynx and upper esophageal sphincter into the upper esophagus. The thoracotomy portion of the esophagectomy is then performed. After completion of the intrathoracic esophagogastric anastomosis, the sump drain is then forwarded through the anastomosis and secured in a proper intragastric position. A heavy silk suture is used to anchor the sump tube at the pharyngostomy site.

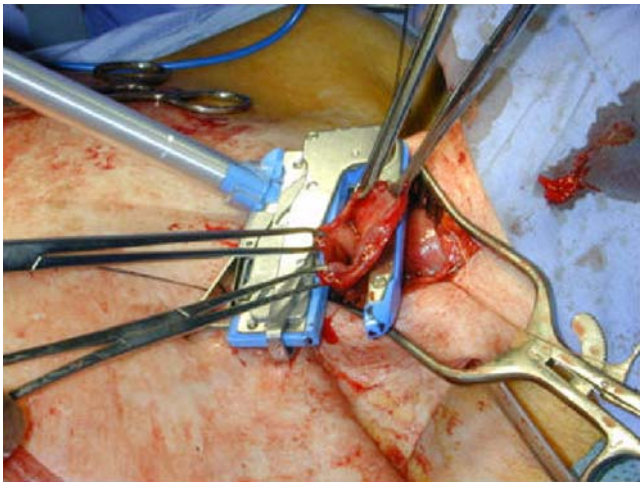


Figure 3 Completion of esophagogastric anastomosis.

Postoperative Course

Patients were typically extubated on the day following surgery. Patients were mobilized out of bed into a chair following extubation on the morning after surgery. The patient's pulmonary hygiene is encouraged and ambulation is established. Cervical drainage tubes were kept to low continuous suction for the first 7 days. The patients were routinely taken off of the suction during the times of physical therapy to enhance mobilization. Jejunostomy tube feeds were initiated at a low rate on postoperative day number 3. A barium swallow was performed on the seventh postoperative day and, if satisfactory, a clear liquid diet was initiated and the transcervical drainage tube was removed. The cervical JP drain was removed the following day. The patients' diet is expanded to a mechanical soft consistency. Patients were typically discharged on the tenth–12th postop-

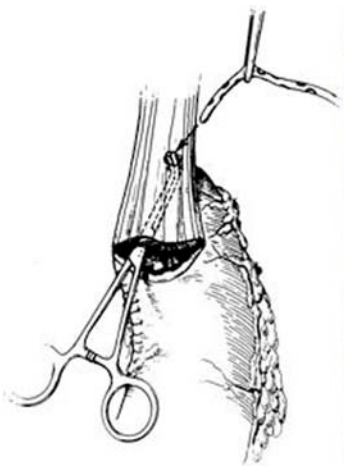
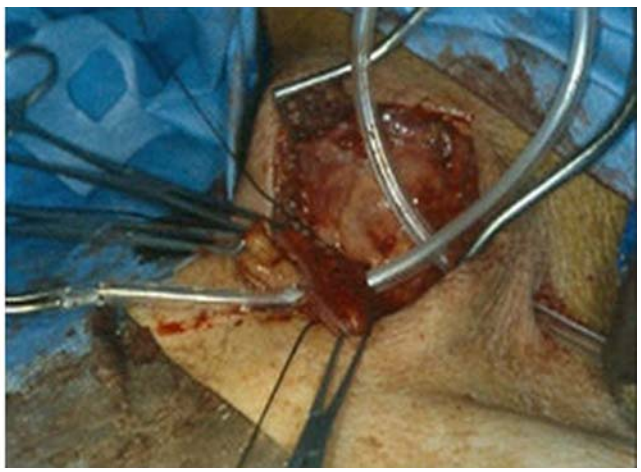


Figure 2 Cervical esophagostomy tube insertion.



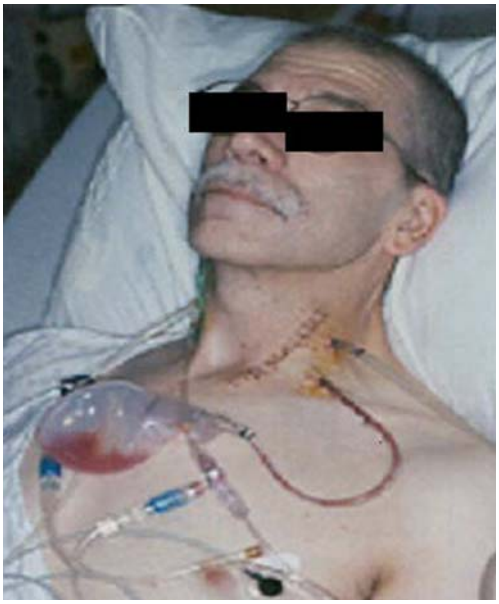


Figure 4 Cervical esophagostomy and JP drain.

erative day. Our current protocol is to evaluate the patients 2 weeks following discharge for the first postoperative visit. The jejunal feeding tube is removed 1 month after surgery if the supplemental feedings are not necessary.

Follow-Up

Clinical follow-up data was successfully acquired in all patients. The primary postoperative outcome variables included operative time, estimated operative blood loss, chest tube days, pharyngostomy tube days, length of stay, overall morbidity and mortality, and specific esophagogastric anastomosis/cervical gastric tube drainage morbidity. The mean postoperative follow-up of our patients was 12.6 months.

Results

Demographics and preoperative data are detailed in Table 1. The majority of patients underwent transhiatal esophagectomy (n=128, 88.3%). The most common indication for surgery was esophageal cancer (n=122, 84.1%), followed by Barrett's esophagus with high-grade dysplasia (n=12, 8.3%). Neoadjuvant chemotherapy was utilized in 22 (15.2%) patients. All patients underwent insertion of either an esophagostomy (THE, 3-hole) or pharyngostomy (Ivor Lewis) tube for gastric decompression.

The median operative time and estimated blood loss was 185 min and 300 ml, respectively. Most patients were extubated on postoperative day 1, and the median intensive care unit (ICU) stay was 4 days. The transcervical gastric drainage tubes were removed at a mean of 8 days. Median length of stay for the entire cohort was 12 days (Table 2). Complications occurred in the 73 (50.3%) patients and are detailed in Table 3. Pneumonia was the most common major complication, occurring in ten patients (6.9%). Anastomotic leaks (n=5, 3.5%) were managed with antibiotics and opening of the neck wound. Gastric tip necrosis was not encountered. Overall mortality for the series was 2.8%. Morbidity and mortality rates of the largest published open series are presented in Table 3 for comparison. Anastomotic strictures were encountered in the 17 (11.7%) patients and were managed with dilation.

Transcervical gastric drains were tolerated extremely well. Patient complaints referable to the tube were not encountered. Four patients (2.8%) developed mild cellulitis of the skin immediately adjacent to the tube, which was easily treated with antibiotics and/or tube removal. No tubes were dislodged prematurely. There were no bleeding complications. Prolonged pharyngocutaneous fistulas were not observed.

Discussion

Esophagostomy and pharyngostomy tubes have been employed for decades in the perioperative management of patients undergoing head and neck cancer surgery.[3,4] Others have reported the use of pharyngostomy drainage following esophagectomy and for the use of long term gastric/intestinal decompression or enteral access for nutrition.[10–12] In all the reported series, the use of this technique has been shown to be safe and effective. Only one death utilizing the pharyngostomy approach due to bleeding has been reported in

Table 2 Postoperative Outcomes

	Open esophagectomy (n=145)
Operative time (min)	185 (80–455)
Estimated blood loss (ml)	300 (50–2,000)
ICU stay (days)	4 (1–30)
Chest tube duration (days)	7 (2–19)
Esophagostomy duration (days)	8 (3–56)
Length of stay (days)	12 (6–63)
Complications (%)	52.6
Major	29.9
Minor	27.0
Esophagostomy problems (%)	
Cellulitis	2.9
Dislodged	0
Mortality (%)	0

Operative time, estimated blood loss, ICU stay, chest tube duration, esophagostomy duration, and length of stay are expressed as median values with associated ranges in parentheses.

Table 3 Complications

Complication	Current series (%) n=145)	Orringer et al. (MI, USA; n=2,007)[20]	Bailey et al. (VA, USA; n=1,777)[21]	Rizk et al. (Sl-Ket; n=510)[22]	Portale et al. (University of California, LA, USA; n=263)[23]
Mortality	2.8	3	9.8	6.1	4.5
Anastomotic leak	3.4	12	NR	21	12
Gastric tip necrosis	0	2	NR	NR	2
Pneumonia	6.9	2	21.4	21	10
Vocal cord palsy	2.2	4.5	NR	4	NR
Chylothorax	0.7	1	0.02	NR	3

the literature, secondary to local erosion into an adjacent blood vessel.[13]

Potential benefits of transcervical gastric drainage in the setting of esophagectomy include the avoidance of gastric distension during the early postoperative period that can result in gastric tip ischemia, prevention of aspiration, avoidance of nasopharyngeal complications, enhanced patient mobilization, and improved pulmonary hygiene.[9,14,15] Potential disadvantages of this technique include the development of local inflammation or cellulitis at the skin entry site, as well as the risk of a pharyngocutaneous fistula subsequent to the tube removal. The incidence of cellulitis in this study was only 2.8% and was easily treated with antibiotics and/or tube removal. Prolonged pharyngocutaneous fistulas were not encountered. Though the subjective assessments and retrospective nature of this series represent limitations of this study, the described technique of transcervical gastric tube drainage is presented as a safe and durable adjunct in the management of patients following esophagectomy. In the current study, patient compliance was found to be exceptional. There were no documented patient complaints related specifically to the tube, and no tubes were dislodged prematurely. Pulmonary and ischemic complications were reduced in the current study, when compared to the largest open series (Table 3).

Cervical esophagostomy tubes are easy to position at the time of surgery and provide a stable, effective means of gastric decompression following esophagectomy. By passing the tube through the sternal head of the sternocleidomastoid, the tube is anchored over a broader plane (muscle and skin) and is thus more difficult to dislodge. The exit site can be exposed to open air (Fig. 4) and should be inspected for the development of inflammation/cellulitis. Meticulous attention to maintaining patency of the tube is essential in ensuring optimal gastric tube decompression. Tubes are routinely flushed with 20 ml of water each nursing shift and whenever appropriate tube sumping is not evident. Inadvertent tube removal was not encountered in this series. If this event should occur, the tube can be either left out or replaced in the operating room by reestablishing the tract and confirming the appropriate intraluminal position by endoscopy. Prior neck radiation may theoretically predispose to local complications but does not represent an absolute contraindication to the use of cervical esophagostomy tubes.

The use of transcervical gastric tube drainage is subjectively tolerated better by patients recovering from esophagectomy. Patients frequently attempt to remove nasogastric tubes in the early postoperative period due to the noxious stimulus of transnasal intubation. Complaints of sinus congestion, headache, sore throat, gagging, and difficulty clearing secretions are common with nasogastric drainage. In addition, accidental dislodgement of the nasogastric tube when the patient is moved or attempts to get out of bed also occurs with an undesirable frequency.

In contrast, patients with cervical drains are visibly more comfortable and mobile. They are relieved of the continuous drive to remove the drain, as seen with nasogastric tubes. When the tubing becomes kinked or entangled, it is easier for the patients to remedy the situation with a cervical drain because they are able to turn their head more comfortably, not being tethered by the nose. The drains are more reliably secured with stitches, as opposed to the tape most commonly used for nasogastric tubes, thus reducing the chances of inadvertent removal during patient transfers and mobilization. These advantages translate into greater patient comfort, ease in patient mobility, and greater tube security, which we think is critical in preventing gastric tube distension and the associated pulmonary complications of regurgitation and aspiration, as well as gastric tube ischemia. Though certainly not establishing a causal relationship, the low rate of pulmonary and ischemic complications seen in this study supports this contention.

We feel that the minimal morbidity, improved anastomotic integrity, and low mortality observed in our experience reflect the impact of several key technical variables. The totally stapled esophagogastric anastomosis technique,[16] which is very similar to that initially described by

Collard et al.,[17] appears to result in improving anastomotic integrity. This may be due to a more uniform tissue closure and tension upon the tissues with the mechanical stapler compared to the hand-sewn techniques for anastomosis.[18] We also believe that effective decompression of the gastric conduit for a period of 5–7 days during the period of greatest gastric tip ischemia may also be beneficial in reducing anastomotic failure and postoperative anastomotic stricturing.[19]

Conclusion

Transcervical gastric tube drainage is easy to perform in the setting of esophagectomy and is tolerated well by the patient. Exceptional patient compliance is the rule. They are associated with improved patient comfort and may thus enhance patient mobilization postoperatively. Local complications related to cervicogastric drainage are rare. Reliable and tolerable gastric tube decompression, as achieved by transcervical gastric drainage, helps to minimize the risk of aspiration and potential gastric tip ischemic complications following esophagectomy.

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Long-term Outcome of Operated and Unoperated Epiphrenic Diverticula

Giovanni Zaninotto · Giuseppe Portale · Mario Costantini · Stefano Merigliano · Emanuela Guirroli · Christian Rizzetto · Sabrina Rampado · Ermanno Ancona

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Abstract
Introduction The natural history of esophageal epiphrenic diverticula (ED) is not entirely clear; the decision whether to operate or not is often based on the personal preference of the physician and patient. The aim of this study was to evaluate the long-term fate of operated and unoperated patients with ED.
Materials and Methods Clinical, radiological, and motility findings, and operative morbidity and long-term outcome of 41 patients with ED (January 1993 to December 2005) were analyzed. All patients were reviewed at the outpatient clinic or interviewed over the phone. A symptom score was calculated using a standard questionnaire and subjective patient assessment. The radiological maximum diameter of the ED was measured.
Results Twenty-two patients (12M:10F; median age, 60 years) were operated. One underwent surgery for spontaneous rupture of a large diverticulum. Operative mortality was nil; postoperative morbidity was 22.7%, the most severe complication being suture leakage (4 patients, all managed conservatively); median follow-up was 53 months. Nineteen patients (9M, 10F; median age 70 years) were not operated: 3 received pneumatic dilations; median follow-up was 46 months. None of the patients in either group died for reasons related to their ED. Symptoms decreased in all operated patients and, to a lesser extent, also in unoperated patients. ED recurrence was observed in one operated patient. Four patients had GERD symptoms with esophagitis and/or positive pH-metry after surgery and 3 patients had persistent dysphagia/regurgitation and were dissatisfied with the outcome of surgery.
Discussion Surgery is an effective treatment for ED, but carries a significant morbidity related mainly to suture leakage. Even in the long-term, unoperated patients do not die of their ED, though a better subjective symptom outcome is reported by operated patients. A non-interventional policy can safely be adopted in cases of small, mildly symptomatic ED.

Keywords Epiphrenic diverticula · Surgery · Conservative treatment · Minimally invasive surgery

Presented as a poster at the SSAT/DDW Meeting in Los Angeles (19–22 May 2006).

G. Zaninotto (✉)
General Surgery, Venice Hospital, ULSS12,
University of Padova School of Medicine,
Via Giustiniani 2,
35128 Padova, Italy
e-mail: giovanni.zaninotto@unipd.it

G. Portale · M. Costantini · S. Merigliano · E. Guirroli · C. Rizzetto · S. Rampado · E. Ancona
Clinica Chirurgica 3º, University of Padova School of Medicine,
Via Giustiniani 2,
35128 Padova, Italy

Introduction

Epiphrenic diverticula are outpouchings of the esophageal lumen originating in the distal third of the esophagus, close to the diaphragm. They have historically been considered as 'pulsion' diverticula due to high intraluminal pressures in a short segment of the esophagus (with or without esophageal wall weakness), unlike mid-thoracic 'traction' diverticula, which are a consequence of chronic inflammatory processes starting in the mediastinal lymph nodes (from granulomatous diseases, such as tuberculosis).[1,2] This anatomical and pathogenic dichotomic classification of the esophageal body diverticula (mid-thoracic traction vs. epiphrenic pulsion diverticula) was challenged by Jordan in 1999: Small diverticula may originate anywhere in the distal half

of the esophagus, and as they become larger, approaching the diaphragm, they acquire 'the status of epiphrenic diverticula.'[3] The true prevalence and, more important, the natural history of ED are unknown, but the most intriguing question regarding ED probably concerns whether or not they *all* need treatment. The decision to operate or not is often based on the personal preference of the physician and patient, and there are only a few reports in the literature of experience and results obtained by the same group with both the surgical and the conservative management of patients with ED.

Thus, the aim of this study was to assess the long-term fate of operated and unoperated patients with ED.

Materials and Methods

Patient Population

Data were collected prospectively on all patients referred to our department and esophageal motility laboratory for ED from January 1993 to December 2005.

Diagnostic Workup

This included clinical history, esophageal manometry and pH-metry, barium swallow, and endoscopy. Clinical data were prospectively collected by means of a symptom questionnaire currently used at our laboratory for patients with benign esophageal diseases and validated in a control group of healthy subjects (unpublished data). Severity and frequency of dysphagia, regurgitation, heartburn, and chest pain were scored respectively from 0 to 3 and from 0 to 5; the sum of the scores for each symptom was considered as the "patient's symptom score": The highest possible score was 32 and the lowest was 0. Surgical or conservative treatments were considered as having failed when the patient's symptom score was 'worse,' exceeding the 25th percentile of the situation prior to treatment (considering scores, 6 or more). A treatment was defined as successful when the symptom score decreased by 50% or more (minimum scores, 0 to 5). If the patient's score remained constant after the treatment, the patient was considered as "unchanged."

A barium swallow study was performed to measure the diameter of the diverticulum. Stationary esophageal manometry, using a pneumohydraulic perfusion system and standard techniques,[4] was performed to detect any underlying motility disorder. In a small group of patients, 24-h motility was also performed.

Twenty-four-hour pH monitoring was performed in operated patients 6 months after surgery to assess any abnormal gastroesophageal reflux, positioning a glass electrode 5 cm above the upper edge of the lower esophageal sphincter (LES), according to the standard procedure used at our laboratory and described elsewhere.[5] Acid exposure in the distal esophagus was considered abnormal when the composite DeMeester pH score was higher than 14.74 (95th percentile of normals).

Surgical Treatment

Diverticulectomy was performed using either an open approach via a thoracotomy or a transabdominal laparoscopic approach. In patients with hypertensive or unrelaxing LES, a cardiomyotomy was added on the opposite side of the esophagus, from the upper margin of the diverticulum down to 1–2 cm below the cardia on the gastric side. Cardiomyotomy was not performed in patients with a hiatal hernia and a normotensive/hypotensive normally relaxing LES. When the laparoscopic approach was used, the choice of antireflux procedure was based on the decision to perform a simple diverticulectomy (adding a Toupet fundoplication) or diverticulectomy plus cardiomyotomy (completing the operation with a Dor hemifundoplication).

One patient presented for emergency surgery due to spontaneous rupture of the diverticulum: She had diverticulectomy and pulmonary lobe resection.

Postoperative Course

To rule out any perforation or leakage, a swallow test with a water-soluble contrast (Gastrografin®) was performed on postoperative day 7. The nasogastric tube was removed, and patients were told only to drink for the next 12 h, to stay on a soft diet for 10–15 days, and then to return to a normal diet.

Follow-up

Patients were followed up by the operating surgeon. They were asked to come to the outpatient clinic 1, 6, and 12 months after surgery, and every 2 years thereafter. A barium swallow was obtained at the first follow-up visit; manometry and pH monitoring were performed immediately before the second checkup, when a second symptom assessment was recorded. Endoscopy was performed 12 months after surgery and then every 24 months, associated with a barium swallow. If patients failed to show up for 12 months or more, they were interviewed over the phone.

Statistical Analysis

Data are expressed as medians and interquartile ranges. Proportions were compared using the chi-square or Fisher's exact tests. Continuous variables were compared using the

Mann–Whitney test. A p value below 0.05 was considered significant.

Results

Demographics and Preoperative Assessment

Of the 41 patients with ED referred to our department from January 1993 to December 2005, 22 (12M, 10F; median age, 60; interquartile range, IQR, 55–69) underwent surgery (group A), and 19 (9M, 10F; median age, 70; IQR, 58–77) were treated conservatively (group B).

The clinical data are summarized in Table 1. There was no statistically significant difference between the two groups of patients in terms of duration of symptoms and symptom score (p=ns). The radiologically evident maximum diameter of the diverticulum was higher in group A patients ($p < 0.01$). All but one patient had manometry, and the motility findings are summarized in Table 2: diffuse esophageal spasm (DES) and non-specific motility disorder (NSMD) were the main motility disorders in both groups.

Surgical Treatment

Data on the surgical treatments for group A patients are summarized in Table 3: Five patients had a transthoracic and 17 a laparoscopic transabdominal approach. Operative mortality was nil. The postoperative morbidity rate was 22.7%. The most severe complication was suture leakage, which occurred in four patients (18%): Three of these patients were asymptomatic, and the leakage was revealed by the Gastrografin control; one developed fever on post-op day 5 and a first Gastrografin swallow was negative for leakage, but she subsequently had a chest CT scan and a second water-soluble contrast swallow that revealed the leakage. These four patients were kept on parenteral nutrition, with the nasogastric tube in place, until the leak healed.

Table 1 Demographics and Preoperative Data

	Surgical treatment (n=22)	Conservative reatment (n=19)	p value
Gender (M/F)	12/10	9/10	0.75
Patient's age (years)	60 (55–69)	70 (58–77)	0.07
Duration of symptoms (months)	12 (8–48)	30 (15–78)	0.56
Symptom score	14 (7–17)	9 (4–15)	0.28
Maximum diverticulum size (cm)	7 (5–9)	4 (3–6)	0.004

Data are expressed as median (IQR)

Table 2 Motility Findings

	Surgical treatment (n=22)[a]	Conservative treatment (n=19)	p value
Achalasia	2 (9.5)	1 (5.4)	0.75
DES or NSMD	9 (42.8)	7 (36.8)	
HLES	2 (9.5)	4 (21)	
Undetected abnormality	8 (38.2)	7 (36.8)	

Data are expressed as N (%).
DES diffuse esophageal spasm, *NSMD* non-specific motility disorder, *HLES* hypertensive lower esophageal sphincter.
[a] Data not available for one patient

Non-surgical Treatment

Reasons for conservative treatment were the presence of small asymptomatic pouches or mildly symptomatic mid-size diverticula (n=14; median symptom score, 7; IQR, 4–13), amenable to medical therapy (mainly antisecretory drugs) or requiring no specific treatment; severe comorbidities (n=2; symptom score, 10 and 14); and symptomatic improvement after pneumatic dilations (n=3; symptom score, 8, 12, and 15). The motility anomalies in the latter were achalasia (1) and HLES (2) on stationary manometry.

Follow-up

After surgery, the clinical follow-up was completed by all 41 patients at a median of 48 months (IQR, 15–81): 53 months (15–77) for group A and 46 months (16–92) for group B, p=0.714. None of the patients in either group died for reasons related to their ED; two group B (unoperated) patients died of unrelated causes at 15 and 63 months.

There was a significant drop in the symptom score after surgery in group A patients [14 (7–17) vs. 10 (0–6); p= 0.0005]. After a median follow-up of 46 months, the symptom score in group B patients was 7 (2–13) as

Table 3 Operations Performed for Epiphrenic Diverticula

	N (%)
Transthoracic	5 (23)
Diverticulectomy[a]	4
Diverticulectomy + cardiomyotomy + Belsey	1
Transabdominal (laparoscopic)	17 (77)
Diverticulectomy + cardiomyotomy + Dor[b]	14
Diverticulectomy + Toupet	3

[a] One patient underwent emergent surgery for spontaneous rupture of large epiphrenic diverticulum.
[b] Two patients required conversion to the right thoracotomy to complete the diverticulectomy after laparoscopic Heller–Dor procedure due to severe adhesions of the epiphrenic diverticulum.

opposed to 9 (4–15) at the first clinical evaluation (p=ns; Fig. 1). Six patients in the operated group complained of postoperative dysphagia and regurgitation; four received pneumatic dilations, with symptom relief in 3; one patient was still complaining of dysphagia despite multiple dilations but refused any further treatment.

In the unoperated group, only the three patients treated with endoscopic pneumatic dilations had an improvement in symptom score (Table 4). Two patients reported significantly worse symptoms and are now scheduled for surgery.

ED recurred in three patients, while four had postoperative heartburn and acid regurgitation with documented endoscopic esophagitis and/or positive pH monitoring. The latter four patients were assigned to proton pump inhibitors therapy, achieving a good symptom control.

Conclusions

Several important observations emerge from this study. First, surgery is an effective treatment for ED but carries a significant morbidity, mainly related to suture leakage.

Second, even in the long term, unoperated patients do not develop severe complications and potentially death from their ED, though a better subjective symptom outcome is reported by operated patients. Third, a conservative policy can be adopted safely for cases of small, mildly symptomatic ED.

Esophageal epiphrenic diverticula are quite rare and their pathogenesis is not entirely understood: They are usually associated with motility disorders, such as achalasia and diffuse esophageal spasm, and non-specific motility disorders, but they are also reported in association with a motility disorder undetectable on manometry.[6–10] The natural history of ED is not clear: The decision whether to

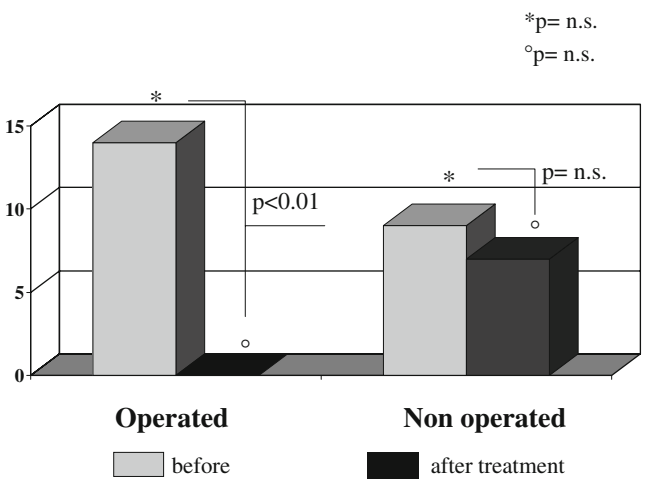

Figure 1 Pre- and post-operative symptom scores in operated and unoperated patients with epiphrenic diverticulum.

Table 4 Subjective Outcome

	Group A (n=22)	Group B (n=19)	p value
Better	19 (86.3)	3 (15.8)	<0.0001[a]
Worse	3 (13.7)	2 (10.5)	
Unchanged	0	14 (73.7)	

Data are expressed as N (%).
[a] Better vs. worse or unchanged

operate or not has been a matter of debate for some time and is still disputed among surgeons dealing with diverticula of the thoracic esophagus. This statement from Orringer has been quoted by many papers addressing the issue: 'A masterful inactivity in asymptomatic or mildly disturbing diverticula is a good practice even if, in this time of minimally-invasive surgery and stapling device, an esophageal diverticulectomy may represent a tempting trophy for an hyperactive surgeon.'[11]

The presence of a diverticulum, per se, cannot be considered an indication for surgery. The surgeon should balance the potential benefit (carefully assessing a patient's symptoms and complaints and the risk of complications related to the presence of the diverticulum) and the surgery-related risks. The proportion of diverticula symptomatic enough to warrant surgery varies considerably, ranging from 0% to 40% in the literature.[12–15] Generally speaking, severe dysphagia, regurgitation, and contrast retention on esophagography, with an implicit or explicit risk of aspiration pneumonia, would suggest pouch resection. In the present series of 41 patients, a third of the patients had severe symptoms and, in one case, spontaneous rupture of the diverticulum necessitated emergency surgical repair.

In our experience, as well as in the literature, the size of the diverticulum does not correlate strictly with the patients' symptom score and consequently should not be used to orient treatment decisions.[16,17] Altorki and Skinner suggested that symptoms may paradoxically improve as the diverticulum becomes larger because it eventually acts as a reservoir.[12] They also pointed out the difference between a significantly dilated esophagus (capable of accommodating the contents of the diverticulum as it spills over into the esophageal lumen) and a minimally dilated esophagus, which carries a higher risk of aspiration. Although there is no demonstrable linear correlation between symptoms and size of diverticulum, it is still common in our own and other series to encounter small, mid-esophageal diverticula that are mildly or not at all symptomatic and rarely require surgery, whereas larger diverticula are often associated with food retention and regurgitation, necessitating surgical diverticulectomy.

The most severe complications related to the presence of a diverticulum in the thoracic esophagus are perforation or

Table 5 Natural History of Epiphrenic Diverticula

Author	No. of patients	Clinical condition	Diameter (cm)	Follow-up (years)[a]	Evolution	
					Progression	Stable
Altorki et al.[12]	3	3 symptomatic	≥3.5	–	1 (liquid diet)	1 MI 1 asp pn
Benacci et al.[13]	42	35 asympt/mild	–	7	35	0
		7 sympt_ref surgery		5	0	7
Nehra et al.[20]	3[c]	1 sympt	–	–	0	1 asp pn[b]
Jordan and Kinner[3]	6[d]	5 asympt	–	6	1 asympt	2 ref surgery
		1 unfit for surgery[d]			2 mild	
Castrucci et al.[14]	16[e]	16 asymptomatic	≥1.5	5.3	13	0
Klaus et al.[21]	5[d]	5 asympt/mild[d]	≤2	–	2 asympt	0
					2 mild	
All authors	68[c–e]	57 asympt/mild	–	–	55 (96.5%)	2 (3.5%)
		11 symptomatic			1 (9%)	10 (91%)

[a] Data are expressed as median
[b] One patient died while waiting for surgery
[c] Two patients refused surgery, lost to follow-up
[d] One patient lost to follow-up
[e] Three patients lost to follow-up

rupture in the mediastinum or, less frequently, progression to carcinoma in the diverticulum.[18,19] Aside from Altorki and Skinner report of high rate of aspiration (9/20 patients) in their series and even one case of tracheo-esophageal fistula, though strongly advocating operative intervention for all epiphrenic diverticula, the natural history of mildly symptomatic or even asymptomatic diverticula is extremely difficult to predict. It has been estimated that fewer than 10% of the patients will develop symptoms or complications relating to their diverticula (Table 5). On the other hand, in cases of moderate-to-severe symptomatic ED, the disease tends to progress, sometimes even to the point of preventing surgery, as reported by DeMeester's group (one patient died of aspiration pneumonia before surgery could be performed).[20] We had one case of rupture of the diverticulum and one patient whose symptoms worsened over a period of 7 years, prompting the patient to request surgical repair. We encountered no cases of esophageal carcinoma arising in the diverticulum among our patients.

Another important aspect to bear in mind when evaluating patients with ED is the risk related to surgical treatment. The overall mortality associated with surgery for ED is nearly 5% and the morbidity nearly 20% (0% and 18%, respectively, in our series). Table 6 shows the mortality and morbidity rates for over 170 patients operated for ED. As expected, the most common complication is suture leakage after diverticulectomy, which has prompted many surgeons to believe that routine distal esophageal myotomy should always accompany diverticulectomy in order to reduce the outflow obstruction and decrease the tension at the suture line, possibly extending the myotomy across the LES into the stomach.[20] Some authors advocate the 'selective' use of myotomy only in cases of evident hypertonic motility in the esophagus based on motility test results.[3–14–15] We are in line with authors advocating the routine use of myotomy, but we do agree that the presence of a hypotonic LES should discourage surgeons from performing a myotomy, which would be of no benefit in this case and merely add to the risk of postoperative gastroesophageal reflux.

According to the medical literature,[6,21–23] the clinical results of minimally invasive surgery to treat ED seem to be just as good as open surgery and the risk of leakage from the suture line is also much the same. However, most papers dealing with this topic report on only a few cases and should be regarded as anecdotal. We support the use of a laparoscopic approach for mid-size diverticula because of the perceived advantages (lower wound-related morbidity and better recovery rates, and compared with the transthoracic approach, the chance to avoid problems relating to single-lung ventilation), but we agree that giant diverticula or those well above the epiphrenic region would be best approached via a thoracotomy or thoracoscopy.

In our series, asymptomatic patients with small, incidentally diagnosed diverticula and mildly symptomatic, medium-size pouches were managed conservatively without any

Table 6 Morbidity and Mortality Following Surgery for Esophageal Diverticula

Author	No. of patients	Mortality[a]	Leaks[a]	Morbidity[a]
Streitzet al.[15]	13	0	1 (7.7)	1 (7.7)
Altorki et al.[12]	17	1 (5.9)	0	0
Benacci et al.[13]	33	3 (9)	6 (18)	11 (33)
Nehra et al.[20]	18	1 (5.5)	1 (5.5)	2 (11)
Jordan and Kinner[3]	19	0	1 (5.3)	1 (5.3)
Castrucci et al.[14]	27	2 (7)	2 (7)	3 (11)
Rosati et al.[22]	11	0	1 (9)	1 (9)
Klaus et al.[21]	11	0	1 (9)	2 (18)
Costantini et al.[23]	8	0	3 (37.5)	4 (50)
Del Genio et al.[24]	13	1 (7.7)	3 (23)	4 (31)
All authors	170	8 (4.7)	19 (11.1)	29 (17.1)

[a] Data are expressed as *N* (%).

specific treatment other than proton pump inhibitors or H_2 blockers in the event of symptoms related to reflux or gastritis. The non-surgical alternative, i.e., endoscopic pneumatic dilations, proved a valuable option in symptomatic patients unfit for surgery or unwilling to submit to surgery, who had an underlying motility disorder (achalasia or hypertensive LES): They all benefited from this treatment and were symptom-free at 2-year follow-up.

In conclusion, when the fate of unoperated patients with ED is compared with the surgical complications encountered, surgery only appears to be justified in patients with moderately or severely incapacitating symptoms or potential life-threatening complications (e.g., recurrent aspiration pneumonia) and existing or impending complications. Patients with no symptoms or mildly symptomatic ED can be managed conservatively (even with endoscopic pneumatic dilations or botulinum toxin injections) and a close symptomatic and radiological/endoscopic follow-up.

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Prospective Assessment of Patient Selection for Antireflux Surgery by Combined Multichannel Intraluminal Impedance pH Monitoring

Gianmattia del Genio · Salvatore Tolone · Federica del Genio · Rajesh Aggarwal · Antonio d'Alessandro · Alfredo Allaria · Gianluca Rossetti · Luigi Brusciano · Alberto del Genio

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Abstract
Introduction Selecting gastroesophageal reflux disease (GERD) patients for surgery on the basis of standard 24-h pH monitoring may be challenging, particularly if this investigation does not correlate with clinical symptoms. Combined multichannel intraluminal impedance pH monitoring (MII-pH) is able to physically detect each episode of intraesophageal bolus movements, enabling identification of either acid or non-acid reflux episodes and thus establish the association of the reflux with symptoms.
Materials and Methods We prospectively assessed and reviewed data from 314 consecutive patients who underwent MII-pH for GERD not responsive or not compliant to proton pump inhibitor therapy. One hundred fifty-three patients with a minimum follow-up of 1 year constituted the study population. Clinical outcomes and satisfaction rate were collected in all patients who underwent laparoscopic Nissen–Rossetti fundoplication. Outcomes were reported for patients with normal and ineffective peristalsis and for patients with positive pH monitoring, negative pH monitoring and positive total number of reflux episodes at MII, and negative pH monitoring and normal number of reflux episodes at MII and a positive symptom index correlation with MII.
Results The overall patient satisfaction rate was 98.3%. No differences were recorded in the clinical outcomes of the patients with preoperative normal and ineffective peristalsis. No differences in patients' satisfaction and clinical postoperative DeMeester symptom scoring system were noted between the groups as determined by MII-pH.
Conclusion MII-pH provides useful information for objective selection of patients to antireflux surgery. Nissen fundoplication provides excellent outcomes in patients with positive and negative pH and positive MII monitoring or Symptom Index association. More extensive studies are needed to definitively standardize the useful MII-pH parameters to select the patient to antireflux surgery.

Keywords Multichannel intraluminal impedance · GERD · Antireflux surgery · Nissen · MII-pH

G. del Genio (✉) · S. Tolone · F. del Genio · R. Aggarwal · A. d'Alessandro · A. Allaria · G. Rossetti · L. Brusciano · A. del Genio
Foregut and Obesity Pathophysiology Study Center,
First Division of General and Gastrointestinal Surgery,
Department of Surgery, University of Naples II,
Via Strettola a Chiaia, 7,
80122 Naples, Italy
e-mail: gdg@doctor.com

Abbreviations

GERD	gastroesophageal reflux disease
MII-pH	combined multichannel intraluminal pH monitoring
LES	lower esophageal sphincter
LNRF	laparoscopic Nissen–Rossetti fundoplication

Introduction

Laparoscopic fundoplication is widely accepted as the treatment of choice for patients affected by gastroesopha-

geal reflux disease (GERD) not responsive to medical treatment. However, selecting these patients for surgery on the basis of standard 24-h pH monitoring may be challenging, especially if this investigation does not correlate with the clinical symptoms. In the past, fundoplication was the absolute indication for patients responsive to proton pump inhibitors (PPIs) and/or with positive 24-h pH monitoring, while the indication was debated in case of patients not responding to PPI and/or with a negative pH monitoring.[1]

Combined multichannel intraluminal impedance-pH monitoring (MII-pH) is able to physically detect each episode of intraesophageal bolus movement, allowing to identify either acid or non-acid reflux episodes and to exactly establish the association of the reflux with symptoms.[2] Since the mechanism of fundoplication is to physically block gastric refluxate to enter into the esophageal lumen by restoring the competence of the lower esophageal sphincter (LES), the routine use of MII-pH in the preoperative evaluation may offer objective parameters for a more accurate indication to surgery. The aim of this study was to verify the efficacy of MII-pH in selecting patients for laparoscopic Nissen fundoplication.

Table 1 Modified DeMeester Clinical Symptoms Score

Symptoms	Score	Description
Dysphagia	0	None
	1	Occasional transient episodes
	2	Require liquids to clear
		Impaction requiring medical attention
Heartburn	0	None
	1	Occasional brief episodes
	2	Frequent episodes requiring medical treatment
	3	Interference with daily activities
Regurgitation	0	None
	1	Occasional episodes
	2	Predictable by posture
	3	Interference with daily activities
Chest pain	0	None
	1	Occasional brief episodes
	2	Frequent episodes requiring medical treatment
	3	Interference with daily activities
Respiratory complications	0	None
	1	Occasional brief episodes
	2	Frequent episodes requiring medical treatment
	3	Interference with daily activities

Materials and Methods

From September 2005 to March 2008, 314 consecutive patients who complained of typical or atypical symptoms of GERD, not-responder, not-satisfied, or not compliant by PPI therapy, underwent MII-pH at the Foregut and Obesity Pathophysiology Study Center of the First Division of General and Gastrointestinal Surgery, University of Naples II. Data were collected prospectively in electronic database (Microsoft Excel® 2003, Microsoft, Redmond, WA, USA).

Preoperative Data

At first visit, demographics, clinical history, and previous instrumental investigation were reviewed. At the same time, patients were invited to define their clinical symptoms (i.e., heartburn, regurgitation, and cough), fulfilling a standardized questionnaire dealing with presence of typical or atypical symptoms based on a modified DeMeester score (Table 1); presence of dysphagia was also evaluated in the preoperative questionnaire for a better comparison after surgery.

Exclusion criteria from the study were previous gastrointestinal surgery, presence of paraesophageal (type II), mixed (type III), or giant hernias (>5 cm), and complications of GERD, like as Barrett's esophagus or peptic stricture. All the patients had to complete at least 12 months follow-up.

Among 314 patients, 153 were eligible for the study. All of the 153 patients underwent outpatient MII-pH at 8:30 A.M. Patients had to observe fasting since the night before and had to be off medication (any kind of PPI or drugs affecting the normal gastrointestinal motility) for at least 7 days. Firstly, all underwent stationary esophageal manometry to localize and evaluate the esophageal sphincter and esophageal motility as previously described.[3] Patients were classified to have ineffective motility when esophageal peristalsis either at 5 or 10 cm above LES was <30 mmHg in ≥30% of liquid swallow.

A dedicated MII-pH catheter (with intraluminal impedance segments positioned at 3, 5, 7, 9, 15, and 17 cm above the LES; Sandhill Scientific Inc., Highlands Ranch, CO, USA) was placed transnasally, with the esophageal pH sensor positioned 5 cm above the manometrical determined LES. Patients were invited to signal three or more predominant symptoms that occurred during the recording time, every meal, and changing position in upright or in recumbent, as on the device and a written diary as well. This information was transmitted by the catheter into software integrated into the device (Sleuth System, Sandhill Scientific Inc.). MII-pH data were acquired and analyzed with the Bioview GERD Analysis Software (Sandhill Scientific Inc.). All tracings were carefully reviewed to check correspondence between the results of the computer

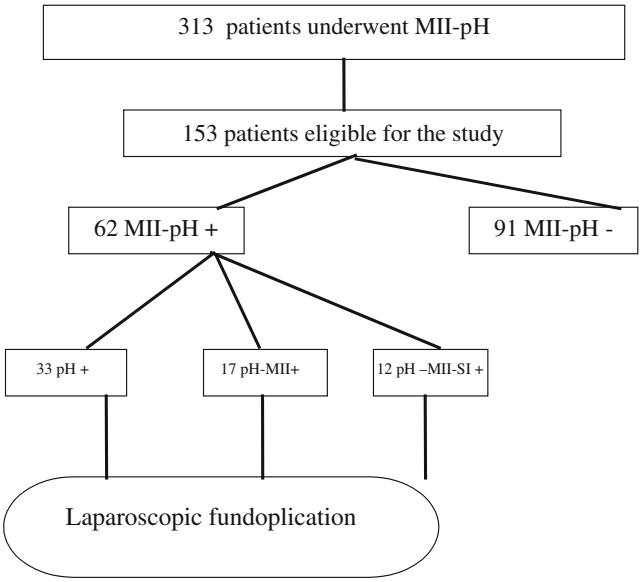

Figure 1 Algorithm of patients selected for laparoscopic Nissen–Rossetti fundoplication.

evaluation and the morphology of each reflux episode. Meal periods and drop in pH, not related to a retrograde movement at impedance (i.e., swallow of acid drink), were excluded from the analysis to improve accuracy of the pH monitoring.

The following variables were assessed: (1) esophageal acid exposure calculated as percentage (%) of time with pH <4 (total, upright, and recumbent), (2) number and quality (acid and non-acid) of reflux detected at MII, and (3) Symptom Index, described according to reported parameters.[4–6] An abnormal % of time with pH <4 in distal esophagus, a total number of refluxes detected at MII >73, a Symptom Index at least 50%, or the presence of two or all three were considered as parameters useful to indicate antireflux surgery.

All patients selected for antireflux surgery underwent laparoscopic Nissen–Rossetti fundoplication (LNRF), as described elsewhere.[7] In short, a 2-cm Nissen–Rossetti fundoplication was performed laparoscopically with an extensive transhiatal mobilization of the esophagus and preservation of short gastrics. Fundoplication was calibrated by intraoperative manometry at 20–40 mmHg. No esophageal bougie was used for calibration of the valve. Intraoperative endoscopy controlled the wrap.

Postoperative Data

Clinical data were collected prospectively at 6 and 12 months after LNRF. Patients were invited to redefine their symptom assessment after surgery, fulfilling the same standardized questionnaire dealing with presence of typical or atypical symptoms and based on the modified DeMeester score (Table 1). Satisfaction of the procedure and the will to undergo the same operation after knowing its effects were defined as excellent outcome.

Based on the results of MII-pH, the patients were divided into positive pH monitoring (pH+) and negative pH monitoring groups (pH−). This latter were further divided in two sub-groups if the total number of reflux episodes at MII was pathologic (pH-MII+) or the total number of reflux episodes were negative, though the Symptom Index was positive (pH-MII-SI+). A comparative analysis was performed between these subgroups and for the groups determined by esophageal manometry (normal vs. ineffective peristalsis).

Statistical Analysis

Statistical analysis was carried out using SPSS for Windows (version 12.0, SPSS Inc. Chicago, IL, USA). Results were expressed as mean±SD unless otherwise indicated. ANOVA analysis, Student's *t* test, the chi-square test, the Fischer's exact test, and the Wilcoxon signed rank test were used as appropriate. P value<0.05 was considered statistically significant.

Table 2 Demographic and MII-pH Outcomes of the Patients Submitted to Laparoscopic Nissen-Rossetti Fundoplication

	Total (N=62)	pH+ (N=33)	pH - MII+ (N=17)	pH-MII-SI+ (N=12)
Mean age	42.1±16.2	40.6±19.3	45.2±12.8	40.5±17.4
Sex ratio (M/F)	1:2.6	1:3.1	1:1.7	1:1.9
Total time pH<4 (%)	3.2±3.9	5.6±2.4	2.6±1.8	1.5±1.9
Upright time pH<4 (%)	4.9±3.5	8.4±2.1	4.1±2.2	2.2±2.4
Recumbent time pH<4 (%)	1.5±1.2	2.8±1.3	0.9±0.3	0.7±0.2
MII total reflux (*N*)	63.7±47.5	54.2±20.5	93.4±17.2	43.5±24.5
MII acid reflux (*N*)	45.3±35.0	43.3±25.3	65.3±15.1	27.3±11.4
MII non-acid reflux (*N*)	18.4±23.0	10.9±14.8	28.1±20.4	16.2±13.2

All data are presented as mean±SD.

Total Total population, *pH+* patients with positive pH monitoring, *pH-MII+* patients with normal pH monitoring and a positive total number of reflux detected at MII, *pH-MII-SI−* patients with normal pH monitoring and total number of reflux detected at MII and a positive Symptom Index correlation

Table 3 Pre- and Postoperative Modified DeMeester Symptom Scoring System

Symptom (mean score±SD)	Preoperative	Postoperative	*P* value
Heartburn	2.3±0.8	0.2±0.2	<0.05
Regurgitation	1.8±0.9	0.3±0.2	<0.05
Solid food dysphagia	0.3±0.5	0.4±0.1	<0.05
Respiratory complication	1.1±0.9	0.3±0.1	<0.05

All data are presented as mean±SD. Comparisons are made between the pre- and postoperative total population of patients

Results

Among 153 patients investigated at MII-pH, 62 patients (40.5%) had one or more MII-pH parameter positive and, for this reason, were submitted to LNRF and 91 patients (59.5%) had a negative MII-pH exam. Of these, 43 patients (47.2%) complained of abdominal pain, with gastritis at esophagogastroduodenoscopy and underwent eradication of *Helicobacter pylori* infection (14/43) and/or started PPI therapy. The remaining 48 (52.7%) patients were non-responders to PPI. In particular, 18 patients (19.7%) with symptoms related to the presence of hiatus hernia underwent laparoscopic hernia repair, hiatoplasty, and fundoplication.[7] Twenty-one (23%) patients complaining of extraesophageal symptoms (i.e., hoarseness, laryngitis, chest pain, and globus) not related to GERD were referred to otolaryngologists, pulmonologists, or other specialists.

In nine cases, the symptoms were suggestive for functional dyspepsia (i.e., bloating, delayed gastric empting), and the patients underwent further clinical–instrumental investigation (i.e., diisopropyl iminodiacetic acid gastric scintigraphy scanning, 24-h intragastric bile monitoring with the Bilitec), and promotility agents like metocloporamide, domperidone, and erythromycin were started.

Preoperative Data

Demographics of LNRF group are shown in Fig. 1. Mean duration of preoperative symptoms was 4.9±3.8 years (range, 1–7). Mean LES pressure was 11.0±1.2 mmHg. Distal esophageal amplitude peristaltic waves were ineffective in 35.5% (22/62) of the cases.

Among the 62 patients, 33 (53.3%) had abnormal pH monitoring (pH+), 17 (27.4%) had a normal pH monitoring and a positive number of MII reflux (>73 episodes; pH-MII+), and 12 (19.3%) had a normal pH monitoring and number of MII reflux (<73 episodes) and a positive Symptom Index. Sixteen patients (25.8%) were positive for all the parameters (e.g., pH-monitoring, number of reflux >73, and Symptom Index). MII-pH outcomes are detailed in Fig. 1.

Postoperative Data

Clinical follow up at 6 and 12 months from intervention was carried in all the patients. At 12 months, 98.3% (61/62) were satisfied of the procedure and expressed the will to undergo the same operation knowing its effects. A significant difference was found comparing the pre- and postoperative modified DeMeester symptom scoring system (Table 2). No differences were recorded in DeMeester symptom scoring system between patients with preoperative normal and ineffective peristalsis. No differences in patients' satisfaction and DeMeester symptom scoring system were noted between the subgroups determined by MII-pH (Tables 3 and 4). Regarding side effects, among 62 patients, one patient complained about bloating and hyperflatulence and one complained about transient dysphagia, totally resolved in 2 months after surgery. All the patients did not restart taking any anti-acid drugs for symptoms above the wrap.

Table 4 Postoperative Comparison of Modified DeMeester Score in the MII-pH Subgroups did not Show Clinical Difference

Symptom (mean score±SD)	pH+	pH-MII+	pH-MII-SI+
Heartburn	0.2±0.1*	0.3±0.2*	0.2±0.2*
Regurgitation	0.3±0.4*	0.3±0.1*	0.2±0.8*
Solid food dysphagia	0.3±0.6*	0.4±0.5*	0.4±0.1*
Chest pain	0.2±0.1*	0.3±0.2*	0.3±0.7*
Respiratory complication	0.3±0.1*	0.2±0.9*	0.3±0.2*

All data are presented as mean±SD.
pH+ Patients with positive pH monitoring, *pH-MII+* patients with normal pH monitoring and a positive total number of reflux detected at MII, *pH-MII-SI−* patients with normal pH monitoring and total number of reflux detected at MII and a positive Symptom Index correlation
**P*=NS. Comparison are made between the postoperative pH+, pH-MII +, and pH-MII-SI+ groups.

Discussion

This study offers objective data to demonstrate that MII-pH used as a routine diagnostic tool for patient candidates for surgery provided a satisfaction rate comparable to classic pH monitoring.[7] It is noteworthy that these positive results were obtained extending the indication to surgery in an additional 40% of patients, with negative pH monitoring. In the pre-MII era, to establish the need for surgery in patients with negative pH monitoring was a challenging decision. Data on non-acid reflux episodes and a more precise symptom index correlation helps the surgeon to decide for an antireflux operation vs. medical treatment. Moreover, the possibility of following up the patients operated on by MII-pH helps the surgeons to distinguish a surgical failure from gastroduodenal-associated symptoms.

In this study, we found that the total fundoplication had an excellent and satisfying rate even in the patients with a preoperative poor motility. This is consistent with the fact that ineffective peristalsis is not an obstacle to bolus transit after total fundoplication[3,8] even when associated with extended Heller myotomy, as previously reported.[9,10]

From a clinical practice standpoint, we identified three useful parameters to select patients for antireflux surgery. The first parameter is the presence of an abnormal time of esophageal exposure to pH <4. This data indicates the total exposure of the mucosa of the esophagus to acid, and its importance is known from the standard pH monitoring.[11] MII-pH improves the affordability of this parameters, giving the opportunity of detecting and excluding the acidification due to the swallow of acid drinks (i.e., coke, lemonade, and orange juice). The second parameter selected is the total number of reflux episodes detected at MII. This parameter indicates how many times the esophageal mucosa is exposed to refluxate from the stomach independently from pH. Because PPI therapy is only able to switch reflux from acid to non-acid without modifying the total number of reflux episodes[12,13] and because the patients with good esophageal clearance are more likely to have negative pH monitoring being more rapid to clean their esophagus, we believe that to find an abnormal number of reflux episodes in non-responder patients is an indicator for antireflux surgery. This is consistent with our positive outcomes in the group of patients with negative pH monitoring and a positive total number of reflux episodes at MII (pH-MII+) and the fact that Nissen fundoplication protects against both acid and non-acid reflux.[14] The last parameter, the Symptom index correlation, helps to identify those patients suffering from a specific symptom. In the case of a repeated disabling symptom correlated to reflux, a patient may be offered the opportunity of surgery knowing the chance of solving it, as demonstrated by our positive clinical outcomes in the pH-MII-SI+ group.

This study however has some limitations related to the short-term follow-up and to the absence of a control group. Another limitation lays on the absence of instrumental follow-up. Further studies are needed to define the standard parameters to predict good results of antireflux surgery. Furthermore, to avoid interferences in pH monitoring, we prefer to perform all MII-pH exams after suspension of anti-acid therapy; this is a not widely accepted method. Moreover, because we use MII-pH to select patients for surgery, the type of reflux (acid vs. non-acid) is not crucial. It is more important to have real quantification of GERD.

In summary, MII-pH provides useful information for an objective selection of patient candidates to antireflux surgery. Nissen fundoplication provides excellent outcomes in patients with positive pH and negative pH and positive MII monitoring or Symptom Index association. More extensive studies are needed to definitively standardize the useful MII-pH parameters to select the patient to antireflux surgery.

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Conflicts of interest None

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The Effects of Vasopressors on Perfusion of Gastric Graft after Esophagectomy. An Experimental Study

Dimitrios Theodorou · Panagiotis G. Drimousis · Andreas Larentzakis · Apostolos Papalois · Konstantinos G. Toutouzas · Stylianos Katsaragakis

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Abstract
Aims To evaluate the impact of the perioperative administration of norepinephrine on the perfusion of the esophageal graft.
Methods This is an experimental study. Six swine underwent transhiatal esophagectomy; the stomach was used to replace the resected esophagus. We provoked hemorrhagic shock to the animals and then we administered noradrenaline to restore the blood pressure. We monitored the graft perfusion perioperatively using the technique of microdialysis.
Results In all animals, the graft experienced severe hypoperfusion after the administration of noradrenaline that was statistically significant.
Conclusions Our data support the hypothesis that norepinephrine should be used with extreme caution in the perioperative setting after esophagectomy. Further studies, however, will be required to evaluate the clinical significance of this finding.

Keywords Esophagectomy · Norepinephrine · Gastric graft perfusion · Experimental study

Introduction

Esophagectomy comprise the main treatment for cancer of the esophagus and cardia.[1] The esophageal resection is associated with high mortality and morbidity rates. In 1940, Oschner and DeBakey reviewed the literature and reported a mortality rate of 72%.[2] Since then, advances in the perioperative management have improved the morbidity in other major operations such as hepatectomy, pancreatectomy and gastrectomy, but the morbidity rate of the esophagectomy remains high. At present, esophagectomy is still an operation that is characterized by very high mortality and morbidity rates, reaching in many reports the percentage of 10% and 40–80% respectively.[3]

Many studies have evaluated several preoperative and perioperative risk factors associated with the morbidity of the esophagectomy.[4] In one report by Law et al.,[5] smoking, history of cardiac or pulmonary disease (decreased forced vital capacity) and malnutrition in preoperative evaluation, have all been related to high mortality and morbidity rates after esophagectomy. Dimick et al.,[6] reviewed the state-wide Maryland experience with two high-risk operations, esophagectomy and hepatectomy. They tried to correlate hospital expenditure to mortality rates and they concluded that quality improvement is feasible after the identification of "the most important complications". Concerning esophagectomy, the most important complications encountered are anastomotic rupture and leakage, usually followed by stricture, which are both related to high morbidity rates.[3,7] To our knowledge, there have been some reports in the literature investigating several risk factors for anastomotic leakage after esophagectomy. Nevertheless, there have been no reports about the risk factors in the immediate postoperative period. Our hypothesis is that beyond factors such as the meticulous surgical

D. Theodorou · P. G. Drimousis · A. Larentzakis · K. G. Toutouzas · S. Katsaragakis
1st Department of Propaedeutic Surgery, Athens Medical School, University of Athens, "Hippocration" General Hospital of Athens, Athens, Greece

A. Papalois
Department of experimental surgery, ELPEN Laboratories, Athens, Greece

A. Larentzakis (✉)
11, 3rd September 1843 Str.,
12242 Egaleo, Attiki, Greece
e-mail: alarentz@med.uoa.gr

technique, the performance of a tension free anastomosis and the assurance of adequate blood flow, there may also be other factors contributing to anastomotic complications after esophagectomy.

In this report we present our data on esophageal substitute perfusion after noradrenaline administration. Based on these data we support the argument that the impact of the drugs, that are administrated during the perioperative period, on anastomotic integrity maybe more important than anticipated till now.

Material and Methods

This was an experimental study. Six domestic Sus scrofa Landrace animals, of 30±2 Kgr and of five to 6 weeks aged were used. The study was performed in accordance with the guidelines of the Institutional Review Board and the directives of the state authorities concerning experimental use of animals.

Food was withheld 12 h before the procedure, while water access was given ad libitum. At the induction of anesthesia, before the intubation, animals received intramuscular ketamine (15 mg/Kgr), midazolam (0.5 mg/Kgr), and atropine (0.04 mg/Kgr). Two marginal ear veins were cannulated as an intravenous access for the continuous infusion of anesthetics. A combination of propofol (15 mg/kgr/h), fentanyl hydrochloride (50 mcg/kgr/h), and cisatracurium (1.5 mcg/Kgr/min) was used to maintain general anesthesia throughout the procedure. Pigs underwent endotracheal intubation with an orotracheal tube of 7 mm in diameter. The mechanical ventilation was established with 15 ml/Kgr of tidal volume and in 60% oxygen concentration of the inspired gas mixture (FiO_2 60%). During the procedure, the temperature of all animals was maintained at 38±1°C, using an electrically warmed blanket.

After the intubation, a right neck incision was made to the swine and the right interior jugular vein and right exterior carotid artery were cannulated for central vein access and invasive blood pressure monitoring, respectively.

Once cannulation of both the jugular vein and the carotid artery was achieved, the animals were subjected to transhiatal esophagectomy. The continuity of the digestive tract was restored using a gastric tube. The blood supply of the graft was based on the right gastroepiploic artery. The gastric tube was placed in an orthotopic position in the posterior mediastinum. A microdialysis catheter (CMA Microdialysis, Sweden) was placed in the gastric mucosa, anteriorly, next to the anastomotic line.

Microdialysis is a technique that enables the monitoring of the composition of extracellular fluids in the living tissues. The microdialysis probe is a double lumen catheter. The outer lumen consists of a semipermeable membrane, which is designed to mimic a blood capillary. The proximal end of the probe is connected to a pump and the distal end is placed in the tissue to be monitored. After the placement of the probe, a normal saline solution is slowly pumped through the inner lumen of the probe to the tissue. Eventually, the concentrations of various solubles in the solution equilibrate with the ones of the surrounding extracellular tissue fluid. The pump extracts the microdialysate to a microvial and a bedside analyzer calculates the concentration of each substance. Lactate, pyruvate, glycerol and glucose are among the common measured molecules. Glucose represents the biochemical matrix for energy production. High concentration of glycerol reflects the initiation of a cell degeneration process. Lactate and pyruvate are products of the glycolysis in the absence and presence of oxygen, respectively. In case of adequate oxygen delivery, the cells transform glucose to pyruvate, which enters the Kreb's cycle for the process of the aerobic glycolysis and the production of ATP. When the oxygen delivery is not sufficient to meet demands, then the pathway of the anaerobic glycolysis is triggered and glucose is transformed to lactate. Therefore, the relation between the concentrations of lactate and pyruvate (the lactate/pyruvate ratio) becomes an index of the adequacy of the oxygen delivery to the tissues.[8–11]

One hour after the end of the operation, the animals were subjected to hemorrhagic shock to a systolic arterial blood pressure of 80 mmHg. This was accomplished with aspiration of blood from the jugular vein (median blood loss, 210 cc; range, 200–265 cc). Then, we used norepinephrine to achieve a systolic blood pressure of 90 mmHg (norepinephrine was infused to a median dose of 0.12γ- range, 0.1–0.5γ- to accomplish this blood pressure). One hour after the restoration of blood pressure all animals were euthanized. Measurements of arterial blood pressure, heart rate, and microdialysis variables were obtained every 30 min from the beginning of the surgical procedure to the end of the experiment.

All data were collected in an electronic database for future review and statistical analysis. Data analysis was performed using the SPSS statistical package version 14.0. Comparison of categorical variables was done by paired *t*-test.

Results

In all animals the transhiatal esophagectomy was technically feasible. The mean operative time from induction of anesthesia to microdialysis catheter placement was 2.1 h (range, 1.8–3 h). There was no major intraoperative complication and all animals survived the esophagectomy. The baseline measurements at the beginning of the procedure and the basic characteristics of all six pigs are shown in Table 1. All animals showed a similar pattern of metabolic response to the operation, with a slight increase of the lactic acid concentration, which was not statistically significant. The hemorrhage provoked a more severe shift to anaerobic metabolism and an increase in the lactate concentration yet not statistically

Table 1 Lactate Concentration, Lactate/Pyruvate Ratio, Heart Rate and Blood Pressure of all six Animals Throughout the Procedure

Animal	Time point 0	Time point 1	Time point 2	Time point 3
Lactate (mg/dl)				
1	0.72	0.95	2.25	2.75
2	0.01	0.01	2.45	1.66
3	0.02	0.05	0.34	0.31
4	0.82	1.46	1.99	1.84
5	10.40	16.83	3.10	3.74
6	0.24	0.73	4.97	4.65
L/P Ratio				
1	379	364	532	1041
2	17	15	27	63
3	36	50	115	197
4	788	712	1048	1153
5	111	95	756	1377
6	150	248	590	925
HR (bits/min)				
1	125	130	140	75
2	92	103	160	157
3	94	101	141	125
4	84	85	100	120
5	115	104	80	85
6	73	69	89	119
SAP/DAP (MAP) (mmHg)				
1	95/71 (82)	91/52 (66)	61/31 (39)	72/40 (52)
2	92/52 (65)	89/59 (72)	70/47 (51)	82/52 (62)
3	79/32 (48)	89/39 (48)	56/25 (31)	82/26 (36)
4	61/40 (46)	46/26 (36)	44/24 (27)	42/22 (26)
5	62/30 (39)	53/24 (32)	37/16 (19)	14/14 (14)
6	75/42 (52)	78/35 (45)	51/27 (33)	82/37 (48)

Time points 0, 1, 2 and 3 represent the zero hour of the measurements, and one, two and 3 h after, respectively
L/P ratio Lactate/pyruvate ratio, *HR* heart rate, *SAP* systolic arterial pressure, *MAP* mean arterial pressure, *DAP* diastolic arterial pressure, *Time Point 0* baseline measurements at the initiation of the transhiatal procedure, *Time Point 1* baseline measurements after the completion of the transhiatal procedure, *Time Point 2* at the end of the hemorrhage period, *Time Point 3* at the end of noradrenalin administration

significant. After norepinphrine was used to restore the blood pressure there was observed increase in lactate concentration and a marked deterioration of tissue perfusion in the gastric graft as monitored by the lactate/pyruvate ratio (L/P ratio). Lactate concentration, L/P ratio, heart rate, and blood pressure of all six animals throughout the procedure are shown in Table 1. Table 2 shows statistical significance (p value) between time points. In Fig. 1, the fluctuation of these variables, throughout the procedure, is presented.

Discussion

Many parameters have been studied and identified as predictive factors for postoperative complications after esophagectomy, such as the malnutrition, the surgical trauma, the surgical technique, and the postoperative care. The most frequently seen surgical complication after esophagectomy is anastomotic leakage which is attributed to poor surgical technique, tension, and anastomotic line ischemia.[4] As surgical technique and perioperative care improve, the incidence of leakage and postoperative stenosis is decreasing in specialized centers, but it is still reported as high as 25%.[12] The anastomotic leakage related mortality is approximately 3%. There are numerous reports in the literature concerning several prevention measures in order to avoid anastomotic leakage.[13–18] Most of them focus on meticulous surgical technique and adequate postoperative care.

Anastomotic line blood flow has been described as a cornerstone of the anastomotic integrity. In this experiment, we aimed to evaluate the impact of perioperative norepinephrine administration to the perfusion of the graft. Norepinephrine is commonly used in the operating room and it has a substantial vasoconstrictive effect on small arteriols. In the operating setting of an esophagectomy, patients often develop hypotension due to either the surgical manipulations or the acute blood loss.

Our hypothesis was that with such a vasoconstrictive effect on small arterioles, the use of norepinephrine has a harsh

Table 2 Mean, Median and Standard Deviation (SD) of the Lactate/Pyruvate Ratio (L/P Ratio) Measurements at each Time Point

Time point	Time (hours)	Mean L/P ratio	Median L/P ratio	SD L/P ratio	*p* value
0	0	247	130	295	
1	1	248	171	263	
2	2	511	561	386	<0.03*
3	3	793	983	536	<0.03**

The changes of the L/P ratio measurements between time points 1 and 2, 1 and 3, and 2 and 3 are statistical significant (p value<0.03)
*p value between time points 1 and 2
**p value between time points 1 and 3, and 2 and 3

effect on the perfusion of the gastric graft after esophagectomy. We chose to use microdialysis technique as the monitoring tool of the tissue perfusion, because it has been reported to be an accurate regional marker of tissue perfusion. Moreover, rather than monitoring global oxygen delivery, we believe that evaluating the regional microenvironment of the transplant is far more accurate.

Microdialysis has been described as a technique that can monitor the metabolic status at the tissue level. Various reports in specific organs have been published, such as the brain, the liver, the skin grafts in plastic surgery, and the small and large intestine.[19] Most of them conclude that microdialysis represents the metabolic status of the examined organ and that microdialysis can be used as a monitoring tool of tissue perfusion. Moreover, microdialysis measurements have been used to illustrate the pharmacokinetics of a variety of drugs, usually antibiotics. There have been no previous reports in regard to the esophagus or the impact of norepinephrine in the esophageal graft perfusion. The physiologic values of L/P ratio in living tissue are not univocally determined, but there is general agreement in the literature that values above 20 are strongly related to poor perfusion of the tissue.

In our experiment, during the operation, all animals experienced initially a moderate lactic acidosis attributable to the surgical trauma. As the operation progressed, L/P ratio was stabilized, a finding that reflects adequate resuscitation in the operating room. When we provoked hemorrhagic shock to the animals to a systolic blood pressure below 80 mmHg, the L/P ratio increased even if the increment did not reach statistical significance. This increment most probably reflects the ongoing metabolic stress as tissue perfusion was impaired. When we administered norepinephrine and restored the blood pressure, the L/P ratio increased further more as appears in Fig. 1. We suspect that the physiologic basis of this event is the vasoconstriction which deteriorates the perfusion of the graft. This phenomenon may be more profound with a gastric pull-up, where the blood supply of the graft depends on a single artery (i.e., the right gastroepiploic artery). If,

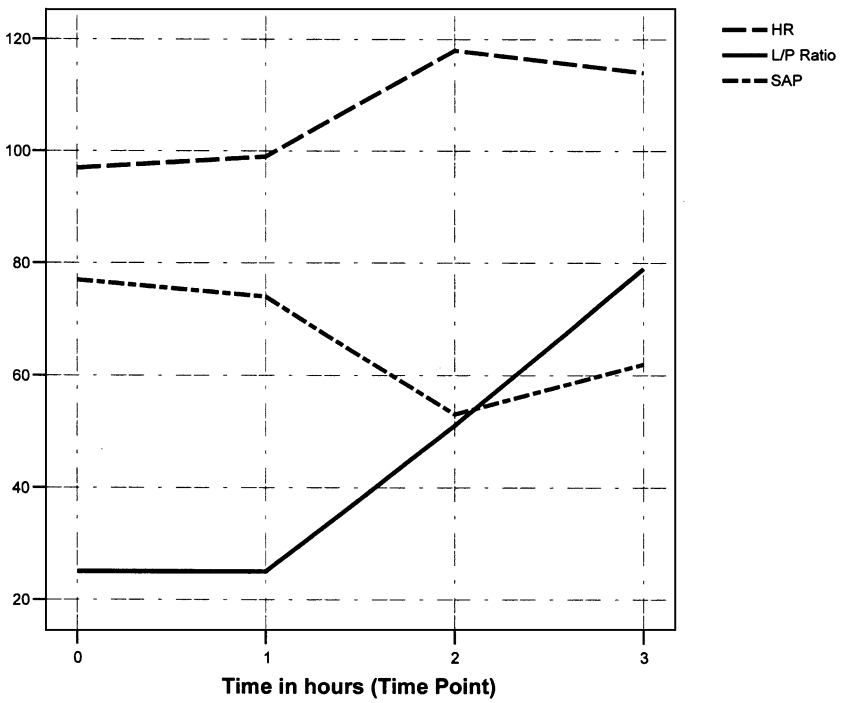

Figure 1 The lactate/pyruvate ratio (L/P ratio x 10^{-1}), heart rate (HR-beats/min) and systolic arterial pressure (SAP—mmHg) mean values of the six animals at each time point.

whatever the cause, the blood flow of this artery is deteriorated, then the graft suffers severe hypo-perfusion.

As already described earlier, the vasoconstriction due to the administration of noradrenaline may be effective in restoring hypotension, but at the same time the effect of vasoconstriction is even more hazardous than the hypotension itself. Nevertheless, hypotension is a common occurrence during the perioperative period of these patients. There are, though, several maneuvers that the physician who cares for the patient may try before using vasoconstrictors. The use of fluids for volume expansion should be the first line of treatment in such patients. Also, attention should be paid to the use of epidural analgesia, especially with local anesthetics, that can cause significant hypotension. We believe that our data support the hypothesis that noradrenaline administration should be cautiously used during the perioperative period of an esophagectomy. Further studies, however, will be required to evaluate the clinical significance of this finding.

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Does Age Matter in the Indication for Laparoscopy-Assisted Gastrectomy?

Masanori Tokunaga · Naoki Hiki · Tetsu Fukunaga · Akira Miki · Shigekazu Ohyama · Yasuyuki Seto · Toshiharu Yamaguchi

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Abstract
Background Laparoscopy-assisted gastrectomy (LAG) is being increasingly performed in Japan. However, the indication of LAG in elderly patients who usually have preoperative morbidities and reduced functional capacities still remains unclear.
Materials and Methods Two hundred eighty-nine patients who underwent LAG at the Cancer Institute Hospital were included in this study. Among them, 240 cases were younger than 75 years old (Y-LAG group), and 49 cases were 75 years old or older (E-LAG group). Early surgical outcomes between the two groups were compared to clarify the feasibility of performing LAG in elderly patients.
Results The E-LAG group had a higher incidence of preoperative morbidities; however, the frequency of intraoperative and postoperative complications in this group was not significantly different from the Y-LAG group (9% vs 11%). The operation time was significantly shorter, and the number of retrieved lymph nodes was significantly smaller in the E-LAG group compared to the Y-LAG group. However, other early surgical outcomes were not significantly different between two groups.
Conclusions LAG proved to be a feasible and safe procedure in elderly patients provided that the patients were selected carefully.

Keywords Laparoscopy-assisted gastrectomy · Elderly patient · Gastric cancer · Laparoscopic surgery

Introduction

The incidence of early gastric cancer (EGC), which is considered a good indication for laparoscopy-assisted gastrectomy (LAG), is increasing in Japan because of a well-developed mass-screening program initiated by the government.[1,2] This trend is observed equally in both elderly and younger patients. Many reports have commented on the superiority of LAG compared with conventional open gastrectomy, with advantages including less intraoperative bleeding, less pain, and shorter postoperative hospital stays.[3–11] On the other hand, disadvantages of LAG such as longer operation times and difficulty in intracorporeal reconstruction were also reported.[4,6,9,12] Furthermore, laparoscopic surgery usually requires a pneumoperitoneum, which can disrupt respiratory or cardiovascular performance.[13–15] These effects are especially enhanced in elderly patients, who usually have preoperative morbidities and reduced functional capacities. Therefore, the feasibility of LAG in elderly patients is still controversial.

In our institute, the age of elderly patients was not always considered a contraindication for laparoscopic surgery unless the patients had severe preoperative cardiopulmonary disease or other comorbidities. Indeed, 49 elderly patients (range, 75 to 89 years old) underwent LAG since April 2005 in our institute.

M. Tokunaga · N. Hiki (✉) · T. Fukunaga · A. Miki · S. Ohyama · Y. Seto · T. Yamaguchi
Department of Gastroenterological Surgery,
Cancer Institute Hospital,
Japanese Foundation for Cancer Research,
3-10-6 Ariake, Koto-ku,
Tokyo 135-8550, Japan
e-mail: naoki.hiki@jfcr.or.jp

In this study, early surgical outcomes including operation time, intraoperative bleeding, postoperative morbidity, and mortality were collected prospectively and compared between elderly and younger patients (less than 75 years old) to clarify the feasibility of performing LAG in elderly patients.

Materials and Methods

Patient Clinical Data

Patients who underwent LAG including laparoscopy-assisted distal gastrectomy (LADG) and laparoscopy-assisted pylorus-preserving gastrectomy (LAPPG) at the Cancer Institute Hospital between April 2005 and June 2007 were included in this study. We collected clinical, surgical, and pathological data concerning these patients from medical, surgical, and pathological record, respectively.

Approval by the Ethics Committee

The present study, including data collection and data analysis, was approved by the review board of the gastroenterological center of our institute.

Evaluation of Preoperative General Conditions

Chest X-rays, laboratory tests, electrocardiograms (ECG), and respiratory function tests using spirometry were examined in all patients to assess preoperative cardio-pulmonary function and other comorbidities. Patients with forced expiratory volume in first second/forced vital capacity (FEV1.0%) less than 0.7 were defined as having chronic obstructive pulmonary disease (COPD). Patients with a vital capacity less than 80% of the expected value were defined as having restrictive lung disease. Patients were also classified according to the American Society of Anesthesiologists (ASA) Classification of Physical Status guidelines so that patient comorbidity could be assessed objectively.

LAG was not indicated if patients had cardiac (greater than New York Heart Association class II), pulmonary (greater than Huge–Jones grade IV), hepatic (Child classes B and C), or renal insufficiencies.

Comparison of Early Surgical Outcomes Between Elderly and Younger Patients

The feasibility of LAG in elderly patients was evaluated by comparing early surgical outcomes between elderly patients (E-LAG group, 75 years old or older) and younger patients (Y-LAG group, younger than 75 years old). Early surgical outcomes included operation time, estimated blood loss, the degree of lymph node dissection, the number of lymph nodes retrieved, the day of first oral intake, the day of first flatus, postoperative morbidity, mortality, and the duration of the postoperative hospital stay.

Lymph Node Station Number

Lymph node station numbers are classified according to the Japanese Classification of Gastric Carcinoma.[16] Station 1 to 6 lymph nodes are regional lymph nodes. Station 7s, 8a, 9, and 11p lymph nodes are second-tier lymph nodes located along the left gastric artery, the common hepatic artery, the celiac axis, and the proximal half of the splenic artery, respectively. Station 12a lymph nodes are classified as second-tier lymph nodes if the tumor is located in the distal two thirds and they are located along the proper hepatic artery. Station 14v lymph nodes are classified as second-tier lymph nodes of lower third gastric cancer and are located along the superior mesenteric vein at the lower border of the pancreas.

Operative Procedure

LAG was performed under a pneumoperitoneum that was created by the injection of carbon dioxide (10–12 mmHg). However, an intraperitoneal pressure of 8 mmHg was sometimes selected if a lower cardiopulmonary reserve was expected. A total of five ports (each 5–12 mm) were inserted, and LAG with extragastric lymph node dissection was conducted as reported previously.[17,18] Extracorporeal reconstruction was performed using a 4- to 5-cm upper midline incision. A Billroth-I reconstruction or Roux-en-Y reconstruction was selected if a distal gastrectomy was performed. In the case of pylorus-preserving gastrectomy, the distal part of the stomach was resected while retaining a 3.5-cm pyloric cuff and reconstructed using hand-sewn sutures.

Statistical analysis

All data are presented as the mean±SD. Results were compared between elderly patients and younger patients. Statistical analysis was performed using the chi-square test, Student's t test, and Mann–Whitney U test. $P<0.05$ was considered significant.

Results

The number of LAGs performed between April 2005 and June 2007 at the Cancer Institute Hospital was 289, and all

Table 1 Patient Characteristics

	Elderly patients	Younger patients	*P* value
N	49	240	
Gender (male/female)	30/19	135/105	0.629
Age (year)			
Mean±SD	78.9±3.9	59.1±9.7	< 0.001
Range	75–89	36–74	
Body mass index (kg/m^2), mean±SD	22.92±3.96	22.79±3.06	0.618
Previous abdominal surgery, *n* (%)			
Yes	23 (47)	64 (27)	
No	26 (53)	176 (73)	0.008
Clinical staging, *n* (%)			
Early gastric cancer	44 (90)	233 (97)	
Advanced gastric cancer	5 (10)	7 (3)	0.053

were included in this study. Among these, 49 cases were 75 years old or older (E-LAG group) and the remaining 240 cases were younger than 75 years old (Y-LAG group).

Patient Demographics

Patient demographics and clinical findings are listed in Table 1. There were no significant differences in gender, body mass index, or incidence of advanced gastric cancer between the two groups. More members of the E-LAG group had a previous medical history of laparotomy (P=0.008) compared with the Y-LAG group.

Preoperative Comorbidities

Patient medical histories and the results of preoperative ECG and spirometry tests are listed in Table 2. The E-LAG group had a higher incidence of hypertension (P<0.001) and ECG abnormalities (P<0.001). The spirometry results also revealed that the elderly patients had a higher incidence of COPD (P=0.047) and restrictive lung disease (P=0.041). ASA Classification of Physical Status classes 2 and 3 were also observed more frequently in members of the E-LAG group, and this difference was statistically significant (P<0.001)

Table 2 Preoperative Conditions

	Elderly patients	Younger patients	*P* value
Preoperative co-morbidities, *n* (%)			
Hypertension	24 (49)	58 (24)	<0.001
Diabetes mellitus	3 (6)	10 (4)	0.823
Respiratory disease	8 (16)	18 (8)	0.090
Ischemic heart disease	2 (4)	2 (1)	0.270
Electrocardiogram abnormality	24 (49)	57 (24)	<0.001
Spirometry results			
COPD	15 (31)	41 (17)	0.049
Restructive lung disease	4 (8)	4 (2)	0.041
ASA physical status classification			
Class 1	5	131	
Class 2	38	99	
Class 3	6	10	
Class 4	0	0	
Class 5	0	0	<0.001

Surgical Outcomes

The operative findings are listed in Table 3. LADG was performed more frequently in the E-LAG group. The conversion from LAG to open surgery was undertaken in four patients in the Y-LAG group. One patient needed open surgery because of severe adhesion due to previous chemoradiotherapy for gastric malignant lymphoma. The reason for the conversion in the remaining three patients was for further lymph node dissections, as pathological examination of frozen second-tier lymph nodes revealed positive results. Open surgery was not required for any of the elderly patients. Conversion to open surgery due to difficulties maintaining general anesthesia during pneumoperitoneum was not required in either group. Intraoperative blood loss was not significantly different between the E-LAG groups (75.5±181.5 ml) and Y-LAG (65.3±133.4 ml). Neither group required blood transfusions during surgery. The operation time was significantly shorter for the E-LAG (215.7±45.6 min) than for the Y-LAG group (242.8±58.2 min; P=0.003). The degree of lymph node dissection was not different between groups; however, the number of lymph nodes retrieved in the E-LAG group (30.5±8.9) was significantly lower than that of the Y-LAG group (36.1±11.3; P=0.003).

Postoperative Clinical Course

Postoperative outcomes are listed in Table 4. The total complication rate was 9% in the E-LAG group and 11% in

Table 3 Operative Data

	Elderly patients	Younger patients	*P* value
Operation performed, *n* (%)			
LADG	42 (86)	136 (57)	<0.001
LAPPG	7 (14)	104 (43)	
No. of cases that required further open surgery	0 (0)	4 (2)	0.810
Bleeding	0 (0)	0 (0)	–
Severe adhesion	0 (0)	1 (0)	0.378
Further lymph node dissection	0 (0)	3 (1)	0.989
Difficulty in maintaining general anesthesia	0 (0)	0 (0)	–
Lymph node dissection, n (%)			
D1+No.7	2 (4)	5 (2)	
D1+No.7, 8a, 9	44 (90)	209 (87)	
D2	3 (6)	26 (11)	0.448
Intraoperative blood loss (ml), mean±SD	75.5±181.5	65.3±133.4	0.633
No. of cases requiring blood transfusion during surgery	0	0	–
Operation time (min), mean±SD	215.7±45.6	242.8±58.2	0.003
Total no. of retrieved lymph nodes, mean±SD	30.5±8.9	36.1±11.3	0.003

the Y-LAG group, which was not a significant different. The frequency of complications, including respiratory or circulatory complications, was not different between the groups and postoperative mortality was zero in both groups. Three patients in the Y-LAG group needed a second operation due to postoperative complications. The first patient required surgery on postoperative day 1 due to ileal perforation, which was attributed to adhesiotomy during LAG. The second patient had surgery on postoperative day 13 due to strangulation ileus. The third patient needed surgical intervention on postoperative day 27 to drain an intra-abdominal abscess caused by a pancreatic fistula. All three patients recovered well after surgery and were discharged 12, 33, and 106 days after their first operation, respectively. The time until commencement of oral intake and first flatus and the duration of postoperative hospital stay were not significantly different between the two groups.

Table 4 Postoperative Outcomes

	Elderly patients	Younger patients	*P* value
Postoperative complications	4 (9)	26 (11)	0.763
Gastric fullness, *n* (%)	0 (0)	5 (2)	0.676
Anastomotic leakage, *n* (%)	0 (0)	0 (0)	–
Anastomotic bleeding, *n* (%)	0 (0)	1 (0)	0.378
Anastomotic stenosis, *n* (%)	0 (0)	0 (0)	–
Intra-abdominal abscess, *n* (%)	0 (0)	4 (2)	0.810
Pancreatic fistula, *n* (%)	0 (0)	4 (2)	0.810
Ileus, *n* (%)	0 (0)	3 (1)	0.989
Cardiovascular complications, *n* (%)	0 (0)	1 (0)	0.378
Respiratory complications, *n* (%)	1 (2)	3 (1)	0.811
Other complications, *n* (%)	3 (6)	5 (2)	0.275
Mortality, *n* (%)	0 (0)	0 (0)	-
Time until start of oral intake (day), mean±SD	2.1±0.2	2.0±0.4	0.599
Time until start of flatus (day), mean±SD	2.6±1.1	2.4±0.9	0.270
Duration of postoperative hospital stay (day), mean±SD	12.7±4.1	13.0±10.8	0.060

Discussion

Gastric cancer is observed more frequently in Japan compared to European countries and the USA. EGC is also observed more frequently because of a well-developed mass-screening system initiated by the government.[1,2] EGC is considered a good indication for minimal invasive approaches such as endoscopic resection or laparoscopic gastrectomy, and the recent advances in laparoscopic instruments and procedures have accelerated the nationwide spread of LAG in Japan.[19,20] LAG has many advantages such as less pain, less intraoperative bleeding, less disturbance of postoperative respiratory function, earlier bowel movements, and shorter postoperative hospital stays and has been accepted as the treatment of choice for EGC.[3–11] However, when compared with conventional open gastrectomy, LAG has some disadvantages including longer operation times.[4,6,9,12] Laparoscopic lymph node dissections and intracorporeal reconstruction of the alimentary tract are also more complex.

Life expectancy has been increasing, and recently, the number of elderly patients with EGC being considered as candidates for LAG is escalating. However, the safety of LAG in elderly patients has not been proved because of the possible adverse hemodynamic and respiratory effects of the pneumoperitoneum on the limited cardiopulmonary reserve of these patients.[13–15] The feasibility of laparoscopic

surgery in elderly patients for diseases other than gastric cancer, such as laparoscopic cholecystectomy or laparoscopic colorectal surgery, has been well documented.[21,22] Mochiki et al.[23] and Yasuda et al.[24] also reported the feasibility of LAG in elderly patient. In both of these studies, elderly patients were defined as being 70 years old or older, although the World Health Organization defines elderly patients as those over 65 years of age.[23,24] We increased the age limit in the present study so that patients aged 75 years old or older were defined as elderly, since life expectancy has been increasing in developed countries. We therefore believe that the feasibility of performing LAG in these older patients should be clarified.

Preoperative comorbidities were observed frequently in elderly patients undergoing conventional open gastrectomy.[25–28] The incidence of postoperative complications after open gastrectomy in elderly patients was also reported more frequently than in younger patients,[25,27] although some reports indicated that there were no differences in the postoperative complication rate between elderly and younger patients.[26,28] The present study also revealed that the E-LAG group frequently had preoperative morbidities including hypertension, COPD, and restrictive lung disease. Furthermore, many patients in the E-LAG group were classified as either class 2 or 3 under the ASA Classification of Physical Status guidelines. Despite these results, there was no significant difference in postoperative complications between the E-LAG and Y-LAG groups in this study. Moreover, postoperative respiratory complications were quite low in the E-LAG group despite many of the elderly patients having preoperative respiratory disease and decreased cardiopulmonary reserve function. We believe that the decrease in postoperative morbidity, especially in respiratory complications is due to the reduced invasiveness of laparoscopic surgery. This is because laparoscopic surgery is less painful and allows earlier mobility, both of which are crucial for better postoperative respiratory function.

Other early surgical outcomes were not significantly different between the two groups except for the operation time and the number of lymph nodes retrieved. D2 lymph node dissections were performed more frequently in the Y-LAG group, although this finding was not statistically significant. According to our experience, when comparing early surgical outcomes between patients who had undergone LAG with D2 lymph node dissection to those who had undergone LAG with less lymph node dissection, the average number of retrieved lymph nodes was significantly larger in the D2 lymph node dissection cases (40.6±2.3) than other cases (35.3±0.6, data not shown). Furthermore, the operation times for both types of lymph node dissection were also different (256.6±9.9 min for D2 dissections vs 235.8±2.8 min for others, data not shown). These data were obtained from our experiences in performing LAG on a total of 370 consecutive cases. Since D2 lymph node dissections were performed more frequently in the Y-LAG group, these results might explain the longer operation time and larger number of lymph nodes retrieved in the Y-LAG group compared to the E-LAG group.

There have been some reports concerning the negative effects of the pneumoperitoneum on cardiopulmonary performance during laparoscopic surgery.[17–19] However, we have never experienced severe accidents related to the pneumoperitoneum such as severe arrhythmia, decreased blood pressure, or decreased respiratory functions during surgery, and conversion to open surgery due to problems with the pneumoperitoneum was not required in this study. An intraperitoneal pressure of 10–12 mmHg, which is normal, was kept during surgery in the present study. However, we sometimes selected an intraperitoneal pressure of 8 mmHg if a lower cardiopulmonary reserve was expected to lessen the negative effect of pneumoperitoneum on cardiopulmonary function. In addition, we usually reconstructed the alimentary tract through a small upper middle line incision, which reduces the time for maintaining the pneumoperitoneum. These conditions might result in less intraoperative pneumoperitoneum-related complications, and allow LAG to be performed safely in elderly patients.

There are some limitations associated with the present study. The feasibility of performing LAG in elderly patients with severe comorbidity was not investigated because patients with severe cardiac disease (greater than New York Heart Association class II) or pulmonary disease (greater than Huge–Jones grade IV) were excluded in the present study. However, LAG might be feasible in these patients if performed by an experienced surgeon, as it is possible that postoperative respiratory function would be less disturbed and early mobility could be achieved. Furthermore, only short-term outcomes were evaluated in the present study. The long-term outcomes of elderly patients still remain unclear. These outcomes need to be investigated in the future.

In conclusion, the present study revealed satisfactory early surgical outcomes after LAG in elderly patients provided that the patients were selected carefully. In addition, lower intraperitoneal pressure and shorter operation times should be achieved whenever possible. In these situations, LAG could be indicated and should be considered as a treatment of choice in elderly patients.

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Behavior of the Infection by *Helicobacter pylori* of the Gastric Remnant After Subtotal Gastrectomy and Roux-en-Y Anastomosis for Benign Diseases

Attila Csendes · Gladys Smok · Ana María Burgos

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Abstract
Introduction Reinfection by *Helicobacter pylori* of the gastric remnant after partial gastrectomy has been implicated in the development of gastric cancer at the gastric stump.
Objective The aim of this study is to determine the rate of infection by *H. pylori* after partial gastrectomy and Roux-en-Y anastomosis for benign disease.
Materials and Methods A total of 79 patients with long segment Barrett's esophagus were submitted to vagotomy, antireflux surgery, two thirds distal gastrectomy, and Roux-en-Y anastomosis 70 cm long. In all preoperative biopsy samples were taken from the antrum. After surgery, four endoscopic studies were performed in different periods of time. Mean follow-up was 98 months after operation (60–240).
Results Three groups of patients were identified: (a) group 1, 43 patients (54%) who had no preoperative infection by *H. pylori* and remained so late after surgery; (b) group 2, 21 patients (27%) who had no preoperative infection by *H. pylori* but presented infection of the gastric remnant that increased parallel to the length of follow-up; (c) group 3, 15 patients (19%) who presented infection by *H. pylori* before surgery. From them, 11 showed reinfection of the gastric remnant, while four patients had no reinfection.
Conclusion After partial gastrectomy and Roux-en-Y anastomosis for benign disease, there are three different patterns of behavior regarding reinfection or not by *H. pylori*. A total of 41% of patients presented *H. pylori* reinfection at the gastric remnant after Roux-en-Y anastomosis, which increased parallel to the length of follow-up.

Keywords *Helicobacter pylori* · Subtotal gastrectomy · Roux-en-Y loop

Several authors have implicated a significant role for *H. pylori* infection of the gastric remnant after partial or subtotal gastrectomy for benign or malignant diseases in the development of gastric cancer late after surgery.[1–4] Even an eradication therapy has been proposed in order to decrease this eventual complication.[1,5] This was specially seen in patients submitted to Billroth I (BI) or Billroth II (BII) anastomosis.

After Roux-en-Y reconstruction, conflicting results have been published. There are authors who reported increased rate of infection after Roux-en-Y anastomosis,[2] similar proportion to BI or BII gastrectomy,[6] or less infection than Billroth anastomosis.[7]

The purpose of this prospective study was to determine the role of infection by *H. pylori* of the gastric remnant after partial or subtotal gastrectomy for benign disease, evaluated several times by biopsy samples after surgery.

Material and Methods

1. *Patients studied*. Patients included in this study are part of a prospective clinical trial that begun on 1987 and was related to the surgical treatment of patients with Barrett's esophagus.[8,9] They were selected from patients who had at least five or more years of follow-up.

A. Csendes (✉) · G. Smok · A. M. Burgos
Clinical Hospital University of Chile,
Santiago, Chile
e-mail: acsendes@redclinicauchile.cl

All patients gave their consent to be included in this investigation. There was no special exclusion in this study except that they had to have preoperative evaluation also.

2. *Endoscopic procedure*. As part of the serial endoscopic control performed to these patients with Barrett's esophagus,[10] two or three biopsy samples from the gastric remnant were taken.
3. *Histological analysis*. The biopsy samples were immediately fixed in paraffin and stained by hematoxylin–eosin. For this particular study, only the presence or absence of *H. pylori* will be reported. The complete and complex histological findings are not the purpose of the present study and have been reported elsewhere.[11]
4. *Surgical technique*. The complete details of the surgical steps have been extensively published previously.[8,9] Basically, patients are submitted to vagotomy, antireflux procedure, two thirds distal gastrectomy, and Roux-en-Y anastomosis 70 cm long.

Results

A total of 79 patients followed more than 5 years and all with preoperative evaluation were included in this study. All details respect to symptoms, and laboratory findings including manometry, 24-h pH monitoring, and 24-h bile monitoring have been extensively reported elsewhere.[10] They had a mean age of 47.9 years (16–70). They were 40 women and 39 men. The mean follow-up of the whole group was 98 months after operation (60–240).

According to the preoperative findings of *H. pylori* at the antrum and the behavior of reinfection or not of the gastric remnant after surgery, patients were divided in three groups, with their main clinical characteristics shown in Table 1.

a. Group 1, 43 patients (54%) who had no preoperative infection by *H. pylori* and remained in the same situation of the late follow-up.
b. Group 2, 21 patients (27%) who showed no preoperative infection by *H. pylori* but presented infection of the gastric remnant at different moments of the follow-up.
c. Group 3, 15 patients (19%) who presented infection by *H. pylori* before operation.

There were no differences in age and gender comparing the three groups. The length of follow-up was similar, up to 20 years. Almost four postoperative endoscopies and biopsy samples were taken in each group, but all had at least three postoperative endoscopies, and 16 patients (20%) had five or more postoperative endoscopies.

Table 2 shows the rate of infection of the gastric remnant in the three groups of patients. Group 1 showed no infection of the gastric remnant late after surgery. Group 2, patients who had no *H. pylori* infection before surgery, showed a progressive increase in the rate of infection by *H. pylori*, according to the follow-up. At 96 months after surgery, 90% had presence of *H. pylori* at the gastric remnant. Two patients presented infection by *H. pylori* 168 and 240 months after surgery. Group 3 of 15 patients corresponded to those with presence of *H. pylori* before operation. Among 11 of them, reinfection occurred, while four patients persisted free of infection late after surgery. The curve of reinfection is similar to patients of group 2. Figure 1 shows the behavior of all three groups according to the length of follow-up.

Discussion

The results of the present study suggest that, after partial of subtotal gastrectomy, with resection of the antrum, where *H. pylori* is mainly located, three different patterns of behavior can be seen in respect to the probability of reinfection by *H. pylori* or not. The purpose of the present study was neither to evaluate the complex and different histologic changes of fundic mucosa after gastrectomy with or without the presence of *H. pylori*, which has been analyzed extensively elsewhere,[11] nor to report clinical and laboratory results after this operation of vagotomy, antrectomy, and Roux-en-Y loop for Barrett's esophagus, which also have been published extensively.[8,9,11] Therefore, we focused only in the behavior of the infection by *H. pylori* after partial gastrectomy.

Table 1 Main Characteristics of Patients with Partial Gastrectomy and Roux-en-Y Anastomosis According to Presence or Not of *H. pylori* Infection Before Surgery

	H. pylori infection before surgery			
	Group 1 (−)	Group 2 (−, +)	Group 3 (+)	*p* value
No. of patients	43	21	15	
Mean age (range)	49.5 (24–70)	44.9 (16–68)	49.7 (36–72)	n.s.
Women	25	8	7	n.s.
Men	18	13	8	
Length of follow-up (months)	99 (60–206)	95 (60–240)	96 (60–180)	n.s.
No. of postop endoscopies/patient	3.7	3.6	4.2	n.s.

n.s. not significative, *postop* postoperative

Table 2 Behavior of the Rate of Infection of Gastric Remnant by *H. pylori* After Partial Gastrectomy

Infection by *H. pylori*	Group 1, *n*=43	Group 2, *n*=21	Group 3, *n*=15
Before operation	0	0	100%
After operation (months)			
12	0	2 (10%)	5 (33%)
24	0	4 (19%)	6 (40%)
48	0	10 (48%)	8 (53%)
60	0	14 (67%)	11 (73%)
96	0	19 (90%)	11 (73%)
>120	0	21 (100%)	11 (73%)

Previous studies are very few and have the same problems: (a) The majority of the publications are related to partial gastrectomy after early or advanced cancer,[1,2,4–7,12] (b) all studies refer to only one endoscopy and biopsy samples after surgery, and (c) the majority of the studies are done 3 to 12 months after surgery, and very few have been performed years after surgery for benign diseases.[3,4,13]

We have tried to overcome some of the difficulties. First, we performed a prospective consecutive evaluation before and late after surgery in a homogenous group of patients with benign disease. Second, we performed nearly four postoperative endoscopic and bioptic studies, which we believe is the major strength of this study.

The first author to postulate some pathogenic effect of *H. pylori* after partial gastrectomy was Dixon in 1989.[14] He postulated that bile reflux was universally related to the presence of *H. pylori* because this organism does not tolerate the presence of bile reflux; therefore, he thought that gastritis due to bile reflux and gastritis due to *H. pylori* infection were different entities. O'Connor[15] demonstrated that *H. pylori* may reinfect gastric remnant after partial gastrectomy. Later, there has been a long debate whether the presence of bile reflux promotes or avoids the probability of reinfection by *H. pylori*. Some authors postulate more reinfection after Roux-en-Y anastomosis,[2] some similar proportion,[6] and some less reinfection compared to Billroth I or II.[7] However, the majority of the studies are related to Billroth I or II anastomosis and the possibility of developing cancer of the gastric remnant late after surgery. The rate of reinfection of the gastric remnant after partial gastrectomy and Billroth II anastomosis has been 39%,[2] 29%,[3] 59%,[5] 65%,[6] and 55%.[7]

Even some authors have postulated that *H. pylori* is responsible of the appearance of cancer of the gastric remnant late after surgery.[3,4] Giuliani et al.[3] performed in 151 gastrectomized patients an endoscopic and histologic study 25 years after surgery. They found 29% of *H. pylori* infection after Billroth II and postulate that both *H. pylori* and enterogastric reflux may have a synergistic causal role in the development of gastric cancer. Sloane et al.[4] studied a very selected group of 73 patients after partial gastrectomy 32 years after surgery and found 20% of carcinoma in the gastric remnant. Obviously, this was a very selected group and does not represent the total group of patients operated for benign disease. Due to this hypothesis, some authors have postulated to perform eradication of *H. pylori* if it is found in an endoscopic study.[1,5] They published 70% eradication with dual therapy and between 83% and 90% with triple therapy.

However, we disagree with this hypothesis. Patients with Roux-en-Y reconstruction have almost the same rate of infection by *H. pylori* than after Billroth II reconstruction.[2,6,11] In our previous study, we observed 57% of infection by *H. pylori* after Billroth II and 42% after Roux-en-Y loop, which was not statistically significantly.

In the present study, we found again 41% of reinfection of the gastric remnant after partial gastrectomy. Therefore, the main difference with Billroth II is the absence of intestinal reflux into the gastric remnant, which is able to produce intestinal metaplasia and probably carcinoma at the gastric remnant. We believe that bacterial overgrowth of enteric fecal bacteria together with bile reflux may be the responsible of the appearance of gastric stump carcinoma. Up to now, after more than 20 years of follow-up, we have never seen carcinoma of the gastric remnant after Roux-en-Y reconstruction, similar to what has been published by other authors.[16,17] Therefore, the question whether to treat or not the infection by *H. pylori* on these patients is open. Up to now, due to the fact that no cases with gastric stump cancer after Roux-en-Y anastomosis have been described, either in the literature or in our patients, our policy has not been to eradicate it 100%, and there are serious collateral effects of the antibiotics in nearly 30% of the patients.[18]

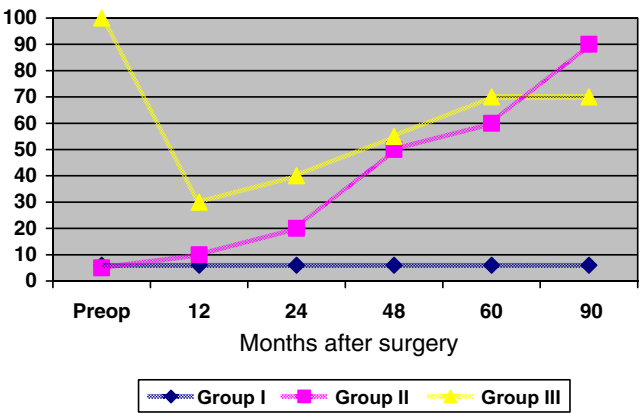

Figure 1 Behavior of the infection or not of the gastric remnant by *Helicobacter pylori* before and late after surgery.

Probably, the most interesting finding that has never been published before is the behavior of the "re-infection" or not by *H. pylori*, according to whether it was present before surgery or not. This was possible due to the performance of nearly four endoscopic and histological studies in all patients after surgery. In our study, a total of 39% of patients had reinfection by *H. pylori* after surgery. However, we could demonstrate three different behaviors:

a. Nearly 55% of the patients had no *H. pylori* infection before surgery and remained negative along the late follow-up.
b. Nearly 27% of the patient who had no infection before surgery and showed a progressive increase in the rate of infection of the gastric remnant after surgery, reaching 90% of the infection 8 years after surgery. This shows a parallel increase of reinfection according to the length of follow-up.
c. Nearly 19% of the patients had presence of *H. pylori* before surgery at the antrum. They were not treated by eradication because 60% distal gastrectomy was performed, including the antrum and therefore, eliminating the infection by *H. pylori*. In these patients, the presence of *H. pylori* at the remaining fundus was 33% 1 year after surgery, and reinfection rate increased progressively up to 5 years after surgery, when it remained stable, because four patients showed no *H. pylori* at the gastric remnant. This behavior has not been described before; therefore, we neither have comparison with other publications nor know if these findings will be reproducible or not in other surgical units. We urge that other groups could perform such a study in order to delucidate the real role of *H. pylori* infection at the gastric remnant and the possible carcinogenetic role, which we do not believe.

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Clostridium difficile Infection: A Surgical Disease in Evolution

Joshua L. Hermsen · Cosmin Dobrescu · Kenneth A. Kudsk

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Abstract
Introduction Several recent publications suggest an increase in the incidence of *Clostridium difficile* colitis. However, such studies commonly lack denominators over which to index this rise. There is also concern in the literature that disease virulence is increasing.
Methods Billing, admission, operative, and infection databases at a single tertiary care center identified patients admitted from 1990 to 2006 with a diagnosis of *C. difficile* infection. Grouped by era, case numbers were indexed against overall hospital, operative, and laboratory volumes. *C. difficile* colectomy cases were individually examined and analyzed.
Results The number of hospitalized patients diagnosed with *C. difficile* colitis increased in a linear fashion during the study period (1990, 14 cases; 2006, 927 cases). The colectomy per *C. difficile* case ratio did not change over the study period (era 1, 0.17%; era 2, 0.20%; era 3, 0.16%). Thirteen patients underwent colectomy with 54% surviving. The increase in patients admitted with a diagnosis of *C. difficile* was significantly associated with hospital volume ($p=0.04$), operative volume ($p<0.001$), and lab testing volume ($p=0.008$).
Conclusion The number of *C. difficile* patients admitted to our hospital is rising at an alarming rate. This reflects national trends and urgent action seems warranted to prevent a *C. difficile* epidemic.

Keywords *Clostridium difficile* · Colitis · Colectomy

Introduction

Clostridium difficile is a gram-positive, anaerobic, spore-forming bacillus which manifests a spectrum of disease, ranging from asymptomatic carrier to *C. difficile*-associated diarrhea to pseudomembranous colitis (PMC) to toxic megacolon with septic shock and death. Infection can begin with small innocula of difficult-to-eradicate spores, which germinate in the host colon. The first reported case of PMC was in 1893 in a 22-year-old woman following gastric polyp resection.[1] In 1943, penicillin was found to induce a lethal penicillin-resistant bacterial infection now presumed to be *C. difficile*.[2] Researchers attributed PMC to a "local toxin" in 1965[3] and described clindamycin-induced PMC in the mid 1970s.[4] Isolation of *C. difficile* toxin provided the biologic link between antibiotic use, unchecked toxin-producing Clostridial overgrowth, and the clinical phenotype known today as *C. difficile*-associated diarrhea.

PMC is a toxin-mediated colonic injury pattern usually caused by *C. difficile*. Two toxins, enterotoxin A and cytotoxin B, cause the severe colonic and systemic illnesses.[5] Typical symptoms include foul smelling diarrhea, fever, and abdominal pain which range from mild disease to fulminant colitis. The process usually occurs with anteced-

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K. A. Kudsk
Veterans Administration Surgical Services, William S. Middleton Memorial Veterans Hospital,
Madison, WI, USA

J. L. Hermsen · C. Dobrescu · K. A. Kudsk (✉)
Department of Surgery, University of Wisconsin-Madison College of Medicine and Public Health,
600 Highland Avenue, H4/736 CSC,
Madison, WI 53792-7375, USA
e-mail: kudsk@surgery.wisc.edu

ent antibiotic use, carries a significant (~20%) rate of recurrent diarrheal illness,[6] and progresses to toxic megacolon in up to 3% of cases.[7] In mild cases, the disease responds to supportive therapy including discontinuation of offending antibiotics, avoidance of narcotics and anti-diarrheal agents, and maintenance of fluid/electrolyte intake. More severe cases require hospitalization for intravenous hydration. A minority of patients (~3%) with *C. difficile*-associated diarrhea develop toxic megacolon. This is a grave disease requiring surgical intervention with a reported mortality rate of 25–40%.[7]

Over the last 3 years, investigators in the US, Canada, and the UK reported increased *C. difficile* rates associated with hypervirulent strains.[8,9] In the US, the estimated colonization rate of hospitalized adults with *C. difficile* is 383 cases per 100,000 hospital discharges.[10] Other reports estimate the incidence of *C. difficile* colonization to be 1% in patients with hospital stays <1 week and 50% if hospital stay exceeds 4 weeks.[11] Additional treatment charges in patients acquiring *C. difficile* infection average over 75,000 US dollars/patient.[12]

Despite study and observations of specific intervention (s) on *C. difficile* infection rates,[13–19] little attention has been paid to long-term trends in disease incidence until recently. Due to a perception of increased refractory *C. difficile* disease requiring colectomy, we investigated the incidence at a major tertiary referral hospital and hypothesized that the number of patients admitted with a diagnosis of *C. difficile* and the number of colectomies performed for fulminant *C. difficile* PMC increased over the last 16 years. Ricciardi et al. recently described such a trend using the Nationwide Inpatient Sample database.[10] One weakness of that study was the lack of denominating factors that may have influenced the observed trend of increasing disease incidence over time. This study evaluates the relationship of refractory *C. difficile* infections indexed by the number of at-risk patients, number of operative cases performed, and number of *C. difficile* assays.

Methods

The Institutional Review Board for Human Subjects at the University of Wisconsin-Madison approved this study. De-identified electronic and paper records of study patients with PMC who underwent operative intervention were examined. Billing, admission, and infection control databases at the University of Wisconsin Hospital (a 465-bed academic tertiary care center) were queried to identify all patients admitted to the hospital with a current or previous (and thus at risk for recurrent disease) diagnosis of *C. difficile* between January 1, 1990 and September 30, 2007. As available, hospital admissions data were analyzed for total hospital admission volume during the study period. Additionally, available data from laboratory and operating room databases were queried for total *C. difficile* tests performed and operative case volumes during the study period.

Patients assigned an ICD-9 diagnosis of *C. difficile* pseudomembranous colitis (008.45) were cross-referenced with patients undergoing colonic surgery (all study years) to identify those with possible fulminant, refractory *C. difficile*. Fulminant, refractory PMC was defined as PMC in a patient with hemodynamic instability. Review of the clinical chart confirmed all diagnoses with one or more of the following indicators: positive *C. difficile* toxin assay, positive colonoscopy, surgical pathology specimens, CAT scans, or autopsy. Due to small annual numbers, surgically treated patients were grouped into three time periods: 1990–1995, 1996–2000, and 2001–2006. The relationships between hospital admission volume, operative case volume, and *C. difficile* laboratory testing volume on the number of *C. difficile*-positive patients admitted and colectomy for fulminant *C. difficile* colitis were analyzed by pairwise linear regression analysis.

Results

Data regarding number of patients admitted to the hospital carrying a diagnosis of *C. difficile* infection and the number of colectomies performed for refractory fulminant *C. difficile* PMC were available for the entire period of study. Data regarding the total number of *C. difficile* tests performed were available from 2001 to 2006. Prior laboratory testing data were unavailable due to a change in lab database management during 2000. Total hospital admissions data were available between 1999 and 2006 and annual operative volume data were available since 1993.

A near-linear increase in patients admitted to the hospital carrying a diagnosis of *C. difficile* infection occurred over the study period. This reflects an increase from 14 such patients in 1990 to 927 patients in the first 9 months of 2006. If grouped by era, this increase is a straight line (Fig. 1, $r^2=0.999$).

Surgeons recommended colectomy for fulminant *C. difficile* colitis for 18 patients during the study period. Three patients declined operation and expired after institution of comfort care measures. Fifteen patients underwent operation identified by the following ICD-9 colectomy procedure codes: 45.79 (partial/subtotal), 45.72 (cecal), 45.75 (left colon), 45.71 (multiple segmental), 45.73 (right colon), 45.76 (sigmoid), 45.8 (total), and 45.74 (transverse colon). Two patients received non-colectomy operations (one transverse colostomy and one cecostomy) and were excluded from this analysis.

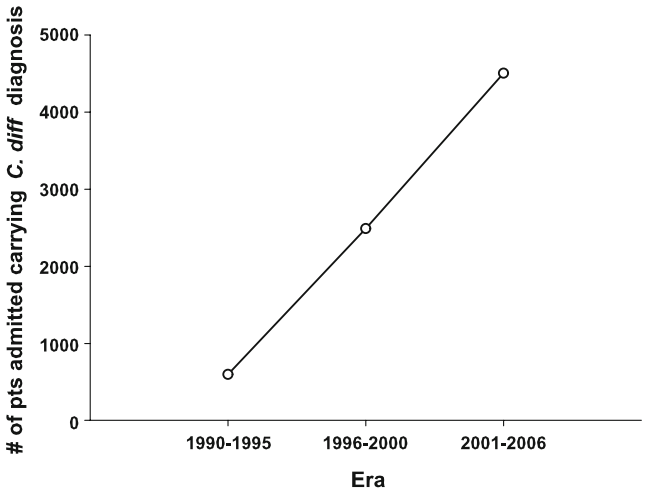

Figure 1 Number of *C. difficile*-positive patients admitted to hospital during the study period.

Thirteen patients underwent total or subtotal colectomy for refractory fulminant PMC during the study period. The mean age of colectomy patients was 56.4±19.9 years and 54% were male. The incidence (by era) increased in parallel with the increase in number of patients admitted carrying a *C. difficile* diagnosis (Fig. 2, r^2=0.993). Interestingly, the ratio of colectomies to *C. difficile*-positive patients did not change over time: 1990–1995=1 colectomy/598 patients (0.17%); 1996–2000=5 colectomies/2,486 patients (0.20%); 2001–2006=7 colectomies/4,504 patients (0.16%), for an average incidence of one colectomy per 583 patients admitted to the hospital with a diagnosis of *C. difficile* (Table 1, 0.17%). Medical comorbidities of these patients are shown in Table 2.

Antecedent antibiotic use (13/13) and exogenous immunosuppression (7/13) preceded development of fulminant disease in patients requiring surgery. Chronic renal insufficiency or end stage renal disease was common (5/13, 38%). Nearly all patients (11/13, 85%) received acid suppression with H_2 blockade or proton pump inhibitors. Most patients also had a recent (within 30 days) history of surgery (8/13, 62%).

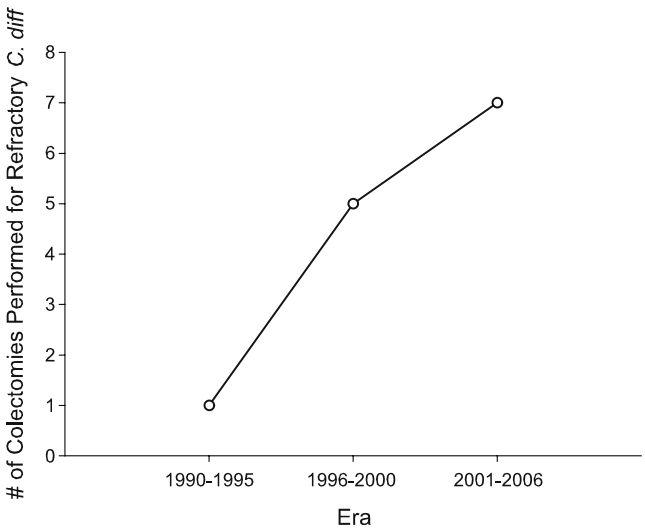

Figure 2 Number of colectomies for *C. difficile* colitis during the study period.

Table 1 Ratio of *C. difficile*-positive Admissions/Colectomy for Refractory C. *difficile*

Era	# *C. difficile* (+) admissions	# Colectomies	Colectomy/ test ratio
1990–1995	598	1	0.17
1996–2000	2,486	5	0.20
2001–2006	4,504	7	0.16
Overall	7,588	13	0.17

Diagnostic features included *C. difficile* toxin positivity in 92% (12/13) and leukocytosis in 85% (11/13, Table 3). Clinicians noted peritonitis in 46% (6/13) of patients. Most (8/13, 62%) had developed acute renal failure and were vasopressor dependent (9/13, 69%) prior to operation (Table 3). Time from patients' first diagnosis of symptomatic *C. difficile* infection to operation varied from 1–138 days (mean 23 days, median 5 days). The time from acute diagnosis (whether initial or recurrent) of *C. difficile* colitis to operation averaged 3 days (range 1–8). Seven patients (54%) had received prior antibiotic treatment specifically for *C. difficile* colitis. Colonoscopy revealed pseudo-membranes in 54% (7/13) of patients and CT scan was diagnostic of colitis in 62% (8/13) of patients.

All colectomy patients initially survived operative intervention but 6/13 (46%) died post-operatively. No significant difference in survival over the three time periods was observed although a trend towards increased survival following colectomy was noted over time: 1990–1995=1/1 (100% survival); 1996–2000=1/5 (20% survival); 2001–2006=7/8 (88% survival). Yearly total hospital admissions increased 9% (21,039 to 22,860) from 1999 to 2006. Yearly total operative volume increased 58% (14,230 to 22,520)

Table 2 Demographics and Comorbidities of Colectomy Patients

Demographics and comorbidities	
Age	56.4±19.9
Gender	54% male
HTN	31%
CAD	38%
COPD	23%
Immunosuppressed	54%
CRI/ESRD	38%
Acid suppressed	85%
Recent operation	62%

HTN, hypertension; *CAD*, coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *CRI*, chronic renal insufficiency; *ESRD*, end stage renal disease

Table 3 Diagnostic and Clinical Features of Patients Undergoing Colectomy for *C. difficile* Colitis

Pt.	Toxin+	Scope+	CT+	Pre-op WBC	Peritonitis	Pressors	ARF	Perforated	Survival
1	+	+	−	51.2	−	+	+	−	−
2	+	+	+	32.1	−	+	+	−	−
3	+	+	−	15.2	+	+	+	−	−
4	+	+	−	5.4	−	−	−	−	+
5	−	+	−	56.6	−	−	−	−	+
6	+	−	+	0.4	+	+	−	−	+
7	+	−	+	44.8	+	+	+	−	+
8	+	+	+	38.7	+	−	+	−	+
9	+	−	+	10	−	+	+	−	+
10	−	−	+	41.7	−	−	−	−	+
11	+	+	−	31.2	−	+	−	−	−
12	+	−	+	45.3	+	+	+	−	−
13	+	−	+	13.7	+	+	+	−	−
Total	85%	54%	62%	29.7±18.7	46%	69%	62%	0%	54%

from 1993 to 2006. Laboratory testing for *C. difficile* increased 59% (1,720 to 2,741) from 2001 to 2006.

Because admission, laboratory, and operative databases were incomplete during the study period, a valid multivariant linear regression analysis was impossible. However, pairwise correlation analysis was performed using available data. Overall, the data was highly co-linear. The number of patients admitted with a *C. difficile* diagnosis was the only factor significantly associated with the increase in colectomies performed (Table 4, $p=0.03$). However; as Table 4 also shows, the increase in number of positive patients was associated with the following factors: number of tests performed ($p=0.008$), hospital admissions ($p=0.04$), and operative volume ($p<0.001$).

Discussion

Between 1990 and September 2006, the number of patients developing or admitted to our hospital with a diagnosis of *C. difficile* increased dramatically. These data support our hypothesis, and other recently published reports, that the incidence of this disease is rising very rapidly. Correspondingly, the increase in *C. difficile* incidence results in more emergent colectomies for refractory *C. difficile* PMC. Our experience argues against increasing disease virulence since the ratio of operative interventions to positive toxin tests remained stable during the study period.

Table 4 Factors Influencing Number of C. *difficile* (+) Patients Admitted and Colectomy Rates

Variable	Vs. # of C. *difficile* (+) pts. admitted	Vs. colectomies
# of + *C. difficile* (+) pts. Admitted	−	0.03*
Total hospital admissions	0.04*	0.13
Operative volume	<0.001*	0.43
No. of *C. difficile* tests performed	0.008*	0.24

There appear to be multiple reasons for this increase in *C. difficile* and its complications. Overall hospital, surgical, and laboratory test volume were examined to explore possible associations with the increase of this diagnosis. The association between admission and operative volumes and *C. difficile* is somewhat intuitive in that as more patients are tested and treated, any given common disease process will be seen more frequently. Total operative volume might *distinctly* influence the incidence of this disease since antibiotic guidelines to reduce surgical site infections have led to more patients receiving "prophylactic" antibiotics prior to most surgical procedures. There is evidence that even a single dose of perioperative antibiotics can alter colonic flora and convert approximately 20% of patients from *C. difficile* negative to positive by culture and toxin although symptomatic disease may not occur.[20] Consistent with other studies, all patients requiring colectomy for refractory *C. difficile* received antecedent antibiotics and a majority of patients were immunosuppressed.

Post-surgical (as well as non-surgical) inpatients remain at risk of contracting the disease simply by their hospital-bound status since *C. difficile* is readily transmissible by fomites, prolonged antibiotics are frequently administered, and environmental eradication and control techniques remain imperfect.[21–23] Perhaps even more intuitive is the association between increased testing and increased number of positive patients, suggesting that the more one looks for *C. difficile*, the more one finds it. Likely this contributes to

a cycle of "self-fulfilling prophecy" as increased testing yields more positives and more positives lead clinicians to consider the diagnosis and test for it more frequently. This phenomenon remains unclear, however, as data from other institutions both support[24] and refute[25] this line of reasoning.

Fulminant, refractory *C. difficile* is a potentially lethal disease. Byrn et al. recently published a single center experience to identify risk factors predictive of mortality in patients undergoing colectomy for *C. difficile colitis*.[26] Our mortality of 46% exceeded the 34% reported by Byrn et al. but there are several potential reasons for this. First, our colectomy rate of 0.17% was lower than the rates reported in studies by Ricciardi (0.28% colectomy rate) or Byrn et al. (1.3% colectomy rate). The decision to operate probably differs between the various sites since hemodynamic instability usually preceded the decision to operate at our institution. Despite a lower resection rate, only the sickest patients were subjected to surgery with a resulting higher mortality rate. Institutions that operate earlier may experience lower mortality due to more frequent operations on less ill patients that may have responded to aggressive medical therapy, i.e., they operated on less ill individuals resulting in an overall reduction in mortality but at the expense of unnecessary colectomies. Since clinical judgment guides the decision to operate without defined guidelines of "medical failure" for "refractory *C. difficile* colitis", it is difficult to state which approach is preferable. Secondly, there appear to be differences between our patient populations with respect to significant pre-existing pulmonary (Byrn et al., 8%; this study 23%) and renal (Byrn et al., 7%; this study 38%) disease system comorbidities. Overall, the trend demonstrated in our study agrees with several recent publications on this topic.

We found no evidence of the hypervirulent strain of *C. difficile* recently reported by other centers since our constant colectomy rate over time suggests that, while the incidence of disease may be rising, the virulence of "normal" bacterial strains remains unchanged over time. Even so, the increasing burden of this disease almost certainly increases overall morbidity, workload, and charges/costs. While not currently included in the list of hospital acquired infections that Medicare will cease reimbursement for beginning October 1, 2008, this is a disease that is largely hospital acquired and a current draft proposal of factors influencing reimbursement considers *C. difficile* a non-reimbursable complication.

No attempt was made to examine trends in antibiotic or antisepsis use and/or protocols during the study period. Many others have studied the effects of antibiotic type and usage patterns on *C. difficile* disease; it seems clear that the "antibiotic variable" influences this disease.[8,16,18–20,27–29] During the final period of study (2001–2006), our hospital instituted several generalized protocols to define, restrict, and monitor antibiotic usage resulting in an overall hospital-wide trend of decreased antibiotic use (personal communication with Barry Fox MD, hospital infection control officer). We cannot address more specific observations on possible relationships between antibiotics and *C. difficile* at our hospital during this study period.

One weakness of this study is that we used admission ICD-9 codes to identify patients admitted with a diagnosis of *C. difficile*. Patients carry this diagnosis over time so some patients counted in the study may have been admitted for reasons unrelated to a prior infection. Also, a patient admitted more than once during the study period would have been counted at each admission since they remained at risk at each admission. If so, our data may overestimate the true incidence of *C. difficile* infections in *individual* patients at our institution. Alternatively, a diagnosis of *C. difficile* may be an indicator of a sicker patient population requiring frequent readmissions and overall increased medical care.

Conclusions

Regardless of current study limitation, there exists a rapidly growing number and/or frequency of patients carrying a diagnosis of *C. difficile* being admitted to the hospital, needing medical attention, and utilizing ever-scarce health-care resources. Using the Nationwide Inpatient Sample Database, Ricciardi et al. recently showed a similar *national* upward trend in the incidence and prevalence of this disease. The trend we confirmed is alarming and likely occurring at many other hospitals. Aggressive study of this disease is urgently needed to prevent a *C. difficile* surgical epidemic.

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ORIGINAL ARTICLE

Laparoscopic Bile Duct Reexploration for Retained Duct Stones

L. T. Chiappetta Porras · E. D. Nápoli · C. M. Canullán · B. M. Quesada · J. E. Petracchi · A. S. Oría

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Abstract
Background Failure of endoscopic sphincterotomy (ES) for retained bile duct stones occurs in 4% to 10% of cases and was traditionally managed with open bile duct reexploration.
Methods This study uses retrospective analysis of a consecutive series of cases of laparoscopic bile duct reexploration for retained bile duct stones after unsuccessful ES.
Results Thirty-one cases were operated over a 7-year period. Seventy percent had a previous open cholecystectomy. Ten cases were successfully treated with a transcystic approach and 19 with laparoscopic choledochotomy. Two patients were converted to open surgery. Morbidity was 3.22% with no mortality.
Conclusion Laparoscopic bile duct reexploration can be safely performed and should be considered as an alternative to open surgery.

Keywords Bile duct stones · Laparoscopy · ERCP

Introduction

Endoscopic sphincterotomy (ES) is the treatment of choice for patients with retained bile duct stones after cholecystectomy. Failure rates of up to 10%, mostly because of incomplete bile duct clearance, have been described, and traditionally, open bile duct reexploration was offered to these patients.[1–3] Since there is good evidence coming from prospective and randomized trials about the safety and efficacy of laparoscopic surgery for choledocholithiasis,[4–6] we started an initial experience with laparoscopic bile duct reexploration for retained bile duct stones after unsuccessful ES.

The objective of this study was to evaluate the results obtained with this initial experience.

Material and Methods

We retrospectively reviewed the prospective data collection of a consecutive series of patients that underwent laparoscopic bile duct reexploration for retained bile duct stones after unsuccessful ES at A Tertiary Care Surgical Department.

Causes of unsuccessful ES included failure of cannulation, occurrence of complications that precluded endoscopic treatment, and incomplete bile duct clearance.

All patients underwent abdominal ultrasound with measurement of bile duct diameter and liver function test at the time of admission. Data analyzed included demographics, morbidity and mortality, success rate for bile duct clearance, operative times, and conversion rate.

L. T. Chiappetta Porras · E. D. Nápoli · C. M. Canullán · B. M. Quesada · J. E. Petracchi · A. S. Oría
Department of Surgery, "Cosme Argerich" Hospital,
Alte. Brown 240,
Buenos Aires, Argentina

L. T. Chiappetta Porras · A. S. Oría
Department of Surgery, University of Buenos Aires,
Buenos Aires, Argentina

B. M. Quesada (✉)
Talcahuano 944 9°A,
CP 1013 Buenos Aires, Argentina
e-mail: bmquesada@hotmail.com

Surgical Technique

Pneumoperitoneum was created with an open technique and a working pressure of 12 mmHg was used for every case. The operation started with three ports: a 10-mm umbilical port, a 5-mm upper right quadrant port and a 10-mm upper left quadrant port.

Adhesions were taken down with harmonic scalpel. Once the right upper quadrant was exposed, identification of the cystic duct stump was attempted. Intraoperative cholangiography was done through the cystic duct whenever possible or through a direct bile duct puncture with a butterfly needle. When the cystic duct was identified, a transcystic approach to the bile duct stones was attempted and included the use of Dormia baskets and the pharmacologic relaxation of the papilla with IV glucagon administration combined with saline solution flushing. Failure of the transcystic approach indicated laparoscopic choledochotomy. Stone extraction was done with Dormia baskets, instrumental maneuvers, or with a combination of both. All procedures were done under direct fluoroscopic guidance. Fiber-optic choledocoscopy was performed to confirm complete clearance of the bile duct after a laparoscopic choledochotomy in most cases. Primary duct closure (PDC) was performed after a normal fiber-optic choledocoscopy and when the bile duct fulfilled Mirrizzi's postulates, which include a bile duct diameter of at least 8 mm, the absence of papillary hypertension, and appropriate bile duct walls to hold sutures.[7] In the absence of fiber-optic choledochoscope for technical failure or when the bile duct did not fulfill Mirizzi's postulates, we closed the bile duct over a T-tube. These were closed after a normal cholangiogram 2 weeks and removed no earlier than 6 weeks after surgery. Suture material used was always 4.0 Vicryl (Ethicon, Somerville , NJ, USA). A hydraulic test through the cystic duct or the T-tube was always done after both types of bile duct closure to detect and treat any leak. A small diameter drain was always left in the right upper quadrant. In cases of giant biliary trees with multiple stones, we chose to perform a laparoscopic choledochoduodenostomy.

Incomplete bile duct clearance after laparoscopic choledochotomy indicated conversion to an open procedure.

Results

Between September 1999 and September 2006, 31 patients underwent laparoscopic bile duct reexploration after unsuccessful ES. Twenty-five were females (80%), with a mean age of 52 years (range 23 to 74 years). Twenty-nine patients (93.5%) underwent cholecystectomy at another institution and were referred for endoscopic treatment of retained bile duct stones. Twenty cases (70%) were open surgeries. The remaining two patients were operated at our hospital and both were laparoscopic cases. Liver function tests were abnormal in all cases, with a median bilirubin value of 8.5± 5.4 mg %. Ultrasound showed bile duct dilation in all cases, except for one, which had a transpapillary stent previously inserted at another institution.

Reasons of ES failure were in 22 cases (71%), incomplete stone extraction, and in 8 cases, (25%) the bile duct could not be cannulated. In one case (4%), the procedure was terminated because of significant bleeding during papillotomy.

In 26 cases (84%), intraoperative cholangiography was done through the cystic duct stump and in the remaining five cases (16%) through a bile duct puncture with a butterfly needle.

Retained bile duct stones were successfully removed through a transcystic approach in ten cases. In nine cases, the stones were removed with a Dormia basket and one case with flushing + IV glucagon. The remaining 21 patients required laparoscopic choledochotomy, mostly because of multiple and big bile duct stones. After complete bile duct clearance, primary duct closure was done in 16 patients, a choledochoduodenostomy in two, and a T-tube in the remaining patient. The remaining two patients were converted to an open procedure (6.5% conversion rate). Both cases had distally impacted stones bigger than 15 mm and were successfully managed with open bile duct exploration and T-tube insertion.

Mean operative time for transcystic approach was 80 min (range 60–105 min) and 120 min (80–160 min) for choledochotomy.

Mean hospital stay was 2 days for transcystic approach and 3.8 days for choledochotomy.

One patient developed a mild wound infection after open T-tube insertion, for a total morbidity rate of 3.22%. There was no morbidity in any of the laparoscopic cases. There was no postoperative mortality.

The mean follow-up is 42.5 months (1–84 months). No retained bile duct stone was detected during the follow-up period.

Discussion

ES is the treatment of choice for retained bile duct stones. Failure rates between 4% and 10% have been reported. The most common reasons cited are difficulties in cannulation, intradiverticular papilla,[8] and incomplete stone clearance.[1–3] Traditionally, these patients were managed with open bile duct reexploration and the laparoscopic approach was not considered.

The discussion of the results obtained in this series is limited because there are only two series dealing with

laparoscopic bile duct reexploration.[9,10] In Dixit et al.[9] experience, the reason for ES failure was incomplete stone extraction. All cases required laparoscopic choledochotomy finishing with two PDC and one with a T-tube insertion. In Chen et al. experience, a total of 26 cases underwent laparoscopic bile duct reexploration. Mean operative time (125 min) and conversion rate (3.84%) are similar to our results. In contrast to our experience, they report the occurrence of three cases (11.5%) of retained bile duct stones successfully removed through the sinus tract of the T-tube.

Laparoscopic bile duct reexploration can be started in most cases with only three trocars because the liver adherences to the anterior abdominal wall give sufficient exposure for a transcystic approach. In our experience, it was necessary to add another trocar only in cases requiring choledochotomy. The location of this additional port varied according to the case and the surgeon's preference, but most of the times, it was located at the right flank to help with the bile duct exposure by lifting the liver up. The same trocar can be use to take the T-tube out of the abdomen.

Cystic duct stump identification was possible in 84% of cases, usually at the cholecystectomy scar base. This allows intraoperative transcystic cholangiography and transcystic lithotomy in favorable cases. The transcystic approach effectivity was 30%, very low compared with our 76.3% in primary cases[11] and is justified by the bile duct stones characteristics, most of them being multiple and larger than 8 mm. This approach is ideal because morbidity, hospital stay, and mortality are significantly lower when compared to laparoscopic choledochotomy and open surgery.

Our results show that laparoscopic bile duct reexploration for retained bile duct stones is safe, with minimal morbidity and a high success rate in duct clearance, even in patients who had previously open cholecystectomy, with a high proportion needing only a transcystic approach. Special populations such as gastrectomized or bariatric surgery patients that have no easy access for the endoscope to the duodenum might benefit from this approach. Laparoscopic bile duct reexploration for retained bile duct stones after unsuccessful ES should be considered before offering open surgery.

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Surgical Resection Versus Radiofrequency Ablation in the Treatment of Small Unifocal Hepatocellular Carcinoma

M. Abu-Hilal · J. N. Primrose · A. Casaril · M. J. W. McPhail · N. W. Pearce · N. Nicoli

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Abstract
Background Hepatocellular carcinoma (HCC) has a high worldwide prevalence and mortality. While surgical resection and transplantation offers curative potential, donor availability and patient liver status and comorbidities may disallow either. Interventional radiological techniques such as radiofrequency ablation (RFA) may offer acceptable overall and disease-free survival rates.
Materials and Methods Sixty-eight cirrhotic patients matched for age, sex, tumor size, and Child–Pugh grade with small (1–5 cm) unifocal HCC were studied retrospectively to find determinants of overall and disease-free survival in those treated with surgical resection and RFA between 1991 and 2003.
Results Multivariate analysis using Cox proportional regression modeling showed that overall survival was related to tumor recurrence (p=0.010), tumor diameter (p=0.002), and treatment modality (p=0.014); overall p=0.008. Recurrence was independently related to the use of RFA over surgery (p=0.023) on multivariate analysis; overall p=0.034.
Conclusion Surgical resection offers longer disease-free survival and potentially longer overall survival than RFA in patients with small unifocal HCC.

Keywords Hepatocellular carcinoma · Radio frequency ablation · Resection

Introduction

Hepatocellular carcinoma (HCC) is a common cause of cancer mortality worldwide.[1,2] It has a high incidence in Southeast Asia and Africa as well as to a lesser extent in Europe and America.[1–3] Hepatic cirrhosis is the most widely recognized condition predisposing to the development of HCC[1,2], and worldwide, 90% of patients with HCC have chronic infection with hepatitis B or C. Its incidence is expected to rise and peak within the next 20 to 30 years mirroring the predicted worldwide epidemiology of viral hepatitis.

Orthotopic liver transplantation (OLT) is the optimal treatment for small-volume HCC in patients with favorable Child–Pugh A or B disease. This can increase 5-year survival up to 75–92%.[4–6] However, the small donor pool and the current guidance ("Milan criteria")[5] that only patients with solitary HCCs of a diameter less than 5 cm or three or fewer tumors of maximum diameter of 3 cm preclude OLT for many patients.

Resectional surgery is the next most effective curative treatment for HCC but this may not always be possible because of the characteristics of the tumor or the grade of cirrhosis in the background liver. Few cirrhotic patients are suitable for radical resection,[4,6–13] and recurrence rates are

M. Abu-Hilal · J. N. Primrose · M. J. W. McPhail · N. W. Pearce
Department of Surgery, HPB Unit,
Southampton General Hospital,
Southampton, UK

A. Casaril · N. Nicoli
Department of Surgery, Liver Surgical Unit, G B Rossi,
Piazzale Scuro,
Verona, Italy

M. Abu-Hilal (✉)
University Surgical Unit, F Level, Southampton General Hospital,
Tremona Road,
Southampton SO16 6YD, UK
e-mail: abu_hlal@yahoo.co.uk

high.[8,10,14] Therefore, parenchymal-sparing alternative or complementary techniques such as radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), percutaneous acetic acid injection (PAI), and cryotherapy have evolved. Radiofrequency ablation has been shown to be more effective than other percutaneous techniques such as PEI and PAI,[15,16] but its role as an alternative to surgery is still unclear. At present, there is only one study[17] which compares percutaneous techniques with surgical resection and three which compare RFA alone with surgery.[18–20]

The aim of this study is to compare the procedural morbidity, mortality, and long-term overall and disease-free survival of patients with hepatocellular cancer who did not undergo OLT and were treated with either surgical resection or RFA in two high-volume liver centers.

Materials and Methods

Patients were treated either in the hepatic unit of the Department of Surgery of Verona, Italy or the hepato-biliary surgical unit at Southampton General Hospital, UK between 1991 and 2003. Only tumors less than 5 cm were included as RFA is not effective in the ablation of hepatoma lesions above this size. All HCC patients meeting Milan criteria were considered for OLT, but if excluded on the basis of age, comorbidity likely to yield poor 5-year survival, alcohol recidivism, or patient choice was eligible for this study. Patients were divided into two groups according to the treatment they had received; group A consisted of patients who had been treated with surgical resection between 1991 and 2003; group B patients had been treated with RFA after its introduction in 1998. Patients were not randomized but allocated to resection or RFA on clinical grounds. The details of both groups for the case control study are shown in Table 1.

Table 1 Characteristics for Patients in Groups A and B

Variable	Group A (Surgery)	Group B (RFA)	*p* value
Number of patients	34	34	–
Mean age	67	65	0.588[a]
Sex (M/F)	26:8	27:7	1[b]
Child's score			
A	25	27	0.775[b]
B	9	7	
C	0	0	
Median tumor diameter (cm)	3.8 (1.3–5)	3 (2–5)	0.053[c]
Median follow-up (months)	43 (2–129)	30 (0–60)	0.017[c]
Median survival (months)	74	N/A	0.302[d]
Median disease-free survival (months)	35	9	0.028[d]

[a] Student's *t* test
[b] χ^2 test
[c] Mann–Whitney *U* test
[d] Log rank test

Therapeutic Techniques

Surgery

In general, a trans-parenchymal surgical technique was used guided by intraoperative ultrasound to identify tumor margins and segmental vascular pedicles. Resections were completed as needed as per tumor location aiming always for 1 cm of clear resection margin. The type and extent of the resection was based on tumor location, parenchymal condition, and patient's general condition and to some extent whether the resection was performed early or late in the study period. In the early period, more extensive radical resections were performed, but more recently, segmental resections were performed if acceptable resection margin could be guaranteed. Later, if a wedge resection with acceptable margins could be achieved, this was performed.

Percutaneous RFA

The technique has been described previously.[21] Between 1998 and 2003, a 460-kHz radiofrequency generator, with maximum power of 150 W and impedence range between 40 and 200 Ω (RITA Medical System, Mountain View, CA, USA) was used. All radiofrequency ablations were performed percutaneously. A repeat ultrasound was performed after the procedure to demonstrate the presence of a hyperechoic spherical area of coagulative necrosis with a diameter greater than the tumor's diameter.

Follow-up in both groups was with a combination of contrast-enhanced abdominal computed tomography scan and alpha fetoprotein levels. These were repeated after 1 month, then every 6 months for 2 years and then at least annually until the fifth year. In the group treated with RFA, the presence of partial or total contrast enhancement at the site of ablation was considered as local recurrence. Recurrences were treated when possible by further surgical resection, repeat RFA, or transarterial chemo-embolization.

Statistical Analysis

Patient data were retrospectively collated. Data gathered included age, sex, etiology of cirrhosis, tumor diameter, treatment method, biochemical profile to calculate Child–Pugh score, timing of intervention, and presence and timing of follow-up, recurrence, and death. Main end points were overall and disease-free survival.

Categorical data were compared using the χ^2 test, and measures of central tendency in parametric and nonparametric continuous datasets were compared using the Student's *t* test and Mann–Whitney *U* test, respectively. Survival and disease-free survival were calculated and presented using the Kaplan–Meier method and comparison of overall and disease-free survival performed (for each relevant stratum) using the log-rank test. Cox regression modeling was used in univariate and multivariate mode to calculate hazard ratios (HR), regression coefficients, and *p* values for independent variables on the dependent variables overall and disease-free survival. Only variables deemed significant or close to significant on univariate analysis were put forward to the multivariate stage. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) v 12 for Windows. Statistical significance was required at the 95% level.

Results

Ninety-eight patients [72 men, 26 women, mean age 67 (95% confidence interval, CI 65–69) years] treated for first presentation, small (1–5 cm) unifocal HCC were identified from our databases and their case notes re-examined. From this unmatched cohort, a second cohort of 68 nontransplanted patients appropriately matched for age, sex, etiology, tumor size, and Child–Pugh grade were identified for analysis. The etiology of the cirrhosis was viral in 59% of cases and alcohol in 31%, the remainder being hemochromatosis, mixed or idiopathic. All patients were graded according to the Child–Pugh classification as all treatments were performed prior to the introduction of Model for End-Stage Liver Disease (MELD) score: 76% were class A, 24% class B. The median diameter of the tumors was 3 (range 1–5) cm.

Treatment Morbidity and Mortality

The overall major complication rate was 21% (27% in group A vs 16% in group B, $p=0.085$). In group A, three patients developed postoperative hepatic failure, and in group B, one patient developed an artero-portal fistula after RFA.

Blood transfusion was required in three patients in group A and was not required in group B. The median duration of hospital stay was 16 [interquartile range (IQR) 12–25] days in group A and 3 (IQR 2–4) days in group B ($p<0.001$, Mann–Whitney *U* test). There was one treatment-related death in this series; in group B, a 65-year-old Child–Pugh B patient with a 3-cm subcapsular nodule in segment V died of complications of peritonitis due to colonic perforation caused by heat transmission after RFA.

Survival Analysis

Overall Survival

The median follow-up for the whole study group was 32 (IQR 19–43) months. In group A, it was 43 (IQR 19–89) months and 30 (IQR 13–40) months in group B ($p=0.017$, Mann–Witney *U* test). Overall, 61% of patients were still alive at the end of the follow-up. The median overall survival (Fig. 1) was 74 (95% CI 42–137) months in group A, but it was not attained in group B due to the difference in duration of follow-up for the two groups. The probability of overall survival at 1, 2, and 5 years was 91%, 81%, and 56% in group A vs 83%, 62%, and 57% in group B ($p=0.302$).

Disease-Free Survival

In total, 28 patients remained disease free (42%), while 40 had recurrence (58%). In group A, the median disease-free survival was 35 (95% CI 28–58) months and in group B 10 (95%CI 6–20) months ($p=0.028$); see Fig. 2. In group A, the probability of disease-free survival at 1, 2, and 5 years was 77%, 67%, and 28% and for group B 42%, 29%, and 21%, respectively. In group A, true local recurrence at the site of resection was documented in 4% of patients, while 57% developed new sites of primary disease within the liver. In group B, local recurrence at the RFA site was seen in 30% of patients, while a further 30% developed new primary hepatic disease away from the site of the treated

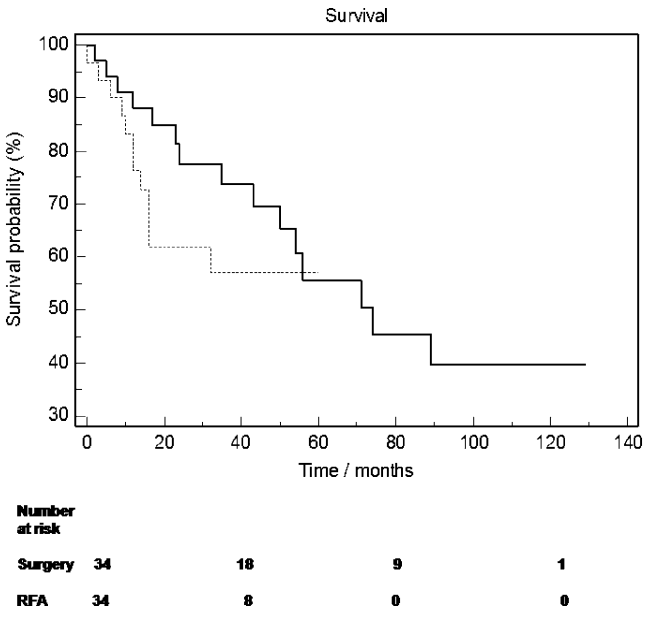

Figure 1 Overall survival for patients undergoing surgical resection (*heavy line*) or RFA (*dashed line*) for HCC ($p=0.302$).

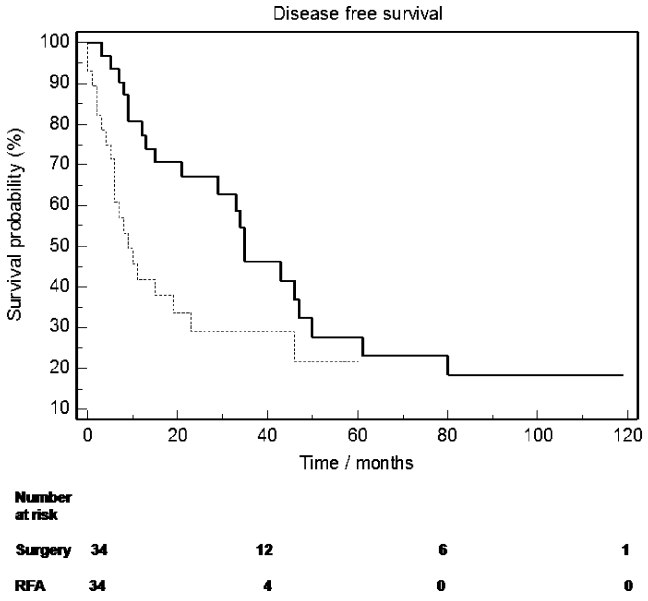

Figure 2 Disease-free survival for patients undergoing surgical resection (*heavy line*) or RFA (*dashed line*) for HCC (p=0.028).

lesion (p<0.001, χ^2 test). The shorter follow-up in group B should lead to caution in interpreting these results.

Univariate Analysis

On univariate analysis for overall survival age, sex, and Child Score did not achieve statistical significance for affecting survival, whereas tumor diameter, treatment method, and the presence of recurrence were associated with increased risk of death. In a similar analysis for disease-free survival, tumor diameter and treatment method were the only variables noted to have a significant effect.

Multivariate Analysis

On multivariate analysis using tumor size, treatment modality, and presence of recurrence, the most significant factor associated with death was the presence of hepatic recurrence (HR=5.4, p=0.010) Other independent risk factors for death identified on the multivariate analysis were: larger primary tumor nodule diameter (HR=2.5, p=0.003), treatment by RFA (HR=4.0, p=0.014). On multivariate analysis of disease-free survival using tumor size and treatment method, only treatment method retained its correlation with disease-free survival (HR=2.3, p=0.022, overall p for the regression model 0.034).

Other Analyses

In smaller tumors where surgery may be thought to be not as advantageous (≤3 cm) compared to larger tumors, median survival was not attained in either group, but median disease-free survival remained significantly different, being 47 months in group A and 8 months in group B (p<0.001).

As RFA is a relatively new procedure and the expertise and technical considerations may have changed during the course of the study, an analysis was performed to determine whether the main outcome measure were related to the number of procedures performed during the time-course of our study. Including procedure number in multivariate analysis of disease-free survival did lead to a significant correlation between disease-free survival (DFS) and procedure performed at a hazard ratio very close to unity (HR 1.03, p=0.003), but this was not replicated in a similar multivariate analysis for overall survival (Table 2). An analysis of overall and disease-free survival in both surgical and RFA groups for the first 25 procedures (group 1) and for later (26 to end of series) procedures (group 2) showed no statistically significant change in the relationship for overall and disease-free survival between the two groups (Table 3).

Discussion

Orthotopic liver transplantation is the gold-standard treatment in HCC with surgical resection a close second. Insufficient donor pool, patient comorbidity (or age in certain countries), alcohol recidivism, and extent of local disease are a cause for these treatment modalities to be impossible in a significant proportion of cases. Of the parenchymal-sparing procedures available, RFA has been demonstrated to be the most useful in early-stage disease for small (<5 cm), localized cancers.[15,22,23] Although the role of RFA when surgery is not possible is well established, its precise role as an alternative to surgery remains debatable.

Vivarelli et al.[18] retrospectively analyzed results for 158 nonrandomized cirrhotic patients, half treated surgically and half with RFA. Surgery demonstrated better results in 1- and 3-year survival, 83% and 65% vs 78% and 33%, and also in 1- and 3-year disease-free survival, 79% and 50% vs 60% and 20%, respectively. The authors noted the advantages of surgery to be more pronounced in Child A

Table 2 Multivariate Analysis of Covariates for Effect on Overall Survival

	Significance	HR	95.0% CI for HR	
			Lower	Upper
Diameter	0.002	2.46	1.38	4.38
Intervention (RFA v surgery)	0.014	3.98	1.33	11.84
Recurrence	0.010	5.39	1.51	19.24

Table 3 Multivariate Analysis of Covariates for Effect on Disease-Free Survival

	Significance	HR	95.0% CI for HR	
			Lower	Upper
Diameter	0.339	1.268	0.780	2.060
Intervention (RFA vs Surgery)	0.022	2.336	1.129	4.837

patients and in those with single, larger (>3 cm) tumors. Our message is similar and has comparable survival statistics (although disease-free survival at 1 year is lower in our cohort for RFA patients) in confirming the superiority of surgical resection, but in addition, we observed increased disease-free survival of patients undergoing resection even in the smaller tumor-size subgroup <3 cm. Since the overall message in this study is that surgery is the better treatment modality in the 1–5 cm tumor-size range, it should be emphasized that this is still true in the lower regions of this range. RFA at present should be considered as an acceptable alternative when surgery is not possible and not in patients who simply have a smaller tumor.

Wakai et al.,[17] in a similar study of 149 patients undergoing surgical resection or percutaneous ablation (either RFA, microwave ablation, or PEI) found that surgery (p=0.006) and smaller tumor size (p=0.017) were associated with better outcomes in a retrospective study of 69 months median follow-up. The study had similar design to the one presented here, but interestingly an analysis of tumor size with a cut-off of 2 cm found that surgical resection was more effective in the larger sizes. In our subgroup analysis, we find that the improved DFS of patients undergoing surgical resection is significant below tumor diameter 3.5 cm. This difference may be a reflection of both the racial differences between the studies (all patients in the Wakai et al. study were Japanese) and different ranges of tumor sizes and may be because three different percutaneous ablative therapies were used in the Japanese study. We preferred to use RFA alone given its proven survival benefit over other ablative therapies in early-stage small HCC. A similar retrospective Asian study[19] in 148 Child–Pugh A patients treated with surgery or RFA showed higher rates of local recurrence in the RFA group but no difference in overall and recurrence-free survival rates.

Only one randomized controlled trial[20] comparing surgery and RFA has been performed comparing Child–Pugh A patients with unifocal HCC less than 5 cm in diameter. Comparing 90 patients in each group, the trial could not detect a difference in overall and disease-free survival between patients treated with surgery or RFA. While KM curves were produced and 1-, 2-, 3-, and 4-year survivals calculated, p values for the log-rank test were not given, and multivariate analysis, while showing that only serum albumin was associated with a difference in survival, was not repeated for disease-free survival. This would be necessary to allow a more detailed comparison with the data presented.

Our study is one of the first to directly compare overall and disease-free survival between surgical resection and RFA alone using both log-rank test against Kaplan–Meier curves and Cox proportional regression modeling of likely determinants of survival and recurrence. The major finding in terms of overall survival following confounding is that surgery, smaller tumors, and no recurrence is associated with improved survival. In multivariate analysis of disease-free survival, the type of intervention is the only independent predictor of improved DFS. The main criticism of our study is its retrospective nature. Furthermore, it should not be read as suggesting surgical resection is a superior treatment modality to OLT in patients meeting Milan criteria.

The contrasting results between the studies discussed in this paper suggest the need for a randomized prospective trial comparing resection with RFA in unifocal HCC (either as a bridge to OLT or where OLT is not possible) to be performed in the Western Hemisphere where etiology of cirrhosis is likely to be more variable and across Child–Pugh classes where surgery may still be offered. This is the second retrospective European study comparing surgery and RFA in the treatment of small HCC, which in the absence of prospective data will help to guide present practice and guide scientific and ethical hypothesis generation for future prospective studies.

At present, it is widely agreed that surgical resection remains the better treatment for discrete, nontransplantable HCC in favorable patients. It offers the best overall survival, and RFA should be considered as the best available option when surgery is not feasible. However, the morbidity and mortality of liver resection in these difficult patients must be borne in mind and, with probe development and adjuvant maneuvers, RFA may yet prove to be equally effective. The use of both treatments can be supported in specialist, multi-disciplinary liver units where the choice of technique at present should be decided on a case-by-case basis.

Conclusion

Surgical resection remains the best treatment for small, unifocal nontransplanted HCC in favorable patients. It offers the best disease-free survival and, through this reduced recurrence, may offer improved overall survival.

RFA should be considered as the best available option when surgery is not feasible.

Summary

Radiofrequency ablation is a potential alternative to surgery in patients with hepatocellular carcinoma. Surgical resection and RFA are compared in 68 nontransplanted cirrhotic patients with small unifocal HCC. Surgery has a clear benefit in preventing recurrence and a small survival benefit which does not preclude future randomized trials.

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Relationship Between Provider Volume and Outcomes For Orthotopic Liver Transplantation

John E. Scarborough · Ricardo Pietrobon · Janet E. Tuttle-Newhall · Carlos E. Marroquin · Bradley H. Collins · Dev M. Desai · Paul C. Kuo · Theodore N. Pappas

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Abstract
Introduction Recent data suggests that the previously demonstrable relationship between hospital volume and outcomes for liver transplant procedures may no longer exist. Furthermore, to our knowledge, no study has been published examining whether individual surgeon volume is associated with outcomes in liver transplantation.
Materials and methods The Nationwide Inpatient Sample database was used to obtain early clinical outcome and resource utilization data for liver transplant procedures performed in the USA from 1988 through 2003. The relationship between surgeon and hospital volume and early clinical outcomes was analyzed with and without adjustment for certain confounding variables such as patient age and presence of co-morbid disease.
Results The in-hospital mortality rate, major postoperative complication rate, and length of hospital stay after liver transplantation did not differ significantly based on hospital procedural volume. These outcome variables did, however, exhibit a statistically significant inverse relationship with individual surgeon volume of liver transplant procedures. A significant relationship between procedure volume and outcomes for liver transplantation cannot be demonstrated at the level of transplant center, but does appear to exist at the level of the individual transplant center.
Conclusion Minimal volume requirements for individual liver transplant surgeons may be justified, pending validation of this volume–outcomes relationship using a clinical data source.

Keywords Liver transplantation · Outcomes assessment · Resource utilization · Provider volume

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J. E. Scarborough (✉) · J. E. Tuttle-Newhall · C. E. Marroquin · B. H. Collins · D. M. Desai · P. C. Kuo · T. N. Pappas
Department of Surgery, Division of General Surgery,
Duke University Medical Center,
Durham, NC Box 102345, 27710, USA
e-mail: scarb005@mc.duke.edu

R. Pietrobon
Department of Surgery, Division of Orthopaedic Surgery,
Duke University Medical Center,
Durham, NC, USA

R. Pietrobon
Center for Excellence in Surgical Outcomes,
Duke University Medical Center,
Durham, NC, USA

Introduction

There is ample evidence linking increased provider volume leads to better patient outcomes and more efficient resource utilization for a number of different surgical procedures. From pancreatic resections to coronary artery bypass grafts as well as certain other oncologic and vascular procedures, this link between outcomes and operative experience has been established at both the level of the hospital as well as the level of the individual surgeon.[1–4] As a result of these data, there has been considerable support by third-party payers and some surgeons for volume-based referral whereby specialized procedures are diverted to high-volume centers.[5] Proponents of volume-based referral initiatives believe that such regionalization will lead to improved patient outcomes and minimization of cost inefficiencies by ensuring that the most complex operations are concentrated into the hands of surgeons and hospitals with the most experience.[6]

Several investigators have previously found that a similar volume–outcomes relationship existed for liver transplantation, although more recent data suggest that this relationship has diminished in significance.[7–10,25] All of these studies, however, confine their analyses to the level of the transplant center. To our knowledge, no study has yet been published which examines the relationship between procedure volume and outcomes at the level of the individual surgeon. This is because most national and international transplant databases, such as the United Network for Organ Sharing Scientific Registry and the European Liver Transplant Registry, collect and report data by center rather than by individual surgeon.

In this study, we use a nationwide inpatient database which tracks both surgeon- and hospital-specific outcomes to characterize the current relationship between operative volume and outcomes for liver transplant procedures.

Materials and Methods

Database Description

The Nationwide Inpatient Sample (NIS) databases for the years 1988 thorough 2003 were used for our study.[11] The NIS is a part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest all-payer inpatient care database that is publicly available in the USA and contains approximately 5 to 8 million records of inpatient stays per year from about 1,000 hospitals, which represent a 20% stratified sample of community hospitals in the USA.[12] To ensure maximal representation of the US hospitals, the following sampling strata, based on five important hospital characteristics, were used for the creation of the NIS: geographic region (Northeast, North Central, West, and South), ownership (public, private not for profit, and private investor-owned), location (urban and rural), teaching status (teaching hospital and non-teaching hospital), and bed size (small, medium, and large).

NIS data sets provide the following information: hospital identifiers (AHRQ-sponsored and American Hospital Association Identifiers), synthetic surgeon identifiers, unique patient visit identifier, patient demographics, and procedure and diagnostic codes classified according to the *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM).[13] Therefore, this database is capable of tracking outcomes specific to both individual surgeons and to hospitals.

The HCUP has assigned validation and quality assessment of these data sets to an independent contractor.[14] The validation was performed by reviewing univariate statistics for all numeric data elements, determining the frequency distributions for all categorical and some continuous data elements, checking ranges against standard norms, and performing edit checks that identify inconsistencies between related data elements. The NIS has also been extensively validated against the National Hospital Discharge Survey and confirmed to perform very well for many estimates.[15]

Sample Selection

Records with valid ICD-9-CM procedure code 50.50 for liver transplant were extracted from the NIS data sets for the years 1988 through 2003. Each record in the data sets represented a single patient encounter and has a unique identification number. Patients with a secondary procedure code of pancreatic transplant (52.80) or kidney transplant (55.60) were excluded from the analysis in order to impart some homogeneity to our study population. In order to confine our study to adult transplant recipients only, we also excluded patients who were under 18 years of age at the time of transplantation. There were 8,054 cases that underwent orthotopic liver transplantation (OLT) after these exclusion criteria were applied.

Outcome Measures

The outcome variables of interest were as follows: (1) length of hospital stay, (2) percentage of discharges which were non-routine (i.e., the patient was discharged to a nursing home, rehabilitation facility, or intermediate care facility rather than to home), (3) postoperative in-hospital mortality, (4) major intraoperative complications, and (5) major postoperative complications. The major intraoperative and postoperative complications were identified using ICD-9-CM diagnostic code and included the following: injury to adjacent structures (998.2); retained foreign body (998.4); hemorrhage complicating a procedure (998.11); primary liver allograft nonfunction or hyperacute rejection (996.8); septic or hypovolemic shock (998.0); mechanical wound disruption (998.3); postoperative infection including intra-abdominal abscesses, wound infection, or septicemia (998.5); systemic inflammatory release syndrome (995.9); hepatic arterial thrombosis (444.9); portal vein thrombosis (452); complications of biliary anastomosis (997.4); pneumonia (997.3); pulmonary embolism (415.1); adult respiratory distress syndrome (518.5); pulmonary edema (518.4); acute respiratory failure (518.81); myocardial ischemia (410); heart failure (428); acute renal failure (639.3); and gastrointestinal bleed (578.9). Because the ICD-9-CM coding system does not include transplant-specific codes for many of the postoperative variables that are of particular

interest, the best available ICD codes were used. For example, in order to identify any reported hepatic arterial thromboses, the code for "thrombosis of unspecified artery" was used.

Primary Predictor Variables

The primary predictor variables were surgeon and hospital volume. The database contains a synthetic primary surgeon identifier for each surgeon and each hospital, which are unique and consistent over the period of 16 years. Each procedure captured by the NIS can be associated with only one surgeon identifier. Therefore, a surgeon who may be serving as an assistant or "co-surgeon" during a procedure will not be recognized by the NIS. Surgeon volume was calculated by counting the number of liver transplant procedure performed during a given year by use of this unique identifier. Surgeon volume was then divided into three categories (low volume, <3 procedures; intermediate volume, 3–9 procedures; and high volume, >9 procedures). Importantly, these surgeon volume categories do not necessarily coincide with the volume used to define the hospital volume categories. Synthetic primary surgeon identifiers were missing for 3,672 (45.59%) of the liver transplant cases examined. There were no missing hospital identifiers. To test the impact of missing surgeon identifiers on our results, a sensitivity analysis was conducted. Imputation by best subset regression of missing values for surgeon volume was used to conduct the sensitivity analysis. We calculated the values for missing surgeon volume based on other characteristics such as hospital volume, hospital location, teaching status of hospital, hospital identifier, hospital bed size, and year of operation. In addition, to test the potential impact of missing surgeon identifiers on our findings, patients with surgeon identifiers were compared with patients without surgeon identifiers in terms of outcomes and demographic variables.

Surgeon and hospital volume categories were chosen to obtain approximately similar percentages of procedures in each category and also to have clinically meaningful cutoff values. This scientifically sound approach has been previously described.[3,16–19] Although the cutoff value for high-volume surgeons seems to be low, it reflects approximately one third of total cases. In other words, approximately two thirds of liver transplant procedures in the USA are performed by surgeons who perform nine or fewer procedures per year. By forming surgeon and hospital volume categories based on an even distribution of the total number of procedures into terciles, we have sought to maximize the statistical validity of our analysis. Similar methodology has been used by other groups performing volume–outcomes analyses.[3,4]

Covariates

Age, sex, race, household income (median household income of patient's ZIP code, three categories: 1=$1–35,999, 2=$36,000–44,999, 3=$45,000 and above, a known proxy for a patient's socioeconomic status), and comorbidity (Index of Charlson et al.[20] modified by Deyo et al.[21]), for each patient were used as confounders in the logistic regression models. The Charlson Index as modified by Deyo et al. measures comorbidity by assigning a score of 1, 2, 3, or 6 to each of the comorbid conditions present in a patient. These scores were then added and translated into a single index score, which measured the overall comorbidity of the patient. To assess the impact of the missing values for the variable race (2,111, 26.21%) and household income (821, 10.19%), logistic regressions were performed separately with and without race or household income as a confounder. The results were then compared for consistency.

Statistical Analysis

Bivariate analyses were performed to assess the unadjusted association between either surgeon volume or hospital volume and outcomes. Multivariable regression analyses were used to examine the risk-adjusted associations between surgeon or hospital volume and outcomes. All multivariable analyses were adjusted for the following potential confounders: age, race, household income, and patient comorbidity. Multivariable regression analyses allow the assessment of the risk-adjusted (independent of other potential confounders) impact of hospital or surgeon volume on the outcomes. Differences between the potential confounders are thus decreased using this method.

Risk-adjusted odds ratios with 95% confidence intervals and p values were used to assess the strength of the association between hospital or surgeon volume and outcomes. Adjusted estimates were calculated for length of stay using linear regression.

Statistical analyses were conducted using Intercooled STATA for Windows (version 7.0; Stata Corporation, College Station, TX, USA) and SAS for Windows (version 8.02; SAS Institute, Cary, NC, USA).

Results

The NIS database contains information on 8,054 patients who underwent orthotopic liver transplantation from 1988 through 2003. Patients in our analysis were predominantly white (4,479, 55.61%), and had a median age of 50.0 years (interquartile range 7.0 years; Table 1).

Table 1 Characteristics of Patients Undergoing Orthotopic Liver Transplantation

Baseline characteristics	OLT patients (n=8,054)
Age[a]—Mean (SD)	49.32 (10.96) years
Gender[a] (%)	
Male	61.09
Female	38.91
Race (%)	
White	55.61
Black	4.51
Hispanic	8.36
Other	5.31
Missing	26.21
Household Income (%)	
$1–35,999	37.21
$36,000–44,999	22.81
$45,000+	29.79
Missing	10.19
Charlson Score[a] (%)	
0	10.49
1	31.39
>1	58.12

[a] There were no missing values.

The in-hospital mortality rate after liver transplantation was 10.06%, the incidence of major intraoperative complications was 5.84%, and the incidence of one or more major postoperative complications was 22.13%. The mean length of hospital stay was 27.62 days, and the percent of patients having routine discharge status to home was 63.32% (Table 2).

Without risk adjustment, low-volume surgeons had significantly higher mortality and major postoperative complication rates followed by surgeons with intermediate caseloads, while high-volume surgeons had the lowest mortality and major postoperative complication rates. Unadjusted length of hospital stay also exhibited an inverse relationship with surgeon volume (Table 3). In risk-adjusted multiple linear regression analysis, the mortality rate and the length of hospital stay were significantly higher for low- and intermediate-volume surgeons when compared to high-volume surgeons, whereas the major postoperative complication rate of low-volume surgeons but not intermediate-volume surgeons was significantly less than for high-volume surgeons (Table 4). There appeared to be no statistically significant relationship between surgeon volume and the rate of major intraoperative complications or the

Table 2 Unadjusted Outcomes of Patients Undergoing Orthotopic Liver Transplantation

Outcomes	OLT patients (n=8,054)
In-hospital postoperative mortality[a]	10.06%
Intraoperative major complications[b]	5.84%
Postoperative major complications[b]	22.13%
Non-routine patient discharge status[c]	26.31%
Length of stay in days (interquartile range)[d]	27.62 (11–33)

[a] Data were missing for 15 patients (0.19%).
[b] There were no missing values.
[c] Data were missing for 835 patients (10.37%).
[d] Data was missing for eight patients (0.10%).

Table 3 Stratified Unadjusted Outcomes by Surgeon Volume

Outcome	Surgeon volume	Unadjusted percentages	p value
In-hospital postoperative mortality	≤2	14.97	0.053
	3–9	12.58	
	>9	6.79	
Intraoperative complications	≤2	4.81	0.151
	3–9	5.92	
	>9	9.88	
Postoperative complications	≤2	34.22	0.026
	3–9	25.66	
	>9	21.60	
Non-routine discharge status	≤2	32.08	0.953
	3–9	31.06	
	>9	30.46	
Length of hospital stay—mean (interquartile range)	≤2	34.27 (13–42)	0.0005
	3–9	26.06 (10–34)	
	>9	24.67 (10–33)	

Table 4 Risk-Adjusted[a] Associations Between Surgeon Volume and Outcomes

Outcome	Surgeon volume	Adjusted odds ratio	(95% confidence Intervals)	p value
In-hospital postoperative mortality	≤2	3.21	(1.39, 7.37)	0.006
	3–9	2.81	(1.18, 6.65)	0.019
	>9	1	–	Ref.
Intraoperative complications	≤2	0.41	(0.16, 1.05)	0.063
	3–9	0.34	(0.12, 0.98)	0.047
	>9	1	–	Ref.
Postoperative complications	≤2	2.18	(1.29, 3.68)	0.003
	3–9	1.23	(0.70, 2.16)	0.480
	>9	1	–	
Non-routine discharge status	≤2	1.08	(0.64, 1.82)	0.758
	3–9	0.72	(0.41, 1.27)	0.259
	>9	1	–	Ref.
Length of hospital stay–mean (interquartile range)	≤2	26.19[b]	(22.88, 29.50)[b]	<0.0001
	3–9	16.18[b]	(12.49, 19.87)[b]	<0.0001
	>9	15.91[b]	(12.47, 19.34)[b]	Ref.

Ref. High-volume providers are the reference category
[a] Risk-adjusted for age, race, household income, and patient comorbidity
[b] Length of hospital stay is expressed as mean number of days.

percentage of patients with non-routine discharge status in either the unadjusted or risk-adjusted models.

In the bivariate, unadjusted analysis of the relationship between hospital volumes and outcomes, the in-hospital postoperative mortality was found to be significantly higher in low-volume hospitals when compared to high-volume hospitals, and the length of hospital stay was longer in low- and intermediate-volume hospitals than in high-volume hospitals (Table 5). When a risk-adjusted multiple linear regression analysis of these relationships was performed, there were no significant relationships between any of the outcome variables and hospital volume (Table 6).

Discussion

In the current study, we have found that hospital volume of liver transplant procedures does not appear to be significantly associated with in-hospital mortality rates. Several other studies have been previously published which also examine the center volume–outcomes relationship for liver transplantation.[7–10,25] Most of these studies have found an inverse relationship between hospital volume and mortality after liver transplantation. For example, Edwards and colleagues examined data from the *1997 Report of Center-Specific Graft and Patient Survival Rates*, a report provided by the United Network for Organ Sharing (UNOS) that provides center-specific outcome data on all liver transplantations performed in the USA between October 1, 1992 and April 30, 1994.[8,9] The investigators found that the 1-year mortality rate after liver transplantation was significantly higher at transplant centers performing 20 or fewer procedures per year than in centers performing more than 20 procedures per year.[9] This center-specific volume effect on outcomes was less significant at 3 years postoperatively, suggesting that the effect of hospital volume on patient outcomes after liver transplantation was more pronounced in the early period after the operation.[8] Studies by Axelrod et al., using UNOS data from 1996 through 2000, and by Adam et al., using European Liver Transplant Registry data from 1988 to 1997, report similar findings.[7,10] More recently, Northup and colleagues found that the previously significant relationship between liver transplant center volume and mortality disappeared when using UNOS data from an 18-month period beginning in 2002.[25] These authors attributed this change in the volume–outcomes relationship for liver transplants to a variety of factors, including improvements in organ allocation policies, government oversight of liver transplant programs, and postoperative management. Our findings support those recently published by Northup and colleagues, although our use of an administrative database limits our ability to draw conclusions about why the center volume–outcomes relationship typical of many other complex procedures does not appear to currently exist for liver transplantation. We would speculate that the increase in government oversight of liver transplant programs that began in the mid-1990s, with centers with consistently poor graft or patient survival rates undergoing intense review, has contributed to the disappearance of the volume–outcomes relationship for liver transplantation.[25] Also, it

Table 5 Stratified Unadjusted Outcomes by Hospital Volume

Outcome	Hospital volume	Unadjusted percentages	*p* value
In-hospital postoperative mortality	≤11	19.80	0.025
	11–30	7.29	
	>30	10.75	
Intraoperative complications	≤11	6.93	0.724
	11–30	6.25	
	>30	4.30	
Postoperative complications	≤11	20.79	0.113
	11–30	14.58	
	>30	26.88	
Non-routine discharge status	≤11	27.16	0.626
	11–30	23.60	
	>30	30.12	
Length of hospital stay in mean days (interquartile range)	≤11	37.24 (10–42)	0.0110
	11–30	32.86 (12–39)	
	>30	19.73 (9–25)	

Table 6 Risk-Adjusted[a] Associations Between Hospital Volume and Outcomes

Outcome	Hospital volume	Adjusted odds ratio	(95% confidence intervals)	*p* value
In-hospital postoperative mortality	≤11	2.35	(0.87, 6.31)	0.091
	11–30	0.65	(0.20, 2.14)	0.478
	>30	1	–	Ref.
Intraoperative complications	≤11	3.14	(0.72, 13.69)	0.127
	11–30	2.46	(0.55, 10.89)	0.235
	>30	1	–	Ref.
Postoperative complications	≤11	0.88	(0.37, 2.09)	0.781
	11–30	0.36	(0.13, 0.96)	0.042
	>30	1	–	Ref
Non-routine discharge status	≤11	1.08	(0.39, 2.98)	0.879
	11–30	0.99	(0.40, 2.54)	0.992
	>30	1	–	Ref.
Length of hospital stay—mean (interquartile range)	≤11	15.45[b]	(10.44, 20.47)[b]	0.2673
	11–30	19.34[b]	(14.41, 24.28)[b]	
	>30	13.94[b]	(9.57, 18.31)[b]	

Ref. High-volume providers are the reference category

[a] Risk-adjusted for age, race, household income, and patient comorbidity

[b] Length of hospital stay is expressed as mean number of days.

has previously been shown that hospitals performing liver transplantation experience a learning curve whereby clinical outcomes and resource utilization begin to improve after a certain minimum cumulative threshold level of procedures have been performed.[23,24] Because our study period encompasses 15 years , the low-volume centers included in our analysis are more likely to have surpassed this minimal threshold volume of transplant procedures, and their outcomes are therefore less likely to reflect the potentially confounding learning curve effects to which those studies performed over shorter periods of time are subject.

To our knowledge, our study is the first to examine whether a volume–outcomes relationship exists at the level of the individual transplant surgeon. We have found that high-volume surgeons, defined in our study as those performing more than nine liver transplants per year, have lower in-hospital mortality rates and lower rates of major postoperative complications than low-or intermediate-volume surgeons. Furthermore, liver transplantations performed by high-volume surgeons appear to result in more efficient resource utilization, as evidenced by decreased length of postoperative hospital stay, than when performed by lower-volume surgeons. The significance of these surgeon volume–outcome relationships is maintained even after adjusting for confounding variables such as patient age, household income, degree of comorbidities, and the procedure volume of the hospital in which the transplant is performed. It appears therefore that individual provider volume is a significant independent determinant of early clinical outcome and resource utilization after liver transplantation.

There are several implications of our study. It has been noted by some authors that hospital volume should not be used as a surrogate for transplant center quality because many low-volume centers have exceptional outcomes.[22] Furthermore, safeguards already exist which subject hospitals that perform liver transplantation to minimum requirements in terms of availability and quality of ancillary medical staff and services. Because many low-volume centers may be staffed with high-volume surgeons, these centers can be expected to achieve acceptable clinical outcomes and efficient resource utilization. The results of our study therefore support using caution with respect to how published data on center volume effects for liver transplantation are interpreted by the public and scientific communities. Such data should only be considered in context of both surgeon and hospital volumes, not just hospital volume alone.

Conversely, our study suggests that while center volume and post-transplant outcomes may not be significantly related, such a volume–outcomes relationship may exist at the level of the individual transplant surgeon. There are many potential implications of this finding. First, high-volume liver transplant surgeons should be able to achieve acceptable outcomes regardless of center volume. Thus, experienced surgeons who wish for whatever reason to move from a high-volume to a low-volume center should be able to do so without compromising their patients' outcomes. Second, the results of our study suggest that low-volume surgeons may not necessarily be "protected" from poor outcomes merely by operating at a high-volume center. Thus, surgeons performing a low annual volume of procedures may benefit from the active assistance of more seasoned or experienced surgeons in areas such as donor selection, intraoperative performance, and postoperative management. This is especially true for low-volume surgeons with minimal cumulative experience, such as those who have recently finished fellowship training. Having a higher-volume surgeon involved as a co-surgeon in the operating room, and available for management advice postoperatively, may help the low-volume surgeon to achieve better patient outcomes. Eventually, as the low-volume surgeon increases their annual volume and improves their cumulative experience, their need for such intensive "hands-on" mentoring should decrease. While such mentoring strategies may already exist at some transplant centers, the results of our study suggest that there is room for improvement and that the development of formal mentoring guidelines for low-volume surgeons by the American Society of Transplant Surgeons may be appropriate.

In order to develop appropriate mentoring guidelines for low-volume surgeons, however, it would be important to validate our findings using a different data source. We used an administrative database for the current study because it enabled us to examine both hospital and surgeon volume and because it has been used to establish a volume–outcome relationship for many other complex surgical procedures. However, administrative databases have much less clinical data available for risk adjustment than clinical databases such as the Scientific Registry of Transplant Recipients (SRTR). Important preoperative information, such as the components of the Model of End-Stage Liver Disease, cannot be obtained from the NIS. Other variables to transplantation, such as the structure of the Organ Procurement Organization, the quality of the donor organ, and the intraoperative surgical techniques used, are also unable to be assessed when using large administrative databases. Unfortunately, the SRTR does not currently provide surgeon-specific volume and outcomes data and thus does not permit an examination of the volume–outcomes relationship at the level of the individual liver transplant surgeon. We believe that the SRTR should collect data on individual surgeon volume and outcomes, subjecting these data to the same robust analysis that is currently

provided for center-specific outcomes. This is the only way to confirm the volume–outcomes relationship that we describe in our study and to establish those practices and operative strategies responsible for this relationship.

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Surgical Specialization and Operative Mortality in Hepato-Pancreatico-Biliary (HPB) Surgery

Nicholas G. Csikesz · Jessica P. Simons · Jennifer F. Tseng · Shimul A. Shah

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Abstract
Introduction Surgeon specialization has been shown to result in improved outcomes but may not be the sole measure of surgical quality in hepato-pancreato-biliary (HPB) surgery. We attempted to determine which factors predominate in optimal patient outcomes between volume, surgeon, and hospital resources.
Methods All non-transplant pancreatic (n=7195) and liver operations (n=4809) from the Nationwide Inpatient Sample (NIS) were examined from 1998–2005. Surgeons and hospitals were divided into two groups, transplant (TX) or non-transplant (non-TX), using the unique surgeon and hospital identifier of NIS. A logistic regression model examined the relationship between factors while accounting for patient and hospital factors.
Results We identified 4,355 primary surgeons (165 TX, 4,190 non-TX) who performed HPB surgery in 675 hospitals across 12 different states. Non-TX surgeons performed the majority of pancreatic (97%) and liver procedures (81%). There was no difference in mortality after HPB surgery depending on surgeon specialty (p=0.59). Factors for inpatient death after HPB surgery included increasing age, male gender, and public insurance (p<0.05). In addition, surgery performed at a TX center had a 21% lower odds of perioperative mortality.
Discussion Non-TX surgeons performed the majority of pancreatic and liver surgery in the US. Hospital factors like support of transplantation but not surgical specialty, appeared to impact operative mortality. Future regulatory benchmarks should consider these types of center-based facilities and resources to assess patient outcomes.

Keywords Liver · Pancreas · NIS · Transplant · Hepato-pancreatico-biliary surgery

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N. G. Csikesz · J. P. Simons · J. F. Tseng · S. A. Shah
Department of Surgery, Surgical Outcomes Analysis & Research, University of Massachusetts Medical School, Worcester, MA, USA

S. A. Shah (✉)
Department of Surgery, University of Massachusetts Medical School, 55 Lake Avenue North, S6-632, Worcester, MA 01655, USA
e-mail: shahs01@ummhc.org

Introduction

The field of hepato-pancreatico-biliary (HPB) surgery has matured significantly in the last 20 years and is now considered by many as its own discipline. Trends from national studies have confirmed that the number of procedures performed are increasing while mortality is decreasing.[1,2] HPB surgery is now commonly practiced by one of three disciplines within general surgery; it may be performed by either a surgical oncologist, a transplant surgeon or a general surgeon without subspecialty training. The extent to which the type of training has influenced practice patterns, patient selection or postoperative outcomes is unknown. In addition, the role of the surgeon's center in patient outcomes is also undefined. While center volume has been shown to be an important factor in perioperative and long-term outcomes,[3–5] hospital size and perioperative resources have never been examined in HPB surgery mortality.

An interest in improving surgical quality and outcomes has been the focus of numerous national, regional, and hospital level projects. For specialized operations like liver and pancreas surgery, standardized definitions of quality may not apply. The common benchmarks such as surgeon volume, access to care, or long-term survival may not be relevant to HPB surgery due to low overall number of cases, specific referral patterns, and poor long-term survival in cancer cases.

There is increasing evidence that surgical sub-specialization translates into improved outcomes following high risk procedures such as pancreaticoduodenectomy and liver resection.[6,7] One may hypothesize that surgeons who do not specialize specifically into HPB disorders may be less proficient and therefore lead to poorer outcomes. Surgeon and center volume have been shown to be important factors for mortality in high risk cancer operations.[5,6,8,9] By using a national discharge registry, we aimed to evaluate the roles of different surgical specialties performing HPB surgery and the impact of surgeon type, hospital size, and hospital type on operative mortality.

Materials and Methods

We used data from the Nationwide Inpatient Sample (NIS) for the years 1998 to 2005. The NIS is the largest national all-payer hospital inpatient care database in the United States. It is supported by the Healthcare Cost and Utilization Project and contains all-payer discharge information for 100% of patient discharges from participating hospitals. Data exist for approximately seven million hospital discharges per year from a stratified sample of 20% of nonfederal US community hospitals from participating states including academic and specialty hospitals. It contains hospital-level information obtained from a direct link to the American Hospital Association's annual survey of hospitals, which includes hospital type (teaching/nonteaching) and geographic region (Northeast, West, South, Midwest as defined by the US Census Bureau). Each record in the NIS represents a single hospital discharge and includes a unique identifier. In addition, some states include a physician identifier that allows one to track the care provided by a practitioner.

The study was reviewed by the University of Massachusetts Institutional Review Board (IRB) as appropriate for exception from IRB oversight as no personal identifiers were used among the registry data.

Study Population

Diagnoses and procedures were identified by the Clinical Modification of the International Classification of Diseases, 9th Revision (ICD-9-CM) diagnostic and procedural codes (Table 1). All patients who underwent either a pancreas or liver operation were identified. ICD-9 procedure codes and unique surgeon and hospital identifiers were then used to construct binary variables identifying either multiorgan transplant (TX) surgeons or non-transplant or general and oncologic surgeons (non-TX). Surgery of the biliary tract was not included in this cohort given its overlap with both liver and pancreas diseases and procedures. In addition, identifiable and comprehensive procedure codes for complex biliary procedures are difficult to identify. Technically less demanding biliary operations like laparoscopic cholecystectomy would not be representative of a typical HPB surgeon's practice. It was not possible to differentiate between oncologic and general surgeons given the overlap in procedures performed.

The median number of states per year with the specific surgeon and state identifier code was eight (range 4–10). A total of 12 different states were included over the course of the study. All years were considered together as one cohort. These variables were assigned to each record designating whether a HPB surgery on a specific patient was under the care of a TX or non-TX surgeon and performed at either a TX or non-TX hospital. Since record sampling in the NIS does not correlate across years, a continuous single surgeon identifier was not possible. Each record or identifier is

Table 1 ICD-9 Procedure Codes

Procedure	ICD-9 Codes	Frequency (%)
Marsupialization of lesion of liver	5021	0.5
Partial hepatectomy (wedge resection)	5022	14.1
Other destruction of lesion of liver (cauterization, enucleation, or evacuation of hepatic lesion)	5029	14.3
Lobectomy of liver	503	11.2
Pancreatotomy—drainage of pancreatic cyst by catheter	5201	7.0
Pancreatotomy—other pancreatotomy (pancreatolithotomy)	5209	2.5
Endoscopic excision or destruction of lesion or tissue of pancreatic duct	5221	0.1
Other excision or destruction of lesion or tissue of pancreas or pancreatic duct	5222	4.3
Marsupialization of pancreatic cyst	523	0.6
Internal drainage of pancreatic cyst	524	2.3
Proximal pancreatectomy	5251	0.5
Distal pancreatectomy	5252	10.1
Radical subtotal pancreatectomy	5253	0.5
Other partial pancreatectomy	5259	2.4
Total pancreatectomy	526	1.5
Whipple	527	24.3
Anastomosis of pancreas (to intestine/stomach)	5296	3.9

considered a unit assigned to a specific surgeon or hospital; therefore, the same surgeon may operate in each year recorded as a different individual surgeon. For example, due to the sampling in the NIS, it is possible for a surgeon's hospital to be included in 1 year and then not included the following year.

We applied several restrictions in order to increase the homogeneity of the study samples and thus minimize the potential for confounding by case mix. We excluded all states which did not provide unique surgeon or hospital identifiers. We also excluded states in which the surgeon identifier could not be tracked across different hospitals. Live donor hepatectomies were not included in the cohort since they are only performed by TX surgeons in transplant centers. Between 1998 and 2005, there were 38,523 HPB operations performed in the US based on discharge records from 39 states and 1,877 hospitals. After eliminating records from states that did not accurately specify surgeon identification, we were left with 12,004 HPB surgeries performed in 12 different states at 675 hospitals by 4,355 surgeons.

Demographic and operative characteristics of patients were captured within NIS. Age was maintained as a continuous variable. Race was divided into white, black, Hispanic or other, which included, but was not limited to Asians, Pacific Islanders, and Native Americans. Hospital size in NIS is reported in tertiles: large, medium, and small. The cutoff for each tertile is different depending on the region, location (rural/urban), and teaching status of the hospital, so that the hospitals are divided approximately equally. Payer type was divided into four groups: Medicare, Medicaid, private insurance or other. Surgeon volume was divided into tertiles to create equal groups for comparison. This translated into volume cutoffs of low (0–2 cases per year), middle (3–14 cases per year), and high (>15 cases per year).

For purposes of risk adjustment, coexisting comorbidity was compiled to create an Elixhauser comorbidity index.[10] This index identifies 29 disease entities that are considered true comorbid diseases associated with adverse outcomes in hospitalized patients. Patients were given a score of 0, 1, 2 or ≥3 based on number of comorbities.

Outcomes

The primary endpoint examined in this study was in-hospital mortality. Mortality was defined as death from any cause prior to discharge regardless of time from operation.

Statistical Analysis

Data was analyzed using SAS software release 8.02 (SAS Institute, Cary, NC, USA). Analyses were performed using SAS survey means command to account for NIS' stratified 2-stage cluster design. Continuous variables were evaluated for normality using Shapiro–Wilks test and tested for statistical significance with a one-way analysis of variance. Categorical variables were tested with χ^2 analysis. Statistical significance was defined by $p<0.05$.

A logistic regression was used to determine the effect of different variables on the probability of mortality while controlling for patient and hospital characteristics. A Hosmer-Lemeshow goodness-of-fit test was performed to confirm the final model. All covariates with $p<0.10$ by univariate analysis were included in the multivariate regression model. These included patient age (continuous variable), race (white, black, Hispanic, other), comorbidity index score (0, 1, 2, ≥3), gender, payer status (private, Medicare, Medicaid, other), and hospital type. All regression models were performed separately with and without variables with missing fields. The data was unchanged in both models.

Results

Demographics and Patient Population

From 1998–2005, 12,004 HPB surgeries were performed by 4,355 surgeons in this cohort from the NIS database (Table 2). Sixty percent of operations in the cohort were pancreatic type (n=7195/12004). TX surgeons only comprised 4% of the total number of surgeon/year combinations (TX 165; non-TX 4190). Although TX surgeons only performed 3% of the pancreas surgeries, they performed a larger percentage of the liver procedures (19%). Specifically, TX surgeons performed 35% and 22% of lobectomies and wedge resections respectively.

HPB surgery was performed in 675 hospitals across twelve different states over the 8-year period. Based on hospital size, 8.9% were small hospitals (lowest tertile), 16.4% were medium sized (middle tertile), and 74.7% were

Table 2 Volume Demographics of Patients who Underwent HPB Surgery

	Liver (n=4,809)	Pancreatic (n=7,195)	Total (n=12,004)
Surgeon type			
GI	3,885 (80.8%)	6,965 (96.8%)	10,850 (90.4%)
Transplant	924 (19.2%)	230 (3.2%)	1,154 (9.6%)
Hospital type			
Non-transplant	2,240 (46.6%)	4,383 (60.9%)	6,623 (55.2%)
Transplant	2,569 (53.4%)	2,812 (39.1%)	5,381 (44.8%)

GI Gastrointestinal

large hospitals (highest tertile). Only 10.0% of the hospitals comprised of TX centers (n=66) while 90.0% were non-transplant hospitals (n=594). In spite of this disparity, 45% of HPB surgeries were performed at TX hospitals. Surgery at a designated TX hospital was more closely associated with a large hospital size. Large hospitals comprised 89.6% of TX hospitals while only 62.6% of non-TX hospitals were in the highest tertile. The majority of operations (70%) were performed at multiorgan TX hospitals that supported both liver and kidney transplantation,

Patient demographics are shown in Table 3. The median age was 57.6 years and half of the patients were female. Almost half of the patients had private insurance (45.6%) and most patients were white (72.1%). Most operations occurred in teaching hospitals in an urban location (96.8%). Unadjusted mortality in this cohort was 4.8%.

Transplant surgeons were most commonly high volume surgeons (60%) (Table 4). Hospital volume also showed different trends when comparing TX hospitals with non-transplant hospitals (Table 5). Non-TX hospitals were most commonly lower volume hospitals (<62 surgeries/year; 87.9%) while more than half of TX hospitals were high volume centers in HPB surgery (≥62 surgeries/year; 59.6%).

Table 3 Demographics of the 12,004 Patients who Underwent HPB Surgery

Variable	Percent
Median age—(years)	60
Female gender	50.3
Race	
White	72.1
Black	11.2
Hispanic	10.5
Other	6.2
Primary insurance	
Medicare	38.5
Medicaid	7.9
Private	45.5
Other	7.9
Elective admission	67.5
Number of comorbidities	
0	20.6
1	29.6
2	24.4
>=3	25.4
Teaching hospital	73.8
Urban hospital location	96.7
Hospital bedsize	
Smallest	8.9
Middle	16.4
Largest	74.7

Table 4 Volume Cutoffs in HPB Surgery, Surgeon Volume

Surgeon volume	GI surgeon (n=10,864)	TX surgeon (n=1,155)	Total
Surgeon volume			
Low volume (<3/yr)	4,097 (38%)	120 (10%)	4,217 (35%)
Middle volume (3–14/yr)	3,477 (32%)	345 (30%)	3,822 (32%)
High volume (>15/yr)	3,290 (30%)	690 (60%)	3,980 (33%)

GI Gastrointestinal, *yr* year, *TX* Transplant

Multivariate Regression

After adjusting for patient and hospital factors, there was no difference in mortality after HPB surgery if performed by a TX or non-TX surgeon (p=0.59; Table 6). Significant factors for inpatient death after HPB surgery included increasing age (Hazard ratio (HR), 1.02; 95% CI, 1.01–1.03), increasing comorbidity (HR, 1.10; 95% CI, 1.03–1.18), male gender (female gender HR, 0.65; 95% CI, 0.54–0.78), and public insurance (HR, 1.4; 95% CI, 1.10–1.81). In addition, surgery performed at a transplant center had a 21% lower odds of perioperative mortality (HR, 0.79; 95% CI, 0.63–0.98). As a sensitivity analysis to see if center and surgeon type were colinear, the analysis was performed without center type included. The type of surgeon still was not an independent predictor of mortality.

Since a large proportion of TX centers were large hospitals (89.6%), we further analyzed the large hospitals (n=8900 patients) specifically to ensure that center size alone was not the factor in improved outcomes. This would further validate that centers which supported transplantation reflected potentially improved perioperative services and practice environment. Logistic regression of mortality confirmed that the benefit of being cared for at a TX center was still preserved (HR, 0.69; 0.54–0.90).

We then analyzed the cohort of large volume surgeons (>15 cases) to determine if different independent predictors of mortality existed in this cohort. Surgeon type was not significant (HR, 1.7; 95% CI, 0.9–3.2). In this cohort, TX hospital was no longer independently associated with

Table 5 Volume Cutoffs in HPB Surgery, Hospital Volume

Hospital volume	Non-transplant hospitals (n=6,623)	TX hospitals (n=5,831)	Total (n=12,004)
Lowest tertile (<15 cases/yr)	3,767 (56.9%)	282 (5.2%)	4,049 (33.7%)
Middle tertile (15–62/yr)	2,055 (31.0%)	1,894 (35.2%)	3,949 (32.9%)
Highest tertile (≥62 cases/yr)	801 (12.1%)	3,205 (59.6%)	4,006 (33.4%)

Table 6 Logistic Regression of Mortality after HPB Surgery (n=12,004)

Variable	Odds ratio	95% CI	p value
Age	1.02	1.01–1.03	<0.001
Female gender	0.65	0.54–0.78	<0.001
Primary insurance			
Private	1.0	–	–
Medicare	1.4	1.10–1.81	0.007
Race			
White	1.0	–	–
Black	1.17	0.88–1.55	0.27
Hispanic	1.31	0.99–1.73	0.06
Admission type			
Elective	1.00	–	–
Urgent	2.08	1.59–2.73	<0.0001
Emergent	3.34	2.72–4.11	<0.0001
Elixhauser index	1.10	1.01–1.22	0.002
Teaching status	0.90	0.73–1.10	0.30
TX surgeon	1.42	0.99–2.05	0.59
Transplant center	0.79	0.63–0.98	0.04

TX Transplant

improved outcomes either (HR, 0.7; 95% CI, 0.4–1.1). This suggests that individual surgeon factor may trump hospital factor.

Discussion

Complex procedures such as HPB surgery require a multidisciplinary approach to achieve optimal outcomes. Surgeons performing these procedures may have trained from a variety of disciplines including oncology, transplantation, or general surgery. Our data from an 8-year period across 12 different states suggests that the in-hospital outcomes currently are similar but not as good as single institution reports for HPB surgery.[11,12] This large cohort suggests that surgeon type is not an important factor in surgical outcome after HPB resections. Non-transplant surgeons performed the majority of pancreatic and liver surgery. In-hospital mortality in this cohort was 4.8%, similar to other population-based studies in HPB procedures.[1,2,8,15,16] HPB surgery most commonly is performed at large hospitals. We found that other demographic factors such as age, public insurance and race may affect surgical results as others have shown from different surgeries.[13–15] Centers with transplantation services have a significant in-hospital mortality benefit to patients.

Despite numerous reports regarding center volume, no previous database studies have examined center resources and perioperative services in HPB surgeries. High volume centers have been shown to be important in not only the postoperative period but also in long-term survival after complex cancer surgery.[2,3,6] We found that the ability to support transplantation provided a survival benefit compared to non-TX hospitals. Given the unique surgeon and hospital identifiers in NIS, we were able to reliably ensure that these hospitals were TX centers that performed either a liver or kidney TX during the course of the study.

Improved outcomes after HPB surgery in centers that support transplantation may reflect differences in perioperative services and practice environment. Support of transplantation may just be a benchmark of a large center; we did not cross-link the centers with other programs that require significant support and resources such as cardiac surgery or complex radiological procedures. Transplant services are an important and relevant benchmark for quality in HPB surgery given its association with these procedures and caregivers. Non-transplant hospitals were more commonly smaller or medium sized centers compared to TX hospitals which likely accounted for a large part of the differences that were observed. In order to account for this, we then examined only patients that were treated at the largest hospitals (third tertile). In this analysis, we still found that the beneficial effect of TX hospitals persisted.

Hospital characteristics were closely examined to ensure that the hospital effect remained. We took into account important characteristics like center size, teaching status and location. Combined with our subgroup analysis these results suggest that the observed mortality variation is due to the difference in hospital types rather than surgeon type or hospital size. Do transplant services account for such a difference in perioperative outcomes? This dataset does not directly address whether transplant services accounted for the difference in mortality; future studies with center specific clinical variables would be necessary at high volume HPB or TX centers. Should minimal volume standards be applied to HPB surgery? Our data would argue that the standards should be applied and focused more to the hospital setting and services. The interplay between volume metrics, patient outcome, and hospital services is still unknown.

Several limitations to this study must be considered. The main outcome measure of this study was in-hospital mortality. This may reflect a lower mortality rate compared with studies using 30-day mortality as most patients were likely discharged from the hospital prior to the potential death (if applicable). Our study used population-based data with only limited information on patient and treatment factors, thereby limiting our evaluation of medical factors such as presence of cancer, cirrhosis, antibiotic use, mechanical ventilation, and prior surgery. The lack of specific clinical information may have led to a case mix between surgeon and center types. We were unable to reliably collect complex biliary cases given the ICD-9 coding ambiguity around these procedures. We felt that

capturing the liver and pancreas procedures would be reliable as markers of HPB surgeons. This study is at risk of a Type II statistical error because the large sample size differences between two groups. We attempted to mitigate this risk by confirming the primary findings in a multivariate analysis that controlled for important risk factors affecting survival. Our data was comprised of only a median of eight states per year. This may not have been a representational cohort of a large population; demographic and practice patterns of surgeons performing HPB procedures may vary from state to state. In order to account for this, we calculated the mortality rates for the whole NIS cohort for HPB surgery and did not find any difference in mortality among states with surgeon/hospital identifiers and those without. We also did not identify any significant regional differences in our cohort and states had uniform distribution of demographic and patient characteristics.

The majority of HPB surgery is being performed by non-TX surgeons in the US today. TX surgeons comprise a small percentage of surgeons performing HPB surgery but achieve a larger volume of such operations per surgeon. The majority of HPB surgery is being performed in large teaching hospitals reflecting the specialized and regionalized nature of HPB surgery today. A center's ability to support transplantation may be an important factor in improved outcomes after HPB surgery; future regulatory benchmarks should consider these types of center-based facilities and resources to assess patient outcomes.

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Clonality Analysis for Multicentric Origin and Intrahepatic Metastasis in Recurrent and Primary Hepatocellular Carcinoma

Qiang Li · Jian Wang · Jonathan T. Juzi · Yan Sun · Hong Zheng · Yunlong Cui · Haixin Li · Xishan Hao

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Abstract
Aims To clarify the incidence of multicentric occurrence (MO) and intrahepatic metastasis (IM) for hepatocellular carcinoma (HCC) related to hepatitis B virus in China and to identify the differences between them.
Methods Histopathologic and genetic features of primary and recurrent tumors in 160 cases with HCC were analyzed. The two groups, the origin of which was definitely determinable as of multicentric occurrence or as of intrahepatic metastasis, were analyzed for their disease-free survival and clinicopathological differences.
Results According to histopathological findings, 27.5% and 59.4% patients were considered to be MO and IM, respectively. By comparing the genetic information of loss of heterozygosity and microsatellite instability for 10 different markers between primary and recurrent tumor, 30.0% and 63.8% patients with recurrent HCC were considered to be MO and IM, respectively. In total, 126 cases with unanimous conclusions from the histopathological and genetic method were selected and divided into the MO group (37 cases) and the IM group (89 cases). Analysis of stepwise regression identified that recurrence time, grading, portal vein invasion, tumor number, and Child's stage were the most important discriminating factors between MO and IM ($p<0.05$). As for their prognosis, Kaplan–Meier and log rank test showed that the disease-free survival in the MO group was significantly better than in the IM group ($p=0.002$).
Conclusions Combined analysis of histopathological and genetic analysis may reflect more exactly the nature of recurrent HCC. The incidence of MO in China is lower than in other countries—30% compared to up to 50% in Japan [Morimoto et al., *Journal of Hepatology* 39:215–221, 2003; Yamamoto et al., *Hepatology* 29;1446–1452, 1999]. Recurrence time, tumor grading, portal vein invasion, tumor number, and Child's stage are the most important discriminating factors between MO and IM. The prognosis (disease-free survival) of patients with MO compared to IM is significantly better.

Keywords Hepatocellular carcinoma · Recurrence · Multicentric occurrence · Intrahepatic metastasis · Loss of heterozygosity

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and is particularly prevalent

Q. Li (✉) · J. Wang · J. T. Juzi · Y. Cui · X. Hao
Department of Hepatobiliary Surgery,
Cancer Hospital of Tianjin Medical University,
Huanhu Western Road, Hexi District,
Tianjin 300060, People's Republic of China
e-mail: jianwang04@yahoo.com.cn

H. Zheng
Institute of Cancer Research,
Cancer Hospital of Tianjin Medical University,
Tianjin, People's Republic of China

Y. Sun
Department of Pathology,
Cancer Hospital of Tianjin Medical University,
Tianjin, People's Republic of China

H. Li
Department of Epidemiology,
Cancer Hospital of Tianjin Medical University,
Tianjin, People's Republic of China

in China.[1,2] The incidence of HCC is prone to increase dramatically over the next few decades due to high infection rates with hepatitis B virus (HBV) and hepatitis C virus (HCV), which are known to be intimately associated with HCC.[3,4] Besides liver transplantation, operation is another preferable effective treatment for this problematic disease at present. Although for cancers accessible by surgery, survival has greatly improved over the last years, the 5-year survival rate still remains as low as 47% after surgical resection.[5] This is much lower when compared to other gastro-intestinal cancers, e.g., gastric[6] and colonic cancer.[7] One of the main reasons for this is that the incidence of intrahepatic recurrence is extremely high, even after curative resection. Recurrence in the remnant liver has two different reasons: it may originate from intrahepatic metastasis (IM) and/or from multicentric occurrence (MO) also known as multicentric carcinogenesis, which is independent from the original primary tumor.

Discriminating them is very important not only for the study of hepatocarcinogenesis, but also for the determination of therapeutic strategies. Some groups have reported the incidence of MO in patients with HCC related to HCV as high as 50%. HCC with IM recurs earlier and has a poorer prognosis than that with MO.[8–11] Aggressive therapy may not be warranted in cases with IM, but in cases with MO, intervention should be taken within the limits of liver functional reserve.[12] Most of these reports refer to HCC related to HCV; however, the incidence and clinicopathologic features of HCC associated with HBV remain unclear.

The diagnosis of IM and MO is mainly based on histopathological findings as reported by the Liver Cancer Study Group of Japan with modifications,[8] but it is relatively subjective.[13] Previous studies had used the integration pattern of HBV-DNA, the X chromosome inactivation assay, and comparative genomic hybridization (CGH) as tumor markers of clone origins.[16–18] However, these methods have their limitations such as being applied only to HCC patients who have integrated HBV-DNA, female patients or expensive equipment and reagents.[14] Besides this, the test of HBV integration with southern blotting needs enough genome DNA. Microsatellite polymorphism, mainly including loss of heterozygosity (LOH) and microsatellite instability (MSI), is an important genetic feature in carcinogenesis. The test of LOH has been reported to be useful for clone discrimination of multiple HCC.[15] This is a simple and inexpensive method and can be applied in studies with large samples.

Materials and Methods

Patients and Samples

Informed consent was obtained from all the patients for the collection of liver specimens, and the study protocol was approved by the Ethics Committee of Tianjin Medical University. The clinical pathological data were collected as described in an earlier study by us.[5] Among the patients with recurrent HCC receiving repeat surgical resection in the Cancer Hospital of Tianjin Medical University, 160 cases were selected between 2001 and 2006 according to the following criteria: (1) diagnosis of HCC confirmed by pathology; (2) second hepatectomy; (3) incisal margins negative; (4) serum hepatitis B surface antigen (HBsAg) positive and hepatitis C virus antibody (anti-HCV) negative; and (5) complete clinicopathologic data of the case. Postoperatively, primary and recurrent HCC tissues as well as corresponding non-neoplastic liver tissue were stored at −80°C in a tissue bank.

Observation of Pathology

The recurrent and primary tumor sections of all patients were collected and the diagnosis of HCC was confirmed by two pathologists according to the diagnostic criteria of primary HCC.[16] The clone relations between recurrent and primary tumor nodules from every patient were determined in accordance with conventional histological criteria.[8]

PCR-based LOH and MSI Analysis

Genomic DNA was extracted from primary and recurrent tumor and non-neoplastic liver specimens by proteinase K/sodium dodecyl sulfate digestion followed by phenol/chloroform/isoamyl and alcohol extraction. It was resolved with sterile water and stored at −20°C.

Ten microsatellite markers on multiple chromosomes (1, 3, 8, 9, 13, 16, and 17) were selected for LOH analysis (Table 1) because of their high frequencies of LOH reported in HCC. These markers were amplified by polymerase chain reaction (PCR) kit (Tanaka Biotech, Japan) performed on PTC-240 (MJ, USA). Annealing temperatures were determined by Oligo software and are listed in Table 1. The PCR products were confirmed by 2% agarose gel electrophoresis.

Loss of heterozygosity (LOH) and MSI were detected by denaturing polyacrylamide gel electrophoresis (PAGE). Amplified DNA was mixed with formamide loading buffer (98% formamide, 1 mM EDTA, 0.025% bromophenol blue, and 0.05% xylen cyanol) and denatured for 5 min at 95°C.

Table 1 Microsatellite Markers for LOH Analysis

No	Markers	Primer sequence	Annealing temperature (°C)	Product (bp)
1	D1S214	3′-CCGAATGACAAGGTGAGACT-5′ 3′-AATGTTGTTTCCAAAGTGGC-5′	51	120–142
2	D1S2797	3′-ATCACATCACACACAATGACTGTGG-5′ 3′-TGTCCATTCAAAGGATTGGTCTC-5′	55	144–180
3	D3S3681	3′-GTGAGAACCATTTGGGGCAG-5′ 3′-GGCGAGCTATCTGTCAGGG-5′	53	210–246
4	D8S277	3′-GATTTGTCCTCATGCAGTGT-5′ 3′-ACATGTTATGTTTGAGAGGTCTG-5′	51	121
5	D9S199	3′-ACACATTCATACCATAGCAGAGG-5′ 3′-GGGGAAAGCATTCAGACTTT-5′	51	144
6	D13S170	3′-GATAAACACATAGGCACATGG-5′ 3′-CCTGCAGAATTGTGAGTAATG-5′	53	234
7	D16S3091	3′-GGGAGATAGCCTTAAACTTTCTTAC-5′ 3′-TGTTGCTAATAACACTAGGCCA-5′	52	115–129
8	D17S796	3′-AATGTGGTCCTTGAAATCCT-5′ 3′-TTACTAGGATCAAGGGGCAT-5′	53	234
9	D17S831	3′-CGCCTTTCCTCATACTCCAG-5′ 3′-GCCAGACGGGACTTGAATTA-5′	55	194–246
10	D17S938	3′-GGACAGAACATGGTTAAATAGC-5′ 3′-ATGCTGCCTCTCCCTACTTA-5′	52	145

LOH loss of heterozygosity

Then, the mixture was cooled immediately on ice and loaded onto a gel composed of 8% acrylamide (19:1 acrylamide/bisacrylamide), 90 mmol Tris (pH 8.3), 89 mmol borate, 2 mmol EDTA, 7 mol ultrapure urea, 1.6% ammonium persulfate (APS), and 5 μl *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TEMED). Samples were electrophoresed at 50 V for 6 h, immersed in ethidium bromide and visualized by Chemidoc.XRS (Bio-Rad, USA).

Follow-up

All patients were followed up at the outpatient clinic every 3 months with measurement of the serum alpha-fetoprotein level and hepatic ultrasonography every 2–4 months from the date of initial treatment up to November 2007, or up to the time of their death. When recurrence was suspected, further evaluations were made by abdominal computed tomography (CT) scan, if necessary, by ultrasound-guided biopsy to confirm the diagnosis. Defined end point was non-survival. Patients who died of another disease were lost to follow-up, which, in total, were 14 (8.8%).

Statistics

The univariate analysis with Student's *t* test, the chi-square test, and Fisher's direct probability test helped us to reduce the number of study variables substantially. For the multivariate analysis, a stepwise regression model was used to identify the most important discriminating factors between two groups. The disease-free survival was calculated by method of Kaplan and Meier, and the differences in survival between them were compared using log-rank test. A p value <0.05 was considered significant.

Results

Clonality Analysis Based on Pathological Features

According to histological findings, 27.5% (44/160), 59.4% (95/160), and 7.5% (12/160) patients were considered to be MO for polyclonal origin, IM for intrahepatic metastases, and indeterminate group without definitive histological differentiation, respectively**.** Both MO and IM types of nodules were presented simultaneously in 5.6% cases (9/160).

Clonality Analysis Based on LOH and MSI

Compared to normal tissue of the same patient, a visually determined reduction of over 50% in allele intensity (allelic loss) was considered as LOH and emerging of additional

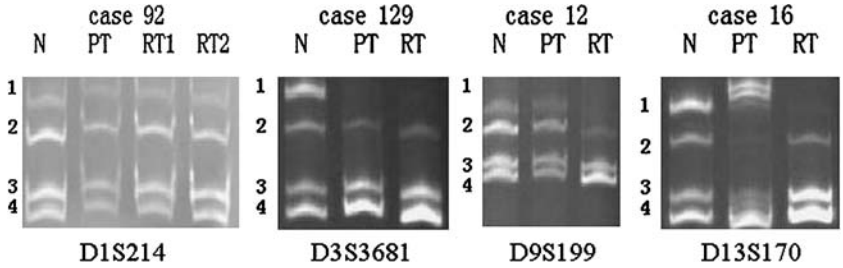

Figure 1 Case 92 showed no LOH and MSI in normal (*N*) tissue, primary tumor (*PT*), recurrent tumor (*RT*) 1 and *RT2* for marker *D1S214* (four bands presented at the same position). Case 129 showed LOH for marker *D3S3681* in *PT* and *RT* (no band 1 in *PT* and *RT* compared to that of *N*). Case 12 showed LOH for marker *D9S199* in *RT* (no band 1 in *RT* compared to that of *N*). Case 16 showed MSI (the positions of bands in *PT* were different from that of *N*) for marker *D13S170* and LOH (no band 1 in *RT* compared to that of *N*). *LOH* loss of heterozygosity, *MSI* microsatellite instability.

band(s) within a certain allele or a shift of an allelic signal was considered as MSI. The LOH pattern between the primary and recurrent tumors from one individual patient was regarded as identical when the same marker demonstrated loss of the same allele or no LOH (Fig. 1). It was regarded as different LOH pattern when the same marker demonstrated loss of one allele in either the primary or recurrent tumor but no loss or loss of the other allele in the other tumor. If the LOH patterns and MSI for the different markers reached 30%,[15] the recurrent nodule was considered of different clonality compared to the primary tumor (MO).

For all the 160 cases, the LOH for the 10 different markers ranged from 17.7% to 53.2% and the MSI from 3.8% to 15.2% (Table 2). In average, the LOH rate and MSI rate for the 10 markers was 35% and 10%, respectively. By comparing the genetic information of LOH and MSI between primary and recurrent tumor, 30.0% (48/160), 63.8% (102/160), and 3.8% (6/160) patients with recurrent HCC were considered to be MO, IM, and indeterminate ones due to insufficient information for some of the markers in the primary or recurrent HCC nodules, respectively. Because another four patients showed both MO and IM in the recurrent nodules, they were also not determinable.

Correlations Between Pathologic Features and Microsatellite Analysis and Grouping

Totally, the result concluded by pathologic features is significantly correlated to that demonstrated by analysis of microsatellite polymorphism (r=0.611, p<0.01). For all the cases where the analysis of clonality from the pathologic features and the microsatellite polymorphism was unanimous, it was possible to select and divide them into the MO and IM group for further study. In total, 126 patients qualified for this, 37 for the MO group, and 89 for the IM group. Thirty-four patients were excluded from further analysis since the origin of recurrent HCC could not be determined or both types were simultaneously present.

Clinicopathologic Features of MO and IM Groups

For further analysis between the two groups, the following clinicopathological variables were investigated: age, gender, Child's stage, platelet count, total bilirubin (TBIL), deconjugated bilirubin (DBIL), albumin, globulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), cholinesterase, cholesterol, tumor number (n<2 versus n≥2), location (recurrent tumor

Table 2 Rates of Heterozygosis, LOH and MSI for the 10 Markers in 160 Patients

Number	Marker	Heterozygosis (%)	LOH (%)	MSI (%)
1	D1S214	76.5	22.8	7.6
2	D1S2797	59.7	32.9	11.4
3	D3S3681	66.2	36.7	6.3
4	D8S277	82.0	40.5	3.8
5	D9S199	68.8	17.7	3.8
6	D13S170	77.6	49.4	8.7
7	D16S3091	70.4	58.2	10.1
8	D17S796	83.7	32.9	12.7
9	D17S831	79.4	25.3	15.2
10	D17S938	86.5	53.2	2.5

Heterozygosis: the alleles of homologous chromosome at the same site are different.

Table 3 The Clinicopathologic Features Between the Groups of MO and IM

Variables	MO group	IM group	*P* value
	n=37 (%)	*n*=89 (%)	
Age (years)	54.4±9.9	51.7±10.3	0.179
Gender (male vs. female)	31(84):6(16)	76(85):13(15)	0.818
Child stage (A, B and C)	14(38):23(62):0(0)	62(70):26(29):1(1)	0.002
Platelet count (10^9/L)	110±40	137±59	0.012
TBIL (umol/L)	14.9±8.3	16.0±9.9	0.560
DBIL (umol/L)	5.4±2.5	6.5±4.3	0.160
Albumin (g/L)	39.9±6.6	42.6±6.7	0.043
Globulin (g/L)	32.8±10.1	34.7±8.3	0.292
ALT (U/L)	57.5±36.6	48.9±33.5	0.206
AST (U/L)	44.3±38.2	52.7±31.6	0.246
ALP (U/L)	101.8±65.1	111.5±80.7	0.522
Cholinesterase (U/L)	6.4±2.8	7.6±3.2	0.047
Cholesterol (mmol/L)	5.9±4.1	6.5±5.2	0.522
Tumor number (*n*=1 vs. *n*≥2)	33(89):4(11)	54(61):35(39)	0.002
Location (same vs. different lobe)	17(46):20(54)	59(66):30(34)	0.033
Tumor size (cm)	2.87±1.46	3.01±1.81	0.673
Capsule (present vs. none)	13(35):24(65)	23(26):66(74)	0.293
Histological grading (1, 2, and 3)	15(41):19(51):3(8)	12(13):53(60):24(27)	0.001
Portal vein invasion (positive vs. none)	5(14):32(86)	36(40):53(60)	0.003
AFP≥100 vs. AFP<100 (ng/ml)	29(78):8(22)	63(71):26(29)	0.382
Recurrent time (months)	23.9±13.0	15.6±11.9	0.001

MO multicentric occurrence, *IM* intrahepatic metastasis, *TBIL* total bilirubin, *DBIL* direct bilirubin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *AFP* a-fetoprotein

same lobe versus different lobe compared to primary tumor), tumor size (primary tumor), capsule (present versus no capsule), histological grading (1:2:3), portal vein invasion (invasion versus no invasion), a-fetoprotein (AFP) (>100 ng/ml versus <100 ng/ml) and recurrent time. The following variables were significantly different between group MO and group IM by univariate analysis: Child's stage, platelet count, albumin, cholinesterase (host factors), tumor number, location (compared to the primary tumor), histological grading, positive portal vein invasion in primary tumor (primary HCC) and recurrent time (factors of recurrent HCC) (Table 3). Analysis of stepwise regression identified that recurrent time (months), grading, portal vein invasion, tumor number, and Child's stage were the most important discriminating factors between MO and IM ($p<0.05$; Table 4). As for their prognosis, Kaplan–Meier and log-rank test demonstrated the disease-free survival in group MO was significantly better than that in group IM ($p=0.002$) (Fig. 2).

Discussion

An accurate method to identify the origin of a recurrent tumor in an individual patient is to determine whether the recurrent tumor and primary one are monoclonal (intrahepatic metastasis, IM) or polyclonal (multicentric occurrence, MO). Distinction between them has conventionally been determined by pathological criteria. Though pathological observation is relatively subjective, it is still the most convenient method in distinguishing MO and IM. Our results based on pathology only showed that 27.5% (44/160) and 59.4% (95/160) patients were MO and IM, respectively. Moreover, in a certain number of cases no

Table 4 The Discriminating Factors Between Group Mo And Group IM By Stepwise Regression

Variables	β	Std. Error	*t*	*P* value
Recurrent time (month)	−0.018	0.004	−4.153	0.004
Grade	0.150	0.053	2.825	0.006
Portal vein invasion	0.179	0.074	2.420	0.017
Tumor number	0.163	0.075	2.168	0.032
Child's Stage	−0.147	0.069	−2.144	0.034

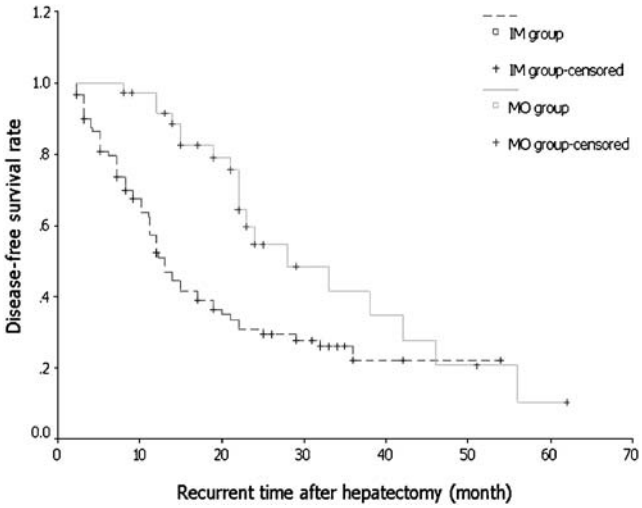

Figure 2 Kaplan–Meier and log rank test demonstrated the disease-free survival in group MO was significantly better than that in group IM (p=0.002). *MO* multicentric occurrence, *IM* intrahepatic metastatic. (Censored means mainly the cases without outcome of recurrence at the end of observation or the patients who were lost to follow-up.)

definitive differentiation between recurrent and primary tumor was possible, which suggested the limitation of this method when used alone.

The most precise and specific methods for assessing tumor clonality depend on the detection of common patterns of aberrations in DNA among the recurrent and primary tumors. Recent studies have indicated that in HCC, frequent aberrations are present in several genomic regions, including 1p, 4q, 5q, 6q, 8p, 8q, 10q, 11p, 13q, 16q, 17p, and 22q.[17–20] It has been suggested that an accumulation of these genetic changes, which affect the expression of oncogenes and tumor suppressor genes, occurs in a stepwise manner during HCC development and progression and can be used to identify the clonality of recurrent tumor. Therefore, in the present study 10 markers with a high frequency of LOH were selected to be amplified, which are located in seven different chromosomes. The extensive distribution may reflect more accurately the nature of the recurrent tumor than when just using markers for fewer chromosomes. With that, 30.0% (48/160) and 63.8% (102/160) of the patients with recurrent HCC were considered to be MO and IM, respectively. Besides LOH for the markers, we also noticed that MSI provides us valuable information in differentiating MO and IM, though its frequency in microsatellite polymorphism is much lower than that of LOH.

Compared with other molecular methods, the test of microsatellite polymorphism with PCR and PAGE showed many advantages as described before. Furthermore, it can be used for small quantities of genome DNA from tiny specimens such as fine-needle biopsy. This makes it possible to perform clone analysis for patients not qualifying for an operation. Meanwhile, it can also be used to study DNA fragments from paraffin-embedded specimen since the microsatellite markers are usually short DNA and can be amplified. In contrast, the test of HBV integration needs large quantities of genome DNA for Southern blotting and presents considerable limitation.

The combined analysis of pathological features and genetic data from LOH and MSI demonstrated that 23.1% (37/160) and 55.6% (89/160) were MO and IM, respectively. The percentage of MO is similar to that reported by Irene et al.,[21] but is less than that of most Japanese studies.[22,23] This may be caused by the different reasons for hepatitis. HCV is the most important risk factor in Japan. HBV, however, is intensively associated with HCC in China. It has been reported that the incidence of MO is much higher in HCV-positive patients than in HBV-positive ones.[24] The precise cause of this higher incidence of MO in HCV-positive patients is unclear. In general, however, it is well-known that cirrhosis due to HCV causes more severe and persistent active inflammation than cirrhosis originating from HBV.[25] Such persistent active inflammation may cause continuous necrosis and regeneration of hepatocytes; this could lead to DNA instability in the hepatocytes and could cause HCC to occur more frequently. Tarao et al.[26] studied DNA synthesis in hepatocytes in cirrhotic livers after hepatectomy for HCC. They reported that in 28 HCCs associated with HCV-related liver cirrhosis, a high labeling index was found in 14 HCCs, and nine of the 14 had recurrence (or new cancer) within 3 years after surgery. On the other hand, in the remaining 14 HCCs (which had a low labeling index) only three had recurrence in the same period. These findings suggested that accelerated hepatocyte regeneration seemed to be closely related to the occurrence of HCC. Their findings also supported the finding of a higher frequency of synchronous or metachronous multicentric occurrence of HCC in HCV-related liver cirrhosis in which persistent liver cell damage and regeneration of hepatocytes are common.[27]

In a further comparison between the MO group and the IM group, the discriminating factors include tumor grade, number, and portal vein invasion. However, without statistical significance, it appears that tumor size was noted to be smaller in the polyclonal group compared to the intrahepatic metastasis group. The different growth velocity may due to the different biological behavior in the two groups (cancer cells in IM showed more powerful invasion and metastasis than those of MO) and also presented in tumor capsule and location besides the three variables above. Meanwhile, the short intervals of follow-up counteract the proliferative dimensional significance in the two groups. As for the non-tumor factor, the distinct Child's stage suggests that liver cirrhosis in patients with MO was

more severe than in IM. It is believed to cause multiple premalignant and malignant nodules in the liver and is considered to be one of the most important factors of simultaneous and metachronous multicentric occurrence of HCCs.[28] The other factors, such as platelet count, albumin, globulin, and cholinesterase, also suggested the poor liver function reserve in the patients of group MO. Nevertheless, in our study the disease-free survival in the MO group is better than in the IM group. This demonstrates that in the determination of patients' prognosis, the biological behavior of a tumor plays a more important role than liver cirrhosis does. Although our study was confined to curative resected patients and excluded unresectable cases and led to some bias in the comparison of variables, the results were considered to be quite reasonable. As we know, many cases in both groups lose the opportunity of surgery because of various factors in which multiple tumors located in both liver lobes and severe liver cirrhosis (Child's C) are the most common reasons in group IM and group MO, respectively.

In conclusion, the combined analysis of pathology and test for microsatellite polymorphism shows much power in the determination of clone origin of recurrent HCC. The incidence of MO HCC was much lower than in Japan due to the different origin of hepatitis. Apart from the appraisal of recurrent time, tumor grade, portal vein invasion, tumor number, and Child's stage, the discrimination between MO and IM for recurrent HCC benefits the evaluation of patients' prognosis.

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Distal Pancreatectomy: Incidence of Postoperative Diabetes

Jonathan King · Kevork Kazanjian · J. Matsumoto · Howard A. Reber · Michael W. Yeh · O. Joe Hines · Guido Eibl

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Abstract
Introduction Distal pancreatectomy is an accepted and safe procedure for lesions of the body and tail of the pancreas. Limited resections, including central pancreatectomy, have recently been advocated as possible strategies to preserve pancreatic endocrine function. The true rate of diabetes after distal pancreatectomy is not known, but we hypothesize that the risk is nominal.
Materials and Methods We reviewed 125 consecutive patients who underwent distal pancreatectomy between January 1, 1992, and March 31, 2006.
Results Of these 125 patients, 27 (21.6%) had an islet cell tumor, 25 (20%) adenocarcinoma, 24 (18.4%) serous cystic neoplasm, 19 (15.2%) mucinous cystic neoplasm, 11 (8.8%) chronic pancreatitis, and eight (6.4%) intraductal papillary mucinous neoplasm. In addition to the distal pancreatectomy, 105 (84%) of the patients underwent splenectomy and 12 (9.6%) a concomitant liver resection. The median operative time was 232 min and median blood loss 250 cc. Postoperative complications occurred in 44 (35.2%) patients (12% fistula), and there was one death. Fourteen patients had known type 2 diabetes preoperatively.
Discussions With a median follow-up of 21 months, 10 (9%) of previously nondiabetic patients developed new onset diabetes. There was a trend toward increased risk of new onset diabetes among patients with pancreatitis (odds ratio, 2.9). In the absence of pancreatitis, the rate was 7.5%. Length of hospitalization was greater for patients with new onset diabetes (9.4 vs 7.5, $P<.05$). Neither demographics, diagnosis, nor operative statistics impacted the risk of postoperative diabetes.
Conclusion We conclude that the rate of clinically apparent new onset diabetes after distal pancreatectomy is minimal. Alternative pancreatic resections aimed at preserving pancreatic mass are likely to be unwarranted.

Keywords Distal pancreatectomy · Postoperative diabetes · Pancreas

Introduction

Distal pancreatectomy (DP) is the standard operation for resection of both neoplastic and non-neoplastic lesions of the body and tail of the pancreas. It can be done with low morbidity and mortality rates, particularly when performed by experienced surgeons at centers with high operative volumes.[1] The resection may include splenectomy, depending on the nature of the underlying lesion and anatomical considerations.

Some controversy has arisen regarding the use of DP for benign lesions involving the proximal body and/or neck of the pancreas. For these, some propose the so-called central pancreatectomy (CP) in an effort to preserve the normal pancreatic tissue in the remaining body and tail of the pancreas that would otherwise be sacrificed. First described by Guilleman and Bessot,[2] the proposed benefits of CP include preservation of pancreatic function and the spleen. Because less pancreas is removed, proponents of this alternative operation hypothesize that patients are less likely to develop diabetes mellitus (DM) postoperatively, which seems logical.[3,4]

However, there are significant limitations to CP.[5,6] Most notable is the need to manage two divided edges of the pancreas, thus creating two opportunities for pancreatic

J. King · K. Kazanjian · J. Matsumoto · H. A. Reber · M. W. Yeh · O. J. Hines (✉) · G. Eibl
Department of Surgery,
David Geffen School of Medicine, UCLA,
10833 Le Conte Ave, CHS 72-170,
Los Angeles, CA 90095-6904, USA
e-mail: joehines@mednet.ucla.edu

Table 1 Published Series of Distal Pancreatectomy (DP)

Author	Study design	Number of patients	Population/pathology	Mortality (%)	Morbidity (%)	Incidence of diabetes (%)
Shankar et al.	Retrospective cohort study	113	Chronic pancreatitis	0.9	13	–
Kajiyama et al.	Retrospective cohort study	394	Not reported (n.r.)	n.r.	n.r.	–
Ohwada et al.	Prospective cohort study	110	Non-panc. malignancy and panc. disease NOS	2	31	–
Lillemoe et al.	Retrospective case series	235	Benign and malignant pancreatic neoplasia	0.9	31	8
Balcom et al.	Retrospective case series	190	Benign and malignant pancreatic neoplasia	3	38	–
Shoup et al.	Retrospective case series	125	Benign or low-grade malignancy	1.6	46	4.8
Bilimoria et al.	Retrospective case series	126	Benign and malignant panc. and non-panc. disease	3.2	114	–
Balzano et al.	Retrospective case series	123	Benign and malignant pancreatic disease	0	49	–
Kleeff et al.	Prospective case series	302	Benign and malignant pancreatic disease	2	35	–
Rodriguez et al.	Retrospective case series	259	Benign and malignant pancreatic disease	0.8	106	–
Sierzega et al.	Retrospective case series	132	Benign and malignant pancreatic disease	4.5	56.8	
McPhee et al.	Meta-analysis	7,872	Benign and malignant panc. and non-panc. disease	5.9	n.r.	–
Current	Retrospective case series	125	Benign and malignant pancreatic disease	0.8	35	8

fluid leak and/or fistula. Indeed, fistula rates published for CP are higher than those typically reported for DP.[7–11] In addition, in the series of CP that have been reported, there are occasional patients who turn out to have had invasive malignancies resected by this approach. This usually occurs because it is impossible to establish the true diagnosis preoperatively in some cases, and not all surgeons obtain frozen section confirmation that the neoplasm was benign at the time of operation.

The minimum amount of residual pancreas necessary to preserve normal glucose homeostasis is unknown. Published results suggest that between 5% and 20% of patients who have a resection of either the pancreatic head or tail for neoplastic disease develop new onset diabetes in the short

Table 2 Demographic and Operative Data of Patients Undergoing Distal Pancreatectomy

	NODM (+)	NODM (−)	*P* value
Age, mean±SEM (years)	60±14.7	57±15.5	0.6148
Sex (no.)			
Male	7	75	0.7600
Female	3	40	
Operative time, mean±SEM (min)	225±66.8	246±74	0.5314
Blood loss, mean±SEM (ml)	641±721	429±555	0.2605
Length of stay, mean±SEM (days)	9.4±4.0	7.5±2.9	0.0550
Type of resection			
Standard	10	111	0.5488
Extended	0	4	
Morbidity (other than NODM), no.	5/10	34/115	0.1810
Mortality	0	1	

term (months after surgery); the number increases to between 40% and 50% up to 7 years after surgery.[12–15] The risk of diabetes also correlates with the volume of pancreas resected, though the effect appears to be nonlinear.[16]

Several reports suggest that many patients who undergo DP or even subtotal pancreatectomy have normal fasting postoperative blood glucose levels.[15,17] To date, few studies exist that report the incidence of postoperative DM in patients undergoing DP for resection of benign or malignant pancreatic lesions. We hypothesized that DP can be performed safely and with low risk of the development of new DM in the postoperative period, and we performed this retrospective analysis of our experience to test that hypothesis.

Materials and Methods

Data Collection

This study was approved by the UCLA Office for Protection of Research Subjects. We retrospectively reviewed data collected from 125 consecutive patients who underwent distal pancreatectomy between January 1, 1992 and March 31, 2006 at the University of California, Los Angeles. The main outcomes measured were morbidity and mortality rates and the incidence of postoperative diabetes. Data was also collected on patient demographics (age and sex), indication for operation (malignant diseases vs benign diseases and chronic pancreatitis), extent and type of resection (extended vs non-extended DP and laparoscopic DP), additional procedures performed (splenectomy or concomitant liver resection), operative factors (time in operating room, blood loss, and management of pancreas remnant), perioperative transfusion requirement, perioperative complications, and length of follow-up. An extended DP was defined as a resection that began to the patient's right of the superior mesenteric/portal vein and included the neck of the pancreas neck. If the neck was not removed, the resections were considered non-extended.

Table 3 Incidence of New-Onset Diabetes Mellitus (NODM) by Pathologic Diagnosis

Diagnosis	Number of patients (%)	NODM (+)	NODM (−)
Islet cell tumor	27 (21.6)	2	25
Adenocarcinoma	25 (20)	0	25
SCN	24 (18.4)	2	22
MCN	19 (15.2)	1	18
IPMN	8 (6.4)	1	7
Chronic Pancreatitis	11 (8.8)	2	9
Other	11 (8.8)	2	9
Total	125 (100)	10	115

Table 4 Concomitant Procedures

Procedure	Number of patients	Percent
None	20	16
Splenectomy	105	84
Liver resection	12	9.6
Cholecystectomy	5	4
Colon resection	6	4.8
Gastrectomy	5	4
Small bowel resection	2	1.6
Adrenalectomy	2	1.6

New onset diabetes mellitus (NODM) was defined by the need for initiation of antihyperglycemic medications (oral agents or insulin) within the median follow-up period of 21 months in patients who had no need for glucose control before the procedure.

Literature Review

A literature review of case series, randomized controlled trials, and cohort studies with the key word "distal pancreatectomy" was performed using the PubMed database. Twelve articles were identified that met the study requirements of greater than or equal to 100 distal pancreatectomies and published in the English language. Data was compiled to generate conglomerate results of mortality and morbidity rates (Table 1).

Statistical Analysis

Data are presented as a mean±SEM. Differences in continuous variables of demographics, operative data, and length of hospitalization were analyzed using analysis of variance and *t* tests. Differences in discrete demographic and operative variables were analyzed with the Fisher exact test. Statistical significance was achieved at $P<0.05$.

Table 5 Postoperative Complications

Complication	Number of patients	Percent
None	81	64.8
One or more	44	35.2
NODM	10	8
Pancreatic fistula	15	12
Intraabdominal abscess	6	4.8
Wound infection	10	8
Genitourinary infection	7	5.6
Pulmonary	7	5.6
Cardiac	5	4
Hemorrhage	3	2.4
Other	3	2.4

Table 6 Management of Pancreatic Distal Remnant

Distal remnant	Number of patients	Percent
Stapled	25	20
Oversewn	16	12.8
Both	81	64.8
Anastomosis	3	2.4
Fibrin Glue	4	3.2

Results

Patient Characteristics and Operative Results

From January 1, 1992 to March 31, 2006, 125 distal pancreatectomies were performed at the University of California, Los Angeles, Medical Center. There was one death (0.8%) and morbidity was 35%. Age, gender, blood loss, operative time, and length of stay were similar in patients who developed NODM and those who did not (Table 2).

Of the 125 patients, 27 (21.6%) had an islet cell tumor, 25 (20%) adenocarcinoma, 24 (18.4%) serous cystic neoplasm (SCN), 19 (15.2%) mucinous cystic neoplasm (MCN), 11 (8.8%) chronic pancreatitis, and eight (6.4%) intraductal papillary mucinous neoplasm (IPMN; Table 3). In addition to DP, 105 (84%) patients underwent splenectomy and 12 (9.6%) had a concomitant liver resection. Another 20 (16%) patients had additional resections involving stomach, large intestine, small intestine, or adrenal gland. Four (3.2%) patients underwent extended DP where resection included tissue to the right of the SMV (Table 4).

Postoperative Outcomes

The median operative time was 232 min and median blood loss 250 cc. Postoperative complications occurred in 44 (35.2%) patients, and there was one death in a patient who was re-operated on for a bleeding duodenal ulcer and had methicillin-resistant *Staphylococcus aureus* pneumonia. Fourteen patients had two or more complications other than NODM. The most common complications were pancreatic fistula (12%), genitourinary infection (5.6%), and pulmonary infection (5.6%; Table 5). The cut end of the proximal remnant of the pancreas was managed by a variety of techniques including stapling, suture oversewing, a combination of both stapling and suture, the application of fibrin glue, and enteric anastomosis (Table 6).

Fourteen (11%) had DM preoperatively. With a median follow-up of 21±36.8 months, of the 111 patients without preoperative diabetes, 10 (8%) patients experienced new onset diabetes. There was a trend toward increasing risk of new onset diabetes in patients with a previous history of pancreatitis (odds ratio, 2.9). Without pancreatitis, the rate of NODM was 7.5%. There was a trend toward a longer inpatient stay in those patients who developed NODM (9.4 vs 7.5, P=0.055). Neither demographics, diagnosis, nor operative statistics (time in operating room, blood loss, type of resection, or method of management of pancreatic remnant) impacted the risk of postoperative diabetes.

Discussion

The choice of operation for a disease that involves the body and tail of the pancreas must consider the location of the lesion and the likely pathology. Certainly, malignant or potentially malignant lesions should not be addressed with a limited resection since a central pancreatectomy would not adequately sample peripancreatic lymph nodes and provide an adequate oncologic resection. But for many other lesions with limited malignant potential, a more limited resection may be appropriate.

Though efforts to maximize residual pancreatic tissue have a certain intuitive appeal, our findings indicate that the risk of clinically apparent diabetes after conventional distal pancreatectomy is low. We report that only 10 (8%) of patients in this series developed NODM after DP. This is

Table 7 Pancreatic Fistula in Central Pancreatectomy

	Number of patients	Type of distal duct anastomosis			Fistula (%)
		Gastrostomy	Jejunostomy	Oversewn	
Adham et al.	50	44	6	0	22
Crippa et al.	100	Distinction not made		0	44
Muller et al.	40	0	40	0	7.5*
Iacono et al.	20	0	20	0	25
Sauvanet et al.	53	25	26	2	30
Total					25.7

[a] Of the study patients, 57.5% had chronic pancreatitis.

particularly striking when considering the cases of extended DP. Although the number is small, none of these four patients developed NODM postoperatively, despite undergoing resection of perhaps 75% to 80% of their pancreatic parenchyma. These data are consistent with other published reports on the incidence of NODM after DP found in the literature.[15,17] Thus, we estimate that no more than 20% to 25% of otherwise normal residual pancreas is required to maintain clinically normal glucose homeostasis.

The fact that more than half of the pancreas can be removed without precipitating NODM also may reflect functional adaptation of the remaining pancreatic islets. Adaptive increases in beta cell mass, which represent a combined effect of increased beta cell proliferation and beta cell hypertrophy, are known to occur in humans and other mammals.[19] If this were the case, measurable impairments in insulin secretion and glucose disposal would be expected in the immediate postoperative period, followed by progressive restoration of normal glucose homeostasis during the period of adaptation. Such detailed data was not collected for this study.

The data on the risk of NODM must be weighed against the incidence of postoperative morbidity (other than NODM) and mortality. Complication rates (most often pancreatic fistula) and mortality in this series compared favorably to those published by others in the past 10 years.[1,15,18,20–28] Furthermore, the increased risk of pancreatic fistula associated with procedures such as CP is a major disadvantage to be considered during preoperative planning. While most such fistulas can be managed without the need for reoperation and few patients die as a result, the economic cost is considerable.[11]

Current series describing experience with central pancreatectomy report fistula rates substantially higher than those seen with distal pancreatectomy (Table 7).[4,9,29–31] Although the study of Muller et al. appears to have remarkably low incidence of fistulae, it should be noted that 57.7% of the patients in that study had surgery for chronic pancreatitis, where fistula rates are typically significantly lower. The remainder of the series describes fistula rates between 22% and 44% with a composite mean of 25%. This is considerably higher than the 12% fistula rate demonstrated by the current study. It is because of this considerable risk of morbidity that central pancreatectomies have been rare procedures in our practice numbering only three during this study period.

These observations should not be misinterpreted to suggest that we favor more extensive pancreatic resections for all lesions that could be removed safely with lesser procedures that spare pancreatic parenchyma. But our data do suggest that the risk of diabetes mellitus after distal pancreatectomy is low and that the desire to avoid new onset diabetes should not be used as a justification for a more limited resection. On occasion, a central pancreatectomy may be appropriate, but consideration of the likely pathology should drive decisions about the extent of resection. Malignant lesions or those with a high likelihood of malignancy should be treated by distal pancreatectomy and splenectomy. Intraoperative frozen section examination of the resected specimen should minimize the frequency with which central pancreatectomy ends up as the "definitive" operation for an invasive malignancy.

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Effect of Medical or Surgical Admission on Outcome of Patients with Gallstone Pancreatitis and Common Bile Duct Stones

Jennifer LaFemina · Suzanne M. Sokal · Yuchiao Chang · Deborah McGrath · David L. Berger

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Abstract
Introduction Management of uncomplicated common bile duct stone (CBDS) and gallstone pancreatitis (GP) presumably varies based on whether a patient is admitted to medicine or surgery. This study evaluates the impact of admitting team on outcome and cost.
Methods Three hundred seventy patients admitted to the Massachusetts General Hospital for CBDS or GP were retrospectively analyzed for demographics, insurance status, procedures, complications, length of stay, readmission, and cost. A multivariable analysis was conducted for outcome and cost measures.
Results Patients admitted to a surgical service were younger than those admitted to a medical service. Gender, race, tobacco use, and the presence of chronic obstructive pulmonary disease and chronic renal insufficiency were not significantly different between groups. Patients admitted to a medical service had a higher incidence of coronary artery disease and diabetes. Despite lower readmission rates for surgical patients, there was no difference in total hospital days between groups. Though total cost of an initial surgical admission was greater than a medical admission, total cost attributable to the index admission diminished over time and ultimately was not significant in follow-up.
Conclusions Despite variations in uncomplicated management of CBDS and GP, there is no difference, in long-term follow-up, in the total number of hospital days or cost for the management of CBDS or GP based on admitting team practices.

Keywords Common bile duct stones · Gallstone pancreatitis · Admitting team · Outcome · Cost

This manuscript is not based on communication to a society or meeting.

J. LaFemina · D. McGrath · D. L. Berger
Department of Surgery,
Massachusetts General Hospital and Harvard Medical School,
Boston, MA, USA

S. M. Sokal
Decision Support and Quality Management Unit,
Massachusetts General Hospital and Harvard Medical School,
Boston, MA, USA

Y. Chang
Department of Medicine,
Massachusetts General Hospital and Harvard Medical School,
Boston, MA, USA

D. L. Berger (✉)
Massachusetts General Hospital,
15 Parkman Street, WAC 4-460,
Boston, MA 02114, USA
e-mail: dberger@partners.org

Introduction

In an attempt to find the balance between the potential morbidity associated with non-therapeutic endoscopic retrograde cholangiopancreatography (ERCP) and the morbidity associated with a failed or unnecessary common bile duct exploration (CBDE), the management of uncomplicated common bile duct stones (CBDS) and gallstone pancreatitis (GP) may proceed down a number of pathways. A number of algorithms using combinations of one- and two-stage surgical and endoscopic approaches that likely yield equivalent success rates have been proposed, but management remains controversial. Some propose a single-staged approach stating that surgical treatment alone is sufficient for the majority of patients and may minimize

morbidity and mortality.[1–11] Others advocate endoscopic-based therapy as a means of decreasing immediate morbidity and mortality particularly in patients who are high-risk surgical candidates, who are in a center with skilled endoscopists, and in whom there is a high suspicion of CBDS.[12–14] Recently, a meta-analysis of 12 studies revealed that outcome—defined as successful duct clearance, mortality, overall morbidity, and need for additional procedures—was not significantly different between surgery-only and endoscopy-plus-surgery-treated groups.[15] In light of variations in treatment and, ultimately, the lack of a consensus about the "best" way to manage these disease processes, many hospitals do not have definitive triage and management pathways for patients admitted with uncomplicated GP and CBDS. Consequently, one might assume that admission to a medical versus a surgical service might result in differences in management and, subsequently, differences in outcome and cost for patients admitted with these disease processes.

The objective of this study was to determine if admission to a medical versus a surgical service, without an established protocol for triage and management, impacts length of stay (LOS), readmission rate, complication rate, and overall cost for patients admitted with a diagnosis of uncomplicated CBDS and/or GP.

Material and Methods

Study Design and Objectives

The study consisted of a retrospective analysis of patients admitted to the Massachusetts General Hospital with a diagnosis of GP or CBDS. The objective of the study was to determine if admission to a medical compared to a surgical team affects (1) LOS and total hospital days, (2) number of procedures (including operations and/or ERCPs), (3) morbidity, and (4) total cost. The study was conducted in compliance with the institutional human research committee procedures.

Identification of Patients

Patients were eligible for inclusion if they were admitted to the Massachusetts General Hospital from September 1999 through December 2004 and if they were diagnosed with GP or CBDS via clinical, radiologic, endoscopic, or surgical means. Five hundred patients were randomly identified. Patients were excluded if they were diagnosed with necrotizing pancreatitis or if they had a cholecystectomy prior to the index admission. During the study period, the hospital did not have a universal algorithm for triage and management of patients with CBDS or GP.

Data Collection

Paper and electronic records were evaluated for subject age, gender, race, tobacco use, comorbid conditions [chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), coronary artery disease (CAD), chronic renal insufficiency (CRI)], admitting service, insurance status (including Medicaid, Medicare, uninsured, private health insurance, unknown), presence of an operation [including type (laparoscopic or open cholecystectomy)], presence of ERCP (including type and complications), LOS, number and types of complications, and cost. Cost is defined as the amount of money billed by the hospital to the insurance company or patient and is reflective of diagnosis-related groups (DRGs).

Follow-up

Paper and electronic records were evaluated for follow-up data for all patients from September 1999 through August 2005. All follow-up data (including outpatient and inpatient encounters) were collected for date of follow-up, reason for follow-up, presence of readmission, LOS (if applicable), presence of an operation or ERCP, presence of pancreatitis, and cost of follow-up admissions. Only visits, procedures, or admissions that were associated with the index admission were identified and used for data analysis.

Statistical Analysis

Baseline characteristics were compared between patients admitted to medical and surgical services using Wilcoxon rank sum tests for continuous variables and Pearson exact tests for categorical variables. A multivariable analysis was conducted on all outcome and cost data. Poisson regression models were used to compare the number of procedures between the two groups adjusting for age, gender, race, insurance status, and comorbidities (COPD, CAD, CRI, and DM). Linear regression models were used for log-transformed LOS and cost data, and logistic regression models were employed for readmission and complication data.

Results

Demographic and Clinical Characteristics

Five hundred patients admitted from September 1999 through December 2004 with a diagnosis with GP or CBDS were identified. Of these, 370 were analyzed; 130 were excluded because of the presence of necrotizing pancreatitis ($N=17$), prior cholecystectomy ($N=112$), or prior inclusion in the data set ($N=1$). The admitting

Table 1 Baseline Characteristics of Retrospective Cohort

Characteristic	Patients with index medical admission (*N*=168)	Patients with index surgical admission (*N*=202)	P value
Age—years			
Mean	66.9	55.1	<0.01
Standard deviation	19.6	21.0	
Gender–number of patients (%)			
Female	89 (53.0%)	120 (59.4%)	0.25
Race—number of patients (%)			
Caucasian	145 (86.3%)	153 (75.7%)	0.09
Prior or current tobacco use—number of patients (%)	63 (37.5%)	66 (32.7%)	0.45
Comorbid conditions			
COPD	19 (11.3%)	14 (6.9%)	0.29
CAD	57 (33.9%)	28 (13.9%)	<0.01
CRI	17 (10.1%)	8 (4.0%)	0.05
DM	31 (18.5%)	20 (9.9%)	0.04

diagnosis was CBDS in 69% (*N*=254) of patients, GP in 15% (*N*=55), and both CBDS and GP in 16% (*N*=61). The mean length of follow-up for 3.63 years (range, 0.97–6.21 years). The average follow-up was 3.61 years (range, 1.18–6.21 years) for medical patients and 3.64 years (range, 0.97–5.91 years) for surgical patients.

Clinical characteristics are summarized in Table 1. Analysis was conducted on 168 medical patients (45% of population) and 202 surgical patients (55% of population). Patients admitted to the medical service were significantly older than those admitted to a surgical service (66.9 vs. 55.1 years; $p<0.01$). There was not a statistically significant difference in gender or race between patients admitted to medicine and those admitted to surgery. Overall, 35% of patients endorsed current or remote tobacco use, but there was no significant difference in incidence between those admitted to surgery and those admitted to medicine (33% vs. 37%; $p=0.45$). The presence of COPD was not significantly different between groups. However, patients admitted to medicine were more likely to have CAD (34% vs. 14%; $p<0.01$) and DM (18% vs. 10%; $p=0.04$). There was a trend towards a greater incidence of CRI in the medicine group (10% vs. 4%; $p=0.05$).

Overall, there was a significant difference in the insurance status between medical and surgical cohorts ($p<0.01$). Patients admitted to medicine were more likely to have Medicare (54% vs. 31% for surgical patients; *N*=153). Surgical patients were more likely to have Medicaid (8% vs. 5% for medical patients; *N*=24), private insurance (49% vs. 39% for medical patients; *N*=164), or a lack of insurance (7% vs. 2% for medical patients; *N*=17). Insurance data were not available for 12 patients (3.2%).

Intervention Differences

Surgical patients underwent a greater number of total procedures (procedures = operation and/or ERCP) with an average of 1.5 procedures per patient during the index surgical admission compared to 1.1 procedures per patient during the index medical admission ($p=0.01$; Table 2). Ninety percent of surgical patients (*N*=182) underwent an operation during their index admission, with the number increasing to 91% within 1 year of initial admission. After adjusting for age, gender, race, insurance status, and comorbid conditions, these values were significantly greater than the 40% of medical patients (*N*=67) who had an operation during their index admission ($p<0.01$) or the 42% of medical patients (*N*=70) ultimately having an operation within 1 year of initial admission ($p<0.01$). The number of ERCPs ranged from zero to three per patient during index admission. Though medical patients underwent an average of 0.7 ERCPs per patient during initial admission, versus 0.6 ERCPs per patient during index admission for surgical patients, the

Table 2 Procedure Differences Between Patients Admitted to Medicine and Surgery

Average number of procedures (ERCPs and operations)	Patients with index medical admission (*N*=168)	Patients with index surgical admission (*N*=202)	*P* value[a]
Average number of procedures per patient (Index)	1.1	1.5	0.01
Average number of procedures per patient (first 365 days)	1.6	1.7	0.48
Average number of procedures per patient (All follow-up)	1.7	1.8	0.62

[a] Adjusted for age, gender, race, insurance status, and comorbidities

difference was not statistically significant (p=0.33). Differences in the total number of procedures and ERCPs were not statistically significant at any time during follow-up.

Length of Stay and Readmission Differences

The mean LOS for all patients at index admission was 5.6 days. There was no difference between LOS at index for a medical or surgical admission (p=0.23; Table 3). Patients initially admitted to surgery ultimately spent fewer days in the hospital related to their initial diagnosis during follow-up; however, the difference did not reach statistical significance after adjusting for age, gender, race, insurance status, and comorbidities (p= 0.74 at 1 year and p=0.46 for all follow-up).

Within the first year after index admission, there were 87 patients (23%) readmitted for reasons related to their initial admission diagnosis. Within the first year, surgical patients were readmitted 27 times (13% of index admissions), while medical patients were readmitted 60 times (36% of index admissions; p<0.01; Table 3). The decrease in readmission rate persisted through all follow-up, as surgical patients were readmitted significantly fewer times (16% of index admissions) than medical patients (40% of index admissions; p< 0.01; Table 3).

Morbidity Differences

There was a 34% overall complication rate during index admission. Patients admitted to surgery were more likely to experience complications (41%; mean 0.6 complications per patient during index admission, range 0–4) than those admitted to medicine (26%; mean 0.3 complications per patient during index admission, range 0–3; p=0.01). While there was no significant difference in the number of complications due to ERCPs between groups (p=0.85), the greater number of complications within the surgical group may be attributed to surgical complications (31% for surgical patients compared to 15% of medical patients who underwent an operation; p=0.01).

Table 3 Length of Stay and Readmission Rates for Patients Admitted to Medicine and Surgery

Variable	Patients with index medical admission (N=168)	Patients with index surgical admission (N=202)	P value[a]
Length of stay—number of days			
Index			
Mean	5.8	5.4	0.23
Standard deviation	7.6	6.9	
First 365 days			
Mean	7.6	5.9	0.74
Standard deviation	10.6	7.3	
All follow-up			
Mean	8.2	6.1	0.46
Standard deviation	11.2	7.9	
Number of readmissions (%)			
First 365 days	60 (35.7%)	27 (13.4%)	<0.01
All follow-up	68 (40.5%)	33 (16.3%)	<0.01

[a]Adjusted for age, gender, race, insurance status, and comorbidities

Table 4 Overall Cost for Patients Admitted to Medicine and Surgery

Overall cost	Patients with index medical admission (N=168)	Patients with index surgical admission (N=202)	P value[a]
Index			
Mean	$9,762	$12,082	<0.01
Standard deviation	$12,581	$20,129	
First 365 days			
Mean	$13,481	$13,090	0.01
Standard deviation	$17,987	$20,549	
All follow-up			
Mean	$14,652	$13,510	0.06
Standard deviation	$19,671	$21,211	

[a] Adjusted for age, gender, race, insurance status, and comorbidities

Cost Differences

Index surgical admissions had a mean total cost of $12,082, while the mean total cost of a medical index admission was significantly less ($9,762; p<0.01; Table 4). However, within the first year, the difference in total cost attributable to the index admission diminished: total cost within the first year after a medical index admission was $13,481, while cost after an initial surgical admission was $13,090 ($p$= 0.01). Similarly, when taking into account all follow-up encounters related to an index admission to medicine ($14,652) or surgery ($13,510), there was not a significant difference in total cost (p=0.06).

Discussion

GP and CBDS are not only disease processes that pose treatment variations but also are significant contributors to healthcare costs. Though studies have directly looked at the role of specific operative and endoscopic interventions on LOS, readmission rate, morbidity, and cost, there are no prior studies that assess the role of the admitting team on

these same outcomes. Consequently, at our institution, like others, no definitive triage or management algorithm—designed to optimize outcome and minimize cost—exists for these two disease processes.

The current study demonstrates risk factors and certain comorbid conditions that may influence medical and surgical admitting patterns for uncomplicated cases of CBDS and GP. At our institution, elderly patients with CAD and DM are significantly more likely to be admitted to a medical service, confirming one's intuition that patients who are sicker are more likely to undergo medical treatment.

Based on prior studies that suggest a non-endoscopic approach to gallstone-related diseases that require common bile duct intervention results in decreased LOS, we hypothesized that patients admitted to a surgical service would be more likely to undergo a definitive operative intervention and more likely to have a shorter LOS, lower total number of hospital days, and decreased readmission rates. After adjusting for age, gender, race, insurance status, and comorbid conditions, our data do in fact demonstrate a significantly lower readmission rate throughout follow-up in those patients initially admitted to surgery. While the decreased readmission rate translates into fewer hospital days, the difference in total hospital days is not significant either at index or in follow-up. The cause of this is not clear. The benefit in terms of lower readmission rate might reflect that the surgical group is more likely to undergo a definitive operative procedure—cholecystectomy—and therefore necessitate fewer readmissions for recurrent disease. However, even if this is the case, it is possible that the type of admitting team and the subsequent differences in management that result—specifically, surgical patients more likely to undergo treatment involving an operation—do not ultimately impact the time of a patient's hospitalization related to uncomplicated CBDS or GP.

Complication rates based on endoscopic- and non-endoscopic-based treatment algorithms for stone disorders requiring a common bile intervention have been reported in a number of past studies. Initial endoscopic sphincterotomy (ES) for the treatment of choledocholithiasis results in a 5.8–24% complication rate.[16–22] The rate of choledochal complications (i.e., recurrent biliary stones, cholangitis) increases to 36% when ERCP is employed for recurrent choledocholithiasis post-ES.[23] Studies evaluating complication rates in a operative-based approach for the management of obstructive choledochal stone disease report similar numbers, with complication rate ranging from 5% to 20%.[24,25] In the current study, patients initially admitted to a surgical service had significantly more complications during their index admission compared to those admitted to medicine. As these patients are also more likely to undergo an operative procedure—both cholecystectomy as a single-staged approach as well as cholecystectomy with perioperative ERCP and/or ES—the greater complication rate for a patient admitted to a surgical team is not unexpected. However, the overall rate of complications was 34% for all patients and is surprisingly high. Causes for this could include not only aggressive inclusion criteria for complications, particularly minor complications such as fever and urinary tract infection, but also a patient population with a greater number of comorbid factors at this referral center.

Finally, no prior studies have evaluated the effect of the type of admitting team, and subsequently the differences in therapy, on total cost in the management of uncomplicated obstructive stone disorders. We hypothesized that there would be a significant difference. Surprisingly, this study suggests that the initial cost benefit of admission to a medical service diminishes with time and ultimately, admitting service does not have an impact on overall cost. By extrapolating the results of prior studies that demonstrated decreased cost with operative-based approaches,[26–28] it would seem that admissions to teams that favor operative approaches (i.e., surgical teams) would therefore result in decreased cost. This study was retrospective in nature and thus eliminated the potential bias of a prospective study in this regard. As no algorithm for the triage and treatment of CBDS and GP exists at our institution, the management decisions made in this study were not affected by either an algorithm or observer bias and reflect the standard practice of numerous physicians involved on the medical and surgical services. It is possible that this would change if all patients were ultimately referred to a small cadre of physicians who followed a defined algorithm. However, this is an accurate reflection of the results at a large teaching institution and the structure that is inherent with that type of hospital.

The current study has a number of flaws. The study is retrospective and thus prone to the inherent bias of retrospective work. We may fail to include procedures or data that we could not identify. We used a standardized complication grid, but we may have been overaggressive in our inclusion of complications. Additionally, our institution does not have a defined protocol for the triage and management of patients admitted with either CBDS or GP, and we excluded complicated cases of GP, namely necrotizing GP. While the lack of a standardized algorithm and the exclusion of the subset of patients with necrotizing disease introduce the possibility of referral and selection biases in the current study, it also allows for a study environment that parallels that found in most institutions. At the same time, though, the lack of a standard algorithm in combination with inclusion of patients with uncomplicated disease parallels the setting that would be witnessed in the non-teaching setting, thereby allowing for the generalizability of the results and conclusions to both

teaching and non-teaching hospitals. Ultimately, independent of standardized protocols and in the setting of the presumed bias for or against operative intervention with a surgical or medical admission, respectively, outcome—in terms of total hospital days and cost—is not influenced by admitting team. Furthermore, at our institution, there are extremely skilled gastrointestinal interventionalists and their success might skew our outcomes. It is also possible that with a longer period of follow-up, the continued prevalence of readmissions in the medical group might result in overall greater costs for the group initially admitted to medicine. Finally, this study does not address the timing of procedures or the specific types of procedures that were performed. It is possible that subset analysis of these specific points will elucidate further information, but the current study's focus was on the role of type of admitting team on outcome and cost.

Conclusion

Ultimately, despite assumptions that differences in admitting team might result in variations in the management of CBDS and GP, and subsequently differences in outcome and cost, differences in admitting team do not significantly impact patient outcome or cost. While differences in inpatient management result in lower readmission rates for patients initially admitted to a surgical service, this difference does not translate either into differences in total hospital days or into a long-term overall cost difference for patients with uncomplicated CBDS and GP.

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Primary Aortoduodenal Fistula: New Case Reports and a Review of the Literature

Francisco S. Lozano · Luis Muñoz-Bellvis · Enrique San Norberto · Asuncion Garcia-Plaza · Jose Ramon Gonzalez-Porras

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Introduction

A primary aortoduodenal fistula (PADF) is a communication between the lumen of the aorta and that of the gastrointestinal tract at duodenal level. Unlike primary fistulas, there are other so-called secondary ones, such as the complication of a previously implanted aortic prosthesis; these are far more frequent.

Since their first description some 100 years ago, more than 200 PADFs have been reported.[1–5] The location between the aorta and duodenum, mainly in its third portion, caused by the evolutionary complication of an aortic aneurysm is the most common situation. Although less frequent, communications also occur between other parts of the digestive tract (esophagus, jejunum, ileum, and colon). These are caused by other reasons (infection, tumor, radiation therapy, foreign bodies, etc.). Apart from their rarity, the interest in PADFs lies in the diagnostic and therapeutic difficulties involved in their handling, which clearly affect their prognosis.

In the present work, we carried out a literature search on Medline using different key words (primary, aortoenteric, aortoduodenal, aortoesophagic, aorto-enteric, aorto-duodenal, aorto-oesophageal, and a combination of these with fistula) between January 2004 and December 2006. This allowed 34 new cases to be added, which together with those from previous reviews[1–4] make a total of 366 primary aorto-enteric fistulas, of which 267 (72.9%) are PADFs. In this paper, we report two new cases and comment on the historical evolution of this pathology.

F. S. Lozano (✉) · L. Muñoz-Bellvis · E. San Norberto · A. Garcia-Plaza · J. R. Gonzalez-Porras
Angiology and Vascular Surgery,
University Hospital of Salamanca,
Paseo de San Vicente, 58-182,
Salamanca 37007, Spain
e-mail: lozano@usal.es

Case Report #1

The patient was a man of 72 who was admitted to the emergency services because of hypogastric pain that also affected his back and which had been present for a week, worsening in the previous 48 h. His previous clinical history included hypercholesterolemia and an episode of acute pancreatitis of lithiasic origin. Two years earlier he had been diagnosed with an infrarenal aneurysm of the abdominal aorta (AAA) with a transverse diameter of 5 cm, for which he had periodically been attending outpatient consultations; no significant worsening in his condition was observed over the previous 5 months.

On examination, the patient's hemodynamics were stable, as were his arterial pressure and heart rate (within normal limits). There was no hematemesis or melena. The abdomen did not show signs of peritonitis; the abdominal mass and peripheral pulses were present. Hemoglobin was 15.2 g/dl; hematocrit 44.6%, leukocytes 15,300/μl, with 87.1% neutrophiles. The rest of the analytical findings were unremarkable.

An abdominal computed tomography (CT) was performed with and without intravenous contrast. This revealed the presence of an infrarenal AAA with a transverse diameter of 7 cm, containing thrombotic material. Small air sacs were seen inside the thrombus. The duodenum was adhered to the wall of the aneurysm, with a peripheral inflammatory reaction (Fig. 1). Surgical intervention was proposed after a diagnosis of an AAA complicated by an aorto-duodenal fistula.

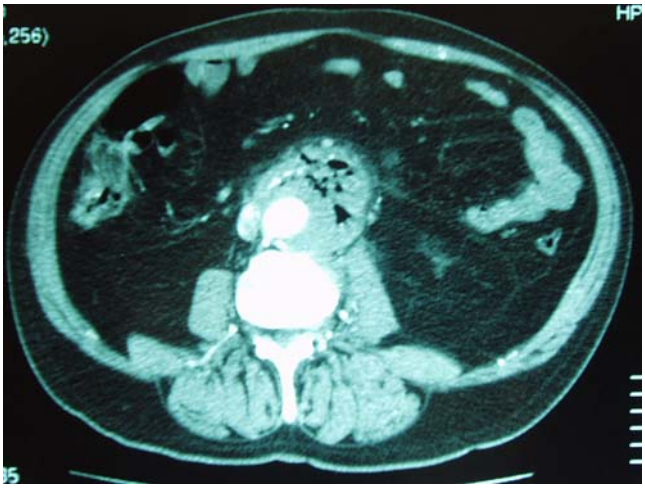

Figure 1 Preoperative (case 1) aneurysm of the abdominal aorta with the presence of gas inside the thrombotic matter and loss of definition between the aorta and the duodenum.

With a median laparotomy, the AAA was exposed together with its fistulization to the fourth portion of the duodenum (Fig. 2). A purulent content was observed in the fistulous zone and the presence of lithiasic chronic cholecystitis was noted. The aorta was cross-clamped below and above the aneurysm, debriding the adherence between the duodenum and the aneurysm (the fistulous zone). The duodenal orifice was sutured, the inferior mesenteric artery was ligated, and the lumbar arteries were sutured. The aneurysm was extirpated, leaving part of the posterior face. The infrarenal abdominal aorta was sutured (two levels) above the aneurysm and above both iliac arteries. Epipoplasty of the duodenal stump was performed, followed by cholecystectomy and closure of the laparotomy. The lower limbs were revascularized with an axilo-femoral bypass.

The microbiological cultures taken during surgery were positive for *Streptococcus viridans*, requiring intravenous treatment, based on the antibiogram, with amoxicillin-clavulanic acid. During the postoperative period, the patient developed a paralytic ileum, but was discharged 12 days after surgery. One year later the patient remains asymptomatic.

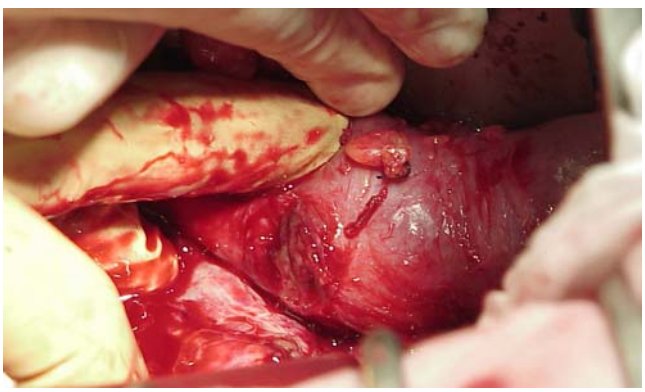

Figure 2 Intraoperative image (case 1) of the fistula between the fourth portion of the duodenum and an aneurysm of the abdominal aorta.

Case Report #2

This patient was a man of 63, who smoked, was hypertensive, had a history of duodenal ulcer, and was diagnosed with AAA, but was being monitored at another hospital. He was sent to our unit after complaining of nausea, vomiting, and epigastric pain irradiating to the right hemithorax. During abdominal exploration, a pulsing tumor was observed. Arterial pressure (AP) was 110/88 mmHg and heart rate was 57 bpm. Hemoglobin was 13.3 g/dl and hematocrit was 39%. The remaining analytical findings were unremarkable.

An abdominal ultrasound was performed, observing a partially thrombosed infrarenal AAA with a lateral right aortic image, suggestive of bleeding; this was confirmed by CT, which revealed a partially thrombosed AAA of 7.5×9.7×13 cm and a lateral right aortic mass that cast doubt on whether we were dealing with chronic bleeding or a tumor in the small intestine (Fig. 3). Esophagogastroduodenoscopy revealed the following: in the second portion of the duodenum was a large infiltrating tumor mass that extended to the third portion, compressing the lumen; the mass had a soft consistency and was covered by mucosa with a normal aspect. Biopsy samples were taken.

During his stay in the hospital the patient developed a picture of melena with no hemodynamic repercussions. Surgery was chosen as the treatment of choice, based on suspicion of an aorto-enteric fistula, although other diag-

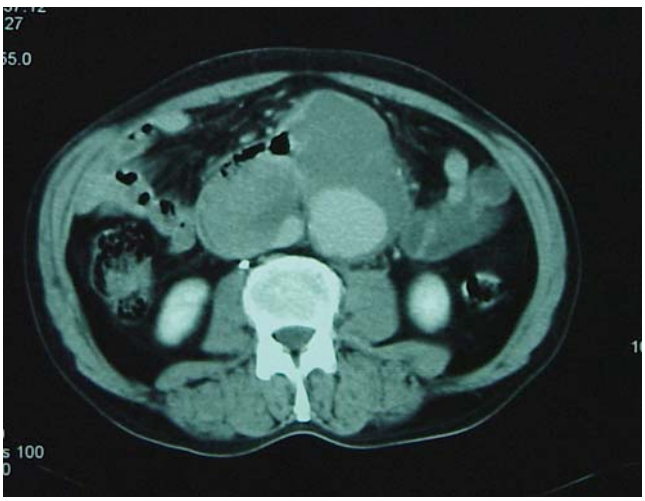

Figure 3 Preoperative CT (case 2): note aneurysm of the abdominal aorta, partially thrombosed, and a lateral right aortic mass.

Table 1 Primary Aortic-enteric Fistulas (Medline: January 2004 to December 2006)

Author (Ref)	Year	Age	Symptoms	Diagnosis	Cause	Location	Outcome
Lawlor et al.[6]	2004	82	H	CT, GDS	AAA	3° Duodenum	Exitus
		55	HC	GDS, C	AAA	Jejunum	Exitus
		72	HC	C, A, CT	IA	Ileon	Exitus
		72	D	CT	AAA	4° Duodenum	Alive
		76	D	CT	AAA	4° Duodenum	Alive
		58	M, H	GDS	AAA	Duodenum	Alive
Tambyraja et al.[7]	2004	–	UGB	–	AAA inflamm	Duodenum	Exitus
Cho et al.[8]	2004	68	M, D	GDS, CT	AAA	3° Duodenum	Alive
Ramanujam et al.[9]	2004	75	H, HC	GDS, A, CT	Tumor	Duodenum	Exitus
Kelliher et al.[10]	2004	73	H, D	GDS, CT	AAA	3° Duodenum	Alive
Wang et al.[11]	2004	74	H, HC	GDS, CT, A	AAA	Jejunum	Exitus
Cendan et al.[12]	2004	–	UGB	CT	AAA	3° Duodenum	–
Tutun et al.[13]	2004	61	D, MP	CT	AAA	Duodenum	Alive
		76	H, HC	CT	AAA	Duodenum	Alive
Cho et al.[14]	2004	71	H	CT	TAA	Esophagus	Alive
Nishibe et al.[15]	2004	71	H	GDS, CT	TAA	Esophagus	Alive
Pirard et al.[16]	2005	74	DF, H	CT	ATA	Esophagus	Alive
Wood et al.[17]	2005	66	D, HC, S	GDS, CT, A	AAA	Duodenum	Alive
Kimura et al.[18]	2005	58	–	–	TAA	Esophagus	Alive
Dagenais et al.[19]	2005	–	–	–	TAA	Esophagus	–
Honjo et al.[20]	2005	52	H, M	CT	AAA	3° Duodenum	Alive
Delgado et al.[21]	2005	78	H, HC	CT, GDS	AAA	3° Duodenum	Exitus
Klonaris et al.[22]	2006	72	HC, D, F	CT, GDS	Psoas abscess	4° Duodenum	Alive
Ikeda et al.[23]	2006	64	DF	CT	Tumor	Esophagus	Alive
Kavanagh et al.[24]	2006	7 cases	–	–	3 AAA	–	1 Alive
Contini et al.[25]	2006	77	H, Dolor torácico	CT, GDS	TAA	Esophagus	Exitus
Aksoy et al.[26]	2006	54	GB Baja	–	AAA	Colon	Exitus
Heikens et al.[27]	2006	78	F, S, Intestinal obstruction	GDS, CT	AAA Mycotic	4° Duodenum	Alive

Symptoms: *H* hematemesis, *HC* hematochezia, *D* abdominal or back pain, *M* melena, *UGB* upper gastrointestinal bleeding, *MP* pulsing mass, *DF* dysphagia, *S* shock, *F* fever
Diagnosis: *CT* computerized tomography, *GDS* gastroduodenoscopy, *C* colonoscopy, *A* angiography
Cause: *AAA* abdominal aortic aneurysm, *IA* iliac aneurysm, *TAA* thoracic aortic aneurysm, *ATA* abdominal-thoracic aneurysm

Table 2 Primary Aorto-enteric (and Aorto-duodenal) Fistulas

Author (Ref)	Period (years)	No. of PAEF	No. of PADF	PADF+AA	Survival	
					PAEF	PADF+AA
Reckless et al.[1]	1940–1972 (33)	131	102 (77.9%)[a]	NA	8 (6.1%)	DNA
Sweeney and Gadacz[2]	1973–1983 (11)	58	55 (94.8%)[b]	NA	14 (24.1%)	DNA
Voorhoeve et al.[3]	1984–1993 (10)	62	50 (80.6%)[c]	36 (72.0%)[f]	27 (43.5%)	DNA
Saers and Scheltinga[4]	1994–2003 (10)	81	44 (54.3%)[d]	38 (86.4%)[g]	44 (54.3%)	22 (57.9%)
Current review	2004–2006 (3)	34	16 (47%)[e]	14 (87.5%)[h]	17 (50.0%)	11 (78.5%)
Total	1940–2006 (66)	366	267/366 (72.9%)	88/110 (80.0%)	110/366 (30%)	33/52 (63.5%)

Case reports in five successive reviews of the literature (1940–2006)
PAEF primary Aorto-enteric fistula, *PADF* primary Aorto-duodenal fistula, *AA* aortic aneurysm, *DNA* data not available
Other locations:
[a, b] Stomach (7); others in small bowel (14) and colon (11)
[c] Esophagus (2); stomach (2); others in small bowel (6), colon (2)
[d] Esophagus (24); stomach (2); others in small bowel (9), colon (1), dual location (2)—one involving duodenum
[e] Esophagus (7); others in small bowel (3), sigmoid colon (1), not referred (7)
Other causes:
[f] Idiopathic (4), tuberculosis (2), inflammation (2), peptic ulcer (2), cystic disease (2), neoplasm (1), radiation (1)
[g] Neoplasm (3), arteritis (1), tuberculosis (1), radiation treatment (1)
[h] Neoplasm (1); abscess (1)

noses (duodenal tumor, contained hematoma) were not ruled out. Surgery revealed an aorto-enteric fistula between the AAA and the third portion of the duodenum. The infrarenal aorta and both primitive iliac arteries were ligated. The AAA was excised, the edges of the fistula orifice were cleaned and suturing was performed in two lines of the duodenum. An epipoplasty was performed on the aortic ligature and duodenal suturing was carried out. Cholecystectomy and appendectomy were performed, followed by an axilo-femoral bypass. The patient was discharged after 11 days and remains asymptomatic 6 months later.

Discussion

The incidence of primary aorto-enteric fistulas (PAEFs) is very low and, according to autopsy studies,[3] lies between 0.04% and 0.07%. Until December 2003, only 332 cases had been reported.[1–5] Between that date and December 2006, 34 new cases have appeared on Medline,[6–27] making a total of 366 PAEFs (Tables 1 and 2). Of these, 267 (72.9%) were of duodenal location (PADFs). For anatomical reasons, the portion most frequently affected is the third (2/3), while the fourth portion of the duodenum is involved in one third of cases.

The most frequent cause of PAEFs is the presence of an infrarenal AAA. Other aetiologies reported are the presence of primary or metastatic tumors, the ingestion of foreign bodies, radiation therapy or infections, such as diverticulitis, appendicitis, or ulcers. Within the aneurysms, those of atherosclerotic origin represent 73% of cases, the rest being of infectious or traumatic aetiology.[28]

The classic triad of PAEFs (gastrointestinal bleeding, abdominal pain, and a pulsing abdominal mass) only occurs in approximately 10% of cases.[4] Other symptoms described include back pain, hematemesis, melena, fever, sepsis, shock, or syncope. Cases involving intermittent bleeding have been reported in which the thrombus closed the fistula intermittently or the intestine contracted about the fistular trajectory around the wall. Accordingly, with such symptoms suspicion of the condition is crucial.

Currently, the diagnostic test of choice is helical CT with intravenous contrast.[29] In comparison with endoscopy of the digestive tract or arteriography, this technique is less invasive, easy to use, and it poses no risks regarding the aortic thrombus. The presence of air in the retroperitoneum and within the thrombus, together with a loss of the fat plane between the aorta and the duodenum, is, in all probability, indicators of a PADF. The visualization of a contrast agent in the gastrointestinal tract is a pathognomonic sign. Endoscopy is of great use for excluding other causes of acute gastrointestinal bleeding,[30] while arteriography is used for planning surgical intervention.[31]

The mortality of this pathology when untreated is almost 100%. After surgical intervention, survival ranges between 18 and 93%,[2–32] although it has improved remarkably in the past half century (Table 2). In any case, mortality mainly depends on the severity of the bleeding (which governs the urgency) and contamination (which governs the type of revascularization to be performed). Classic treatment consists of closure of the duodenal orifice, aortic ligation to exclude the aneurysm, and an extraanatomical bypass, although in cases of minimal contamination *in situ* repair is feasible. The classic treatment leads to higher percentages of mortality than *in situ* repair with prostheses. This is because of the first technical option, having been accomplished on occasions in which the anatomical field is most infected. Some authors have reported cases treated with endoprostheses, all of them followed up over a little more than 1 year, but without the appearance of complications.[33–34] This procedure can be posited as an initial therapeutic option in unstable patients, allowing control of the bleeding and the recovery of the patient for a second, definitive operation.

The clinical cases reported in this report offer a further reference to be added to the low number of patients with this pathology reported in the literature. In addition, the concise review of what has been published to date may be of great use in clinical practice.

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CASE REPORT

Autoimmune Pancreatitis and Concurrent Small Lymphocytic Lymphoma: Not Just a Coincidence?

Tad Kim · Stephen R. Grobmyer · Lisa R. Dixon · Robert W. Allan · Steven N. Hochwald

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Abstract
Case A 76-year-old gentleman presented with painless jaundice, weight loss, and anorexia. Computed tomography imaging revealed fullness of the pancreatic head and multiple enlarged retroperitoneal lymph nodes. Cholangiogram revealed a distal common bile duct stricture. Due to concerns of malignancy, the patient underwent operative exploration. Several enlarged lymph nodes in the aortocaval region and a firm hard mass in the pancreatic head were found. Frozen section from one of the lymph nodes was suspicious for low-grade lymphoma. A pancreaticoduodenectomy was performed. Histologic analysis of the pancreatic head revealed a lymphoplasmacytic infiltrate with stromal fibrosis consistent with autoimmune pancreatitis. The retroperitoneal lymph nodes were involved by small lymphocytic lymphoma.
Discussion Autoimmune pancreatitis is the most common benign diagnosis after pancreatic resection for presumed malignancy. It has a well-documented association with autoimmune conditions, such as Sjögren's syndrome, inflammatory bowel disease, and sclerosing cholangitis. Additionally, chronic lymphocytic leukemia–small lymphocytic lymphoma is often associated with autoimmune phenomena, most notably autoimmune hemolytic anemia. However, an association between autoimmune pancreatitis and small lymphocytic lymphoma has not been previously described. To our knowledge, this is the first reported case of a patient with concurrent autoimmune pancreatitis and small lymphocytic lymphoma.

Keywords Autoimmune pancreatitis · Lymphoplasmacytic sclerosing pancreatitis · IgG4 · Small lymphocytic lymphoma · Chronic lymphocytic leukemia

Introduction

Autoimmune pancreatitis (AIP), also termed lymphoplasmacytic sclerosing pancreatitis, is a rare disease of the pancreas that has become more widely recognized. It is typically characterized by irregular narrowing of the main pancreatic duct, enlargement of the pancreas, and lymphoplasmacytic inflammation. The first report suggesting its existence was published in 1962 and noted a chronic inflammatory sclerosis of the pancreas.[1] In 1992, Toki et al.[2] described AIP as a characteristic chronic pancreatitis with narrowing of the main pancreatic duct. Kawaguchi et al.[3] attributed this narrowing to an intense periductal inflammatory infiltrate consisting primarily of lymphocytes and plasmacytes. Due to the suggestion of an autoimmune mechanism, this disease was designated as autoimmune pancreatitis in 1995 and has since been increasingly recognized.[4,5]

AIP presents most commonly with obstructive jaundice, weight loss, and abdominal pain and can clinically mimic pancreatic adenocarcinoma or cholangiocarcinoma.[6,7] AIP presents most often in the head of the pancreas but can also present atypically with discrete tail lesions.[8] It has been shown that approximately 2.5% of pancreaticoduodenec-

T. Kim · S. R. Grobmyer · S. N. Hochwald (✉)
Division of Surgical Oncology,
University of Florida College of Medicine,
1600 SW Archer Road, Room 6165, P.O. Box 100286,
Gainesville, FL 32610, USA
e-mail: hochwsn@surgery.ufl.edu

L. R. Dixon · R. W. Allan
Department of Pathology, Immunology, and Laboratory Medicine,
University of Florida College of Medicine,
Gainesville, FL, USA

tomies performed for presumed malignancy were in fact cases of AIP.[9] Demonstration of serum immunoglobulin G4 (IgG4) elevations can help confirm the diagnosis and possibly help avoid unnecessary surgery.[10,11]

Various criteria exist for diagnosing AIP. Of note, the histology, imaging, serology, other organ involvement, and response to steroid therapy (HISORt) diagnostic criteria for AIP from the Mayo Clinic suggest that AIP may be a pancreatic manifestation of a systemic "IgG4-related sclerosing disease."[12] This is evidenced by the many reports of AIP and associated extrapancreatic disease with infiltration by IgG4-positive cells.[13,14] Currently, the significance of high serum IgG4 in the pathogenesis or pathophysiology of AIP is unclear. Furthermore, up to 40% of AIP cases are associated with autoimmune diseases[15] such as sclerosing cholangitis,[16,17] Sjögren's syndrome,[18,19] Crohn's disease and ulcerative colitis,[16,20] primary biliary cirrhosis,[21] rheumatoid arthritis, retroperitoneal fibrosis, Hashimoto's thyroiditis,[22] Graves' disease, and Riedel's thyroiditis.[7]

Small lymphocytic lymphoma (SLL) is a mature B cell lymphoma that represents the lymph node component of chronic lymphocytic leukemia (CLL). A small minority of patients (fewer than 10%) present with exclusive node-based disease; these often progress to leukemic involvement. Presenting symptoms include painless generalized lymphadenopathy, splenomegaly, and, in less than one-third of patients, fever, night sweats, weight loss, and extreme fatigue ("B" symptoms).

It has long been documented that CLL–SLL is often associated with autoimmune phenomena,[23] most notably autoimmune hemolytic anemia (AIHA) and thrombocytopenia (AITP),[24,25] neutropenia,[26] and, rarely, pure red cell aplasia.[27] Barcellini et al. studied 194 cases of autoimmune complications in CLL patients and found 30 other autoimmune diseases in addition to AIHA and AITP. These included bullous pemphigus, Hashimoto's thyroiditis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and ulcerative colitis.[28] The cause of autoimmune phenomena is unclear but is hypothesized to be due to aberrant APC activity by the leukemic B cells.[29]

The relationship between SLL–CLL and AIP is uncertain. We present the first report of a patient with concurrent AIP and SLL and discuss a possible relationship between these disorders.

Case

Clinical Information

A 76-year-old gentleman with a past medical history of type II diabetes mellitus presented with painless jaundice, weight loss, and anorexia. His blood glucose levels had also become increasingly uncontrollable. He had no known history of cancer or autoimmune disease.

Radiological Findings

Computed tomography imaging demonstrated fullness of the pancreatic head and multiple mildly enlarged retroperitoneal lymph nodes (Fig. 1). After attempted endoscopic retrograde cholangiopancreatography, we performed percutaneous transhepatic cholangiography which revealed a distal common bile duct stricture (Fig. 2). An internal–external drainage catheter was placed for decompression of the biliary tree.

Laboratory Findings

Initial serum CA 19-9 (23 units/mL, range 0–37 units/mL) and serum IgG4 levels (61 mg/dL, range 7–89 mg/dL) were normal, while total IgG was elevated at 1,811 mg/dL. However, on repeat testing 7 days later, IgG4 levels were markedly elevated at 533 mg/dL, and total IgG levels were elevated at 2,012 mg/dL (ARUP Labs, Salt Lake City, UT, USA). The patient did not experience any allergic event that may have accounted for this elevation.

Intraoperative Details

Due to the concern for pancreatic malignancy and conflicting values on preoperative laboratory studies, the patient underwent open exploration which revealed several enlarged 3-cm lymph nodes in the aortocaval ridge. An aortocaval lymphadenectomy was performed, and one of the lymph nodes was sent for frozen section pathologic analysis. There was no evidence of carcinoma, but there was evidence for a probable low-grade lymphoma.

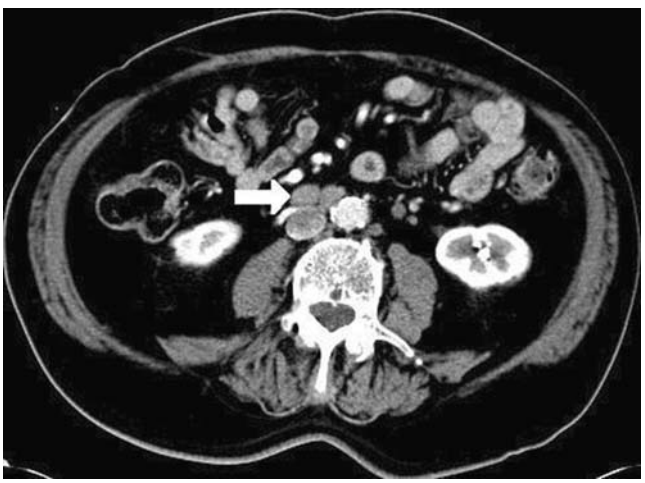

Figure 1 CT scan demonstrating enlarged lymph node in the aortocaval ridge. Enlarged lymph node (*white arrow*).

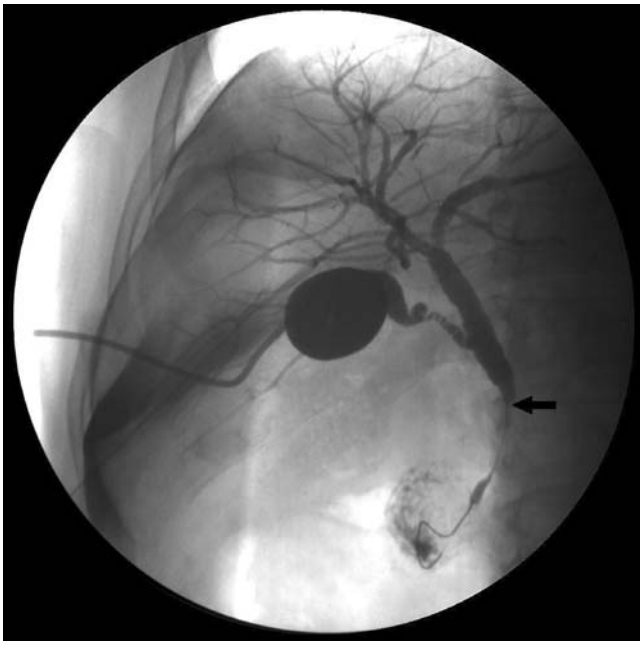

Figure 2 Cholangiogram demonstrating distal common bile duct stricture. Common bile duct stricture (*black arrow*).

Next, we evaluated the pancreatic head and noted a firm hard mass with significant scarring. Biopsy of this mass was preliminarily reported as pancreatitis with possible plasma cells. The mass was intimately adherent to the portal vein and was surrounded by a dense fibrotic process. A diagnosis of autoimmune pancreatitis was considered likely, and a limited pancreaticoduodenectomy was performed.

Pathology

Evaluation of the pancreas specimen revealed a pattern of lymphoplasmacytic infiltrate with eosinophils and stromal fibrosis. Immunohistochemical characterization of the inflammatory infiltrate showed mostly CD3+ and CD5+ T cells with scattered CD20+ B cells. Additionally, double immunohistochemical staining showed that there was not coexpression of CD5 on the OCT-2+ B cells. These findings were consistent with AIP (Fig. 3). There was no evidence of carcinoma or lymphoma in the pancreas. The retroperitoneal lymph nodes were frozen intraoperatively and found to be involved by a lymphoma. The lymph nodes were then sent for flow cytometric analysis.

Evaluation of the retroperitoneal lymph nodes by flow cytometry revealed a dominant population of clonal B cells with a typical immunophenotype for CLL–SLL: CD19+, dim expression of CD20, coexpression of CD5, and CD23. Cyclin D1 immunohistochemistry was negative. Cytogenetic studies were not performed. Histologic sections of the retroperitoneal lymph node showed the typical pseudofollicular growth pattern with scattered prolymphocytes seen in low-grade CLL–SLL.

Postoperative Course and Follow-up

The patient's postoperative course was unremarkable, and he was discharged home on postoperative day 7. On follow-up, he reported feeling well. He has not developed any other autoimmune diseases in the following 5 months.

Discussion

AIP is a rare disease of the pancreas affecting patients anywhere from 14 to 70 years of age, with most patients being older than 50 years.[13] There is a slight predominance (2:1 to 4:1) in men.[6,7,13] The clinical presentation is variable but is most commonly obstructive jaundice, weight loss, and abdominal pain.[13] AIP can thus present similarly to a pancreatic or biliary malignancy. There are limited data suggesting that AIP may be successfully treated with steroids, obviating the need for surgical resection.[30,31]

There are numerous reports of AIP complicated by extrapancreatic lesions with the same infiltration by IgG4-positive plasmacytes as seen in the pancreas.[13,14] AIP may be a pancreatic manifestation of what is truly a systemic IgG4-related fibroinflammatory process. Furthermore, AIP has been associated with various autoimmune conditions such as sclerosing cholangitis,[16,17] Sjögren's syndrome,[18,19] ulcerative colitis,[16,20] and Riedel's thyroiditis.[7]

CLL–SLL has also been associated with autoimmune conditions such as autoimmune hemolytic anemia and less commonly autoimmune thrombocytopenia. A relationship between AIP and CLL–SLL has not been previously documented. Our patient had no prior history of autoimmune disease or malignancy and was found to have AIP and concurrent SLL involving the retroperitoneal lymph nodes. It is possible that these two disease entities were

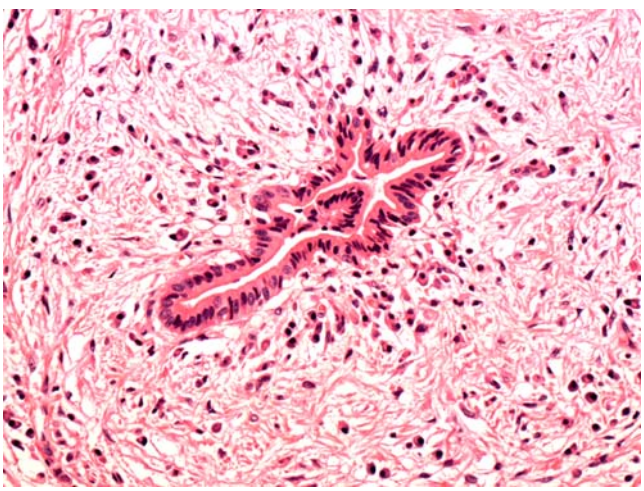

Figure 3 Histopathologic findings in AIP. Dense fibrosis of the pancreas with lymphoplasmacytic infiltrate containing scattered eosinophils centered around a pancreatic duct (H & E, ×200).

related in our patient. A study of 15 patients with lymphoproliferative disorders by Polliack and Lugassy[32] suggests that manifestations of autoimmunity may precede the development of lymphoid neoplasias. Our patient may have had a preexisting autoimmune IgG4-related systemic disease which increased his likelihood of developing SLL. We also recognize that CLL–SLL is not uncommon in 75 year olds, and the two disease entities could be a chance association in our patient. Interestingly, CLL–SLL is less common in Japan compared to the US, even though the incidence of IgG4-related sclerosing disease is higher.

There are emerging data that suggest that AIP can be diagnosed by detecting IgG4 increases in the serum.[10] Our previous studies have suggested the limitations of IgG4 testing in the preoperative assessment of patients with AIP.[17] The case presented here suggests the potential for error in IgG4 testing in the US. While total IgG levels were elevated on two serum tests spaced 1 week apart, IgG4 was initially reported as normal (61 mg/dL) while upon repeat testing it was noted to be markedly elevated (533 mg/dL). Due to the potential for preanalytic or analytic error in utilizing reference laboratories, repeat testing is warranted in select cases with a high clinical suspicion for AIP. The ability to make the diagnosis of AIP prior to surgery can obviate the need for surgery as treatment with steroids may relieve the biliary obstruction associated with this condition.[17]

In conclusion, this is the first reported case to our knowledge of concurrent AIP and SLL. The role of IgG4 and autoimmune mechanisms in the pathogenesis and pathophysiology of AIP is unclear. Further investigation into the immunohistochemical and molecular changes in AIP may improve our understanding of this rare disease.

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Diagnosis and Management of the Symptomatic Duodenal Diverticulum: a Case Series and a Short Review of the Literature

Beat Schnueriger · Stephan A. Vorburger · Vanessa M. Banz · Alain M. Schoepfer · Daniel Candinas

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Abstract
Introduction The incidence of duodenal diverticula (DD) found at autopsy may be as high as 22%. Perforation is the least frequent but also the most serious complication. This case series gives an overview of the management of this rare entity.
Methods This study is a case series of eight patients treated for symptomatic DD.
Results Two patients had a perforated DD. One perforation was in segments III–IV, which to our knowledge is the first published case; the other perforation was in segment II. A segmental duodenectomy was performed in the first patient and a pylorus-preserving duodeno-pancreatectomy (pp-Whipple) in the second. A third patient with chronic complaints and recurring episodes of fever required an excision of the DD. In a fourth patient with biliary and pancreatic obstruction, a pp-Whipple was carried out, and a DD was discovered as the underlying cause. Four patients (one small perforation, one hemorrhage, and two recurrent cholangitis/pancreatitis caused by a DD) were treated conservatively.
Conclusions Symptomatic DD and, in particular, perforations are rare, encompass diagnostic challenges, and may require technically demanding surgical or endoscopic interventions. The diagnostic value of forward-looking gastroduodenoscopy in this setting seems limited. If duodenoscopy is performed at all, the use of a side-viewing endoscope is mandatory.

Keywords Duodenal diverticulum · Perforation · Operative management

Introduction

Duodenal diverticula (DD) were first reported by Chomel in 1710.[1] The incidence of DD found at autopsy may be as high as 22%.[2] Similar incidences have been described during endoscopic retrograde cholangiopancreatography (ERCP).[3,4]

Most DD are asymptomatic; only 5% of patients experience symptoms resulting from compression of neighboring organs, hemorrhage, or inflammation and perforation.[5]

Diverticula of the small intestine are largely pseudodiverticula,[2,6,7] with the duodenum being the second most frequent location.[8,9] These are typically located in the second portion of the duodenum within 2.5 cm of the ampulla of Vater.[8]

Up until 2005, 115 cases of perforated DD have been published.[9–11] In 57% of all cases, the possible cause of duodenal perforation was peptic digestive processes as a result of the retention of food in the diverticula.[12] Other causes, such as ulcerations, enterocoliths, blunt abdominal trauma, or iatrogenic perforation during an ERCP, have also been described.[12–15]

B. Schnueriger (✉) · S. A. Vorburger · V. M. Banz · D. Candinas
Department of Visceral and Transplantation Surgery,
University Hospital Bern,
CH-3010 Bern, Switzerland
e-mail: beat.schnueriger@insel.ch

A. M. Schoepfer
Department of Gastroenterology, Bern University Hospital,
Bern, Switzerland

Here, we summarize the history of eight patients with symptomatic DD while reviewing the appropriate diagnostic steps and surgical therapy.

Materials and Methods

From January 2003 to December 2006, a total of eight patients with symptomatic DD were treated at our facility. Four patients required surgical intervention, and four patients were treated conservatively. Prehospitalization data, inpatient chart records, and radiological and endoscopic findings were collected and analyzed retrospectively. We then compared our results with the existing literature.

Results

Case Report #1 A 68-year-old man was admitted with acute abdominal pain accompanied by nausea and bilious vomiting, which he had experienced for 6 h. The patient's personal history included Crohn's disease, which was in complete clinical remission under daily therapy with 150 mg of azathioprine. The clinical examination showed a patient with diffuse pain in the lower abdomen radiating to both flanks as well as sparse bowel sounds. Blood analysis showed an elevated white blood cell count with 15 g/l and a normal C-reactive protein (CRP) level. The result of an abdominal radiography was also normal. Twelve hours after admission, the CRP level increased to 210 mg/l (normal<4 mg/l). The abdominal computed tomography (CT) scan is shown in Fig. 1. A forward-looking gastroduodenoscopy was carried out in order to locate the site of perforation. The examination revealed macroscopically normal mucosa up to 40 cm past the ligament of Treitz, without detecting any perforation site. In this setting, we opted for laparotomy and surgical revision. After mobilization of the duodenum (Kocher maneuver), pus was found dorsal to duodenal segment III/IV, coming up from behind the pancreas. Further examination showed a macerated 5-cm-large DD in segment IV with multiple perforation sites (Figs. 2 and 3). This was accompanied by a retroperitoneal phlegmona that extended to the left pararenal region. The pancreas itself was normal. In this setting, we carried out a pancreas-preserving duodenectomy of segments III and IV with an end-to-end duodeno-jejunostomy (Fig. 4) 3 cm distal of the ampulla of Vater. The azathioprine treatment was paused so that the patient could be treated for 5 days with imipenem. After 15 days, the patient was dismissed from hospital in good health.

Case Report #2 A 70-year-old woman presented with epigastric pain that was ongoing for 4 h and radiating to the right hemiabdomen. Nausea was followed by bilious vomiting. The clinical examination revealed peritonitis in the right upper quadrant. Her white blood cell count was elevated (16.8 g/l), whereas the CRP level was normal. Result of a plain abdominal X-ray was normal. Due to persistent abdominal pain, we carried out a CT scan which showed a retroperitoneally perforated DD in segments II–III. Because of her increasing abdominal discomfort, we performed an emergency laparotomy. Complete duodenal mobilization revealed a very firm pancreatic head. Intraoperative sonography showed a nondilated pancreatic duct and homogenous pancreatic parenchyma. An intraoperative gastroduodenoscopy was carried out, allowing for maximal diagnostic security in order to rule out further pathologies. Intraoperative gastroduodenoscopy failed to locate the DD. Due to the ambiguous findings in the pancreatic head, we carried out a pp-Whipple. A DD, covered in pus and fibrinous strands, was located between segments II and III of the duodenum. Dissection of the 5×5-cm-large diverticulum showed an opening of 7 mm towards the duodenal mucosa that was filled with partially digested food. The patient's further recovery was uneventful.

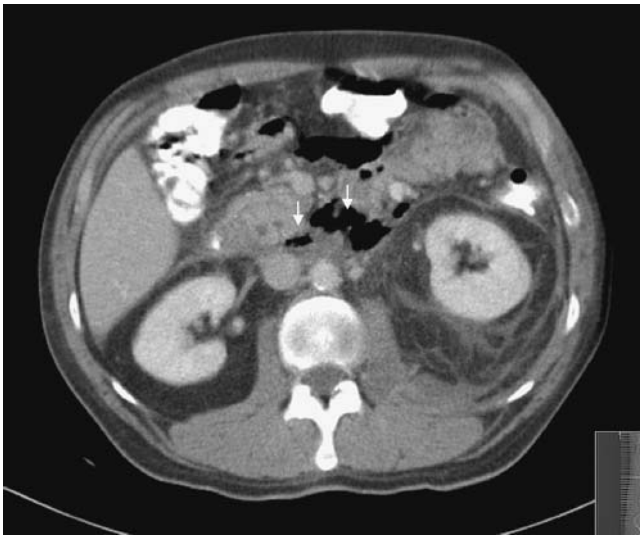

Figure 1 Abdominal CT scan of a 68-year-old man with a perforated duodenal diverticulum. The scan shows extraluminal retroperitoneal air around the ascending duodenal segment (segment IV) (*white arrows*) as well as minimal retroperitoneal, pararenal fluid with an impressive fat stranding in a 68-year-old male patient with a perforated duodenal diverticulum.

Case Report #3 A 68-year-old man presented to his physician with a feeling of general illness, nonspecific upper abdominal pain, as well as vomiting and diarrhea which had been ongoing for several days. A colonoscopy showed no pathology. Due to persistent epigastric abdominal pain, intermittent lack of appetite, and a dislike for meat, a gastroduodenoscopy was performed. The examination revealed a grade II reflux esophagitis with a small axial hernia and minimal antrum gastritis. Besides these findings,

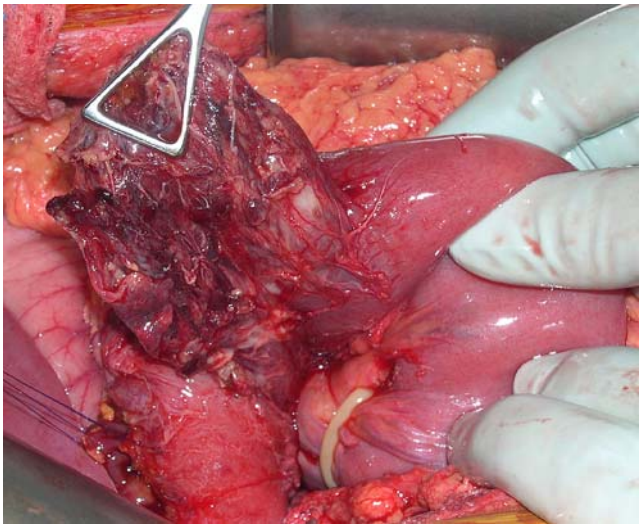

Figure 2 Macerated 5-cm-large duodenal diverticulum in segment IV with multiple perforation sites.

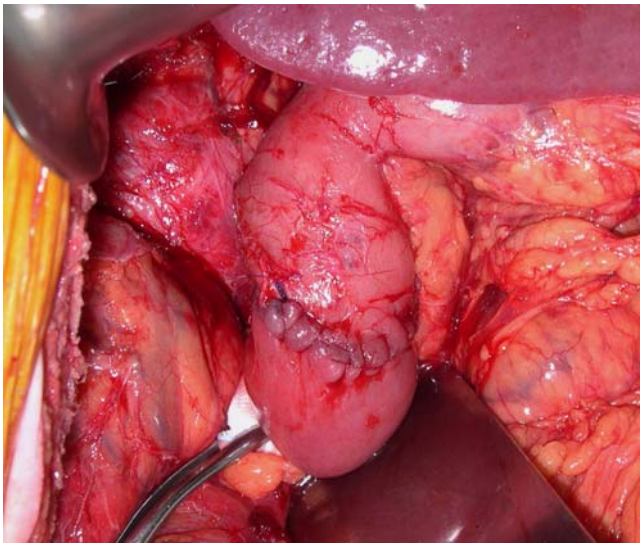

Figure 4 Hand-sewn end-to-end duodeno-jejunostomy after segmental duodenectomy of segments III and IV.

no further pathologies were detected. In the course of time, the patient developed recurrent fever. A CT scan of the abdomen revealed a heterogeneous zone in the transition area between the head and the neck of the pancreas. Endosonography confirmed this finding, but needle biopsy was inconclusive. The patient was referred to our clinic. At the time of examination, the patient was in good general health without abdominal pain. A magnetic resonance imaging (MRI) of the abdomen showed a heterogeneous zone of the pancreatic body without obstruction of the surrounding structures. As malignancy could not be ruled out with certainty, we opted for surgical exploration. The intraoperative aspect revealed a normal pancreas. Sonography and multiple biopsies were without pathology. As a possible cause for the recurrent fever, we found a DD located in segment II. The diverticulum was excised and the duodenum repaired with full-thickness sutures. Due to its proximity to the ampulla of Vater, we carried out a biliodigestive anastomosis according to Roux-en-Y. Definitive histological examination confirmed the duodenal pseudodiverticulum without acute inflammation. Postoperative recovery was uneventful, and the patient was dismissed on the 12th postoperative day.

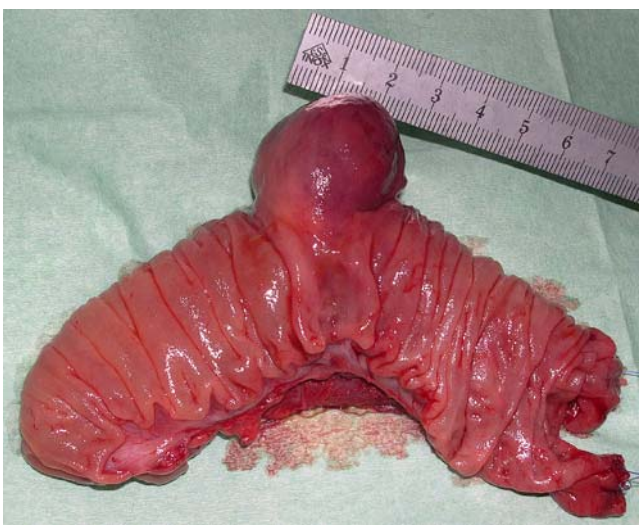

Figure 3 Resected segments III and IV duodena everted duodenal diverticulum.

Case Report #4 A routine medical checkup of a 65-year-old man with no complaints revealed slightly elevated blood amylase and lipase values. Six months later, an ERCP was performed because the elevated values had persisted. The ERCP showed a significant stenosis of the Wirsungian duct, 3–4 cm proximal to the ampulla of Vater. The orifice of a DD was located immediately proximal to the ampulla. A CT of the abdomen failed to clearly identify the boundaries of the head of the pancreas, with a small bubble of air visible in direct proximity to the pancreatic duct. A cholangio-MRI revealed a dilated pancreatic duct of 1 cm right up to the ampulla of Vater. The results were discussed with the patient, and the necessity for explorative laparotomy was agreed upon, as a tumor could not be ruled out with certainty. Furthermore, chronic outlet obstruction of the pancreatic duct may have led to secondary exocrine and endocrine problems with the pancreas.

Intraoperative findings revealed a markedly enlarged pancreatic head and uncinate process. Gradual resection of the pancreatic head revealed a 3–4-cm-large periampullary DD with compression of the pancreatic duct. In such a setting, a pp-Whipple operation was carried out. Definitive histological examination confirmed the presence of a periampullary duodenal pseudodiverticulum with a narrow opening and minimal chronic–atrophic partially fibrosing

pancreatitis. The patient was dismissed without complications on the 11th postoperative day. No signs of endocrine or exocrine pancreatic insufficiency were found upon follow-up.

Of the four patients not requiring surgery, patient 5 had a DD located in duodenal segment III with a small iatrogenic perforation, which occurred during an ERCP because of biliary obstruction. We treated this patient conservatively by a temporary percutaneous transhepatic cholangio drainage (PTCD) inserted under CT guidance and a course of antibiotics and parenteral nutrition.

Patient 6 had a hemodynamically relevant hemorrhage from a DD due to coagulopathy in a Child C hepatopathy. The bleeding and the DD were diagnosed by ERCP, but a treatment by endoscopic clipping or sclerotherapy was not possible. Finally, the bleeding stopped after correction of the coagulopathy by the substitution with fresh frozen plasma.

Patients 7 and 8 suffered from cholangitis caused by an infected DD. Both received an ERCP with papillotomy with insertion of a temporary naso-biliary drainage and a treatment with antibiotics. Table 1 gives an overview of our eight patients with symptomatic DD.

Discussion

This case series shows a wide spectrum of diagnostic and therapeutic problems DD can give. To the best of our knowledge and after an extensive search of the literature, we report here the first patient with perforated DD in duodenal segments III–IV.

Clinical Symptoms and the Diagnosis of Complicated DD Clinical symptoms are usually nonspecific. In the case of a perforation, patients often experience a per-acute onset of pain followed by nausea and vomiting. Furthermore, chronic progression with pain and fever due to recurrent episodes of cholangitis or pancreatitis or by the inflammation of the DD itself are possible symptoms, as was also seen in our patients 3, 4, 7, and 8. Additionally, anorexia and steatorrhoe due to duodeno-colic fistulas have also been described.[16]

Correctly diagnosing the complications associated with DD, especially duodenal perforation, poses several difficulties. Fifty percent of all conventional radiological examinations show no abnormalities.[10] An abdominal CT scan is the most sensitive examination if there is suspicion that a DD perforation may have occurred. Findings consist of a thickened bowel wall, mesenteric fat stranding, and an extraluminal, retroperitoneal collection of air or fluid.[17,18] Occasionally, a contrast-enhanced CT scan can directly depict a DD.[13] Duarte et al. and Juler et al. reported 101 cases of duodenal perforation, of which only 13 were diagnosed preoperatively.[12,19] Because there are no pathognomonic signs, even making the correct intraoperative diagnosis requires a high index of suspicion.

The Value of Endoscopy The diagnostic value of the forward-viewing gastroduodenoscopy remains doubtful, as was seen in three of our four surgically managed patients, where repeated gastroduodenoscopies failed to reveal any pathology. This can be explained by the difficulty of the forward-viewing endoscope to reliably assess the concavity of duodenal segment II retroperitoneal in the vicinity of the ampulla of Vater where most (75%) of the DD are located.[11] Additionally, an acute diverticulitis causes mucosal swelling and narrowing of the diverticular orifice that further hampers the diagnostic yield of forward upper endoscopy. Our experience shows that forward-viewing

Table 1 Overview of All Patients with Symptomatic DD

Patient	Location of DD	Complication	Treatment
1	Segments III–IV	Acute retroperitoneal perforation	Segmental duodenectomy
2	Segment III	Acute retroperitoneal perforation	Pylorus-preserving duodeno-pancreatectomy (pp-Whipple)
3	Segment II	Chronic complaints and recurring episodes of fever	Excision of the diverticula
4	Segment II	Chronic biliary and pancreatic obstruction with chronic-atrophic pancreatitis	Pylorus-preserving duodeno-pancreatectomy (pp-Whipple)
5	Segment III	Small iatrogenic perforation caused by an ERCP (biliary obstruction)	PTCD, period of parenteral nutrition and antibiotics
6	Segment II	Hemorrhage (Child C hepatopathy)	Conservative, fresh frozen plasma
7	Segment II	Infection and biliary obstruction	ERCP with papillotomy and insertion of a naso-biliary tube, antibiotics
8	Segment II	DD infection with biliary obstruction and cholangitis	ERCP with papillotomy and insertion of an naso-biliary tube, antibiotics

DD Duodenal diverticulum, *PTCD* percutaneous transhepatic cholangio drainage, *ERCP* endoscopic retrograde cholangiopancreatography

endoscopy can exclude other pathologies, such as ulcers, but has a low negative predictive value in diagnosing DD. A side-viewing duodenoscope (as was used in our fourth to eighth patients) may be of benefit and allow for a correct diagnosis as shown previously by Leivonen et al.,[3] who demonstrated that, in 1,735 ERCPs, DD were found in 123 patients (7.1%). Jin et al. found DD in 129 of 527 patients (24.6%) upon ERCP.[4]

ERCP not only has its own diagnostic value but may provide endoscopic therapy options in some patients with symptomatic DD. Up until 2006, there were nine reported cases of endoscopic treatment of hemorrhage from a DD and one documented endoscopically drained retroperitoneal abscess which occurred after DD perforation.[20, 21] Lee et al. presented another 11 patients with endoscopic treatment of symptomatic DD (obstruction, pain, pancreatitis).[22] Several other unusual case reports can be found, including a bezoar in a periampullary DD causing pancreatitis[23] or a vegetable stalk as a nidus for gallstone formation in a DD.[24] Both could be removed during ERCP.

Surgical Treatment Surgical intervention is usually only required when there are complications, whereof perforation is the least frequent but also one of the most serious complications.[25] However, nonoperative or endoscopic treatment of perforations has also been described.[20] An additional example is our fifth patient. However, care must be taken not to delay the surgical treatment of a perforated DD, as this condition is associated with a mortality of up to 13%.[12] More often than perforation are symptoms from the pancreaticobiliary system, such as recurrent cholangitis or pancreatitis, as a result of increased pressure in a poorly emptying and inflammed DD.[25] Harthun et al. published another unusual indication for surgery: a duodenal obstruction caused by an intraluminal DD, which was resected through a longitudinal duodenotomy.[26]

Concerning surgical techniques and options, detailed recommendations or even guidelines are lacking. Because of the rare appearance of symptomatic DD, only case reports or case series up to four patients have been published until now. In case of perforation, surgical options range from local excision of the diverticulum to a pp-Whipple, depending on the site of the DD and the grade of inflammation. Most frequently, resection of the DD after Kocher maneuver with one- or two-layer closure of the duodenum has been described in this context.[7,18,27] As a third option, we describe here a segmental duodenal resection of a perforated DD in segments III–IV. This option can only be considered in the rare case of a DD located in segments III and IV. A pp-Whipple may be necessary when the sac of the DD lies in close proximity to the common bile and pancreatic ducts, and quite frequently the ampulla of Vater is found within the diverticulum.[28] Either a pp-Whipple or a segmental duodenal resection with removal of the nectrotic tissue must be considered in case of perforation which leads to severe retroperitoneal inflammation.

If the leading symptoms of DD are obstruction of the biliary tract (cholangitis) or the pancreatic duct (pancreatitis), a resection of the duodenum is not required. In the absence of other risk factors and the presence of a DD, exclusion of the duodenum by means of Roux-Y-choledochojejunostomy (biliodigestive anastomosis) and duodeno-jejunostomy has warranted satisfactory results.[29,30]

All the above procedures are technically challenging and carry the risk of potential injury to the pancreatic duct and parenchyma as well as to the extrahepatic bile ducts. Other potential complications are duodenal fistulas, sepsis, intra-abdominal abscesses, and pancreatitis.

Conclusion

Complications caused by DD and, in particular, perforations are rare and encompass diagnostic challenges requiring immediate and usually technically demanding surgical interventions. A high index of suspicion is required for the correct diagnosis. In our opinion, if the presence of a DD seems likely, the side-viewing duodenoscope should be preferred to the forward-viewing endoscope for higher diagnostic yield.

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Biliary Injury After Laparoscopic Cholecystectomy in a Patient with Right Liver Agenesis: Case Report and Review of the Literature

Ryan C. Fields · Jay P. Heiken · Steven M. Strasberg

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Abstract
Introduction An 87-year-old man underwent attempted laparoscopic cholecystectomy.
Material and Methods The procedure was characterized by significant inflammation and bleeding requiring conversion to an open procedure. Postoperatively, the patient had continued bile drainage from his surgical drain. He was referred to our institution and found to have complete transection of his common bile duct. Incidentally, he was noted on imaging studies to have absence of his right liver with associated left liver hypertrophy. This was characterized by complete absence of the right portal vein and right bile duct. Review of his preoperative imaging confirmed this finding of right liver agenesis and very unusual hepatic vein anatomy.
Conclusion This represents the first reported case of bile duct injury in the setting of right liver agenesis. We review the details of the case and the natural history of agenesis of a hemiliver.

Keywords Laparoscopic cholecystectomy · Biliary injury · Liver agenesis

Case Report

An 87-year-old man presented to his primary physician with biliary colic. An ultrasound revealed cholelithiasis with no evidence of acute cholecystitis or biliary ductal dilatation. Past health was significant only for coronary artery disease and a left hemicolectomy for a T2N0 adenocarcinoma. He was evaluated and felt to be a candidate for laparoscopic cholecystectomy. A laparoscopic cholecystectomy was performed approximately 1 month later. The operative report noted "considerable inflammation" requiring conversion to an open procedure. A portion of the gallbladder wall was left adherent to the liver due to "excessive bleeding in the bed of the gallbladder" requiring a two-unit blood transfusion intraoperatively. A drain was left in the gallbladder fossa. The patient tolerated the procedure well. However, starting on the first postoperative day, 800–1,000 mL/day of bilious output came from his abdominal drain. One week postoperatively he underwent endoscopic retrograde cholangiopancreatography (ERCP), which revealed an acute cutoff of the common bile duct consistent with common bile duct injury. A stent was left in place. The patient was transferred to our hospital for further treatment 10 days after the cholecystectomy.

On admission, the patient was stable and afebrile. Abdominal examination was in keeping with his postoperative state. Blood count was within normal limits, serum albumin was 3.1 g/dL, total bilirubin 1.1 mg/dL, alkaline phosphatase 222 IU/L, and serum transaminase levels were normal. A computed tomography (CT) scan was performed demonstrating changes consistent with cholecystectomy,

R. C. Fields · S. M. Strasberg
Department of Surgery, Barnes-Jewish Hospital,
Washington University School of Medicine,
St. Louis, MO 63110, USA

J. P. Heiken
Mallinckrodt Institute of Radiology, Barnes-Jewish Hospital,
Washington University School of Medicine,
St. Louis, MO 63110, U.S.A.

S. M. Strasberg (✉)
Department of Surgery, Barnes-Jewish Hospital,
Washington University School of Medicine,
Campus Box 8109, St. Louis, MO 63110, U.S.A.
e-mail: strasbergs@wustl.edu

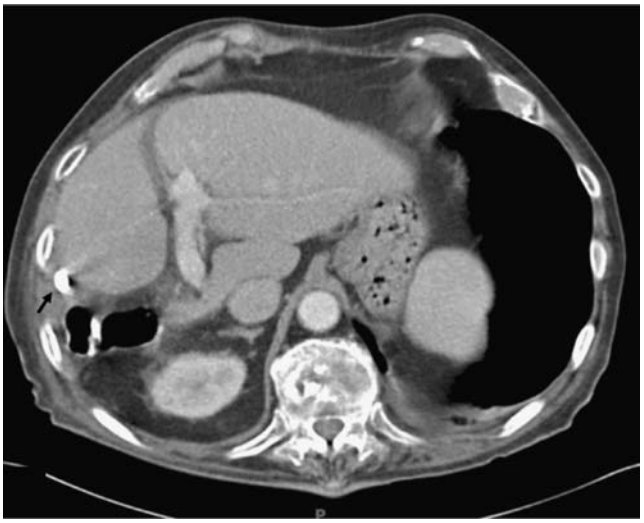

Figure 1 Computed tomography scan obtained on admission to our institution demonstrating changes consistent with cholecystectomy. A drain (*arrow*) is seen in the right upper quadrant. The right hemiliver is absent, and no right portal vein is identified. The left portal vein is large and enters the umbilical fissure from the left instead of from the right.

i.e, a drain in the gallbladder fossa (Fig. 1) and surgical clips. No bile duct dilatation was seen. The right hemiliver was absent and no right portal vein could be identified. The left portal vein was large and swung into the umbilical fissure from the left instead of from the right. The left liver and caudate lobe were hypertrophied. An magnetic resonance image (MRI) showed no evidence of an associated vascular injury.

It was discovered that a CT scan had been performed 3 months prior to the cholecystectomy for vague abdominal pain, and copies of this examination were obtained (Fig. 2). That CT scan confirmed that complete agenesis of the right liver was present prior to operation and showed the unusual position of the gallbladder on the underside (right side) of the hypertrophied left liver in the preoperative state. The enlarged left portal vein and its unusual entry into the umbilical fissure from the left were confirmed. The branches of the left portal vein to segments 2–4 were large and easily seen.

The hepatic veins, which were in a very unusual position, were seen much better on the preoperative CT (Fig. 3). The middle hepatic vein was rotated counterclockwise from its normal position to lie in the horizontal plane at 8o'clock, much in the same position as a normal right hepatic vein, although its entry point on the cava and its fusion with the left hepatic vein clearly identify it as a middle hepatic vein. There was no right hepatic vein. A thin layer of liver tissue lay behind (i.e., to the right side) of the middle hepatic vein. This might represent a hypoplastic right liver or a portion of the caudate lobe. Given that no veins could be seen to enter the middle hepatic vein from this section of liver, it is more likely that this tissue is part of a hypertrophied caudate lobe. The left hepatic vein was also rotated counterclockwise and pointed to 10 o'clock rather than 1 o'clock. The umbilical vein, which drained a portion of segment 4, was also rotated counterclockwise and as usual drained into the left hepatic vein. Its course was unusually long (Fig. 3).

A transhepatic cholangiogram was performed after first injecting contrast via the drain tract to cause retrograde filling of the biliary tree in order to guide placement of the percutaneous catheter. The cholangiogram demonstrated filling of the left ducts with complete obstruction of the duct system just below the entry of the duct from segment 4 (Fig. 4). The stent placed at ERCP could also be seen, but there was no communication between the upper ducts and this stent. No right ductal system was visualized.

It was elected to do a delayed repair given that it was now 11 days after the difficult surgery in a patient with abnormal anatomy. The initial stay in our hospital was 6 days during which it was established that the patient could replace drain losses orally. He was readmitted 10 weeks later, and a bile duct reconstruction was performed. The Hepp–Couinaud technique was used. After clearing adhesions from segment 4, the hilar plate was lowered, the left duct opened on its anterior surface, and a side-to-side hepaticojejunostomy performed. The postoperative course was uneventful, and the patient was discharged after 8 days. The postoperative cholangiogram is shown (Fig. 5). There was good emptying of the left hepatic ducts into the jejunal

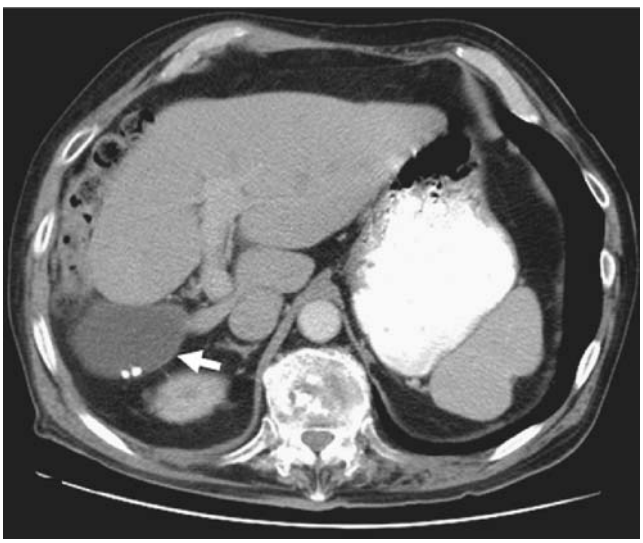

Figure 2 Computed tomography scan performed approximately 3 months prior to cholecystectomy. This demonstrates agenesis of the right liver and the unusual position of the gallbladder (*arrow*) on the underside of the hypertrophied left liver. The enlarged left portal vein and its unusual entry into the umbilical fissure from the left were confirmed.

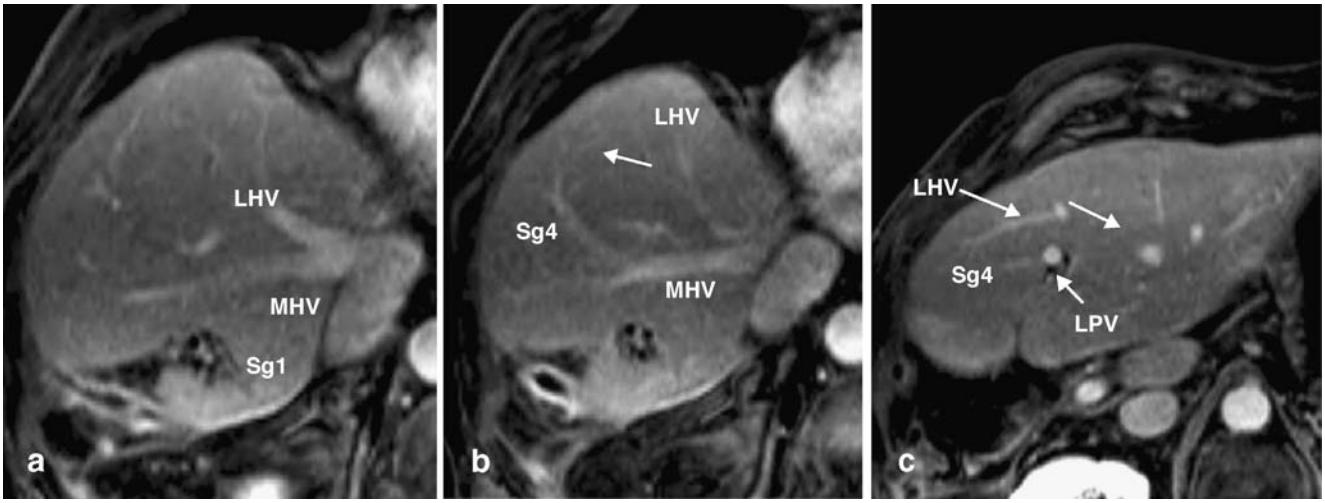

Figure 3 Three images from a magnetic resonance imaging (MRI) examination performed prior to cholecystectomy demonstrating position of hepatic veins. A is the most superior and C the most inferior image selected. Note tissue posterior to middle hepatic vein (MVH), which might be a hypoplastic right liver or part of segment 1. The long course of one of the tributaries of the left hepatic vein (LVH) is indicated by the *dotted arrows*. This tributary is likely the umbilical vein. *LPV* left portal vein, *Sg4* segment 4.

Roux loop. The stent was removed. The patient is well after a short follow-up of 3 months.

Discussion

Agenesis of the right lobe of the liver is a rare condition with approximately thirty cases reported in the literature.[1–11] To our knowledge, this represents the only case in the literature of biliary injury after laparoscopic cholecystectomy in the setting of complete agenesis of the right hemiliver. It also seems to be the only description of the unusual hepatic vein anatomy in this condition.

Early reported cases were discovered on autopsy and reported in the 19th and early 20th century,[12,13] Later cases were usually discovered by imaging. There is a slightly higher incidence in males (~60% of cases). As with our patient, approximately one third of patients are diagnosed after the sixth decade of life. There are no reports of this condition discovered incidentally on autopsy. Table 1 summarizes the modern reported cases of liver agenesis. Many patients have been diagnosed with agenesis after

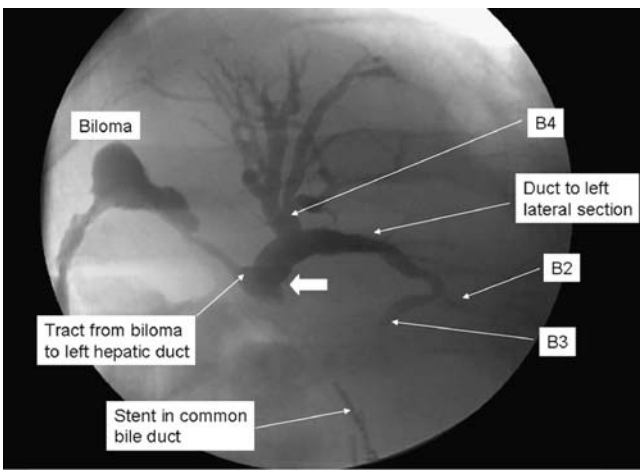

Figure 4 Images from a percutaneous transhepatic cholangiogram demonstrating filling of the left ducts with complete obstruction of the duct system just below the entry of the duct from segment 4 (*arrow*). The biloma and biloma tract are indicated. The stent placed at ERCP can be seen, but there was no communication between the upper ducts and this stent. No right ductal system was visualized.

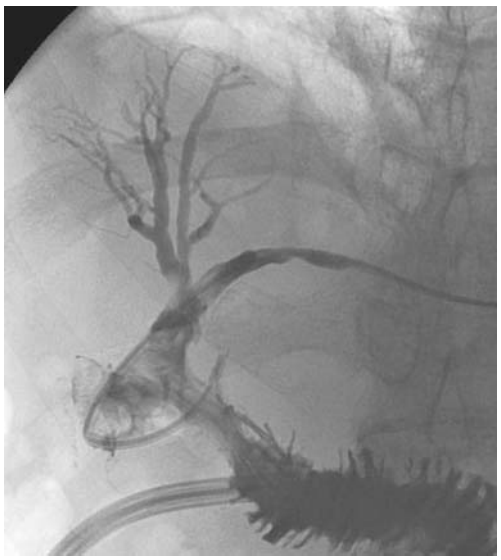

Figure 5 Postoperative cholangiogram after side-to-side hepaticojejunostomy bile duct reconstruction. Contrast is seen in the left-sided bile ducts. The anastomosis is widely patent, and contrast flows well into the jejunal Roux loop. No leakage is seen.

Table 1 Summary of Case Reports of Liver Agenesis, 1985 to Present

Author	Year	Case	Comments
Radin, et. al[1]	1987	5 patients, right liver agenesis 3 male (ages 29, 61, 57) 2 female (ages 60, 45)	2 with RUQ pain, 3 with gallstones. All diagnosed on imaging.
Kanematsu, et. al[8]	1991	Right liver agenesis 58 yo male	Abdominal pain, diagnosed on imaging.
d'Araujo, et. Al[7]	1992	Right liver agenesis 62 yo male	RUQ pain, suprahepatic gallbladder, underwent open cholecystectomy.
Lee, et. Al[6]	1993	Right liver agenesis 48 yo female	RUQ pain, diagnosed on imaging.
Hsu, et. al[5]	1994	Right liver agenesis 71 yo male	RUQ pain, suprahepatic gallbladder with gallstones, underwent cholecystostomy.
Harada, et. al[10]	1995	Right liver agenesis 51 yo male	Obstructive jaundice, bile duct carcinoma, diagnosed on imaging.
Ishibashi, et. al[17]	1995	Right liver agenesis 53 yo female	Choledocholithiasis, liver scarring.
Cesani, et. Al[4]	1996	Right liver agenesis 70 yo male	Incidental finding on imaging.
Karaman, et. al[3]	1997	Right liver agenesis 44 yo male	Hydatid cyst, Chiliaditi syndrome*, diagnosed on imaging.
Maeda, et. Al[29]	1998	Left liver agenesis 71 yo female	RUQ pain, Hepatitis C, diagnosed on imaging.
Sato, et. Al[2]	1998	Right liver agenesis 60 yo female	Gastric cancer, diagnosed on pre-op imaging
Noritomi, et. al[30]	2004	Left liver agenesis 71 yo female	Acute cholecystitis, diagnosed intra-operatively during laparoscopic cholecystectomy (converted to open).
Ianelli, et. al[26]	2005	Right liver agenesis 68 yo female	RUQ pain, gallstones, diagnosed intraoperatively during laparoscopic cholecystectomy.

*Interposition of the hepatic flexure of the colon between the liver and right hemidiaphragm.
yo year old, *RUQ* right upper quadrant

presenting with biliary colic as in our case.[13–16] Whether this represents an increased tendency to form stones or simply that patients with stones get imaging that identifies the problem is unclear and likely will remain so due to the rare incidence of this condition. It is possible that there are a number of people remain asymptomatic who lead a completely normal life with unilateral liver agenesis.

Classically, imaging reveals that the right liver is absent and the left liver and caudate lobe are hypertrophied. However, there are variations. Sometimes the left medial section (segment 4) is hypoplastic, and then the left lateral section is usually very large.[1,11,17] The caudate lobe is absent in about half of the reported cases. Other associated anomalies include diaphragmatic defects[18–21] and abnormalities of embryologic rotation (i.e., situs inversus).[15,16,22,23] Sometimes the left liver does not hypertrophy, and such cases may be associated with portal hypertension, characterized by hypersplenism, esophageal varices, and ascites.[12,24,25] The development of portal hypertension may be due to a fixed reduction in the intrahepatic vascular bed.

The anatomical arrangement in this condition is such that a resection of a portion of segment 4 or the caudate lobe should be possible if necessary, e.g., in case of tumor development. Awareness of the unusual position of the hepatic veins should be helpful in planning safe surgery.

A prior report by Iannelli et al.[26] described a case of laparoscopic cholecystectomy in the setting of right liver agenesis. However, in contrast to this case, there was minimal inflammation, and the aberrant anatomy was rapidly identified by the absence of the right liver with the falciform ligament in a "near frontal plane" with concurrent left liver hypertrophy. The surgeons modified the port placement and continued with the procedure, noting that on intraoperative cholangiogram the right bile ducts were absent. Postoperative magnetic resonance (MR) cholangiogram confirmed right liver agenesis.

Absence or hypoplasia of the left lobe of the liver is also a rare anomaly that has been described in less than 20 patients, often associated with left-sided or absent gallbladder and other congenital anomalies, such as *situs inversus*.[11,27] Alternatively, it can be the result of various acquired etiologies, such as portal vein obstruction.[11]

This case report highlights that partial liver agenesis can increase the possibility of intraoperative difficulty and injury. Surgeons operating on the biliary tree must be mindful of the fact that this area of the body is one in which surgically important anomalies are common. Every cholecystectomy should be performed using a standard approach to anatomical identification of ductal and vascular structures such as the critical view of safety method.[28] When doing a laparoscopic cholecystectomy, the surgeon may be alerted to the presence of agenesis of the right liver by the unusual posterior position of the gallbladder. Before diagnosing congenital agenesis of the right liver, atrophy due to unilateral obstruction of a portal vein or bile duct, and reduced liver size due to cirrhosis or other conditions should be eliminated. Should agenesis be suspected consideration should be given to performing the cholecys-

tectomy as an open procedure. If severe inflammation is present or anatomical identification is not achievable, then termination of the procedure by cholecystostomy and referral to a hepatobiliary center for delayed cholecystectomy is a safe option.

In summary, we report a case of biliary injury after laparoscopic cholecystectomy in the setting of right liver agenesis. Although congenital anomalies of the liver should not represent a contraindication to laparoscopic cholecystectomy, it is important for the operating surgeon to be aware of such anatomical variants (either via preoperative imaging or upon initial inspection of the liver and gallbladder), as the incidence of biliary injury has been shown to be increased in other settings in which the biliary anatomy is unclear or aberrant, such as in the setting of acute cholecystitis. If such an anomaly is appreciated, the treating surgeon should modify the operative approach or refer the patient to a tertiary care center for definitive care.

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Technical Aspects of Performing Transduodenal Ampullectomy

Shishir K. Maithel · Yuman Fong

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Abstract Transduodenal ampullectomy is a procedure that can be used to remove either benign or malignant tumors arising from the ampulla of Vater. Specific indications for performing this procedure remain controversial. In this report, we describe the technical details necessary for successfully completing an ampullectomy.

Keywords Ampulla of Vater · Ampullectomy · Transduodenal · Periampullary neoplasm · Technique

Introduction

Although malignant tumors arising from the ampulla of Vater exhibit more favorable biological behavior compared to other periampullary tumors, specifically cholangiocarcinoma and pancreatic adenocarcinoma, pancreaticoduodenectomy (Whipple procedure) still remains the standard surgical approach.[1–3] However, a transduodenal ampullectomy may be an alternative, and at times, a more appropriate procedure for the management of benign neoplasms of the ampulla or for those rare patients with an obstructing adenocarcinoma not deemed fit to undergo a pancreaticoduodenectomy.[4] Intraoperative frozen section evaluation can be used with ampullectomy for benign lesions to determine if a pancreaticoduodenectomy is warranted for an adequate oncologic resection of an adenocarcinoma.[5] In the following report, we describe our technique for performing a transduodenal ampullectomy, including some pearls that will promote success.

S. K. Maithel · Y. Fong (✉)
Department of Surgery,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, NY 10065, USA
e-mail: fongy@mskcc.org

Transduodenal Ampullectomy

Preoperative Evaluation

Patients usually come to medical attention with complaints of nonspecific abdominal pain, pancreatitis, or obstructive jaundice. Upper gastrointestinal (GI) endoscopy, with or without retrograde cholangiopancreatography, facilitates visualization and biopsies of the ampullary mass. Axial imaging with computed tomography (Fig. 1) and/or magnetic resonance cholangiopancreatography (MRCP) is obtained to assess for locoregional and systemic disease. Histopathologic analysis revealing a benign ampullary adenoma is especially amenable to transduodenal ampullectomy. *Pearl*: Tell the GI imager the goal of the study. If they concentrate on the duodenum and produce distention of this part of the small bowel (often best with oral water, not contrast), much improved detail can be obtained (Fig. 1).

Operative Technique

The patient is positioned supine on the operating room table. An upper midline or extended right subcostal incision is used, depending on the patient's body habitus and previous incisions. A complete visual and manual abdominal exploration is performed upon entering the peritoneal cavity to assess for systemic spread. A self-retaining retractor suited for the exposure of the central abdomen, such as the Bookwalter or Thompson retractor, is used to provide adequate exposure. Once the colonic hepatic flexure is mobilized, a complete Kocher maneuver is performed to

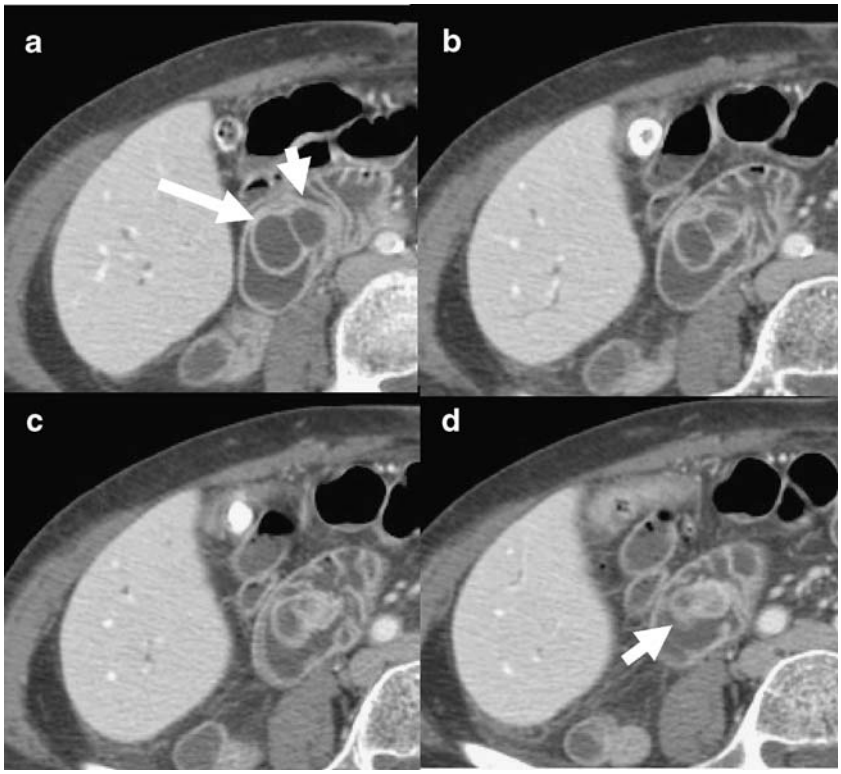

Figure 1 Computed tomography showing ideal ampullary tumor for local excision. Tumor is demonstrated best in **d** (*arrow*). In **a**, **b**, and **c**, the bile duct (*long arrow*) and pancreatic duct (*short arrow*) are easily visualized. There are clearly normal-looking, thin-walled ducts immediately above a relatively small tumor.

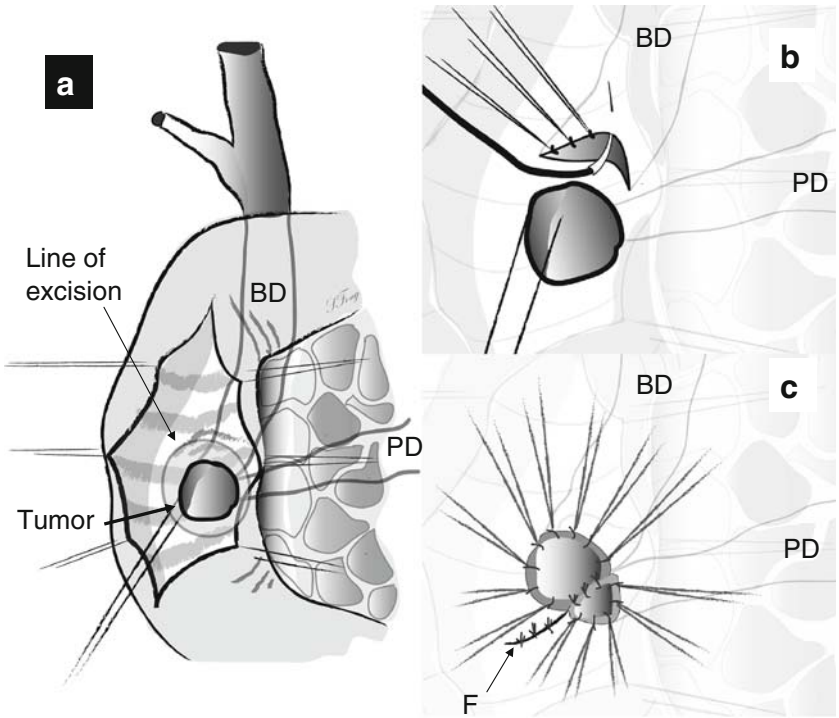

Figure 2 Schematic demonstrating ampullectomy. **a** Demonstrates the surgical field after the duodenum has been opened. Stay stitches on each side hold the duodenotomy open for access. The pancreatic duct (*PD*) and bile duct (*BD*) are outlined. **b** Shows progress of the procedure. After the bile duct is identified with incision into the posterior wall of the duodenum, serial sutures are placed to approximate the bile duct to the duodenal mucosa. Traction on the tumor is achieved by pulling a stay stitch on the tumor downward. **c** Demonstrates the field at the end of the procedure. The reapproximated bile and pancreatic ducts are shown. Note the fold (*F*) shown. This is redundant mucosa that is approximated by simple stitches.

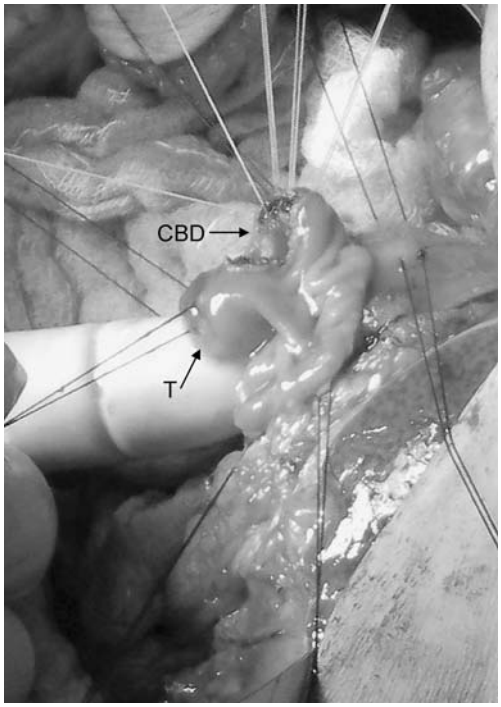

Figure 3 Beginning the tumor excision. This operative photograph shows the ampullary tumor (*T*) being retracted downward. Depicted is the incision into the posterior duodenal surface, identification of the *CBD*, and immediate reapproximation. Sew as you go. This photo parallels Fig. 2b.

fully expose the posterior aspect of the duodenum and facilitate bimanual palpation of the ampulla. *Pearl*: Extend the Kocher maneuver inferomedially to the junction of the superior mesenteric and middle colic vessels. A full Kocherization also facilitates subsequent safe and tension-free closure of the duodenotomy.

An approximately 4 cm longitudinal duodenotomy is made along the lateral wall of the second portion overlying the area of the ampullary tumor. It is important to remember that the duodenotomy will "stretch" so as not to be overly aggressive with the initial duodenotomy that may make subsequent closure difficult. Serial stay sutures (2-0 silk) are placed on either side of the duodenotomy to facilitate exposure of the ampulla (Fig. 2). Once the ampulla is directly visualized, the tumor is usually readily visible. *Pearl*: This operation is much easier technically if the biliary obstruction has not been relieved. If the bile duct is small because the patient previously had a papillotomy or drainage, there may be great difficulty in identifying the bile duct. In that case, a cholecystectomy can be performed to enable transcystic catheterization of the common bile duct (CBD). The catheter can be brought through the ampulla to help in identifying the bile duct during the transection.

A figure of eight suture (2-0 silk) is placed directly through the mass to facilitate its lateral distraction away from the common bile and pancreatic ducts (Figs. 2 and 3). Electrocautery is used to excise the mass. A needle-point electrocautery tip allows for precision and minimizes thermal injury to the CBD and pancreatic duct. Excision begins at the eleven o'clock position. With the lesion retracted inferiorly, the electrocautery is used to cut the posterior duodenal tissues directed toward the CBD until the bile duct is encountered (Figs. 2 and 3). Once the lumen of the CBD is entered, a 4-0 or 5-0 absorbable suture (PDS or vicryl) is used to approximate the bile duct to the medial duodenal wall (Fig. 3). The suture should be placed by first entering the CBD lumen, incorporating the full thickness of the CBD and medial duodenal wall, and finally exiting through the duodenal mucosa. The dissection is then continued in a clockwise fashion. *Pearl*: If the bile duct had not been previously drained, a spurt of bile will announce entry of the bile duct and facilitate visualization. Some have advocated excising the entire tumor before suturing the bile duct to the duodenum. We advocate suturing as you go. If the bile duct is sutured to the duodenum as the duct is opened, it will prevent retraction of the CBD.

As the dissection is continued, the pancreatic duct will be encountered at approximately the two o'clock position along with the effluence of clear pancreatic secretions. The pancreatic duct is approximated to the duodenal wall in the same manner as described for the CBD. It is important to maintain constant maximal lateral traction on the mass itself to facilitate obtaining a negative medial margin. Using this technique, the dissection is continued in a circumferential clockwise manner until the ampullary mass is completely excised. The sequential sutures placed to approximate the CBD and pancreatic duct to the duodenal wall should resemble the spokes of a wheel when excision is complete (Figs. 2 and 4). At this time, depending on the clinical situation, the specimen can be sent for frozen section evaluation. *Pearl*: The defect in the duodenum is always

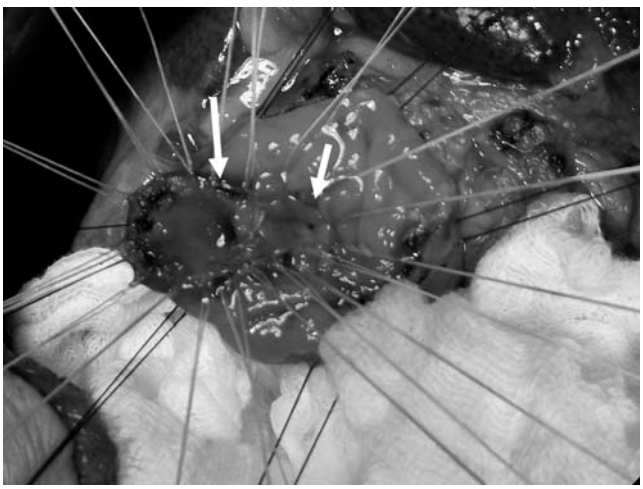

Figure 4 Completed reconstruction of the bile duct (*long arrow*) and pancreatic duct (*short arrow*). This operative photograph parallels Fig. 2c.

bigger that the sum of the size of the bile duct and the pancreatic duct. Thus, there will always be an extra fold of tissue. This is closed with simple duodenal stitches (Fig. 2c).

Once all of the outer sutures are secured, the common walls of the pancreatic duct and CBD are approximated with two to three interrupted 5-0 absorbable sutures, placing the knot in the duodenal lumen (Fig. 4). At this time, the excess suture material is cut, and the excision and reconstruction are now complete. Visualization of biliary and pancreatic drainage confirms patency of both ductal systems.

Duodenal closure is performed in a transverse orientation so as to avoid narrowing the lumen. The stay sutures placed at the initiation of the procedure are removed, except for the two that are located at the midpoint of the anterior and posterior edges, thus converting the longitudinal duodenotomy to a transverse orientation. We prefer to close the duodenotomy in one layer of 3-0 suture (silk, PDS, or vicryl). The decision to leave a closed suction drain is at the surgeon's discretion; we prefer to not leave drains after an uncomplicated procedure. The fascial and skin closure is performed in the usual fashion.

Postoperative Care

Oral intake is resumed once the patient displays a return of bowel function. Routine oral contrast swallowing evaluation to assess for leak before initiating oral intake is usually not necessary. If a closed suction drain was left at the time of operation, a normal drain amylase level (less than three times serum level) may guide drain removal, but usually is unnecessary.

Conclusion

Transduodenal ampullectomy is a less morbid procedure compared to pancreaticoduodenectomy that can be used to resect ampullary neoplasms. Specific clinical situations, such as operating for benign pathology, warrant employing this technique to accomplish an adequate resection. Transduodenal ampullectomy should remain in the armamentarium of any hepatopancreaticobiliary surgeon.

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Laparoscopic Heller Myotomy: Technical Aspects and Operative Pitfalls

Khashayar Vaziri · Nathaniel J. Soper

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Abstract Achalasia is a rare motor disorder of the esophagus characterized by aperistalsis and impaired relaxation of the lower esophageal sphincter (LES). The etiology of this disease remains unknown. The current treatment is palliative and relies upon surgical disruption of the fibers of the LES. The technical aspects and operative pitfalls of laparoscopic Heller myotomy are described in this article.

Keywords Achalasia · Heller myotomy · Laparoscopic surgery · Esophagus

Introduction

Achalasia is a rare motor disorder of the esophagus characterized by the absence of peristalsis and impaired relaxation of the lower esophageal sphincter (LES). First recognized 300 years ago as "cardiospasm", it was then described as a functional esophageal obstruction at the cardiac sphincter. The understanding of this disease has evolved over time and is currently termed "achalasia", derived from the Greek term "chalasis" or relaxing.[1]. Achalasia is rare, affecting approximately one per 100,000 individuals in the United States. The etiology remains unknown, but multiple theories involving viral, inflammatory, and autoimmune processes targeting esophageal ganglion cells have been proposed. Most physiologic studies support the theory of dysfunction or loss of the esophageal myenteric plexus.

K. Vaziri · N. J. Soper (✉)
Department of Surgery,
Northwestern University Feinberg School of Medicine,
201 E. Huron Street, Galter 10-105,
Chicago, IL 60611, USA
e-mail: nsoper@nmh.org

Clinical Evaluation

Common symptoms include dysphagia, chest pain, regurgitation, and heartburn. The most common symptom is dysphagia, but chest pain and heartburn lead many physicians to an erroneous diagnosis of gastroesophageal reflux disease (GERD) and a delay in diagnosis. Antireflux medications are unsuccessful in relieving symptoms and over time esophageal dilatation results. The diagnosis is confirmed by functional studies. Esophageal fluoroscopy and manometry are the best diagnostic tests. The two key manometric findings are absence of esophageal body peristalsis and failure of the LES to relax in response to swallowing. The resting pressure of the LES may be normal or elevated. Barium swallow usually demonstrates a dilated esophagus with a "bird's beak" narrowing at the level of the gastroesophageal (GE) junction. Endoscopy should also be performed to exclude causes of pseudoachalasia such as peptic strictures and carcinoma.

Treatment

Current treatments of achalasia do not address the underlying neuropathology and are aimed at relaxation or disruption of the dysfunctional LES. Medications that reduce LES pressure such as isosorbide dinitrate have been used in the past with transient results. Other more successful methods involve intersphincteric injection of botulinum toxin (botox), forceful endoscopic balloon

dilatation (pneumatic dilatation), and surgical myotomy. Although endoscopic therapy offers a less invasive approach, results are generally not as durable as myotomy and repeat treatments are often necessary. Multiple controlled trials between these three treatment modalities have been performed. Botox was found to be less successful than balloon dilation with 12-month success rates of 32% and 70%, respectively.[2] Similarly, the probability of remaining asymptomatic at a 2-year follow-up favors surgical myotomy over botox, 87.5% versus 34%.[3] A prospective randomized trial comparing forceful balloon dilatation and open surgical myotomy reported symptom resolution in 51% of endoscopic patients and 95% in the surgical group after 5 years.[4] First line treatment of achalasia has traditionally been pneumatic dilatation, but the introduction of laparoscopic Heller myotomy with its reduced surgical morbidity has led to a paradigm shift. Laparoscopic Heller myotomy offers the most effective and durable treatment of achalasia. Nonsurgical candidates can benefit from repeated balloon dilatation, which carries a low but finite risk of esophageal perforation.

Surgical management requires a delicate balance of relieving esophageal outflow obstruction while maintaining a protective antireflux mechanism. Myotomy performed without an antireflux procedure is associated with increased esophageal acid exposure and esophagitis.[5] Heller myotomy with partial fundoplication significantly reduces esophageal acid exposure and the overall relative risk of postoperative GERD when compared to myotomy alone.[6] Studies have shown that both the Dor and Toupet fundoplications are effective with low morbidity and short-term failure rates.[7–11] We describe in this paper the technical aspects of laparoscopic Heller myotomy with partial fundoplication, and common operative pitfalls are discussed. As we preferentially perform a Toupet fundoplication after the myotomy, this will be the focus of the technical description.

Operating Room Setup

Patient positioning, operating room setup, communication, and an experienced operating room team are key elements in achieving successful and reproducible results. A general anesthetic and good muscle relaxation is required to ensure an adequate intraabdominal working space. Rapid sequence intubation is preferred as many achalasia patients will have retained food or secretions in their esophagus. The patient is placed supine on the operating room table with legs abducted on flat padded leg boards to minimize the likelihood of lower extremity neurovascular injury. The right arm is tucked at the patient's side and the left arm remains on an arm board. The patient should be well secured, as steep reverse Trendelenberg is needed for the majority of the operation, displacing the intraabdominal organs from the subdiaphragmatic area, and bringing the operative site closer to the surgeon. This is achieved with the use of a vacuum beanbag mattress. The surgeon stands between the abducted legs allowing easy access to the upper abdomen and minimizing muscle strain and fatigue. The first assistant stands to the right of the patient and the scrub nurse to the left. The camera operator assumes a seated position to the surgeon's right allowing for a comfortable camera operation throughout the procedure. A laparoscopic monitor is placed directly above the patient's head for easy and ergonomically neutral visualization by the operative team. An endoscopic monitor is positioned above the patient's right shoulder to have a side-by-side view with the laparoscope during endoscopy. Two 11-mm and three 5-mm ports are used in a laparoscopic Heller–Toupet operation. Instrumentation includes a 10-mm 30-degree laparoscope, atraumatic graspers, a Babcock grasper, a liver retractor, a needle driver, hook cautery, and ultrasonic shears.

Surgical Procedure

Access to the abdominal cavity is attained approximately 12 cm inferior to the xiphoid process and slightly to the left of midline with a Verress needle. A pneumoperitoneum is established, an 11-mm port is placed and the laparoscope is introduced. This camera port is almost always superior to the umbilicus and care must be taken to ensure that this port is not placed too low, making visualization of the hiatus difficult. A 5-mm port is placed at least 15 cm from the xiphoid process and 3–4 cm below the right costal margin for the liver retractor. The assistant's 5-mm port is placed midway between the camera and liver retractor ports. The surgeon's right hand port is placed approximately 10 cm from the xiphoid process and 3–4 cm below the left costal margin. An 11-mm port is used in this location to facilitate laparoscopic suturing with curved needles. The left lateral segment of the liver is lifted and fixed anteriorly using a self-retaining retractor before placing the final 5-mm port. This port, for the surgeon's left hand, varies depending on the edge of the retracted liver and the location of the esophageal hiatus. Optimally, this 5-mm port is placed in the right subxiphoid area allowing for the camera to look between the surgeon's left and right hands for optimal instrument manipulation (Fig. 1).

Dissection begins by dividing the gastrohepatic ligament just superior to the hepatic branch of the vagus nerve using the ultrasonic shears. This dissection is carried up to the level of the right crus of the diaphragm. The surgeon must be aware of the possibility of an aberrant left hepatic artery,

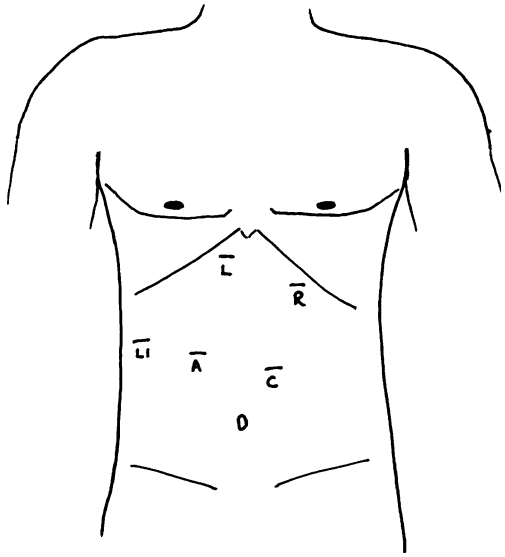

Figure 1 Port placement: *LI*—liver retractor port, *A*—assistant's port, *C*—camera port, *L*—surgeon's left hand port, *R*—surgeon's right hand port.

as incidental transaction can compromise arterial blood flow to the left lateral segment of the liver. Once the right crus is reached, the phrenoesophageal ligament is divided transversely. Only the superficial layers of the phrenoesophageal ligament are divided to avoid injury to the underlying anterior wall of the esophagus and anterior vagus nerve. The assistant provides adequate countertraction by grasping the GE fat pad and retracting caudally. As dissection continues transversely toward the left crus, the fundus and GE fat pad are retracted inferiorly and to the patient's right facilitating mobilization of the cardia.

Following this initial mobilization, a careful hiatal dissection is performed. The assistant provides traction on the esophagus by retracting the GE fat pad caudally. The hiatal dissection begins at the medial border of the right crus. With appropriate tension on the distal esophagus provided by the assistant, the plane between the esophagus and the medial border of the right crus is entered with a blunt instrument. The right crus is then grasped with the surgeon's left hand and retracted to the patient's right. The esophagus is gently swept away in the opposite direction by the surgeon's right hand instrument. The esophagus is gradually and bluntly mobilized in this fashion and the posterior vagus nerve is identified. The posterior vagus nerve is kept with the esophagus and swept away from the periesophageal tissues until the base of the right crus is seen. Tissue between the base of the right crus and esophagus is divided to visualize the origin of the left crus. This blunt dissection is then continued anteriorly along the medial border of the right crus generously mobilizing the mediastinal esophagus (Fig. 2). As the apex of the hiatus is reached, the surgeon's left hand instrument is slipped into this plane and elevates the anterior crural fibers while the esophagus is gently swept away in a blunt fashion with the right-hand instrument. The left-hand instrument continues to retract the crural fibers moving in a clockwise fashion along the hiatus, effectively dissecting ahead of the right hand. The anterior vagus is identified and swept away from the hiatus and toward the esophagus. As the dissection is carried around to the left of the esophagus, the surgeon's left hand instrument is used to bluntly retract the esophagus as the right hand instrument sweeps the hiatus away toward the base of the left crus. Once the base of the left crus is visualized, attention is turned to the short gastric vessels.

The fundus is mobilized by retracting the gastrosplenic ligament to the left and the lateral border of the fundus to the right. The short gastric vessels and all fundal attachments are divided starting approximately 10–15 cm inferior to the angle of His. Adequate mobilization of the fundus is important to ensure a tension-free fundoplication. The ultrasonic shears are used to divide the short gastric vessels up to the angle of His. This dissection plane joins the previous hiatal dissection at the base of the left crus. This allows visualization of the retrogastric space and facilitates the creation of a retroesophageal window. After the fundic mobilization, the hiatal dissection is re-inspected and adequate esophageal dissection is ensured. The GE fat pad is then divided with the ultrasonic shears to expose the GE junction anteriorly, and the anterior vagus nerve is mobilized to avoid injury during the myotomy.

A 6–7 cm esophageal myotomy is planned along the anterior aspect of the esophagus extending onto the gastric

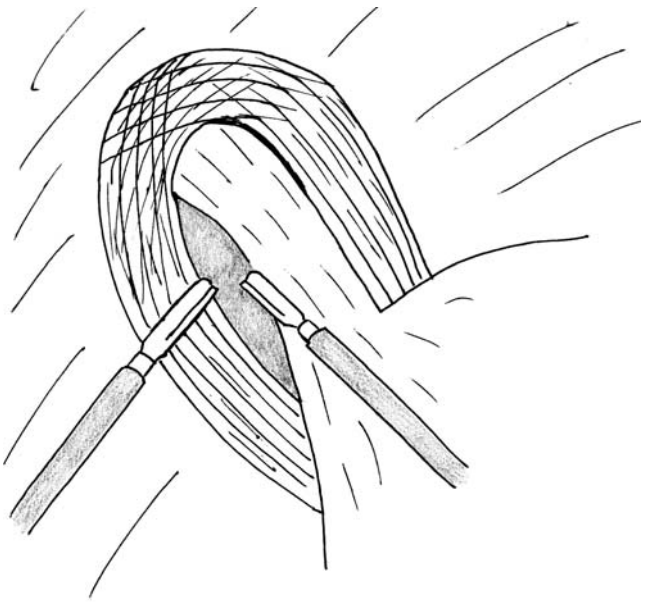

Figure 2 Hiatal Dissection—The hiatal dissection begins at the medial border of the right crus. This dissection can be performed in a blunt fashion.

wall 2–3 cm below the GE junction. Hook cautery is used to deliver low-wattage energy to "map out" and initiate the myotomy. Once the myotomy has been started on the distal esophagus, the edges are grasped with atraumatic graspers, elevated away from the underlying tissue and gently peeled away from the submucosa (Fig. 3). Hook cautery can also be used to lift and then divide/cauterize circular muscle fibers. The myotomy is extended in a cephalad direction and then caudad onto the gastric wall. Care must be taken during the myotomy to avoid injury to the anterior vagus nerve, esophageal perforation, and spiraling of the myotomy. After the myotomy is completed and all muscle fibers are divided, upper endoscopy is performed to ensure adequacy of the myotomy and to identify any mucosal injury. Completeness of the myotomy is confirmed by comparing laparoscopic and endoscopic views. Before constructing the fundoplication, the hiatus is inspected and reapproximated posteriorly with interrupted permanent sutures. The hiatal closure must not impinge on or angulate the esophagus. A 50 French bougie is then passed perorally into the stomach and remains in place during creation of the fundoplication. The leading edge of the lateral aspect of the fundus is then passed through the retroesophageal space. When mobilized properly, this portion of the fundus should sit comfortably to the right of the esophagus. The posterior aspect of the fundus is secured to the right crus. The leading edge of the wrapped fundus is then sutured to the right side of the myotomy over a length of 3 cm using interrupted 2–0 braided polyester suture. Similarly, the anterior fundus is secured to the left side of the myotomy over a length of 3–4 cm. The most cephalad sutures on each side also incorporate the crura. It is important to prevent redundancy in the fundoplication and to avoid snaring the anterior vagus nerve during suturing. A completed Heller–Toupet fundoplication is shown (Fig. 4).

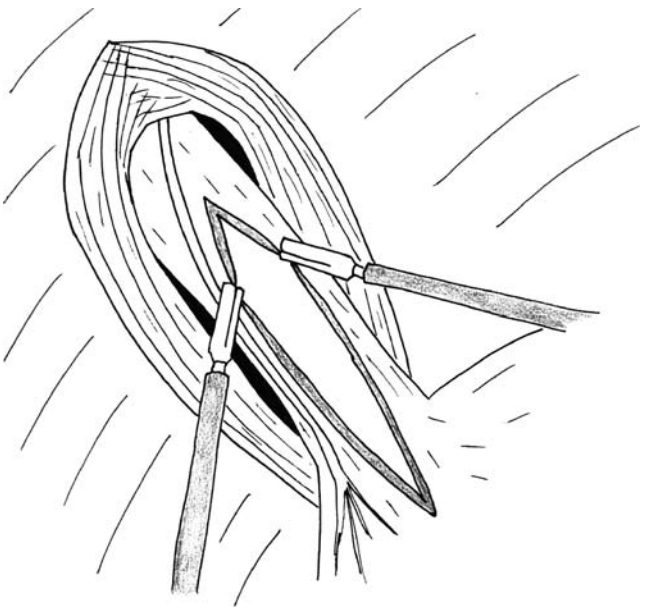

Figure 3 Laparoscopic Heller Myotomy—The edges of the myotomy are grasped and separated. Both longitudinal and circular muscle layers are divided revealing the submucosa. The anterior vagus nerve is seen coursing across the esophagus and not included in the myotomy. The myotomy is extended below the GE junction.

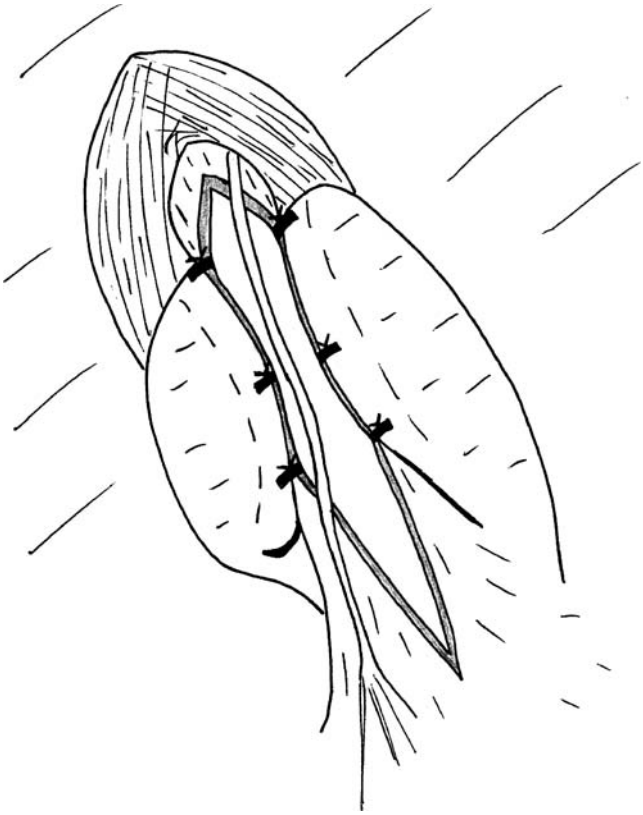

Figure 4 Completed Heller–Toupet Fundoplication—The superior sutures in the partial fundoplication incorporate the crus, myotomy, and stomach. The vagus nerve is seen lying anteriorly and not included in the fundoplication. The fundoplication is positioned above the GE junction.

When the posteriorly wrapped fundus appears to result in excessive anterior esophageal angulation, and in the rare instance of esophageal perforation during myotomy, we perform a Dor fundoplication instead of the Toupet. If a Dor fundoplication is planned preoperatively, the posterior esophageal dissection is unnecessary. The fundus is mobilized and the myotomy is performed as described above. The leading edge of the lateral aspect of the fundus is pulled anteriorly to the right side of the hiatus, effectively covering the myotomy. An inner row of interrupted sutures is placed to fix the inner medial aspect of the fundus to the left side of the myotomy over a 3-cm length as it is being folded over anteriorly. The leading edge of the fundus is then sutured to the right side of the myotomy over 4 cm. The fundus is also sutured to the left and right crura.

Once the myotomy and partial fundoplication is completed, the bougie is removed. The liver retractor is

removed under direct laparoscopic visualization, and hemostasis is assured. All laparoscopic ports are removed under direct vision and the pneumoperitoneum is released. The fascia of the camera port can be reapproximated in interrupted fashion, taking care not to incorporate any intraperitoneal structures in the closure. The fascia of the 11-mm subxiphoid port (surgeon's left hand) does not need to be reapproximated as this incision will commonly migrate above the costal margin when the pneumoperitoneum is released. All skin incisions are closed in subcuticular fashion.

Pitfalls

Previous Surgery or Endoscopic Treatments

Patients with previous upper abdominal or hiatal surgery should be approached with caution. As in any reoperative field, the risk of organ injury, bleeding, and poor outcomes are increased. Access to the peritoneal cavity can be performed using the Verress needle in an area away from the previous operative site, or an open Hasson approach can be used. The left lateral segment of the liver may be densely adherent to the distal esophagus and proximal stomach. Care must be taken to avoid excessive bleeding while mobilizing the liver. The risk of esophageal and gastric perforation is increased, as is the rate of conversion to an open procedure. These risks must be taken into consideration and select patients may benefit from a transthoracic approach. Many patients have undergone endoscopic treatments for achalasia before seeking surgical myotomy. Controversy exists as to whether previous endoscopic treatments increase operative complications and poor outcomes.[12, 13] It has been our experience that prior Botox treatment leads to a more difficult myotomy with longer operative times but otherwise equivalent outcomes to the untreated patient.[10]

Adequacy of Myotomy

The purpose of surgical myotomy is to disrupt the LES fibers and relieve symptoms of dysphagia. Adequacy of the myotomy has been a point of controversy. When the myotomy was performed via a transthoracic approach, it was extended just across the GE junction.[8] With the advent of laparoscopy, most surgeons extend the myotomy onto the gastric wall for 1–2 cm. A recent study advocates that an extended myotomy (>3 cm) provides superior symptomatic relief of dysphagia when compared to a standard myotomy of 2 cm.[9] Unfortunately, this study had sequential patient accrual and compared standard myotomy with Dor fundoplication to extended myotomy with Toupet fundoplication; it is unclear whether long-term symptomatic relief is caused by the myotomy or improved reflux protection. Until more definitive studies are performed, we believe the myotomy should extend onto the gastric wall for at least 2 cm and intraoperative endoscopy should be used to gauge its adequacy.

Esophageal Perforation

Hiatal dissection and mobilization of the mediastinal esophagus can result in an esophageal or gastric injury. At no time should the esophagus be grasped directly. A careful and meticulous dissection should be performed in all patients especially the elderly, immunosuppressed, and reoperative patients. If recognized, gastric perforation or serosal tears can generally be easily repaired at the time of surgery. Esophageal perforations can be handled in a similar fashion by suturing with fine absorbable sutures. If an anterior esophageal injury is created at the time of myotomy, the surgeon can elect to buttress the repair with a Dor fundoplication as opposed to a Toupet. The true danger lies in unrecognized injuries. Unrecognized injury can result in peritonitis and/or mediastinitis and may require diversion and gastrostomy tube placement or esophagectomy. For this reason, some surgeons advocate the routine use of a Dor fundoplication to cover the myotomy, and this approach obviates the need for the posterior esophageal dissection. Despite this theoretical advantage, the Heller–Toupet operation has been shown to be safe and effective in experienced hands.[9, 10, 14]

Postoperative Management

A nasogastric tube is not used routinely, and patients are hospitalized overnight. A clear liquid diet is started on the afternoon of the operation and a soft diet the morning after. Adequate pain control is achieved using oral (liquid) analgesics. Intravenous anti-emetic medications are given as needed to prevent retching and vomiting to avoid stress on the newly created fundoplication. An esophagram is not routinely performed, and obtained only if there is clinical suspicion of a perforation, or to evaluate for herniation and disruption if the patient retches or vomits. Patients are discharged home on the first postoperative day on a diet of soft foods for 2–4 weeks. Bread, bread products, hard fruits and vegetables, and coarse meats should be avoided for this time period. Patients are seen on an outpatient basis at 2–4 weeks, 6 months, and yearly thereafter. We generally perform a timed barium swallow to evaluate gastric emptying and a 24-hour pH test to assess for silent GE reflux at 6–12 months postoperatively.

Conclusion

Surgical myotomy is the most effective and durable treatment for achalasia. The use of laparoscopy has decreased operative morbidity, which has led to the laparoscopic Heller myotomy becoming the first line treatment.[15] A partial fundoplication should be performed in conjunction with the myotomy to minimize postoperative GE reflux, a harmful occurrence in an esophagus with poor clearance capabilities. The ideal fundoplication awaits the performance of prospective randomized trials. We have found the combined laparoscopic Heller–Toupet procedure to be a safe and effective treatment of achalasia.

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How I Do It: Surgical Management of Gastrointestinal Stromal Tumors

Chandrajit P. Raut · Stanley W. Ashley

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Abstract The surgical management of gastrointestinal stromal tumors (GISTs) has been impacted by the development of tyrosine kinase inhibitors (TKIs), advances in surgical technique, and a better understanding of the natural history of this unique disease. In this article, we review the technical aspects of the operations, the expanding role of laparoscopy, and the indications for neoadjuvant and neoadjuvant TKI therapy in primary GIST. Furthermore, we explore the rationale for and incorporation of surgery in the multidisciplinary management of advanced GIST.

Keywords Gastrointestinal stromal tumor · Surgery · Adjuvant therapy · Metastases · Sarcoma

Advances in the Management of Gastrointestinal Stromal Tumors

The management of gastrointestinal stromal tumors (GISTs) has evolved considerably over the last decade. Before 2001, the only proven therapy was surgery. The recent development of clinically effective inhibitors targeting the transmembrane receptor tyrosine kinase KIT radically changed the management of advanced (locally advanced and metastatic) disease and provided an opportunity for adjuvant or neoadjuvant therapy for localized disease. To date, two tyrosine kinase inhibitors (TKIs) have been approved by the United States Food and Drug Administration for the treatment of advanced GIST: imatinib mesylate (Gleevec, Novartis Pharma, Basel, Switzerland) and sunitinib malate (Sutent, Pfizer Inc, New York, NY). Neither drug has been approved for adjuvant/neoadjuvant use in primary GIST.

Given this progress, it is imperative that surgeons understand the salient features in the diagnosis and multidisciplinary management of this neoplasm. This review will focus on our current surgical management of GIST.

C. P. Raut (✉) · S. W. Ashley
Department of Surgery, Brigham and Women's Hospital,
75 Francis St,
Boston, MA 02115, USA
e-mail: craut@partners.org

C. P. Raut · S. W. Ashley
Department of Surgery,
Dana-Farber Cancer Institute, and Harvard Medical School,
Boston, MA, USA

Diagnosis and Evaluation

We rely on contrast-enhanced computed tomography (CT) of the abdomen and pelvis to characterize an abdominal mass suspicious for GIST and to evaluate the extent of disease. Though lung metastases are rare, CT of the chest completes the routine imaging studies. Magnetic resonance imaging (MRI) may clarify the scope of disease at sites such as the liver or the perirectal tissues. We selectively employ functional imaging with [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) to determine the extent of disease, evaluate ambiguous masses, and monitor response to medical therapy and emergence of drug-resistant clones.[1] However, for primary, localized, resectable GIST, routine use of PET is neither necessary nor indicated.

We do not believe a preoperative tissue diagnosis is necessary for a primary, resectable neoplasm suspicious for GIST. However, if the diagnosis is in doubt, if neoadjuvant therapy is under consideration, or if there is metastatic disease, then fine-needle aspiration (FNA) or biopsy is essential.

Table 1 Risk Stratification for GIST

Mitotic Rate	Tumor Size	Percent of Patients with Progressive Disease/Risk Classification, Based on Site of Origin			
		Stomach	Duodenum	Jejunum/Ileum	Rectum
≤5 per 50 HPF	≤2 cm	0	0	0	0
	>2, ≤5 cm	1.9/very low	8.3/low	4.3/low	8.5/low
	>5, ≤10 cm	3.6/low	–[a]	24/moderate	–[a]
	>10 cm	12/moderate	34/high	52/high	57/high
	≤2 cm	–[a]	–[a]	–[a]	54/high
>5 per 50 HPF	>2, ≤5 cm	16/moderate	50/high	73/high	52/high
	>5, ≤10 cm	55/high	–[a]	85/high	–[a]
	>10 cm	86/high	86/high	90/high	71/high

Adapted from Miettinen and Lasota (with permission).[2] The risk of recurrence is based on review of data from the pre-TKI era.
HPF High-power field
[a] Insufficient data

Prognostic Factors

We increasingly rely on the presence or absence of established prognostic factors to guide treatment decisions. The accepted risk factors for GIST predictive of aggressive behavior are tumor size, mitotic count, and site of tumor origin.[2] The current risk stratification of primary GIST is listed in Table 1. In general, GISTs originating in the small bowel (30% of all GISTs) demonstrate more aggressive behavior than those of comparable size and mitotic rate originating in the stomach (60% of all GISTs).[2]

Management of Primary GIST

Surgical Technique

Surgery remains the principal and only potentially curative treatment for localized, resectable, primary disease. Specific technical considerations are listed in Table 2. The goal of the operation is complete macroscopic resection with an intact pseudocapsule and a negative microscopic margin (R0 resection).

At laparotomy, we thoroughly explore the abdomen to identify and remove any previously undetected peritoneal

Table 2 Technical Considerations Regarding Surgery for Localized Primary GIST

Surgical Approach	Goals and Guidelines
Laparotomy	Complete macroscopic resection with negative microscopic margins (R0 resection)
	Intact pseudocapsule
	Thorough abdominal exploration for peritoneal or liver metastases
	Wedge or segmental resection of site of origin
	Extensive resection when required
	En bloc contiguous organ resection when required
	Lymphadenectomy not indicated
	Wide margins not indicated
	Resect all non-gastric GISTs
	Consider management of positive microscopic margins on a case-by-case basis
Laparoscopy	Acceptable when R0 resection is feasible
	Oncologic principles apply (used of protective plastic bag to minimize risk of port-site recurrences)
	Feasible for tumors <8 cm (data for larger tumors not available)
	No data available for laparoscopic or laparoscopy-assisted resection of non-gastric GIST
Endoscopy	Endoscopy useful for surveillance of gastric GIST≤1 cm
	Endoscopic resection not indicated
Neoadjuvant therapy	No data yet available
Adjuvant therapy	Consider for all tumors ≥3 cm in size on a case-by-case basis; refer to specialty sarcoma center

metastatic deposits. In general, primary neoplasms tend not to invade surrounding organs despite CT appearance. Wedge or segmental resection of the involved stomach or bowel usually suffices. However, anatomic considerations may require a more extensive resection to completely remove the neoplasm. For instance, large proximal gastric GISTs may mandate a total gastrectomy, periampullary GISTs may necessitate a pancreaticoduodenectomy, and rectal GISTs at the level of the levator ani muscles may require an abdominoperineal resection (APR). In a series of 140 patients with gastric GISTs, 68% underwent wedge resections, 28% underwent partial gastrectomies, and only 4% needed total gastrectomies.[3] Lymphadenectomy is generally not indicated as lymph nodes are rarely involved.

Indications for Laparoscopy

A minimally invasive approach may be considered for appropriate primary GISTs. We perform laparoscopic or laparoscopy-assisted resections for neoplasms less than 5 cm in size situated along the greater curvature of the stomach. Standard oncologic principles still apply. The abdomen should be thoroughly explored, and the tumor should be placed into a protective plastic bag to minimize the risk of port-site recurrence. We confirm with the pathologist that adequate margins were achieved before the operation is terminated. A laparoscopic approach knowingly resulting in a positive microscopic margin (R1 resection) should never be accepted when conversion to a laparotomy will guarantee an R0 resection.

The supporting data are limited. Otani and colleagues removed 35 gastric GISTs 2–5 cm in size via laparoscopic wedge resections.[4] With a median follow-up of 53 months, no local or distant recurrences were noted for neoplasms under 4 cm in size. Novitsky and colleagues performed margin-negative laparoscopic or laparoscopy-assisted resections of 50 gastric GISTs measuring 1.0–8.5 cm in size.[5] With a mean follow-up of 3 years, 92% of patients remained disease-free, and there were no local or port-site recurrences. There are no series reporting long-term outcomes with laparoscopy for resection of GISTs at other sites.

Microscopic GIST: When is Observation an Option?

We believe that all GISTs 2 cm in size or greater should be resected, barring prohibitive comorbidities. None of these should be considered benign (Table 1). Management of GISTs under 2 cm in size is more controversial, and the natural history of such neoplasms is unknown. Subcentimeter "microscopic" gastric GISTs are common, reported in 22.5% of autopsies in German adults older than 50 years and in 35% of Japanese patients undergoing gastrectomy for gastric cancer.[6,7] Yet, few of these neoplasms ever become clinically relevant. In the absence of sufficient data to guide therapy, management of such neoplasms remains undefined. Small gastric GISTs are generally less aggressive than comparable neoplasms in the small bowel. Thus, gastric GISTs under 1 cm in size identified incidentally (usually on imaging or endoscopy) may be followed with serial endoscopy or imaging. Any that are symptomatic (for instance, hemorrhage from erosion through the mucosa) or increase in size on serial endoscopy or imaging should be resected. Endoscopic resection of small gastric GISTs has been reported.[8] However, these neoplasms frequently involve the muscularis propria. Thus, endoscopic resection may increase the risk of a positive peripheral margin, and we do not encourage this approach.

GISTs between 1 and 2 cm in size pose an even more difficult management dilemma. We favor resection, particularly when laparoscopy is possible. However, the natural history of such neoplasms is not known. One could argue that with the very low risk of recurrence in patients with neoplasms under 2 cm in size and a low mitotic rate (Table 1), all GISTs in this category may be observed. However, the mitotic rate cannot be estimated reliably on biopsy or FNA, and thus observation cannot be recommended based on size alone. Ultimately, the surgeon should carefully discuss the pros and cons of operation versus observation with the individual patient.

We do not consider any non-gastric GISTs "benign," given their higher risk of aggressive behavior, and recommend resection irrespective of size.

Margin: What is Enough?

The management of surgical margins is not well defined for GISTs. There are no data to support the belief that the wide margins of resection typically recommended for adenocarcinomas or other sarcomas reduce the risk of recurrence in GIST.[9] There is also no evidence that patients who have undergone complete resection of all macroscopic disease but who still inadvertently have positive microscopic margins (R1 resection) require re-excision.[10] As margins may retract after resection, or the pathologist may trim away the staple line (converting a negative margin into a positive one), all such cases should be carefully evaluated by a multidisciplinary team of surgeons, pathologists, and medical oncologists to assess the need for re-excision.

Neoadjuvant and Adjuvant Therapy for Primary Disease

While patients with resectable disease should undergo an operation, single-institution retrospective series have demonstrated that recurrence rates are high. In patients undergoing R0 or R1 resections, 5-year overall survival (OS) rates ranged from 42% to 54% in the pre-TKI era.[11–13] Conse-

quently, investigators are evaluating TKIs for neoadjuvant or adjuvant use.

The Radiation Therapy Oncology Group (RTOG) 0312 trial is the only study to examine the use of imatinib as a neoadjuvant agent (eligibility criteria in Table 3). This study has completed accrual, and preliminary data are expected in the near future.

Four trials evaluating imatinib in the adjuvant setting have completed or nearly completed accrual (Table 3). Results are not available for three of these trials. The results of the American College of Surgeons Oncology Group (ACOSOG) multicenter Z9001 trial were recently reported.[14] In this study, patients with KIT-positive primary GISTs at least 3 cm in size were randomized to either 400 mg of imatinib daily or placebo for 1 year after R0/R1 resection. The trial was closed early after planned interim analysis identified significant improvement in recurrence-free survival (RFS) in the experimental arm. There was no difference in OS. The trial did not stratify patients based on the prognostic factors mitotic rate or site of origin, so treating clinicians should carefully consider the risk of recurrence in their patients before starting adjuvant imatinib. Future trials should address the optimal duration of adjuvant therapy with imatinib.

The success of TKI therapy should not change the approach to the operation. Despite the results of the Z9001 trial, the availability of TKIs does not release surgeons from their responsibility in performing an oncologically appropriate operation for localized, resectable, primary GIST.

Management of Locally Advanced or Metastatic Disease

Medical Management

Patients who have unresectable or marginally resectable primary tumors or those in whom resection could lead to considerable morbidity or functional deficit should be considered as having "locally advanced" GIST. At our institution, such patients are managed by a multidisciplinary team. They may be candidates for TKI therapy on an individual basis and may be treated like those with metastatic disease. Therapy with imatinib (first-line TKI) may cause the tumor to shrink to the point that resection may be

Table 3 Clinical Trials of Surgery and Imatinib in Primary Gastrointestinal Stromal Tumor

Trial	Imatinib Therapy	Eligibility	Dose	Status
RTOG S0132	Neoadjuvant	Any of the following: 1. primary tumor ≥ 5 cm 2. recurrent tumor ≥ 2 cm Potentially resectable	600 mg daily × 8–10 weeks preoperatively + 600 mg daily × 24 months postoperatively	Completed accrual
ACOSOG Z9000	Adjuvant	Any of the following: Tumor≥10 cm Rupture/hemorrhage Multiple tumors (<5) Complete resection	400 mg daily × 12 months	Completed accrual
ACOSOG Z9001	Adjuvant	Tumor≥3 cm Complete resection	400 mg daily v. placebo × 12 months	Reported
SSG XVIII	Adjuvant	Any of the following: Tumor≥10 cm Rupture Mitotic rate>10 Tumor>5 cm+mitotic rate>5 Primary tumor + liver/peritoneal metastases Complete resection	400 mg daily × 12 months or 36 months	Open
EORTC 62024	Adjuvant	Any of the following: Tumor>5 cm Mitotic rate>10 Tumor<5 cm+mitotic rate 6–10 Complete resection	400 mg daily v. no treatment × 24 months	Open

Adapted from van der Zwan and Dematteo (with permission)[26]. Mitotic rate expressed per 50 high-power fields
RTOG Radiation Treatment Oncology Group, *ACOSOG* American College of Surgeons Oncology Group, *SSG* Scandinavian Sarcoma Group, *EORTC* European Organization for the Research and Treatment of Cancer

reconsidered. However, there are no trial data to provide further guidance.

Presently, a patient with locally advanced or metastatic disease ("advanced" GIST) should first receive imatinib dosed at 400 mg daily.[10] When unequivocal progression is observed, the dose may be escalated incrementally up to 800 mg daily, although the side effects may become more pronounced. Alternatively, the patient may be switched to sunitinib at 37.5 mg daily.[10] Those experiencing disease progression on sunitinib should be referred to centers specializing in the management of sarcomas, where protocol therapy may be available. Further details on nonsurgical therapy may be found in the recently published revision of the National Comprehensive Cancer Network (NCCN) guidelines and on the NCCN website (http://www.nccn.org).[10]

Rationale for Surgery for Advanced Disease After TKI Therapy

With the advent of TKIs, the philosophy on the role of surgery in the management of advanced GIST changed. The majority of patients with advanced GIST experience long periods of partial response (PR) or stable disease (SD) on TKI therapy. Furthermore, despite the fact that over 80% of treated patients respond to imatinib, tumors still remain viable, and fewer than 5% experience pathologic complete responses.[15,16] Those who respond to imatinib develop secondary resistance to the drug after a median of 2 years of therapy.[17] When drug resistance develops, disease progression may be either limited or generalized.[18,19] Limited disease progression refers to progression at one site of tumor, with other tumor deposits showing ongoing response to TKI therapy. Generalized disease progression describes progression at more than one site. Experience with sunitinib is more limited, but again, drug resistance develops after initial response, leading to disease progression.[20]

Surgical Technique

The effectiveness of TKI therapy has provided an opportunity to reconsider surgery with cytoreductive rather than palliative intent. Recently, six institutions reported their rates of progression-free survival (PFS) and OS after operations in patients with advanced GIST treated with TKI therapy.[18,19,21–24] Such operations are typically extensive and thus should only be undertaken at institutions and by surgeons with considerable experience. The goal of these operations should be an R0 or R1 resection, though the former is only rarely possible. There are no data establishing the superiority of an R0 over an R1 resection in the setting of metastatic disease in the post-TKI era. In the various series, the R0/R1 resection rate ranged from 48% to 91% (Table 4).[18,19,21–24]

Patients with advanced disease may have peritoneum-only, liver-only, or combined peritoneum–liver disease. Specific technical considerations are listed in Table 5. In our experience, liver resections were required in nearly 40% of such cytoreductive operations, and over 60% included peritonectomy and/or omentectomy.[19] Bowel resections were common, and over 60% of patients underwent multivisceral resections.[19] Aggressive, complex GI operations, including total gastrectomy, pancreaticoduodenectomy, APR, and hepatic lobectomy were occasionally necessary to remove all visible disease. Radiofrequency ablation may be considered for bilobar liver disease. Lymphadenectomy is not required. Again, standard oncologic principles apply, with every attempt made to avoid tumor rupture.

Complications rates approaching 60% were reported, though the majority were minor.[18] Perioperative deaths were rare, usually in the setting of emergency procedures.[22,24] These issues underscore the need for additional multidisciplinary support with experienced anesthesia, nursing, and critical or intensive care unit.

Table 4 Resection Rates During Cytoreductive Surgery for Advanced GIST After TKI Therapy

First Author	Number of Pts	TKI Therapy	Response[a] to TKI (%)	Progression[a] on TKI (%)	R0/R1 (%)
Raut[19]	69	IM/SU	33	Limited 47 Generalized 20	83
Rutkowski[24]	24	IM	75	25	91
Andtbacka[21]	46	IM	45	55	48
Bonvalot[22]	22	IM	95	5	68
DeMatteo[18]	40	IM/SU	50	Limited 33 Generalized 17	80
Gronchi[23]	38	IM	71	Limited 21 Generalized 8	82

[a] Response or progression at the time of surgery

TKI Tyrosine kinase inhibitor, *IM* imatinib, *SU* sunitinib, *Limited* limited disease progression, *Generalized* generalized disease progression

Table 5 Technical Considerations Regarding Surgery for Advanced GIST

Issues	Guidelines
Timing of Surgery	When maximal response to TKI is observed
	After a minimum of 6 months of TKI therapy
Candidates for surgery	Patients with ongoing response (PR or SD) to TKI therapy
	Patients with limited disease progression on TKI therapy may be considered
	Patients with evolving necrosis or other impending emergency
Details of surgery	Complete macroscopic resection (R0/R1 resection)
	Resect all progressing lesions if operating on patient with limited disease progression
	Resect lesions of concern (impending emergencies)
	Liver resection when required
	En bloc contiguous organ resection when required
	Peritonectomy/omentectomy when required
	Lymphadenectomy not indicated
	Wide margins not indicated
TKI therapy	Resume postoperatively

TKI Tyrosine kinase inhibitor, *PR* partial response, *SD* stable disease

Timing of Surgery Based on Resectability and Survival

From the collective experience of the six institutions, we can derive several guidelines for determining the optimal timing of surgery. First, we found that the ability to remove all macroscopic disease was greatest in patients demonstrating ongoing response to TKI therapy. After operation, there was no evidence of any disease in 78%, 25%, and 7% of patients with PR/SD, limited progression, and generalized progression, respectively.[19] On the other hand, bulky residual disease remained postoperatively in 4%, 16%, and 43% of patients with PR/SD, limited progression, and generalized progression, respectively.

Second, the highest rates of PFS and OS were seen when cytoreductive surgery occurred while the patients were still responding to TKI therapy. Rates of PFS for patients responding to TKI therapy were 70% to 96% at 1 year after surgery and as high as 72% at 4 years from the start of imatinib therapy.[18,19,23] In contrast, the 1-year PFS for patients with generalized progression was only 0% to 14%. OS rates approached 100% at 1-year after surgery in patients responding to TKI therapy. In the setting of generalized progression, the OS rates were more variable, ranging from 0% to 60%. Although patients with limited progression had lower rates of PFS than those with PR/SD, the rates of OS were not consistently different.

Third, the optimal time interval from start of TKI therapy to surgery (when considered) is unclear, but is probably under 24 months. Radiographic response to imatinib identifiable on CT may take 3 to 6 months. In fact, tumors that are responsive to therapy may appear to even grow in part due to cystic degeneration within the tumor. Such change in size may be indistinguishable from primary resistance to imatinib (tumors which do not respond to imatinib). Thus, we believe it is prudent to wait at least 6 months before undertaking surgery to be certain that the tumors are responding. Little incremental tumor shrinkage is observed after 9 months of imatinib.[18] The median time to progression on imatinib is approximately 2 years. Thus, we prefer to operate between 6 and 12 months or at a point when there is no significant change between sequential staging CTs and certainly before 24 months. Similar data for sunitinib are not available, as only two of the reported series included patients on this agent.[18,19]

Based on these data, the patients who seemed to derive the most benefit from surgery were the ones still responding to TKI therapy at the time of the operation; such patients should be considered for operation on a case-by-case basis. Though patients with limited progression recurred more quickly than those with responsive disease, the rates of OS were not different, and thus, operation should be considered in these patients as well. Finally, those with generalized progression did not appear to derive much benefit from an operation, and we believe they are best treated with nonoperative therapies.

It is crucial to understand that though an operation is feasible, there is still no evidence that outcomes are superior or even equal to those who continue on TKI therapy without an operation. This can only be answered in a randomized clinic trial; such trials are under development in both the United States and Europe.

Resumption of TKI Therapy Postoperatively

After cytoreductive surgery, patients should resume TKI therapy. Failure to resume imatinib or sunitinib postoperatively may lead to rapid recurrence of disease. In a report out of Poland, the first five patients undergoing cytoreductive surgery did not restart imatinib, and four developed recurrent disease.[24] The next 19 patients resumed imatinib,

and only one developed recurrence. An unresolved issue is the length of time to continue TKI therapy postoperatively. Data from the French Sarcoma Group demonstrated that interruption of imatinib therapy in patients with advanced GIST resulted in rapid progression; these patients did not undergo surgery as part of this trial.[25] Extrapolating from this experience, we recommend continuing TKI therapy indefinitely after resuming it postoperatively.

Specific details about TKI selection and dosing postoperatively are best managed by a multidisciplinary team. After reviewing the operative findings, the treating surgeon and medical oncologist may determine whether the patient is best served by dose escalation of current TKI, switching from imatinib to sunitinib, or consideration of protocol therapy.

Management of Emergencies

Patients with advanced GIST on TKI therapy may develop complications such as intraluminal or intraperitoneal hemorrhage, rupture, abscess, fistula, or obstruction secondary to the tumor requiring emergency surgery. An operation in this setting is associated with higher rates of complications than elective cytoreductive surgery.[19] Furthermore, all three postoperative deaths in one series occurred in patients undergoing emergency surgery.[22] Consequently, an operation should be considered preemptively in patients considered "high-risk" for impending emergencies. While the specific findings concerning for impending emergency have not been completely outlined, patients with evidence of fistulization to bowel, evolving necrosis, or self-limited hemorrhage should be evaluated for surgery to reduce the risk of sepsis, further tumor rupture, or hemorrhage.[22]

Surveillance

Postoperatively, all patients should undergo surveillance CT of the chest, abdomen, and pelvis to monitor for recurrent or metastatic disease every 3 to 6 months for the first 5 years and then yearly thereafter. Those with very low risk GISTs may undergo less frequent follow-up. We do not routinely use PET for surveillance, but it may help characterize ambiguous masses seen on follow-up CT. Further guidelines may be found on the NCCN website.

Conclusion

Surgery remains the primary and only potentially curative therapy for GIST. The development of the effective TKI inhibitors imatinib and sunitinib has altered the prognosis of metastatic disease. Use of imatinib as a neoadjuvant and adjuvant agent remains an area of active investigation. Operations may be considered in select patients with advanced GIST on TKI therapy. However, there is no evidence establishing the superiority of operation plus TKI therapy over TKI therapy alone for advanced disease. Given the increasing complexity in the management of GISTs, affected individuals should be referred to experienced centers for optimal multidisciplinary management.

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Neoadjuvant Therapy for Pancreatic Cancer

Andrew M. Lowy

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Abstract Surgical resection is necessary but generally insufficient as curative treatment for pancreatic cancer. Traditionally, postoperative (adjuvant) therapies have been utilized in an attempt to improve outcome, yet these efforts have met with extremely limited success. As preoperative (neoadjuvant) treatment strategies have evolved for the treatment of other malignancies, preoperative therapy for pancreatic cancer has been investigated by several groups over the past decade. At this time, no randomized trials comparing adjuvant and neoadjuvant therapies have been performed, nor have there been any large multicenter trials of neoadjuvant therapy for pancreatic cancer. In this manuscript, the rationale for neoadjuvant strategies are discussed in the context of the available data on both adjuvant and neoadjuvant therapy and clinical trials currently in development.

Keywords Pancreatic cancer · Neoadjuvant therapy · Adjuvant Therapy · Chemotherapy · Radiation · Chemoradiation

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States, with an incidence of 37,000 that nearly matches its mortality rate.[1] Despite advances in surgery and perioperative care that have resulted in markedly reduced postoperative mortality after pancreaticoduodenectomy, the median survival for pancreatic cancer patients has changed minimally over the past two decades. These distressing facts become even more so when viewed in the context of significant progress in the treatment of other epithelial malignancies. For example, the median survival for patients with Stage IV colorectal cancer has doubled during the last decade and now exceeds that of patients with resected pancreatic cancer. The fact that roughly 85% of patients with resected pancreatic cancer will ultimately recur and die of their disease argues strongly that in most cases, pancreatic cancer is a systemic disease at the time of diagnosis. As such, surgical resection alone is inadequate therapy, and multimodality treatment must be effectively applied to achieve cure. In pancreatic cancer treatment, the addition of chemotherapy, chemoradiation or some combination, to surgery has traditionally been delivered in the postoperative (adjuvant) setting. In recent years, however, there has been increasing interest in the delivery of preoperative (neoadjuvant) therapy for patients with pancreatic cancer as this approach offers hypothetical advantages over postoperative treatment. This article will review the available data on adjuvant and neoadjuvant therapy for pancreatic cancer and consider these treatment strategies in the context of currently accepted standards and ongoing clinical trials.

A. M. Lowy (✉)
Surgery, University of California, San Diego,
3855 Health Sciences Drive,
La Jolla, CA 92093-0987, USA
e-mail: alowy@ucsd.edu

Adjuvant Therapy for Pancreatic Cancer

Historically, the use of chemoradiation for pancreatic cancer, both in the adjuvant and neoadjuvant setting, can be traced to studies by Moertel et al.[2] In these trials, the use of 5-FU-based chemoradiation improved the median survival of patients with locally advanced unresectable

pancreatic cancer from 6 to 10 months. As both local and distant failure is common after pancreatic resection, adjuvant therapy strategies initially used both chemotherapy and chemoradiation. The Gastrointestinal Tumor Study Group (GITSG) performed the first prospective randomized trial for resected pancreatic cancer, examining the efficacy of 2 years of systemic 5-FU and 5-FU based chemoradiation using 40 Gy of split-course radiotherapy.[3] Because of poor accrual, ultimately the trial consisted of only 22 patients in the surgery control arm and 21 patients in the study arm. Despite this, a marked survival advantage was conferred to the treatment group, as 2-year survival was increased from 15% to 42%. The split course chemoradiation regimen used in this study is now viewed as substandard, but it is often overlooked that patients in this trial received a considerable amount of 5-FU as systemic treatment. It is important to note that one reason for poor accrual to the GITSG trial was the slow recovery many patients faced after pancreaticoduodenectomy and that 25% of patients entered did not receive adjuvant therapy for more than 10 weeks after their operation. Subsequent retrospective single institution studies were offered as confirmation of the benefits of 5-FU-based chemoradiation until the European Organization for Research and Treatment of Cancer (EORTC) reported a randomized trial for resected periampullary cancer[4,5] The EORTC study regimen again utilized split course, 5-FU-based chemoradiation, this time without additional systemic therapy. The study was not powered to examine pancreatic cancer patients alone and in this subset, chemoradiation resulted in a modest, but statistically insignificant benefit in survival, (median 17.1 vs. 12.6 months median, $p=0.09$). The European Study Group for Pancreatic Cancer (ESPAC) performed a larger Phase III trial to examine the benefit of chemotherapy, and chemoradiation in resected pancreatic cancer patients.[6] This trial initially consisted of 285 patients randomized in a 2×2 factorial design. Subsequently, 256 patients were added in randomizations to either chemotherapy vs. observation or chemoradiation versus observation. The outcome of the trial was reported for all patients and than again for the 2×2 factorial randomization groups alone. Ultimately, the authors concluded that patients who received chemotherapy alone enjoyed a survival advantage (median 19.7 vs. 14 months), although chemoradiation conferred no advantage and, as described by the authors, may have in fact had a "deleterious effect". This trial has been criticized for the randomization scheme, and for a lack of quality control for pathology and radiotherapy. In addition, patients receiving radiotherapy may have had a poorer performance status as they began adjuvant treatment an average of 2 weeks later than those receiving chemotherapy. Regardless of the controversies, the ESPAC-1 study demonstrated a benefit to systemic chemotherapy after a resection of pancreatic cancer. This concept was again tested in the CONKO-001 trial, which examined the benefit of adjuvant Gemcitabine after pancreatectomy.[7] Three hundred fifty-four patients were randomized to adjuvant gemcitabine versus observation after surgery. At the time of publication, the treatment group enjoyed a prolonged disease-free survival (13.4 vs. 6.9) months, but as yet there was no difference in overall survival. The authors speculated that his may have been caused by the use of Gemcitabine as salvage post recurrence. Importantly, both margin negative and margin positive patients benefited from adjuvant gemcitabine. The last randomized trial to be reported was Radiation Therapy Oncology Group (RTOG) 9704, which examined the use of adjuvant Gemcitabine versus 5-FU given before and after 5-FU-based chemoradiation.[8] This study, not yet published in manuscript form, revealed a benefit in overall survival for patients with pancreatic head cancers receiving gemcitabine (median 20.6 vs. 16 months). An ongoing study by the EORTC is evaluating the benefit of chemoradiation added to gemcitabine vs. gemcitabine alone, a point of continuing controversy. At present, the available data would suggest a benefit to adjuvant chemotherapy for resected pancreatic cancer patients (Table 1). The role of chemoradiation remains less clear and may be more important in patients with microscopically positive margins. Whereas the optimal adjuvant regimen for pancreatic cancer remains undefined, it is clear that one problem common to all adjuvant protocols is slow patient recovery after pancreaticoduodenectomy. Most studies have revealed that approximately 25% of patients will experience a delay or not receive adjuvant therapy because of difficulty returning to adequate performance status. A recent study revealed that in the United States, less than half of resected pancreatic cancer patients receive any form of adjuvant therapy.[9]

Neoadjuvant Therapy for Resectable Disease

The most certain advantage of neoadjuvant therapy for pancreatic cancer is that it obviates the issue of postoperative recovery and insures delivery of treatment to nearly all patients. Neoadjuvant therapy offers other hypothetical benefits including: 1) delivery of treatment to well-oxygenated tissue which enhances efficacy of chemoradiation, 2) downstaging can enhance ability to achieve a negative margin resection and thereby reduce local recurrence, 3) avoidance of surgery in patients with rapidly progressive disease, 4) preoperative radiotherapy may decrease the risk of pancreatic anastomotic leak. Definitive proof for many of these hypotheses requires a randomized prospective trial; however, to date, there have been no randomized comparisons of the adjuvant and neoadjuvant

Table 1 Prospective Randomized Trials of Adjuvant Therapy for Pancreatic Cancer

Trial	*N*	Design	Outcome	Author's Conclusions	Flaws
GITSG	43	Observation vs. split course 5-FU-based chemoradiation (40 Gy) +2 years systemic 5-FU	Improved median survival c20 vs. 11 mos. 2 yr. survival 42% vs. 15%	Chemoradiation/5-cFU improves survival	Small study, long time to accrue, suboptimal radiation regimen, no stratification for prognostic factors, no data on margin status
EORTC	114	Observation vs. split course 5-FU-based chemoradiation	No statistically significant difference in survival (17.1 vs. 12.6 mos., p=0.09)	Chemoradiation not of benefit	Underpowered study, suboptimal radiation therapy regimen
ESPAC1	541	5-FU chemotherapy and/or 5-FU-based chemoradiation	Improved median survival for chemotherapy alone (19.4 mos. vs.) No benefit for chemoradiation	Chemotherapy of benefit, chemoradiation is not and may be deleterious	Randomization schema, no quality control for radiotherapy, high local recurrence rates, ?difference in performance status for chemotherapy and chemoradiation groups
CONKO-001	354	Gemcitabine (24 weeks vs. observation)	Improved median dse-free survival (13.4 vs 6.9 mos.)	Gemcitabine of benefit to margin positive and margin negative groups	Restricted entry based on CA19-9 levels
RTOG 9704	442	Gemcitabine vs. 5-FU pre and post-5-FU-based chemoradiation	Gemcitabine improved survival for pancreatic head cancer patients	Gemcitabine of benefit for resected pancreatic head cancer	High rate of positive or unknown margins

approach. Therefore, at this time, neoadjuvant treatment for patients with potentially resectable pancreatic cancer remains investigational. Although feasibility has clearly been demonstrated by multiple single institution and a few multicenter trials, it is not clear if the hypothetical benefits of neoadjuvant approach actually translate into better outcomes (Table 2). Critics of the neoadjuvant approach cite several concerns: 1) the possibility that patients who

Table 2 Recent Neoadjuvant Trials for Potentially Resectable Pancreatic Cancer

Author	*N*	Regimen	No. of patients resected (%)	Median survival of resected patients (months)
Yeung et al. 1993 [10]	26	XRT (50.4 Gy) 5-FU Mitomycin C	10 (38%)	12
Staley et al. 1996 [11]	39	XRT (30, 50.4 Gy) 5-FU	33 (85%)	19
Spitz et al. 1997 [12]	91	XRT (30, 50.4 Gy) 5-FU	41 (45%)	19
Hoffman et al. [29] 1998	53	XRT (50.4 Gy) 5-FU Mitomycin C	24 (45%)	16
Pisters et al. [30] 1998	35	XRT (30 Gy) 5-FU IORT	20 (57%)	25
Pisters et al. 2002 [14]	37	XRT (30 Gy) Paclitaxel	20 (54%)	19
Wolff et al. 2002 [15]	86	XRT (30 Gy) Gemcitabine	63 (73%)	36
Meszoely et al. 2004 [31]	63	XRT Gemcitabine	41 (65%)	20
Moutardier et al. [32] 2004	61	XRT (30 Gy) 5-FU Cisplatin	40 (66%)	27
White et al. 2004 [21]	96	XRT (45 Gy) 5-FU Cisplatin Mitomycin C	53 (55%)	23
Mornex et al. 2005 [33]	41	XRT (50 Gy) 5-FU Cisplatin	26 (63%)	13
Talamonti et al. 2006 [16]	20	XRT (36 Gy) Gemcitabine	17 (85%)	26

XRT: radiation therapy; 5-FU: fluorouracil

are operable may progress to inoperability during the period of preoperative treatment, 2) the need for a tissue diagnosis in all patients, and 3) the requirement for preoperative biliary stenting in most patients and its association with an increased risk of postoperative complications. Advocates of neoadjuvant therapy argue that those patients who progress during treatment almost certainly harbored occult metastases and are in fact benefited by being spared what would likely be a nontherapeutic operation. Tissue diagnoses can now generally be obtained in more than 95% of cases via endoscopic ultrasound-directed biopsy. As this is a transgastric or transduodenal biopsy, the risk of peritoneal seeding is minimal. Finally, the risk of preoperative biliary stenting does likely increase the risk of postoperative wound infection, but proponents of the neoadjuvant approach argue this is a small price for the other benefits conferred by neoadjuvant treatment.

The first neoadjuvant trials for potentially resectable disease were performed in the early to mid-1990s. A Phase II trial from Fox Chase Cancer Center reported in 1993 demonstrated feasibility of a 5-FU/mitomycin C-radiotherapy regimen in 26 patients.[10] Of this cohort, 10 patients had been deemed unresectable at laparotomy. In total, 10 of the 26 (39%) patients ultimately were resected. Although the investigators concluded their results were encouraging, it is difficult to judge the efficacy this or any neoadjuvant regimen in the absence of preoperative staging that uses objective criteria to classify patients as potentially resectable, borderline or locally advanced. Using objective CT criteria to define resectability, investigators at MD Anderson treated 39 patients with resectable tumors with infusional 5-FU-based chemoradiation using either a standard 50.4 Gy or a hypofractionated regimen of 30 Gy in 10 fractions.[11] Ultimately, all 39 patients completed protocol therapy and 33 (85%) of patients underwent resection. The median survival for resected patients was 19 months, results similar to those seen in treatment arms of the randomized adjuvant trials previously discussed. The predominant site of failure was the liver, and the number of patients with involved lymph nodes and with positive margins was greatly reduced compared to historical controls, all suggesting the effects of neoadjuvant treatment. Importantly, this study demonstrated that the use of high-quality computed tomography (CT) imaging, with objectively defined criteria, was associated with a high resectability rate in patients treated with neoadjuvant therapy. A subsequent report from MD Anderson compared patients treated with preoperative versus postoperative 5-FU-based chemoradiation.[12] Of the 142 patients, 91 underwent neoadjuvant treatment, of whom 52 (57%) were resected, whereas 25 patients underwent surgical resection followed by adjuvant therapy. No patient receiving preoperative therapy experienced a delay in surgery because of chemoradiation toxicity. Six of the 25 patients receiving postoperative therapy (24%) did not receive postoperative therapy because of delayed recovery from surgery. No patient who received preoperative therapy developed local recurrence versus 21% of patients who received postoperative treatment. Despite this, overall recurrence rates were similar and no complete pathologic responses were achieved, suggesting that 5-FU-based regimens have insufficient activity. The Duke University experience has also been predominantly with 5-FU-based chemoradiation regimens. They have treated 96 potentially resectable patients and 53 (55%) underwent resection.[13] Patients who underwent neoadjuvant therapy followed by resection had an overall median survival of 23 months. Treatment-related morbidity, specifically complications related to endoscopic stenting for biliary decompression, occurred in 34% of patients, with 15% requiring hospitalization. Neoadjuvant trials have investigated the use of other systemic agents in conjunction with radiation. One such trial evaluated the efficacy of paclitaxel-based radiation given with a hypofractionated radiation regimen of 30 Gy in 10 fractions.[14] This regimen was associated with a 46% incidence of Grade 3 toxicity. Of the 37 patients enrolled, 20 ultimately underwent resection (54%). The median survival of resected patients was 19 months. Again, no pathologic complete responses were achieved and given the higher incidence of toxicity compared to 5-FU, this regimen was not investigated further. With the approval of Gemcitabine for Stage IV pancreatic cancer and the recognition that it is a potent radiation sensitizer, there have now been several neoadjuvant trials using this agent. The first study by Wolff et al. examined 86 patients treated with weekly gemcitabine at a dose of 400 mg/m^2 and 30 Gy of radiation.[15] All patients received the prescribed radiation therapy; gemcitabine was held or the dose reduced in 47 patients secondary to either drug-related toxicity or biliary stent-related morbidity. Ultimately, 61 patients underwent resection (71%), a higher resectability than has been seen in many neoadjuvant trials. Of greatest interest was the 36-month median survival of resected patients, vastly superior to that seen in prior regimens using 5-FU or paclitaxel as the radiation sensitizer. Analysis of the specimens revealed two pathologic complete responses and more than 50% nonviable tumor cells in 36 (59%). A gemcitabine-based regimen was also used in a multiinstitutional study of 20 patients reported by Talamonti et al.[16] This group used full-dose gemcitabine (1,000 mg/m^2) and limited field radiation to 36 Gy (2.4 Gy/fraction). The authors described 14 patients as resectable and six as borderline resectable. Ultimately, all patients were explored and 17 resected (85%), again representing a very high rate of resectability. A single pathologic complete response was observed and, in 24% of tumors, greater than 90% of the tumor cells were felt to be nonviable. Also notable was the low incidence 6% of margin positivity in this trial. The

median survival in the resected patients was 26 months. Based on the results of these initial trials, gemcitabine-based neoadjuvant regimens remain of considerable interest. The Eastern Cooperative Oncology Group is currently planning to evaluate the feasibility and efficacy of limited field radiation and gemcitabine in a multicenter trial.

Pretreatment Staging and the Need for Uniform Definitions of Disease Status

To discuss neoadjuvant trials in locally advanced disease, it is important to put the subject in the context of clinical trial design. One of the initial promises of neoadjuvant therapy was to increase the number of pancreatic cancer patients who could ultimately undergo surgical resection. This promise has largely gone unfulfilled for two reasons: 1) lack of sufficiently active agents against pancreatic cancer, and 2) lack of objective definitions of disease status in clinical trial design. Obviously, the search for more active drugs continues. In the meantime, we can advance pancreatic cancer treatment by improving clinical trial design, as we can only reach meaningful conclusions regarding treatment efficacy from well-designed studies. It is clear that the performance of high-quality clinical trials in pancreatic cancer is critically dependent on the accuracy of pretreatment staging and the use of objective definitions based on cross-sectional imaging. This issue is most significant in neoadjuvant trials, where pathologic staging and margin status are not available. Resection is the only therapy associated with the opportunity for long-term survival in pancreatic cancer, and subtotal resections are associated with median survivals that approximate those achieved with nonsurgical therapies. Cross-sectional imaging provides the most objective picture of the relationship of the pancreatic tumor to the surrounding SMV-PV, SMA, celiac axis and its branches. The use of CT scan has allowed for the identification of objective criteria associated with a high likelihood of achieving a margin-negative resection, namely, those without extrapancreatic disease and a demonstrable fat plane between the pancreatic tumor and the superior mesenteric vessels, hepatic artery, and celiac axis. Traditionally, tumors in which there is loss of this plane have been termed locally advanced. Long recognized, but largely ignored in trial design, has been the fact that tumors that abut major vessels have a different likelihood of being rendered operable compared with those that encase vessels. High-quality imaging has led to the more ready identification of borderline resectable or marginally resectable tumors; tumors, although perhaps technically removable, are more likely to be removed with positive surgical margins.

Although several groups have put forth definitions, there is no consensus definition of borderline resectable pancreatic cancer, and there are no published studies examining its treatment as a distinct entity. A consensus conference on pancreatic cancer will be held in 2008 by the American Hepatopancreaticobiliary Association (AHPBA), with one goal being to address this issue. Currently, the National Comprehensive Cancer Network classifies a tumor as borderline resectable if one of the following conditions are met: 1) tumor abutment of the SMA, 2) severe unilateral SMV or PV impingement, 3) GDA encasement to its origin, 4) invasion of the transverse mesocolon.[17] The major problem with this definition relate to the inability to objectively quantify "severe" impingement and the fact that transverse mesocolon involvement is not clearly associated with risk of a margin positive resection, nor is it always easily identifiable by CT. Investigators at MD Anderson have proposed the following definition: any tumor in which there is 1) short segment occlusion (<2 cm) of SMV-portal vein allowing for resection and venous reconstruction, 2) short segment involvement of hepatic artery allowing reconstruction, or 3) abutment of the superior mesenteric artery along <180°.[18] Of note, this definition excludes tumors with >180 abutment of the SMV-PV, instances which are technically challenging for most surgeons. Several reports have suggested decreased resectability or a high likelihood of R1/R2 surgery in such instances, particularly when neoadjuvant therapy is not administered.

Neoadjuvant therapy for Locally Advanced Disease

The lack of consistently applied definitions based on the degree of vessel involvement has led to the variable inclusion of patients with borderline resectable tumors into neoadjuvant studies of both resectable and locally advanced disease. This issue is readily demonstrated by the studies performed at many outstanding institutions (Table 3). Snady et al. reported on 159 patients with locally unresectable disease treated with either surgery, with or without postoperative chemoradiation (N=91), vs. neoadjuvant 5-FU/streptozotocin/cisplatin/54 Gy radiation therapy followed by selective surgical resection (N=68).[19] Ultimately, 20 patients in the neoadjuvant group underwent resection. The median survival in the neoadjuvant group was 23.6 months compared to 14.0 months for the adjuvant treatment group, leading the investigators to conclude that the neoadjuvant regimen could result locally advanced disease and improve survival. Unfortunately, the study methods comprise this interpretation in that patients were initially staged using a variety of methods, and there were no objective, uniform designation for resectable versus locally advanced disease. Investigators from Memorial

Table 3 Selected Trials of Neoadjuvant Therapy for Locally Advanced Pancreatic Cancer

Author	*N*	Regimen	No. of patients resected (%)	Median survival after Neoadjuvant treatment (months)
GITSG 1981	169 (arm1) 25 (arm 2)	XRT (40–60 Gy) 5-FU vs. XRT alone (60 Gy)	NA	10[c] 5.3[c]
Kamthan et al. [34] 1997	35	XRT (54 Gy) 5-FU Cisplatin Streptozocin	5 (14%)	15[a] 31[b] 11[c]
Snady et al. 2000 [19]	68	XRT (54 Gy) 5-FU Streptozocin Cisplatin	20 (29%)	23.6[a] 32.3[b] 21.2[c]
Ammori et al. [35] 2003	67	XRT (50 Gy) Gemcitabine ± Cisplatin	9 (13%)	11.9[a] 17.6[b]
Aristu et al. [36] 2003	47	XRT (45 Gy) 5FU Cisplatin ± Paclitaxel or Gemcitabine or Docetaxel	9 (19%)	11[a] 23[b] 10[c]
Joensuu et al. [37] 2004	28	XRT (50 Gy) Gemcitabine	20 (71%)	25[a] 25[b] 14[c]
White et al. 2004 [21]	88	XRT (45 Gy) 5-FU Cisplatin Mitomycin C	18 (20%)	23[b]
Pipas et al. 2005 [23]	24	XRT (50.4 Gy) Gemcitabine Docetaxel	13 (54%)	14[a]

NA surgery not attempted, *XRT* radiation therapy, *5-FU* fluorouracil
[a] All patients
[b] Resectable patients
[c] Unresectable patients

Sloan-Kettering treated 87 patients with locally advanced, unresectable pancreatic cancer utilizing 5-FU-based regimens. They found that only a single patient was downstaged sufficiently to undergo resection.[20] In this study, all patients underwent surgical staging and had "extensive" major vessel involvement. In contrast, at Duke University, of 88 patients with locally advanced disease treated with a regimen of 5-FU/cisplatin/mitomycin C-based chemoradiation, 16 (18%) underwent resection.[21] All 16 patients who were resected had locally advanced disease defined by arterial abutment rather than encasement. A recent study from the Southwest Oncology Group examined a chemotherapy only regimen of infusional 5-FU, leucovorin, mitomycin C, and dipyridamole in patients with locally advanced disease, Stage II or III.[22] In this study, locally advanced was defined as total occlusion or encasement of greater than 75% of the superior mesenteric or portal vein, superior mesenteric, celiac, or hepatic artery. It is worth noting that also included were patients with pancreatic tail lesions greater than 5 cm, regardless of vascular involvement. Currently, such patients would not be considered locally advanced by most investigators. In this study of 50 patients, 26% of patients had objective responses and the median survival was 13.8 months. Six responders (12%) underwent margin negative resections and all survived greater than 12 months with two patients alive at 51 and 71 months after initiation of therapy. This study is provocative in that it did not incorporate radiation therapy. Two small studies have attempted to differentiate patients with locally advanced versus borderline resectable disease. Pipas et al. treated 24 patients with a neoadjuvant regimen of docetaxel/gemcitabine followed by gemcitabine-based chemoradiation therapy.[23] Of the 24 patients, four were initially considered resectable, seven were designated borderline resectable, and 13 patients were deemed locally advanced unresectable. After neoadjuvant therapy, 17 patients underwent resection. According to pretreatment designation, 4/4 resectable patients were resected, versus 6/7 borderline and 7/13 locally advanced patients. It is important to note, however, that 3/7 patients with locally advanced disease had margin-positive resections versus 1/6 and 0/4 in the borderline and resectable groups, respectively. Massucco et al. treated 28 patients with locally advanced tumors with gemcitabine-based chemoradiation.[24] Of these 28 patients, 18 were classified as borderline resectable. Ultimately, seven of 18 borderline resectable tumors were successfully resected versus only one of 10 locally advanced unresectable tumors. Only one patient treated with neoadjuvant therapy had a positive margin resection. The investigators concluded that conversion of locally advanced unresectable tumors was rare, but that borderline resectable tumors could be successfully resected in one third of cases after neoadjuvant therapy. Each of these studies serves to demonstrate that the outcome of most neoadjuvant trials for locally advanced disease has been primarily dependent on pretreatment stage rather than the actual treatment regimen. Neoadjuvant therapy clearly can allow some patients with borderline resectable pancreatic cancer to be resected with

negative pathologic margins, whereas downstaging patients with major vessel encasement to allow margin-negative resection is exceedingly rare. The natural history of borderline resectable tumors resected after a response to neoadjuvant therapy is not well-defined at this time. As uniform definitions of borderline resectable and locally advanced disease are incorporated into clinical trial design, it will greatly enhance our ability to compare the effects of various neoadjuvant regimens on survival and patterns of failure.

Future Directions

To date, neoadjuvant therapy trials for pancreatic cancer have largely been restricted to large academic institutions with a focused interest in this strategy. Neoadjuvant therapy poses unique challenges in patient care, such as the need for a pretreatment tissue diagnosis, the management of biliary stenting, and uniformly high-quality imaging. Because of the multidisciplinary interactions required, it remains to be proven that neoadjuvant treatment of the pancreatic cancer patient can be delivered safely and effectively in centers across the U.S. The feasibility of a multiinstitutional neoadjuvant trial is a primary endpoint of a proposed Phase II trial sponsored by the American College of Surgeons Oncology Group. This study will attempt to examine the feasibility and efficacy of a regimen of neoadjuvant gemcitabine and erlotinib in patients with radiographically resectable pancreatic head cancer. A randomized multicenter Phase II trial comparing neoadjuvant gemcitabine/cisplatin-based chemoradiation with adjuvant gemcitabine is being conducted in Germany, Switzerland, and Austria as coordinated by the Interdisciplinary Study Group of Gastrointestinal Tumors.[25] This would be the first randomized trial of any kind directly comparing the adjuvant and neoadjuvant approach.

Of great interest remains the investigation of novel agents to be incorporated into neoadjuvant protocols. This includes the use of targeted therapies such as Epidermal Growth Factor Receptor (EGFR) inhibitors, anti-angiogenesis agents in combination with chemotherapy and/or radiation. Several groups have begun investigations of bevacuzimab-based chemoradiation that suggest interesting activity and a Phase I trial of 10 patients has been performed with capecitabine, radiation, and the EGFR inhibitor gefitinib.[26,27]

Evaluation of the numerous novel targeted agents may be best performed using a neoadjuvant trial design as this permits an in vivo assessment of response and allows for studies of both untreated (obtained at biopsy) versus treated tumor. Such studies would allow for the development of biomarkers, which could predict the risk of recurrence and chemosensitivity before and after neoadjuvant therapy. Few such studies have been performed to date. A recent study by White et al. investigated the prognostic significance of histologic responses to neoadjuvant chemoradiation.[28] The surgical specimens from 70 patients who underwent resection after 5-FU-based chemoradiation were scored for differentiation, the degree of necrosis, fibrosis, and residual tumor burden. Higher degrees of necrosis and residual tumor as well as poor differentiation were associated with decreased survival. Future studies investigating the molecular events, which underlie these pathologic findings, are critical to improving pancreatic cancer therapeutics.

Conclusions

Neoadjuvant therapy for pancreatic cancer remains a theoretically attractive treatment strategy. Single-institution studies confirm that treatment compliance is a major benefit to this approach and suggest that even marginally active agents such as 5-FU when combined with radiotherapy can reduce the incidence of margin positivity and likely local recurrence. Many neoadjuvant studies, particularly those in locally advanced disease, have been hindered by poor design, predominantly with respect to uniformity of inclusion criteria and pretreatment staging. The neoadjuvant approach may be ideally suited to test the efficacy of novel agents and to biomarker discovery. Ultimately, multicenter prospective randomized trials comparing the adjuvant and neoadjuvant approach must be performed to determine the ideal treatment strategy for pancreatic cancer patients.

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Malignant Peripheral Nerve Sheath Tumor: An Unusual Cause of Intussusception

Dana A. Telem · David Pertsemlidis

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Abstract Malignant peripheral nerve sheath tumors (MPNST) are defined as any tumor arising from a peripheral nerve or showing nerve sheath differentiation. The majority of these tumors arise on the trunk, extremities, or head and neck region. The literature to date has fewer than 14 cases of MPNST arising in the gastrointestinal tract, and only two cases were ever reported in the small intestine, one of which was a recurrent disease. In this paper, we report the first US case of an MPNST arising in the small intestine and presenting as intussusception.

Keywords Malignant peripheral nerve sheath tumor · Intussusception · Small bowel tumor · Gastrointestinal neoplasm

Case Report

This is a case report on a 71-year-old woman seen by her primary care physician for a 1-week history of moderate epigastric pain accompanied by nausea. Her past medical history is significant for a motor vehicle accident in 1956 requiring exploratory laparotomy, a left hemicolectomy in 1992 for carcinoma in-situ with negative subsequent colonoscopies, and gastroesophogeal reflux disease. Family history was notable for a mother who died of colon cancer at age 44.

The patient was found to be Hemoccult-positive on rectal exam and was referred to a gastroenterologist for further evaluation. An upper and lower endoscopy was performed and was within normal limits. Shortly after the endoscopy, the patient began vomiting and her pain acutely worsened. She was sent to the emergency department where an abdominal computed tomography (CT) scan was obtained. The CT demonstrated an intussusception in the proximal jejunum immediately distal to the ligament of Treitz with a smooth enhancing 3.7-cm mass suspicious for neoplasm (Figs. 1 and 2).

The patient was taken to the operating room where a laparoscopic-assisted small bowel resection with extensive lysis of adhesions was performed. The lesion was identified approximately 10 cm distal to the ligament of Treitz. Under the presumption, the lesion was cancer; no attempt to reduce the intussusception was made. The bowel was resected 3 cm proximal and 8 cm distal to the lesion. No lymphadenopathy was appreciated, and the mesentery was divided close to the bowel. An end to side jejunojejunostomy was performed. The resected specimen revealed a $3.6 \times 3.6 \times 2$ submucosal mass.

The histopathologic examination revealed a polypoid lesion with surface mucosal ulceration. The lesion had white-tan homogenous and myxoid cut surface and extended beyond the muscle wall into the intestinal adipose tissue. The tumor showed dense cellularity and approximately 20 mitoses per 50 high power fields. On immunohistochemical staining, the tumor stained positive for CD34 and S100 protein but negative for actin, desmin, NSE, and CD117. Based on these findings, the tumor was identified as a malignant peripheral nerve sheath tumor (MPNST).

The patient had an unremarkable postoperative course and was discharged home on postoperative day 4. A full metastatic workup was obtained as an outpatient, which demonstrated no evidence of metastatic disease.

D. A. Telem (✉) · D. Pertsemlidis
The Mount Sinai Hospital, Department of Surgery,
One Gustave Levy Plaza Box 1259,
New York, NY 10029, USA
e-mail: dana.telem@mssm.edu

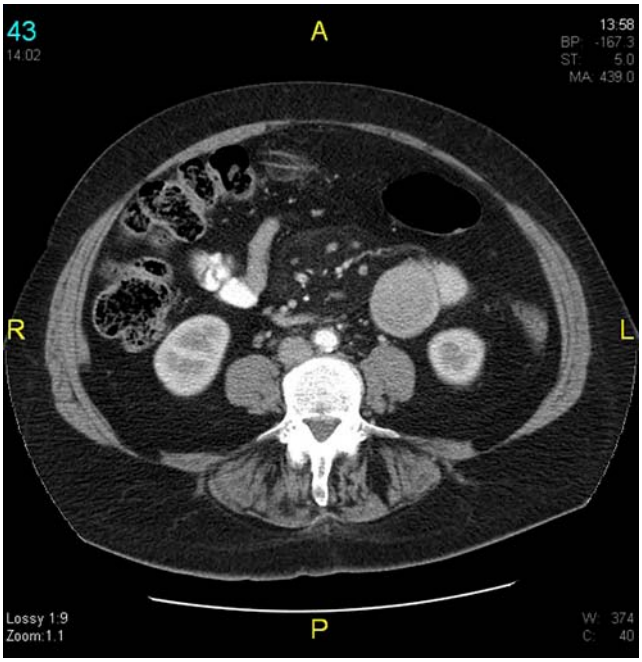

Figure 1 CT scan showing intussusception in the proximal jejunum.

Discussion

The World Health Organization defined the term MPNST as any tumor arising from a peripheral nerve or showing nerve sheath differentiation. The majority of these tumors arise on the trunk, extremities, or head and neck region. The literature to date has fewer than 14 cases of MPNST arising in the gastrointestinal tract, and only two cases were ever reported in the small intestine, one of which was recurrent disease.[1,2]

These tumors are typically associated with neurofibromatosis 1 (NF-1), which is an autosomal dominant disorder characterized by the formation of neurofibromas in the skin, subcutaneous tissue, cranial nerves, and spinal root nerves caused by a mutation in the NF-1 tumor suppressor gene. Approximately 25 to 50% of observed MPNST occur in patients with NF-1 and, depending on the series, the lifetime risk of developing MPNST in this patient population is 5 to 26%.[3] Approximately 0.001% of these tumors are sporadic and present in adults in the third to sixth decade of life.[4]

MPNST of the gastrointestinal tract appear to present similarly to other primary malignancies of the intestine. The most common presenting symptoms include abdominal pain (63%), emesis (43%), weight loss (44%), and gastrointestinal bleed (23%).[5] These tumors may also initially present as a painless mass.

Pathologic diagnosis of MPNST is facilitated by features such as palisading arrangement, nuclear atypia, bizarre giant cells, mitotic figures, and necrosis. These tumors possess well-described morphological heterogeneity, and staining reveals highly cellular spindle cell tumor in fascicles.[6]. There are no specific histological or immunohistochemical markers for MPNST. S-100 is highly characteristic of neural-derived neoplasms; however, it is limited secondary to its expression in a wide range of tissues.[7]. High levels of P53 and Ki67 may also be related to MPNST.[8]

The prognosis and initial treatments for MPNST of the small bowel remains unknown. A recent study published investigated the overall prognostic factors and survival of patients with MPNST in all locations. The study suggests an overall poor prognostic clinical outcome with 43% mortality rate at 10 years and continuous disease-free survival rate of less then 40% within that time frame. The strongest independent predictors of survival were primary vs recurrent disease, tumor size, tumor site, and margin status.[9] In addition, most case series demonstrated limited benefit and high morbidity with the use of adjuvant radiotherapy or chemotherapy. The current recommendation is that this therapy be reserved for recurrent tumors, suspicion of residual microscopic disease, and high-grade tumors.

To date, little is known regarding MPNST of the small bowel. Current recommendations and treatment plans may be based only on what is known regarding the behavior of this tumor in other locations of the body. Based on the literature available, we recommend wide excision of these tumors with very close postoperative follow-up imaging. Adjuvant therapy should be used in cases of positive

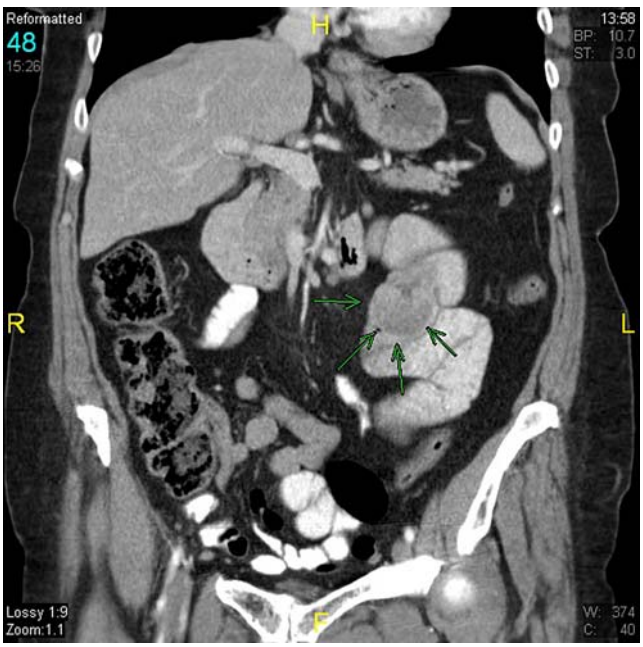

Figure 2 CT scan also showing intussusception in the proximal jejunum with a mass suspicious for neoplasm.

margins, recurrent disease, or when wide local excision is unfeasible.

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Rapunzel Syndrome: A Case Report and Review

Catherine Western · S. Bokhari · S. Gould

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Abstract We report a 14-year-old girl who presented with epigastric pain, vomiting, and an upper abdominal mass. A diagnosis of trichobezoar was made on ultrasound and she went on to have a laparotomy, where a large trichobezoar was extracted with a tail that extended into the small intestine.

Keywords Rapunzel syndrome · Bezoar · Trichotillomania · Trichobezoars

Introduction

Bezoars are collections of indigestible matter within the gastrointestinal tract. They come in many forms, the commonest being phytobezoars, which consist of plant material. Trichobezoars result secondary to ingestion of hair and are associated with trichotillomania, where sufferers have an irresistible urge to pull out their hair to the point of alopecia.[1,2]

Rapunzel syndrome is a very rare complication of trichobezoar formation in which the mass of hair extends through the pylorus into the small bowel and can even reach the colon. Originally named by Vaughan et al. in 1968,[3] it gets its name from the longhaired tower-bound character in Grimm's Fairy Tales.[4] There are only 27 recorded cases in the literature worldwide.[5]

C. Western (✉)
Department of General Surgery, North Devon District Hospital,
Raleigh Park,
Barnstaple, Devon EX31 4JB, UK
e-mail: catherinewestern@yahoo.co.uk

S. Bokhari · S. Gould
Department of General Surgery, Northwick Park Hospital,
Middlesex, UK

We present the case of a 14-year-old girl of Asian origin who presented to her GP with a few-weeks history of epigastric pain of increasing severity. She had also been nauseous and vomiting for 2 days prior to presentation but had had no change in her bowel habit. She was a vegetarian and had a 2-year background of poor appetite, fatigue, and failure to thrive. Of note, she also had a 2-year history of pica and was reported to have eaten hair and plastic in the past. Previous abdominal ultrasound was normal.

On referral to pediatric services at the local District General Hospital, she was found to be anemic (Hb=7.3, mean corpuscular volume=60.9), with a palpable mass 8× 6 cm in the epigastric region that was dull to percussion, nonmobile, and nontender. The rest of the abdominal examination was unremarkable. A general surgical opinion was sought and an ultrasonography was arranged, which revealed a large midline mass, likely to be within the stomach. CT confirmed this finding.

Miss A.P. underwent an upper midline laparotomy, and an extensive trichobezoar was removed, which formed a complete cast of the stomach and the proximal duodenum, up to D2 (see Figs. 1 and 2). She made a good postoperative recovery and at follow-up clinic was found to have recovered her appetite and to be gaining weight. She was referred for outpatient psychiatric input.

Discussion

Trichobezoars occur far more commonly in girls. Of the 27 recorded cases of Rapunzel syndrome, only one was

Figure 1 Trichobezoar removed at laparotomy.

diagnosed in a male patient.[5] They arise as the human body is unable to digest hair and, due to its smooth surface, it is not propelled by peristalsis but instead becomes matted together in a ball. This can reach sizes sufficient to distend the stomach and inhibit gastric emptying. The condition is linked to pica and other psychiatric conditions, learning disabilities, and emotional disturbance.[6–8]

Diagnosis

Trichobezoar formation and its most extreme form, Rapunzel syndrome, have variable presentation from chronic anorexia and failure to thrive to abdominal pain, vomiting, and acute obstruction. Clinically, Lamerton's sign[9] may be present, with an indentable palpable mass in the upper abdomen. It is difficult to diagnose by plain film, but barium meal (with the characteristic honeycomb appearance), ultrasound, CT, MRI, and of course endoscopy can all prove useful.

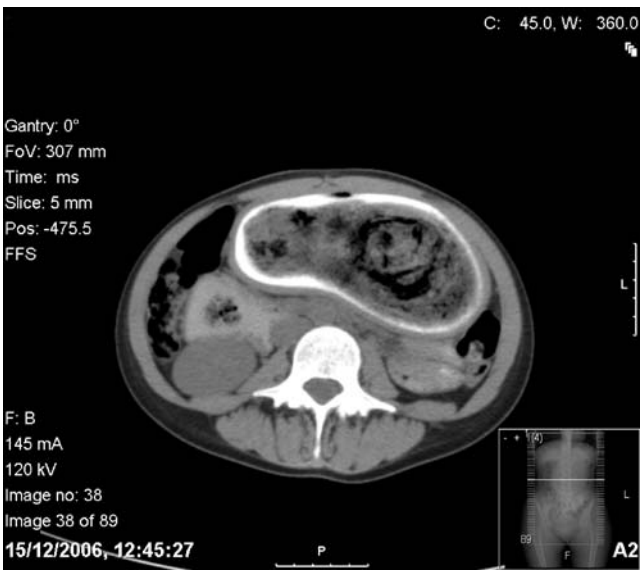

Figure 2 CT abdomen demonstrating extent of bezoar within stomach.

Various criteria have been used to define Rapunzel syndrome, ranging from a trichobezoar with a tail that extends through the pylorus[1,6,10,11] to a tail extending to the large bowel.[12–14] Some define it by presentation with obstruction, regardless of extension of the tail.[15]

Treatment

It is sometimes possible to endoscopically or laparoscopically extract the hairball. However, lithotripsy/laser therapy may be required preprocedure to first fragment the mass.[16,17] If large (greater than 20 cm has been quoted in one reference[2]), open removal is required. This may require both gastrotomy and enterotomy if particularly extensive.

Other methods have been employed, such as enzymic digestion (e.g., with pancrealipase), lavage,[12] or the use of drugs to increase gastric emptying such as metoclopramide.[6] However, effectiveness of these methods is obviously limited by bezoar size.

It is important to refer for psychotherapy/psychiatric input after removal due to the risk of recurrence. Follow-up barium meals/endoscopy have also been advised if trichotillomania is suspected.[5]

Complications

Failure to thrive, chronic gastritis resulting anemia and hypoalbuminemia,[9] perforation, intussusception, intestinal and biliary obstruction, and pancreatitis[12] can all result from both simple trichobezoar formation and Rapunzel syndrome.

Conclusion

Although rare, this diagnosis should be considered in children with gastrointestinal symptoms, particularly those in high-risk groups.

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Hepatic and Splenic Hydatidosis Managed with Percutaneous Aspiration, Injection, and Reaspiration (PAIR) of the Hepatic Cyst and Laparoscopic Splenectomy

P. Marco Fisichella · Kristen Donaldson · W. Scott Helton

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Abstract The treatment of hydatidosis traditionally consisted of surgery with a perioperative course of anthelmintic medications. However, percutaneous aspiration, injection, and reaspiration (PAIR) combined with oral albendazole has been recently shown to be as effective as surgery in the treatment of liver hydatidosis. We report a 20-year-old female immigrant from Western Europe who presented with discomfort in her upper abdomen. Computed tomography revealed a 5.7×7×5.9-cm cyst in segment 7 of the liver and a 17×15-cm cyst in the spleen in contiguity with the hilar vessels. Indirect hemaglutination test confirmed hydatidosis. A strategy with two different surgical approaches was designed to treat her condition: laparoscopic splenectomy and ultrasound-guided PAIR of the liver cyst. The patient was discharged on postoperative day 5, and at 18 months follow-up, she is free of symptoms.

Keywords Hydatid disease · Spleen · Liver · Laparoscopy · Cysts · PAIR · Echinococcus

Case Report

A 20-year-old female from Western Europe presented with left-sided abdominal discomfort. For many years, she was exposed to her paralyzed dog that needed assistance to clear its bowels. Moreover, during her childhood, she and her family lived in a cottage in the countryside surrounded by many sheep and cows. Abdominal computed tomography revealed a 5.7×7×5.9-cm cyst in segment 7 of the liver and a 17×15-cm cyst in the spleen in contiguity with the hilar vessels (Fig. 1). Indirect hemaglutination test confirmed hydatidosis. An endoscopic retrograde cholangiopancreatography (ERCP) showed no communication between the biliary ductal system and the echinococcal hepatic cysts (Fig. 2).

Surgical intervention consisted of a tailored approach that included a laparoscopic splenectomy followed by ultrasound-guided percutaneous aspiration, injection, and reaspiration (PAIR) of the echinococcal cyst in segment 7 of the liver. Preoperatively, the patient was administered prophylactic antibiotics (cephazolin 1 g) and steroids (hydrocortisone 100 mg IV) together with H_1- and H_2-blockers (Benadryl 50 mg IV and famotidine 20 mg IV) to minimize the risk of anaphylaxis from the potential leakage of hydatid cystic fluid into the abdomen. The patient was positioned on a beanbag in the right lateral decubitus for the laparoscopic splenectomy. A pneumoperitoneum with 14 mm of CO_2 was established with a Veress needle placed in the left subcostal margin lateral to the rectus muscle. Using a 5-mm 30° laparoscope, a 15-mm trocar was inserted at the umbilicus under direct vision. Three additional 5 mm trocars were placed along the left subcostal border in the midline, in the left midclavicular line, and in the left posterior axillary line. The colonic flexure and the splenocolic ligaments were taken down with the Harmonic Scalpel (Ethicon-Endo Surgery™). The lesser sac was opened and the short gastric vessels were divided to gain access to the splenic hilum. The splenic vessels were transected with the Endo-GIA 60 (Ethicon-Endo Surgery™) using a 2.5-mm staple load. The

P. Marco Fisichella · K. Donaldson · W. Scott Helton
Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA

P. Marco Fisichella (✉)
Department of Surgery, University of California, San Francisco, 4 Koret Way LR -101, San Francisco, CA 94143, USA
e-mail: Marco6370@yahoo.com

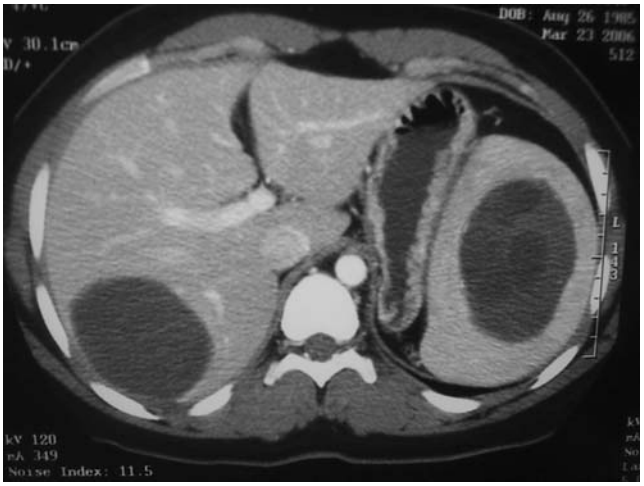

Figure 1 Abdominal CT showing a 5.7×7×5.9-cm cyst in segment 7 of the liver and a 17×15-cm cyst in the spleen in contiguity with the hilar vessels.

superior pole of the spleen was separated from its attachments with the left hemidiaphragm, and the specimen was retrieved using an Endobag (ENDO CATCH™– Autosuture™) to avoid any potential contamination of the abdomen with the cystic fluid. The umbilical port incision was then enlarged to a 6-cm midline incision to extract the spleen in the EndoBag. After completing the laparoscopic splenectomy, the patient was placed supine and sterilely draped for the PAIR of the hepatic cyst. Using extracorporeal ultrasound guidance, a 20-gauge needle was inserted into the hydatid cyst in segment 7 of the liver. Using the Seldinger technique, a 6-French sheath was introduced over a 0.018-guidewire. The 6-French sheath was oversized to accept a 10-French pigtail catheter, which was used to aspirate the cyst, inject it with a scolicidal hypertonic, 23% NaCl, sterile solution, and reaspirate it again. This was followed by the injection and aspiration of 50 ml of ethyl alcohol. The pigtail catheter was removed and a closed suction drain was placed next to the pancreatic tail.

Recovery was uneventful and the patient was vaccinated and discharged on postoperative day 5 with a 4-week course of oral albendazole 400 mg twice a day. At 18 months follow-up, the patient had no abdominal discomfort. The family was counseled to undergo testing for hydatidosis.

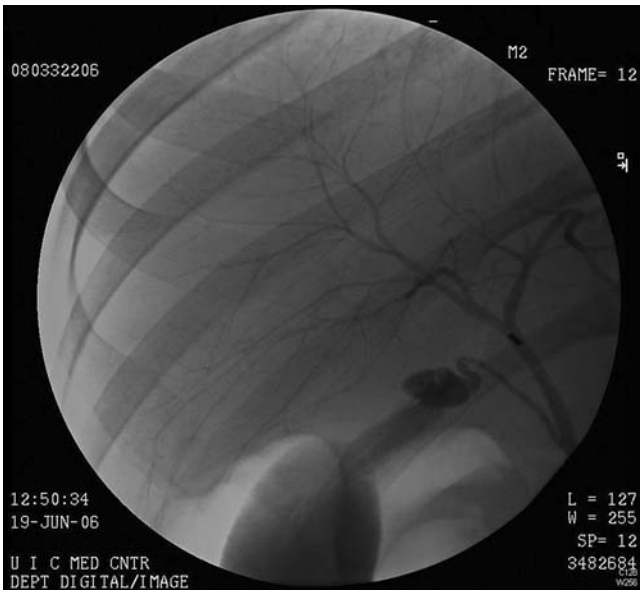

Figure 2 ERCP showing no communication between the biliary ductal system and the echinococcal hepatic cysts.

Discussion

The liver is the most common sites of echinococcal infection (60–70% of all cases), whereas infection of the spleen is rare (0.5–8% of all cases).[1–3] We were unable to find cases in the literature that described our patient's combined presentation of liver and splenic hydatidosis. Therefore, a strategy was designed to include two surgical approaches to treat her unusual condition: laparoscopic splenectomy and PAIR of the liver cyst.

Splenic hydatidosis is treated with surgery for symptomatic cysts or cysts larger than 5 cm.[4] The surgical approach is based on size and location, and spleen sparing procedures should be considered.[5,6] Total or partial splenectomy has traditionally been the treatment of choice for splenic hydatidosis.[2,4] Hand-assisted laparoscopic splenectomy and laparoscopic excision of splenic hydatid cysts have also all been reported.[7,8] In this patient, the splenic cyst encompassed the majority of the splenic parenchyma and was in contiguity to the hilar vessels (Fig. 3). Therefore, partial splenectomy or PAIR was not considered a safe surgical option. Although we found no reported cases of total laparoscopic splenectomy for hydatidosis, Hansen and Moller stated that this option may be safe even for gigantic splenic cysts.[4]

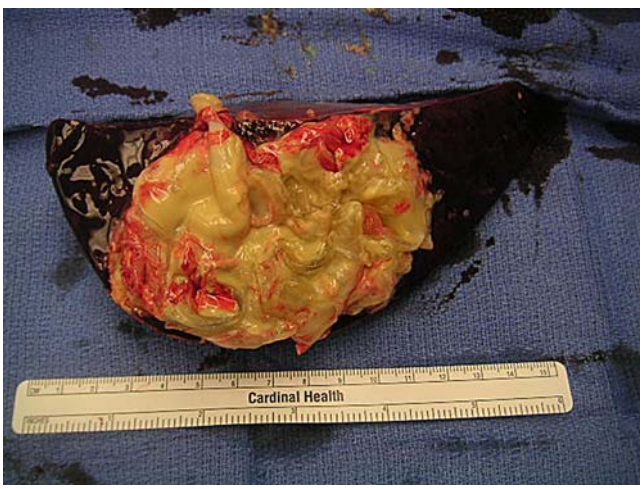

Figure 3 Specimen section showing the splenic cyst encompassing the majority of the splenic parenchyma.

PAIR followed by treatment with albendazole was chosen over surgical excision of the liver cyst in the light of the reports that have shown this technique to be safe and efficient for the treatment of hepatic hydatidosis if preoperative ERCP shows no communication between the biliary ductal system and the cysts.[9–13] Khuroo et al. reported that PAIR has similar results to surgery in terms of cyst disappearance and reduction of cyst size, but fewer complications (32% vs 84%, $P<0.001$) and shorter hospital stays (4.2±1.5 vs 12.7±6.5 days, $P<0.001$).[10]

In conclusion, a combined organ-specific tailored approach to hydatidosis in multiple organs should be considered to treat patients with unusual presentations. We feel that splenic hydatidosis may be safely treated using laparoscopic splenectomy, if precautions are taken to prevent complications from the possible puncture of a hydatid cyst. Given the minimal evidence regarding the laparoscopic approach to hydatidosis, further research should be done to evaluate its safety and effectiveness and to establish standard techniques.

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Is Vena Cava Resection Justified for Hydatid Liver Cyst?

Cuneyt Kayaalp · Cemalettin Aydin · Aydemir Olmez

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Dear Sir,

We read with interest the article entitled "Combined resection of the liver and the inferior vena cava for hydatid disease" by Mekeel and Hemming[1] in the 2007 November issue of the *Journal of Gastrointestinal Surgery*. The authors presented a patient with hydatid liver cyst, which occluded the retro-hepatic inferior vena cava at the junction of hepatic veins. The cyst had a calcified wall with a solid component and serologically negative. The authors detected vena cava obstruction and portal hypertension and treated the patient with right hepatic trisegmentectomy, vena cava resection, and Gore-Tex graft replacement.[1]

We believe that the symptoms of the patient cannot be attributed to the vena cava obstruction and portal hypertension. The symptoms of the patient were severe right-upper-quadrant pain and fullness, shortness of breath, and weight loss. Otherwise, he was reported as healthy. He did not have any lower-extremity swelling or edema with normal creatinine level. Figures in the paper do not demonstrate any splenomegaly. There are no mentioned ascites, esophageal varices, or manometric studies. Liver function tests, which should be significantly influenced in hepatic portal hypertension, were normal. The described cyst is old (type IV or V) and has a low intracystic pressure.[2,3] These all demonstrate that venous collaterals compensate portal hypertension and caval flow effectively, and the symptoms were not related to the radiological findings. We believe that, for a benign disease, the procedure for this case is excessive and will require lifelong anticoagulant for venous grafting in a 38-year-old man.

C. Kayaalp (✉) · C. Aydin · A. Olmez
Department of General Surgery, Turgut Ozal Medical Center,
Inonu University,
Malatya, Turkey
e-mail: cuneytkayaalp@hotmail.com

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Is Vena Cava Resection Justified for Hydatid Liver Cyst. Reply

Alan W. Hemming · Kristin L. Mekeel

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In their letter, Dr. Kayaalp et al. take issue with the management described in a case report of hydatid disease that resulted in inferior vena cava (IVC) and hepatic vein obstruction and stenosis with subsequent portal venous hypertension.[1] They state that they do not believe the patients' symptoms can be attributed to portal hypertension and believe that lifelong anticoagulation is required for a Gortex graft placed in the retrohepatic, suprarenal position. They also state that they believe the cyst must have had a low intracystic pressure since it was old and calcified. As a general comment, we would state that the requirement for resection of the IVC for hydatid disease should be incredibly rare, hence our belief that the case report might be of interest.

At the operative procedure, it was clear that there was a tremendous inflammatory response to the cyst that might explain the symptoms. In our case report, we did not state that the patient had any symptoms related to portal hypertension, only symptoms of pain and shortness of breath, which we would assume most people know are not symptoms of portal hypertension. While we did not measure intracystic pressures, on opening the cyst, the contents appeared to be under relatively high pressure. We, in fact, initially believed that simply reducing the pressure by decompressing what appeared to be a high-pressure hydatid cyst might relieve the hepatic venous outflow obstruction and relieve the portal venous hypertension. When this did not occur, we believed that shunting of total IVC flow through the large inferior hepatic vein across the liver and out a stenotic left hepatic vein that was unable to accommodate the high flow of combined portal and caval flows was the cause of the portal venous hypertension. Resecting the cyst/liver effectively removed the source of inflammation, interrupted the collaterals through the liver, and replaced the completely occluded IVC. It allowed reduction of flow through the only remaining hepatic vein and relieved the portal hypertension. We felt that leaving a correctable form of portal hypertension uncorrected at operation would be inappropriate. We have reported previously on a moderately large series of combined liver and IVC resections for malignancy.[2] Current combined liver and IVC resections, including malignant and nonmalignant cases, at our institution now number over 30 cases. All grafts are patent with follow-up from 3 months to 8 years, and no patients with a Gortex ring graft have been placed on any anticoagulation after their procedure apart from a daily baby aspirin. There is no evidence that lifelong anticoagulation is required for Gortex grafts placed in the retrohepatic suprarenal position. After the surgery, the patient was symptom-free for the first time in over 3 years, has returned to work for the first time in 2 years and has a patent graft on no anticoagulation. Since both symptoms and portal hypertension are gone and the patient is not on anticoagulation, we feel we made an appropriate choice.

A. W. Hemming (✉)
Division of Transplantation & HPB Surgery,
University of Florida,
Gainesville, FL, USA
e-mail: hemming@surgery.ufl.edu

K. L. Mekeel
Department of Surgery, Mayo Clinic,
Scottsdale, AZ, USA

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