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2009 SSAT PLENARY PRESENTATION

Endoluminal Fundoplication (ELF) for GERD Using EsophyX: a 12-Month Follow-up in a Single-Center Experience

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Abstract
Background Several endoscopic antireflux therapies have been proposed to reduce the need for chronic medical therapy or laparoscopic fundoplication for gastroesophageal reflux disease (GERD). Aim of this study was to evaluate the short- and mid-term clinical results of endoluminal fundoplication (ELF) with EsophyX™.
Patients and Methods From June 2006 to April 2008, 20 patients were enrolled in the study. All the ELFs were performed under general anesthesia.
Results The mean duration of the procedure was 63 min (range 38–105). A median of 14 fasteners was placed. There were no major intraoperative complications. Two patients developed early complications and were treated conservatively. Four patients underwent, within the first year post-ELF, a laparoscopic fundoplication because of persistence of symptoms. One patient was lost to follow-up between 6 and 12 months. Among the other 15 patients who completed 12 months follow-up, the GERD health-related quality of life score decreased from a median of 40 to a median of 10 ($p<0.05$), and seven patients were still off proton pump inhibitor. An improvement in esophageal acid exposure was recorded in 16.6% of patients, while in 66.7%, it worsened.
Conclusions ELF induced improvement of GERD symptoms and patients quality of life in a subgroup of patients with a reduced need for medication. However, it did not significantly change esophageal acid exposure in these patients. The need for revisional standard laparoscopic fundoplication was high.

Keywords Gastroesophageal reflux disease (GERD) · Endoluminal fundoplication (ELF) · EsophyX

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Introduction

The gastroesophageal reflux disease (GERD) is an extremely diffuse pathological condition in the Western countries that significantly impairs patients' quality of life and increases the risk for the development of complications including Barrett's esophagus and adenocarcinoma.[1–4] Patients with symptomatic GERD are typically managed with lifestyle modifications and acid suppressant or acid neutralizing agents. Those who experience persistent symptoms despite daily drug use can be offered a laparoscopic fundoplication, which has proved to be safe and efficacious,[5] but in a subset of patients, new symptoms arise postoperatively (e.g., dysphagia and bloating).[6] For these reasons, a minimally invasive totally endoscopic antireflux treatment could be an appealing alternative approach.

In the past 15 years, there has been a considerable effort by intervention-inspired endoscopists to develop and establish new endoscopic techniques for intraluminal treatment of GERD. These endoscopic procedures use three different approaches to improve the antireflux barrier function: (1) delivery of radio frequency energy to the cardia,[7–11] (2) creation of gastroplications,[12–15] or (3) injection of inert polymer materials into the muscle layer.[16–18] All these endoluminal techniques may theoretically provide an attractive alternative to long-term maintenance therapy with proton pump inhibitors (PPI) or surgery. Several trials evaluated these new procedures—mostly focusing on technical feasibility. Unfortunately, at present time, the majority of these studies have not provided a sufficient clinical and instrumental evidence to determine the safety and efficacy of endoscopic procedures for GERD, particularly in the long term.[19] Moreover, some of the devices have been retired from the market for unsafety reason, and the techniques have been abandoned.

A novel instrument for antireflux endoluminal fundoplication (ELF), EsophyX (EndoGastric Solutions, Redmond, WA, USA), was designed to endoscopically construct a full-thickness valve at the gastroesophageal junction through tailored delivery of multiple fasteners during a single-device insertion. The experimental results and the first clinical application of this device have shown extremely encouraging results: the physiopathologic studies showed a reflux control in 80% of patients, at 6 months, without significant intra- and postoperative morbidity.[20]

The present prospective, single-arm study has the purpose to evaluate the safety and the 12-month efficacy of this new endoscopic suturing device that allows the creation of an antireflux plication at the GE junction.

Patients and Methods

This prospective, single-arm, independent study was conducted at the Department of Gastroenterology of Istituto Clinico Humanitas under a common protocol which was approved by the Ethics Committee and financially supported by the own Foundation for the Research. Informed consent was obtained before enrolling patients in the study. From June 2006 to April 2008, 64 consecutive patients with a history of chronic reflux esophagitis (>6 months), needing long-term acid suppressive therapy, were considered for the study. During the initial screening phase, patients were evaluated for their medical history including GERD medication usage, and they completed the GERD health-related quality of life (HRQL) questionnaire while on PPI therapy. The use of PPIs was then discontinued for 21 days, at least. While off all GERD medications, the GERD-HRQL questionnaire was re-administered, and esophageal pH was assessed over a 24-h period by pH–impedance monitoring. Normal manometry and pH–impedance values were as follows: basal LES pressure from 8 to 26.5 mmHg, residual LES pressure <4 mmHg, acid percent time <1.1%, and all reflux percent time <1.4%. Stationary manometry and 24-h pH–impedance monitoring were performed at screening and at 12 months. Inclusion criteria were age 18–75 years, symptomatic gastroesophageal reflux defined by a GERD-HRLQ score >20 off acid suppressive therapy, ability to be clinically followed for 2 years, and a signed informed consent. To be included, patients were also required to have a deteriorated GE junction with Hill grade II, III, or IV.[21] Patients with a hiatal hernia larger than 3 cm, esophageal motility disorders, diverticula, strictures, previous gastroesophageal surgery, or Barrett's esophagus were excluded. Twenty patients (15 males/five females, median age 47.5 years, range 26–68) were included into the study while the other 44 did not meet the inclusion criteria and were therefore addressed either to continuous medical therapy or to Nissen fundoplication. The patient population is shown in Table 1.

Study Objective

The hypotheses tested in this study were that endoscopic fundoplication would decrease the use of antisecretory drug, decrease GERD symptoms, improve quality of life, and reduce esophageal acid exposure.

Description of the Device and Technique

EsophyX is a device aimed at reconstructing the one-way flow characteristics of the gastroesophageal valve (GEV). The device functions by retracting the portion of the gastric cardia making up the angle of His and firing full-thickness "H" tacks through a plicated fold of the gastric wall, thus lengthening the GEV and restoring antireflux characteristics to the gastroesophageal junction.[22] The procedure begins

Table 1 The Patient Population

Males/females	15/5
Median age (years)	48 (26–68)
Hiatal hernia <3 cm	11 (55%)
Esophagitis	
No/Los Angeles grade A	15 (75%)
Los Angeles grade B/C	5 (25%)
24-h pH–impedance monitoring	
All reflux % time (mean; normal value <1.4)	3.8 (±3.4)
Acid reflux % time (mean; normal value <1.1)	2,8 (±2.9)
Number acid reflux (mean)	55.5 (±29)
Number nonacid reflux (mean)	29.6 (±22.4)

with an endoscopic examination to determine the anatomy of the gastroesophageal junction, the esophagitis degree according to Los Angeles classification, and the degree of the valve tightness according to the Hill classification (Table 2). All procedures were performed under general anesthesia with orotracheal intubation with the patient placed on the operating table in left lateral decubitus. Two physicians (an endoscopist and an surgeon in our study) composed the operating team: the endoscopist (AR) had experience on endoluminal fundoplication with Endocinch, and the surgeon (RR) had experience in laparoscopic fundoplication. Before doing the first cases in humans, both of them performed several cases of ELF in live animals (dogs and pigs). The first physician controls the implantation of fasteners using the EsophyX device, and the second operates the endoscope and ensures continuous direct visualization. The device is inserted transorally into the esophagus as a normal "overtube". At the level of the Z-line, suction is applied to the device, and as it is advanced into the stomach, the Z-line is displaced caudally. Under direct endoscopic guidance, an helical retractor is deployed and screwed into the gastric wall just distal to the Z-line. As the helix is retracted, the tissue is drawn into the device's jaws for a length of 2–3 cm. The jaws are then closed, apposing the two walls GE junction and gastric wall. The technique used in these series is defined as transoral incisionless fundoplication (TIF) 1, as opposed to a different newer technique which is defined as TIF 2. In TIF 1, deployment of the fastener initiates on the greater curvature and continues anteriorly and posteriorly to create a 200–300° omega shape valve over a length of 3–5 cm. Fasteners are applied 2–3 mm caudally to the squamocolumnar junction, which is easily recognizable through the transparent window of the device, and the stomach wall. The polypropylene fasteners are delivered serially across the full thickness of the two walls, esophagogastric (EG) junction and stomach, respectively. The technique recreates a full-thickness GEV, similar to those resulting from surgical fundoplication. The number of polypropylene sutures for the realization of the antireflux valve varies normally from seven to eight couples (therefore from 14 to 16 sutures). Following the procedure, patients were admitted overnight and discharged on the following day after a clinical examination and a radiologic gastrographin swallow. They were instructed to consume a soft diet during the first 2 weeks and a regular diet afterward.

Table 2 Hill Grading System of the Esophagogastric Valve

Grade I valves: presence of a prominent tissue fold surrounding the endoscopic shaft
Grade II valves: presence of a moderately prominent tissue fold; rarely opens with respiration and closes promptly
Grade III valves: a barely present fold; fails to close around the endoscope
Grade IV valves: lack of a muscular fold; lumen of esophagus stays open all the time, allowing the squamous epithelium to be viewed from below

Follow-up

Patients were instructed to discontinue PPI drugs from day 5 after the treatment. If symptoms returned, PPI treatment (maintenance or on demand) was restarted without consulting the study investigators. Patients were free to increase or reduce the daily PPI dose as desired, depending on their GERD symptoms. Use of other antacids was discouraged. One month after treatment, patients underwent either a clinic or a telephone interview, during which the GERD-HRQL and a symptom severity scale were administered as well as PPI consumption, present symptoms, and the occurrence of adverse events (i.e., sore throat, dysphagia, retrosternal pain, and nausea) were evaluated. The patients were then evaluated 6 and 12 months after the procedure: the GERD-HRQL questionnaire was administered; endoscopy, stationary manometry, and ambulatory 24-h pH–impedance monitoring were then performed.

Statistical Analysis

The statistical analysis was carried out using Stat Software for Windows (StatSoft. Inc., Tulsa, OK, USA). The Mann–Whitney U test was used to compare two independent groups of data. $p<0.05$ was considered statistically significant.

Results

Eleven patients (55%) had a small hiatal hernia (<3 cm); five (25%) had a grade B/C esophagitis according to Los Angeles classification. Eight patients had a Hill grade II valve, ten patients had a Hill grade III, and only two patients had a grade IV. Pretreatment mean pressure of the lower esophageal sphincter was 10.5±2.7 mmHg (range 6–15). The mean preoperative total reflux time was 3.8% (normal value 1.4%), and the mean acid reflux time was 2.8% (normal value <1.1%; Table 1).

The mean duration of the procedure to construct a 220° valve (range 180–270°) was 62 min (range 38–105). A median of 14 fasteners (range 6–18) was placed. There were no major intraoperative complications. Two serious adverse events were recorded in the early postoperative period: two patients had a hematemesis, on the first and eighth postoperative day, respectively. They needed either prolonged or rehospitalization and were both treated conservatively. Six months follow-up was completed by

all patients included in the study. At 6 months follow-up, 11 patients (55%) were off PPIs and free of GERD symptoms while nine patients had resumed PPI or H2 blockers. Endoscopy showed grade B esophagitis in one patient (5%). Most of the ELF were Hill grade I (12 patients) or II (6 patients) while Hill grade III was observed in 2 patients (10%; Fig. 1). GERD-HRQL score decreased from a median of 40 to a median of 7 ($p<0.05$, Mann–Whitney U test). Stationary manometry did not show significant variations in mean LES pressure. The pH impedance report did not show significant changes 6 months after fundoplication (Table 3). At 6 months follow-up, four patients (20%) with persistence of GERD symptoms despite the use of standard doses of PPI were scheduled for laparoscopic fundoplication; they were excluded from further follow-up. At reoperation, fasteners were found partially extruded as if the stomach wall had disengaged from the H suture, which was still present of the esophageal side. Fasteners were easily removed. One patient was lost to follow-up after 6 months. Therefore, 15 patients completed 1-year follow-up. Among them, seven were still off PPIs. Eleven patients (73.3%) had an improvement of GERD-HRQL score of more than 50% ($p<0.05$, Mann–Whitney U test). Again, mean LES pressure did not show significant changes from preoperative values. Total and acid reflux esophageal exposures were, respectively, 3.3% and 2.7%, without significant differences from preoperative values (Table 3). Two further patients were scheduled for laparoscopic surgery after the 12-month follow-up for persistance of symptoms associated to pathologic acid esophageal exposure.

Discussion

The idea to realize a stable antireflux mechanism through a totally endoscopic procedure is very attractive, and in the past 15 years, considerable efforts have been done by interventional endoscopists to attain these results. However, all these endoscopic procedures proved either unsafe or uneffective.

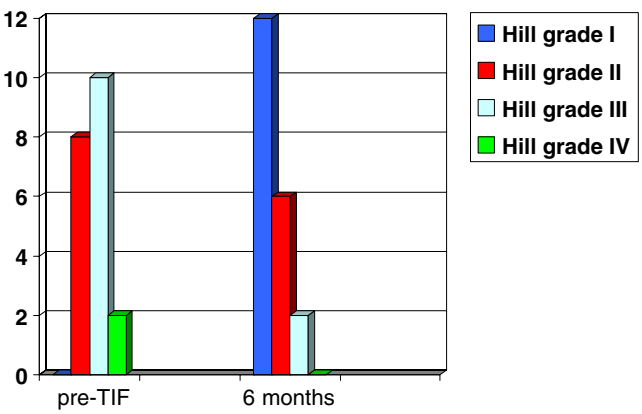

Figure 1 Changes of the Hill grades before and 6 months after TIF.

EsophyX is a novel transoral device which has been developed in an attempt to mimic antireflux surgery through constructing a valve at the GE junction, restoring the angle of His, and reducing a small hiatal hernia with fewer side effects and without incisions.

Differently from previously described endoscopic systems for the treatment of GERD, the EsophyX device was designed to construct an anterior partial fundoplication of 270° by attaching the fundus to the anterior and left lateral wall of the distal esophagus slightly below the esophagogastric junction. The feasibility of the procedure has already been described, and its safety was already demonstrated even if some serious adverse events with this procedure were described. In previous animal studies, histological analysis of TIF-created valves have revealed serosal fusion at 4 weeks,[23] thus confirming that the device is able to create a full-thickness omega-shaped valve very similar to a laparoscopic fundoplication.

A large multicenter clinical trial investigated the safety and early (12 months) and late (24 months) outcomes of ELF in treating patients with chronic GERD[24]: 86 patients underwent ELF. Unfortunately, the data from this study are inconclusive because the reported reduction of PPI use and improvement of GERD-related quality of life score were not accompanied by a significant reduction of distal acid exposure. Moreover, two cases of esophageal perforation have been reported.

The efficacy of ELF in the control of GERD is not clear: an improvement on symptoms and a relief from PPI use had been reported by others in 80% of patients at 6 months follow-up, but functional results are contradictory. In the multicenter study,[24] postoperative pH report demonstrated a reduction of esophageal acid exposure in 31% of patients and normalization in 40%. Cadiére, in a personal experience,[20] reported that 63% out of 19 patients had normal pH study at 1-year follow-up. In the present study, we could not confirm these favorable reports: a mild symptom improvement was recorded with 55% and 46% of patients that could remain off PPI at 6 and 12 months follow-up, respectively. Objective evaluation, however, showed that

Table 3 pH–Impedance Monitoring Report

	6months follow-up		12months follow-up	
	Mean	SD	Mean	SD
All reflux % time	3.2	±2.1	3.3	±1.2
Acid reflux % time	2.6	±1.9	2.7	±1.2
No. acid reflux	48.2	±30.9	37.4	±22.6
No. nonacid reflux	21.5	±15.1	15.4	±14.8

esophageal acid exposure did not change significantly after the endoscopic fundoplication. Only a minority of patients showed a slight reduction in the number of acid and total refluxes and a minor reduction of acid exposure time was observed, and both findings were not significant; most of the patients had unchanged and some had worsened pH–impedance evaluation. Moreover, it should be considered that six patients out of 20 needed a revisional laparoscopic Nissen for persistent or worsened symptoms: at surgical exploration, a large number of fasteners were visible from the peritoneal side, meaning an incomplete plication or a valve partial disruption. Reasons that might explain our unsatisfactory results are difficult to clarify. A possible explanation of failure might be related to the first generation prototype used in the experimentation: the device was large with a rough shape. The articulation made the advancement through the hypopharynx and the upper part of the esophagus difficult. Its positioning in front of the cardia at the time of tissue approximation and fasteners delivery is difficult. Moreover, the fasteners needed to be charged manually resulting in a time-consuming procedure. The consequent incorrect placement of the fasteners through the gastroesophageal junction may result in an incompetent valve. With time loosening of the anterior and posterior fastener sets may cause a worsening of the antireflux mechanism. Also, we used the so-called TIF 1 technique, in which construction of the valve starts centrally at the greater curvature side and moves anteriorly and posteriorly: with this technique, probably the valve results not so adherent to the endoscope and virtually too low on the cardia since the fasteners are a couple of millimeters caudally to the EG junction. A technical evolution has been proposed called TIF 2 technique in which the deployment of fasteners starts on the anterior and posterior corners of the gastric wall closer to the lesser curvature, then moves centrally, and the fasteners are placed just above the squamocolumnar junction. With this technique, a more tightened and adherent to the endoscope valve might be constructed. An experimental study on dogs[25] has compared the TIF 1 and TIF 2 procedure: in this experimental setting, TIF 1 did not significantly reduce distal esophageal acid exposure when compared with baseline, whereas the TIF 2 procedure markedly reduced the DeMeester score in all animals with a tridimensional evaluation of the neo-lower esophageal sphincter truly mimicking the neo-sphincter after a Nissen fundoplication.

In conclusion, the ELF procedure using the EsophyX device is a new attractive technique aiming at the control of GERD. Although feasible, the technique can be associated with serious adverse events. The results of our study with the TIF 1 procedure indicate that the valve can ameliorate GERD symptoms, but the esophageal acid exposure does not change significantly at 1-year follow-up. One third of patients experienced unchanged or worsened symptoms that demanded a standard laparoscopic fundoplication. Basing on our experience, ELF with EsophyX™ should still be considered an investigational procedure with no role in routine treatment of GERD. The TIF 2 technique may indeed improve the results of ELF, and more clinical experience should be made with this technique.

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Discussant

Dr. Brant Oelschlager (University of Washington, Seattle, WA): The search of the holy grail for incisionless endoscopic antireflux surgery is a journey littered with failed devices, procedures, and bankrupt companies.

The EsophyX procedure, as you presented it today, seems like it is kind of off to have a shaky start. It suggests that the procedure has some inherent risk as you describe with your bleeding episodes, and maybe a modest improvement in symptoms and minimal effect on gastroesophageal reflux disease, at least pH monitoring.

I have a few questions. You included patients with hiatal hernias up to 3 cm. How did you measure the hiatal hernias? And do you really think that we can fix gastroesophageal reflux disease endoscopically without a hiatal hernia repair with these endoscopic procedures. Should we not concentrate, if we are going to be successful, on moderate refluxers without hiatal hernia?

By the same token, you said all of your patients had esophagitis and I saw some conflicting information. Patients with esophagitis seem to be on the far end of the GERD spectrum.

Does that partially explain why your results were not better because you are attacking patients with too high a burden of disease?

Finally, one of the critiques of the original TIF 1 procedure is that it does not really recreate the esophagogastric plication the way that a Nissen fundoplication would. Instead, it has more of a gastrogastric plication. The newer TIF 2 procedures that you alluded to tries to do a better job of recreating the esophagogastric plication.

Can you comment on the limitations and whether you think this new procedure is going to be—allow the EsophyX to proceed on in the treatment of gastroesophageal reflux disease?

Closing Discussant

Dr. Uberto Fumagalli (Milan, Italy): Thank you, Dr. Oelschlager, for your comments and questions.

We think that this procedure probably should be considered only for the treatment of reflux disease in patients without hiatal hernias or with very small ones. The device realizes an endoluminal fundoplication: The endoscopic aspect of the valve is similar to the endoscopic view after a laparoscopic Nissen fundoplication, but nothing is done on the diaphragmatic crura during the endoluminal procedure, and a crural plasty may be needed in patients with hiatal hernias. For this reason, we included in our series only patients with small hernias. The hernias were measured endoscopically.

In our series, five out of 20 patients had a LA B or LA C esophagitis. Since the total number of patients evaluated was small, we could not compare the results obtained in patients with different grades of esophagitis; the results on the whole series were disappointing in terms of control of esophageal acid exposure. The reason of this has probably, at least in part, to do with technical reasons: The TIF 2 modification of the procedure may be able to give improved results, mimicking better what we do with a Nissen fundoplication.

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Detection of Free Peritoneal Cancer Cells in Gastric Cancer Using Cancer-Specific Newcastle Disease Virus

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Abstract
Introduction Cytologic detection of peritoneal gastric cancer cells by Papanicolaou staining offers important prognostic information but has low sensitivity. We evaluated a novel detection technique using Newcastle disease virus expressing the enhanced green fluorescent protein (NDV-GFP) gene.
Methods NDV-GFP was tested on MKN-1 human gastric adenocarcinoma cells plated upon rat hepatocytes to determine tumor-specific infection and GFP expression. Malignant ascites infected with increasing doses of virus was evaluated for NDV-GFP dose determination. Peritoneal lavage samples from 30 patients with gastric adenocarcinoma undergoing staging laparoscopy were evaluated with NDV-GFP.
Results NDV-GFP can specifically detect one MKN-1 cell among one million benign rat hepatocytes. NDV-GFP at 5×10^6 plaque-forming units (PFU) produced optimal GFP expression in malignant ascites. Noncancerous cells were non-GFP expressing. GFP-expressing cells counterstained positive for carcinoembryonic antigen expression, confirming their cancerous origin. Furthermore, in patients with advanced gastric cancer, GFP expression was markedly enhanced over cytology. Of six patients with M1 disease discovered during laparoscopy, only 50% were cytology positive. All six, however, were NDV-GFP positive. Cytology was positive in 9% of patients with T3 disease, 8% with N1 disease, and 50% with N2 disease. In contrast, NDV-GFP was positive in 95% of T3 patients and 100% of patients with N1 or N2 disease.
Conclusions NDV-GFP can specifically infect and detect peritoneal gastric cancer cells and offers a more sensitive method compared with conventional cytology. This novel modality may offer enhanced detection of intraperitoneal cancer spread and provide important prognostic information.

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Keywords Newcastle disease virus · Detection · Gastric cancer · Peritoneal lavage

Introduction

Gastric cancer is the fourth most common cancer globally[1] and is particularly prevalent in Asian countries. Within the USA, over 21,000 new cases were estimated to occur in 2008 alone.[2] Staging of gastric cancer is currently done by endoscopy with biopsy and various imaging modalities, including endoscopic ultrasound (EUS) and computed

tomography (CT).[3,4] Diagnostic laparoscopy has emerged as a better means of excluding metastases in the peritoneum while also enabling the procurement of lavage washings for cytologic examination. Positive cytologic washings, as determined by the Papanicolaou (Pap) stain, confer the same poor prognosis as overt metastases.[5–7] Cytology, however, is not always positive in cases of obvious metastatic disease and has a low sensitivity of 54–59%.[8,9] A more sensitive means of diagnosing free peritoneal cancer cells would allow for identification of those patients who may benefit from adjuvant therapy.

Newcastle disease virus (NDV) is a member of the Paramyxoviridae family, is replication competent, and contains a nonsegmented, negative-stranded RNA genome.[10] It is known to be pathogenic in birds but does not cause toxicity in humans. Several trials have noted clinical benefit after administration of naturally occurring NDV in metastatic or malignant tumors refractory to standard care, such as melanoma and various solid tumors.[11,12] The recent establishment of the reverse-genetics system has allowed for genetic manipulation of the NDV virus, thereby enhancing its oncolytic effect, as well as inserting a reporter gene, such as the enhanced green fluorescent protein (eGFP).[13,14] The NDV containing the eGFP marker gene, NDV-GFP, may offer a novel diagnostic modality in evaluation of peritoneal lavage fluid from patients with gastric cancer.

This study set out to determine whether the recombinant NDV-GFP virus, which has been designed to specifically target and infect gastric cancer cells, could be used diagnostically. Virally mediated detection of free peritoneal cancer cells from patients undergoing staging diagnostic laparoscopy for gastric cancer was then investigated as a means of detection and compared with cytologic examination by the Pap stain.

Materials and Methods

Cell Culture

The MKN-1 cell line, an adenosquamous cell carcinoma, was kindly provided by Dr. T. Suzuki (Fukushima Medical College, Japan) and was cultured in Roswell Park Memorial Institute (RPMI) medium supplemented with 10% fetal bovine serum (FBS), 1% penicillin, and 1% streptomycin.

Virus

The attenuated NDV Hitchner B1 strain (NDV-B1) was modified with the reverse-genetics system.[15,16] To generate NDV expressing GFP, a GFP DNA fragment flanked by the appropriate NDV-specific RNA transcriptional signals was inserted into the *Xba*I site created between the P and M genes of pT7NDV of F3aa. Viruses were rescued from complementary cDNA using methods described previously and sequenced by reverse transcription–polymerase chain reaction for insert fidelity.

Rat Hepatocyte Study

All animal studies were done in accordance with Memorial Sloan–Kettering Cancer Center's (MSKCC's) Institute of Animal Care and Use Committee under an approved protocol. Adult male Sprague Dawley rats were anesthetized using 2% inhalational isoflurane mixed with 3 l of oxygen. A midline laparotomy was performed and the liver isolated. The portal vein was cannulated and perfused with warm liver perfusion medium followed by Liver Digest Medium (Gibco, Grand Island, NY, USA). Rat hepatocytes were isolated and cultured according to the manufacturer's protocol on six-well plates coated with 1% rat tail collagen and incubated at 37°C. Four hours after plating the hepatocytes, MKN-1 cells were added at a ratio of one cancer cell against a background of one million rat hepatocytes. Twenty-four hours later, the plates were infected with NDV-GFP at a dose of 5×10^6 PFU and evaluated for GFP expression.

Patient Study

All patient samples were collected under an Institutional-Review-Board-approved tissue collection protocol with patient consent. Thirty patients underwent diagnostic laparoscopy at MSKCC for biopsy-proven gastric adenocarcinoma. Normal saline was instilled into the peritoneal cavity, and lavage samples were collected from the right upper quadrant, left upper quadrant, and pelvis. Duplicate samples from each site were obtained from every patient; half were sent to the pathology department for evaluation, and the other half were transported to the laboratory on ice. The lavage fluid was combined and placed in 50-ml conicals and centrifuged at 800 rpm for 5 min to obtain a cell pellet. This pellet was then washed once with phosphate-buffered saline (PBS), resuspended in 1-ml RPMI media containing 10% FBS and 1% penicillin and streptomycin, plated in four-well chamber slides, and incubated at 37°C.

NDV-GFP Dose Optimization

A sample of grossly malignant ascites was obtained from the operating room and processed in the above-described fashion. Wells were incubated with single doses of NDV-GFP ranging from 5×10^3 to 5×10^7 PFU. Fluorescence microscopy was performed after 12 h of incubation to evaluate for number of green fluorescent cells visualized per high-powered field.

Viral Infection and Costaining for CEA

After a minimum of 6 h and up to 24 h of incubation, 500 μl of media was aspirated carefully from each well of the chamber slide. NDV-GFP 5×10^6 PFU was added to the remaining media and left at room temperature. Five hundred microliters of media was added back after 30 min, and the chamber slide returned to 37°C. Samples were also counter-stained with phycoerythrin–anti-carcinoembryonic antigen (CEA; BD Pharmingen, Franklin Lakes, NJ, USA).

Fluorescence Microscopy

All samples were evaluated with an inverted microscope (Nikon Eclipse TE300, Nikon, Tokyo, Japan) using phase contrast and fluorescence microscopy. A GFP emission filter was used to detect green fluorescence and a TRIT-C filter for the red fluorescent CEA antibody. Images were obtained using NIS software.

Immunofluorescent Staining

Samples were washed with PBS and fixed with 4% paraformaldehyde for 20 min. The cells were lysed with 1% Triton-X and incubated in rabbit anti-NDV antibody for 2 h. Incubation for 1 h with Alex-fluor 532 secondary antibody followed. The slide was then mounted with mounting medium containing 4′,6-diamidino-2-phenylindole (DAPI) and evaluated with fluorescence microscopy.

Results

Detection of MKN-1 Cells Against Benign Hepatocytes

To confirm that NDV-GFP infects cancer cells but not cells of noncancerous origin, one MKN-1 cell was plated on a background of one million benign rat hepatocytes and infected with NDV-GFP. At a dose of 5×10^6 PFU, NDV-GFP was able to detect one cancer cell against a background of one million benign rat hepatocytes (Fig. 1). GFP expression was seen as early as 6 h and continued for over 24 h. This demonstrated that NDV was both sensitive and specific for gastric cancer cell detection.

Dose Optimization

To optimize the dose of NDV for maximum detection benefit, grossly positive ascites were infected with different doses of NDV, and the numbers of cancer cells that were detectable by GFP expression among the different groups were compared. NDV-GFP produced detectable GFP expression with as low a dose as 5×10^3 PFU after 12 h of incubation. The number of GFP-positive cells increased with increasing doses of virus from one GFP-positive cell per high-powered field at a dose of 5×10^3 PFU to nine GFP-positive cells per high-powered field with a dose of 5×10^7 PFU (Fig. 2). A dose of 5×10^6 PFU, which produced five GFP-positive cells per high-powered field, was chosen as the dose of NDV-GFP with which to proceed, since this dose was the most practical and provided the best balance of viral dose and number of green-fluorescent-positive cells. Also noted were that noncancerous cells, such as erythrocytes and fibroblasts, determined by phenotypic appearance, were also non-GFP expressing.

Evaluation of Peritoneal Washing Samples

We proceeded to evaluate the detection of gastric cancer cells in peritoneal washings using the NDV-GFP virus. GFP-positive cells were found in both cytology-negative and cytology-positive samples (Fig. 3a, b). Other cell types, such as red blood cells and dendritic cells, were GFP negative. GFP-positive cells were detected in 29 of 30 (97%) samples. Cytology, in comparison, was positive in three of 30 (10%). Of the six patients found to have metastatic disease at laparoscopy, GFP-positive cells were found in all washing samples. Cytology, however, was positive in only half of these cases. Overall, NDV-GFP offered a greater sensitivity in detecting gross disease, $p<0.01$ (Table 1).

There was no correlation between patient gender or tumor location and the detection of free peritoneal cancer

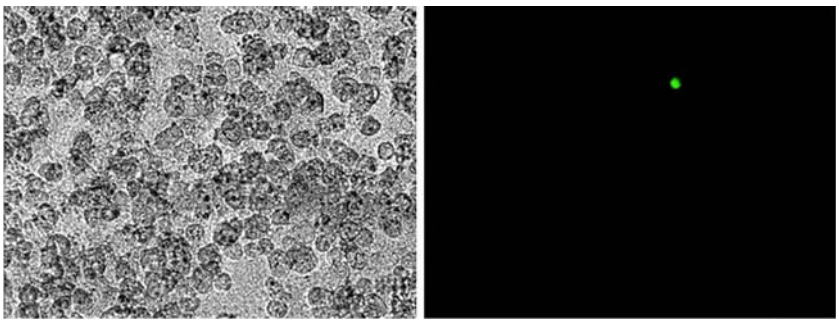

Figure 1 Representative phase contrast and GFP images of MKN-1 gastric adenocarcinoma cells against benign rat hepatocytes after infection with NDV-GFP for 24 h. NDV-GFP can detect one MKN-1 cancer cell against a background of one million benign hepatocytes.

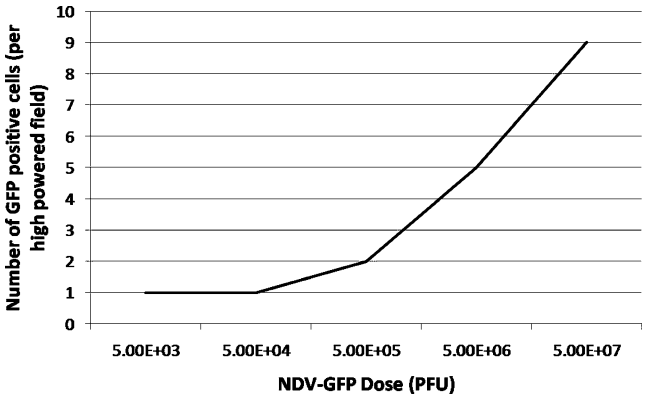

Figure 2 Dose optimization of NDV-GFP. A grossly malignant sample of ascites was processed and divided into multiple aliquots, incubated with increasing doses of virus, and evaluated with fluorescence microscopy after 12 h.

cells, either by cytology or by NDV-GFP (Table 1). Based on EUS, CT, and diagnostic laparoscopy findings, 13 patients were considered stages 1 or 2, while 17 patients were considered stages 3 or 4. NDV-GFP was positive in 100% of stage 3–4 patients, while cytology was positive in only 18% (Table 1). Additionally, 22 patients were determined to have T3 disease or tumors that penetrated the serosa. Of these, two of 22 (9%) were cytology positive, while 21 of 22 (95%) were found to be NDV-GFP positive. Fifteen patients were determined to have N1 or N2 disease. Of these, two of 15 (13%) were cytology positive, while all 15 (100%) of patients were NDV-GFP positive (Table 1).

Table 1 Relationship Between NDV-GFP and Cytology Detection of Cancer Cells in Peritoneal Washings and Clinical Features of the Gastric Cancer Cohort

Clinicopathologic features	NDV-GFP+ *N*=29/30	NDV-GFP+/cytology+ *N*=3/30
Gender		
Male	67%	10%
Location		
GE junction	17%	7%
Cardia	13%	0%
Fundus	3%	0%
Body	33%	3%
Antrum	30%	0%
Differentiation		
Well	7%	0%
Moderate	33%	3%
Poor	57%	7%
EUS/CT/laparoscopy		
Stages 1–2	92%	0%
Stages 3–4	100%	18%
T1/T2 (*N*=6)	100%	0%
T3/T4 (*N*=22)	95%	9%
N1/N2[15]	100%	13%
M1 (*N*=6)	100%	50%

GE gastroesophageal, *EUS* endoscopic ultrasound, *CT* computed tomography

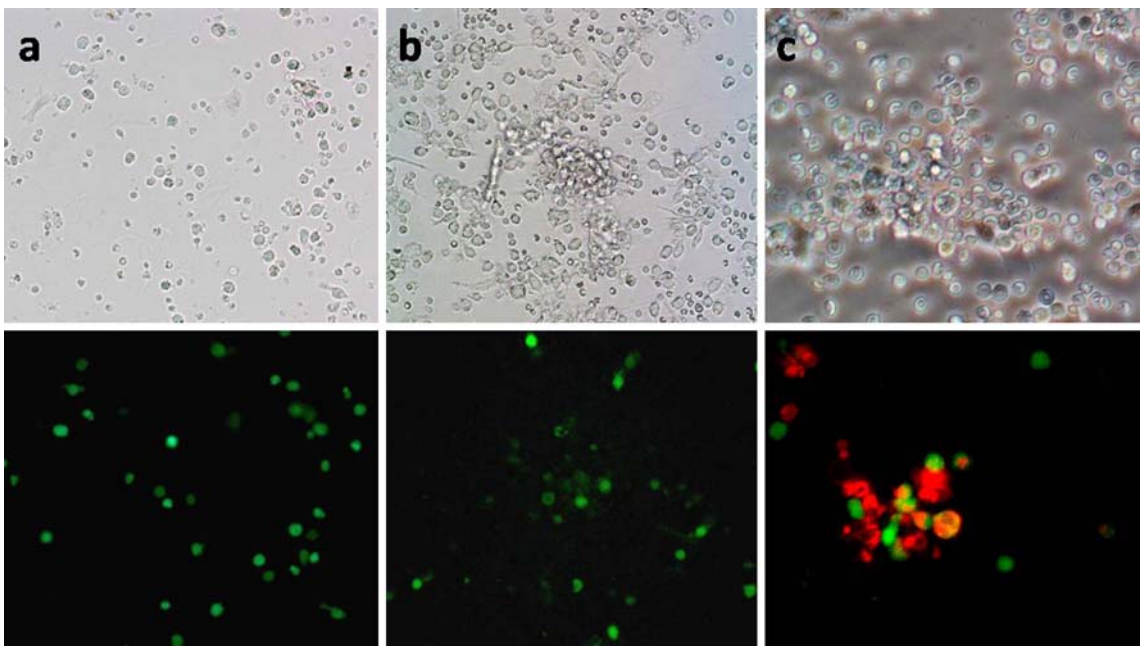

Figure 3 Phase contrast and GFP images of human peritoneal washing samples after infection with NDV-GFP and counterstaining for CEA. Peritoneal washings processed with NDV-GFP from a cytology-negative patient (**a**) and from a cytology-positive patient (**b**). Both samples demonstrated GFP-positive cells. Counterstaining for CEA (*red*) confirms the GFP-positive cells are cancer cells (**c**).

Table 2 Relationship of NDV-GFP Detection and Clinical Indicators of Poor Prognosis in Gastric Cancer Patients at the Time of Resection

Pathologic features of resected specimens	NDV-GFP+ *N*=22/23	Cytology+ *N*=0/23
Vascular invasion	17/17 (100%)	0/17 (0%)
Perineural invasion	9/9 (100%)	0/9 (0%)
Positive margins	7/7 (100%)	0/7 (0%)

After diagnostic laparoscopy, 23 patients ultimately underwent resection. Of these, 22 of 23 (96%) had GFP-positive cells as detected by NDV-GFP. None of the patients were cytology positive. Of the 17 patients found to have vascular invasion on pathology, all were NDV-GFP positive (Table 2). Similarly, all nine patients found to have perineural invasion and all seven patients found to have positive margins on pathologic examination were also found to be NDV-GFP positive and cytology negative.

Counterstaining for CEA

To confirm that these GFP-positive cells were indeed cancer cells, the samples were costained with anti-CEA antibody. Using fluorescence microscopy, the GFP-positive cells were shown to costain for CEA (Fig. 3c), further confirming their cancerous origin.

Immunofluorescent Staining

To confirm that the GFP-positive cells were fluorescent due to NDV-GFP infection, human samples were processed in the manner described above, evaluated with fluorescent microscopy for GFP and CEA expression, and then fixed with 4% paraformaldehyde. These samples were then stained with anti-NDV antibody, anti-CEA antibody, and appropriate secondary antibodies. As can be seen in Fig. 4, cells that were stained for NDV antigens also costained for CEA, confirming that only cancer cells were infected with NDV.

Discussion

Gastric cancer is the fourth most common cancer globally.[2] While metastatic disease still carries a median survival of less than a year with chemotherapy,[17] patients who can be preoperatively identified as having high risk for advanced disease would benefit from a treatment paradigm that differs from the treatment plan for patients with early-stage disease. Diagnostic laparoscopy has proven to be both a useful tool in diagnosing subradiologic metastatic disease, as well as providing a means to evaluate peritoneal lavage cytology.[9] Multiple studies have demonstrated that positive peritoneal cytology, as determined by the Pap stain, confers the same prognosis as does gross metastatic disease.[5,7]

NDV has been studied for its natural tumor specificity and oncolytic properties since the late 1950s.[18] The establishment of the reverse-genetics system for the virus has allowed for modifications enhancing cancer specificity and incorporation of marker genes, such as GFP, thereby allowing for tracking of viral replication.[14] The current study set out to determine if virally mediated detection of free peritoneal cancer cells in patients undergoing diagnostic laparoscopy for biopsy-proven gastric adenocarcinoma would offer a more sensitive method of detection, as compared to conventional Pap staining.

The results of this study demonstrated that NDV-GFP was able to specifically detect cancer cells and express GFP upon a background of benign rat hepatocytes, as well as in human peritoneal lavage samples. Noncancerous cells, such red blood cells and fibroblasts, were non-GFP expressing. Counterstaining for CEA in the human lavage samples

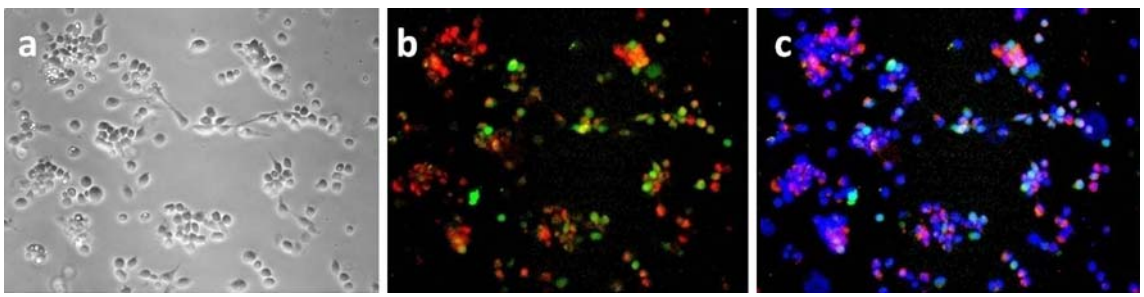

Figure 4 Immunofluorescent staining for Newcastle disease virus and CEA. Peritoneal washings from a cytology-positive patient were processed and fixed with 4% paraformaldehyde. Phase-contrast image (**a**), immunofluorescent staining for CEA (*red*) and NDV (*green*) show double-positive staining (**b**), and overlay with DAPI stain for nuclei (**c**).

confirmed the cancerous origin of the GFP-positive cells. NDV-GFP-mediated detection offers significantly more sensitivity compared with conventional cytology. Even in patients who were found to have gross peritoneal disease during laparoscopy, NDV-GFP detected positive cells in all cases, while Pap staining was positive in only 50% of those patients.

NDV-GFP was also able to identify free peritoneal gastric cancer cells in the majority of those patients found to have more advanced disease, such as stage 3–4 disease, T3, and N1 or N2 tumors. Positive gastric cancer cells were also identified in the peritoneal washings of all patients found to have vascular invasion, perineural invasion, and positive margins within the resected specimen, while Pap staining was negative. These results suggest that NDV-GFP may better identify those patients who have risk factors for recurrence. Future clinical follow-up is needed to determine the prognostic significance of finding free peritoneal gastric cancer cells by this more sensitive, virally mediated method and how the identification of these cells may affect treatment.

Conclusion

NDV-GFP-mediated detection of gastric cancer cells offers a rapid and more sensitive method of identifying free peritoneal gastric cancer cells in peritoneal lavage fluid compared with conventional Pap staining. While positive peritoneal cytology by Pap staining confers the same poor prognosis as does metastatic disease, long-term clinical follow-up is needed to ascertain the prognostic impact of positive NDV-GFP status.

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Discussant

Dr. Sarah Thayer (Massachusetts General Hospital, Boston, MA): First, may I congratulate you on a job well done for your work, which was very well presented.

I think that your study has nicely shown another enhanced detection technique for these free peritoneal cells using the Newcastle disease virus. I think what you have shown is an extraordinarily sensitive technique.

But the question still remains, how specific is this technique? And can the specificity be used to ascertain those patients who are at high risk of recurrence or at advanced stage of disease?

I think the difficulty in making any conclusions actually stems from your data—that nearly 100 percent of your patient population was GFP-positive.

So it comes as no surprise, then, that positive GFP cells were found in advanced-stage disease. It's also true, if you think about it, that 100 percent of your patients with very early-stage disease and good prognostic factors were also GFP-positive. So this raises the specter of specificity with

this particular enhanced detection technique.

So my questions are three, and they really focus around the specificity of this technique. The first: Your control experiment done on the patient revealed that your virus was sensitive; however, the contaminating cells in cytology are mesothelial and inflammatory cells. Did you perform any control to make sure your Newcastle disease virus did not stain mesothelial or inflammatory cells?

Closing Discussant

Dr. Joyce Wong: Interestingly, if you were to look at the washing specimens, sometimes you see macrophages or dendritic cells exhibit very low fluorescence. But with fluorescence microscopy, you can actually gait the level that you determine GFP to be positive. So when you raise the threshold, you will gait out all sort of cells that exhibit low-level fluorescence, such as dendritic cells or macrophages, which you can confirm phenotypically.

The GFP or fluorescence that the dendritic cells show could be autofluorescence. The GFP expression is much lower than what you see in the cancer cells, which you can also detect morphologically.

Discussant

Dr. Sarah Thayer: My second question is: Going back looking at your patient samples again, you showed very nicely that the CEA-positive cells were, in fact, green fluorescent protein-positive. However, also in the same field, we saw a lot of GFP-positive cells that were not CEA-positive; there were also a lot of CEA-positive cells that didn't co-localize with GFP. So I wonder whether or not you went ahead and looked at those significant GFP-positive cells and confirmed that in fact they were cancer, and if so, what methodology you used to confirm that they were cancer.

Closing Discussant

Dr. Joyce Wong: I think what we need to do is actually go back and look at markers other than CEA. There is also an interesting time correlation between GFP and CEA expression. With viral infection, as the virus gets taken in by the cell and starts to replicate, the cancer cells actually lose CEA expression. So there is a very definite window of time between administering our virus and evaluating with microscopy where you can see the co-localization of CEA and GFP. We also used a dose of virus that was low enough that we did not infect every cell at once.

So we believe that the CEA positive cells are just not infected with virus yet. I think that in those particular panels, the GFP positive cells could have been either at one point CEA positive, or they are cancer cells, or we believe them to be cancer cells, that would be positive by a marker other than CEA. We are currently investigating other markers.

Discussant

Dr. Sarah Thayer: My final question actually has to do with this virus. It's an incredibly interesting virus when you go back to its history. I'm surprised that we can have access to it and use it.

The reason why, as you said, is that clearly it's an avian virus. But it has the capability of infecting human cells, and there are spontaneous mutants that affect the neurons and respiratory epithelia. And, actually, if you look at the history of this virus, it was studied by the U.S. Defense Department as an agent of biological warfare.

So now I ask you how you modify this virus so that it appears to have a sensitivity to (now) gastric cancer epithelia, and whether you also then plan to use it for its oncolytic properties, and not as a marker?

Closing Discussant

Dr. Joyce Wong: There actually have been a number of studies in our lab that have used it against melanoma, mesothelioma, and gastric cancer. The NDV virus specifically targets cancer cells because of the defective interferon pathways within tumor cells that are not present in normal cells. So normal cells are not able to replicate NDV, and NDV does not infect them.

We have been able to insert various proteins and various genes within the NDV genome that makes it more oncolytic, so the idea would be to eventually use it as a cancer therapeutic agent and not just a diagnostic tool. We use the GFP marker gene in this situation purely for diagnostic reasons.

Closing Discussant

Dr. Michael Sarr (Mayo Clinic, Rochester, MN): Let me ask you a couple of things. I am also going to talk about the specificity.

First, concerning your hepatocyte co-culture. How do you know that cell was one of the cancer cells? You showed us a photomicrograph with one green cell image.

Closing Discussant

Dr. Joyce Wong: I don't have the data here, but you can tell cancer cells morphologically when zoomed in on the background. Hepatocytes are a little bit difficult to culture because they are not grown in monolayers. They are actually quite large cells relative to the cancer cells. So we determined the cancer cells by morphologic analysis.

Discussant

Dr. Michael Sarr: Can't you separate the cells and then do a FACS analysis to look for specific markers?

Closing Discussant

Dr. Joyce Wong: Correct.

Discussant

Dr. Michael Sarr: What's the efficiency of your transfection? Some of your positive figures looked like there were a lot of cells but only a few showed positive transfection.

Closing Discussant

Dr. Joyce Wong: In the washings, we basically used as high a dose as we could use to try and detect as many

cancer cells as possible. When we receive washings, we don't know the number of cancer cells that would be contained in that washing. Not all of the cells that you see will be malignant cells. There will be blood cells and other types of cells.

When we talk about viral infections, typically we talk about multiplicity of infection, or the MOI, which is the number of viral particles relative to cancer cells. When we screened gastric cancer cell lines, we found that there was a great deal of uptake with an MOI of one. So, for example, in this situation we really are talking about MOIs of 100 or 1,000. So the efficiency should be quite high.

Discussant

Dr. Michael Sarr: Then why weren't more cells stained? The number of cancer cells were few?

Closing Discussant

Dr. Joyce Wong: Right. Number one, the number of cancer cells were so few. Secondly, the timeline to evaluating washings is after about 12 hours of incubation. If you were to allow the virus time to replicate more, say at 24 hours or 48 hours, you would, probably, see higher degrees of GFP-expressing cells. But then the optimal balance between viral infection, replication, and lysis would have to be determined.

Discussant

Dr. Michael G. Sarr: You saw so many positive cells with stage one and stage two. How can you use this then, clinically.

Closing Discussant

Dr. Joyce Wong: I think we need longer-term follow-up. Basically, we may be, perhaps, understaging patients. If we can detect peritoneal cancer cells in the lavage specimens, perhaps these patients are not, in fact, stage 1 and stage 2 patients. I think, ultimately, we need to follow these patients out to see if there is disease recurrence or survival.

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2009 SSAT PLENARY PRESENTATION

Improvement in Peripheral Glucose Uptake After Gastric Bypass Surgery Is Observed Only After Substantial Weight Loss Has Occurred and Correlates with the Magnitude of Weight Lost

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Abstract
Introduction Altered gut and pancreatic hormone secretion may bolster resolution of insulin resistance after Roux-en-Y gastric bypass (RYGB), but the independent effects of weight loss and hormonal secretion on peripheral glucose disposal are unknown.
Methods Two groups of nondiabetic morbidly obese patients were studied: RYGB followed by standardized caloric restriction (RYGB, $n=12$) or caloric restriction alone (diet, $n=10$). Metabolic evaluations (euglycemic–hyperinsulinemic clamp, meal tolerance test) were done at baseline and 14 days (both groups) and 6 months after RYGB.
Results At baseline, body composition, fasting insulin, and glucose and peripheral glucose disposal did not differ between groups. At 14 days, excess weight loss (EWL) was similar (RYGB, 12.7% vs. diet, 10.9%; $p=0.12$), fasting insulin and glucose decreased to a similar extent, and RYGB subjects had altered postmeal patterns of gut and pancreatic hormone secretion. However, peripheral glucose uptake (M value) was unchanged in both groups. Six months after RYGB, EWL was 49.7%. The changes in fasting glucose and insulin levels and gut hormone secretion persisted. M values improved significantly, and changes in M values correlated with the % EWL ($r=0.68$, $p=0.02$).
Conclusions Improvement in peripheral glucose uptake following RYGB was observed only after substantial weight loss had occurred and correlated with the magnitude of weight lost.

This paper was presented at the 50th Annual Meeting of the Society for Surgery of Alimentary Tract during Digestive Disease Week, Chicago, IL, June 2009.

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Keywords Bariatric surgery · Insulin resistance · Obesity · Morbid obesity · Gastric bypass · Weight loss · GLP-1 · Insulin · Type 2 diabetes · Diabetes · Calorie restriction · Incretin

Introduction

Several bariatric surgical techniques originally designed to promote weight loss offer a variable but impressive rate of cure for type 2 diabetes mellitus (T2DM). In 80% of patients who undergo Roux-en-Y gastric bypass surgery (RYGB), T2DM resolves or improves significantly.[1,2] RYGB is the most common bariatric surgical technique used in the USA and seems to provide better weight loss and higher rates of resolution of T2DM than purely restrictive techniques such as laparoscopic gastric banding.[3–5]

The proposed mechanisms to account for why RYGB offers this remarkable rate of resolution of T2DM have been under extensive scrutiny in both animals and humans.[1,6–12] At the center of the debate is the relative contribution of greater and sustained weight loss, or to an altered pattern of gut and pancreatic hormone secretion, frequently called the "incretin effect", or other factors.[13,14] RYGB creates an anatomical rearrangement that delivers a partially digested food bolus directly into the second portion of the small bowel while avoiding contact with a large portion of the stomach and the duodenum.[15–17] This, in turn, results in altered glucose kinetics[18] and altered secretion of many gut and pancreatic hormones known to affect glucose metabolism[6,19] and has additional effects on gastric emptying[20] and on neurohormonal gut–brain signaling that regulates energy homeostasis and hunger–satiety mechanisms.[10,20,21] However, to date, there have been few detailed and controlled metabolic studies of the interplay and independent effects of RYGB on the many factors that affect insulin resistance and glucose metabolism, such as beta cell function, the associated changes on gut and pancreatic hormone levels, the magnitude and rate of weight loss, energy balance, changes in body composition, and other factors. Information from such studies might help clinicians and patients in choosing among available surgical treatments for morbid obesity and guide the search for novel surgical procedures to treat obesity-associated T2DM in patients with lower body mass indices (BMI). Therefore, the goal of this study was to delineate short-term changes in total body glucose disposal, gut and pancreatic hormone secretion, and body composition, while controlling for energy balance and delineate the same changes after more substantial weight loss had occurred 6 months after RYGB.

Patients and Methods

Morbidly obese patients, selected to undergo gastric bypass surgery (RYGB), were recruited at the University of California, San Francisco's (UCSF) Bariatric Surgery Program. They met the National Institute of Health and UCSF Bariatric Surgery Program criteria for bariatric surgery: age 21 to 65 years old, BMI either >40 or >35 kg/m^2 with high-risk comorbidities, documented desire to undergo bariatric surgery, well informed and motivated, acceptable operative risks, evaluated and cleared for the procedure by a certified dietitian and a psychiatrist or psychologist, documented repeated failure of nonsurgical supervised weight loss programs, documented BMI >35 kg/m^2 for more than 5 years, and ability and willingness to provide informed consent. Exclusion criteria included previous weight loss surgery; a previous esophageal, gastric, pancreatic, adrenal, small bowel, large bowel, thyroid, or central nervous system operation; diagnosis of thyroid, liver, pancreatic, adrenal, hypothalamic, pituitary, ovarian, and chronic renal disease; diagnosis of T2DM; use of insulin or any oral medications for T2DM; or unwillingness or inability to give informed consent. This project was approved by the UCSF Committee of Human Research and the UCSF Clinical and Translational Science Institute Clinical Research Center (CRC) Advisory Committee.

Randomization and Metabolic Evaluation

Twenty-two patients were allocated to two groups: One underwent immediate laparoscopic RYGB surgery followed by standardized calorie restriction (RYGB, N=12), and the other underwent caloric restriction only (diet, N=10). Allocation to either group was determined by randomization in the initial 17 patients studied and then by CRC and surgery date availability in the last five patients.

All participants underwent the same baseline metabolic evaluation (visit 1, V1). Subjects were admitted to the CRC at 7:00 p.m. on study day 0 for an initial complete medical history and physical examination. On that day, they began an "ad libitum" diet up to a maximum intake of 25 kcal/kg/24 h. Each morning upon arising, they were weighed on a calibrated scale after voiding.

Meal Tolerance Test On day 1, participants underwent a meal tolerance test (MTT), which consisted of a standardized 300 kcal in 100 mL liquid meal containing 50% carbohydrate, 30% protein, and 20% fat with 9.9 g of simple sugars in a total of 38 g carbohydrate, 10 g of fat, and 15 g of protein. Participants were asked to consume this meal within a maximum of 20 min. Blood samples, obtained through an intravenous catheter inserted in the forearm, were drawn at −120, −60, −5, 0, +5, +15, +30, +60 +120, and +180 min relative to the start of the meal. After collection, the samples were processed on site and stored at −70°C for subsequent batch analysis of glucose, insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP; formerly known as gastric inhibitory polypeptide).

Euglycemic–Hyperinsulinemic Clamp On day 2, after an overnight fast, peripheral glucose uptake was measured by the hyperinsulinemic–euglycemic clamp method.[22] Insulin (Humulin R, Eli Lilly, Indianapolis, IN, USA), bound to albumin, was administered intravenously at a rate of 40 mU/m^2/min for 120 min. Blood was drawn by intravenous catheter in a heated vein, and glucose concentrations were measured at 5-min intervals. Infusion of 20% dextrose was adjusted to maintain a whole-blood glucose level of 90 mg/dL. Peripheral glucose uptake (M value) was calculated according to the method of DeFronzo et al.[22], based on steady-state glucose infusion rates.

Body Composition Total body fat and lean body mass were measured by dual-energy X-ray absorptiometry (Hologics Discovery Wi, Bedford, MA, USA). Scanning was not performed in subjects who weighed >350 lbs, the weight limit for the scanner.

Surgery The participants assigned to immediate surgery were discharged from the CRC and admitted for surgery the next day. The RYGB was performed in a standardized fashion by one author (GC); the technique has been described in detail previously.[23,24] In brief, RYGB was performed laparoscopically with six to seven ports. A 3.5-mm linear stapler transected the stomach to create a 30-mL gastric pouch. An antecolic gastrojejunostomy route was always used. A circular gastrojejunal anastomosis with a 25-mm stapler was used. A biliopancreatic limb of 50 cm and an alimentary limb of 100 cm were measured, and a completely stapled side-to-side jejunojejunostomy was created. Patients were discharged on postoperative day 2, and none had perioperative complications.

Participants were then followed as outpatients for 14 days, during which they consumed a standardized low-calorie diet: Optifast HP (Novartis Nutrition Corporation), which provides 800 kcal/day (25% carbohydrate, 48% protein, and 27% fat). Different flavors were available, and participants were allowed to consume no-calorie, non-carbonated soft drinks and water ad libitum. They were given prepackaged servings and instructed to follow a specific feeding schedule. Each participant had met with the CRC dietitian during the baseline inpatient admission for individualized instructions regarding the diet and counseling. During the 14-day outpatient period, participants were asked to fill out daily logs of all food, water, and drinks ingested and were contacted every other day by a research fellow or coordinator from the Bariatric Surgery Clinic. Adherence to the diet was assessed by alternate-day phone calls from the research dietitian.

Follow-up in Patients Undergoing Diet Alone After completing the baseline evaluation and discharge from the CRC, participants assigned to the diet group started the 14-day diet period at home, following the identical diet routine as described for the RYGB group above.

Follow-up Metabolic Assessments (Visit 2 and Visit 3) After 14 days, all participants were readmitted to the CRC and underwent the same metabolic assessments performed at baseline (visit 2, V2). They were then discharged and continued their standard medical treatment. Six participants in the diet group underwent RYGB after completing the V2 assessment. A total of 12 subjects (nine originally assigned to RYGB and three to diet who subsequently underwent RYGB) had a third inpatient evaluation 6 months after RYGB (visit 3, V3).

Laboratory Analyses Whole-blood and plasma glucose levels were measured by the glucose oxidase method (YSI 2300 STAT-Plus Glucose Analyzer, YSI Inc., Yellow Springs, OH, USA). Serum insulin concentrations were measured by radioimmunoassay (Millipore, St. Charles, MO, USA). Active GLP-1 and GIP concentrations were measured by enzyme-linked immunosorbent assay (Millipore, St. Charles, MO, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: fasting plasma glucose (millimoles per liter)× fasting serum insulin (microunits per milliliter)/22.5.[25]

Statistical Analysis

Data are summarized as mean and standard deviation unless otherwise stated. The unadjusted association of proportions and the distribution of continuous variables between groups and the association of each variable with outcomes were determined by two-sided *t* test and chi-square tests. Area under the curve (AUC) was calculated using the trapezoidal rule. Linear associations were measured using the Pearson's correlation coefficient. Statistical significance was considered to be $p<0.05$. SPSS, version 13.0.1 (SPSS Inc, Chicago, IL, USA), was used for all statistical analyses.

Results

From October 2007 to January 2009, 59 patients met the study criteria, 28 initially agreed to participate, and 22 completed the evaluation procedures. Twelve patients were randomized or assigned to RYGB followed by standardized caloric restriction (RYGB) and ten to caloric restriction only (diet). The two groups did not differ with respect to baseline demographics, body composition (Table 1), fasting glucose and insulin, HOMA-IR, peripheral glucose disposal (*M* value), or hormonal secretion during the MTT (Table 2).

Table 1 Demographic and Clinical Characteristics of the RYGB and Diet Groups

	RYGB (n=12)	Diet only (n=10)	p value
Female/Male	9:3	6:4	0.65
Age (years)	47.4±8.7	40.2±13.4	0.16
Weight (kg)	138.0±21.6	134.7±16.9	0.70
BMI (kg/m^2)	48.4±6.8	48.3±6.6	0.99
% Excess body weight	55.4±6.4	55.3±6.8	0.96
% Fat (by DEXA)	48.6±6.8	46.8±4.7	0.53

RYGB Roux-en-Y gastric bypass surgery, *BMI* body mass index, *DEXA* dual-energy X-ray absorptiometry

Table 2 Changes in Body Composition, and Baseline and Changes in Fasting Glucose and Insulin, HOMA-IR, AUCs for Insulin, GLP-1, and GIP During a Meal Tolerance Test at Baseline and 14 days

	RYGB (N=12)	Diet only (N=10)	p value
Weight loss (kg)	9.9±2.4	8.2±2.3	0.11
% Excess weight loss	12.7±2.4	10.9±2.8	0.12
% of weight lost as fat	40.4±16.2	29.9±16.8	0.22
Fasting glucose (mg/dL), baseline	94.8±12.0	99.6±14.7	0.41
Change in fasting glucose	−7.8±10.1	−13.1±17.7	0.40
p value	0.02	0.04	
Fasting insulin (μU/mL), baseline	22.4±14.4	34.1±20.1	0.15
Change in fasting insulin	−7.7±7.5	−13.7±15.9	0.29
p value	<0.01	0.02	
HOMA-IR, baseline	5.1±2.9	8.9±7.0	0.14
Change in HOMA-IR	−1.9±1.4	−4.6±6.2	0.22
p value	0.01	0.04	
AUC insulin, baseline	196±70.6	276±89.3	0.03
Change in AUC insulin	33±131.6	−21±114.5	0.32
p value	0.40	0.57	
AUC GLP-1, baseline	5.1±4.1	3.5±1.2	0.59
Change in GLP-1 AUC	13.4±11.0	0.5±1.6	<0.01
p value	<0.01	0.24	
AUC GIP, baseline	226.0±93.1	201.0±67.4	0.59
Change in GIP AUC	−11.4±80.1	132.0±40.3	<0.01
p value	0.63	0.02	

HOMA-IR homeostasis model assessment, *AUC* area under the curve, *MTT* meal tolerance test

At baseline, peripheral glucose uptake determined by the euglycemic–hyperinsulinemic clamp was profoundly impaired in all subjects; average M value was about one third of that for lean controls in our laboratory (2.1±0.9 vs. 7.6± 2.3 mg/kg/min, p<0.01).[26]

Metabolic Changes

After the 14-day diet period, the magnitude of weight loss and changes in body composition did not differ between groups. Fasting glucose, insulin, and HOMA-IR decreased similarly in both groups (Table 2). M values did not change in either group (RYGB (n=10), V1=2.4±0.9 vs. V2=2.3± 0.7 mg/kg/min, p=0.80 and diet (n=8), V1=1.8±1.0 vs. V2=2.0±1.0 mg/kg/min, p=0.57; Fig. 1).

Insulin secretion over the 3-h postmeal period was similar for V1 vs. V2 in both groups at baseline (Table 2), but after RYGB, serum insulin levels in the first 30 min after the meal were higher than for the diet group (RYGB, V1=107±44 vs. V2=181±137 μU/mL; p=0.01 and diet, V1=117±40 vs. V2=133±90 μU/mL, p=0.83; Fig. 2). GLP-1 postmeal AUC increased significantly following RYGB, whereas it did not change after diet only (Table 2). GIP AUC increased after diet, whereas the values remained low in the RYGB patients (Table 2). The increase in GLP-1 AUC in the RYGB group paralleled the early increase in insulin release after RYGB (Fig. 2).

Metabolic Changes 6 Months After RYGB

Six participants in the diet group underwent RYGB after completing V2 assessment. A total of 12 subjects underwent a third inpatient evaluation 6 months after RYGB (V3): nine subjects from the original RYGB group and three from the diet group who underwent RYGB after completing V1 and V2. Six months after RYGB, this group of subjects had sustained significant weight loss (weight loss=28.4±4.6 kg; EWL=49.7%, p<0.01 vs. V1) of which 74.5% was fat and had significant changes in fasting glucose, insulin, and HOMA-IR compared to baseline (Table 3). The magnitude of changes in fasting glucose, insulin, and HOMA-IR observed at 6 months (V1–3) for the patients originally assigned to RYGB was similar to changes observed at 14 days (V1–2): change in glucose V1–2=−7.8±2.9 vs. V1–3=−9.6±4.1 mg/dL, p=0.73; change in insulin V1–2=−7.7±2.2 vs. V1–3=−12.6± 3.5 μIU/mL, p=0.25; and change in HOMA-IR V1–2= −1.9±0.4 vs. V1–3=−3.0±0.7, p=0.25. The changes in the postmeal serum levels and AUCs of GLP-1, GIP, and insulin 6 months after RYGB remained similar to those observed at 14 days (Tables 2 and 3). In contrast, peripheral glucose uptake (M value) increased in all subjects at 6 months, reaching the upper boundary for the lowermost quartile of values in healthy control subjects (Fig. 3). Notably, the changes in M values correlated significantly with the magnitude of weight lost (r=0.68, p=0.02; Fig. 4).

Discussion

Operations such as RYGB that bypass the duodenum and/or stomach, thus allowing for early delivery of the food bolus to the small intestine and preventing food bolus contact with the duodenum, offer a unique opportunity for identifying weight loss independent mechanisms for resolution of diabetes.[9] Consequently, a variety of novel surgical and endoscopic gastrointestinal procedures are under investigation for use as therapeutic options in treating T2DM.[27–31] Critical unanswered questions remain as to whether or to what degree the altered patterns of gut and pancreatic hormone secretion known to occur with bypass operations bolster beta cell function and ultimately improve peripheral glucose disposal and promote resolution of T2DM independent of weight loss.[9] The fact remains, however, that bariatric operations that result in greater

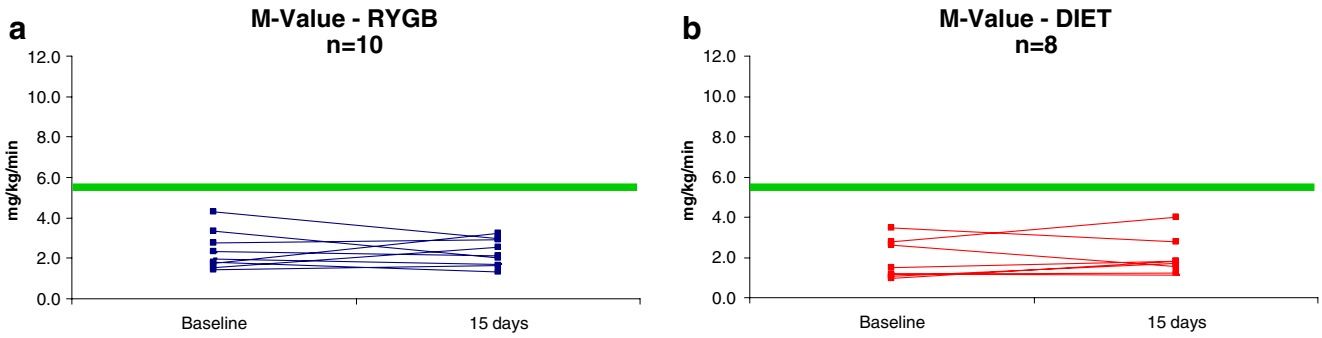
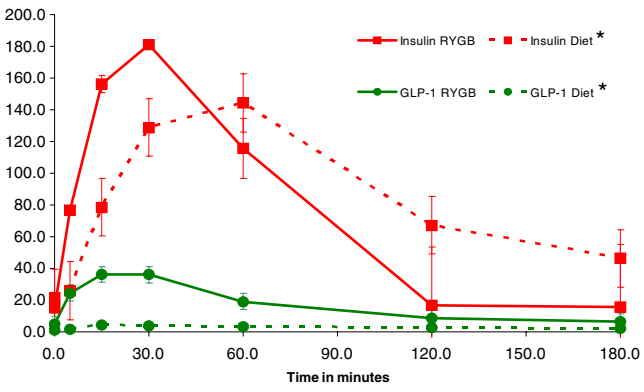


Figure 1 Peripheral glucose uptake (*M* value) by euglycemic–hyperinsulinemic clamp before (baseline) and 14 days after either RYGB (**a**) or caloric restriction (**b**). The *horizontal line* indicates the upper boundary for the lower-most quartile of values seen in healthy control subjects.[26]

weight loss are still associated with greater rates of T2DM improvement or cure.[1] In a recent systematic review and meta-analysis, Buchwald and colleagues[1] showed that excess weight loss and diabetes resolution in the first 12 months after surgery were the highest for patients undergoing biliopancreatic diversion/duodenal switch (BPD/DS; 64% excess weight loss, 95% diabetes resolution) followed by RYGB (60% excess weight loss, 80% diabetes resolution) and the least for banding procedures (46% excess weight loss, 57% diabetes resolution). However, BPD/DS and RYGB may impact and alter mechanisms other than weight loss that play an independent role in improving insulin resistance and allow for this high rate of resolution of T2DM. The intricate interplay among insulin sensitivity/resistance, glucose metabolism, and insulin secretion is affected by many factors: beta cell function; quality, distribution, and total fat mass; energy balance and the magnitude of calorie restriction; hepatic glucose and insulin metabolism and kinetics; quality and quantity of nutrient intake and absorption; associated diseases and stressors such as sleep apnea, liver fat, and adipocytokines; and gut and pancreatic hormone secretion and metabolism, among others.[9,32]



RYGB= Roux-en-Y gastric bypass surgery
* Insulin in microU/mL ** GLP-1 in pM

Figure 2 Insulin and GLP-1 secretion after a meal, 14 days after RYGB and calorie restriction or diet alone.

In this study, we sought to delineate short-term changes in peripheral glucose disposal, fasting measures of glucose and insulin, gut and pancreatic hormone secretion in response to a meal challenge, and body composition, while controlling for energy balance, and to evaluate these same changes after more substantial weight loss had occurred 6 months after RYGB. We confirmed previous studies in showing that, after RYGB, the pattern of gut and pancreatic hormone secretion following a meal is altered compared to

Table 3 Baseline Fasting Glucose, Insulin, HOMA-IR, AUCs for Insulin, GLP-1, and GIP During a Meal Tolerance Test and Changes 6 Months After RYGB

	RYGB (N=12[a])
Fasting glucose (mg/dL), baseline	91.9±10.3
Change in fasting glucose	−9.6±14.2
p value	0.03
Fasting insulin (μU/mL), baseline	22.9±14.0
Change in fasting insulin	−12.6±12.3
p value	<0.01
HOMA-IR, baseline	5.1±2.8
Change in HOMA-IR	−2.9±2.6
p value	<0.01
AUC insulin, baseline	191±62
Change in AUC Insulin	2.1±103
p value	0.95
AUC GLP-1, baseline	3.7±2.2
Change in GLP-1 AUC	11.6±5.4
p value	<0.01
AUC GIP, baseline	207.4±65.8
Change in GIP AUC	−4.5±89.9
p value	0.87

HOMA-IR homeostasis model assessment, *AUC* area under the curve, *MTT* meal tolerance test

[a] A total of 12 subjects underwent a third inpatient evaluation 6 months after RYGB (visit 3): nine subjects from the original RYGB group and three from the diet group who underwent RYGB after completing V1 and V2

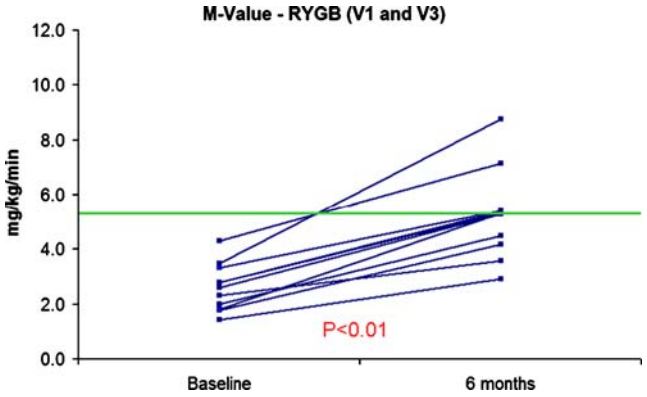


Figure 3 Peripheral glucose uptake (*M* value) by euglycemic–hyperinsulinemic clamp before and 6 months after RYGB (n=11).

controls[10,11,30,33] and that RYGB patients have early improvements in fasting glucose, fasting insulin, and, thus, in calculated HOMA-IR. Notably, the magnitude of improvement in fasting glucose homeostasis was similar in the group that underwent diet alone, indicating that weight loss, rather than the surgical procedure, results in these early changes. We also found that soon after RYGB and before massive weight loss occurs, peripheral glucose disposal (measured by euglycemic–hyperinsulinemic clamp) was not improved. Taken together, these results suggest that in the nondiabetic morbidly obese with severe insulin resistance, the short-term effects of gastric bypass surgery can improve glucose homeostasis under fasting conditions before substantial weight loss occurs but are not sufficient to improve peripheral glucose disposal during hyperinsulinemia. Other investigators, using a variety of techniques to study glucose metabolism, have documented

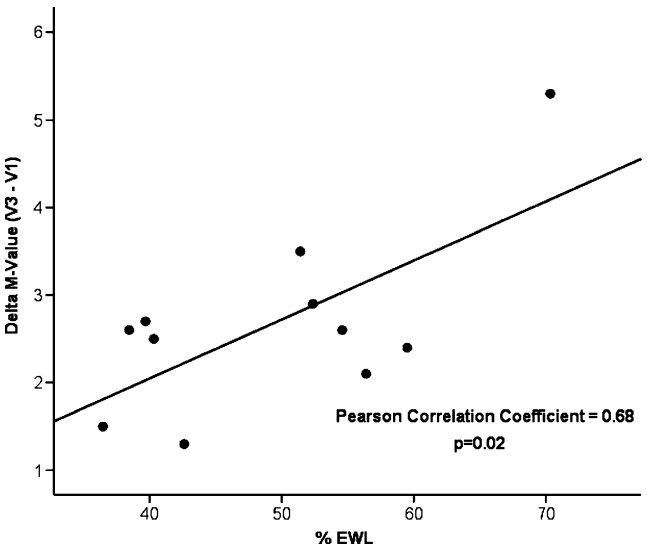


Figure 4 Correlation in between changes in peripheral glucose uptake (*M* values) and percent excess weight loss at 6 months after RYGB (n=11).

improvements in insulin resistance from 1 week to 1 month after BPD/DS[34] and also RYGB with weight loss varying from 9 to 15 kg.[34–37] In contrast to our study, these studies were done in diabetic subjects and most were performed without a diet-only control group. Nevertheless, these differences support the notion that diabetic patients may respond differently to these procedures than nondiabetics.

The altered pattern of gut hormone secretion may result in amelioration of glucose disposal independently of weight loss by many mechanisms. For example, GLP-1 reduces elevated fasting and postprandial blood glucose levels in diabetic humans; leads to glucose-dependent insulin secretion, induction of beta-cell proliferation and expansion of the beta-cell mass, and enhanced resistance to beta-cell apoptosis; inhibits gastric emptying and acid secretion; and reduces food ingestion and glucagon secretion, among other functions.[20,38] We and others demonstrated that RYGB is associated with an increased release of postprandial GLP-1.[13,20,33,39] While the more rapid delivery of glucose and other nutrients to the proximal intestine may partially explain the rapid and robust insulin and GLP-1 responses following RYGB, the magnitude of the exaggeration of the GLP-1 response suggests that other unique features with RYGB also contribute to this increase. In another example, GIP, which is released from the duodenum and proximal small bowel K-cells in response to glucose and fat ingestion, augments glucose-stimulated insulin secretion in healthy humans but almost completely loses its insulinotropic effect in patients with T2DM.[20,33] Others have shown a blunted recovery of GIP levels in obese diabetic patients, but not in obese nondiabetics, after RYGB.[17,33,40] Patients in our current study, although not classified as diabetics, had markedly impaired glucose disposal, and the recovery of GIP secretion in diet-only subjects after minimal weight loss and maintenance of low levels of GIP in the RYGB group were similar to those observed in diabetics in other studies.[17,33,40]

A unique strength of our study was the use of the hyperinsulinemic–euglycemic clamp and repeated testing under controlled conditions. The clamp technique is widely accepted as the reference standard for directly determining insulin sensitivity and peripheral glucose disposal in humans[41] and offers, in the research setting, significant advantages over the commonly used technique for assessing insulin sensitivity, such as HOMA-IR. The hyperinsulinemic–euglycemic clamp leads to a steady-state condition in which the glucose infusion rate during the clamp must be equal to the glucose disposal rate. Thus, the clamp estimates insulin sensitivity/resistance in humans and directly measures peripheral glucose disposal at a given level of insulinemia under steady-state conditions.[22,41] In addition, the glucose clamp has excellent test characteristics. Peripheral glucose uptake typically has a coefficient

of variation of 0.10 and a discriminant ratio of 6 (a measurement of both reproducibility and the ability to distinguish individual results).[42] On the other hand, HOMA-IR, which has been used in many other studies of the metabolic effects of bariatric surgery, is a simple surrogate index for insulin resistance that is derived from blood insulin and glucose concentrations under fasting conditions and reflects mostly hepatic insulin sensitivity. The main limitations of the glucose clamp approach are that it is time-consuming, labor-intensive, expensive, and requires an experienced operator to manage the technical difficulties, but these were overcome by the use of CRC resources and the experienced group of endocrinologists. Moreover, because glucose and insulin are administered parenterally during the clamp, thus bypassing the gut and splanchnic metabolism, this technique measured peripheral glucose uptake independent of any potential influence of altered nutrient delivery to the small intestine or changes in incretin secretion following RYGB.

Evidence from our study and others leaves little doubt that calorie restriction alone can improve fasting glucose and insulin levels and is an important factor leading to the rapid changes observed after RYGB. However, as detailed above, RYGB provides mechanisms that are independent of weight loss and impact and/or bolster the ability of morbidly obese patients to experience a more rapid amelioration of glucose metabolism. However, fasting glucose and insulin measurements, which are usually obtained as a surrogate for insulin sensitivity in most studies performed to date and were the measures that improved similarly at 14 days after RYGB or calorie restriction only, are mostly a reflection of hepatic insulin sensitivity. The *M* value obtained during the clamp study provides the best estimate of peripheral glucose homeostasis, and as we demonstrate, *M* values improved only after significant weight loss and correlated with the magnitude of weight loss.

Limitations of our study include small differences between RYGB and diet groups in gender distribution, weight loss, percentage of weight loss as fat, average daily energy intake, and possible differences in diet absorption that, although not statistically significant, when combined may have impacted the results. Nevertheless, these differences in changes would have led to improvement in glucose metabolism in the RYGB group. On the other hand, the surgical insult and trauma of a laparoscopic operation for RYGB may have had a negative impact, in the 14 day analyses, on glucose homeostasis and disposal. Lastly, we may have not been able to identify a differential and earlier improvement in peripheral glucose disposal in the RYGB group because we studied only nondiabetic participants and studied them only at three time points. Although our participants were profoundly insulin resistant, they may have had effective counter-regulatory mechanisms that successfully forestalled progression to diabetes, and thus, we may have observed a different result had we studied patients with diabetes.

With these limitations in view, we conclude that in nondiabetic morbidly obese subjects under similar caloric restriction and weight loss, peripheral glucose disposal is not improved early after RYGB or calorie restriction. Improvement in peripheral glucose disposal following RYGB was observed only after substantial weight loss had occurred and correlated with the magnitude of weight lost. These findings suggest that weight loss is a critical component for complete restoration of glucose homeostasis in the morbidly obese with insulin resistance.

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Discussant

Dr. Bruce M. Wolfe (Portland, OR): Dr. Campos and colleagues demonstrated that 2 weeks postgastric bypass, GLP-1 and insulin secretion were enhanced, but peripheral insulin resistance as reflected by glucose uptake did not decrease until substantial weight loss occurred at 6 months postoperatively. I have the following questions: First, you indicated that all subjects demonstrated insulin resistance prior to operations. Would you comment on the importance of this finding?

Second, HOMA, a measure of insulin resistance calculated from fasting glucose and insulin decreased at 2 weeks, but the clamp derived *M* score of glucose uptake and

peripheral insulin resistance did not. Is HOMA a useful parameter in these studies or will further studies require the extensive and burdensome clamp studies?

Finally, are you confident that the insulin infusion was effective in shutting down hepatic gluconeogenesis allowing you to draw conclusions regarding peripheral glucose uptake?

Closing Discussant

Dr. Guilherme M. Campos (San Francisco, CA): Thank you, Dr. Wolfe. Your questions highlight the need to clearly understand the definition of diabetes and prediabetes and that diabetes is a spectrum of a disease. What is interesting in our patient population of morbidly obese individuals is that none had a diagnosis of diabetes. All their fasting glucose measures were below 105 and with normal hemoglobin A1c, thus fitting the current criteria for nondiabetics. However, when we studied and challenged them using the hyperinsulinemic–euglycemic clamp, they uniformly had peripheral insulin resistance and poor peripheral glucose disposal. How to incorporate and apply these tests in other studies? The clamp technique is widely accepted as the reference standard for directly determining insulin sensitivity and peripheral glucose disposal or uptake in humans and offers, in the research setting, significant advantages over the commonly used technique for assessing insulin sensitivity, such as fasting measurements like HOMA-IR. However, it cannot be used in large epidemiological studies as it is indeed labor-intensive and expensive. Thus, surrogate indices of insulin resistance, such as HOMA-IR, are an acceptable alternative, but as shown in our study, it will not identify all patients with impaired glucose metabolism.

Lastly, was the amount of insulin chosen during the clamp effective in suppressing hepatic gluconeogenesis?—the answer is we do not know. We would have to have radiolabeled glucose tracer studies to study hepatic glucose production to see if the effect was indeed enough to suppress hepatic gluconeogenesis. But that does not affect our results and conclusions as we use the same amount of intravenous insulin in all three evaluations using standard dosing per square meter. So, even if hepatic gluconeogenesis was not suppressed, the observed values and changes are still valid and reliable.

Discussant

Dr. Nils Lambrecht (Los Angeles, CA): Do you have any data on gastric sleeve surgery because the physical removal of a large portion of the gastric oxyntic mucosa including most ghrelin containing endocrine cells may play a big role in changes in food intake and dietary behavior?

Closing Discussant

Dr. Guilherme M. Campos (San Francisco, CA): No, we do not have data on gastric sleeve.

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2009 SSAT POSTER PRESENTATION

Subclinical Intestinal Inflammation in Patients with Crohn's Disease Following Bowel Resection: A Smoldering Fire

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Abstract
Background/Aims Fecal lactoferrin is the direct expression of intestinal inflammation in Crohn's disease (CD). The aim of this study was to analyze the in vivo intimate correlation between intestinal and systemic inflammation in CD patients in clinical remission following bowel resection. The secondary end point was to evaluate the prognostic value of lactoferrin levels and serum cytokines in terms of need of surgery for recurrence in these patients.
Patients and Methods Fecal lactoferrin and serum cytokine (interleukin (IL)-1β, IL-6, IL-12, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β1) levels were assessed; hematological and biochemical investigations were carried out, and Crohn's Disease Activity Index was evaluated in the 36 patients who had undergone bowel resection. The prognostic value of lactoferrin and cytokine levels in terms of surgical recurrence was assessed by re-calling patients after 24 months from the enrolment in the study.
Results All patients, evaluated after a follow-up of 36±5 months, were in clinical remission. Fecal lactoferrin levels were found to be significantly correlated with IL-6 (R=0.431, p=0.025) and C-reactive protein (CRP; R=0.507, p=0.007), while no correlation was observed between lactoferrin and IL-1β, IL-12, TNF-α, or TGF-β1. Reoperation for anastomotic recurrence tended to occur significantly more frequently in patients with higher IL-6 (p=0.10).
Conclusions Subclinical intestinal inflammation, expressed by fecal lactoferrin, seems to keep the systemic inflammation alive in CD patients through the IL-6-CRP cascade. IL-6 seems to be predictive of the outcome of CD patients undergoing surgery.

Keywords Crohn's disease · Recurrence · Lactoferrin · Interleukin-6

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Introduction

Several studies on the differential diagnosis of intestinal inflammatory conditions have shown that fecal lactoferrin is a reliable marker of bowel inflammation having a sensitivity of 90% and a specificity of 98%.[1,2] According to a recent study, fecal lactoferrin is a more sensitive surrogate marker of endoscopic Crohn's disease (CD) activity than is Crohn's Disease activity index (CDAI) or C-reactive protein (CRP), and it is a useful tool in clinical practice to estimate disease activity and to monitor treatment response.[3]

The main component of the secondary granules of activated neutrophils that degranulate during inflammatory processes, lactoferrin has an important role in the innate immune system.[4,5] We found lactoferrin levels three times higher than normal[6] in a previous study on 63 CD patients in clinical remission who had undergone an ileocolonic resection more than 3 years earlier. Such elevated values seemed to suggest that the subclinical inflammation was still active in the remaining part of the bowel, probably affecting the systemic inflammatory status of those patients.

CD has traditionally been considered a typical T-helper-1 (Th1) condition mediated by interleukin (IL)-12 and tumor necrosis factor (TNF) axis.[7] Transforming growth factor (TGF)-β1 also appears to be important in controlling CD, and its dysregulation may be implicated in the disease's pathogenesis.[8–11] The upregulation of natural immunity could be quantified by the analysis of TNF-α, IL-1β, and IL-6, known to contribute to the intestinal lesions characteristic of CD.[11,12] Furthermore, in a previous study, we demonstrated that mucosal levels of IL-6 are predictors of recurrence and of need for surgery in perianal CD patients.[13]

The aim of the present study was to analyze the in vivo intimate correlation between intestinal inflammation (expressed by lactoferrin levels) and systemic inflammation mediated either by the innate immune system or T-cell-mediated immunity in CD patients who had undergone bowel resection and were in clinical remission. The secondary end point was to evaluate the prognostic value of lactoferrin levels and serum cytokines in terms of need of surgery for recurrence in these patients.

Methodology

Patients

Thirty-six consecutive patients who had undergone bowel resection for CD in our institute with a follow-up of *36± 4 months* were contacted from April 2006 to April 2007: 27 patients had undergone ileocolonic resection and nine partial or total colectomy. This time period was chosen since Rutgeerts et al. demonstrated that that the endoscopic recurrence rate 3 years after ileal resection for CD increases to 85%, and symptomatic recurrence occurred in 34%.[14] All gave their informed consent to the collection and evaluation of their clinical and laboratory data. Exclusion criteria were: a CDAI score above 150, active extra intestinal CD complications such as arthritis, perianal CD, uveitis, stomatitis and erythema nodosum, or recent infections. Patients who presented other bowel diseases were also excluded. Details concerning the patients' clinical and surgical follow-up were obtained and reviewed. All of the patients were examined; blood and fecal samples were collected, and their CDAI scores were calculated[15,16] on the basis of an interview focusing on their current health status, recurrent symptoms, reoperation, and therapy.

The prognostic value of lactoferrin and cytokine levels in terms of surgical recurrence was assessed by re-calling patients after 24 months from the enrolment in the study. All small procedures performed in outpatient setting and in local anesthesia (such as stenosis dilatations) were excluded.

Blood Tests

Blood samples were taken from fasting patients. Inflammatory activity was assessed on the basis of erythrocyte sedimentation rate (ESR), white blood cell count (WBC), platelet blood count (PLT), and CRP. ESR was measured by the Westergren method. CRP was detected by immunonephelometry (normal <6 mg/l; pathological >6 mg/l). Total protein and albumin were assessed using the biuret assay. WBC, PLT, and hemoglobin were obtained using a standard full blood cell count.

The serum levels of the following cytokines were determined: IL-1β, IL-6, IL-12, TNF-α, and TGF-β1. IL-1β, IL-6, and TNF-α were measured with immunometric assays (Immulite analyzer; Diagnostics Products Corporation DPC, Los Angeles, CA, USA). Serum levels of IL-12 and TGF-β1 were measured with enzyme-linked immunosorbent assay (ELISA) procedures (Bender MedSystems, Vienna, Austria). The sensitivity of the assays was 1.5 pg/ml (IL-1β), 2 pg/ml (IL-6), 12.6 pg/ml (IL-12), 1.7 pg/ml (TNF-α), and 0.1 ng/ml (TGF-β).

Fecal Tests

All the stool samples were immediately frozen at −20°C until analyzed by a quantitative lactoferrin ELISA (IBD-SCAN; TechLab, Blacksburg, VA, USA). The assay used a rabbit polyclonal antibody specific for human lactoferrin. Stool samples were serially diluted at 1:10 and lactoferrin levels, reported as microgram per gram of feces, were determined by measuring the optical density at a 450/630-

nm wavelength. Human lactoferrin standards from 6.25 to 100 μg/g were used to create a standard curve for linear regression. Fecal lactoferrin concentrations were calculated using the highest sample dilution within the linear portion of the standard curve (the normal value reported by the kit's producer <7 μg/g; pathological >7 ng/g).[2,4]

Statistical Analysis

Data were expressed as the median and interquartile range unless otherwise specified. As the level of statistical significance for two-tailed tests was set at 0.05, the 1-beta power was set at 0.20, and the expected correlation coefficient was set at 0.05, we calculated that the minimum sample size required was 26 patients. Spearman's rank correlation test was used to assess the correlation between lactoferrin and the inflammatory parameters. The Mann–Whitney *U* test was used for comparisons. Variables were considered statistically significant at the $p<0.05$ value. Surgical recurrence-free survival was calculated using actuarial (Kaplan–Meier) analysis with the time at risk ending at first reoperation or at last available follow-up, whichever came first. Data were considered as complete when patients had a surgical evidence of anastomotic recurrence

Results

Patient Characteristics

The patients' characteristics are summarized in Table 1. The male-to-female ratio in our group of patients was 24:12, and the median age at the time of surgery was 39 (24.5–46) years. Indications for resection had been: CD of the terminal ileum refractory to medical therapy or with "critical" stenosis (13 patients), recurrent CD of the terminal ileum (nine subjects), CD of the terminal ileum complicated by a fistula or an abscess (five patients), CD of the colon refractory to medical therapy or with "critical stenosis" (six patients), and late diagnosis of CD after restorative proctocolectomy for ulcerative colitis (three patients). Ileocolonic resection was carried out using the open technique in 20 patients and with laparoscopy assistance in seven patients. Fifteen patients underwent a

Table 1 Patients' Characteristics

	Median or frequency	Interquartile range or %
Demographic data and medical history		
Patients' number	36	
Male/female ratio	24/12	70/30
Age at diagnosis (years)	26	20–39
Age at operation (years)	39	24.5–46
Disease duration prior to operation (months)	79	12–132.8
Current medical status		
Current medical therapy (no/5ASA/AZA/5ASA+ budesonide)	10/22/2/2	
CDAI	72	57.4–112.3
Weight (kg)	65	53–70
Bowel movement /day	3	2–4.3
Hb (g/dl)	14.1	13.0–15.1
Ht (%)	43.6	39.7–44.9
WBC (/ml)	6,390	5,715–8,055
CRP (mg/l)	3.2	3.1–6.1
ESR (mm/h)	22.0	9.0–35.0
Albumin (g/l)	44.0	41.5– 46.0
Serum iron (μmol/l)	14.1	8.7–19.6
Ileocolonic resection		
Indication: recurrent CD/1st operation ratio	9/18	33/67
Indication: fistulizing CD/obstructing CD ratio	5/22	19/81
Access: laparoscopy/laparotomy	7/20	26/74
Partial or total colectomy		
Indication: recurrent CD/1st operation ratio	3/6	33/67
Access: laparoscopy/laparotomy	2/7	22/78

Table 2 Comparison between Patients Operated on for Colonic and Ileocolonic CD

	Colonic CD			Ileal CD			
	Pts	Median	IQR	Pts	Median	IQR	*p* level
Hb	9	135	129–141	26	144	131–151	0.364
Ht	6	42.35	39–45	26	43.65	39.9–44.9	0.664
WBC	9	6.18	4.65–8.04	26	6.505	5.83–8.07	0.385
PMN	6	4.23	2.74–4.36	26	4.095	3.53–5.22	0.412
CRP	9	3.3	3.17–7.73	27	3.17	3.13–5.57	0.179
ESR	8	27.5	9–37.5	26	21	9–33	0.583
Serum iron	9	19.3	15.4–20.7	26	13	7.4–18.1	0.151
Albumin	9	44	44–48	25	43	41.3–45.9	0.203
Lactoferrin	9	97	40–100	27	11.53	3.83–51	0.059
IL-1	9	5	5–5	27	5	5–5	
IL-6	9	2.2	2–5.6	27	3.7	2.7–7.1	0.082
TNF-α	9	9.5	4.8–13.4	26	7.5	4–11.3	0.342
TGF-β	6	104.5	98–158	26	117.5	101–135	0.828

stapled side-to-side ileocolic anastomosis, six a stapled end-to-side anastomosis, and six a hand-sewn side-to-side anastomosis. In the colonic CD group, two patients underwent laparoscopic sigmoid resection with a stapled end-to-end anastomosis; three patients underwent total proctocolectomy with end ileostomy, and four patients, including those three patients that later on had a diagnosis of CD, underwent restorative proctocolectomy with ileal J pouch and stapled ileoanal anastomosis. A comparison between patients that underwent operations for ileocolonic and colonic CD are shown in Table 2. All of the patients were in clinical remission and therefore did not have active intestinal disease at the time of this study. The median CDAI was 72 (57.4–112.3), and the median CRP was 3.17 mg/l (3.16–6.13). The different levels of lactoferrin and cytokines in patients with remission CD and in those with subactive CD (CDAI 130–150) were shown (Table 3).

Lactoferrin and Systemic Cytokines Network in CD Patients

The median lactoferrin level was 37.5 μg/g (4.01–75.91). Fecal lactoferrin levels correlated directly and significantly with CRP (R=0.41, p=0,013). The median serum levels of IL-6, IL-12, TNF-α, and TGF-β1 were 3.55 pg/ml (2.38–5.72), 76.0 pg/ml (62.0–232.0), 8.1 pg/ml (4.3–11.9), and 115 ng/ml (100.25–135.5), respectively. Serum IL-1β was found to be undosable. Serum IL-6 levels correlated significantly and directly with polymorphonuclear leukocyte (PMN; R=0.38, p=0.031) and WBC (R=0.52, p=0.001) and indirectly with serum iron (R=−0.46, p=0.005). Correlation analyses are shown in Table 4.

In the ileocolonic resection group, fecal lactoferrin levels correlated directly and significantly with serum IL-6 (R=0.431, p=0.025; Fig. 1) and CRP (R=0.507, p=0.007), and they were inversely correlated with albumin (R=−0.443, p=0.027) and serum iron (R=−0.546, p=0.004). Correlation analyses are shown in Table 4. Fecal lactoferrin levels were significantly higher in patients taking 5-aminosalicyclic acid (5-ASA) compared to those receiving 5-ASA and budesonide (p=0.037).

In the ileocolonic resection group, the median serum levels of IL-6, IL-12, TNF-α, and TGF-β1 were 3.7 pg/ml (2.7–7.1), 76.0 pg/ml (60.0–234.0), 7.5 pg/ml (4.0–11.3), and 117.5 ng/ml (101.0–135.0), respectively. Serum IL-1β was found to be undosable. Serum IL-6 levels were significantly higher in the female patients (p=0.038), in those operated on for the first time compared to patients with recurrences (p=0.009), and in the patients on 5-ASA compared to those receiving azathioprine (p=0.019).

Table 3 Comparison Between Patients with Active and Subactive CD

	CDAI<130			CDAI>130			
	Pts	Median	IQR	Pts	Median	IQR	*p* level
Lactoferrin	29	11.53	4–51	7	101	21–100	0.056
IL-6	29	3.7	2.4–5.6	7	3.4	2.1–13	0.548
TNF-α	28	7.5	4.1–11	7	10.2	4.3–120	0.309
TGF-β	26	115	101–137	6	111	86–122	0.411

Table 4 Correlation Between Fecal Lactoferrin and Serum Cytokines in Patients Operated on for Colonic and Ileocolonic CD and Between Fecal Lactoferrin and Inflammatory Parameters in Patients Operated on for Ileocolonic CD

		Pts	Spearman's ρ	p level
Correlation between fecal lactoferrin and serum cytokines in patients operated on for colonic and ileocolonic CD				
Lactoferrin	CRP	37	0.41	0.013
IL-6	Serum iron	36	−0.46	0.005
	PMN	33	0.38	0.031
	WBC	36	0.52	0.001
TGF-β	Serum iron	32	−0.36	0.043
	WBC	32	0.47	0.007
Correlations between fecal lactoferrin and inflammatory parameters in patients operated on for ileocolonic CD				
Lactoferrin	Age at the time of surgery	26	−0.054	0.793
	Age at diagnosis	23	−0.068	0.759
	CD duration	20	−0.106	0.656
	daily bowel movements	27	0.239	0.230
	Body weight	27	−0.207	0.301
	CDAI	26	0.103	0.615
	Hemoglobin	26	0.125	0.543
	Hematocrit	26	0.169	0.408
	WBC	26	0.203	0.321
	PMN	26	0.114	0.579
	CRP	27	0.507	0.007
	ESR	26	0.031	0.880
	Serum iron	26	−0.546	0.004
	Albuminemia	25	−0.443	0.027
	Serum IL-6	27	0.431	0.025
	Serum TNF-α	26	−0.244	0.231
	Serum TGF-β1	26	0.056	0.786
	Serum IL-12	14	−0.385	0.174

Prognostic Value in Terms of Surgical Recurrence

Six patients underwent a reoperation in the observation period of 24 months. Reoperation occurred significantly more frequently in patients with higher TNF-α (p=0.03)

In the ileocolonic resection group, three patients underwent reoperation for anastomotic recurrence, respectively, 1, 5, and 22 months from the enrolment in our study. All three patients had a stapled anastomosis in the first operation, and all of them had a re-ileocolonic resection with stapled anastomosis in the second operation. In one patient, the lactoferrin level was high (100.00), in the second moderately high (41.47), and in the third normal (3.47), but these data were not statistically significant. In this group, reoperation for anastomotic recurrence tended to occur significantly more frequently in patients with higher IL-6 (p=0.10).

In the colectomy group, two patients who had undergone restorative proctocolectomy with ileal J pouch and stapled ileoanal anastomosis with a late diagnosis of CD and one patient that had undergone total proctocolectomy with end ileostomy underwent a reoperation, respectively, 5, 7, and 12 months after enrolment. One of the first two patients underwent excision of the pouch and creation of end ileostomy for persistent perianal fistulas resistant to medical and surgical therapy, and the second patient underwent drainage of perianal abscesses due to fistula. The last patient underwent multiple stricture plasties for jejunal CD.

Discussion

Several studies on the differential diagnosis of intestinal inflammatory conditions have reported that fecal lactoferrin is a reliable marker of bowel inflammation, having a sensitivity of 90% and a specificity of 98%.[1,2,17] Released by activated PMN, its presence is proportional to the neutrophil flux to the gastrointestinal tract. Playing an important role in the innate immunity as a bactericidal agent,[4,5] lactoferrin is a 76-kDa iron-binding glycoprotein

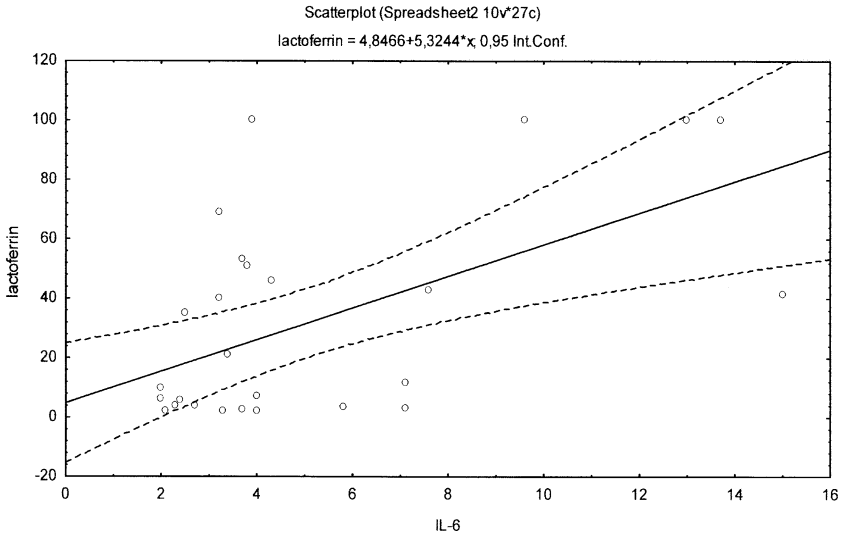

Figure 1 Fecal lactoferrin levels of patients that underwent ileocolonic resection significantly correlated with serum IL-6 (R=0.431, p=0.025).

that is the main component of the secondary granules of the neutrophils that degranulate during inflammatory processes. It is converted into lactoferricin by pepsin cleavage in the digestive tract.[5] A recent study demonstrated that fecal lactoferrin is a more sensitive marker of endoscopic CD activity than is CDAI or CRP and serves as a useful tool in clinical practice to estimate disease activity and to monitor treatment response.[3] It was also found to be a useful marker of mucosal healing after anti-TNF-α treatment by another study which reported significantly lower levels after therapy. Extensively assessed as a disease activity marker, it may be useful in detecting CD recurrence.[18] In the present study, lactoferrin levels were higher than normal in CD patients after ileocolonic resection, thus confirming that a subclinical inflammation was still present despite the patients' apparent good health that was confirmed by their low CDAI scores and undosable IL-1β levels.

Lactoferrin was significantly correlated with the IL-6-CRP axis in particular in the ileocolonic resection group, demonstrating that it is not only a marker of intestinal inflammation but also reflects the systemic inflammatory status of these patients. In our previous study,[6] a significant correlation between fecal lactoferrin and CRP was observed, but the correlation with IL-6 presently noted confirms that the axis was activated and suggests that it may have a primary role in CD inflammation. In fact, some studies had shown that high levels of serum IL-6 in CD patients who are in remission predict inflammatory activity, and this high expression also yields a prognostic value.[19–21] Nancey et al. demonstrated that plasma IL-6 concentrations correlated significantly with serum CRP in CD patients.[22] Moreover, the frequency of recurrence in patients with CD is correlated with the mean serum level of IL-6 during remission.[20] Even though a recent study has shown that lactoferrin can identify postoperative recurrence in CD in symptomatic postoperative patients,[23] the present data did not demonstrate that fecal lactoferrin is a marker of clinical recurrence. Probably, since patients were subclinical in this study, the data did not show the usefulness of lactoferrin levels in these patients.

In the present pilot study, the fact that serum IL-12 did not seem to correlate with fecal lactoferrin could be due to the lower number of patients who were analyzed or could confirm what we had already observed in perianal CD: there is no correlation between serum and mucosal IL-12 and the histological grade of disease activity.[13] Furthermore, at first, it seemed that IL-12 production by antigen-presenting cells stimulates Th1 responses in the bowel of CD patients,[11] but the recent identification of a new pathway may have implications on CD pathogenesis. This pathway is induced by IL-23, a heterodimeric cytokine that shares the p40 subunit with IL-12, but it couples with the p19 instead of the p35 subunit.[24] IL-23 drives a population of T lymphocytes that produce IL-17, IL-6, and TNF-α (Th17 cells). Recent publications have reported that the Th17 pathway may be of cardinal importance during chronic intestinal inflammation.[25]

Reoperation occurred significantly more frequently in patients with higher TNF-α.This association could be due to the reoperation for perianal fistulas of two patients who had had colectomy. In a previous study, TNF-α was significantly higher in the presence of perianal fistulas.[26] Fecal lactoferrin levels and serum TNF-α were not correlated in these patients. Some studies have shown high mucosal TNF-α secretion in CD even in the absence of patent inflammation, thus demonstrating a sustained local immune stimulation.[20,27] Higher serum levels were not, however, demonstrated.[20,28]

No correlations were observed between serum TGF-β1 and fecal lactoferrin levels. This was not surprising since no correlation was observed in our previous study between mucosal TGF-β1 levels and the histological grade of disease

activity.[9] Endogenous healing pathways mediated by TGF-β1 are probably unrelated to mucosal neutrophil infiltration and depend entirely on T cell regulatory activation.

The role of IL-6 as a systemic mediator for chronic inflammation was first confirmed in a previous study[26]. Then, we also demonstrated that mucosal levels of IL-6 are predictors of recurrence and of need for surgery in perianal CD patients.[13] In the ileocolonic resection group, three patients underwent a reoperation for anastomotic recurrence after enrolment in this study, and serum IL-6 levels tended to be significantly higher in these patients at enrolment. IL-6 seems to be predictive of the outcome of CD patients undergoing surgery as demonstrated in previous studies already mentioned above.[19,20] Furthermore, Yamamoto et al. demonstrated that IL-6 in the ileal mucosa during remission after resection for ileal or ileocecal CD is an independent significant predictor for future relapse.[29]

Conclusion

Subclinical intestinal inflammation in CD, expressed by fecal lactoferrin, seems to keep the systemic inflammation smoldering through the IL-6-CRP cascade. IL-6 levels seems to be predictive of the outcome of CD patients undergoing ileocolonic resection. TNF-α seems to be predictive of the outcome of CD patients undergoing bowel resection in particular in the presence of perianal fistulas. The role of IL-1β, IL-12, and TGF-β1 is probably more complex and less directly related to mucosal neutrophil infiltration.

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ORIGINAL ARTICLE

Surgical Treatment and Prognosis of Esophageal Cancer After Distal Gastrectomy

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Abstract
Background The purpose of the present study was to explore the clinicopathological characteristics and operative therapeutic efficacy of thoracic esophageal cancer after gastrectomy and compare with those without gastrectomy.
Methods From January 2000 to June 2007, 28 esophageal cancer patients with a history of distal gastrectomy underwent subtotal esophagectomy. Vascularized pedicle colonic conduit was most commonly used for esophageal substitution. Six hundred seventeen patients without a history of gastrectomy treated in the same period form the control group. After the operation, pathological characteristic, tumor staging, and survival statistics were analyzed.
Results Of those patients with esophageal cancer associated with gastric remnant, the majority were male. There was an average of 16.5 years for diagnosing esophageal cancer from the initial partial gastrectomy, 75% (21/28) of them were patients with Billroth I anastomosis. The proportion of lower-third tumors in patients after gastrectomy (12 of 28 patients, 43%) was significantly higher compared with that of the patients with intact stomachs (124 of 617 patients, 20%; P=0.004). After surgical treatment, the overall 1-, 3-, and 5-year survival rates of gastrectomized and nongastrectomized patients were 100%, 35.00%, and 23.33% versus 98.93%, 59.42%, and 30.85% in stages I–II and 80.00%, 30.00%, and 0% versus 98.59%, 62.03%, and 21.03% in stages III–IV. The log rank test of equality of survival distribution for the gastrectomized vs nongastrectomized patients was not significant in stages I–II (P=0.5692) but was significant in stages III–IV (P=0.0166).
Conclusions The patients with partial gastrectomy for more than 5 years, having upper gastrointestinal symptoms, should be considered having the risk of esophageal cancer associated with gastric remnant. For patients with a history of distal gastrectomy, a vascularized pedicle colonic conduit was most commonly used for esophageal substitution. Surgical efficacy was similar with the no-gastrectomy group in early stages I–II of esophageal cancer associated with gastric remnant but was lower compared with the no-gastrectomy group in stages III–IV. So, early diagnosis and an aggressive surgical approach may be crucial to achieve better outcomes for esophageal cancer patients with gastrectomy.

Keywords Esophageal cancer · Gastric remnant · Gastrectomy · Reoperation · Surgery

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Introduction

Patients with a history of distal gastrectomy are an interesting group to study because duodenogastroesophageal reflux is thought to be common. It has been postulated that the reflux of gastroduodenal contents may contribute to the pathogenesis of esophageal cancer.[1,2] Esophageal cancer after partial gastrectomy is the malignant changes of mucous membrane of esophagus, which occur in patients with distal gastrectomy for benign gastrointestinal diseases or early radical gastrectomy for gastric cancer for more than 5 years.[3,4] Although conservative treatment with alternative

routes of drug administration of upper gastrointestinal ulcer has replaced partial gastrectomy, the incidence of esophageal cancer after partial gastrectomy does not decrease for its long incubation period. In addition, at present, the intractable gastrorrhagia and pyloric obstruction caused by recurrence of gastric ulcer still have the indication of distal gastrectomy. The incidence of gastrointestinal ulcer is more common; therefore, some patients still need partial gastrectomy, which gives a chance of developing esophageal cancer after gastrectomy in the future. For extended lymph node metastases, infiltration of adjacent organs, and low rate of early diagnosis, most patients with a history of distal gastrectomy are diagnosed with advanced esophageal cancer; so, their removal rate and survival rate (SR) were lower than in patients without such a history.[5] The reported 5-year overall SR ranged from 7% to 20%, but it was also reported that early detection of esophageal cancer after gastrectomy would lead to long-term SR.[6] This study determines if there is any difference in the clinicopathological features and clinical outcome of esophageal cancer in patients with a history of distal gastrectomy compared with those without such a history.

Patients and Methods

Clinical Data

From January 2000 to June 2007, 28 esophageal cancer patients with a history of distal gastrectomy underwent subtotal esophagectomy at the Department of Cardiothoracic Surgery, Changzheng Hospital, Second Military Medical University. Their data were reviewed retrospectively. The Institutional Review Board of Changzheng Hospital, Second Military Medical University, Shanghai, China, also approved this study. Over the same time period, another 617 consecutive patients with primary thoracic esophageal cancer but without any history of gastrectomy also had an operation. The clinicopathological data of these patients were examined. Excluded from this study were patients who underwent gastrectomy for cancer of the stomach less than 5 years before the diagnosis of esophageal cancer. Patients without a history of gastrectomy treated in the same period form the control group.

Preoperative Examinations

Preoperative examinations included thoracic X-ray (plain film), pulmonary function, endoscopy, upper gastrointestinal barium meal examination, computed tomography (CT), and ultrasound gastroscopy. Exclusion of cerebral, abdominal, skeletal, and other distal metastases (M1) was accomplished with CT and emission CT. The patients were then selected.

Surgical Treatment

The choice of surgical approach depended on the location of the tumor, the extent of the tumor, and the cardiovascular assessment of the patient. All patients underwent radical en bloc esophagectomy with a two-field lymph node dissection in the upper abdomen and mediastinum. Transthoracic resection via a right-sided thoracotomy was preferred. In patients with compromised cardiopulmonary functions, a transhiatal esophagectomy was performed. Reconstruction of the nongastrectomized patients was carried out with a gastric tube through the posterior mediastinum route. When the stomach was used for reconstruction for middle- and lower-third tumors, the esophagogastrostomy was usually placed in the right thoracic cavity, and for some lower-third tumors, the esophagogastrostomy was placed in the left thoracic cavity. In those with tumors of the superior mediastinal segment, a three-phase esophagectomy was performed, with reconstruction to the neck. For patients with a history of distal gastrectomy, a colonic conduit was most commonly used for esophageal substitution; the transverse colon and descending colon were preferred, based on the middle or left colonic vessels. The vascularized pedicle colon was raised to left neck behind the sternum for end-to-end or end-to-side anastomosis with the esophagus under cervical incision, and the inferior colon underwent end-to-side anastomosis with residual stomach or jejunum. The reconstruction of colon conduits was mostly in isoperistaltic orientation.

Statistical Analysis

Continuous variables are expressed as mean±SD and nonparametric data as median (range). Statistical differences between groups were determined by analysis of variance, Mann–Whitney test, χ^2 test, and Fisher exact test, where appropriate. Survival was calculated with the Kaplan–Meier method, and differences were compared with the log rank test. Statistical Program for Social Sciences V12.0 software was applied in statistical analysis; SR was calculated with survival curves; $P<0.05$ was defined as statistical significance.

Patients were followed up monthly for the first year and every 3 months thereafter. Follow-up was complete up to Dec 2008. The data of clinical pathological characteristics, depth of invasion, lymph node metastasis, distant metastasis, survival time, recurrence, etc. were collected.

Results

Of the 28 gastrectomized patients, there were 23 men and five women with an average age of 59.6 years. Twenty-one

patients underwent a Billroth I and seven patients a Billroth II anastomosis, and distal gastrectomy was performed on all patients. The mean interval between previous gastrectomy and diagnosis of esophageal cancer was 16.5 years (range 5~32 years). The indications for previous gastrectomy were gastroduodenal ulcer in 20 (gastric ulcer in ten, duodenal ulcer in seven, and complex gastroduodenal ulcer in three) and adenocarcinoma of the stomach in eight patients. In the 1~15 months preceding diagnosis (average 8.2 months), all patients had different levels of clinical symptoms. Choking when eating and abdominal satiety were the most common. The other symptoms included abdominal pain, nausea, vomiting, melena, belching, poor appetite, weight loss, and anemia. All cases were confirmed consistently with the pathological changes by gastroscopic biopsy. All patients underwent two to four courses of chemotherapy after surgery; the patients with N1, T3, or more underwent radiation therapy first. Radical surgery was performed.

After operation, TNM staging was done according to the International Union Against Cancer classification (sixth edition).[7] Postoperative pathological information included distribution of the tumor, the extent of tumor invasion, lymph node metastases, and distant metastasis, as shown in Table 1. The proportion of lower-third tumors in patients after gastrectomy (12 of 28 patients, 43%) was significantly higher compared with that of the patients with intact stomachs (124 of 617 patients, 20%; $P=0.004$). There was no surgery-related mortality. The histological subtype for tumors was squamous cell in all cases of the gastrectomized and the nongastrectomized patients. None of the patients manifested adenocarcinoma. In the pathological staging, the gastrectomized patients showed a tendency to prophase cancers of a less advanced pathological stage. That is to say, there were more stage I and II cases and fewer stage III and IV cases ($P=0.034$) compared to the nongastrectomized patients. Although superficial cancer (T1) and node-negative observations were slightly more frequent for the gastrectomized patients, there was no difference in the depth of tumor invasion ($P=0.124$) and frequency of lymph node metastasis ($P=0.397$) compared with those of non-gastrectomized patients.

Within 30 days postoperatively, complications occurred in 11 (39.3%) of 28 gastrectomized patients, including cervical esophagocolonic anastomotic leaks in three cases (10.7%), pulmonary infection in two (7.1%), bleeding in one (3.6%), vocal cord paralysis in two (7.1%), chylothorax in one (3.6%), multiple-organ dysfunction syndrome (MODS) in two (7.1%), all of whom completely recovered with medical treatment except for one death (3.6%) occurring due to MODS. The MODS patient died 42 days

Table 1 Clinical Pathological Characteristics of Patients with Esophageal Cancer with and Without Gastrectomy

Characteristics	Gastrectomized pts ($n=28$)	Nongastrectomized pts ($n=617$)	P value
Age	54.8±6.5	58.5±8.5	0.020
Sex			
Male	23 (82%)	523 (85%)	0.707
Female	5 (18%)	94 (15%)	
Tumor location			
Cervical	0	54 (9%)	0.102
Upper thoracic	2 (7%)	78 (13%)	0.388
Middle thoracic	14 (50%)	361 (58%)	0.372
Lower thoracic	12 (43%)	124 (20%)	0.004
Pathological changes	Squamous cell carcinoma	Squamous cell carcinoma	
Depth of invasion			
T1	7 (25%)	89 (14%)	0.124
T2	15 (54%)	316 (51%)	0.807
T3	5 (18%)	127 (21%)	0.727
T4	1 (3%)	85 (14%)	0.120
Lymph node metastasis			
N0	24 (86%)	488 (79%)	
N1	4 (14%)	129 (21%)	0.397
Disease stage			
I	8 (29%)	96 (16%)	
II	15 (53%)	289 (47%)	
III	5 (18%)	193 (31%)	0.034
IV	0	39 (6%)	

after operation. There was an important difference in the postoperative complications between gastrectomized and nongastrectomized patients, especially in MODS (Table 2). The postoperative hospital stay was significantly longer in gastrectomized patients than in nongastrectomized ones (median 46 days vs. 22 days, $P<0.001$). Anastomotic leakage was the highest risk factor for prolonging the hospital stay of the gastrectomized patients, with the median postoperative hospital stay of three patients with leakage being 88 days.

The whole group was followed up. The follow-up results demonstrated that the overall 1-, 3-, and 5-year SRs of gastrectomized and nongastrectomized patients were 100%, 35.00%, and 23.33% versus 98.93%, 59.42%, and 30.85% in stages I–II and were 80.00%, 30.00%, and 0% versus 98.59%, 62.03%, and 21.03% in stages III–IV. The median survival time of gastrectomized and nongastrectomized patients was 28 versus 43 months in stages I–II and 25 versus 41 months in stages III–IV. The survival curves are shown in Fig. 1. The log rank test of equality of survival distribution for the gastrectomized vs nongastrectomized patients was not significant in stages I–II ($P=0.5692$) but was significant in stages III–IV ($P=0.0166$). The log rank test of equality of survival distribution was not significant for the gastrectomized patients in stages I–II vs stages III–IV ($P=0.1597$) but was significant for the nongastrectomized patients in stages I–II vs stages III–IV ($P=0.0404$).

Discussion

Carcinogenetic Effects on Esophageal Cancer Patients After Distal Gastrectomy

The association between previous gastrectomy and the subsequent development of esophageal cancer remains controversial. In a recent study, 3~9% patients with esophageal cancer had a history of gastrectomy, and in more than half the patients the tumors were located in the lower or middle esophagus.[2,8] The incidence of previous gastrectomy among patients with esophageal cancer in the present series is 4.3%, comparable to that reported in the literature. These workers pointed to the possible association between gastroesophageal reflux and development of cancer in the esophagus. In the present study, for patients who had undergone distal gastrectomy, the subsequent esophageal cancers seemed to have a propensity to develop in the distal esophagus compared with those patients who did not undergo gastrectomy. The type of reconstructive method was largely responsible for the observed difference, with distal tumors more likely in the patients who underwent Billroth I rather than Billroth II gastrectomy.[9] Esophageal mucosal changes resulting from persistent regurgitation of gastric and duodenal contents, including bile, into the lower esophagus may occur at higher frequency in patients with partial gastrectomy or gastroenterostomy than in patients with intact stomach. In Chinese populations, patients with adenocarcinoma of the esophagus are rare (less than 1%).[10] In this study, the histological subtype for tumors was squamous cell cancer in all cases—gastrectomized and nongastrectomized. None of the patients had adenocarcinoma. There was no observed increase in adenocarcinomas. There is no apparent explanation. Animal studies have shown that gastroesophageal reflux can increase the incidence of esophageal squamous cell carcinoma, even without the administration of any carcinogen.[11,12] Considering the high proportion of patients with esophageal cancer in the lower thoracic esophagus who had undergone gastrectomy and the presence of esophagitis in patients with lower thoracic esophageal cancer who had undergone gastrectomy, esophagitis may be associated with the development of esophageal cancer.[13] In histologic investigation of the resected specimens, we noted cases of lower esophageal cancer with previous gastrectomy, with evidence of esophagitis. Gastric remnant has been recognized as a precancerous condition. After partial gastrectomy, esophagus of patients with gastrointestinal diseases was prone to canceration.[3,14] Therefore, patients with partial gastrectomy ought to have a long-term follow-up so as to facilitate early diagnosis and treatment.[3,6]

Table 2 Postoperative Complications of Radical Operation for Esophageal Cancer Patients with and Without Gastrectomy

Postoperative complications	Gastrectomized pts ($n=28$)	Nongastrectomized pts ($n=617$)	P value
Anastomotic leak	3 (10.7%)	27 (4.4%)	0.119
Infection	2 (7.1%)	30 (4.9%)	0.587
Bleeding	1 (3.6%)	19 (3.1%)	0.883
Vocal cord paralysis	2 (7.1%)	36 (5.8 %)	0.774
Chylothorax	1 (3.6%)	11 (1.8%)	0.493
Failure of organ function	2 (7.1%)	8 (1.3%)	0.014
Postoperative hospital stay median (days)	46	22	<0.01

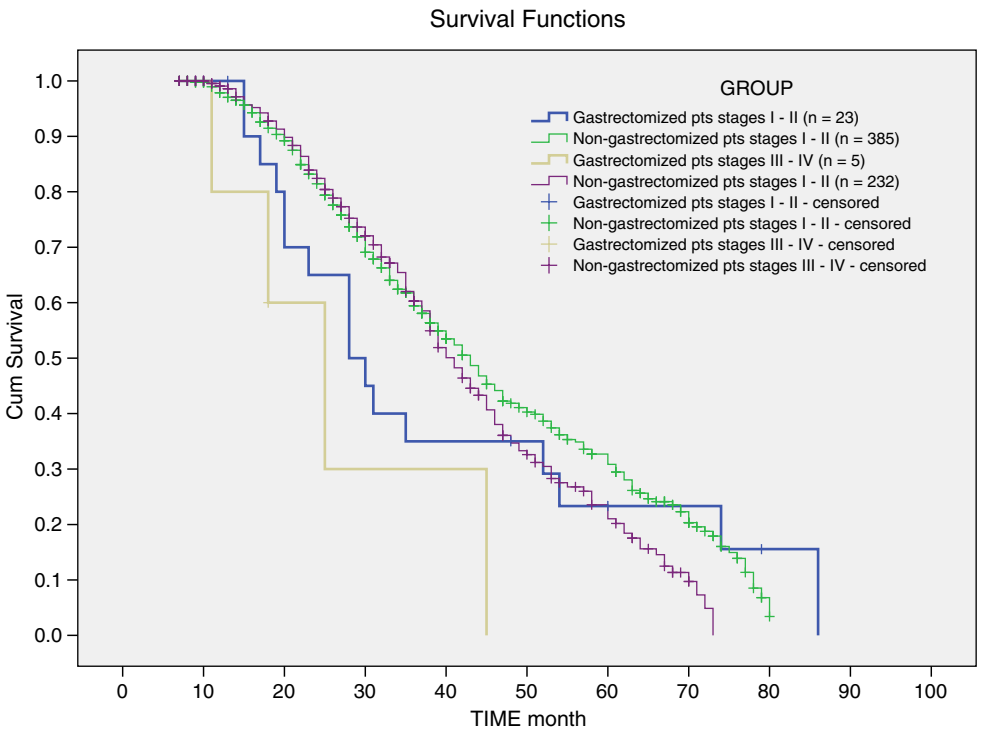

Figure 1 Kaplan–Meier survival curves in gastrectomized and nongastrectomized patients after surgical resection.

Diagnosis of Esophageal Cancer Associated with Gastric Remnant

After partial gastrectomy, patients paid little attention to symptoms of digestive tract, making early diagnosis of esophageal cancer difficult. In the literature, the average duration of symptoms was 9.5 months before the diagnosis of esophageal cancer after partial gastrectomy[15]; in this study, it was 8.2 months. Early esophageal cancer associated with gastric remnant lacks any specific clinical manifestation and is thus easily misdiagnosed as postgastrectomy syndrome or the recurrence of gastric ulcer, anastomosis, etc. According to the literatures, the incidence of esophageal cancer associated with gastric remnant has the following features: it is discovered more than 5 years after the initial operation; it frequently occurs after Billroth I anastomosis; it is more common in male patients than in female.[1,2] The diagnosis of esophageal cancer associated with gastric remnant depends mainly on barium examination and gastroscopy. However, due to anatomical changes of gastric remnant, using barium examination to diagnose early esophageal cancer associated with gastric remnant is difficult. Fiber endoscopy and biopsy are the primary means of diagnosis for esophageal cancer associated with gastric remnant, with a diagnostic rate of over 90%. However, the anatomical changes due to the gastrectomy (including swelling and reactive changes of the anastomotic stoma, reflux esophagitis, stomach volume reduction, etc.) are easily confused with esophageal cancer and swelling lesions.[8,15] In recent years, exploration of submucosal invasion depth through ultrasound endoscopy has also been used to further assist diagnosis.

Surgical efficacy on esophageal cancer patients with gastrectomy was compared with nongastrectomized patients.

The lifetime limits of esophageal cancer patients who had undergone distal gastrectomy are not much different from those of esophageal cancer patients who did not undergo gastrectomy. Therefore, we should take a positive attitude towards esophageal cancer patients who have undergone distal gastrectomy. Once diagnosed, if the general conditions permit, we should seek surgical treatment as soon as possible.[3] A history of abdominal surgery should not be considered a contraindication to surgery, although esophageal cancer associated with gastric remnants belong to an advanced stage, with a removal rate of 30–50%.[3,5] In our study, one of the strictly selected 28 cases was resected, which related to the case selection. More importantly, with the continuous improvement of auxiliary examination techniques—particularly with the universal application of fiber endoscopy—the early diagnosis of esophageal cancers associated with gastric remnants has become possible, thus increasing the removal rate. Even when faced with advanced cases, we should be active in exploration and employ surgical resection to prolong the survival time as far as possible. In recent years, thanks to developments in endoscopy and other surgical techniques—in particular, with the extensive application of stapler and anastomat—the removal rate of esophageal cancer associated with gastric remnant has seen a substantial increase.

It has been reported that the prognosis of early esophageal cancer associated with gastric remnant was better than primary esophageal cancer at the same stage, while esophageal cancer patients who did not undergo gastrectomy in progression had the same poor prognosis as the esophageal cancer patients with a history of distal gastrectomy in advanced stage. It is thought that the abruptly terminated and obstructed lymphatic flow at the anastomotic line and scar tissue at the previous surgical resection site may possibly result in low incidence of lymphatic spread and improved prognosis when the cancer is treated at an early stage, which permitted a better prognosis.[16] In our study, we also found that the overall 5-year SR of gastrectomized patients reached 19.68%. The survival distribution for the gastrectomized and nongastrectomized patients was not significant in stages I–II, but was significant in stages III–IV (P=0.0166). So surgical efficacy was similar with the no-gastrectomy group in early stages I–II of esophageal cancer associated with gastric remnant but was lower compared with no-gastrectomy group in stages III–IV. The power analysis shows that much higher than 28 patients were necessary in the study to permit reliable estimate differences in long-term outcomes between esophageal cancer patients with and without gastrectomy groups. Analysis of the entire clinical data in strict accordance with the statistical methods might be difficult, so clinical data and not the most rigorous statistics could have a certain degree of clinical significance.

It is most appropriate to apply the colon to replace the esophagus in esophageal cancer associated with gastric remnant. We believe that the transplanted colon can be anastomosed with the neck behind the sternum, which can prevent the transplanted intestine swimming in the chest; even if anastomotic fistula occur, intestinal contents will not easily leak to the chest. Whether after Billroth I or II anastomosis, it is easy to educe the colon. During the operation, paying special attention to preventing the injury to the pedicled vessel and colon vascular network can ensure the survival and anastomotic stoma healing of transplanted intestine.[4]

In summary, early diagnosis and an aggressive surgical approach may be crucial to achieve better outcomes for esophageal cancer patients with gastrectomy. Enhancing the awareness of esophageal cancer associated with gastric remnant and following up gastrectomy patients with regular endoscopy for more than 5 years, as well as drawing the materials from suspicious lesions at every opportunity, can all improve early diagnosis and treatment, removal rates, and 5-year SRs for patients with esophageal cancer associated with gastric remnant.

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ORIGINAL ARTICLE

The Size of the Esophageal Hiatus in Gastroesophageal Reflux Pathophysiology: Outcome of Intraoperative Measurements

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Abstract
Objective The aim of the study was to investigate the impact of the size of the esophageal hiatus on lower esophageal sphincter pressure (LESP) and acid reflux.
Methods Patients with gastroesophageal reflux disease who underwent Nissen fundoplication in 2006–2008 were included. All underwent esophageal manometry and 22 had 24-h pH monitoring. The area of the esophageal hiatus was calculated from a photograph shot during surgery. A hiatal index was calculated via division of hiatal area with body mass index (BMI). Correlation and logistic regression analysis were performed.
Results Twenty-eight patients (average age 44, 14 males) were enrolled. The mean BMI, LESP, DeMeester score, hiatal area, and hiatal index were 27±3.9 kg/m^2, 11.7±6.6 mmHg, 43±34, 3.83±1.24 cm^2, and 0.143±0.048, respectively. There was a significant negative correlation between hiatal area, hiatal index and LESP (−0.513, p=0.005, r=−0.439, p=0.019 respectively). Additionally there was a negative correlation between hiatal area and total LES length (r=−0.508, p=0.013) and a significant positive correlation between hiatal area, hiatal index, and DeMeester scores (0.452, p=0.035, 0.537, p=0.01, respectively). Height and hiatal area were significant factors in multiple linear regression.
Conclusions The size of the esophageal hiatus significantly affects LESP and acid reflux, and hiatal index is a new value, which appears to reflect the amount of acid reflux. Total LES length is also shortened in patients with a large hiatus.

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Keywords Gastroesophageal reflux disease · Hiatal hernia · Esophageal hiatus · Intraoperative measurement

Introduction

Existence of a hiatal hernia is one of the most important factors in the pathophysiology of gastroesophageal reflux disease (GERD).[1] Presence of hiatal hernia with low lower esophageal sphincter (LES) pressure and resultant esophagitis is commonly associated with GERD.[1–3]

Esophageal hiatus is mainly formed by the right crus of the diaphragm and the crural diaphragm arises from the dorsal mesentery of the esophagus.[4] It is innervated separately from the costal part of the diaphragm and acts in harmony with the LES. The crural diaphragm is in an oblique plane, which results in uneven pressure distribution around the esophagus with mainly anterior and lateral compression.[4] This anatomic association is disrupted in the presence of GERD and hiatal

hernia, and in a study using high-resolution manometry, a larger separation of LES and crural diaphragm was detected during inspiration in patients with GERD which results in less inspiratory pressure augmentation of the LES.[5]

The enlargement of the esophageal hiatus results in intrathoracic migration of the abdominal esophagus and LES, which causes induced or free reflux.[3] As an initial observation, endoscopic assessment of gastroesophageal flap valve, which is an indirect assessment of the size of the esophageal hiatus, showed a strong correlation with the presence of GERD.[6] A recent study that evaluated the cardia circumference by endoscopic measurement showed a direct positive correlation between cardia circumference and the presence and grade of GERD and Barrett's esophagus.[7] Another study showed that dilatation of the gastroesophageal junction or cardia is a progressive phenomenon and results in disruption of the clasp and sling fibers that form the LES.[8]

Surgical exploration during antireflux surgery allows direct visualization of the esophageal hiatus (Fig. 1). Surgical findings vary from a simple enlargement of the esophageal hiatus with minimal herniation to a 4–5-cm-large hiatal hernia and severe periesophageal fibrosis.[9]

Almost all of the criteria used for the diagnosis of GERD rely on intraluminal findings. Little is known about the size of the esophageal hiatus in GERD patients and its effects on LES pressure and other GERD parameters. This prospective study analyzes the impact of the size of the esophageal hiatus on LES pressure and acid reflux and discusses its potential as a clinical evaluation criterion.

Patients and Methods

Patients who have undergone laparoscopic Nissen fundoplication in our department during 2006–2009 were included in the study. Routine preoperative workup included upper gastrointestinal endoscopy, esophageal manometry, and 24-h pH monitoring. Demographic data, body mass index (BMI), and duration of symptoms were also recorded. Surgical treatment was offered to the patients with the conjoint decision of the surgeon (HFB) and gastroenterologists (OUB, AG) following assessment of the symptoms and preoperative findings. The ethics committee of the Marmara University Faculty of Medicine approved our study, and informed consent was obtained from all patients.

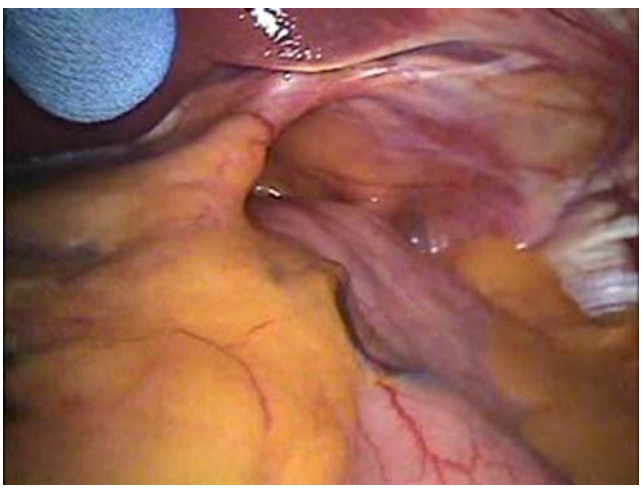

Figure 1 Laparoscopic view of a large esophageal hiatus in a 65-year-old female patient with significant reflux and periesophageal fibrosis.

Measurement of Esophageal Hiatus

Laparoscopic Nissen fundoplication was performed in all patients through five-port incisions using 30° scope (Fig. 2). A photograph of the esophageal hiatus was either shot during surgery or captured from video recording of the operation. A surgical instrument of known size was used as a scale. The photograph was always from the right side of the esophageal hiatus following hiatal dissection and from the same angle to prevent any calculation bias. The circumferential margin of the esophageal hiatus (square centimeter) was drawn by the surgeon using a graphics program. The depiction starts from the posterior crural triangle, and the edges of the crural fibers were outlined as the esophageal hiatus. The surface area was blindly calculated by one of the authors (BE) using a graphics program. The hiatal area was divided by BMI to calculate an individualized value, which was named as hiatal index.

Statistics

Pearson correlation analysis, independent samples Student's *t* test, and multiple stepwise linear regressions were performed. Age, height, weight, hiatal area and hiatal index, and total and abdominal LES lengths were analyzed for their role on LES pressure and 24-h pH scores. $p<0.05$ values were considered statistically significant. All values are expressed as arithmetic mean and standard deviation. The data were analyzed using SPSS (15.0) software.

Results

Twenty-eight patients were included in the study. All underwent esophageal manometry and endoscopy. Twenty-four-hour pH monitoring was performed in 22 patients. It could not be performed in six patients due to patient incompliance. The average age was 43.6±11.8 years (14 males).

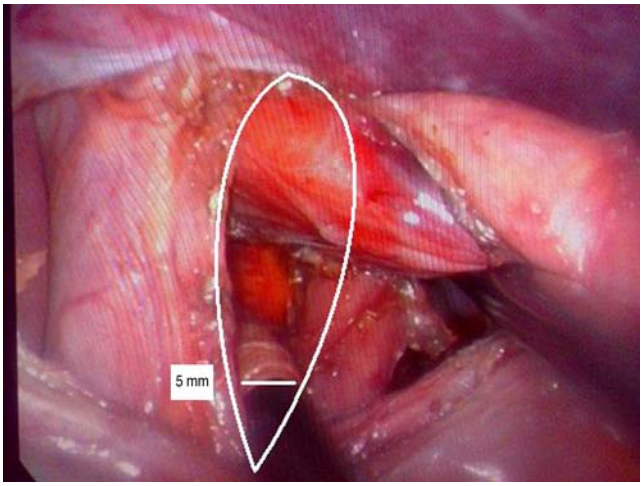

Figure 2 Intraoperative photograph of the esophageal hiatus following dissection. The instrument used for surgical manipulation has been used as the scale for calculation of the outlined area.

Endoscopy, Esophageal Manometry, and 24-h pH Monitoring Findings

Twenty-five patients had endoscopic findings of different sizes of hiatal hernia. Fifteen patients had various grades of esophagitis; six patients had antral gastritis or pangastritis. Mean LES pressure was 11.7±6.6 mmHg. LES pressure was less than 10 mmHg in 16 patients and less than 7 mmHg in seven patients. Average DeMeester score was 43.3±33.8 (9.5–111.4). Five patients had scores over 85. Average total and abdominal LES lengths were 2.87± 0.83 cm (1.5–4.5) and 2±0.98 cm (0–3.5).

Hiatal Area and Hiatal Index

Average hiatal area was 3.83±1.24 cm^2 (1.94–6.91), and average BMI was 27.2±3.9 kg/m^2 (20.6–35.9). BMI was over 30 in six patients. Average hiatal index was 0.143± 0.048.

Effects of Hiatal Area and Hiatal Index on LESP and 24-h pH Scores

In our study group, we had a group of patients with normal LES pressure (n=7) and normal pH values (n=4). These patients were operated on mainly due to the clinical symptomatology. Patients with normal LES pressures (n=7) were compared with the remaining patients (n=21), and there was a significant difference of hiatal index (0.114±0.026 vs 0.152±0.05, p=0.04). The difference of hiatal area was very close to significance (2.87±0.51 vs 4.15±1.26, p=0.07).

This difference was more profound when patients with abnormal pH values (n=18) were compared with patients with normal pH scores (n=4). We found significant difference of hiatal area (2.39±0.22 vs 4.04±1.05, p<0.001) and hiatal index (0.089±0.015 vs 0.153±0.042, p<0.001) between the two groups.

Correlations

The correlations are listed in Table 1. There was a significant negative relationship between hiatal area and LES pressure (r=−0.513, p=0.005; Fig. 3). This relationship was still significant with hiatal index (r=−0.439, p=0.019; Fig. 4).

There was no correlation between the duration of symptoms and LES pressure (r=−0.339, p=0.26). There was also a significant positive correlation between hiatal area and 24-h pH monitoring scores (r=0.452, p=0.035; Fig. 5). This relationship was even more significant with hiatal index (r=0.537, p=0.01; Fig. 6).

LES pressures and 24-h pH monitoring scores did not have any correlation (r=−0.317, p=0.15). There was no correlation between BMI and hiatal area and hiatal index (r=0.083, p=0.68; r=−0.323, p=0.09, respectively). There was also a significant negative correlation between total LES length and hiatal area (r=−0.508, p=0.013) and hiatal index (r=−0.435, p=0.038), and as expected, there was also a very strong positive correlation between LES pressure and total LES length (r=0.649, p=0.001).

Multiple Linear Regression Analysis

Among LES pressure, 24-h pH scores, age, hiatal area, hiatal index, weight, height, and total LES length, only height was found to be a significant determinant of 24-h pH scores (p=0.002), and its overall contribution to the pH scores was found to be 37% (adjusted R square value 0.37). In both models, hiatal area was the only factor that had a significant impact on LES pressure (p=0.008) and contributed an overall 27% to LES pressure (adjusted R square value 0.27). However, when total LES length was added to

Table 1 Results of Pearson Correlation Analysis

Criteria	Correlation coefficient (r)		Significance (p)	
	LESP	pH score	LESP	pH score
Age	−0.181	0.037	0.36	0.87
Weight	−0.330	0.258	0.09	0.25
Height	−0.250	0.630	0.20	0.002
Body mass index	−0.172	−0.233	0.38	0.30
Hiatal area	−0.513	0.452	0.005	0.035
Hiatal index	−0.439	0.537	0.02	0.01
LES length	0.649	−0.107	0.001	0.66

LES lower esophageal sphincter

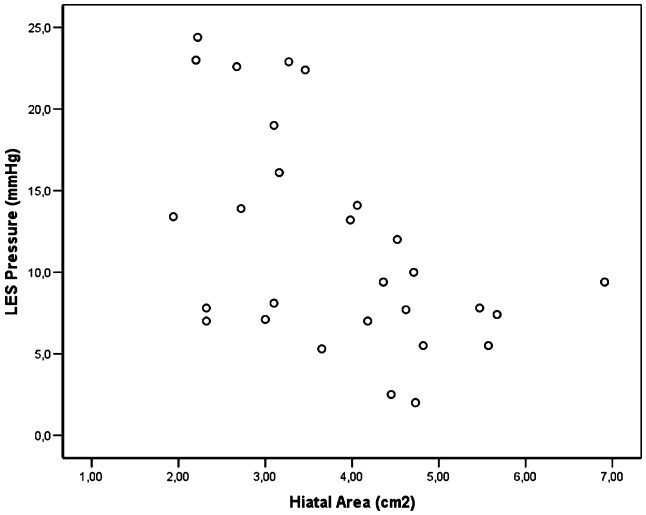

Figure 3 The scatter plot of hiatal area and lower esophageal sphincter (*LES*) pressure showing a very significant negative correlation ($r=-0.513$, $p=0.005$).

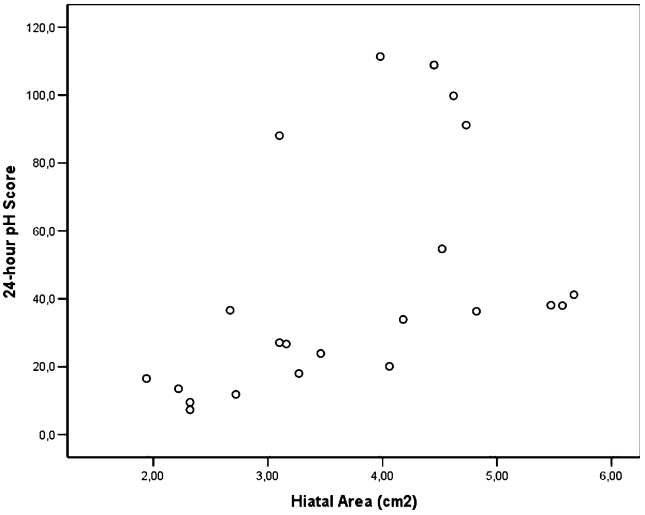

Figure 5 The scatter plot of hiatal area and 24-h pH scores showing a significant positive correlation ($r=0.452$, $p=0.035$).

the model, hiatal area and total LES length both became significant factors affecting LES pressure ($p=0.04$, $p=0.02$ respectively).

Discussion

The pathophysiology of GERD is very complex and the extent of contribution of different anatomic structures is unknown. However, most of the recent data show that the anatomic configuration of the esophageal hiatus of the diaphragm has a critical role in the pathophysiology of GERD.[1,3,10–12]

Three major mechanisms, namely transient LES relaxations, strain-induced reflux in the setting of low or normal LES pressure, and free reflux during periods of low LES pressure or deglutitive relaxation, have been described in the pathophysiology of reflux.[11] The latter two mechanisms are frequent in patients with hiatus hernia.[3] It has been shown that small increases in intra-abdominal pressure easily overcome the low resting LES pressure leading to reflux in patients with hiatal hernia.[10,11] Additionally, the esophagogastric junction opens wider in these patients leading to increased refluxate volume.[3] This has been clinically confirmed where more reflux occurred in patients with hiatal hernia, compared with GERD patients without

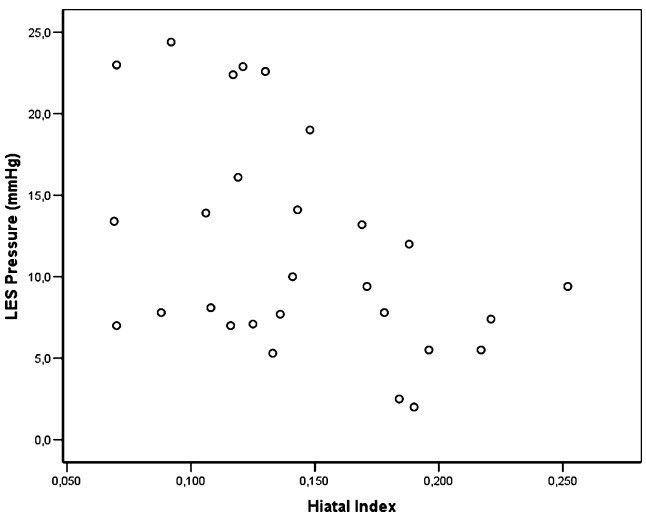

Figure 4 The scatter plot of hiatal index and lower esophageal sphincter (*LES*) pressure showing a significant negative correlation ($r=-0.439$, $p=0.019$).

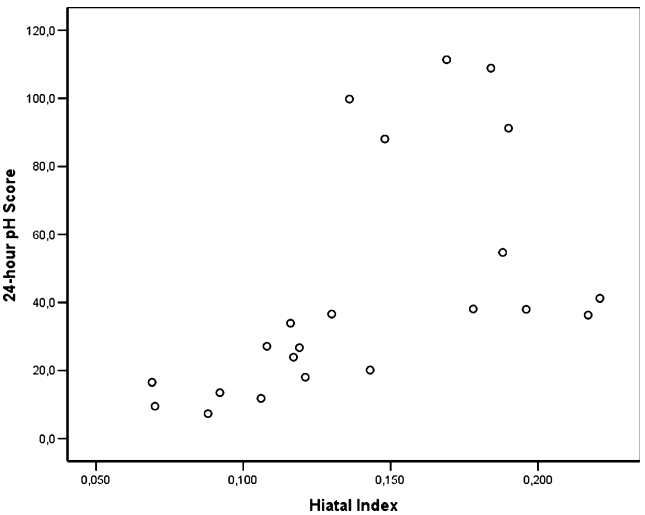

Figure 6 The scatter plot of hiatal index and 24-h pH scores showing a very significant positive correlation ($r=0.537$, $p=0.01$).

hiatal hernia and normal subjects.[11] The lack of crural support for the LES leads to reflux in any occasion with low LES pressure or swallow-induced relaxation. In patients with hiatal hernia during straining, gastric distention, deep inspiration, and swallow-induced LES relaxation, LES malfunctions lead to more severe reflux than other GERD patients.[3,12,13] It has been observed that increased refluxate volume leads to erosive esophagitis and different grades of Barrett's esophagus.[2,14,15,16] Hiatal hernia is also associated with shortened total and abdominal LES length, and presence of a hiatal hernia and a defective LES are important predictors of abnormal esophageal acid exposure.[17]

Our results also show that a large esophageal hiatus leads to diminished LES pressure, acid reflux, and a shortened total LES length. Also, a low LES pressure and decreased esophageal motility are usually associated with a large esophageal hiatus. In our study, we had five patients with a low LES pressure (<10 mmHg) and decreased esophageal motility. In those patients, the average hiatal area was 5.1 cm^2 and HI was 0.189. These values were significantly higher than other patients in the study (p=0.02, both) indicating a more severe GERD.

During expiration, the hiatus narrows and double pressure peak can be observed with manometry.[1,18] Even though LES pressure may be within normal values during manometry, any change in intra-abdominal pressure during daily activities can induce reflux when there is no crural support.[1,19]

In our study, the height of the patient had a strong correlation with pH score, and it was also found to be important in linear regression analysis. This finding may be coincidental, as we did not find the same relationship with weight or BMI. In patients with a 24-h pH scores over 80 (five patients on the top of Figs. 5 and 6), the only significant difference with the remaining patients was height (1.79±0.1 m vs 1.66±0.09 m, p=0.01). We believe that this may be due to the changes in the anatomic configuration of the diaphragm in tall patients leading to easier and more frequent increases in intra-abdominal pressure.

Anatomic investigations of the esophageal hiatus showed that the diaphragmatic crura of the neonates are hypertrophied, and in adults, the crura become thinner and smaller.[20] During this transition, factors (straining, weight lifting, pregnancy), which increase intra-abdominal pressure in a thin and tall patient, may lead to permanent hiatal enlargement. Also, recent research showed that during normal inspiration, the hiatus enlarges; however, with deep inspiration, it narrows.[10] In the situation of a large hiatus with thin crura, this diaphragmatic support is lacking.

We do not have adequate information about the size of esophageal hiatus in normal people and GERD patients. In a study focusing on gastroesophageal junction anatomy and its clinical consequences, a detailed intraoperative measurement of extraluminal cardia perimeter was performed. The average cardia perimeter was 6.3 cm in control subjects, 8.9 cm in GERD patients, and 13.8 cm in patients with Barrett's esophagus.[8] Similar findings were observed with endoscopic assessment of the circumference of the cardia, where the length of the circumference showed a direct correlation with esophagitis and Barrett's esophagus.[7] Granderath et al. performed several studies to tailor the hiatal closure according to the size of the esophageal hiatus in order to improve postoperative dysphagia.[21,22] In their study of 55 patients, mean size of the esophageal hiatus was 5.09 cm^2.[21] They recommended reinforced hiatal closure in patients with hiatal sizes more than 5 cm^2. Intraoperative measurement of the esophageal hiatus was also recommended by Reardon for the same purpose.[23] Currently, a study is underway which aims to calibrate the esophageal hiatus with an inflatable silicon balloon pre- and postcrural repair to prevent postoperative dysphagia and long-term intrathoracic migration.[24] The expected diameter of an esophageal hiatus postcrural repair is 18–20 mm in these studies, which results in an estimated hiatal surface area of 2.5–3 cm^2.[23,24]

In our study, BMI had no correlation with hiatal area and hiatal index, which are unexpected findings. This is may be due to our patient group who had patients with relatively normal BMIs and severe GERD. From these findings, we think that it should be very important to have 5-cm^2 hiatus in a patient with a BMI of 20. In our patients with a BMI≤ 25, five patients had hiatal areas ≥3.83 cm^2 (cohort average) and six patients had HIs≥0.143 (cohort average). In these patients, average DeMeester score was 82 (36–111), and all had esophagitis despite being on proton pump inhibitors. Thus, in thin patients, reflux is more severe in the setting of a large hiatus, probably due to the low pressure threshold to overcome the resting LES pressure in a small abdomen.

Our study evaluated the intraoperative hiatus size; however, with current radiologic methods, the esophageal hiatus can be reconstructed using computerized tomography or magnetic resonance imaging. We may be able to have inspiratory and expiratory size measurements with these radiologic methods. When the hiatal area is corrected with BMI, a specific individualized value is obtained, and the role of this new value is still to be investigated in further studies.

An objective preoperative assessment of the size of the esophageal hiatus can help us stratify patients to appropriate treatment options, rather than recommending fundoplication for all patients with GERD. Current surgical principles of antireflux surgery include repair of the hernia, reduction of the esophageal hiatus to a normal size, division of short gastric vessels, and formation of a total or partial

fundoplication.[25] But there is a subgroup of patients who have normal LES pressures despite hiatal enlargement. We had five patients with pathologic pH scores and LES pressures >15 mmHg. Average hiatal area and hiatal index in these patients were 3.13 cm^2 and 0.127, respectively, which are both lower than our cohort averages. In these patients, do we really need to add a fundoplication to hiatal repair or can we use endoscopic antireflux methods or techniques that will lead to crural hypertrophy? This issue was studied by a group in Germany on the basis of preventing postoperative unwanted side effects (lifelong inability to vomit, gas bloating) of conventional antireflux surgery, and two prospective trials were carried out.[26,27] They applied reinforced hiatal closure without fundoplication in the management of gastroesophageal reflux and both of the studies showed improvement at 3 months postoperatively. But long-term results are lacking.

Our study is limited by two-dimensional image measurements. We tried to overcome this by taking the photograph from the same angle. Another limitation was abdominal CO_2 insufflation, which obscures the respiratory changes in the hiatal area during expiration and inspiration.

Conclusion

This is one of the first studies to show a direct correlation between the surgically measured size of the esophageal hiatus and the acid reflux, LES pressure, and total LES length. The size of the esophageal hiatus significantly affects LES pressure and acid reflux. Hiatal area is especially important with its significant contribution to an effective LES mechanism. When hiatal area is divided by BMI, it gives a new value, which appears to reflect the amount of acid reflux and may have a role in the preoperative assessment and decision making.

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ORIGINAL ARTICLE

Airway Infection Predisposes to Peristomal Infection after Percutaneous Endoscopic Gastrostomy with High Concordance Between Sputum and Wound Isolates

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Abstract
Background Peristomal infection is common after percutaneous endoscopic gastrostomy. This study aims to evaluate the correlation between airway and peristomal infected pathogens.
Methods Before the procedure, sputum cultures were prospectively performed for the patients with airway symptoms. All the patients received prophylactic antibiotics. Once peristomal infection occurred, the wound cultures were obtained to analyze the antibiotic susceptibilities of the pathogens. The paired isolates, with concordance between sputum and wound cultures, were validated for their clone identity using pulsed-field gel electrophoresis.
Results One hundred twelve patients were enrolled, and 30 patients had peristomal infection. The 31 patients with airway pathogens had a 10-fold higher risk of peristomal infection than the other 81 without airway pathogens (95% CI, 3.85–26.4, $p<0.001$). Among patients collected with paired isolates from wound and sputum, 85% had concordant microorganism species. In the paired concordant isolates, 94% had indistinguishable antibiogram, and nearly 90% were clonally identical in pulsed-field gel electrophoresis.
Conclusions Patients with airway infection have an increased risk of peristomal infection after percutaneous endoscopic gastrostomy. Concerning the high concordance between infected wound and sputum isolates of such patients, the selection of appropriate prophylactic antibiotics could be individual to cover the microorganisms isolated from sputum.

Contribution of authors: Chuang CH: concepts, design, acquire data, manuscript preparation; Hung KH & Wu JJ: microbiological support; Chen JR, Chen CY, Kao AW & Chang WL: case collection and acquire data; Sheu BS: design refine, and critical revision of the manuscript for important intellectual content.

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Keywords Percutaneous endoscopic gastrostomy · Peristomal infection · Isolates concordance · Airway infection

Introduction

Peristomal wound infection after percutaneous endoscopic gastrostomy (PEG) is common with variable incidences up to 36%.[1–5] Even though covering pull-type PEG tube or push-type method may prevent infection, the standard "pull method" is still the most widely used technique because it is well established.[5–8] In the procedure, the gastrostomy catheter will be passed through the mouth and oropharynx until reaching the abdominal wall. Thus, oropharyngeal microorganisms may be transported to cause peristomal infection. This possibility is supported by a study that showed patients with methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in nasal or oral cavity also developed PEG-site infection from the same bacteria.[2] Moreover, there seems to be a higher risk of early peristomal infection in the patients with oropharyngeal cancer, who usually have poor oral hygiene.[4] Nevertheless, large-scale validation is necessary to determine whether the microorganisms of the oral cavity, or even those exploded from airway, could be related to the consequent peristomal infection after PEG.

The penicillin or cephalosporin-based prophylaxis is usually suggested to decrease the peristomal infection after PEG.[9–12] However, such broad-spectrum antibiotics may be limited to cover certain common pathogens of peristomal infection, such as MRSA and *Pseudomonas aeruginosa*.[2,5,13] This raises a clinical concern about whether the selection of prophylactic antibiotics should be variably based on the different clinical backgrounds of the patients. This study recognized the high concordance between the pathogens of airway infection and peristomal infection. Appropriate choice of prophylactic antibiotics to cover the airway pathogen may be promising to decrease the peristomal infection in certain risky subgroups with airway infection.

Materials and Methods

Patient's Inclusion and PEG Procedure

The patients who received PEG *by pull method* in a tertiary transferring center were included. One exclusion criterion for entry was the inability to place the gastrostomy for technical reasons, such as oropharyngeal deformity or esophageal stricture. One patient who received PEG by percutaneous push method for preventing migration of his esophageal stent was excluded. The patients were also excluded if active infection and fever were identified, and the PEG was delayed until the infection was brought under control. Before PEG, each patient was evaluated with regards to demographic background and airway condition. If the patient had received proton pump inhibitor or H_2 receptor antagonist, those will be hold 2 days ahead of the procedure.

After giving informed consent, PEG was conducted with the standard pull technique to insert a 24-Fr gastrostomy tube (Kimberly-Clark Corp., Roswell, GA, USA) in each patient. In brief, after local sterilization and anesthesia, a needle cannula was then punctured into the stomach for the insertion of the guiding wire through it. The wire was then caught to be pulled out from the mouth. The PEG tube was tied with the guiding wire to be pulled through the mouth into stomach and then out of the abdominal wall. The PEG wound was cared for once daily by beta-iodine and sterile saline with coverage of dry gauze placed between the external fixing device and the skin.

Grouping of Study Subjects by Airway Pathogens and Antibiotics Prophylaxis

In the pre-PEG visits, the patients' airway conditions were carefully evaluated. If patients had airway symptoms, sputum culture was prospectively performed to identify the microorganisms in the airway. In the first 20 consecutive patients, the oral swabs were routinely done to recognize the possibly colonized microorganisms. Because cultures of the oral swab showed numerous mixed floras, such as non-predominant commensal species of *Streptococcus*, *Lactobacillus*, and *Staphylococcus*, the oral swab was not done in the latter enrolled patients.

An intravenous prophylactic antibiotic was given to each patient within 3 h prior to PEG and maintained for 2 days after PEG placement. The choice of prophylactic antibiotics could be either penicillin- or cephalosporin-based, randomly decided on by the in-charge physicians. If the patients had already used antibiotic for other diseases, the antibiotic would be kept and attributed as with prophylactic antibiotics for PEG. The patients were defined as the "no airway pathogen group" if they had not airway symptoms or had airway symptoms but negative sputum culture. The other patients with positive sputum culture were defined as the "airway pathogen group" and further subgrouped into those with appropriate or inappropriate antibiotics prophylaxis. The "appropriate prophylaxis" was defined as the prophylactic antibiotics adequately covering all the isolated microorganisms of sputum culture according to the antibiogram.

Peristomal Wound Evaluation

Within 1 week after PEG procedure, the investigators evaluated the peristomal area on a daily basis for erythema (0=none, 1=<5 mm, 2=6–10 mm, 3=11–15 mm, 4=>15 mm), induration (0=none, 1=<10 mm, 2=11–20 mm, 3=>20 mm), and exudate (0=none, 1=serous, 2=serosanguinous, 3=sanguinous, 4=purulent). This validated scoring system has been used previously.[11,14] A patient was considered to have an early peristomal infection if the combined score was greater than 8 or presence of purulent discharge. For the infected wounds, the peristomal discharge was collected for culture to recognize the infected microorganisms.

Phenotype and Genotype Analysis of the Isolated Microorganisms

All the cultured isolates from either airway or peristomal wound were analyzed for the antibiogram, using the disc diffusion method. The susceptibility to each tested antimicrobial agent in the antibiogram was reported as susceptible, intermediate, or resistant. In each patient, the paired isolates from sputum and peristomal wound were validated for antibiotic susceptibility patterns, defined as "indistinguishable pair" or "different pair" by the presence or absence of complete match on susceptibility, respectively.

This study further validated the nine concordant pairs of the collected isolates from sputum culture and the infected peristomal wound with pulsed-field gel electrophoresis (PFGE). The chromosomal DNA of the isolated strains was digested by restriction enzyme overnight with *Sma*I for *S. aureus*, *Apa*I for *Acinetobacter baumannii*, *Xba*I for *Klebsiella pneumoniae*, *Not*I for *Proteus mirabilis*, and *Spe*I or *Xba*I for *P. aeruginosa*. Both the paired strains within one individual patient were placed on the same gel for PFGE. The pulse time ramped from 5 to 35 s over 20 h at 6 V/cm. PFGE pattern were considered as identical clones if no differences in the band pattern, as similar clones if only one to three different bands between two strains, and as distinct clones if there were more than three bands different between the two strains.[15,16]

Statistical Analysis

The difference in the demographic characteristics, length of antibiotics use, and hospital stay between the patients with and without PEG wound infection were analyzed by the Student's *t* test, chi-square's test, or Fisher's exact test as appropriate. The relative risks of peristomal wound infection among the different categories were analyzed by the two-tailed Fisher's exact test to estimate relative risk with a 95% confidence interval (95% CI). A $p<0.05$ was considered as significant.

Results

Demographic Characteristics of Study Subjects

This study enrolled 112 patients, including 31 women and 81 men, with a median age of 66 (range, 38–89) years. The underlying diseases indicated for PEG included neurological disorder in 75 patients, oropharyngeal cancer in 31 patients, and esophageal cancer in six patients. Thirty-four patients had received tracheotomy before they received PEG. Excluding 18 patients recruited from the outpatient clinics, 94 patients received PEG during hospitalization for other underlying diseases. Based on the airway symptoms and the results of sputum culture, there were 31 patients placed into the group with airway pathogen and 81 placed into the group without airway pathogen.

The Rate and Relevant Factors Related with Peristomal Infection of PEG

There were 26.8% (30/112) of the enrolled subjects confirmed as having peristomal infection of PEG occurring

Table 1 Demographic Characteristics, Length of Antibiotic Use, and Hospital Stay in the Patients with or Without PEG Wound Infection

(Mean±SD)	With infection (*n*=30)	Without infection (*n*=82)	*p* value
Age (year),	63.2±14.4	67.9±13.4	NS
Gender (Female/Male)	7/23	24/58	NS
Indication for gastrostomy			NS
Neurological disorder (*n*)	18	57	
Oropharyngeal cancer (*n*)	10	21	
Esophageal cancer (*n*)	2	4	
Tracheostomy, % (*n*)	33.3 (10)	29.3 (24)	NS
Positive sputum culture, % (*n*)	63.3 (19)	14.6 (12)	<0.001
Antibiotic use after PEG (day)	12.7±7.5	3.2±3.7	<0.001
Hospital stay after PEG (day)	16.6±11.3	7.3±7.4	<0.001

Table 2 The Peristomal Wound Infection Rate, Relative Risk, Length of Antibiotic Use, and Hospital Stay Between the Patients Without and with Airway Pathogen

	Peristomal infection		Antibiotic use after PEG (day)	Hospital stay after PEG (day)
	N (%)	Relative risk (95% CI)		
Without airway pathogen (*n*=81)	11 (13.5%)	1	4.0±4.7	8.8±10.1
With airway pathogen (*n*=31)	19 (61.3%)	10.1 (3.85–26.4)	9.8±8.4*	12.3±8.0
Appropriate prophylaxis (*n*=13)	5 (35.4%)	3.9 (1.–14.3)	5.6±4.1	10.4±8.0
Inappropriate prophylaxis (*n*=18)	14 (77.7%)	22.2 (6.1–80.1)	12.9±9.5**	13.8±7.9

*p=0.001, significant longer antibiotic use, comparing with the group without airway pathogen

**$p \leq 0.003$, significant longer antibiotic use than those with appropriate prophylaxis and those without airway pathogen

within 1 week after PEG. In Table 1, there were no difference in the age, sex/gender, indications for PEG, and status as with tracheotomy between the patients with and without peristomal infection of PEG ($p>0.05$). There was a significantly higher rate having a positive sputum culture of patients with peristomal infection of PEG than that of those without PEG wound infection (63.3% vs. 14.6%, $p<0.001$). Accordingly, both the length of antibiotic use after PEG and hospitalization duration were significantly higher in the patients with PEG wound infection than in those without ($p<0.001$). All the peristomal infection improved after antibiotics treatment and frequent wound care.

As patients with peristomal infection of PEG have a higher rate of a positive sputum culture (Table 1), this study further analyzed whether the airway pathogen of sputum culture could be related with the peristomal infection of PEG. In Table 2, the patients with positive airway pathogen in sputum culture had close to a 10-fold higher risk of having PEG infection than those without airway pathogen in sputum culture (95% CI, 3.85–26.4, $p<0.001$). There were 31 patients with positive airway pathogen in sputum culture, including 13 and 18 patients with appropriate and inappropriate antibiotic prophylaxis, respectively. Also in Table 2, referring to the patients without airway pathogen, the risk of the patients having peristomal infection after PEG was stepwise increased 3.9-fold for the patients with airway pathogen and with appropriate antibiotic prophylaxis ($p=0.02$). Moreover, the risk even increased up to nearly 22-fold for the patients with airway pathogen and with inappropriate antibiotic prophylaxis ($p<0.001$). It is not striking to show that the patients with inappropriate antibiotic prophylaxis also had a longer duration of antibiotic usage during admission ($p<0.003$).

Microorganisms Isolated from Airway and PEG Wound

Twenty-eight of 30 patients with peristomal infection have been obtained with microorganisms from would cultures. A total of 48 microorganisms were isolated from these 28 patients with wound infection. The wound cultures from the other two patients yielded too much mixed flora to identify of the specific infected pathogens. In Fig. 1, the PEG wound isolates included *P. aeruginosa* in 46.4% (13/28) of patients, *S. aureus* in 39.3% (11/28) patients, and *K. pneumoniae* in 32.1% (9/28) patients. Nine of the 11 strains were MRSA.

There were 19 patients with paired isolates collected from wound and sputum cultures (Table 3). On average, each patient had 1.7 microorganisms isolated from the wound and 2.1 from sputum. Among these patients, 84.2% (16/19) patient had concordant strains between the infected wound and sputum. Moreover, among the 16 patients with concordant pairs of infected microorganisms between wound and sputum cultures, nearly all except one pair had indistinguishable antibiotic susceptibility patterns. In

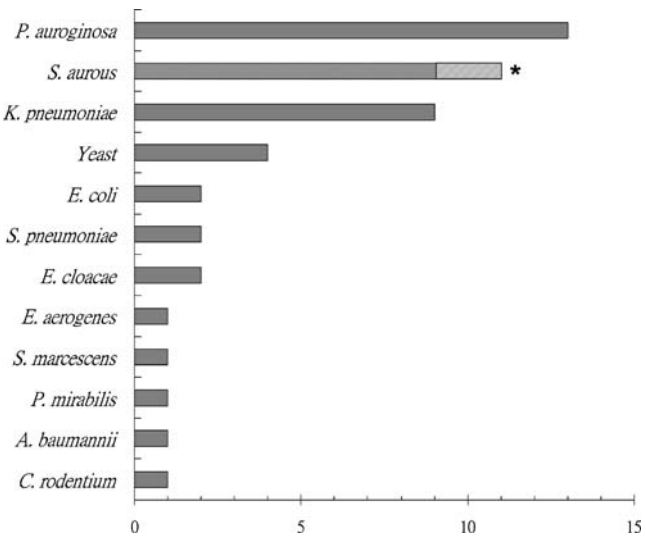

Figure 1 A total of 48 microorganisms were isolated from the wound culture in 28 out of the 30 patients with peristomal infection after percutaneous endoscopic gastrostomy. *P. aeruginosa* and *S. aureus* were the leading two common pathogens. *Asterisk* In 11 *S. aureus* infection, nine were methicillin resistant and two were methicillin susceptible.

Table 3 The Numbers of Concordant Microorganisms Within the 19 Patients with Paired Sputum and Infected Wound Cultures

	Wound isolates	Concordance[a]	Airway isolates
P. aeruginosa	9	7	8
S. aureus	8	5	7
K. pneumoniae	5	1	4
Yeast	4	4	8
E. cloacae	2	2	1
E. coli	1	0	1
E. aerogenes	1	1	3
S. marcescens	1	1	1
P. mirabilis	1	1	1
A. baumannii	1	1	1
F. meningosepticum	0	0	1
S. pneumoniae	0	0	3
A. hydrophila	0	0	1
Patients[b]	19	16	19

[a] Except one pair of *P. aeruginosa*, the other 22 concordant pairs had indistinguishable antibiotics susceptibility patterns

[b] Within the 19 patients, 16 had concordant microorganism species between wound and sputum.

Fig. 2, the PFGE analysis was shown for the randomly selected nine paired isolates with concordance between wound and sputum cultures. Nearly 90% (8/9) of paired isolates had identical clones, and only one pair had a similar clone in the PFGE pattern.

Discussion

Antibiotic prophylaxis has been shown to be effective to reduce peristomal infection.[9–11] The penicillin- or cephalosporin-based antibiotic prophylaxis are usually used with similar efficacy.[12] The European Society of Gastrointestinal Endoscopy guideline recommends a single dose of intravenous cephalosporin or penicillin as preparation before PEG.[17] The updated practice guidelines of American Society for Gastrointestinal Endoscopy and British Society of Gastroenterology also recommend cefazolin, cefuroxime or co-amoxicalv as prophylactic antibiotics.[18,19] However, *P. aeruginosa* and MRSA are common infected pathogens of peristomal infections after PEG.[2,5,13] Thus, the ordinary prophylactic antibiotics that are recommended in the guidelines are not enough to overcome these pathogens.

In the present study, we also disclosed a rather high incidence with 46% of patients having *P. aeruginosa* and 31% of patients having MRSA isolated from the infected wounds (Table 3). These data suggested that certain risk difference in host background may lead into a high incidence of *P. aeruginosa* and MRSA. Therefore, the risk factor of host background should be helpful when selecting the prophylactic antibiotics to cover these specific pathogens of PEG.

The present study further shows the links between peristomal wound's isolates and airway pathogen. In 85%

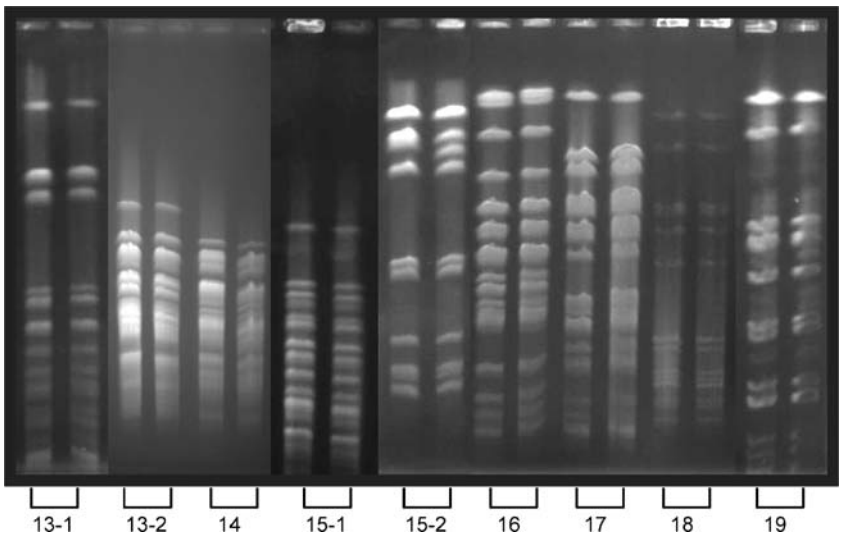

Figure 2 The paired concordant strains from sputum and wound in the last seven patients with peristomal wound infection were analyzed by pulsed-field gel electrophoresis. The macro-restriction patterns were all clonally identical, except one (strain 15–2) which had similar pattern.

of patients, concordant isolates could be found in both sputum and wound cultures. Most paired concordant strains had indistinguishable antibiotic susceptible pattern and identical PFGE patterns (Table 3 and Fig. 2). Our results demonstrate that the airway colonized microorganisms had a high concordance to predispose peristomal infection.

Pre-procedure MRSA screening from nose, throat, perineum, and broken skin with decontamination in the patients who tested positive appears to be effective in reducing MRSA peristomal infection.[18,20] However, excluding MRSA, *P. aeruginosa* are also a common pathogen of peristomal infection in our study and also previous studies.[2,5,13] A single antibiotic did not properly cover both common microorganisms as prophylaxis. Based on our results, the prophylactic antibiotics could be chosen individually, according to patient's airway condition and isolated microorganisms.

Moreover, in Table 2, the patients with airway pathogen had a 10-fold higher risk of getting peristomal infection. For those with inappropriate antibiotic prophylaxis, the risk increased up to nearly 22-fold. Even though the airway pathogens were adequately covered by appropriate antibiotics, the patients with airway pathogen still had 3.9-fold risk. Therefore, it is strongly suggested that it may be suitable to delay PEG until control of the patient's airway infection.

The patients receiving PEG in-hospitalized with other illness had a higher risk for peristomal infection[21] because these patients may have more hospital-acquired airway infection. Published studies show that infection rates could be reduced if patients had a 14–30-day discharge period before PEG placement.[22,23] We suppose that the discharge period gives time to make adequate resolution of airway infection and subsequently reduce infection rates. However, most of our patients hesitated to PEG placement on initial recommendation. They usually received PEG while they were hospitalized for other diseases. Moreover, in the 19 patients with airway pathogens, 13 had sputum cultures of *S. aureus or P. aeruginosa* infection. It indicated that most our patients with airway infection had hospital-acquired pathogens, which cannot be covered by standard prophylactic antibiotics. These may explain the relatively higher infection rate (26.8%) in the present study.

Throat swab is another way to get the infected pathogen in oropharynx. However, there are limits in most of our patients, who were bed-ridden and unconscious. Thus, oral swab culture was applied as an alternative, yielding a mixed flora resulting to the difficulty in differentiating the dominant flora. Moreover, not all isolates from infected wounds had concordant strain in the paired sputum. This indicates that other infectious sources may exist, offering colonized flora leading to peristomal infection, such as patient's skin and mouth, or exogenously acquired from healthcare worker's hands.

Nevertheless, our study had some limitations. The choice of prophylactic antibiotics was not randomly designed and not tailored to the sputum culture. We only collected the sputum cultures in symptomatic patients. Thus, our study cannot clarify how the infection rate could be improved if tailored antibiotic prophylaxis was given. We neither know if the airway or oropharynx colonized microorganisms in asymptomatic patients could also lead into peristomal infection.

In conclusion, patients with airway infection have an increased risk of peristomal infection after PEG. Concerning the close linkage between the microorganisms from PEG wound and sputum cultures of such patients, the selection of prophylactic antibiotics could be individualized to cover the microorganisms isolated from airway. Further intervention study will be conducted to compare standard antibiotic to tailored antibiotic prophylaxis.

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ORIGINAL ARTICLE

Clinicopathological Properties of the Superficial Spreading Type Early Gastric Cancer

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Abstract
Introduction We investigated differences in characteristics between the superficial spreading type early gastric cancer (EGC) characterized by a wide and superficial extension and the common type EGC.
Patients and Methods Between 1982 and 2008, we retrospectively reviewed clinical reports of patients with the EGC treated at Kochi Medical School.
Results Sixty-one patients (9.6%) out of 646 patients had the superficial spreading type EGC. The occurrences of diffuse type histology and lymph node metastasis were significantly greater in the superficial spreading type than in the common type. The incidence of EGC confined to the mucosa was significantly greater in the lymph node-positive superficial spreading type than in the lymph node-positive common type.
Conclusions In patients with the superficial spreading type EGC, lymph node metastasis was more prominent regardless of the degree of tumor invasion. Therefore, appropriate extensive lymph node dissection and wide surgical resection are required for the curative resection of the superficial spreading type EGC.

Keywords Superficial spreading type · Early gastric cancer · Gastrectomy · Lymph node metastasis

Introduction

Early gastric cancer (EGC) is defined as a lesion confined to the mucosa or the submucosa, regardless of the presence of lymph node metastases, and has a good prognosis with surgical curative resection. Previous studies have reported that the incidence of lymph node metastasis of EGC is 15–20% and the recurrence rate is 1.4–2.7%; thus, the 5-year survival rate is approximately 90%.[1,2,3] The superficial spreading type of EGC is characterized by the wide and superficial spreading activity of the cancer but with a more limited depth of vertical invasion compared with the common type of ECG.[4] According to Yasui et al., EGC is classified as a superficial spreading type of tumor when the area of the tumor is equal to or greater than 25 cm^2.[5] As the superficial spreading type of EGC is a rare disease, there have been few studies of its clinicopathological details. Therefore, we attempted to elucidate the clinicopathological features of patients with the superficial spreading type of EGC in comparison to the common type of EGC.

Patients and Methods

Between 1982 and 2008, a total of 646 patients who underwent surgery as an initial treatment for EGC were studied at Kochi Medical School. The standard operation for EGC was a distal, proximal, or total gastrectomy with a

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D2 lymph node dissection in accordance with the rules of the Japanese Gastric Cancer Association (JGCA).[6] Of these patients, 427 were men and 219 were women, ranging in age from 20 to 98 years (mean 65.8 years). Sixty-one patients out of 646 patients had the superficial spreading type lesions, which were defined as cancer lesions with an area equal to or greater than 25 cm^2. There were 30 patients with tumors which were confined to the mucosa, whereas the remaining 31 patients had submucosal involvement. Eleven patients (18.0%) had lymph node metastases, and among them, the median positive lymph node number was 5.5. In contrast, the common type of EGC was defined as cancer lesions with an area smaller than 25 cm^2.

Statistical Analysis

The Mann–Whitney *U* test was used to assess correlations among the mean values for each group. The Pearson chi-square test was applied to qualitative variables. All values are expressed as mean ± standard deviation. *P* values of less than 0.05 were considered significant.

Results

Clinical Characteristics

Patients with the superficial spreading type EGC accounted for 9.6% of all EGCs in the study. Table 1 shows the results of the clinical characteristics for superficial spreading type cancer and common type cancer. No significant differences in age, gender, gross appearance, and tumor location were found between the superficial type and the common type. The mean tumor diameter of the superficial spreading type was 7.1±2.2 cm, and the common type was 2.3±1.3 cm. The tumor diameters were significantly different between the two groups ($P<0.001$).

Table 1 Clinical Characteristics of the Superficial Spreading Type and the Common Type of EGC

Characteristics	Superficial spreading type (n=61)	Common type (n=585)	*P* value
Age in years (mean ± SD)	65.5±12.8	65.8±11.8	0.871
Gender (%)			0.511
Male	38 (62.3)	389 (66.5)	
Female	23 (37.7)	196 (33.5)	
Gross appearance (%)			0.315
Elevated type	16 (26.2)	98 (16.7)	
Depressed type	35 (57.4)	373 (63.8)	
Mixed type	8 (13.1)	96 (16.4)	
Flat type	2 (3.3)	18 (3.1)	
Tumor location (%)			0.352
Upper third	10 (16.4)	78 (13.3)	
Middle third	28 (45.9)	230 (39.3)	
Lower third	23 (37.7)	277 (47.4)	
Tumor diameter in cm (mean ± SD)	7.1±2.2	2.3±1.3	<0.001

Pathological Findings

Table 2 shows the results of the pathological characteristics for superficial spreading type cancer and common type cancer. According to the histoclinical classification devised by Lauren,[7] we found that the incidence of diffuse type histology was significantly higher in the superficial spreading type compared with the common type (45.9% vs. 29.6%; $P=0.009$). The incidence of lymph node metastasis was significantly higher in the superficial spreading type than in the common type (18.0% vs. 7.7%; $P=0.006$). There were no significant differences between the two types with regards to the depth of invasion, venous invasion, and lymphatic invasion.

Clinical Characteristics of ECG with or Without Nodal Metastasis

Among 646 patients, lymph node metastasis was found in 56 patients. Clinical characteristics of the superficial spreading type of EGC with or without lymph node metastasis and the common type of EGC with lymph node metastasis are shown in Table 3. There were no significant differences in age, gender, gloss appearance, and tumor location among the three groups. There was also no significant difference in the tumor diameter between the lymph node-positive superficial spreading type and the lymph node-negative superficial spreading type.

Pathological Findings According to the Presence or Absence of Node Metastasis

Pathological findings for the superficial spreading type of EGC with or without lymph node metastasis and the common type of EGC with lymph node metastasis are shown in Table 4. The incidence of EGC confined to the mucosa was significantly greater in the lymph node-positive superficial spreading type than in the lymph node-positive common type (36.4% vs. 6.7%; $P=0.008$). Although the incidence of the superficial spreading type of EGC confined to the mucosa was slightly higher in the lymph node-negative group than in the lymph node-positive group, there was no significant difference between the two groups. The incidence of lymphatic invasion was more prominent in the lymph node-positive superficial spreading

Table 2 Pathological Findings of the Superficial Spreading Type and the Common Type of EGC

Characteristics	Superficial spreading type (n=61)	Common type (n=585)	P value
Histological classification (%)			0.009
Intestinal	33 (54.1)	412 (70.4)	
Diffuse	28 (45.9)	173 (29.6)	
Depth of invasion (%)			0.945
Intramucosal	30 (49.2)	285 (48.7)	
Submucosal	31 (50.8)	300 (51.3)	
Metastases to lymph node (%)			0.006
Positive	11 (18.0)	45 (7.7)	
Negative	50 (82.0)	540 (92.3)	
Venous invasion (%)			0.124
Positive	12 (19.7)	74 (12.6)	
Negative	49 (80.3)	511 (87.4)	
Lymphatic invasion (%)			0.683
Positive	20 (32.8)	177 (30.3)	
Negative	41 (67.2)	408 (69.7)	

type than in the lymph node-negative superficial spreading type (72.7% vs. 24.0%; P=0.002). There were no significant differences in histological classification, venous invasion, and number of positive lymph node among the three groups.

Survival Analysis

The 5-year cumulative survival curves for 61 patients with the superficial spreading type and 585 patients with the common type are shown in Fig. 1. The overall 5-year survival rate of patients with EGC was 93.2% (91.8% for patients with the superficial spreading type and 93.3% for the patients with the common type). There was no significant difference between the two groups. The overall 5-year survival rate for patients with lymph node-positive superficial spreading type was 72.7%, which was slightly lower than that (84.4%) for patients with lymph node-positive common type. However, there was no statistically significant different between the two groups. The overall 5-year survival rate for patients with EGC according to the

Table 3 Clinical Characteristics of the Superficial Spreading Type of EGC with or without Node Metastasis and the Common Type of EGC with Node Metastasis

Characteristics	Node-positive superficial spreading type (n=11)	Node-negative superficial spreading type (n=50)	Node-positive common type (n=45)	P value
Age in years (mean ± SD)	62.1±11.9	66.3±13.0	64.3±12.2	NS
Gender (%)				NS
Male	5 (45.5)	33 (66.0)	33 (73.3)	
Female	6 (54.5)	17 (34.0)	12 (26.7)	
Gross appearance (%)				NS
Elevated type	1 (9.1)	15 (30.0)	10 (22.2)	
Depressed type	10 (90.9)	25 (50.0)	23 (51.1)	
Mixed type	0 (0)	8 (16.0)	11 (24.5)	
Flat type	0 (0)	2 (4.0)	1 (2.2)	
Tumor location (%)				NS
Upper third	1 (9.0)	9 (18.0)	4 (8.9)	
Middle third	5 (45.5)	24 (48.0)	19 (42.2)	
Lower third	5 (45.5)	17 (34.0)	22 (48.9)	
Tumor diameter in cm (mean ± SD)	7.4±1.8	7.0±2.1	3.0±1.5	<0.001[a]

NS no significant difference

[a] Node-positive superficial spreading type vs. node-positive common type and node-negative superficial spreading type vs. node-positive common type

Table 4 Pathological Findings of the Superficial Spreading Type of EGC with or without Node Metastasis and the Common Type of EGC with Node Metastasis

Characteristics	Node-positive superficial spreading type (n=11)	Node-negative superficial spreading type (n=50)	Node-positive common type (n=45)	P value
Histological classification (%)				NS
Intestinal	5 (45.5)	28 (56.0)	27 (60.0)	
Diffuse	6 (54.5)	22 (44.0)	18 (40.0)	
Depth of invasion (%)				0.048[a], <0.001[b]
Intramucosal	3 (27.3)	27 (54.0)	3 (6.7)	
Submucosal	8 (72.7)	23 (46.0)	42 (93.3)	
Venous invasion (%)				NS
Positive	2 (18.2)	10 (20.0)	14 (31.1)	
Negative	9 (81.8)	40 (80.0)	31 (68.9)	
Lymphatic invasion (%)				0.002[c], <0.001[d]
Positive	8 (72.7)	12 (24.0)	37 (82.2)	
Negative	3 (27.3)	38 (76.0)	8 (17.8)	
Lymph node-positive number	5.5±8.3	–	2.5±2.0	0.285

NS no significant difference

[a] Node-positive superficial spreading type vs. node-positive common type

[b] Node-negative superficial spreading type vs. node-positive common type

[c] Node-positive superficial spreading type vs. node-negative superficial spreading type

[d] Node-positive superficial spreading type vs. node-positive common type and node-negative superficial spreading type vs. node-positive common type

depth of invasion in the superficial spreading type and the common type were 92.1% and 94.7% for EGC confined to the mucosa and 91.3% and 92.3% for EGC with submucosal invasion, respectively. No significant difference between the groups was noted for depth of invasion.

Discussion

In the present study, we found that the superficial spreading type of EGC has a significantly higher incidence of diffuse type histology and lymph node metastasis than the common type of EGC. Previous studies have reported that the superficial spreading type accounted for 5.46% to 11.0% of all EGC,[8–11] and the incidence of lymph node metastasis in the superficial spreading type of EGC was 20.3% to 30.0%.[8,9] Our results were also almost compatible with these previous reports. These studies also revealed a significantly higher incidence of diffuse type histology and lymph node metastasis in the superficial spreading type than in the common type of EGC.

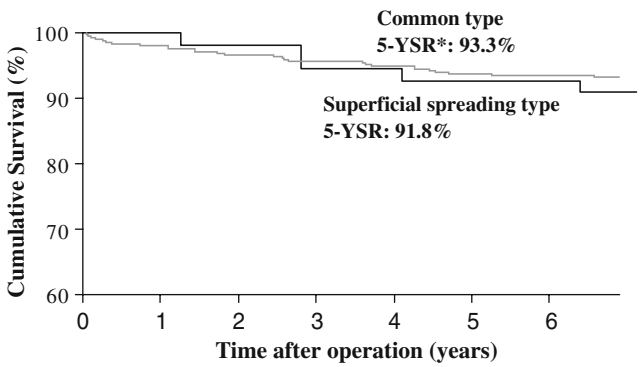

Figure 1 Survival curves of the 61 patients of the superficial spreading type of early gastric cancer (*solid line*) and the 585 patients of the common type of early gastric cancer (*dotted line*). There was no statistical difference in survival between the two groups. **5-YSR* 5-year survival rate.

In general, although EGC has an excellent prognosis, previous reports reveal that the prognosis of gastric cancer patients is mostly affected by the depth of invasion, followed by lymph node metastasis.[2,12] Regarding the depth of invasion, our study demonstrated that there was no significant difference between the superficial spreading type and the common type of EGC. However, some investigators have reported that the superficial spreading type has a higher incidence of submucosal invasion than the common type.[8,9] In addition, the same studies showed no significant differences in the recurrence rate or survival rate between the two groups,[8,9] which agree with our findings. Although the 5-year survival rate for EGC is 90% or greater,[1–3,13] complete surgical extirpation of gastric cancer, with a sufficient resection margin from the tumor and removal of metastatic lymph nodes, is necessary for a good prognosis in all EGC cases.[1,13,14] Thus, if EGC is treated

with the appropriate surgical strategy, the outcome of treatment is excellent, even in patients with the superficial spreading type.[8,9]

Regarding the correlation between tumor size and prognosis, it has been previously reported that tumor size is not an independent prognostic factor.[15] The tumor diameter in gastric cancer is currently not included in the staging system according to the TNM classification of the International Union Against Cancer or the JGCA classification. Kunisaki et al. indicated that tumor size in gastric cancer is a reliable prognostic factor that could be a suitable candidate for use in the staging system, in addition to conventional factors such as the presence of lymph node metastasis and depth of invasion.[16] However, these findings were particularly more prominent in patients with tumors at stage II and III; thus, it may not apply to the superficial spreading type of EGC. Furthermore, EGC with a diameter greater than 3.5 cm has been identified as an independent factor for the occurrence of lymph node metastasis in the superficial spreading type of EGC.[2]

Interestingly, the present study also revealed a significantly higher incidence of EGC confined to the mucosa in the superficial spreading type with lymph node metastasis than the common type with lymph node metastasis. Moreover, lymphatic invasion in the superficial spreading type of EGC was more prominent in the lymph node metastasis group than in the lymph node-negative group. However, there was no significant difference of depth of invasion in the superficial spreading type of EGC between the lymph node-positive group and the lymph node-negative group. In addition, Kasakura et al. have reported that there was no significant difference in the depth of invasion between the superficial spreading type with lymph node metastasis and the small-sized type with lymph node metastasis, which was defined as a cancer lesion of 2 cm or less in diameter.[8] The number of patients with lymph node metastasis may be too small to provide significant results. As with the results of the present study, we suggest that the superficial spreading type of EGC may have a greater lymphogenic malignant potential with lymph node metastatic capability regardless of the depth of invasion which is confined to mucosa or submucosal invasion. Meanwhile, recent advances in mucin histochemical and immunohistochemical methods employing cell markers have enabled to elucidate the biological behavior of the gastric cancer.[17,18] Namely, gastric mucin phenotype expression represents malignant potential in the incipient phase of invasion and metastasis, or difficulties in clinical and pathological diagnoses.[18,19] Mucin phenotype expression in EGC may be helpful in the biological differences between superficial spreading type and common type.

Recent advances in limited surgery, including endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), now offer a better quality of life to patients with EGC.[14] EMR should be indicated to patients with small mucosal cancer with no lymph node metastasis. According to guidelines for diagnosis and treatment of carcinoma of the stomach edited by the JGCA, the indications for EMR or ESD tend to be intestinal type mucosal cancer less than 2 cm in diameter without ulcer. Many investigators are now trying to extend the indications for these procedures. However, the indistinct tumor margin characteristic of superficial spreading tumors in EGC can lead to discrepancies in the tumor area between surgical findings and the pathological diagnosis.[9,11] Kasakura et al. reported that despite extensive preoperative examination, determination of the tumor margin was not possible in 26 of the 59 patients with the superficial spreading type of EGC.[8] Yoshimura et al. reported that endoscopic findings in 11 of the 28 patients with the superficial spreading type of EGC did not correspond clinicopathologically to the infiltrated lesions.[20] In addition, we have previously reported that the superficial spreading type of EGC adjacent to the pyloric ring correlates positively with a more extensive duodenal invasion.[21] Furthermore, Kunisaki et al. reported that the number of metastatic lymph nodes was greater in the superficial spreading type of EGC than in the common tumor type.[10] Recurrence of EGC was shown to be significantly higher in the patient group with submucosal, node-positive, and undifferentiated tumors.[1,3] Sufficient resection margins are necessary to prevent the reappearance of EGC as inadequate resections that do not maintain surgical margins free of cancer can lead to disease recurrence. Accordingly, gastrectomy with an extensive lymph node dissection and with a wide and sufficient surgical margin seems to be a highly appropriate treatment for the superficial spreading type of EGC.

Conclusion

The superficial spreading type of EGC, even if cancer invasion is confined to the mucosa, has more potential for lymph node metastasis than the common type of EGC. Therefore, a sufficient lymph node dissection in addition to a wide surgical resection may be required to achieve no recurrence of the disease.

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ORIGINAL ARTICLE

Laparoscopic Resection for Inflammatory Bowel Disease: Outcomes from a Nationwide Sample

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Abstract
Background and Aims A significant proportion of patients with inflammatory bowel diseases (IBD) require surgery. While the majority of these are open procedures (OP), there is recent interest in laparoscopic resection (LS). There are no nationwide comparison of outcomes between LS and OP.
Methods We used data from the Nationwide Inpatient Sample 2004 and identified patients with IBD who underwent ileocolonic/colonic resection using appropriate ICD-9 codes. Procedures were considered to be laparoscopic if they had concomitant codes for laparoscopy (*International Classification of Diseases, Ninth edition, clinical modification* 54.21/54.51). Multivariate regression was performed to identify independent predictors and outcomes.
Results There were 209,206 IBD hospitalizations included in the study among whom, 884 underwent laparoscopic resections (5.3%). On multivariate analysis, fistulizing disease (odds ratio (OR) 0.35, 95% confidence interval (CI) 0.21–0.59) and emergent admission (OR 0.59, 95% CI 0.39–0.90) were negative while annual hospital IBD surgical volume of >50 procedures (OR 2.0, 95% CI 1.14–3.52) were positively associated with LS. LS was associated with a significantly lower proportion of postoperative complications (27.1% vs 35.4%, $p<0.001$) and shorter postoperative length of stay compared to OP (−1.9 days, 95% CI −3.2 to −0.6 days). Propensity score adjustment for nonrandom allocation of patients into the treatment groups neutralized the OR for postoperative complication (OR 0.82) but not length of stay (−1.7 days).
Conclusion LS had no increase in rate of complications and was associated with a shorter postoperative length of stay.

Keywords Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Colectomy · Terminal ileal resection · Laparoscopic surgery

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Introduction

Inflammatory bowel diseases (IBD) frequently require hospitalization and surgery.[1] In Crohn's disease (CD), up to 70% of patients eventually require surgery with 45% requiring more than one surgical procedure during their lifetime.[2] The frequency of colectomy in ulcerative colitis (UC) is lower, but still significant with a 30% lifetime risk.[3] Recent estimates have placed direct healthcare costs attributable to IBD to be in excess of $6 billion in the United States, with surgical costs accounting for 12.4% for CD and 15.9% of costs for UC.[4] Estimates from Canada and other countries in Europe and elsewhere have also identified similar high costs associated with IBD. Thus, the expenditure related to surgical procedures in IBD is substantial, further making it essential to examine outcomes in the cohort of surgical IBD hospitalizations.

Over the past decade, there has been a growing interest in the use of laparoscopic resection (LS) for IBD, specifically colectomy or terminal ileal resection (TIR).[5–18] LS requires advanced technical expertise, longer operative time, a learning curve prior to improvement in outcomes, and significant IBD-related surgical experience.[6,9] However these disadvantages may potentially be offset by benefits such as superior cosmetic results, reduction in postoperative complications, specifically gastrointestinal (GI) complications such as ileus, short post-op length of stay, and better quality of life (QOL).[6,19,20] The published literature on LS in IBD has been from single tertiary referral centers,[10,14,15,21,22] from academic institutions outside the United States[7,8,11–13] or have been restricted to ileocecal Crohn's disease.[23] To our knowledge, there have been no studies on predictors and outcomes of LS from a nationwide representative US sample incorporating patients with both UC and CD.

We performed the present study with the following aims: (1) to examine frequency of use of LS among colectomy/ileocolonic resections (open procedures, OP) for IBD; (2) to identify positive and negative predictors of undergoing LS compared to OP; and (3) to compare outcomes of LS to OP, specifically post-op length of stay and occurrence of post-op complications.

Methods

Data Source

We utilized data from the Nationwide Inpatient Sample (NIS) 2004 in our analysis. The NIS is a national discharge database maintained by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. It consists of hospitalizations from a 20% stratified sample of hospitals from 37 states and contains information from nearly 1,000 hospitals and over 8 million discharges. The HCUP NIS has been described in detail elsewhere[24,25] including in publications from our center[26–28] and provides reliable estimates of disease burden. Briefly, each hospitalization is treated as an individual record and is coded with one primary discharge diagnosis, up to 14 secondary diagnoses and up to 15 procedures associated with the hospitalization.

Study Population

Our study population consisted of all patients with a primary or a secondary discharge diagnosis of IBD identified through appropriate *International Classification of Diseases, Ninth edition, clinical modification* (ICD-9-CM) codes for CD (555.x) or UC (556.x). Hospitalizations were included in the present analysis if they had any of the following surgical procedure codes associated with the hospitalization: (1) terminal ileal resection (TIR)/cecectomy (45.62, 45.72), (2) right hemicolectomy (45.73), (3) left hemicolectomy (45.75), (4) sigmoidectomy (45.76), or (5) total colectomy (45.8) with or without ileoanal pouch formation (45.95). Patients were included in the laparoscopic resection (LS) group if they also had associated codes for either laparoscopy (54.21) or laparoscopic lysis of peritoneal adhesions (54.51), a method that has been followed by previous publications.[22,29] Patients who underwent one of the surgical procedures listed above but had no associated codes for laparoscopy were included in the open resection group (OP).

Definition of Variables

Age, gender, insurance status, and race were obtained from the NIS. Comorbidity burden was assessed using the Deyo modification of the Charlson comorbidity index, a validated and widely used measure of comorbidity burden.[30,31] The overall comorbidity score was then classified into four groups, based on scores of 0, 1, 2, and 3 or more, with higher scores indicating greater comorbidity. The presence of associated anemia (ICD-9-CM codes 280, 280.1, 280.9, 285.1, and 285.9) or malnutrition (263.9, 263, 263.0, 263.1, 263.8) was also ascertained through discharge codes. Admission type was coded as elective, urgent, or emergent as available in the NIS. The annual volume of IBD-related surgical hospitalizations was calculated for each hospital by summing up the total number of bowel resection procedures (small bowel/colonic) performed in that hospital during that calendar year on patients with a listed discharge diagnosis code of CD or UC. Hospitals were then divided into three groups by volume (low, medium, and high) based on volume cut-offs of 0–25, 26–50, and 51 or more annual surgeries on IBD patients.

Outcomes

Our primary outcomes of interest were postoperative complications and length of stay. The post-op length of stay was calculated by subtracting the day of the procedure from the overall length of stay.[27] Post-op complications were identified through previously used ICD-9-CM codes[32] and consisted of mechanical wound complications, infectious, urinary, pulmonary, gastrointestinal, and cardiovascular complications. We also examined frequency of requiring reopening of a recent laparotomy site. Secondary outcomes of interest included in-hospital mortality and total hospitalization charges.

Statistical Analysis

Data analysis was performed using Stata 9.2 (Stata Corp, College Station, TX) using appropriate survey estimation commands. Analysis was performed using the weighted estimates, and unless specified otherwise, all numbers provided in the manuscript reflect this practice. Chi square and *t* tests were used to perform between group comparisons for categorical and continuous variables, respectively. Univariate logistic regression was used to identify factors associated with undergoing laparoscopic (compared to open) resection. Variables significant on univariate analysis at $p<0.1$ were included in the final multivariate regression model where a $p<0.05$ was used to identify significant independent predictors. This analysis was stratified by IBD type (CD vs UC).

Univariate and multivariate regressions were performed for other outcomes including post-op complications (logistic) and postoperative length of stay (linear). One major confounder for postoperative outcomes could be the nonrandom selection of patients for laparoscopic vs open resection. To decrease this effect, we constructed propensity scores.[33] This score describe the likelihood of a patient undergoing LS (vs OP) given their baseline characteristics. The information used to construct this propensity score included age, gender, insurance status, Charlson comorbidity index, presence of malnutrition, fistulizing, or penetrating disease and admission type (elective, urgent, emergent). The calculated propensity score was then divided into quartiles. Propensity score analysis has been described in several previous publications to minimize the bias due to nonrandom allocation of treatment group from observational studies.[33] The adjusted analysis for postoperative outcomes was then performed in two different ways. In the first method, traditional multivariate analysis was carried out after adjusting for age, gender, comorbidity, and underlying complications such as fistulizing disease or malnutrition. In the second method, the analysis was carried out after adjusting for the propensity score quartiles in the model, thus decreasing the effect of nonrandom selection of patient for LS vs OP.

Sensitivity analysis was performed using log transformation of continuous outcomes of length of stay and hospitalization charges. Subgroup analysis was performed by disease type (CD vs UC), surgery, and admission type.

The study was approved by the Institutional Review Board of the Medical College of Wisconsin.

Results

Utilization of Laparoscopic Resection

There were a total of 209,206 IBD hospitalizations that were eligible for inclusion in the study among whom 16,713 (8%) underwent colon/ileocolonic resection. There were 180 laparoscopic resections from 81 hospitals, which corresponded to a national estimate of 884 laparoscopic resections for IBD during the study period (LS group). The remaining 15,829 resections were included in the OP group. LS thus accounted for 5.6% of all colon/ileocolonic resections with a slightly higher proportion for CD (6.3%) compared to UC (3.1%, $p<0.0001$).

Predictors of Laparoscopic vs Open Resection

There were a few significant differences in the characteristics of patients undergoing LS vs OP procedures (Table 1). There was a slightly higher proportion of patients in the age-group 18–35 years in the LS (40.6%) compared to the OP group (32.0%, $p<0.0001$). In contrast, the proportion of patients older than age 50 in the LS group was 31.9% compared to 40% in the OP group ($p<0.0001$). Comparing the two groups, patients in the LS group were more likely to be white or have private insurance while patients in the OP group were more likely to be self-pay or have public insurance. The comorbidity burden was higher among the OS group with a smaller proportion of patients having a Charlson comorbidity score of 0. LS also tended to be done at centers with higher IBD-related surgical volume. About 43.2% of LS were done at centers with at least 50 IBD-related surgeries annually compared to 30.9% of OP at centers with a similar volume ($p<0.0001$).

The most frequent surgical procedures in the LS group were cecectomy/terminal ileal (TIR) resection (39.6%) and right hemicolectomy (37.8%; Table 1). In the OP group, similarly cecectomy/TIR (40.7%, $p<0.0001$) and right hemicolectomy (25.9%) were the most common resections with total colectomy being performed in 17.1% of LS and 25.4% of OP group (p value<0.0001; Table 1). Conversely, 7.4% of right hemicolectomies were laparoscopic compared to 3.6% of total colectomies ($p<0.0001$) and 5.2% of cecal/TI resection ($p<0.0001$). Among UC patients who underwent total colectomy, ileoanal pouch formation was more common in the OP (24.1%) compared to LS group (12.9%, $p=0.007$).

Table 2 presents the multivariate analysis of predictors of LS for Crohn's disease. Age was not an independent predictor of undergoing LS vs OP, neither was comorbidity nor insurance type. Fistulizing disease (odds ratio (OR) 0.35, 95% confidence interval (CI) 0.21–0.59) and emergent admission (OR 0.59, 95% CI 0.39–0.90) were negatively associated with undergoing LS, while annual hospital IBD-related surgical volume of at least 50 (OR 2.0, 95% CI 1.14–3.52) were predictive of LS. Neither hospital teaching status nor bed size was predictive of LS (data not shown). For patients with UC, there were no variables that predicted LS and achieve statistical significance. Emergent

Table 1 Differences in Characteristics Between Patients Undergoing Laparoscopic and Open Colon Resections for Inflammatory Bowel Disease

Characteristic	Laparoscopic resection (n=884; %)	Open resection (n=15,829; %)	p value
Age-group (in years; %)			
18–35	40.6	32.0	<0.0001
36–50	27.5	28.0	0.75
51–65	19.5	23.3	0.009
66+	12.4	16.7	0.0001
Sex			
Male	42.5	49.5	0.0001
Female	57.5	50.5	0.0001
Race			
White	73.9	66.8	<0.0001
Black	4.3	5.0	0.35
Hispanic	1.6	3.0	0.02
Other	2.0	1.9	0.83
Missing	18.3	23.4	0.0005
Insurance			
Private	74.5	64.6	<0.0001
Medicare	12.7	20.9	<0.0001
Medicaid	6.7	7.4	0.44
Self-pay	2.8	3.6	0.21
Other/Missing	3.4	3.6	0.76
Charlson comorbidity index			
0	83.5	77.9	0.0001
1	11.5	14.2	0.02
2	2.2	4.3	0.002
3+	2.8	3.6	0.21
Disease complications			
% Fistulizing Crohn's disease	15.3	35.0	<0.0001
% Colon cancer	2.9	2.7	0.72
Center IBD surgical volume			
0–25	31.9	44.7	<0.0001
26–50	24.9	24.4	0.74
51+	43.2	30.9	<0.0001
Admission type			
Elective	75.1	57.9	<0.0001
Urgent	8.1	13.8	<0.0001
Emergent	16.8	28.3	<0.0001
Mean time to surgery from admission (in days)	0.89	2.63	0.001
Type of surgery			
Cecectomy/terminal ileal resection	39.6	40.7	<0.001
Right hemicolectomy	37.8	25.9	<0.0001
Left hemicolectomy	2.8	3.6	<0.001
Sigmoid colectomy	2.8	4.6	0.01
Total colectomy	17.1	25.4	<0.0001
Total colectomy with pouch formation (in UC only)	12.9	24.1	0.007

Table 2 Multivariate Analysis of Predictors of Undergoing Laparoscopic Resection (vs Open Resection) Among Patients with Crohn's Disease Undergoing Colectomy/Ileocolonic Resection

Predictor	Odds ratio	95% CI
Age-group		
18–35	1.0	
36–50	0.79	0.52–1.20
51–65	0.72	0.44–1.20
66+	1.14	0.40–3.27
Sex		
Male	1.0	
Female	1.26	0.92–1.72
Insurance type		
Private	1.0	
Medicare	0.46	0.18–1.21
Medicaid	0.77	0.38–1.57
Self-pay	0.82	0.30–2.25
Charlson comorbidity index		
0	1.0	
1	0.91	0.52–1.61
2	0.74	0.23–2.39
3+	1.23	0.48–3.12
Malnutrition		
No	1.0	
Yes	0.49	0.18–1.30
Fistulizing disease		
No	1.0	
Yes	0.35	0.21–0.59
Admission type		
Elective	1.0	
Urgent	0.58	0.27–1.27
Emergent	0.59	0.39–0.90
Center IBD surgical volume		
0–25	1.0	
26–50	1.49	0.81–2.72
51+	2.00	1.14–3.52

IBD inflammatory bowel disease

admission showed a trend towards lower utilization of LS (OR 0.35, 95% CI 0.08–1.94, p=0.15) but was not statistically significant.

Postoperative Outcomes of Laparoscopic vs Open Resection

Length of Stay

The mean postoperative length of stay for patients undergoing LS was 5.6 days compared to 8.4 days for those in the OP group. After adjusting for age, gender, comorbidity burden, and admission type, LS was still associated with a nearly 2-day shorter hospital stay (−1.9 days, 95% CI −3.2 to −0.6 days). As type of surgery

correlated with post-op length of stay, we further adjusted for type of resection in our multivariate analysis, which yielded similar estimates (−1.7 days, 95% C −3.0 to −0.3 days). Adjustment for undergoing pouch construction also did not significantly affect our regression estimates. Log transformation of length of stay did not result in significantly different estimates. Adjustment for propensity score quartiles also did not affect the estimates of lower postoperative sat in the LS group (−1.7 days, 95% CI −3.0 to −0.4 days).

Postoperative Complications

The frequency of postoperative complications was significantly lower for LS compared to OP (27.1% vs 35.4%, OR 0.68, 95% CI 0.48–0.96) (Table 3). Post-op infections (9.2% vs 2.4%, p=0.0003) and surgical complications (5.6% vs 3.6%, p=0.01) were more in common in OP compared to the LS group. There was no difference in any of the other post-op complications; specifically post-op GI complications were similar between the two groups (21.1% vs 19.3%, p=NS). On multivariate analysis, after adjusting for age, comorbidity, and admission type, the risk of post-op complications was not different between the two groups (OR 0.77, 95% CI 0.55–1.08). Similarly adjusting for the propensity score quartile also neutralized the lower complication rate in the LS group (OR 0.82, 95% CI 0.59–1.15).

Relation between Surgical Volume and Outcomes

As stated above, LS was more common in hospitals with a higher annual IBD-surgical volume than in those with lower volumes. We examined outcomes of LS performed at high volume hospitals compared to low volume hospitals. There was no difference in the occurrence of any postoperative complication (OR 0.92, 95% CI 0.42–2.01 for high volume vs low volume hospital), but post-op length of stay was shorter on univariate analysis at high surgical volume hospitals (−2.6 days, 95% CI −4.8 to −0.5 days). After adjusting for age, comorbidity, admission type, and gender, this difference was no longer statistically significant (−1.4 days, 95% CI −3.0 to 0.3 days, p=0.1) but suggested a trend.

Other Outcomes

Adjusted in-hospital mortality was similar between the two groups (OR 0.45, 95% CI 0.06–3.36). Total hospitalization charges were lower in the LS compared to the OP group after adjusting for age, sex, comorbidity, and admission type (−$8,327, 95% CI −$15,544 to −$1,109). However, restricting this analysis to patients who underwent surgery within 2 days of hospitalization, the difference was no longer statistically significant (−$4,065, 95% CI −$11,417 to $3,288) suggesting that the difference in mean hospitalizations costs could be due to LS being performed earlier in the hospital course, especially for elective patients.

Discussion

The past decade has seen a growing interest in the use of LS for IBD[6,9] and non-IBD intestinal surgeries.[22,34,35] In the present study, we show that LS still forms only a small portion (5.3%) of surgical resection procedures within the universe of all IBD-related surgeries in the US. However there appears to be higher utilization of LS at high-volume surgical centers and for elective hospitalizations. We also demonstrate that LS is associated with a nearly 2-day

Table 3 Postoperative Outcomes in Patients with Inflammatory Bowel Disease Undergoing Laparoscopic or Open Colectomy/Ileocolonic Resections

Parameter	Laparoscopic resection (LS; n=884)	Open resection (OP; n=15,829)	p value
Mortality	0.6%	2.3%	0.12
Mean post-op length of stay	5.5	8.4	<0.0001
Postoperative complications			
Any	27.1	35.4	0.03*
Cardiac	1.7	2.3	0.74
Pulmonary	3.6	5.6	0.26
Urinary	3.0	1.1	0.01*
Gastrointestinal	19.3	21.1	0.58
Wound infections	2.4	9.2	0.0003*
Surgical complications	1.1	4.8	0.10
Reoperation	0.6	1.8	0.25
Mechanical wound complications	1.8	3.6	0.23

*p value<0.05

shorter postoperative length of stay and lower overall post-op complications.

Post-op length of stay is a key measure in comparing outcomes between surgical procedures. Indeed, one of the purported theoretical benefits of LS is earlier return of bowel function leading to a lower postoperative ileus, earlier resumption of oral intake and thus, shorter post-op length of stay. There has been conflicting published data on this outcome. Some of the earlier studies reported longer length of stay after LS;[15] others found comparable length of stay in CD after LS compared to OP procedures. However, more recently other authors demonstrated a significantly lower post-op length of stay associated with LS. Bemelman et al., in an examination of 30 laparoscopy-assisted ileocolonic resections compared to 48 open resections found a shorter post-op length of stay in the LS group (5.7 days) compared to open procedure group (10.2 days, $p<0.007$).[7] Similarly, Alabaz et al. found a mean 2.6 day shorter length of stay for laparoscopic ileocolonic resection compared to open resections.[36] Recent randomized controls trials in IBD[11] and non-IBD populations[37] have also confirmed similar shorter length of stay for LS. Consistent with these recent results, we found in our analysis, using both unadjusted and adjusted estimates, LS was associated with a significantly shorter post-op length of stay by nearly 2 days (−1.9 days, 95% CI −3.2 to −0.6 days). From a societal viewpoint, these results have the potential for significant healthcare cost savings that merit further cost-effectiveness analyses.

On univariate analysis, we found that LS was associated with a significantly lower frequency of post-op complications (OR 0.68, 95% CI 0.48–0.96). However, after adjusting for admission type, age, and comorbidity, three key predictors of post-op complications, this difference was no longer significant suggesting that the apparently lower complication rate with LS may be in-part related to selection of relatively healthier, elective patients for LS. While initial reports of LS identified a high rate of complications with LS,[38] this has not been substantiated in later reports.[6,7] Several authors have reported similar or lower morbidity for laparoscopic compared to open procedures[11,36,37] suggesting a learning curve with increasing familiarity with these procedures.

Along the same theme, we found that higher IBD-related surgical volume was predictive of patients undergoing LS compared to OP (OR 1.84, 95% CI 1.03–3.31). Among patients who underwent LS, there was no difference in post-op complications between high and low volume hospitals, but high volume hospitals did have a trend towards a shorter post-op stay that was statistically significant on univariate analysis.

We found that only 16.8% of LS were for admissions coded as "emergent" compared to 28.3% for OP. This is similar to the available literature where there are only a few studies examining LS for emergent indications for severe colitis compared to a larger number of reports for elective resections.[6] Dunker et al. compared outcomes of ten patients undergoing emergency laparoscopic-assisted colectomy for acute severe IBD colitis to 32 patients undergoing an open procedure for a similar indication.[8] They found that despite a longer operative time for LS procedures, they were associated with shorter hospital stays (14.6 vs 18.0 days, $p=0.05$). Restricting our analysis to emergent hospitalizations, LS was associated with similar frequency of post-op complications (OR 0.57, 95% CI 0.25–1.31). This supports the fact that LS may be safe and not associated with a higher immediate complication rate in patients with IBD who required emergent hospitalization, but this merits further examination through prospective multicenter studies in this cohort.

There are a few limitations to our study. First, while our approach has been used for other authors previously to identify laparoscopic surgery, this has not been validated specifically in IBD. This may lead to undercounting of the actual number of laparoscopic resections among IBD patients. However, while this may mean that our percentage of LS may be an underestimate, we do not expect this to significantly alter the analysis of predictors or outcomes after LS. We were not able to examine conversion rates from LS to OP, with historically quoted rates for IBD-related surgeries ranging from 2.5–22%.[6,9] However, in determining predictors of undergoing LS, we believe that the intention to treat (i.e., intent to perform LS) is more important than subsequent need for conversion. We also did not have information on the operating time, which has been noted to be between 0.5–2 h longer for LS.[6,9] In our analysis, we included patients having discharge procedure codes for colectomy or ileocolonic resection and laparoscopy/laparoscopic lysis of adhesions in the LS group. It is possible that this cohort includes a small number of patients who initially underwent diagnostic laparoscopy and subsequently underwent resection later on during the same hospitalization. However, our methodology is similar to that used by previously published studies from non-IBD populations.[22,29] Reliance on ICD-9-CM codes from administrative databases is also susceptible to bias related to miscoding with the possibility of terminal ileal and cecal resections being coded as either small bowel resection or a partial colectomy. In addition, there may be inter-surgeon variation in the practice of both open and laparoscopic procedures, ranging from different incisions (right lower quadrant, midline, pfannensteil) to different anastomotic techniques (intracorporeal vs extracorporeal). Such differences could account for some of the differences in outcomes and would not be captured in administrative databases. They should also be taken into

account in future studies comparing open vs laparoscopic resections.

Our study has several strengths. To our knowledge, it is the first study using a nationwide representative administrative database to compare predictors of and outcomes after LS in patients with IBD. Using national databases limits the potential for referral or selection biases from single center studies, especially tertiary referral centers. It also provides us with a broad overview of practice patterns from different regions and hospital settings in the US. Use of propensity score analysis also decreases the bias due to nonrandom allocation of patients to each of the two treatment groups.

There are a few implications to our results. LS appears to be safe for ileocolonic resections or colectomy in IBD, at least in the elective population. There is need for further prospective research into examining its outcomes in patients requiring urgent surgery. Also, a majority of the literature comparing laparoscopic to open resections have focused on operative morbidity and short-term complications. Long-term outcomes (including need for repeat surgery and quality of life) are essential in chronic diseases such as CD where there is risk of disease progression or recurrence despite an initial "curative" resection. Further, surgical volume and experience with techniques may play a role in determining outcomes after LS exhibiting a learning curve phenomenon, thus, interpretation of results must take this into account.

In conclusion, we found that laparoscopic resections account only for a small proportion of colectomy/ileocolonic resections in IBD nationwide. LS is associated with a lower rate of post-op complications, which may in part be due to patient selection. However, adjusting for age, comorbidity and admission type, LS was associated with a nearly 2-day shorter post-op length of stay compared to OP. Further research into long-term outcomes of LS are essential in the IBD population.

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ORIGINAL ARTICLE

Malignant Transformation in Perianal Fistulas of Crohn's Disease: a Systematic Review of Literature

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Abstract
Introduction Malignant transformation of perineal fistula in Crohn's disease has rarely been reported. The aim of this study is to define the patient's characteristics and clinical presentation of this rare disease.
Methods A systematic review of case series and reports published in English language between 1950 and 2008 was conducted. All cases with malignancy in low pelvic/perineal fistula in patients with Crohn's disease were included. All selected cases were then analyzed with respect to age, gender, duration of Crohn's disease and fistula, location of fistula, presenting symptoms, method of diagnosis, delay in diagnosis, histopathology, treatment, and outcome. Data analyses were done using chi-squared or Fisher's exact test and the Mann–Whitney test.
Results Literature review revealed 61 cases of carcinomas arising in perineal fistulas in Crohn's disease. Sixty-one percent (37) of the patients were females. Females were significantly younger than males at the time of diagnosis of cancer (47 vs. 53 years, $P<0.032$). Males were also noted to have significantly longer duration of Crohn's disease compared to females (24 vs. 18 years, $P=0.005$). However, females were noted to have the fistula for significantly shorter duration prior to cancer transformation when compared to males (8.3 vs. 16 years, $P=0.0035$). On initial examination, malignancy was suspected and proven only in 20% of patients ($n=12$). Adenocarcinoma was the most common histology (59%, $n=36$), followed by squamous cell carcinoma (31%, $n=19$). In most patients (59%, $n=36$), the fistula was rectal in origin.
Conclusions A high suspicion for malignancy in chronic perineal fistulas associated with Crohn's disease should be maintained in spite of negative biopsies. Especially in women, the shorter duration of Crohn's fistulas prior to malignant degeneration necessitates an aggressive approach to rule out cancer.

Keywords Crohn's · Fistulas · Anorectal · Perirectal · Perineal

Introduction

The association between colorectal cancer (CRC) and inflammatory bowel disease has been well established, especially with ulcerative colitis. The relationship between Crohn's disease and the development of gastrointestinal carcinoma has been less consistently reported. Emerging literature suggests that Crohn's disease (CD) may also be associated with a comparable risk of colorectal cancer as in ulcerative colitis. Cancer in the case of CD is most commonly noted in the large intestine in patients with extensive Crohn's colitis. However, cancers arising within perineal CD have been reported rarely. This may be due to the fact that the incidence of perianal problems in CD varies greatly among the reported series and may be as low as 5%. Therefore, the risk of carcinoma formation in patients with perianal CD may

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Table 1 Patient Characteristics of 61 Cases

Reference no.	Author and year	Institution	Number of patients	Location of fistula (*N*)	Cancer detected at initial exam (*N*)	Pathology (*N*)
1	Ky et al. 1998	Lenox Hill Hospital, New York, NY	8	Anorectal = 7 Rectovaginal = 1	Yes = 2 No = 5 Unknown = 1	Adenocarcinoma = 3 Squamous cell carcinoma = 5
2	Gilbert et al. 1991	St. Mark's Hospital, London, UK	7	Anovaginal = 1 Perineal = 6	Yes = 1 No = 6	Adenocarcinoma = 7
3	Ficari et al. 2005	University of Florence, Italy	6	Anorectal = 6	Unknown = 6	Unknown = 6
4	Korelitz 1999	Lenox Hill Hospital, New York, NY	3	Perirectal = 3	Unknown = 3	Adenocarcinoma = 2 Squamous cell carcinoma = 1
5	Church et al. 1985	Cleveland Clinic, Foundation, OH	3	Perineal = 3	No = 3	Adenocarcinoma = 1 Squamous = 2
6	Moore-Maxwell and Robboy 2004	Duke University, Medical center, Durham, NC	2	Rectovaginal = 2	Yes = 2	Adenocarcinoma = 2
7	Buchman et al. 1991	UCLA Medical Center, Los Angeles, CA	2	Rectovaginal = 1 Perineal = 1	No = 2	Squamous cell carcinoma = 2
8	Ball et al. 1988	University Hospital of S. Manchester, UK	2	Anorectal = 1 Perineal = 1	No = 2	Adenocarcinoma = 2
9	Wyatt et al. 1987	Bristol Royal Infirmary, Bristol England	2	Anorectal = 1 Rectovaginal = 1	No = 1 Yes = 1	Adenocarcinoma = 2
10	Slater et al. 1984	Mount Sinai Medical Center, New York, NY	2	Perineal = 2	Unknown = 2	Squamous cell carcinoma = 2
11	Smith et al. 2008	Roswell Park Cancer Institute, Buffalo, NY	1	Perineal	Yes	Adenocarcinoma
12	Tokunaga et al. 2008	Osaka North Japan Post Hospital, Osaka, Japan	1	Anorectal	No	Adenocarcinoma
13	Zagoni et al. 2006	Semmelweis University, Budapest, Hungary	1	Rectovulvar	No	Adenocarcinoma
14	Devroe et al. 2005	AZ Klina, Brasschaat, Belgium	1	Anorectal	No	Adenocarcinoma
15	Kazama et al. 2005	Yaizu Municipal Hospital, Yaizu, Japan	1	Perineal	No	Adenocarcinoma
16	Kuhlgatz et al. 2005	Albert Schweitzer Hosp, Northeim, Germany	1	Perineal	No	Squamous cell carcinoma
17	Laurent et al. 2005	Cliniques Universitaires, Mont-Godinne, Belgium	1	Rectovaginal	Yes	Adenocarcinoma
18	Keese et al. 2005	University Hospital of Mannheim, Mannheim, Germany	1	Perineal	No	Adenocarcinoma
19	Fox et al. 2005	Yale University, School of Medicine, New Haven, CT	1	Rectovaginal	No	Squamous cell carcinoma
20	Bahadursigh and Longo 2004	Saint Louis University, St. Louis, MO	1	Perineal	Yes	Squamous cell carcinoma
21	Wong et al. 2002	WGH and University of Bristol, UK	1	Anorectal	No	Adenocarcinoma
22	Cirincione et al. 2000	Mount Sinai Medical Center, New York, NY	1	Rectovaginal	No	Squamous cell carcinoma
23	Kulaylat et al. 1999	Buffalo General Hos, Buffalo, New York	1	Anorectal	Yes	Squamous cell carcinoma
24	Vervana 1999	St. Louis University, Saint Louis, MO	1	Perianal	No	Adenocarcinoma

25	Inamdar et al. 1995	Houston Health Science Center, Houston, TX	1	Perineal	No	Adenocarcinoma
26	Kyle and Ewen 1992	University of Aberdeen, UK	1	Anorectal	Unknown	Adenocarcinoma
27	Lumley and Stitz 1991	R N. Brisbane Hos, Herston Queensland Australia	1	Rectovaginal	No	Adenocarcinoma
28	Kwan and Freeman 1991	University of British Columbia, Vancouver, Canada	1	Perineal	No	Adenocarcinoma
29	Roe and Mortensen 1989	John Radcliffe Hospital, Oxford, UK	1	Perineal	Yes	Adenocarcinoma
30	Somerville et al. 1984	City Hospital, Nottingham, UK	1	Perineal	Yes	Squamous cell carcinoma
31	Chaikhouni et al. 1981	Medical College, Toledo, Ohio	1	Anorectal	No	Adenocarcinoma
32	Buchmann et al. 1980	General Hospital, Birmingham, UK	1	Rectovaginal	No	Adenocarcinoma
33	Daly and Madrizo 1980	Beekman Downtown Hospital New York, NY	1	Perineal	Yes	Squamous cell carcinoma
34	Lightdale et al. 1975	Memorial Sloan-Kettering Cancer Center, New York, NY	1	Rectogluteal	No	Adenocarcinoma
Totals			61	All anal and perineal fistulas = 25	Yes = 13	Adenocarcinoma = 36
				All rectal Fistulas = 36	No = 35	Squamous = 19
					Unknown = 13	Unknown = 6

be even lower. The aim of this study is to define characteristics and clinical presentation of patients with carcinomas arising within perineal and perirectal fistulous CD.

Materials and Methods

Ovid MEDLINE, Pubmed, and EBSCOhost were searched for case series and reports published in English using a combination of the keywords "fistula", "cancer", and "Crohn's disease". The search was conducted between 1950 and June 2008. One hundred sixty-seven articles were identified in English language. The abstract of all 167 articles were reviewed. All case reports with low rectal, perianal, and anal fistulas were included into this study. All other Crohn's fistulas with malignancy were excluded. The reference lists of these collected articles were screened for further relevant citations. Forty articles met these criteria and were reviewed thoroughly by authors 1 and 5.[1–40] The original institution where the report originated, the author lists, and patient characteristics were scrutinized to identify duplicated cases. An additional six articles were excluded. The final list included both case series and individual case reports by 34 different primary authors.[1–34] Missing data were categorized as not available.

From Lenox Hill Hospital in New York, Korelitz published seven cases of cancer originating from Crohn's perianal fistulas.[4] Four of those cases were also published by Ky et al.[1] from the same institution and were excluded. A total of three publications were identified from St. Marks Hospital in London.[2,35,36] Publication from Gilbert et al. included all the patients,[2] and the other manuscripts were excluded.[35,36] Although other cases were identified by citations and otherwise, including 14 in the Japanese literature[12,37] and two in European literature,[38,39] these were not included as they were not published in the English language.

A total of 61 cases from 34 different studies were then analyzed with respect to age, gender, duration of CD and fistula, location of fistula, presenting symptoms, delay in diagnosis, method of diagnosis, histopathology, treatment, and outcome. Diagnosis was considered to be delayed if it was mentioned as such in the case report, or if the patient presented more than once with the same complaints, within 2 years before a diagnosis of cancer was made. The Mann–Whitney test was used to compare the averages. Categorical and nominal data were analyzed using chi-squared test or Fisher's exact test. Statistical significance was accepted for P values less than 0.05.

Results

A total of 61 cases of cancers in perineal fistulas associated with CD were identified (Table 1).[1–34] One patient who

developed two separate primary anal cancers 11 years apart was analyzed as two individual cases.[1] A summary of our results is shown in Tables 2 and 3.

There were 24 (39%) male and 37 (61%) female patients. The mean age of patients when first diagnosed with cancer was 49.5 years (median 47.5, range 22 to 79 years), and average duration of CD prior to detection of cancer was 20 years (median 17, range 3 to 50 years). The average age at the diagnosis of cancer was 47 years for females (median 44, range 22 to 79 years) and 53 years for males (median 52, range 36 to 75 years; $P<0.032$; Fig. 1). Average duration of fistula prior to cancer detection was 11.5 years (median 10, range 6 months to 50 years). These data were missing in 17 patients. The mean duration of fistula prior to detection of cancer was 8.3 years (median 8.5, range 1 to 23) for females and 16 years (median 16, range 6 months to 50 years) for males ($P=0.034$; Fig. 1). The average duration of CD prior to cancer detection in females was 18 years (median 19, range 3 to 31) and for males was 24 years (median 25, range 10 to 50; $P<0.001$; Fig. 1). Thirty-nine patients (64%) had some form of prior major abdominal surgery ranging from small bowel resections to total proctocolectomy. Four patients (7%) did not have prior surgeries, while in the remaining 18 patients (29%), past surgical history was not mentioned.

The most common fistula origin was rectal including anorectal, rectovaginal, rectovulvar, and rectogluteal in 36 (59%) patients, followed by all anal and perineal sites in 25 (41%). There was no significant association between the site of fistula and the duration of fistula.

The most common presenting complaints were pain and persistent fistula in 39% ($n=24$) and 25% ($n=15$) of patients, respectively. An abscess was reported at the time of examination in 41% ($n=25$) of patients. Twelve (20%) patients did not have an abscess, and in the rest, it could not be determined based on report. In 59% ($n=36$) of patients, cancer was not detected at the time of initial examination. There was a suspicion of cancer on physical examination in only a small percentage of patients (20%; $n=12$) and proven with biopsy.

Table 3 Summary of Results in All Patients

Summary		Total *N* (%)
Cancer type	Adenocarcinoma	36 (59)
	Squamous cell carcinoma	19 (31)
Fistula site	All anal and perineal sites	25 (41)
	All rectal fistulas	36 (59)
Delay in detection	Yes	21 (34)
	No	6 (10)
	N/A	34 (66)
Cancer detected at initial exam	Yes	13 (21)
	No	35 (58)
	N/A	13 (21)
Most common symptom	Pain	24 (39)
	Persistent fistula	15 (25)
Abscess	Yes	25 (41)
	No	11 (18)
	N/A	25 (41)
Previous biopsy	Yes	16 (26)
	No	13 (21)
	N/A	32 (52)
Outcome	Died	20 (54)
	Recurrence	5 (8)
	NED	18 (30)
	N/A	12 (20)

Adenocarcinoma was the most common histology and was present in 36 patients (59%). Squamous cell carcinoma (SCC) was diagnosed in 19 patients (31%), and the type of cancer was not mentioned in six (10%) patients. There was no association between the types of carcinoma and age at diagnosis of cancer. The average age at diagnosis of adenocarcinoma was 51 years (median 50.5, range 22 to 79), and squamous cell carcinoma was 47 years (median 47, range 26 to 77). There was no significant difference in the type of cancer based on gender. The average duration of CD was 20 years in patients with adenocarcinoma and 19 years with patients with SCC. There was no association between the type of carcinoma and the site of fistula.

Table 2 Summary of Results by Gender

	All patients ($n=61$)	Female ($n=37$) (61%)	Male ($n=24$) (39%)	*P* value
Mean age at diagnosis of cancer (years)	49.5	47	53	<0.032
Mean duration of Crohn's disease (years)	20	18	24	0.005
Mean duration of fistula (years)	11.5	8.3	16	0.034
Delay in diagnosis (months)	5.7	4	9	NS
Cancer not detected at initial examination	35	18 (49%)	17 (71%)	NS
No. of adenocarcinomas	36	23 (62%)	13 (54%)	NS
No. of squamous cell carcinomas	19	11 (30%)	8 (33%)	NS

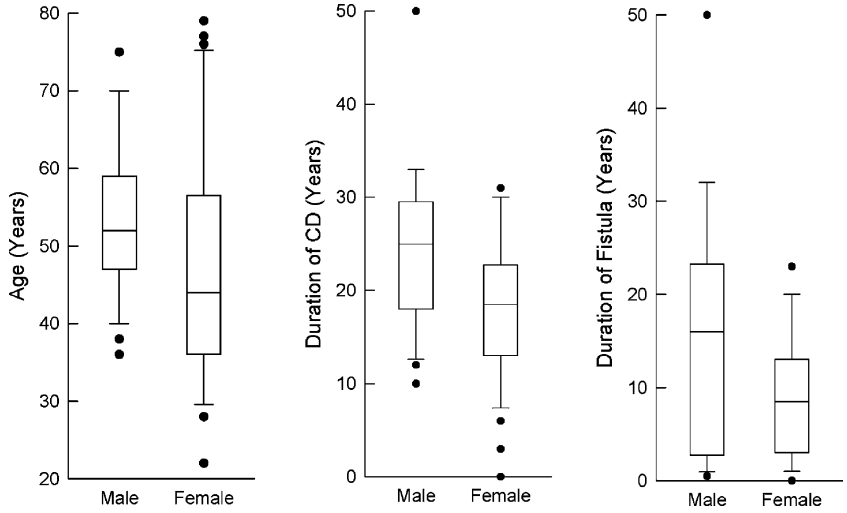

Figure 1 Graphs representing age at diagnosis, duration of Crohn's disease, and fistula prior to detection of cancer.

The relationship between duration of fistula and type of carcinoma was also reviewed. The average duration of fistulas was 12.2 years (median 13, range 0.5 to 50 years) in 27 patients with adenocarcinoma and 9.5 years (median 8 years, range 0.5 months to 30 years) in 19 patients with SCC. The duration of fistula was not clear in nine patients with adenocarcinoma and in ten patients with SCC.

Cancer was detected at the first visit and diagnosed with biopsy in only small number of patients (n=12, 20%). In 36 (59%) patients, the cancer was detected anywhere between 1 month to 2 years after the initial presentation. The average delay in diagnosis of carcinoma in fistula tract was 5.8 months (median 3 months). In patients with adenocarcinoma, the average delay in diagnosis was 6.2 months whereas in patients with SCC was 5.4 months. The average delay in diagnosis in females was 4 months but in males was 9 months. Although cancer was diagnosed later in males than females, this was not statistically significant. In 12 patients (20%), the time to diagnosis was not mentioned in the reports.

Medical treatment for CD was identified in 39 patients in 22 publications.[2,3,5–9,11–14,16–18,20,22,24–26,30,32,33] Corticosteroids were the most commonly used medication in 15 patients. Azathioprine or 6-mercaptopurine was used in seven patients. Only two patients were treated with infliximab. In 22 patients, there was no mention of any medication. Twenty-four (39%) patients died from their cancer, all within 4 years. Half these patients died in 1 year or less from the diagnosis. Recurrent carcinoma was mentioned in three other patients, who were still alive at the time the case reports had been published. Nineteen patients (31%) had no evidence of disease at follow-up intervals ranging from 6 months to 5 years. One patient had a second primary anal cancer at 11 years and had no evidence of disease 18 months after treatment for his second tumor.[1]

Discussion

Our extensive review of the cases published in the literature reveals differences between males and females with cancers in perianal fistulas of CD. The average age of all patients at the time of diagnosis is similar to that observed in smaller studies. However, in our analysis, cancer was detected at an earlier age in women when compared to men. The average duration of CD is also similar to prior studies when all patients are considered, but a significant gender difference was again observed. Female patients on the average had a shorter duration of both CD and fistula prior to detection of cancer. Possible reasons for this gender difference include either earlier detection or earlier malignant transformation in females. We favor the latter explanation as the likelihood of a long quiescent phase in males appears unlikely, given the aggressive nature of this cancer.

The quality of systematic review is influenced by the quality of the primary studies being reviewed. Our study included ten case series with small number of patients (between two and eight) and a total of 24 case reports. On the other hand, very narrow selection criteria were used in order to decrease the heterogeneity of our patient population. This review included only retrospective clinical reports published over 30 years duration. Medical management of CD has evolved considerably, especially over the last decade. Very limited treatment and follow-up data were available in the publications that were reviewed. Our study should be viewed in the light of these limitations that could possibly have influenced the accuracy of the survival and recurrence.

The presence of a perianal fistula in a patient with CD was first described by Penner and Crohn in 1938.[41] Perianal fistulas are found in 20% to 25% of patients with CD limited to the ileum and in 60% when the rectum is involved.[35,42] Increased risk of CRC has been associated

with CD,[43] but cancers arising in perineal fistulas in patients with CD have been infrequently reported. Malignancy arising within Crohn's colocutaneous fistula was first reported in 1975 by Lightdale et al.[34]

Recent literature suggests a stronger association between colorectal cancer and CD than was previously reported. The incidence of colorectal cancer in patients with CD is estimated to be six times the incidence in the general population.[4] The location and extent of CD appears to be important in assessing the risk of CRC. Gyde et al. reported the relative risk of CRC in CD to range from 4.3 in the general Crohn's population to 23.8 in the presence of colitis.[44] Greenstein et al. calculated a relative risk of 6.9 for developing CRC in isolated colonic CD.[45] A Swedish study demonstrated a relative risk of CRC of 5.6 for those with exclusively colonic involvement, as compared to a relative risk of 3.2 for patients with ileocolitis and 1.0 for patients with ileal involvement only.[46] The same study also revealed an increased relative risk associated with diagnosis of inflammatory bowel disease prior to age 30 compared to diagnosis at an older age.[46] A meta-analysis of 12 hospital-based and population-based studies of CRC risk in CD revealed that the cumulative risk of CRC for all patients with CD, regardless of disease distribution, was 2.9% after 10 years, 5.6% after 20 years, and 8.3% after 30 years of disease.[47]

When compared to the overall incidence of anal cancers in CD, the incidence of cancer in perineal fistulas appears to be quite small. In patients with CD, the relative incidence of anal cancer as a proportion of all colorectal cancers is 14%, compared to 1.4% in the general population.[10] Ky et al. followed more than 1,000 patients with long-standing CD complicated by perirectal fistulas over a period of 14 years and demonstrated carcinoma related to fistula eight times in seven patients. This incidence was estimated to be only 0.7% of CD patients. The same authors also reviewed 33 other reported cases of anorectal carcinoma in CD and found that 45% were clearly associated with fistulas.[1] Connell et al. reported four cases of cancers in anorectal fistulas out of some 1,250 patients with CD, an incidence of 0.3%.[35]

Various hypotheses regarding the etiology of this complication of CD have been put forward. Traube et al. suggested constant mucosal regeneration in chronic fistulas as the reason for malignant degeneration, otherwise known as "scar tissue carcinoma".[43] On the other hand, Church et al. thought that it was more likely that carcinoma caused the fistulas in patients with shorter duration of fistulas.[5] Ball et al. suggested long-standing immunosuppression in CD patients as a mechanism for carcinogenesis.[8] Vernava used special mucin stains to demonstrate primary anal gland carcinoma as the possible origin of fistula-related adeno-carcinomas in CD.[25] Human papillomaviruses (HPV) 16 and 18 have been shown to be associated with the majority of anal carcinomas not associated with CD.[48] A study of eight anorectal adenocarcinomas and two anal squamous cell carcinomas in patients with CD found no evidence of HPV 16.[2] However, Kuhlgatz et al. recently reported the presence of HPV 6 initially and HPV 16 subsequently in a CD patient with SCC arising in chronic perineal fistula.[16] This raises the possibility of a different viral etiology (HPV 6) in such cancers.

Immunosuppressants such as infliximab are being increasingly used for management of fistulas in CD and are reported to be effective in controlling inflammation.[49] Current studies using endoscopic ultrasound and magnetic resonance imaging have demonstrated that even when fistulas stop draining externally, inflammation persists within the tract.[50,51] It is possible that delays in diagnosis may have occurred from malignant transformation taking place in the presence of such covert inflammation. However, this hypothesis could not be studied further because only very small percentage of patients received immunosuppressant therapy as treatment of fistulas.

Almost all the above-referenced authors agree that anal strictures and pain may limit proper examination without anesthesia and in some cases even with anesthesia. This may lead to a delay in diagnosis ranging from a few months to a few years as seen in our study. Some authors have suggested initiating a surveillance protocol in Crohn's patients to detect malignancies.[4,40] The cost-effectiveness of such surveillance programs has not been studied yet.

Conclusion

Although malignancy arising in chronic perineal fistulas associated with Crohn's disease is rare, a high suspicion for malignancy should be maintained. Persistent or new symptoms should be thoroughly investigated. The shorter duration of Crohn's disease and fistulas in females prior to development of malignancy requires a more aggressive approach in this group to rule out cancer.

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ORIGINAL ARTICLE

Clinical Significance of the Upregulated Osteopontin mRNA Expression in Human Colorectal Cancer

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Abstract
Objective Osteopontin (OPN) is a phosphorylated glycoprotein which is associated with tumor progression, development, and metastasis. Recently, it has been reported that OPN is highly upregulated in a variety of human malignancies. The aim of this study is to investigate the clinical significance of OPN mRNA expression in colorectal cancer (CRC).
Material and Methods Conventional reverse transcription polymerase chain reaction (RT-PCR) and Western blot assays were performed to detect the expression of OPN mRNA and protein in human CRC cell lines and normal cell line. Real-time quantitative RT-PCR assay was performed to analyze the expression of OPN mRNA in 82 CRC tissue samples and corresponding non-tumor tissues. Immunohistochemistry was also performed to detect the expression of OPN protein in above tissues. Finally, the correlation between the status of OPN mRNA expression and clinicopathological factors and clinical outcome was evaluated.
Results Compared with normal human intestinal epithelial cell line, human CRC cell lines showed high level of OPN gene expression at both transcriptional and translational levels. Moreover, the results of real-time quantitative RT-PCR and immunohistochemistry showed that the expression levels of OPN mRNA and protein in tumor tissues were significantly higher than those in the corresponding non-tumor tissues ($P<0.001$). The expression level of OPN mRNA was significantly correlated with lymph node metastasis, lymphatic or venous invasion, and TNM stage ($P=0.0033$, 0.0061, 0.0008, and 0.0012, respectively). Moreover, we also observed that the disease-free and overall survival rates in patients with high OPN mRNA expression were significantly shorter than those in patients with low OPN mRNA expression ($P=0.0047$ and 0.0125). Additionally, the status of OPN mRNA expression was an independent prognostic factor for the prognosis of CRC patients ($P=0.008$; RR, 2.775; 95% confidence interval, 2.334–3.811).
Conclusion OPN might play an important role in CRC progression and the status of OPN mRNA expression could be a novel prognostic molecular marker for CRC patients.

Keywords Osteopontin · Colorectal cancer · Tumor marker · Prognosis · Survival

Introduction

Colorectal cancer, also called colon cancer or large bowel cancer, is the third most common malignant tumor worldwide and the incidence rate of this disease in China increases year by year.[1]

Despite the advances in early diagnosis and clinical treatment, the prognosis of CRC patients especially with metastasis still remains very poor.[2] Annually, over 945,000 people develop colorectal cancer around the world, and around 492,000 patients die from the disease. Colon carcinogenesis is a complicated and incompletely understood process which is determined by environmental and genetic factors. Thus, it is then necessary to identify new molecular markers underlying the development of this tumor and predicting its poor prognosis in CRC patients.

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Osteopontin, a secreted multifunctional glyco-phosphoprotein, is found in various tissues and plays important roles in a wide range of biological processes such as inflammation, angiogenesis, and tissue remodeling.[3,4] The constitutive expression of OPN has been reported to be involved in the process of tumor carcinogenesis and metastasis.[5] Moreover, OPN also can stimulate various signaling pathways by binding to various cellular receptors including integrins and CD44 variants.[6,7] The overexpression of OPN has been found in a variety of human cancers such as lung cancer, breast carcinoma, esophageal cancer, endometrial cancer, gastric cancer, and malignant pleural mesothelioma.[8–13] Some researchers have shown that inhibition of OPN could suppress the growth, migration, and invasion of tumor cells.[14,15] Although OPN regulates multiple functions contributing to human colon cancer development and progression,[16] the clinical significance of OPN mRNA expression in CRC remains unclear.

To the best of our knowledge, the prognostic significance of the OPN mRNA expression status has not previously been determined in CRC. Therefore, the present study aimed to determine the expression of OPN mRNA or protein in colorectal cancer cells or tissue samples and evaluate the clinical significance of OPN mRNA with regard to predicting prognosis of in CRC patients on a large prospective cohort of a patient population.

Material and Methods

Cell Lines and Cell Culture

Three colorectal cancer cell lines (HT-29, SW480, and HCT-8) and a normal human intestinal epithelial cell line (HIEC) were purchased from Shanghai Institute of Cell Biology (Shanghai, China). All cell lines were cultured in RPMI 1640 (GIBCO-BRL) medium supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin in humidified air at 37°C with 5% CO_2.

Patients and Tumor Tissues

Primary colorectal cancer tumor tissues (T) and corresponding non-tumor tissues (N) were obtained by surgical excision from 84 patients at the Department of General Surgery, Nanjing Hospital (Nanjing, China) between 1998 and 2003. None of the patients had received chemotherapy or radiotherapy before surgery. The original histopathological slide sets and reports were obtained from each case and these were reviewed to confirm the diagnosis of colorectal cancer. Samples were snap-frozen in liquid nitrogen and stored at −80°C until RNA extraction. Informed consent was obtained from all patients before surgery. The ethics committee of Jiangsu Province Institute of Medicine approved the study protocol. The median age of the patients was 54 years (range, 38–68 years). Patients were followed postoperatively every 3 months. Written informed consent, as required by the institutional review board, was obtained from all patients. Complete follow-up was available for all study patients. Follow-up was calculated from the date of surgery.

Total RNA Extraction and cDNA Synthesis

Total RNA was extracted from cells or tissues using TRIzol (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. The RNA was reverse transcribed using reverse transcription polymerase chain reaction (RT-PCR) kits (Applied Biosystems, Foster City, CA, USA) with an oligo d(T)16 primer under standard conditions as described previously.

Conventional RT-PCR Assay

OPN-specific primers (GeneBank NM_000582.2) were designed as follows: sense 5′-*AGTTCTGAGGAAAAG CAGC*-3′; reverse, 5′-*CCCCTACCGGAACATACG*-3′ (a predicted product is 480 bp); to verify integrity of OPN expression, β-actin gene was used as an internal control and the sequences of primers were as follows: sense, 5′-*TGACGGGGTCACCCACACTG-TGCCCATC*-3′; reverse, 5′-*CTAGAAGCATTTGCGGTGGACG*-3′ (a predicted product is 610 bp). PCR conditions were 30 cycles consisted of denaturation at 94°C for 30 s, annealing at 56°C (58°C for β-actin) for 30 s, and extension at 72°C for 30 s. Each PCR product was separated by 1.5% agarose gel electrophoresis and visualized by ethidium bromide staining.

Real-Time Quantitative RT-PCR Assay

Total RNA was isolated and reverse-transcribed from tissue samples as previously described. Quantitative real-time RT-PCR assay was performed to detect β-actin expression that was used to normalize the amount of cDNA for each sample. β-actin primers were as follows: sense, 5′-*TGACGGGGT CACCCACACTGTGCCCATC*-3′; reverse, 5′-*CTAGAAG CATTTGCGGTGGAC-G*-3′. Equal amounts of cDNA from each sample were amplified using the following primers to detect the expression of OPN: sense 5′-*AGTTCTGAG GAAAAGCAGC*-3′; reverse 5′-*CCCCTACCGGAACA TACG*-3′. Two independent experiments were performed in triplicate and PCR products were measured using an ABI PRISM 7700 sequence detection system and analyzed with ABI PRISM 7000 SDS software (Applied Biosystems, USA). Expression of OPN mRNA was normalized by that of β-actin mRNA. Cutoff point selection for the OPN

mRNA was carried out by searching for a cut point yielding the smallest log-rank *P* value and divided to the high and low OPN expression levels.

Western Blot Assay

Cells were treated with lysis buffer [50 mmol/L Hepes (pH 7.0), 250 mmol/L NaCl, 0.1% Nonidet P-40, 5 mmol/L EDTA, 1 mmol/L PMSF, 1 mmol/L DTT, and protease inhibitor cocktail (EMD Biosciences, Inc., USA)]. After centrifugation at 12,000×*g* 4°C for 30 min, the supernatant was collected and protein concentration was determined by the Bradford assay (Bio-Rad Laboratories, Hercules, CA, USA). Equal amounts of proteins were separated electrophoretically on 12% SDS/polyacrylamide gels and transferred onto polyvinylidene membranes (Amersham Biosciences, Piscataway, NJ, USA). The membrane was probed with an anti-OPN rabbit polyclonal antibody (1:1,000; R&D Systems, Minneapolis, MN, USA). Expression of OPN was determined with horseradish peroxidase-conjugated anti-rabbit immunoglobulin G (1:3,000; Amersham Pharmacia Biotech) and enhanced chemiluminescence (Amersham Pharmacia Biotech) according to the manufacturer's instructions. An anti-β-actin mouse monoclonal antibody (1:1,000; Santa Cruz Biotechnology, Santa Cruz, CA, USA) was used to confirm equal loading.

Immunohistochemical Staining

Three-micrometer-thick sections sliced from paraffin-embedded tissues samples were prepared on glass slides. The sections were then deparaffinized in a xylene series graded with ethanol. The sections were placed in 0.1 mol/L citrate buffer (pH 6.0) and autoclaved at 121°C for 10 min. They were treated with 3% H_2O_2 for five min. Then, they were incubated with normal goat serum for 15 min to block non-specific antibody binding. The primary antibody reaction used a primary rabbit polyclonal anti-OPN antibody (R&D Systems, Minneapolis, MN, USA) and anti-β-actin antibody diluted 1:10 (Santa Cruz Biotechnology) for 30 min at room temperature. Thereafter, immunoperoxidase staining was performed with the Envision kit (DAKO, Kyoto, Japan) according to the manufacturer's instructions.

Statistical Analysis

The difference of OPN mRNA expression levels among tumor tissue samples and corresponding non-tumor tissue samples was examined by using the Student *t* test. Disease-free and overall survival rates were calculated actuarially according to the Kaplan–Meier method. A probability level of 0.05 was chosen for statistical significance. Statistical analysis was done with the SPSS software package (version 6.1, SPSS, Inc., Chicago, IL, USA).

Results

The Expression of OPN mRNA and Protein in Cell Lines

Firstly, conventional RT-PCR and Western blot assays were performed to detect the expression of OPN mRNA and protein in human colorectal cancer cell lines (HT-29, SW480 and HCT-8) and normal intestinal epithelial cell line (HIEC). As shown in Fig. 1a and b, the expression levels of OPN mRNA and protein were significantly higher in colorectal cancer cell lines, but there was no detection of OPN mRNA and protein expression in normal intestinal epithelial cell line.

The Expression of OPN mRNA in CRC Tumor Tissues or Non-tumor Tissues

To evaluate the relationship between the expression of OPN mRNA and CRC tumorigenesis and progression, the expression of OPN mRNA in tumor tissue samples and corresponding no-tumor tissue samples from 84 CRC patients was detected. The expression of OPN mRNA expression in tissue samples by conventional and real-time quantitative RT-PCR assays was shown in Fig. 2. Seventy-two of 84 patients (85.7%) showed a higher level of OPN mRNA expression in CRC tumor tissues than in the corresponding non-tumor tissues. The mean expression level of OPN mRNA (0.425±0.321) in tumor tissues was significantly higher than that in the corresponding non-tumor tissues (0.034±0.081; $P<0.001$). In the present study, patients with OPN mRNA expression levels in

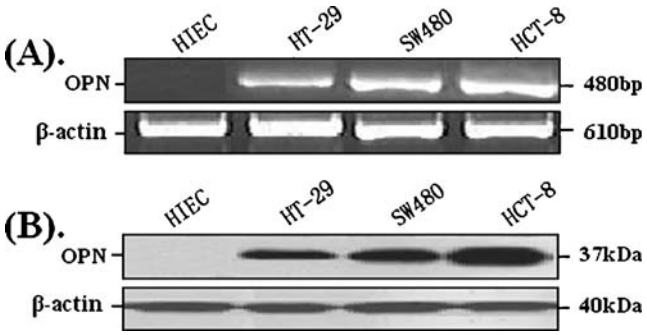

Figure 1 OPN expression in three CRC cell lines and a normal intestinal epithelial cell line by RT-PCR (**a**) and Western blot assays (**b**). The expression levels of Aurora-A mRNA and protein were significantly higher in four tumor cell lines than those in normal cells. To normalize OPN mRNA and protein expression, β-actin was used to normalize for any differences in mRNA and protein loading between lanes.

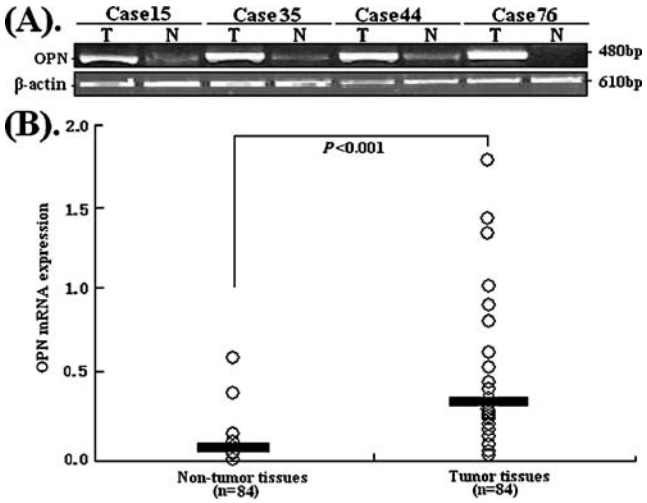

Figure 2 OPN mRNA expression in CRC tissues (*T*) and corresponding non-tumor tissues (*N*). **a** Gel images of electrophoresis. **b** Real-time quantitative RT-PCR assay. OPN mRNA expression in tumor tissue was significantly higher than that in the corresponding non-tumor tissues. To normalize OPN expression, β-actin was used to normalize for any differences in mRNA and protein loading between lanes. Student's *t* test showed a significant difference ($P<0.001$).

tumor tissue less than the median value of 0.276 were considered as the low expression group ($n=42$), while patients with OPN mRNA expression levels in tumor tissue equal to or greater than 0.276 were considered as the high expression group ($n=42$). The cutoff value was the most significant one for prognostic prediction by log-rank plot analysis.

Immunohistochemistry of OPN Protein Expression in Tissue Samples

To determine the localization of OPN protein, immunohistochemistry was performed in the resected CRC tissue samples and corresponding non-tumor tissue samples. Immunohistochemical analysis revealed that OPN staining was predominantly stronger in the cytoplasm of CRC cells than in the cytoplasm of non-tumor intestinal epithelial cells (Fig. 3). These results were consistent with the results from real-time RT-PCR analysis of OPN mRNA expression in tissue samples.

Correlation Between OPN Expression and Clinicopathological Factors

Table 1 summarized the correlation between the clinicopathological factors and OPN mRNA expression in tumor tissue samples from the 84 CRC patients. The expression level of OPN mRNA was significantly correlated with lymph node metastasis ($P=0.0033$), lymphatic invasion ($P=0.0061$), venous invasion ($P=0.0008$), and TNM stage ($P=0.0012$). No significant correlation was observed between the expression level of OPN mRNA and clinical–pathological variables including gender, age, tumor size, tumor location, and tumor location.

Correlation Between OPN Expression and Patient's Survival

To determine the effect of OPN mRNA expression on CRC patients' survival, the disease-free and overall survival rates for all patients were then assessed. Figure 4a and b showed the disease-free and overall survival curves obtained by the Kaplan–Meier method, with statistical significance evaluated using the log-rank test. The cases with high OPN mRNA expression had significantly shorter disease-free and overall survival time than those with low OPN mRNA expression ($P=0.0047$ and 0.0125, respectively). In addition, the overall and disease-free survivals of TNM stage (I+II) cases with high OPN mRNA expression were significantly shorter than TNM stage (I+II) cases with low OPN mRNA expression ($P=0.0347$ and 0.0056, respectively). In TNM stage (III+IV), the overall and disease-free survivals of those cases with high OPN mRNA expression were also significantly shorter than those cases with low OPN mRNA expression ($P=0.0008$ and 0.0113, respectively; Fig. 5).

Multivariate Analyses for Prognosis of CRC Patients

Multivariate analyses were performed using the Cox proportional hazards model to determine the prognostic value of OPN mRNA expression (Table 2). In the multivariate analysis, potential prognosis factors such as age and gender of the patient, tumor size, tumor differentiation, lymph node metastasis, lymphatic invasion, venous invasion, TNM stage, and OPN mRNA expression were included in the Cox proportional hazards model. Results showed that, in addition to TNM stage and lymph node metastasis, the status of OPN mRNA expression was an independent prognostic factor for human CRC (RR, 2.775; 95% confidence interval, 2.334–3.811; $P=0.008$).

Discussion

Colorectal cancer has become one of the most prevalent cancers in the world. Although current clinical practice in colorectal cancer screening has contributed to a reduction in mortality, the prognosis of CRC patients remains very poor in bulky or locally advanced disease.[17] Many clinicopathological parameters including carcinoembryonic antigen (CEA) and CA19–9 are commonly used in CRC clinics;[18,19] however, their clinical usefulness remains contro-

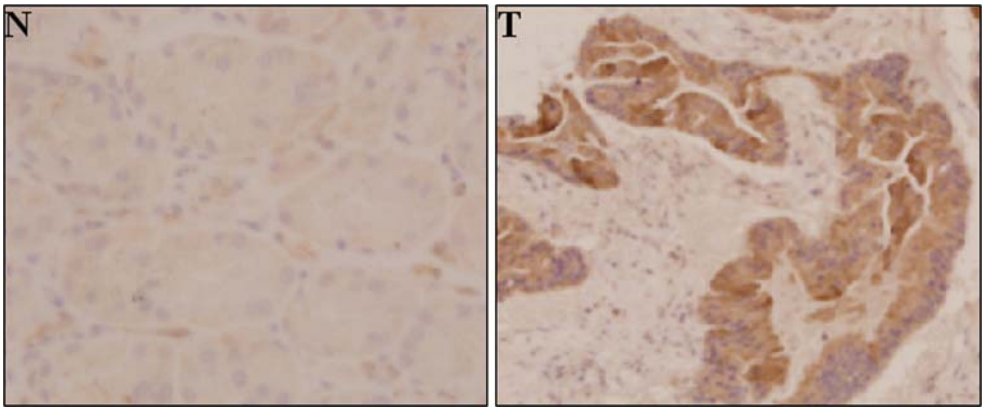

Figure 3 Immunohistochemical analysis of OPN protein expression in tissue samples. OPN immunostaining was strongly positive in the cytoplasm of the CRC cells. *N* non-tumor tissue, *T* tumor tissue.

versial from diagnostic, prognostic, and surveillance points of view. Novel molecular markers to improve the prediction of patient's clinical outcome could appear to be of considerable value when designing individualized treatment procedures, which will be helpful in reducing negative side effects for patients with a good prognosis. With the advent of genomic and proteomic technologies, it has become possible to explore novel cancer-related genes to serve as diagnostic markers and molecular targets for predicting the treatment response and prognosis of CRC patients.

Recently, many studies showed that OPN gene was highly expressed in many human cancers and the high levels of OPN expression could promote tumor progression and cell survival through Akt activation and the induction of HIF-1α expression.[20] Moreover, OPN has been proved to regulate cell motility, invasion, and metastasis formation of tumor cells.[21,22] Therefore, targeting OPN with RNA aptamers or small interference RNA (siRNA) may have therapeutic benefit for tumor patients in the future.[23–25]

Table 1 Clinicopathological Factors and the Expression of OPN mRNA in 84 CRC Tissues

Factors	OPN expression		*P* value
	High (*n*=42)	Low (*n*=42)	
Sex			0.0784
Male	25	22	
Female	17	20	
Age (year)			0.1034
≤55	13	18	
>55	29	24	
Tumor size (cm)			0.2130
≤5.0	16	19	
>5.0	26	23	
Tumor differentiation			0.0912
Well	11	12	
Moderate	26	26	
Poor	5	4	
Lymph node metastasis			0.0033
Absent	13	24	
Present	29	18	
Lymphatic invasion			0.0061
Absent	12	27	
Present	30	15	
Venous invasion			0.0008
Absent	17	26	
Present	25	16	
TNM stage			0.0012
I/II	15	30	
III/IV	27	12	
Tumor location			0.2015
Colon	28	31	
Rectum	14	11	

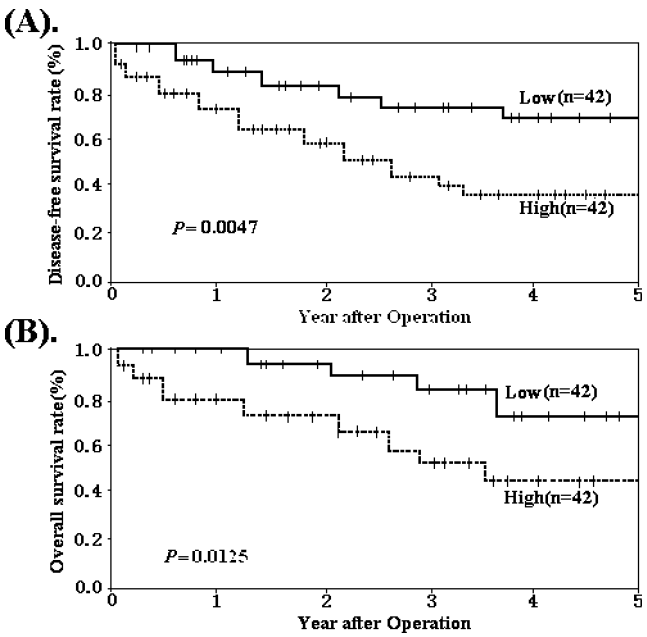

Figure 4 Kaplan–Meier disease-free (**a**) and overall (**b**) survival curves of CRC patients according to OPN mRNA expression. The CRC patients with high OPN expression showed significantly shorter disease-free survival and overall survival rates than those with low OPN expression (*P*=0.0047 and 0.0125, respectively; log-rank test).

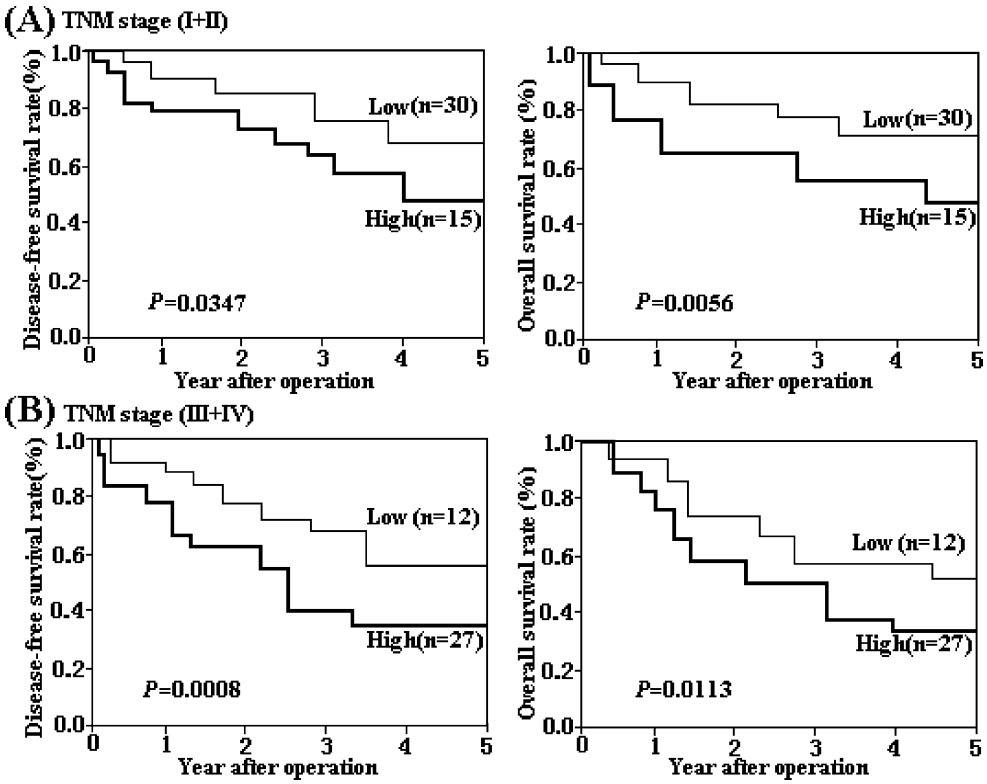

Figure 5 The overall and disease-free survivals of those cases with TNM stage (I+II) and (III+IV).

Moreover, cyclooxygenase-2 inhibitors downregulate osteopontin and Nr4a2-new therapeutic targets for colorectal cancers, which might be associated with blockade of NR4A2 and Wnt signaling.[26] Yeatman et al. reported that osteopontin might be correlated with colon cancer progression.[27] Rohde et al. also reported that expression of osteopontin, a target gene of de-regulated Wnt signaling, could predict survival in colon cancer.[28] Wai et al. showed that osteopontin silencing by small interfering RNA suppresses in vitro and in vivo CT26 murine colon adenocarcinoma metastasis.[29] All these findings suggest that OPN expression may play an important role in colorectal cancer progression and metastasis. Recently, although osteopontin has been identified as lead marker of colon cancer progression, using pooled sample expression profiling,[30] little is known about clinical significance of OPN mRNA expression in CRC.

In the present study, this is the first time to apply the real-time RT-PCR method to quantify expression levels of OPN mRNA in paraffin-embedded tumor tissues obtained by initial biopsy and to elucidate the correlation of OPN mRNA expression with clinicopathologic features and prognosis in human CRC. It has recently become possible to isolate RNA from formalin-fixed paraffin-embedded tissue and to perform RT-PCR assay using this RNA.[31,32] In fact, several reports have described gene analyses using RNA extracted from paraffin-embedded tissues from various tumor tissues described quantitative analysis of mRNA in archived and routine diagnostic tissues. Our study is the largest series to date examining OPN mRNA

Table 2 Multivariate Analysis of CRC Prognosis by Cox Analog

Variables	β	*P* value	RR	95% CI
Gender (female versus male)	0.678	0.426	1.124	0.783–1.341
Age (≤55 versus >55)	−0.232	0.157	2.036	0.923–3.156
Tumor size (≤5.0 versus >5.0)	0.456	0.172	1.089	0.433–1.088
Tumor differentiation (well/moderate + poor)	−0.007	0.885	0.935	0.776–2.453
Lymph node metastasis (absent/present)	0.338	0.015	1.057	1.873–3.045
Lymphatic invasion (absent/present)	0.545	0.508	1.676	0.378–2.885
Venous invasion (absent/present)	0.326	0.155	0.783	0.232–1.784
TNM stage (I+II/III+IV)	0.107	0.026	1.812	1.763–2.112
Tumor location (colon/rectum)	−0.113	0.107	1.066	0.211–1.987
OPN expression (low/high)	0.335	0.008	2.775	2.334–3.811

RR risk ratio, *95% CI* 95% confidence interval

expression in CRC patients and its correlation with clinical parameters, and the first investigation evaluating patients in China. Firstly, we observed that the expression levels of OPN gene in human colorectal cancer cell lines were significantly higher than those in normal human intestinal epithelial cell line at both transcriptional and translational levels. Moreover, we also found that CRC tissues showed significantly higher expression levels of OPN mRNA than non-tumor tissues by conventional or real-time quantitative RT-PCR assays, suggesting that OPN might be used as a diagnostic marker for CRC. Data generated from the immunohistochemistry analyses also further testify the results of RT-PCR. Additionally, our study provided evidence that the high level of OPN mRNA expression in CRC was closely correlated with lymph node metastasis, lymphatic or venous invasion, and TNM stage. The disease-free survival and overall survival rates of CRC patients with high OPN expression were significantly shorter than those of CRC patients with low OPN expression. The disease-free survival and overall survival rates of TNM stage (I+II) or (III+IV) cases with high OPN mRNA expression were also significantly shorter than those cases with low OPN mRNA expression. To our knowledge, this is the first report showing an association between OPN mRNA expression and prognosis. Multivariate analysis showed that the status of OPN mRNA expression might be a prognostic marker for CRC patients. Further studies are needed to validate results of the present report in order to establish the role of OPN mRNA as a prognostic marked in CRC. In addition whether functional analyses of OPN will have utility in human CRC treatment remains to be proven.

Conclusion

In conclusion, our study indicates that the expression of OPN mRNA in CRC is significantly associated with prognosis and has probability of being a clinical prognostic marker for CRC. Since the number of patients in the present study is small, further study of a larger case population is necessary to confirm clinical significance of OPN mRNA expression in human CRC.

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ORIGINAL ARTICLE

Evolution of Surgical Treatment of Amebiasis-Associated Colon Perforation

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Abstract
Background Amebiasis is a worldwide health problem that mainly affects developing countries. Invasive amebiasis tends to develop complications, and among these, perforation of the colon, although infrequent (1.9–9.1%), is the most lethal. Surgical treatment in these cases should be carried out in a timely fashion prior to the presentation of systemic repercussions or death. In the present study, we analyzed a total of 122 cases of invasive amebiasis-associated colon perforation.
Methods and Study Design We conducted a clinical, retrospective, and observational study and presented cases of colonic perforation observed over the past 30 years at the Medical-Surgical Emergency Service of the Mexico City-based Hospital General de México OD during the 1970–1999 period.
Results During this time, a total of 19,916 emergency abdominal surgeries were performed. One hundred twenty-two of these procedures corresponded to cases of colon perforation by ameba, which represents 0.6%; 80 patients were men (65.6%) and 42 were women (34.4%), with an average age of 48 years. Multiple colon perforation was 74%, with right colon the most affected (90.5%). Depending on the perforation's extension and localization, right hemicolectomy with ileostomy were performed in 53 patients (43.45%), subtotal colectomy with ileostomy in 43 (35.25%), left hemicolectomy with transverse colostomy in 12 (9.83%), exteriorization of perforated left colon (stoma) in 13 (10.65%), and primary closure with exteriorization in one patient (0.8%). Post-operative complications were present in 48 patients (39.3%), and 20 cases were related with the creation of a stoma. Eighteen of these cases were due to persistent abdominal sepsis and ten due to toxic colon; the latter correspond solely to patients with initial nonresective treatment. General mortality was 40%, with 32% (17 of 53 cases) of mortality in those submitted to right hemicolestomy, 16.7% (two of 12) of left hemicolestomy, 44.2% (19 of 43) in those in whom a subtotal colectomy was performed, with 76.9% (ten of 13) patients with exteriorization of the perforated right colon, and with 100% (one of one patient) mortality with primary closure.
Conclusions Perforation is the most frequent surgical complication of invasive amebiasis of the colon, occurring principally in masculine gender and in the fourth decade of life. Resection and stoma creation is the procedure of choice that can resolve the septic focus from the first surgical procedure, depending on the general status of the patient. However, morbidity and mortality are high, and there is a tendency for these to be lower on comparing initial cases with those with recently conducted surgical procedures.

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Keywords Colon · Mortality · Perforation · Amebas · Amebiasis · Surgery · Colostomy · Sepsis · Metronidazole · Mexico

Introduction

Amebiasis is the second most frequent parasitosis worldwide,[1,2] affects approximately 10% of the population,[3,4] and is the second or third cause of death due to parasitosis.[5,6] In Mexico, it is considered that the population is the carrier of 20% but that only 2% suffer from the disease; however, it is thought that this number is underestimated because a prevalence has been found of up to 55% in some low-socioeconomic-level zones in Mexico City.[2,6–8] The range of the invasive disease comprises from a clinical symptom of slight diarrhea up to fulminating events of colon and liver; within this range, we find the intestinal and hepatic forms as well as the most important complications for its potential mortality.[4] The colon is the main organ affected, and colitis can present in five different forms: asymptomatic colonization, acute amebic colitis, fulminating colitis, appendicitis,[9,10] and ameboma.[11] Intestinal perforation is the most serious complication of fulminating colitis and can eventually be fatal; fortunately, these cases of fulminating or necrotizing colitis occur in only 1.9–9.1% of cases; however, they cause very high mortality.[12,13] Thus, it is indispensable to suspect the disease, to detect the disease as well as its complications, and to treat the disease in a timely fashion to be able to diminish high morbidity and mortality to the maximum degree. In the present study, we evaluated the frequency of ameba-associated colon perforation, its tendency over the past three decades, and the different surgical procedures utilized for its treatment.

Methods

There were a total of 19,916 abdominal surgery procedures performed at the Emergency Unit of General del Hospital General de México OD Surgery Service during a 30-year period (1970–1999). We conducted a retrospective, transversal, and descriptive review of cases of ameba-associated colon perforation confirmed by histopathologic study, found 122 patients with complete records, and studied the following variables: age, gender, socioeconomic condition, preoperative signs and symptoms, surgical procedure, associated complications, preoperative mortality, days of hospital stay, and days in intensive care. Patients were excluded who were <16 years of age and those without a diagnosis confirmed by the pathology.

Histopathologic Study

We systematically reviewed the biopsies performed prior to the procedure with micro- and macrosurgical analyses of the small and large intestine. These samples were added to 10% formol and performed with hematoxylin and eosin stain.

Study Population

This included all patients with a surgical intervention for acute abdominal pathology during the period from January 1970 to December 1999 with transoperative findings of colon perforation-associated peritonitis.

Results

We obtained a total of 122 patients who were submitted to ameba perforation-related surgery during a 30-year study period (1970–1999). These patients represented 0.61% of all abdominal surgery cases with emergency abdominal surgery.

With respect to gender, we found 82 men (65%) and 45 women (35%), with an average age of 48 years (range, 16–89 years).

Regarding antecedents of importance, we found alcoholism in 36% and smoking in 25% of the total number of patients.

Preoperative Signs and Symptoms

Forms of clinical presentation varied widely, with atypical clinical symptoms predominating with an interval of 5–25 days of evolution characterized by diarrheic syndrome with bloody mucus in evacuations, rectal straining at stool, rectal tenesmus, an attack on the patient's general health status, and abdominal pain. Generalized abdominal pain predominated in 95% of cases, distension in 80%, data on peritoneal irritation in 89%, acute diarrhea in 60%, and chronic diarrhea in 5%.

Fever in 30% was quantified as >37.5°C, with an average of 5 days prior to hospital admission, with slight dehydration in 20% of patients, severe dehydration in 50%, and type 1 hypovolemic shock-state hemodynamic data in 23% of patients.

Radiological Findings

Results showed intestinal occlusion in 48% and pneumoperitoneum in 35%, with the former associated with free subdiaphragmatic air, corroborated by X-ray of thorax and abdomen.

Average Days of Hospital Stay

There was an average of 10 days of total hospital stay per patient. The average stay in the intensive care unit was 4 days in each patient.

We found signs of peritoneal irritation in all cases. Cases of severe colitis (toxic colon or fulminating colitis) were present with systemic repercussion fundamentally with systemic inflammatory response, high blood pressure, and data of abdominal sepsis.

Laboratory studies showed leukocytosis, albumin <3 mg/dL in 84% of cases, and 15,000–21,000 leukocytes in 76% of cases.

Histopathological Study

We analyzed biopsies of small intestine and colon, primarily in lesions corresponding, in the great majority, to colon. In their diverse anatomical presentations, we observed macroscopically that initial lesions demonstrated colonic ulcer covered with necrotic material (Fig. 1). Other cases presented extensive destruction of the colonic mucosa with numerous confluent ulcerated areas (Fig. 2). On analyzing the surgical pieces microscopically, we observed an ulcerative lesion that extended to the muscle layer, with diffusion toward the submucosa. In the fundus of the ulcer, there was a group of amebas, as can be appreciated in Fig. 3. With greater augmentation, we were able to observe trophozoites of *Entamoeba histolytica*, which are characteristic of this type of colon (Fig. 4).

Multiple colon perforation was present with greater frequency, corresponding to 75% of cases (92 cases) and unique perforation in 25% (30 cases). Evaluation of surgical risk in all patients was carried out according to American Society of Anesthesiologists (ASA) criteria; we found that cases with surgical procedures were classified as ASA II in 33 patients (27%), ASA III in 55 patients (45%), and ASA IV in 34 patients (26.8%). From 1990 on, the Acute Physiology and Chronic Health Evaluation II disease classification was employed in ten patients, who obtained an average score of 18 (range, 5–29), finding that 50% had a score of >15. Diagnosis of invasive ameba-associated colon perforation was suspected in only 55 cases, that is, in 45% of cases; however, in no case was it suspected that the preoperative diagnosis would be associated with invasive amebiasis, rendering a preoperative diagnostic accuracy of 0% for invasive amebiasis.

With regard to surgical treatment for control of intra-abdominal septic foci, this was as follows: right hemicolectomy with ileostomy and Hartmann procedure in 53 of 122 patients (43.4%); left hemicolectomy with transversal colostomy of the transverse colon and Hartmann procedure in 12 of 122 patients (9.83%); subtotal colectomy with ileostomy and Hartmann procedure in 43 of 122 patients (35.25%); exteriorization and colostomy at perforation site

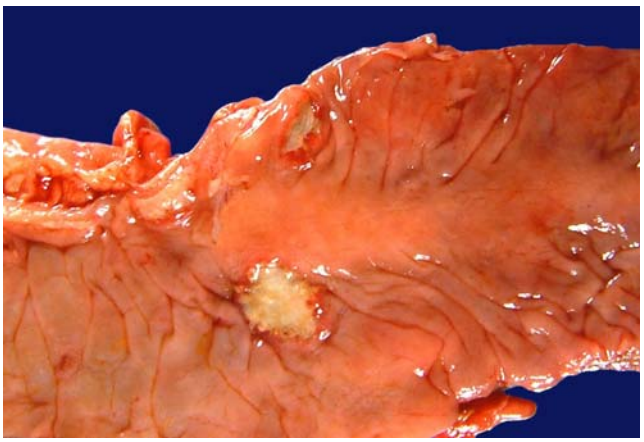

Figure 1 Initial lesions, with ulcer covered with necrotic material.

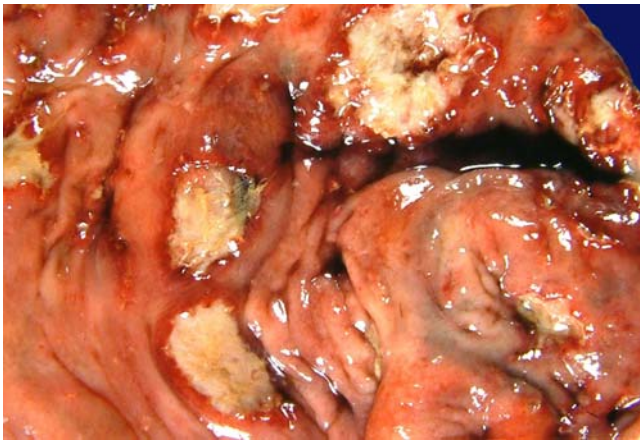

Figure 2 Extensive destruction of the colonic mucosa by numerous confluent ulcerated areas.

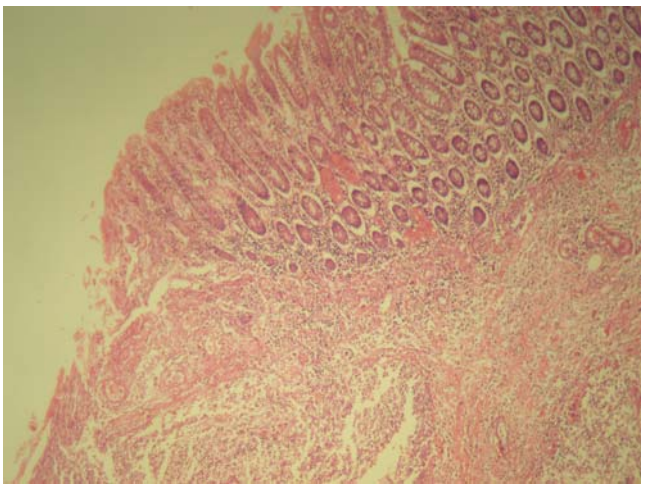

Figure 3 We are able to observe microscopically an ulcer that extends to the muscle layer, with diffusion toward the submucosa. A group of amebas is observed at the fundus of the ulcer.

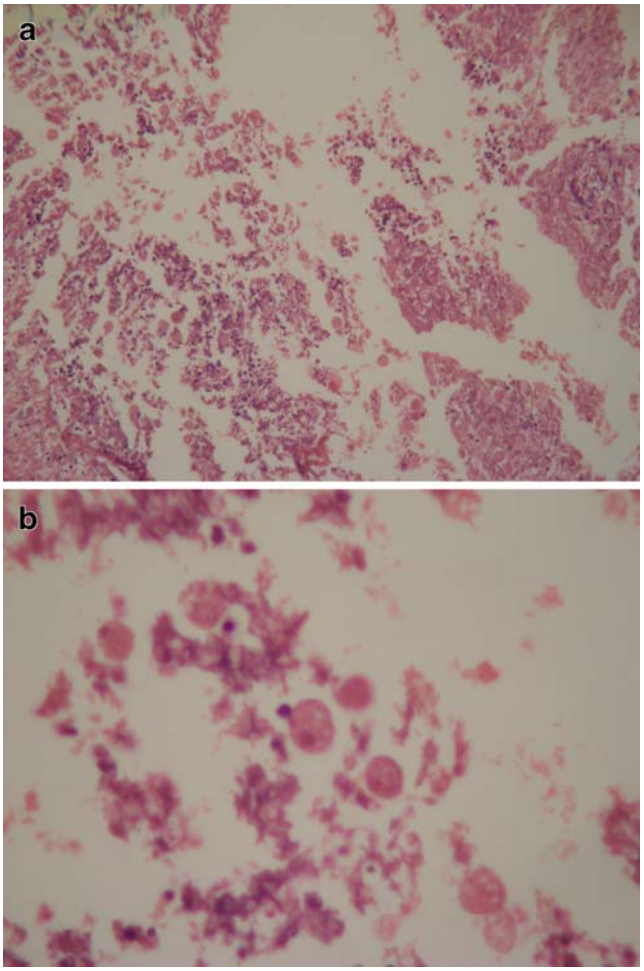

Figure 4 **a**, **b** *E. histolytica* trophozoites are observed in greater detail.

in 13 of 122 patients (10.6%), and primary closure in one patient (0.8%). Therefore stoma formation was carried out in 121 cases (99.2%), and in 35 patients (28.7%), two to five multiple reinterventions were performed as needed for control of abdominal sepsis.

Mortality according to the surgical procedure conducted was as follows: right hemicolectomy, 32% (17 of 53); left hemicolestomy, 16.7% (two of 12); subtotal colectomy, 44.2% (19 of 43); exteriorization and colostomy, 76.9% (ten of 13), and primary closure in one patient, yielding a general mortality of 49 patients (40%); these can be observed in Table 1 under headings for each decade and according to each surgical procedure. The patient who underwent primary closure was excluded from Table 1 (column 3, total of 121 cases) due to being the sole patient with this treatment type. The general mortality of the present study was 40%, this being a total of 48 patients. According to the ASA classification, two patients were classified preoperatively with ASA II, 16 with ASA III, and 30 cases with ASA IV.

Number and cases distributed by decade and their associated mortality are shown in Table 2.

Discussion

The frequency of colon perforation by amebiasis in Mexico has diminished considerably according to data provided in the present study on the decades of the 1970s, 1980s, and 1990s. According to our survey, late complications of the surgical event reflect greater mortality at the beginning of the study time period (1970s), reaching alarming numbers of 50% of deaths associated with complications as compared with complications observed in the 1990s of 10%. Among causes for this tendency, we find greater knowledge of amebic pathology, adequate antibiotic scheme (mainly with the use of metronidazole), medical care and advances in intensive therapy, and a colostomy-derived surgical procedure, which in the majority of cases have provided a lower rate of mortality and complications in these patients.

E. histolytica is a protozoan that evolves in cyst form, which is resistant to gastric secretion up to the trophozoite form and possesses lytic and destructive capacities in the colon. Infection is related with multifactorial mechanisms including the following: (1) the ability for motility and trophozoite phagocytosis and (2) the release of preformed peptides and proteases that produce lethal effects in white cells,[14] carried out by means of an adherence sequence, tissue invasion, cytolysis, and inflammatory response.[7] The trophozoite adheres to the cells of the mucosa by means of a cell surface protein denominated adherence lectin (Ga1/Ga1 NAc), amebopores, protein kinases that degrade extracellular protein and that give rise to disruption of the colonic mucosa, and the epithelial barrier.[15–19] Amebapores are polypeptides that are associated with amebic virulence and comprise pore-forming cells in the white cell with cytolytic activity that induce the release of Na^+, K^+, and Ca^+ from the soft cell and, finally, cytolysis.[18] The inflammatory response is mediated by amebic phospholipases; however, the response is observed to be potentiated by cytolysis of epithelial and inflammatory cells, which add another proinflammatory mechanism.[20] Adherence and the inflammatory response is followed by an intracellular increase of calcium in the white cell until their destruction—in seconds and up to 20 min—of adherence.[20] Microscopically, ulcerations are caused that extend into the submucosa, provoking abundant micro-hemorrhages that progress underneath the mucosa, forming the characteristic "shirt-button ulcers."[13] Progression of these lesions can result in loss of the mucosa and submucosa and can eventually reach the serose and fracture it. All of these effects interact synergically with the bacterial flora and with the host (susceptibility, age, nutrition, and immunity).[4,21]

Table 1 Mortality by Decade and by Surgical Procedure

Surgical procedure	Decade	Number of cases	Mortality (%)	Mortality ASA stage
Right hemicolectomy	1970–1979	35	13 (37)	13 patients: ASA II, 1; ASA III, 5; ASA IV, 7
	1980–1989	15	4 (26.7)	4 patients: ASA III, 1; ASA IV, 3
	1990–1999	3	0 (0)	No deaths
Total		53	17 (32)	
Left hemicolectomy	1970–1979	4	1 (25)	1 patient: ASA IV, 1
	1980–1989	6	0 (0)	No deaths
	1990–1999	2	1 (50)	1 patient: ASA III, 1
Total		12	2 (16.7)	
Subtotal colectomy	1970–1979	31	15 (48.4)	15 patients: ASA II, 1; ASA III, 6; ASA IV, 8
	1980–1989	10	4 (40)	4 patients: ASA III, 1; ASA IV, 3
	1990–1999	2	0 (0)	No deaths
Total		43	19 (44.2)	
Exteriorization and colostomy	1970–1979	8	6 (75)	6 patients: ASA III, 1; ASA IV, 5
	1980–1989	4	3 (75)	3 patients: ASA III, 1; ASA IV, 2
	1990–1999	1	1 (100)	1 patient: ASA IV, 1
Total		13	10 (76.9)	
Total		121[a]	48 (40)%	ASA II, 2; ASA III, 16; ASA IV, 30

ASA American Society of Anesthesiologist

[a] The patient who underwent primary closure was excluded due to being the sole patient with this treatment type

These intestinal lesions, characteristic on healing, leave minimal or null scarring.[13]

The prevalence of amebiasis in our environment continues to be high;[5,22] however, we appreciate in this report a progressive diminution of the number of cases of invasive amebiasis with the passing of the decades,[23] in agreement with present-day amebiasis in Mexico, possibly related with medical care programs, of medical care, amebiasis detection, and facility of access to antimicrobial drugs. It is considered that approximately 90% of patients with *E. histolytica* colonization are healthy carriers and can be cured spontaneously; however, 10% of the remaining trophozoites invade the colon and cause colitis in diverse degrees in blind colon, ascendant colon, and/or rectosigmoids, in segmentary fashion and combined, and this can come to affect the entire colon.[24,25] Fulminating colitis with perforation takes place in 0.5% of cases and is the most dangerous complication of invasive amebiasis, thus requiring emergency surgical treatment.[13,26,27]

Surgical treatment was directed toward removing or controlling the infection foci, as well as the effects of the associated peritonitis, and consisted of procedures conducted according to the conditions of the colon and the patient's general health status. Right hemicolectomy was carried out in the majority of cases, followed by subtotal colectomy and left colectomy; however, a small group of very grave patients required exteriorization and in-site perforation colostomy as part of damage-control surgery in critical-state patients, who despite maximal-benefit surgery had very high mortality. Progressive diminution is appreciated in mortality from the decade of the 1970s toward lower mortality in the 1990s (Table 2), which is related with timely diagnosis, present-day peri-operative management and intensive therapy, as well as the effectiveness of antiamebic and antimicrobial drugs.

In terms of acute clinical symptoms with an evolution time of <48 h, we are able to note that patients presented a smaller percentage of complications and morbimortality.

Table 2 Number of Cases by Decade and Their Mortality

Decade	Number of cases	Number of deaths	Mortality (%)
1970–1979	76	36	47.3
1980–1989	37	8	21.6
1990–1999	9	1	11
Totals	122	45	36.9

In conclusion, the invasion of the colon by amebas is a frequently found disease in Mexico and in countries with a high incidence of amebiasis. However, as described in the present study, a diminution has been observed in the number of cases of amebiasis in recent years. Colon perforation is the most serious complication. The most frequent data that characterize this pathology were severe systemic response, hypoperfusion, and abdominal sepsis. Colon perforation is the result of the necrosis on the colony wall, with destruction of the colonic mucosa and the presence of amebas. We must consider that a sole patient died, this a case with unique perforation that was sutured with primary closure, given that the remainder of the mucosa was found to be eroded in the postmortem study, with necrosis, tissue invasion, cytolysis, and microhemorrhagic zones that at the very short term ended in colon perforation. Thus, surgical treatment is wide resection of colon and stoma, not carrying out primary anastomosis, and primary closure of the perforation is contraindicated in general. In very grave patients with high trans-operative risk, we found very high mortality despite loop colostomy at the perforation site and later programmed reintervention.

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ORIGINAL ARTICLE

Enhanced Recovery After Surgery (ERAS) Versus Conventional Postoperative Care in Colorectal Surgery

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Abstract
Background Enhanced Recovery After Surgery (ERAS) programs are associated with reduced hospital morbidity and mortality. The aim of the present study was to evaluate whether the introduction of ERAS care improved the adverse events in colorectal surgery. In a cohort study, mortality, morbidity, and length of stay were compared between ERAS patients and carefully matched historical controls.
Methods Patients were matched for their type of disease, the type of surgery, P-Possum (Portsmouth-Possum), CR-Possum (Colorectal-Possum) Physiological and Operative Score for Enumeration of Mortality and Morbidity (POSSUM), gender, and American Society of Anesthesiologists (ASA) grade. The primary outcome measures of this study were mortality and morbidity. Secondary outcome measures were fluid intake, length of hospital stay, the number of relaparotomies, and the number of readmissions within 30 days. Data on the ERAS patients were collected prospectively.
Results Sixty-one patients treated according to the ERAS program were compared with 122 patients who received conventional postoperative care. The two groups were comparable with respect to age, ASA grade, P-Possum (Portsmouth-Possum), CR-Possum (Colorectal-Possum) score, type of surgery, stoma formation, type of disease, and gender. Morbidity was lower in the ERAS group compared to the control group (14.8% versus 33.6% respectively; P=<0.01). Patients in the ERAS group received significantly less fluid and spent fewer days in the hospital (median 6 days, range 3–50 vs. median 9 days, range 3–138; P=0.032). There was no difference between the ERAS and the control group for mortality (0% vs. 1.6%; P=0.55) and readmission rate (3.3% vs. 1.6%; P=0.60).
Conclusion Enhanced Recovery After Surgery program reduces morbidity and the length of hospital stay for patients undergoing elective colonic or rectal surgery.

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Keywords Enhanced recovery · Colorectal surgery · Abdominal surgery · Fast track · Mortality · Morbidity

Introduction

Colorectal resections are associated with an in-hospital stay of 6 to 11 days and a complication rate of 15% to 20%. "Fast-track" or enhanced recovery programs are developed to improve perioperative care in these patients.[1–3]

Enhanced Recovery After Surgery (ERAS) protocols aim at reducing the surgical stress response and optimizing recovery, thus reducing the length of hospital stay. All elements in ERAS separately have been shown to improve patient outcome. Preoperative education about the ERAS program diminishes anxiety and is associated with an earlier return of gastrointestinal motility after surgery.[4] Preoperative carbohydrate loading is associated with earlier return of gastrointestinal motility and a significantly shorter hospital stay.[5] Colonic lavages are associated with patient discomfort and electrolyte disturbances and can safely be avoided in elective colonic surgery.[6–10] Epidural analgesia provides better treatment of postoperative pain and leads to an earlier gastrointestinal motility.[11,12] Hypotension, a common physiologic side effect of epidural analgesia, can be treated safely with a vasopressor.[13] Postoperative pain relief is best managed without opioid analgesia because of the adverse effects it has on the central nervous system, respiratory function, and gastrointestinal function.[14]

Intraoperative fluid management aiming at a zero balance reduces the number of patients who experience morbidity and shortens the time to the recovery of gastrointestinal motility and reduces hospital stay.[15,16] Early postoperative enteral feeding shows a reduction in the risk of postoperative complications, hospital stay, and mortality.[17] Bed rest after surgery is undesirable because it impairs pulmonary function and tissue oxygenation and predisposes to pulmonary complications.[18] To avoid this, mobilizing patients as soon as possible is an important factor in improving postoperative care.

The aim of the present study was to compare mortality, morbidity, and in-hospital stay in a cohort of carefully matched patients receiving conventional postoperative care and the ERAS program to evaluate the clinical relevance of the improved perioperative care.

Methods

Identification of Patients

A cohort of consecutive patients that underwent elective open colonic or rectal resection following the ERAS regime was compared with a matched historical cohort who underwent colonic or rectal resection with conventional perioperative care. Between May 2006 and July 2008, patients who were above 18 years of age and were scheduled for any colonic or rectal resection and had an American Society of Anesthesiologists (ASA) grade of 1–3 were treated according to an ERAS program. In all patients, a colorectal resection was performed, with or without primary anastomosis. A loop ileostomy was created in any low rectal anastomosis and in patients with a high estimated risk to develop anastomotic leakage.

Running two protocols of postoperative care in one surgical ward would be prone to bias in a randomized trial. For this reason, a matched cohort study was performed. Since all eligible patients operated in the time span mentioned above received ERAS, a historical control group was used, composed of patients that would have been eligible for ERAS in the successive period. Patients in the control group were operated from January 2003 to May 2006. The latter group was obtained from a surgical database. All procedures were performed by the same team of surgeons.

Each patient from the ERAS group was matched with two patients from the control group on age, gender, P-Possum (Portsmouth-Possum), CR-Possum (Colorectal-Possum) Physiological and Operative Score for Enumeration of Mortality and Morbidity (POSSUM), American Society of Anesthesiologists grade, type of disease, and surgical procedure.

Criteria of Exclusion

Patients with an ASA grade 4–5 and younger than 18 years were excluded from analysis.

ERAS Protocol

In the outpatient clinic, patients who were treated according to the ERAS protocol were informed about the operative procedure and rehabilitation program. Before surgery, patients were consulted by an anesthesiologist and if necessary by a dietitian. All patients were admitted the day before surgery and could eat until midnight, including four drinks of carbohydrate (PreOP®, Nutricia; Numico, Zoetermeer, the Netherlands). Patients could drink water freely until 2 h before surgery. Two hours before surgery, patients received two drinks of PreOP®.

In the case of a planned left-sided resection, a phosphate enema was given the evening before and on the day of surgery. Thrombotic prophylaxis (nadroparin 2850 IE) was started the day before surgery. Antibiotic prophylaxis (cefazolin 2 g and metronidazole 500 mg intravenously) was given 30 min before incision. A transverse incision was preferred, except in Crohn's disease and rectal surgery. In order to maintain a normothermic body temperature, the temperature in the operating theatre was increased to 22°C, and a Bair hugger and warmed intravenous fluids were

applied. Anesthesia consisted of a combination of epidural analgesia and general anesthesia. Before the induction of anesthesia, an epidural catheter was inserted at level Th7/8. After the confirmation of proper placement by a test dose (Lignocaine 2% 3 ml), bolus infusion of 4 ml sufentanil produced sufficient analgesia for the first 30 min of surgery. Afterwards, repeated bolus infusion of 2–3 ml bupivacaine 0.5% maintained the operative analgesia. No additional opioids were given intravenously. At the end of surgery, continuous epidural infusion of 6 ml/h of ropivacain 0.2% with 1 μg/ml sufentanil was started for postoperative analgesia. This infusion lasted for 2 days postoperatively.

During and after surgery, hypotension was preferably treated with a vasopressor agent (ephedrine 5 mg or phenylefrine 0,1 mg) instead of intravenous fluid bolus in order to maintain a neutral fluid balance throughout the perioperative period. No drains were used except in rectal surgery, and the nasogastric tubes were removed immediately after surgery. To prevent postoperative nausea and vomiting, 4 mg ondansetron was administered intravenously at the end of surgery. After surgery, the patient was allowed to drink water, and, if tolerated, patients received two drinks of PreOP®. On postoperative day 1, patients were offered a normal diet. Intravenous fluid administration aimed at a urine production of at least 0.5 ml/kg and the total fluid intake should not exceed 2 l/24 h. Fluid balances were recorded daily. A structured mobilization program was also included in the ERAS protocol. Patients were encouraged to sit out of bed on the day of surgery and to walk the length of the ward on the first postoperative day. The inserted urinary catheter was removed at the same time as the thoracic epidural catheter. Subsequently, pain was managed with paracetamol and nonsteroidal anti-inflammatory drugs. The use of oral opioid analgesics was limited to relieve breakthrough pain.

Each protocol item and any deviation from the protocol was noted on a bedside checklist. Discharge criteria were: adequate pain relief on non-opioid oral analgesia, normal food intake, and return to preoperative mobility level.

Conventional Postoperative Care Protocol

The perioperative care, before the ERAS program was implemented, was according to the surgeon's preference. Thrombotic and antibiotic prophylaxis was given and the practice of bowel preparation was largely abandoned. Discharge criteria were identical to the ERAS.

Data Extraction

After retrieving all reports and information from paper and electronic patient files, the following data were extracted: sex, age, indication for surgery, type of surgery, ASA grade, POSSUM score, P-POSSUM score, CR-POSSUM score,

Table 1 Definitions of Separate Complications

Surgical complications	
Wound hemorrhage	Local hematoma requiring evacuation
Deep hemorrhage	Postoperative bleeding requiring re-exploration
Burst abdomen	Deep wound breakdown, requiring surgical closure of the abdominal wall
Deep infection	The presence of an intra-abdominal collection confirmed clinically or radiologically
Anastomotic leak	Discharge of bowel content via the drain, wound, or abnormal orifice
Wound infection	Wound cellulitis or the discharge of purulent exudate and the necessity of opening the wound
Medical complications	
Chest infection	Production of purulent sputum with positive bacteriological cultures, with or without chest radiography changes or pyrexia or consolidation seen on chest radiograph
Urinary infection	The presence of $>10^5$ bacteria/ml with the presence of white cells in the urine in previously clear urine
Septicemia	Positive blood culture
Pyrexia of unknown origin	Any temperature above 37°C for more than 24 h occurring after the original pyrexia following surgery (if present) had settled, for which no obvious cause could be found
Deep venous thrombosis and pulmonary embolus	When suspected, confirmed radiologically by venography or ventilation/perfusion scanning or diagnosed at post mortem
Cardiac failure	Symptoms or signs of left ventricular or congestive cardiac failure (alteration from preoperative measures)
Impaired renal function	Arbitrarily defined as an increase in blood urea of >5 mmol/l from preoperative levels
Hypotension	A fall in systolic blood pressure below 90 mmHg for more than 2 h as determined by sphygmomanometry or arterial pressure transducer measurement
Respiratory failure	Respiratory difficulty requiring emergency ventilation

Complications had to occur within 30 days after surgery

Table 2 Patient Characteristics and Types of Surgery

	ERAS (%) (n=61)	Control (%) (n=122)	P value
Characteristic			
Male[a]	36.1 (n=22)	50.8 (n=62)	0.06
Female[a]	63.9 (n=39)	49.2 (n=60)	
Age (years)[b]	57 (17.6)	60 (17.4)	0.39
POSSUM[b]	7.50 (6.1)	8.37 (6.7)	0.37
P-POSSUM[b]	2.59 (2.9)	2.57 (2.8)	0.92
CR-POSSUM[b]	2.75 (3.2)	2.79 (3.2)	0.93
Stoma formation[a]	11.5 (n=7)	9.0 (n=11)	0.60
Type of surgery[a]			0.95[c]
Ileocecal resection	21.3 (n=13)	19.7 (n=24)	
Right hemicolectomy	37.7 (n=23)	39.3 (n=48)	
Left hemicolectomy/resection of sigmoid	3.3 (n=2)	3.3 (n=4)	
(Low) anterior resection	24.6 (n=15)	24.6 (n=30)	
Subtotal colectomy	13.1 (n=8)	13.1 (n=16)	
Type of disease[a]			0.83[c]
Cancer	75.4 (n=46)	77.1 (n=94)	
Inflammatory bowel disease	23.0 (n=14)	21.3 (n=26)	
Diverticulitis	1.6 (n=1)	1.6 (n=2)	
ASA grade[a]			0.1[c]
1	29.5 (n=18)	25.4 (n=31)	
2	59.0 (n=36)	53.3 (n=65)	
3	11.5 (n=7)	21.3 (n=26)	

[a] The first number is the percentage, and the number in between the brackets is the absolute number

[b] The first number is the mean, and the number in between brackets is the standard deviation

[c] These P values represent the overall similarity of the two groups in these characteristics

stoma formation, type of medication, oral and intravenous fluid intake, urinary output, stoma production, nasogastric tube production, length of stay in the hospital, number of readmissions, complication, and mortality rate.

In the ERAS group, additional data were prospectively collected: first day of defecation, length of epidural analgesia, first day of mobilization, and the number of days that oral analgesia was used.

Table 3 Morbidity Rates in the ERAS and Control Group

	ERAS%;(n)	Standard care%; (n)	P value
Surgical complications[a]			
Wound hemorrhage	0	0	
Deep hemorrhage	4.9 (3)	0.8 (1)	0.11
Anastomotic leak	3.3 (2)	7.4 (9)	0.34
Wound infection	4.9 (3)	11.5 (14)	0.18
Deep infection	1.6 (1)	6.6 (8)	0.28
Burst abdomen	1.6 (1)	4.1 (5)	0.67
Medical complications[a]			
DVT/embolus	0	0	
Chest infection	1.6 (1)	4.1 (5)	0.67
Cardiac failure	0 (0)	2.5 (3)	0.55
Urinary infection	0 (0)	6.6 (8)	0.05
Septicemia	0 (0)	3.3 (4)	0.30
Pyrexia of unknown origin	0 (0)	0 (0)	
Impaired renal function	0 (0)	2.5 (3)	0.55
Hypotension	0 (0)	0 (0)	
Respiratory failure	1.6 (1)	2.5 (3)	0.99
Total number of complications[b]	12	63	0.0001
Patients with complication(s)	14.8 (9)	33.6 (41)	0.008

[a] First number is percentage, and the number in brackets is absolute number

[b] Only the absolute number is shown

Outcome Measures

The primary outcome measures were mortality and morbidity. Mortality was defined as death within 30 days after surgery. A complication was defined as an unfavorable postoperative course with the need for an intervention to prevent further harm, according to the definition of the Dutch Association of Surgeons. Individual complications were defined as stated in Table 1. Secondary outcome measures were fluid intake, reinsertion of nasogastric tubes, number of relaparotomies, length of hospital stay, and number of readmissions within 30 days.

Analysis

The analysis was by intention-to-treat principles. No patients were excluded for reasons of protocol violations.

Statistical analyses were performed with SPSS® version 16.0(SPSS, Inc., Chicago IL) for Windows® and STATS direct® (Altrinchem, UK). Medians and ranges or means and standard deviations are presented for all continuous outcome measures. Comparisons between the ERAS and conventional postoperative care group were made using the chi-square test for binary outcomes, and the Student's *t* test was used for continuous outcomes. Nonparametric tests were carried out to calculate statistical differences in POSSUM scores.

Results

Sixty-one patients, treated according to the ERAS program, were matched with 122 historical controls who had conventional postoperative care.

The two groups were similar with respect to age, ASA grade, P-Possum (Portsmouth-Possum), CR-Possum (Colorectal-Possum) score, type of surgery, stoma formation, and type of disease (Table 2). Women were slightly overrepresented in the ERAS population (63.9% vs. 36.1%; P=0.06). Fifty-seven patients (93%) who were treated in the ERAS group had an epidural catheter until the second postoperative day (median; range, 1–4). Four patients in whom placing the epidural catheter could not be realized received a patient-controlled analgesia pump. Patients were mobilized out of bed on the first postoperative day (median; range, 0–3). The stools were passed on day 3 (median; range, 0–11) versus 4 days (median; range, 1–8) in the control group. Nonsteroidal anti-inflammatory drugs were used until day 4 (median; range, 0–15). Paracetamol was used until day 6 (median; range, 0–40). In the control group, 77 patients had epidural anesthesia (63%).

The morbidity rate was higher in the control group than in the ERAS group (33.6% vs. 14.8%; P<0.01). Total number of complications amounted 63 in the control group versus 12 in the ERAS group (P=<0.01). Corrected for gender, the control group had a 3.4 times higher risk to develop an unfavorable postoperative course than the ERAS group. Individual complications were similar in both groups, except for urinary tract infections. None of the patients in the ERAS group developed a urinary tract infection versus 6.6% of the

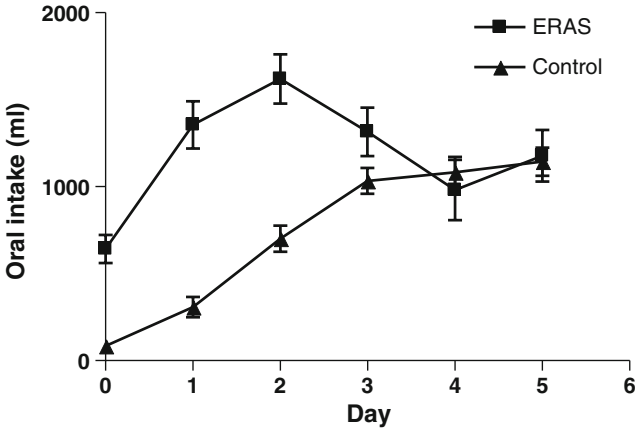

Figure 2 Oral fluid intake (ml/day).

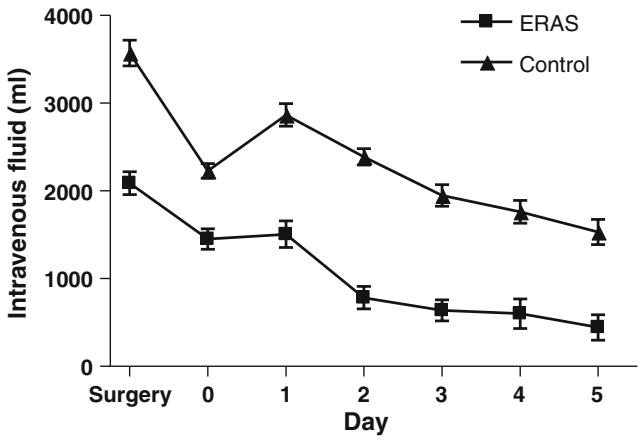

Figure 1 Intravenous fluid intake (ml/day).

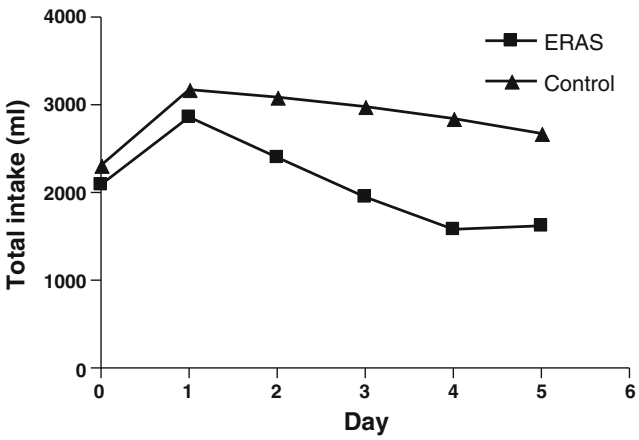

Figure 3 Total fluid intake (ml/day).

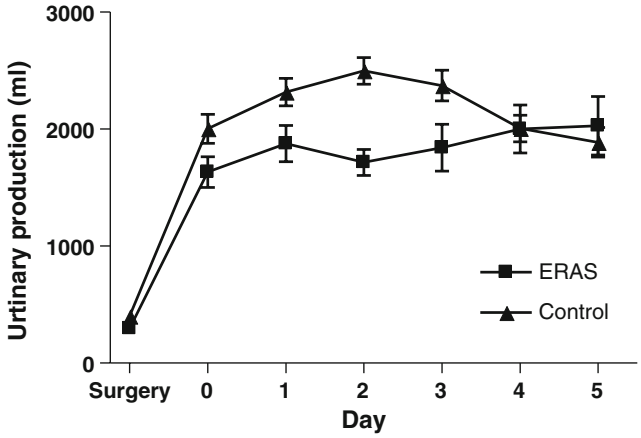

Figure 4 Urinary output (ml/day).

patients in the control group (P=0.05). Septicemia occurred in none of the patients in the ERAS group; the incidence was 3.3% in the control group (P=0.30). Of the patients in the ERAS group, 4.9% developed a wound infection versus 11.5% of the patients in the control group (P=0.18). In the control group, 6.6% of the patients developed a deep surgical site infection. For ERAS, this amounted 1.6% (P=0.28). Anastomotic leakage occurred more often in patients who had conventional postoperative care (7.4% vs. 3.3%; P= 0.34). A dehiscence of all layers of the abdominal wall was seen in 1.6% in the ERAS group and in 4.1% of the patients in the control group (P=0.67; Table 3).

No patient died in the ERAS group within 30 days after surgery. Two patients in the control group died (1.6%; P=0.55). One patient developed congestive heart failure after fluid resuscitation for hypotension. Eight days later, she became septicemic, a laparotomy was carried out, and bowel ischemia was found. The other patient also received an excess of fluid because of her low urine output and low fluid intake. Nevertheless, her renal function deteriorated. Four days later, she also developed fatal heart failure.

Patients receiving ERAS postoperative care were administered significantly less intravenous fluid during (day of) surgery and postoperative day 1 till 5 (P<0.001). Oral intake was higher than in the control group on day of, first, and second postoperative day (P<0.001). This led to a larger urinary production on the first three postoperative days in the control group (P<0.05). Total fluid intake was higher in the second and third postoperative days (P<0.05; Figs. 1, 2, 3, and 4).

Reinsertion of nasogastric tubes were similar in both populations (P=0.85; Table 4). Patients treated according to the ERAS regime spent significantly fewer days in the hospital (median 6; range 3–50) than the control group (median 9; range 3–138 ; P=0.032). The number of readmissions was similar in both groups (3.3% ERAS vs. 1.6% control; P=0.60; Table 4). Two patients in the ERAS group were readmitted with surgical site infections. One developed a presacral abscess which was drained transrectally. The other patient developed a wound abscess which was incised and drained. One patient in the control group developed an intra-abdominal abscess which was treated conservatively. The other patient had successful conservative treatment for a gastro paresis.

Discussion

The results of this study suggest that the Enhanced Recovery After Surgery program is superior to conventional postoperative care for patients undergoing elective colonic or rectal resection. Patients treated according to an ERAS program develop significantly less complications and have shorter hospital stay.

This study is a historic cohort study with carefully matched controls. The control group was chosen from years prior to the introduction of the ERAS program. Because the discharge criteria were identical in both groups, further reduction of bias was achieved. Observer bias was avoided, though awareness about early recovery may have influenced decisions on early discharge. On the other hand, data in the ERAS group were collected prospectively. The historic nature of the control group is likely to have caused the underreporting of complications, thus leading to an overestimation of the beneficial effect of ERAS. Since patients in both groups were operated by the same team of surgeons, selection bias is thought to be small. A randomized trial on ERAS is difficult to perform because running traditional and ERAS care simultaneously carry the

Table 4 Mortality and Secondary Outcomes of the Patients in the ERAS and Control Group

	ERAS % (n)	P value % (n)	Control
Mortality[a]	0 (0)	1.6 (2)	0.55
Number of reinserted nasogastric tubes[a]	19.7 (12)	21.3 (26)	0.85
Time to first defecation (days)[b]	3 (0–11)	4 (1–8)	
Length of hospital stay (days)[b]	6 (3–50)	9 (3–138)	0.021
Number of readmissions[a]	3.3 (2)	1.6 (2)	0.60
Number of relaparotomies[a]	14.8 (9)	17.2 (21)	0.83

[a] First number is percentage, and the number in brackets is absolute number

[b] First number is median, and the number in brackets is range

risk of mixing elements of both regimens. Blinding of nursing and medical staff would be impossible. To overcome these flaws, the design of such a study is challenging. In our study, patients were carefully matched. Women were slightly overrepresented in the ERAS group ($P=0.06$). Literature states male gender predisposes to an increased incidence of anastomotic leakage after colorectal surgery. One of the main theories is the higher levels of estrogens in women and anatomical differences of the pelvis.[19] Further analysis of the data excluded gender as a risk factor for the development of complications. There were less ASA 3 in the ERAS population (not significant). After excluding ASA 3 patients from analysis, significant differences in total number of complications and number of patients with one or more adverse events persisted.

In this study, the targets of ERAS were obtained. All ERAS patients were informed in a standardized way in the outpatient clinic. They received a daily perioperative schedule. Patients knew what was expected and allowed. In the conventional group, it is likely information was not uniform due to variance in information between the individual surgeons. Second, all patients of ERAS received preoperative carbohydrate loading where none of the conventional treated patients had Pre-Op. Since it was policy not to apply colonic lavages before the ERAS era, there was no difference between both groups. Epidural use was good practice in the conventional group; however, in the ERAS protocol it was one of the key elements. This led to a higher epidural use in the ERAS population (93% vs. 63%, respectively; $P<0.001$). Epidural analgesia, one of the main issues in fast track protocols, has been suggested to provide an optimal pain relief, thus reducing surgical stress response, and may reduce postoperative morbidity and mortality.[3,20–22] Rodgers et al.[23] found a significant reduction in deep vein thrombosis (DVT), pulmonary embolism, transfusion requirements, pneumonia, other infections, and respiratory depression in patients with neuroaxial blockade. It is likely that this difference contributes to a reduced complication rate in ERAS. Patients in the ERAS group received less fluid intravenously and started drinking sooner after surgery. Total fluid intake and urinary production was higher in the control group. In our findings, morbidity was higher in the control group. Excessive fluid administration is thought to contribute to an increased complication rate.[24–27] It is important to realize more elements than mentioned above may contribute to improved outcome: the use of short-acting and oral anesthetics and prokinetics, lack of premedication and nasogastric tubes, early removal of catheters and drains, minimal length incisions, early mobilization, and the preservation of normothermia.[20]

It is likely that the combination of elements in ERAS favored uncomplicated outcome after colorectal surgery. Mortality did not differ between both groups. Two patients (83 and 85 years old) in the control group died because of cardiac complications. Patients in the control group had an almost threefold risk to develop one or more complications. Individual complications failed to reach significance. Since data collection in the historic group could lead to underreporting of minor complications, this is less likely for major complications, e.g., anastomotic leakage, surgical site infections, and burst abdomen failed significance. All, however, tend to be more frequent in the conventional care group.

Although this ERAS program is evidence-based, some improvements can be made. Recent evidence suggests that perioperative supplemental oxygen administration reduces the incidence of surgical wound infections.[28] It exposes the patient to little or no risks, has little associated costs, while it reduces the incidence of wound infections by half.[29] The addition of specialized nutritional products to the standard carbohydrate drinks, offered to patients in the used ERAS program, also shows promising results towards reducing complications after gastrointestinal surgical procedures. The specialized nutritional products are the amino acids arginine and glutamine, omega-3 fatty acids, and nucleotides in the form of RNA. Wound infections, anastomotic leakage, abdominal abscesses, and pneumonia were significantly reduced.[30]

Patients who were treated according to the ERAS program spent significantly less time in the hospital. This did not result in more readmissions which reflects early recovery, probably due to a more favorable postoperative course. Besides, this implies benefit for the hospital resources because with the implementation of the ERAS program a higher level of cost-effectiveness can be reached.

This study demonstrates that the program as a whole is clearly beneficial and not flawed with unexpected negative effects. Epidural analgesia and a restricted fluid administration are thought to be the main contributing factors to a favorable outcome. More research is necessary to optimize perioperative care.

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ORIGINAL ARTICLE

Preoperative Chemoradiotherapy Does Not Necessarily Reduce Lymph Node Retrieval in Rectal Cancer Specimens—Results from a Prospective Evaluation with Extensive Pathological Work-up

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Abstract
Purpose Preoperative chemoradiotherapy (CRT) is supposed not only to reduce lymph node metastases but also lymph node recovery in rectal cancer specimens. The objective of this prospective study was to determine the effects of chemoradiation on mesorectal lymph node retrieval under terms of a meticulous histopathological evaluation.
Methods Specimens from 64 consecutive patients with stage II/III rectal cancer receiving preoperative 5-FU-based CRT were investigated. All patients were treated within the German Rectal Cancer Trial CAO/ARO/AIO-04. After surgery (including quality assessed total mesorectal excision), extensive pathological diagnostics was performed with embedding and microscopic evaluation of the whole mesorectal soft tissue compartment.
Results A total number of 2,021 lymph nodes were recovered (31.6 per specimen) within pathological work-up. There was no significant correlation between the number of retrieved nodes and patient- as well as tumor-dependent parameters. Lymph node size constantly amounted for less than 0.5 cm. Twenty patients (31.3%) had persistent nodal metastases. A considerable incidence of residual micrometastatic involvement in lymph nodes <0.3 cm (in 9.4% of all patients) was detected by extensive pathologic work-up.
Conclusion Reliable nodal staging with high numbers of detected nodes was feasible after neoadjuvant CRT. Micrometastases frequently occur in small lymph nodes detected by microscopic evaluation.

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Keywords Locally advanced rectal cancer · Preoperative chemoradiotherapy · Total mesorectal excision · Pathologic diagnostics

Introduction

Rectal cancer is the second most malignant disease in European countries with an annual incidence of about 70,000 cases.[1,2] Distinct progress in therapy of rectal cancer has been achieved within the last 15 years by implementation of appropriate surgical techniques such as total mesorectal excision (TME)[3] and neoadjuvant treatment strategies.

The German Rectal Cancer Study Group has recently demonstrated significant improvements in local control, a higher rate of sphincter preservation, and decreased toxicity by preoperative in contrast to postoperative chemoradio-

therapy (CRT). A combined neoadjuvant 5-fluorouracil (5-FU)-based CRT is thus considered as standard therapy in locally advanced (stage II/III) rectal cancer.[4] Local recurrence rates were significantly reduced, and in subgroup analyses, a distinct improvement in overall survival was achieved in patients with optimal and good response to applied CRT.[5]

A benefit of a general application of adjuvant chemotherapy in individual patients remains unclear, and advices for detection of patients with higher risk of cancer relapse are imperatively needed.[6–9] Lymph node status after preoperative CRT has repeatedly been described as a strong prognostic factor in patients with locally advanced rectal cancer.[10–12]

Thus, the evaluation of an accurate nodal status is an essential task for both surgeon and pathologist because significant correlations between the number of retrieved nodes and survival of patients have frequently been demonstrated.[12–17] Several investigations have been published within the last years showing that preoperative CRT decreases the number of lymph nodes detected in the surgical specimen.[18–20] Some authors report a consistent remission of lymph nodes below the least number of 12 nodes, recommended by the International Union against Cancer (UICC), or even a complete deletion of lymph nodes in the surgical specimen.[21,22]

We summarize results from 64 consecutive patients with locally advanced rectal cancer from our institution. All patients were participants of the randomized phase III German Rectal Cancer Trial CAO/ARO/AIO-04 and received standardized 5-FU-based long-term CRT, curative surgical resection including TME, and extensive macroscopic and histopathological diagnostics.

The aim of this prospective study was to clarify the effects of preoperative CRT on quantities of lymph nodes within the mesorectal soft tissue compartment. Therefore, we meticulously explored rectal cancer specimens with particular focus on small nodes unlikely to be detected by standard manual lymph node retrieval as predominately performed in the retrospective analyses published in this subject.

Material and Methods

Sixty-four consecutive patients with resectable stage II/III rectal adenocarcinoma located no more than 12 cm above the anocutaneous verge and treated within the protocol of the ongoing CAO/ARO/AIO-04 trial of the German Rectal Cancer Study Group between October 2006 and September 2008 were analyzed prospectively.

All patients were medicated at the Department of General and Visceral Surgery, University Medical Center Göttingen, Germany.

Rigid rectoscopy with endorectal ultrasound (ERUS), magnetic resonance imaging (MRI) of the pelvis, computed tomography (CT) of the pelvis, abdomen, and thorax were performed to confirm locally advanced tumor stage and to exclude patients with evidence of distant metastases.

Except for one female patient with a squamous cell carcinoma of the larynx more than 20 years earlier, no patient had previous cancer or received cancer-related chemo- or radiotherapy. There were no contraindications to CRT at the time of staging in any patient. The trial was approved by the Ethics Committee of the University of Göttingen.

Treatment

Sixty-four eligible patients (48 male and 16 female) with a median age of 65 years (36–82 years) underwent standardized preoperative CRT with a total irradiation dose of 50.4 Gy (in multiple three and four-field technique, delivered in 28 fractions of 1.8 Gy) and a simultaneous 6-week course of 5-FU-based chemotherapy.

Radical oncologic surgery was performed 6 weeks after completion of preoperative treatment and actual clinical restaging by experienced colorectal surgeons including quality assessed TME in all cases.

Surgical procedures consisted of 46 (72%) low anterior resections, 16 (25%) abdominoperineal resections, and two (3%) discontinuous resections (Hartmann's procedure).

Immediately after removal of the specimen, a perioperative quality control of TME was performed by a surgeon not involved in the actual surgical intervention.

This procedure consisted of methylene blue injection into the inferior mesenteric artery and revealed smaller surgery-related defects in pelvic fascia and mesorectal surfaces by selective colorant escape.

Macroscopic and Histopathological Evaluation

After surgical quality control, the specimens were committed to the pathologist for macroscopic examination of mesorectal surfaces according to a quality assessment system based on the MERCURY criteria.[23] All 64 specimens of this study were completely worked up by the same gastrointestinal pathologist (H. R.).

Histopathological staging was realized according to the tumor–node–metastasis (TNM) classification of the UICC and comprised an evaluation of the circumferential resection margins (CRM) concerning tumor distance of ≤1 mm or tumor perforation.[24]

The macroscopic work-up procedure consisted of a ventral longitudinal opening of the specimen along the rectal lumen excluding the tumor region and a fixation of the draft-free needle-fixed specimen for at least 72 h in 5% formalin solution.

After fixation and colorant inking of the mesorectal surface, the specimen was cut in consecutive transversal 5-mm sectional slices, beginning at the distal resection margin and comprising the region proximally of the tumor at least up to the lateral vessel branching of the inferior mesenteric artery.

The cross-sectional slices were re-divided into 2.5-mm slices and completely paraffin embedded. Beside ypTNM staging with assessment of the proximal, distal, and circumferential resection margins, it was thus possible to detect structures of microscopic dimension including any residual tumor manifestation, i.e., very small and atrophic lymph nodes below 0.1 cm in diameter with or without micrometastases and isolated tumor cells, intra- or extramural vascular and perineural invasion and mesorectal tumor cell foci, which were presumably left behind after CRT.

Within this procedure, fat clearance methods for detecting lymph nodes were not used as the mesorectal soft tissue was embedded completely.

Additionally, irradiation-induced tumor regression was denoted on the basis of a semi-quantitative five-point grading system according to established methods.[25,26]

Microscopic Lymph Node Evaluation and Count

In order to evaluate the entire mesorectal soft tissue compartment for available lymph nodes after preoperative CRT, a complete paraffin-embedding of the rectal specimens has been implemented. As unencapsulated lymphoid aggregates with follicles are verifiable in pericolic and perirectal tissue, histopathological criteria of a lymph node have been defined prospectively. Only entirely encapsulated lymphatic tissue with marginal sinus and at least residual lymph follicles were—independently of size—counted as lymph node. To prevent double-sectioning of individual—particularly smaller (<2.5 mm)—nodes two optimal section levels from each tissue block were examined consecutively after cutting the block.

A median number of 147 standard sized tissue blocks were examined per case (range, 119–213). Including 3 days of formalin fixation, the median turn-around time from surgical excision of the specimen to completion of final diagnosis was 6 days.

Statistical Analysis

Correlations between numbers of detected mesorectal lymph nodes and various patient- and tumor-related clinicopathological findings were assessed by the function cor. test of the statistical software R (version 2.8; www.r-project.org).

The significance level was set to α=5% for all tests.

Results

Sixty-four surgical specimens with low and mid-third rectal cancers (located within 12 cm from anal verge) were investigated. Average tumor size (longitudinal dimension) after treatment was 2.51 cm (0–8 cm; median, 2.5 cm), and average tumor level was 6.4 cm from anal verge (0–12 cm; median, 6.0 cm). Thirty tumors were located in the lower third of the rectum (0–6 cm), 34 were positioned in the mid-third (6–12 cm).

A histopathologically confirmed complete resection (R0 status) of proximal and distal resection margins was achieved in all cases. Circumferential resection margins (CRM) were free of vital tumor cells with a minimum distance of ≥1 mm in each specimen. Seven patients (11.7%) with no evidence of distant metastatic disease in pretherapeutic CT scans presented with liver (six cases; detected by intraoperative ultrasound) and peritoneal (one case) metastases at the time of surgery. Due to their consistent small size, the liver metastases might represent systemic tumor progression during preoperative treatment as well as misdiagnosis in initial clinical staging (Table 1).

Tumor regression parameters became apparent by T-level downsizing (comparing cT and ypT) in 25 patients (39%). T-level was decreased by one level in 11 patients (17.1%) and by two or three levels in seven patients each (10.9%).

UICC downstaging (comparing cUICC and ypUICC) was performed in 36 patients (56.3%). In 18 patients (28.1%), the tumor stage was reduced by one, 11 patients (17.1%) were downstaged by two, and finally, seven patients (10.9%) were downstaged by three stages.

Tumor regression grading resulted in three patients (4.6%) with low tumor regression (TRG 1). Fifty-three patients (82.8%) had intermediate regression (TRG 2+3), and eight patients (12.5%) presented with pathological complete regression of the primary tumor (TRG 4).

Pathological quality assessment was performed according to modified MERCURY criteria[23] respecting surgical standard of our institution and resulted in the following findings.

Thirty-six specimens (56.3%) showed optimal quality of TME with no defects and smooth surfaces (grade 1). In 21 cases (32.8%), postsurgical mesorectal integrity was given but with very little irregularities of the mesorectal surfaces (grade 2), and seven (10.9%) specimens underwent TME with focal defects and lacerations of mesorectal soft tissue but, in all cases, without visible muscularis propria (grade 3).

An intra- or extramural vascular invasion was identified in nine patients (14.1%). Perineural invasion appeared with considerable frequency in 24 patients (37.5%) after preoperative CRT (Table 2).

A total number of 2,021 lymph nodes were recovered (mean, 31.6 nodes per patient; range, 12–81; median, 30.0). Twenty patients (31.3%) had persistent nodal metastases in

Table 1 Clinicopathological Findings

Feature	Number of Patients $n=64$	Percent
Gender		
Male	48	75
Female	16	25
Age (years)		
Median	65	
Range	36–82	
Tumor Distance from Anal Verge (cm)		
0–6	30	47
>6–12	34	53
cT stage		
1	0	0
2	2*	3
3	60	94
4	2	3
cN Stage		
Positive	51	80
Negative	13	20
cUICC Stage		
I	0	0
II	13	20
III	51	80
IV	0	0
Neoadjuvant treatment		
50.4 Gy+standard 5-FU	34	53
50.4 Gy + intensified 5-FU/oxaliplatin	30	47
Surgical procedure (including TME)		
Low anterior resection	46	72
Abdominoperineal resection	16	25
Hartmann's procedure	2	3
Resection status		
R0	64	100
R1	0	0
Circumferential resection margin (CRM)		
Negative	64	100
Positive	0	0
TME quality (modified Mercury criteria)		
1 Optimal	36	56
2 Good	21	33
3 Moderate	7	11

Patients had uN+ status according cUICC III

cumulative 53 lymph nodes. The mean number of involved nodes was 2.65 per patient (range, 1–8 nodes; median, 1.0). Among these 53 lymph node metastases, 15 manifested as micrometastases (not larger than 0.2 cm). Three additional patients (4.6%) showed evidence of isolated tumor cells (ITC, not larger than 0.02 cm) in one lymph node each. According to the current TNM classification, the latter were classified as "ypN0" or "ypN0 (i+)" respectively, characterizing ITC as cells without yet known specific metastatic attributes.[27]

Lymph node size including non-metastatic and metastatic nodes was below 0.5 cm in all but one case. The majority of nodes ranged between 0.1 and 0.2 cm.

One exceptional patient with mucinous differentiated adenocarcinoma had lymph nodes ranging from 0.5 to 1 cm without viable tumor cells but, instead, large mucinous

lakes, indicating complete regression of previous tumor infiltration.

The detected mesorectal lymph nodes were unequally distributed over the specimen.

The majority of 1,395 nodes (69%) were located proximally to the tumor region along the trunk of the superior rectal artery within the upper radiation field.

Four hundred forty-nine nodes (22%) were located within the tumor region and therewith in the central radiation field, and finally, 177 (9%) nodes could be detected in the mesorectal tissue below the tumor region and in the lower radiation field.

There was no significant correlation between the numbers of detected mesorectal lymph nodes and patient-dependent variables (gender and age). Tumor-related variables (tumor size, ypTNM status, number of lymph node metastases, histopathological tumor regression grade, tumor differentiation, lymph and blood vessel invasion, and perineural invasion) did also not affect the number of available lymph nodes within the perirectal tissue (Table 3).

Due to the reduced lymph node size after preoperative CRT, micrometastases (<0.2 cm) accounted for 28.3% of all lymph node metastases. In detail, 30% of ypN+ patients had *exclusive* micrometastatic involvement. Based on the total study population, the proportion of patients with solely micrometastases was 9.4% after CRT.

Under terms of extensive pathological work-up and microscopic evaluation of the entire mesorectum, higher numbers of identified lymph nodes per specimen were not correlated with increased detection of nodal metastases. The 44 patients without nodal involvement had a median number of 30 detected nodes, whereas patients with lymph node metastases had 29.5 nodes. Interestingly, in patients with solely micrometastatic involvement, the median retrieval accounted for only 24.5 nodes.

In pretherapeutic staging (ERUS, CT, and MRI), 13 patients (20.3%) turned out to have no evidence of mesorectal lymph node metastases (clinical stage II). In pathological staging, altogether, four (31%) of 13 patients with previous (clinical) stage II actually had ypN+ status comprising four micrometastases in a single lymph node each, indicating the potential incertitude of pretherapeutic nodal staging.

Table 2 Post-therapeutic Parameters

Feature	Number of patients n=64	Percent*
Tumor size (cm)		
Median	2.5	
Range	0–8	
Vascular invasion		
Yes	9	14
No	55	86
Perineural Invasion		
Yes	24	38
No	40	62
Tumor regression grading		
0	0	0
1	3	5
2	20	31
3	33	52
4	8	13
ypT stage		
0	8	13
1	7	11
2	9	14
3	36	56
4	4	6
ypN stage		
0	44	69
1	15	23
2	5	8
ypM stage		
0	57	89
1	7	11
ypUICC stage		
0	8	13
I	12	19
II	21	33
III	16	25
IV	7	11
T-level downsizing		
Yes	25	39
No	39	61
UICC-downstaging		
Yes	36	56
No	28	44

Discussion

Lymph node status is currently the strongest prognostic factor in rectal cancer after neoadjuvant CRT. A valid statement concerning nodal involvement is of outstanding importance for individual prognosis and further treatment strategies of patients with locally advanced rectal cancer. Reliable nodal staging of colorectal cancer requires a certain number of detected and evaluated nodes and—as a guideline, not as a precondition—lymphadenectomy should ordinarily include 12 regional lymph nodes to validate pN0 status.[27] There are no particular recommendations concerning effective lymph node retrieval in rectal cancer specimens after preoperative CRT (ypN status) yet. Several

Table 3 Correlations Between Lymph Node Numbers and Different Variables

Variable	Correlation	95% Confidence Interval	*p* value
Gender	−0.11	−0.34; 0.12	0.34
Age	−0.2	−0.41; 0.04	0.098
Surgical procedure	0.2	−0.03; 0.42	0.085
Tumor level	0.1	−0.13; 0.33	0.38
Tumor size	0.04	−0.2; 0.27	0.76
ypT	−0.2	−0.41; 0.04	0.098
ypN	0	−0.23; 0.23	0.99
ypM	−0.08	−0.3; 0.16	0.52
No. of nodal metastases	0.02	−0.21; 0.25	0.85
Tumor grading	−0.2	−0.41; 0.03	0.089
Blood vessel invasion	0.07	−0.17; 0.29	0.59
Lymph vessel invasion	0.07	−0.16; 0.3	0.55
Perineural invasion	−0.12	−0.34; 0.12	0.32

studies independently investigated the number of retrieved lymph nodes in patients being treated with combined long-term CRT and showed a continuous decrease in the number of lymph nodes compared to non-irradiated specimens. Mean numbers of detected nodes varied between 4 and 14 per specimen.[18–20,28] In our prospectively evaluated collective with standardized preoperative and surgical treatment as well as pathological procedures, a mean number of 31.6 nodes were recovered per specimen.

Interpreting our results, we cannot disprove the assumption that preoperative long-term CRT reduces the cumulative number of lymph nodes within the rectal specimen, although we detected surpassingly more mesorectal nodes than any other investigation even without preoperatively applied CRT.[10,13,18,19,21,29]

This might be rationalized for one thing by standardized and quality-controlled surgery and a high rate of optimally performed TME within this study. The removal of the entire mesorectal soft tissue compartment within its intact envelope fascia not only ensures minimal local recurrence rates and functional preservation of pelvic structures but also guaranties a complete regional lymphadenctomy. Moreover, optimized and extensive macro- and histopathological diagnostic procedures are responsible for the detection of more than an allegedly representative number of lymph nodes from a rectal cancer specimen.

Under the terms of an extensive pathological work-up, the rationale of nodal staging within this investigation has been altered from evaluating a representative consensus-agreed number of mesorectal nodes to evaluating the (near-) total number of available rectal lymph nodes.

A significant reduction of lymph node count in rectal cancer specimens has been reported after long-term radiation (doses ranging from 45 to 50.4 Gy) with different concomitant chemotherapy regimes[18–20,22,30] as well as after short-term radiotherapy.[31,32] Only one single investigation did not find significant differences of mesorectal lymph node retrieval in patients after neoadjuvant treatment compared to patients who underwent primary surgical treatment. However, in this study, altogether, only 17% of the study population had neoadjuvant therapy comprising both long-term 5-FU-based CRT as well as short-term radiation.[29]

Perez et al. evaluated rectal specimens from 18 cadavers without evidence of colorectal disease regarding number and distribution of mesorectal lymph nodes. They found a mean number of 5.7 nodes per specimen and concluded that the absence of pathological alterations within the rectum might cause lower lymph node count in contrast to other investigations.[33]

Anyway, concerning mesorectal lymph node numbers, we did not find any correlation neither with patient-related factors like gender and age nor tumor-related pathological characteristics like individual stage or therapy-induced tumor regression.

Additionally, our investigation indicates that neoadjuvant CRT appears to have an important effect on mesorectal lymph node size. We noticed that the majority of nodes varied between 0.1 and 0.2 cm, which we consider to be a consequence of applied CRT, in accordance with others who also described a significant reduction of nodal size.[32,34,35] Changes in morphology and function after radiation of lymph nodes have also been described with decreased numbers of CD4+ lymphocytes and dendritic cells in paracortical areas of the irradiated nodes. This might implicate a reduced immune and tumor suppressive function as well as reduced mechanical filter function for tumor cells.[36,37]

It appears to us that radiation-related reduction of lymph node size might be the main reason for a reputedly reduction of lymph node numbers in irradiated specimens worked up with conventional (manual) retrieval because of the apparent difficulty to detect lymph nodes smaller than 0.2 cm.

Murphy et al.[38] recognized lymph node size as an independent prognostic indicator for survival in node-negative rectal cancers after primary surgery. They supposed small nodes, measuring <2 mm less likely to be infiltrated and suggest a consideration of lymph node size within the staging systems for rectal cancer.

As opposed to this, in 31% of our patients, lymph node metastases have been detected, among these, 15 micrometastases (28.3%) in lymph nodes with constantly <0.3 cm. Regarding other investigations using immunohistochemistry to determine occult lymph node micrometastases in stage II rectal cancers after neoadjuvant CRT, there is a comparatively high incidence of micrometastases detected with conventionally hematoxylin–eosin staining in our collective.[39]

Although their prognostic role has not been clarified, finally, we consider them as important findings, which need to be investigated further on to reveal individual tumor biology and distant metastatic potential. We suppose an appreciable number of mesorectal micrometastases in lymph nodes below 0.5 cm not being detected by manual lymph node recovery and standard pathological diagnostics.

Concerning the minimum number of lymph nodes needed to stage patients with locally advanced rectal cancer, statistical analyses indicated that the probability of detecting a single lymph node metastasis increases with the number of retrieved nodes and amounts to 46% when 18 nodes have been recovered.[40] This resulted in the recommendation of finding smaller nodes ranging from 0.1 or 0.2 cm in diameter. Nevertheless, other investigations revealed that more than 60% of institutions in the USA fail to generally achieve the controversial benchmark of 12 lymph nodes per specimen.[41]

Extensive pathological diagnostics with microscopic evaluation of the entire lymph node containing mesorectal compartment leads to obvious higher lymph node recovery after preoperative CRT than conventional pathological work-up. This has distinct clinical implications because several investigations have shown the prognostic relevance of enhanced lymph node retrieval in stage II colorectal and rectal cancer patients.[13–15] Kim et al., who reported the results of 900 node negative rectal cancer patients, postulated a minimum number of 23 evaluated nodes to stratify patients for low and high risk of cancer-specific survival.[42] As nodal status—particularly after preoperative CRT—is a major decision criterion for the need of adjuvant treatment, it should be based on a stable diagnostic fundament.[43]

We are very well aware that the meticulous lymph node evaluation in our study is hardly convertible in pathological routine diagnostics in rectal cancer specimens. However, it shows that adequate nodal staging is feasible after applied CRT with consequently more than the consensual number of 12 nodes per specimen. In summary, reliable lymph node recovery emphasizes the role of the surgeon and especially of the pathologist. Their role exceeds patient- and therapy-dependent factors by far. These results of our evaluation are supported by another large prospective investigation on more than 7,000 colorectal specimens.[44]

In conclusion, our study reveals that the diligence and accuracy of the pathologist—beside the surgeons obligation to supply high-quality TME specimens—is essential for sufficient lymph node retrieval and valid nodal staging after preoperative RCT.

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ORIGINAL ARTICLE

Risk Factors for Anastomotic Leakage Following Intersphincteric Resection for Very Low Rectal Adenocarcinoma

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Abstract
Background The aim of this study was to perform a retrospective analysis of the risk factors for anastomotic leakage following intersphincteric resection (ISR) for very low rectal cancer.
Methods Between 1993 and 2007, 120 patients with T1–T3 rectal adenocarcinomas located 1 to 5 cm (median 3 cm) from the anal verge underwent ISR without radiotherapy. Univariate and multivariate analyses of 47 prospectively recorded parameters were conducted.
Results All patients had total mesorectal excision after complete bowel preparation. Of them, 103 underwent partial resection, and 17 underwent complete resection of the internal sphincter. Some 108 patients had a defunctioning stoma. Morbidity and mortality rates were 33% and 0.8%, respectively. Fifteen patients (13%) developed clinical leakage, and six (5%) had severe leakage causing relaparotomy, permanent stoma, or death. Univariate analysis of risk factors for clinical leakage revealed tumor annularity, intraoperative blood transfusion, and pulmonary disease to be significant. Multivariate analysis showed transfusion (hazard ratio, 6.5 [95% confidence interval, 1.4 to 30]; p=0.018) and pulmonary disease (6.3 [1.6 to 26]; p=0.009) to be independently significant. Moreover, transfusion (71 [3.0 to 1000]; p=0.008), colonic J-pouch (32 [1.8 to 500]; p=0.018), and pulmonary disease (32 [1.1 to 1000]; p=0.044) were independently associated with severe leakage.
Conclusions This study suggests intraoperative blood transfusion and pulmonary disease as independent risk factors for clinical and severe leakage following ISR and colonic J-pouch as that for severe leakage. By considering these factors, we may be able to stratify high-risk patients and prepare countermeasures.

Keywords Rectal cancer · Surgery · Intersphincteric resection · Anastomotic leakage · Risk factor

Introduction

Although abdominoperineal resection is standard surgery for patients with massively invasive rectal adenocarcinomas located within 5 cm from the anal verge,[1] intersphincteric resection (ISR) has recently been considered as an alternative option to avoid permanent colostomy for selected patients.[2–4] ISR is defined as a procedure obtaining sufficient margins by removing part or whole of the internal sphincter and restoring bowel continuity for patients with rectal cancers involving or neighboring the anal canal.

Careful performance of ISR has been reported to allow satisfactory results both in the short and long term.[4–11] Furthermore, reported rates of anastomotic leakage follow-

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ing ISR have been as comparatively low as 5% to 16% in experienced hands.[7–11] However, anastomotic leakage after rectal cancer surgery can result in reoperation, morbidity, mortality, permanent stoma, prolonged hospitalization, anal stenosis, and anal dysfunction and may be associated with a higher local recurrence rate.[12,13] To reduce such complications, clarification of the risk factors for anastomotic leakage should help in identifying high-risk patients and planning countermeasures. The aim of this study was, therefore, to perform a retrospective exploratory analysis of risk factors for anastomotic leakage following ISR for very low rectal adenocarcinomas.

Patients and Methods

Between October 1993 and February 2007, 122 patients with T1 to T3 rectal adenocarcinomas located within 5 cm from the anal verge underwent ISR at the National Cancer Center Hospital, Tokyo. All of the T1 tumors were accompanied by massive submucosal invasion. Selection criteria for ISR were as follows: (1) sufficient medical fitness; (2) normal sphincter function; (3) distance between the tumor and the anorectal junction (upper edge of the surgical anal canal) less than 2 cm; (4) no involvement of the external sphincter; and (5) no signs of disseminated disease. Preoperatively, the patients were assessed with chest and abdominal computed tomography (CT), digital anorectal examination, and radiological studies, including endorectal ultrasonography, thin-section helical CT, or high-resolution magnetic resonance imaging.

Univariate and multivariate analyses of 47 prospectively recorded clinicopathologic variables were conducted for the 120 consecutive patients who did not receive neoadjuvant radiotherapy. Data from the remaining two given radiotherapy were excluded from the present analysis. Approval by the institutional review board was not required for the observational study. All patients gave informed consent for usage of their data for analysis.

Surgical Procedures

The day before surgery, bowel lavage with 2 L of polyethylene glycol was carried out, and all patients received parenteral antibiotic prophylaxis no more than 30 min before skin incision. The surgical procedures were as described previously[11] and basically similar to those originally documented by Schiessel et al.[4,7] The intersphincteric plane between the puborectalis and the internal sphincter was dissected cautiously as caudad as possible under direct vision, using long right-angle retractors and electrocautery. When the lower edge of the tumor was reached, the anal canal was closed just below the tumor and then irrigated with povidone iodine followed by saline. After retractors were applied to the anal canal, the anal canal mucosa and internal sphincter were circumferentially incised, and the intersphincteric plane was dissected cephalad. A resection margin of at least 1 cm was always attempted. If the rectum was not closed in the abdominal phase, it was closed using sutures during per-anal dissection. After removal of the rectum, the pelvic cavity and anal canal were washed, and then a coloanal anastomosis was made using 3-0 absorbable vertical mattress sutures. A pelvic drain was placed, and a defunctioning stoma was made.

Definition of Anastomotic Leakage

Clinical anastomotic leakage was defined as clinically apparent leakage including gas, pus, or fecal discharge from the pelvic drain or peritonitis. All anastomotic leakages were confirmed as extravasation of endoluminally administered water-soluble contrast material on radiography or computed tomography. An abscess around the anastomosis or a rectovaginal fistula was also considered as leakage. Radiological examination was performed by the surgeon and only when there was clinical suspicion of anastomotic leakage. Pouch fistula, pouch necrosis, and necrosis of neorectum were also regarded as evidence of a leakage. Severe leakage was defined as causing emergency relaparotomy, permanent stoma, or death.

Statistical Analysis

The chi-square test was used to compare proportions. The influence of each variable on the risk of clinical anastomotic leakage or severe leakage was calculated using the chi-square test. All variables associated with clinical leakage or severe leakage at $p<0.05$ were entered in a multivariate analysis using the multiple logistic regression model with the forward stepwise method (likelihood ratio). All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc., Japan). A two-sided p value of less than 0.05 was considered significant.

Results

Of 39 patients (33%) who suffered complications, 30 were treated conservatively and nine received reoperations. Fifteen patients (13%) had clinical anastomotic leakage, and six underwent an emergency relaparotomy (Table 1). Five of those six had permanent stoma and one dying of

Table 1 Details of the Patients with Anastomotic Leakage

Severity	Reconstruction	Site of leakage	Treatment
Severe[a]	Colonic J-pouch (5)[a]	Pouch necrosis (2)[a] Anterior wall of pouch (1)	Pouch resection, colostomy and drainage (3)[a]
		Pouch anal anastomosis (1)	Ileostomy and drainage (1)
		Pouch-vaginal fistula (1)	Drainage and fistulectomy (1)
	Straight end to end (1)	Anovesical fistula (1)	Drain irrigation and fistulectomy (1)
Minor	Straight end to end (6)	Anastomosis (6)	Transanal drainage (3), Observation (2), Drain irrigation (1),
	Transverse coloplasty (3)	Anastomosis (3)	Drain irrigation (1), Transanal drainage (1), Observation (1)

Numbers in parentheses are numbers of patients

[a] One patient died

anastomotic leakage and sepsis (30-day mortality rate= 0.8%). Seven patients had permanent stoma due to complications (six patients) or local recurrence (one). Other complications included wound infection (nine patients), bowel obstruction (six), urinary tract infection (four), anal pain (two), cholecystitis (two), anastomotic stenosis (one), anal prolapse (one), peristomal hernia (one), and thrombocytopenia (one).

Of the 47 variables analyzed, 28 are summarized in Table 2. The remaining 19 variables were tumor size, pT, pN, pM, lateral pelvic lymph node metastasis, preoperative vital capacity, serum carcinoembryonic antigen, CA19-9, C-reactive protein, hemoglobin A1c levels, white blood cell count, hamatocrit, lymphocyte count, arterial blood oxygen tension, carbon dioxide tension, bicarbonate, base excess, liver disease, and drinking habit.

There were 92 male and 28 female patients with a median age of 57 years (range 26 to 75 years). Thirteen had pulmonary disease including chronic obstructive pulmonary disease in eight patients and restrictive respiratory disease in five. The median distance from the anal verge to the tumor was 3 cm (range 1 to 5 cm).

All patients underwent total mesorectal excision. In addition, 46 patients received extended lateral pelvic lymph node dissection. Sixty-seven patients underwent high ligation of the inferior mesenteric artery. A total of 103 patients underwent partial resection of the internal sphincter, and 17 underwent complete resection. A small part of the external sphincter was resected in six patients to obtain sufficient surgical margins. Combined resection of adjacent organs was performed for 12 patients. Two patients with solitary liver metastases and one with a solitary lung metastasis underwent complete resection of their metastases. Mobilization of the splenic flexure was performed for 35 patients. A colonic J-pouch was constructed for 24 patients, a transverse-coloplasty pouch for 38, and a straight anastomosis for 58. Some 108 patients had a defunctioning stoma which was closed 3 months after ISR. Median operating time was 339 min (range 200 to 590 min). Median blood loss was 462 mL (range 45 to 3,644 mL), and nine patients received intraoperative blood transfusions (Table 2).

The median tumor diameter was 3.7 cm (range 1 to 12 cm). Pathologic findings are shown in Table 2. Resection margins were macroscopically negative in all patients but microscopically positive in four. The median number of lymph nodes removed at surgery was 29 (range 4 to 88), and 108 patients (90%) underwent dissection of 12 or more.

Univariate Analysis

Clinical anastomotic leakage was statistically significantly associated with tumor annularity, intraoperative blood transfusion, and pulmonary disease (Table 2). Severe leakage was significantly associated with tumor annularity, extended lateral pelvic lymph node dissection, a colonic J-pouch, intraoperative transfusion, preoperative serum total protein and albumin levels, the preoperative platelet count, and pulmonary disease (Table 2). Neither overall clinical leakage nor severe leakage showed significant association with the 19 variables not shown in Table 2.

Multivariate Analysis

In a multivariate analysis for clinical leakage, the significant variables in the univariate analysis were entered. Pulmonary disease (hazard ratio, 6.3 [95% confidence interval, 1.6 to 26]; $p=0.009$) and intraoperative transfusion (6.5 [1.4 to 30]; $p=0.018$) were found to be independently significant. The incidences of clinical leakage for patients with 0, 1, and 2 positive risk factors were estimated to be 8%, 28%, and 100%, respectively.

In a multivariate analysis for severe leakage, the eight significant variables in the univariate analysis were used.

Table 2 Univariate Analyses of 28 Clinicopathologic Variables Related to Clinical Anastomotic Leakage and Severe Leakage

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Gender					
Male	92	12 (13)	1	5 (5)	1
Female	28	3 (11)		1 (4)	
Age					
<60 years	71	6 (8)	0.16	2 (3)	0.22
≥60 years	49	9 (18)		4 (8)	
Distance of the tumor from the anal verge					
<2.5 cm	21	1 (5)	0.47	0 (0)	0.59
≥2.5 cm	99	14 (14)		6 (6)	
Tumor annularity					
<3/4	101	10 (10)	0.033	3 (3)	0.033
≥3/4	16	5 (31)		3 (19)	
Unknown	3				
Histopathologic grade					
Well-differentiated	59	9 (15)	0.62	3 (5)	1
Moderately differentiated	53	6 (11)		3 (6)	
Poorly differentiated	8	0 (0)		0 (0)	
Pathological UICC TNM stage					
Stage I	50	7 (14)	0.91	1 (2)	0.23
Stage II	21	3 (14)		3 (14)	
Stage III	46	5 (11)		2 (4)	
Stage VI	3	0 (0)		0 (0)	
Microscopic resection margins					
Negative	116	15 (13)	1	6 (5)	1
Positive	4	0 (0)		0 (0)	
Internal sphincter resection					
Partial	103	15 (15)	0.13	6 (6)	0.59
Complete	17	0 (0)		0 (0)	
Combined resection					
No	108	15 (14)	0.36	6 (6)	1
Yes	12	0 (0)		0 (0)	
Extended lateral pelvic lymph node dissection					
No	74	8 (11)	0.57	1 (1)	0.03
Yes	46	7 (15)		5 (11)	
High ligation of the inferior mesenteric artery					
No	50	6 (12)	1	3 (3)	1
Yes	67	9 (13)		3 (4)	
Mobilization of the splenic flexure					
No	63	8 (13)	1	1 (2)	0.129
Yes	35	5 (14)		3 (9)	
Reconstruction					
Straight anastomosis	58	7 (12)	0.18	1 (2)	0.001
Transverse coloplasty	38	3 (8)		0 (0)	
Colonic J-pouch	24	5 (21)		5 (21)	
Defunctioning stoma					
No	14	1 (7)	1	0 (0)	1
Yes	106	14 (13)		6 (6)	
Anastomosis height from the anal verge					
<2.0 cm	57	5 (9)	0.28	1 (2)	0.21
≥2.0 cm	63	10 (16)		5 (8)	

Table 2 (continued)

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Operating time					
<6 h	68	8 (12)	0.79	1 (1)	0.084
≥6 h	52	7 (13)		5 (10)	
Blood loss					
<500 mL	64	6 (9)	0.29	2 (3)	0.42
≥500 mL	56	9 (16)		4 (7)	
Intraoperative blood transfusion					
No	111	11 (10)	0.014	2 (2)	<0.001
Yes	9	4 (44)		4 (44)	
Preoperative body mass index					
<25	89	10 (11)	0.53	4 (4)	0.65
≥25	31	5 (16)		2 (6)	
Preoperative FEV_1 (%)					
<70%	8	3 (38)	0.061	2 (25)	0.051
≥70%	112	12 (11)		4 (4)	
Preoperative serum total protein level					
Normal (6.3–8.3 g/dL)	113	13 (12)	0.21	4 (4)	0.039
Abnormal	7	2 (29)		2 (29)	
Preoperative serum albumin level					
Normal (3.7–5.2 g/dL)	110	12 (11)	0.11	3 (3)	0.007
Abnormal	10	3 (30)		3 (30)	
Preoperative blood hemoglobin level					
Normal (11.3–14.9 g/dL)	85	8 (9)	0.13	2 (2)	0.059
Abnormal	35	7 (29)		4 (11)	
Preoperative platelet count					
Normal (125,000–375,000/μL)	115	13 (11)	0.12	4 (3)	0.02
Abnormal	5	2 (40)		2 (40)	
Diabetes mellitus					
No	106	12 (11)	0.38	6 (7)	1
Yes	14	3 (21)		0 (0)	
Cardiovascular disease					
No	98	10 (10)	0.15	4 (4)	0.30
Yes	22	5 (23)		2 (9)	
Pulmonary disease					
No	107	10 (9)	0.011	3 (3)	0.017
Yes	13	5 (38)		3 (23)	
Smoking habit					
No	79	11 (14)	0.58	6 (8)	0.094
Yes	41	4 (10)		0 (0)	

The remaining 19 variables not shown here did not demonstrate any significant association

FEV_1 forced expiratory volume in the first second of expiration

Intraoperative transfusion (hazard ratio, 71 [95% confidence interval, 3.0 to 1,000]; $p=0.008$), a colonic J-pouch (32 [1.8 to 500]; $p=0.018$), and pulmonary disease (32 [1.1 to 1,000]; $p=0.044$) were independently associated with adverse outcomes. The incidences of severe leakage for patients with 0, 1, 2, and 3 positive risk factors were estimated to be 0%, 6%, 67%, and 100%, respectively.

Discussion

In this study, the incidences of clinical anastomotic leakage and mortality after ISR were 13% and 0.8%, respectively. These are comparable to the respective incidences of 5% to 16% and 0 to 0.8% in recent ISR series.[7–11] Since these figures are even comparable to the 2.8% to 19.2% and 0%

to 2.5% observed with anterior resection,[14–26] appropriately administered ISR can be regarded as safe in terms of leakage and mortality. However, such figures should be interpreted cautiously because incidences of anastomotic leakage depend on the definition, patient selection, and treatment details. Patient factors like gender,[15,16,18,22,25] age,[25] American Society of Anesthesiology score,[25] heart disease,[26] malnutrition,[17] weight loss,[17] obesity,[15] smoking habit,[26] and alcohol abuse[17] have been reported to independently influence the incidences of leakage after anterior resection, and so have treatment factors such as neoadjuvant chemoradiotherapy,[18,22] bowel preparation,[19] timing of surgery,[25] surgeon caseload,[25] anastomotic level, [14,15,18,19,22] intraoperative contamination,[17,18] pelvic drainage,[21] defunctioning stoma,[16,20,21,24] operation time,[17] and blood transfusion.[17,19]

To our knowledge, there have only been few studies addressing risk factors for anastomotic leakage following ISR. Rullier et al.[15] investigated 272 anterior resections for rectal cancer, in which 131 anastomoses were situated 5 cm or less from the anal verge. Multivariate analysis of their overall population showed that male sex and the level of anastomosis were independent factors for leakage. In a second analysis of 131 very low anastomoses, obesity was an independent factor. The authors concluded that a protective stoma is suitable after anastomoses situated at or less than 5 cm from the anal verge, particularly for men and obese patients.

In the present study, all of the patients had undergone complete bowel preparation, elective surgery by high-volume colorectal specialists, and pelvic drainage, all of which have been reported to be independently beneficial for reducing leakage.[19,21,25] Most had a defunctioning stoma as well.[16,20,21,24] None had received neoadjuvant chemoradiotherapy considered to be an independent risk factor for leakage.[18,22] Therefore, these already known significant factors could not be evaluated in this study. Our multivariate analysis revealed intraoperative blood transfusion and pulmonary disease to be independently associated with overall clinical leakage and severe leakage, and a colonic J-pouch was associated with severe leakage. These results suggest that under the circumstances prevailing in our institution, we can stratify high-risk patients by using these factors and prepare countermeasures against them.

Although the exact mechanism whereby anastomotic leakage may be related to blood transfusion is unclear, it is known that allogeneic blood transfusion induces immunosuppression and predisposes to postoperative infection.[27] Allogeneic leukocytes have a critical role in the induction of transfusion-induced immunosuppression.[27] Tang et al.[27] reported that intra- or postoperative blood transfusion was an independent risk factor for overall surgical site infection, incisional infection, and organ/space infection with and without clinical anastomotic leakage in a prospective study of 2,809 consecutive patients undergoing elective colorectal resection. Therefore, susceptibility to infection induced by transfusion may promote development of anastomotic leakage.

To avoid intraoperative transfusion, it is preferable to treat anemia before surgery using oral and parenteral iron therapy. Transfusion should be reserved for patients with cardiovascular instability and continued and excessive blood loss. Furthermore, it should be given before the operation because deleterious effects appear to be more likely with intra- or postoperative transfusion.[27] Operative blood loss should be minimized by cautious procedures. If excessive blood loss is expected, autologous blood transfusion should be considered, especially in the presence of other risk factors.

In line with previous reports on intestinal anastomotic leakage, we found an independent association with pulmonary disease. Jonsson et al.[28] measured oxygen tension and collagen deposition in subcutaneous wounds in 33 postoperative patients and found that this and the resultant tensile strength are limited by perfusion and tissue oxygen tension. Hopf et al.[29] measured subcutaneous wound oxygen tension in 130 surgical patients and observed that this factor is a strong predictor of infection. Millan et al.[23] determined intramucosal pH at colorectal anastomoses, which reflects blood supply and oxygenation of the mucosa, and found that it can accurately predict the risk of anastomotic leakage. Smoking is a major cause of chronic obstructive pulmonary disease and is known as an independent risk factor for anastomotic leakage after anterior resection.[26] Therefore, although the exact pathophysiology remains to be clarified, it is reasonable to speculate that pulmonary disease predisposes to anastomotic hypoxia which in turn hinders wound healing, aggravates infection, and promotes anastomotic dehiscence.

Because of their chronic and irreversible nature, the chronic obstructive pulmonary disease and restrictive respiratory diseases seen in our series are difficult to treat. However, intensive respiratory management including continuous pulse oximetry monitoring, supplemental oxygen, appropriate analgesia, bronchoscopy when needed, and early mobilization, similar to the management applied after esophageal cancer surgery,[30] may prevent the respiratory complications and hypoxemia which can lead to anastomotic leakage.

Although the incidence of leakage with a colonic J-pouch was reported to be significantly lower than with straight coloanal anastomosis[31] and transverse coloplasty[32] in anterior resection, we paradoxically found a J-pouch to be an independent risk factor for severe leakage in our ISR series. Of the five patients who underwent J-pouch construction and suffered severe leakage, four were male, four received an intraoperative transfusion, and two had

pulmonary disease. Therefore, it appears that a colonic J-pouch reconstruction after ISR may confer extra risk on males with intraoperative transfusion and/or pulmonary disease. Since males have a longer anal canal than females, the presence of a bulky J-pouch and anastomosis may increase the sphincteric squeeze pressure and worsen anastomotic blood and oxygen supply, thereby predisposing to leakage. Thus, in the presence of other risk factors, countermeasures including a switch to other reconstruction methods may need to be considered.

There are limitations to the present study. First, the study design is retrospective, and this may cause biases. Especially, because all or nearly all patients had complete bowel preparation, elective surgery by high-volume colorectal specialists, pelvic drainage, and defunctioning stoma and did not have neoadjuvant chemoradiotherapy, the significance of these factors could not be evaluated in this study. Second, because the numbers of events were limited particularly for severe leakage, many other risk factors which were significant in the previous studies on leakage after anterior resection were not significant in this study. Thus, further confirmation with a larger number of patients would be preferable.

In conclusion, the present retrospective exploratory study suggests that intraoperative blood transfusion and pulmonary disease are independently significant risk factors for overall and severe anastomotic leakage after ISR, and a colonic J-pouch was associated with severe leakage. By taking account of these factors, we may be able to stratify high-risk patients and prepare countermeasures. However, because numbers of patients and events in this study were limited, further investigation and validation are warranted with larger datasets or in future prospective trials.

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ORIGINAL ARTICLE

Can Superselective Embolization be Definitive for Colonic Diverticular Hemorrhage? An Institution's Experience over 9 Years

Ker-Kan Tan · Vigneswaran Nallathamby · Daniel Wong · Richard Sim

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Abstract
Introduction Superselective mesenteric embolization is effective in arresting colonic diverticular hemorrhage with minimal complications, but long-term results are lacking. We aimed to review the short- and long-term outcome of superselective embolization in arresting colonic diverticular hemorrhage in an Asian population.
Methods A retrospective review of all patients who underwent superselective embolization for bleeding colonic diverticula from December 2000 to March 2009 was performed. These cases were drawn from a database of embolization for active gastrointestinal hemorrhage. Short-term outcomes (≤30 days from procedure) identified included rebleeding, ischemia, or any further intervention for any of these two complications. Readmission for rebleeding and/or definitive surgery after 30 days (long-term outcome) was also documented.
Results Twenty-three patients, median age 65 years (range 41–79 years), formed the study group. Nineteen (82.6%) patients had active hemorrhage from right colonic diverticula while four (17.4%) had left-sided diverticular bleeding. Technical success was achieved in all 23 (100%) patients.
Short-term outcome Five (21.7%) patients rebled within the same admission, and all underwent surgery. One patient perished from ensuing anastomotic dehiscence and septic shock and accounted for the only mortality (4.3%) in our series. There was no patient with ischemic complications. Another two (8.7%) patients underwent elective surgical resection on the advice of their surgeons in the absence of rebleeding.
Long-term outcome The median follow-up was 40 months (5–99 months). Of the remaining 16 (69.6%) patients for whom the procedure was definitive initially, four (25.0%) rebled within 2 years from the primary procedure, and elective surgery was performed in one of them. Another had repeat embolization, while the other two were successfully managed conservatively. These three patients refused surgical intervention. One patient was lost to follow-up, and the remaining 11 patients had no further complications.
Conclusion Superselective embolization for active colonic diverticular hemorrhage is safe and effective and should be considered as a first line treatment if possible and available. The procedure could act as a bridge to a subsequent more definitive elective surgery or be definitive as seen in over 50% of our patients over a period of 40 months.

Keywords Embolization · Colonic · Diverticular · Hemorrhage · Definitive · Treatment

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Introduction

Colonic diverticular bleeding is one of the common causes of lower gastrointestinal hemorrhage. Though the bleeding ceases spontaneously in most patients, life-threatening hemorrhage is not uncommon, and any ensuing emergency surgery is often fraught with abysmal results.[1]

The dismal morbidity and mortality rates from emergency surgery had led to the advent of superselective embolization as an alternative to rapidly arrest the active

hemorrhage in these high-risk patients. Numerous reports had cited its high-safety profile and efficacy rates.[2–4]

As most of the literature has been focused on the complications of left-sided colonic diverticulosis as right-sided disease is rare in the West, contrary to its high prevalence in Asians,[5] limited data exist on the implications of right colonic diverticulosis. However, right-sided diverticulosis has been shown to be associated with more massive hemorrhage than left-sided disease.[6]

While some institutions had advocated superselective embolization as a temporary measure before more definitive resection of the diseased segments can be performed, recent data have suggested that this technique could be definitive without any further surgical intervention.[7,8] All the above issues prompted us to review our institution's experience in superselective embolization for colonic diverticular hemorrhage in an Asian population, with special emphasis on the short- and long-term outcomes.

Methods

Study Population

Tan Tock Seng Hospital is a 1,300-bed hospital, the second largest in Singapore, and provides secondary and tertiary medical care for about 1.5 million people. Our department managed an average of 100 patients yearly who presented with lower gastrointestinal hemorrhage from colonic diverticulosis.

A retrospective review of all patients who underwent superselective embolization for bleeding colonic diverticula from December 2000 to March 2009 was performed. These cases were drawn from a database of superselective embolization for active gastrointestinal hemorrhage. Diagnosis of diverticular disease was confirmed through colonoscopy, computed tomographic (CT) scans or barium enema, or a combination of the above, either pre- or post-embolization. Right-sided pathologies were regarded if it was located from the cecum until the transverse colon, while left-sided lesion commenced from the splenic flexure.

The data collected included age, gender, comorbid conditions, presenting signs and symptoms, and clinical parameters. Investigations such as full blood count, gastroscopy, or colonoscopy were also documented. Technical success was defined as the cessation of bleeding seen on completion angiography. The type of embolic agent was determined by the interventional radiologist with both microcoils and polyvinyl alcohol particles used in our series.

The following short-term outcomes (≤30 days from procedure) were identified: rebleeding, evidence of ischemia, or any further intervention such as surgery or repeat embolization for any of these two complications. Readmission for rebleeding and/or definitive surgery after 30 days (long-term outcome) was also documented.

Rebleeding was defined as a drop in hemoglobin ≥1 g/dL in the presence of overt gastrointestinal hemorrhage, while ischemic event was defined as bowel ischemia or infarction that necessitated surgery

Results

Study Group

Twenty-three patients, median age 65 years (range 41–79 years), formed the study group. All these patients presented with hematochezia and ten (43.5%) patients were hypotensive, while 12 (52.2%) were tachycardic just prior to the procedure. Sixteen (69.6%) patients had at least two comorbid conditions. Eight (34.8%) patients had previous admissions for lower gastrointestinal hemorrhage from presumptive colonic diverticulosis and were successfully treated conservatively.

Laboratory Values and Investigations

Pre-embolization gastroscopy and colonoscopy were performed in 14 (60.9%) and ten (43.5%) patients, respective-

Table 1 Characteristics of these 23 Patients Who Underwent Superselective Embolization for Colonic Diverticular Hemorrhage

Characteristic	Results
Median Age (years)	65 (41–79)
Median Follow Up (months)	40 (5–99)
Gender	
Male	−15 (65.2%)
Female	−8 (34.8%)
Type of comorbidities	
Hypertension	−20 (87.0%)
Diabetes mellitus	−9 (39.1%)
Ischemic heart disease	−10 (43.5%)
Cerebrovascular accident	−4 (17.4%)
Renal impairment	−2 (8.7%)
Number of comorbidities	
≤1 Comorbid condition	−7 (30.4%)
≥2 Comorbid conditions	−16 (69.6%)
Previous admission for bleeding gastrointestinal tract	8 (34.8%)
Hypotensive (Systolic BP<90 mmHg) just before the procedure	10 (43.5%)
Tachycardia (Heart rate >100 bpm) just before the procedure	12 (52.2%)

Table 2 Details of the Superselective Embolization

Embolic agents used	
Microcoils only	−21 (91.3%)
Microcoils and particles	−1 (4.3%)
Particles	−1 (4.3%)
Site of bleeding	
Right side	−19 (82.6%)
Left side	−4 (17.4%)
Technical success	23/23 (100%)

ly. Their median hematocrit before the procedure was 22.6% (range 10.4–44.3%) (Table 1).

Superselective Embolization

Microcoils alone were used in the majority of the patients (n=21, 91.3%). Nineteen (82.6%) patients had active hemorrhage from right colonic diverticula, while four (17.4%) bled from left-sided disease. Technical success was achieved in all 23 (100%) patients. None of the patients experienced significant complications from the procedure apart from groin hematoma in one patient that resolved spontaneously (Table 2; Figs. 1 and 2).

Short-Term Outcome

Five (21.7%) patients rebled during the same admission and all underwent surgical resection of the diseased colonic segment. All except one were discharged well. Superselective embolization for bleeding caecal diverticular disease was performed for this patient initially, but when bleeding recurred, he underwent emergency right hemicolectomy. This was complicated by an anastomotic leak due to ischemic segments for which further surgery was performed. This patient eventually succumbed from the ensuing septicemia and accounted for the only mortality (4.3%) in our series (Table 3).

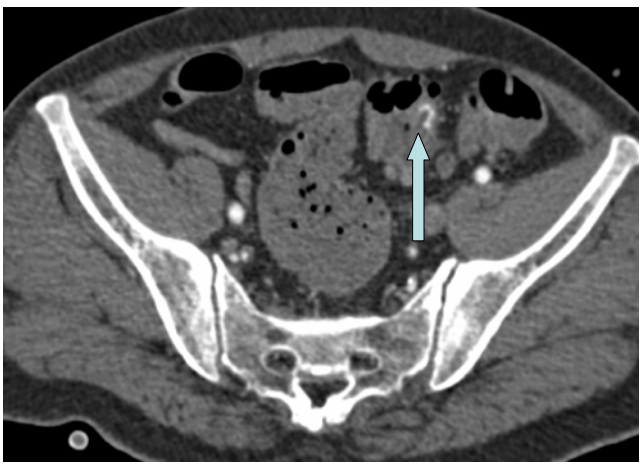

Fig. 1 CT angiography showing extravasation of contrast into sigmoid diverticula.

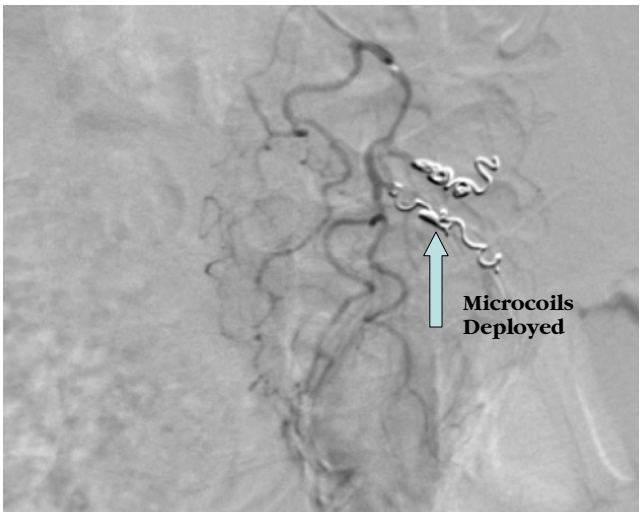

Fig. 2 Completion angiogram showing cessation of hemorrhage and coil deployment.

The remaining two (8.7%) patients underwent surgical resection on the advice of their surgeons in the absence of rebleeding. One patient already had previous episodes of lower gastrointestinal hemorrhage but refused any prior surgery, while the other patient had numerous comorbidities and presented with a very low hematocrit level of 15.4% before the procedure.

The median amount of red blood cells transfused in our series was 2,756 ml (range 389–5,635 ml), and the median length of stay in the hospital was 8 days (range 4–57 days).

Long-Term Outcome

The median follow-up was 40 months (5–99 months). Of the remaining 16 (69.6%) patients for whom the procedure was definitive initially, 11 (68.8%) were well without any further complications, one (6.3%) was lost to follow-up while the remaining four (25.0%) were readmitted for rebleeding. The first patient rebled 2 years post-procedure and required repeat embolization as emergency surgery was

Table 4 Long-Term Outcome of the 16 Patients with Successful Initial Superselective Embolization

Readmission for rebleeding	4 (25.0%)
Underwent elective surgery	−1 (6.3%)
Require re-embolization	−1 (6.3%)
Conservative management	−2 (12.5%)
Lost to follow-up	1 (6.25%)
No further complication	11 (68.8%)

Table 3 Short-Term Outcome of the Study Group

Rebleeding	5 (21.7%)
Ischemic complications	0 (0.0%)
Surgical intervention	7 (30.4%) (5 for rebleeding, 2 on advice of surgeons)
Mortality rate	1 (4.3%)
Median amount of red blood cells transfused	2,756 ml (389–5635)
Median length of stay in hospital	8 days (4–57)

deemed too high risk. Fortunately, the repeat embolization was successful, and the patient was discharged well (Table 4).

Another patient rebled about 8 months post-procedure and was managed conservatively. He underwent right hemicolectomy several months after optimization of his pre-morbid conditions. The other two patients who rebled were successfully managed conservatively without requiring blood transfusion. Both refused definitive surgery. All these three patients had repeat colonoscopy to exclude any other pathology. The six (26.1%) patients (excluding the one that died) who had surgery initially had no further complications.

Review of Our Experience

Figure 3 illustrates our institution's experience in superselective embolization for colonic diverticular hemorrhage. Also seen in Table 5, we reviewed our institution's experience over two time periods. It would appear that patients from the first time period (2000–2004) had worse short-term outcome compared to patients from the second time period (2005–2009). There were higher incidences of rebleeding and associated surgical intervention.

Discussion

Angiographic diagnosis and treatment of gastrointestinal hemorrhage has been described since 1974,[9] but initial attempts were met with high recurrence rates and complications.[10] Significant advances in micro-catheter technology, digital fluoroscopy, and increased technical expertise of the interventional radiologists have resulted in vast improvement and increased adoption of superselective embolization for massive gastrointestinal hemorrhage. Numerous recent reports have cited its high-safety profile and efficacy rates.[2,3,11] Also seen in our series, we were able to achieve a technical success rate of 100%, while the mortality rate was only 4.3%.

Though there were no ischemic complications in our series, we had several patients who rebled after the procedure. Interestingly, all the patients who rebled within 30 days had right-sided diverticula. The authors postulated

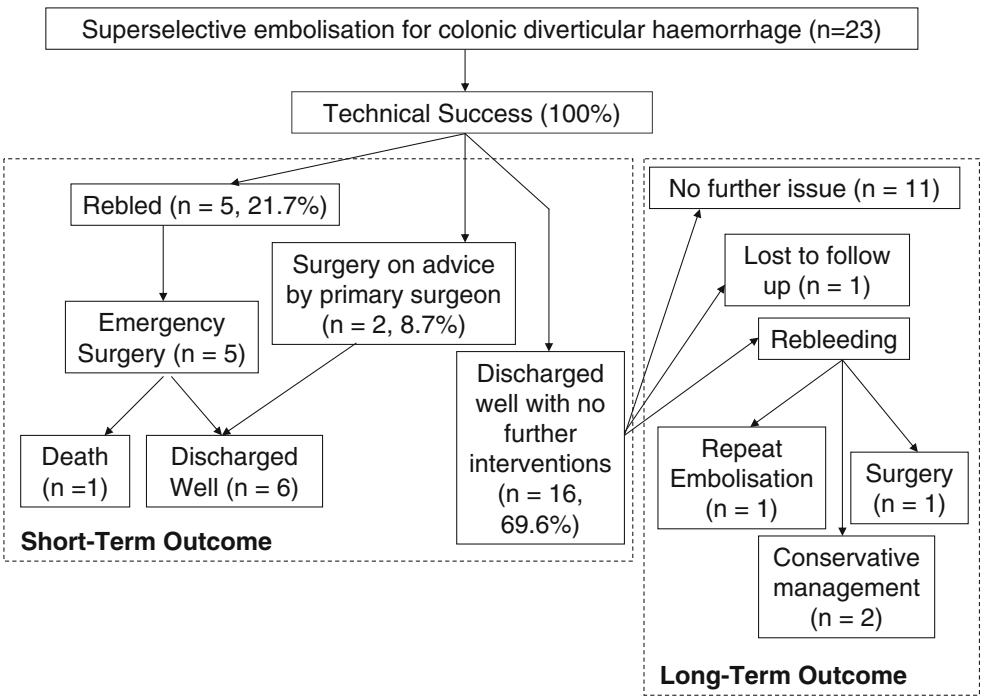

Fig. 3 Summary of short- and long-term outcome of using superselective embolization in colonic diverticular hemorrhage in our institution.

Table 5 Overview of our Institution's Experience over the Two Time Periods

Time period	Technical success	Rebleeding (short-term)	Surgery (short-term)	Rebleeding (long-term)	Surgery (long-term)
1st 5 years (2000–2004)	8/8 (100%)	4/8 (50.0%)	6/8 (75.0%)	1/2 (50.0%)	0/2 (0.0%)
2nd 4 years (2005–2009)	15/15 (100%)	1/15 (6.7%)	1/15 (6.7%)	3/15 (20.0%)	1/15 (6.7%)

that this propensity might actually be genetically linked. While right-sided diverticulosis has been shown to be much more prevalent in Asians, one local study actually highlighted that right-sided diverticula often resulted in more massive bleeding than left-sided lesions.[6] This tendency of right-sided diverticula to bleed more massively has also been reported in the Western population.[12,13] This observation has been postulated to be due to the thinner colonic wall in the right colon resulting in the vessels being more vulnerable to injury and bleeding.[6]

The exact role of superselective embolization in colonic diverticular hemorrhage has been controversial. While some advocate the procedure as a bridge to a subsequent more definitive elective surgical procedure, others had suggested that it could be definitive obviating the need for surgery entirely.[13,14]

As shown in our series, three of our patients (two during the first admission, while the third was readmitted for rebleeding 8 months after the procedure) had elective surgery after successful embolization of the bleeding site and were all discharged well. Superselective embolization allowed ongoing resuscitation, closer monitoring, and preoperative optimization of the numerous risk factors often seen in these patients. This is exemplified by our series, with over 69% of our patients having at least two comorbid conditions.

On the other hand, mesenteric embolization was shown to be definitive in over half of our patients without the need for surgery or any rebleeding episodes. This is an attractive option as it eliminates the risk of surgery in these high-risk patients.

From our series, it was interesting to note that over the two time periods, patients in the earlier period (2000–2004) had worse short-term outcome, with higher incidences of rebleeding and surgery. The authors postulated that this could be because of the continual improvement in embolization technology such as better micro-catheters, advancement of digital fluoroscopy technology, and increased experience and expertise of our interventional radiologists.

Based on our results, superselective embolization was definitive in selected patients and eliminated the need for surgical intervention. However, this must be weighed

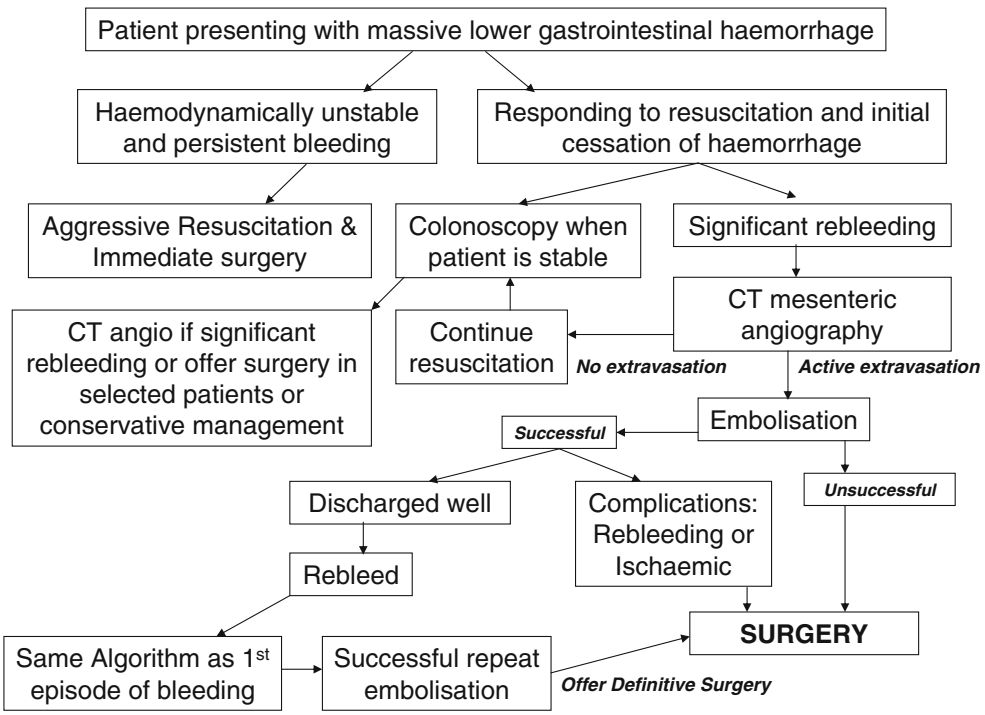

Fig. 4 Suggested algorithm in the management of massive lower gastrointestinal hemorrhage.

against the risks of a second episode of massive gastrointestinal hemorrhage and its ensuing complications in these high-risk patients. Hence, considering all the risks of nonoperative management against that of surgical intervention, our institution has currently adopted superselective embolization as the first-line treatment of active colonic diverticular hemorrhage, if possible, reserving definitive surgery for those patients who rebleed.

In addition, one of our patients had a successful repeat embolization and did not suffer from any ischemic complications. The role of repeat embolization has been briefly mentioned in the literature, but more information would be required to achieve any definitive conclusion on its role.[7,8,13,14]

Based on information from our series and data from the literature, our institution has currently adopted the following algorithm as shown in Fig. 4 below in the management of massive lower gastrointestinal hemorrhage.

Similar to our institution, numerous institutions have also adopted multidetector CT angiography as the radiological investigation of choice in patients with massive gastrointestinal hemorrhage.[15,16] Some of its advantages would include its rapidity, noninvasiveness, high sensitivity, and ease of operation. Apart from localizing the bleeding site accurately, it could also determine the underlying cause of the bleeding lesion and help guide subsequent management, which may include surgery or embolization.[15,16] On the other hand, catheter-directed angiography is more invasive and associated with several complications arising from the vascular access or the catheter. But it does allow immediate therapeutic intervention upon detection, which is the main drawback of CT mesenteric angiography in such situations.[15,16] The data from the literature and our experience led us to include this in the algorithm (Fig. 4).

As with most studies, there were several limitations in the present study. This series of patients was enrolled from a single institution, and any retrospective study has inherent flaws. Even though our study is one of the larger series in the literature analyzing the long-term durability of mesenteric embolization for colonic diverticular hemorrhage in an Asian population, the sample size is still extremely small. Furthermore, there was no prior fixed protocol adopted in our institution in the management of these patients. Moreover, right-sided colonic diverticulosis was the underlying pathology in most of our patients which is much rarely seen in the West. However, several reports based on the Western population have also cited the high prevalence of right-sided colonic diverticulosis in massive lower gastrointestinal hemorrhage and also reinforced the high-safety profile and efficacy of superselective embolization in such situations, even in left colonic diverticula.[12–14]

Though the limitations are significant, our series reinforced the limited data in the current literature on the high-safety profile and long-term durability of superselective embolization in colonic diverticular hemorrhage. Even if surgical resection is deemed necessary for rebleeding or surgeons' advice, this procedure is still invaluable as it allows adequate resuscitation of the patients, proper preoperative optimization, and appropriate preparation for the subsequent surgery. It can also limit the extent of resection. All these serve to reduce the resultant morbidity and mortality in these patients. The authors believed that with the increased awareness and adoption of superselective embolization, more data would be available to reaffirm its long-term efficacy in the management of colonic diverticular hemorrhage.

Conclusion

Superselective embolization for active colonic diverticular hemorrhage is safe and effective and should be considered as a first line treatment if possible and available. The procedure could act as a bridge to a subsequent more definitive elective surgery or be definitive as seen in over 50% of our patients over a period of 40 months.

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ORIGINAL ARTICLE

Endoscopic and Percutaneous Preoperative Biliary Drainage in Patients with Suspected Hilar Cholangiocarcinoma

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Abstract
Introduction Controversy exists over the preferred technique of preoperative biliary drainage (PBD) in patients with hilar cholangiocarcinoma (HCCA) requiring major liver resection. The current study compared outcomes of endoscopic biliary drainage (EBD) and percutaneous transhepatic biliary drainage (PTBD) in patients with resectable HCCA.
Methods One hundred fifteen consecutive patients were explored for HCCA between 2001 and July 2008 and assigned by initial PBD procedure to either EBD or PTBD.
Results Of these patients, 101 (88%) underwent PBD; 90 patients underwent EBD as primary procedure, and 11 PTBD. The technical success rate of initial drainage was 81% in the EBD versus 100% in the PTBD group (P=0.20). Stent dislocation was similar in the EBD and PTBD groups (23% vs. 20%, P=0.70). Infectious complications were significantly more common in the endoscopic group (48% vs. 9%, P<0.05). Patients in the EBD group underwent more drainage procedures (2.8 vs. 1.4, P<0.01) and had a significantly longer drainage period until laparotomy (mean 15 weeks vs. 11 weeks in the PTBD group; P<0.05). In 30 patients, EBD was converted to PTBD due to failure of the endoscopic approach.
Conclusions Preoperative percutaneous drainage could outperform endoscopic stent placement in patients with resectable HCCA, showing fewer infectious complications, using less procedures.

Keywords Endoscopic · Percutaneous · Biliary drainage · Cholangiocarcinoma · Preoperative

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Introduction

Hilar cholangiocarcinoma (HCCA) remains one of the most difficult tumors in terms of staging and radical surgical treatment.[1] The optimal mode of preoperative management is still under debate. Most patients with HCCA show liver dysfunction caused by obstructive jaundice, which has proven to be a significant risk factor in major liver resection.[2–4] A potentially fatal complication of extended liver resection in a jaundiced patient is failure of the remnant liver. Therefore, preoperative biliary drainage (PBD) has been devised for jaundiced patients undergoing major hepatic resection to improve the surgical outcome.[5,6]

Controversy exists regarding the preferred technique of PBD, either via endoscopic retrograde biliary drainage (EBD) or using antegrade percutaneous transhepatic biliary drainage (PTBD). PTBD is the preferred method in Japan for relief of obstructive jaundice due to proximal obstruction.[7,8] In Europe and the USA, EBD is usually performed as primary intervention and is followed by PTBD only

when EBD has failed. Internal drainage by EBD, although a less invasive technique, carries increased risk of developing cholangitis due to bacterial contamination from the duodenum and increased risk of procedure-related complications such as duodenal perforation and post-EBD, acute pancreatitis.[9,10] Drainage by means of PTBD is associated with hemobilia, portal vein thrombosis, cancer seeding, and potentially more patient discomfort.[11–13]

The three published prospective randomized controlled trials comparing EBD versus PTBD, included patients with unresectable bile duct tumors or carcinoma of the gallbladder and pancreas showing conflicting results.[14–16] These studies address palliative treatment and, although important in the context of biliary drainage no, distinction was made between distal and proximal bile duct obstruction. In patients with HCCA with usually involvement of the segmental biliary ducts, drainage of the intrahepatic biliary tree is challenging and mostly requires multiple drains or stents. However, in patients with a distal bile duct obstruction, usually caused by a tumor in the region of the pancreatic head, drainage is more straightforward and requires a single drain or stent. In the latter category of jaundiced patients in whom partial liver resection is usually not undertaken, PBD remains a controversial issue.[17,18]

To date, no studies have been performed regarding the optimal route of drainage in patients with a potentially resectable HCCA. Therefore, the aim of the present study was to compare success rate and complications of EBD and PTBD in patients eligible for resection of a suspected HCCA.

Materials and Methods

Patients

A total of 115 patients underwent an explorative laparotomy under the suspicion of HCCA between January 2001 and July 2008, of which 101 (88%) underwent PBD and were included in the present study (Fig. 1). Fourteen patients did not undergo drainage as their bilirubin level did not exceed 40 μmol/L. Usually, resectional surgery was performed when serum bilirubin levels had decreased to ≤40 μmol/L. When feasible, hilar resection with complete lymphadenectomy of the hepatoduodenal ligament was performed, usually en bloc with (extended) hemihepatectomy, caudate lobe resection and the portal vein bifurcation when involved by tumor.[19] Unresectable disease, due to vascular ingrowth and/or (extra) hepatic metastases, was confirmed histologically. Patients were divided into two groups according to the primary drainage procedure; PTBD or EBD. In the majority of the included patients, the initial diagnostic evaluation and drainage procedures were performed in the referring hospitals. Medical data of patients collected from these hospitals and from our tertiary referring center included demographic features, laboratory investigations, results of imaging studies, results of EBD and PTBD, and intra-operative findings.

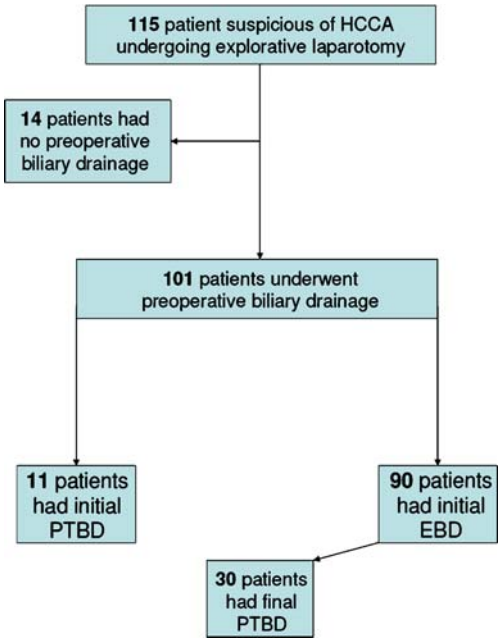

Figure 1 Flow chart of patients eligible for resection of hilar cholangiocarcinoma (HCCA) in the period from January 2001 to July 2008.

Staging of HCCA

Proximal obstruction in the biliary tract was staged according to the Bismuth–Corlette classification based on all available imaging studies.[20] Bismuth type I and II tumors obstruct the proximal common hepatic duct or hepatic duct confluence, but do not extend into the intrahepatic segmental ducts; Type IIIa/b tumors involve the hepatic duct confluence and extend into the right or left segmental intrahepatic branches; Type IV tumors involve the hepatic duct confluence with extension into both the right and left segmental branches.

Biliary Decompression

The technique of PTBD in this series involves the use of ultrasound guidance, a thin Chiba needle and a 0.014-in. guidewire to gain access to the biliary system. Antegrade cholangiography was performed to localize the site of obstruction, after which the guidewire was advanced through the stenosis. Thereafter, a catheter was placed with its distal end in the duodenum for internal–external drainage. The bile was collected for the first 48 h, after which the catheter was closed in order to achieve internal drainage.

For EBD, straight Amsterdam type polyethylene stents were used.[21] After a small sphincterotomy to facilitate introduction of the various catheters a retrograde cholangiography was performed to localize the site of obstruction. The guidewire was maneuvered through and above the biliary stenosis followed by a catheter. The endoprosthesis was then pushed in position over the catheter. The guidewire, catheter, and endoscope were removed, leaving the polyethylene stent in situ. When insertion of two stents was required during the same session, two guidewires were placed before insertion of the first stent. Radiological imaging was not part of routine drainage procedure planning.

Definition of Events

Technical success was defined as stent/catheter insertion across the stricture with appropriate position and immediate biliary decompression. Infectious complications comprised cholangitis and/or cholecystitis. Cholangitis was defined as a temperature >38.5°C without another demonstrable cause that persisted for longer than 24 h, together with biochemical evidence of cholestasis and infection (increased C-reactive protein and leucocytes). Cholecystitis was diagnosed on the basis of right upper quadrant pain, along with supportive evidence on imaging studies. Acute pancreatitis was defined as persistent abdominal pain with three times or more elevation of serum amylase levels.[10] Stent dysfunction (occlusion, migration, or failure) was scored when persistence or recurrence of jaundice was determined and/or imaging studies showed evidence of dilated segmental biliary ducts. Biliary re-intervention was defined as any type of endoscopic or percutaneous procedure that was required to improve biliary drainage after stent insertion. Finally, therapeutic success was defined when an almost normal range bilirubin level (≤40 μmol/L) was achieved at the time of last plasma bilirubin measurement before surgery. All abovementioned events were taken into account during the period from the first attempt of drainage until explorative laparotomy.

Intention to Treat Analysis

We assessed the effect of the biliary drainage procedures using the following variables: technical success of stent insertion, infectious complications, stent migration, number of procedures, interval from first drainage attempt until explorative laparotomy, and therapeutic success. For the intention-to-treat analysis, we assigned subjects by initial drainage procedure (n=101) to the EBD group or PTBD group. The EBD group included also patients in whom EBD was finally converted to PTBD, because of technical failure (including no drainage of the future remnant liver) and/or recurrence of complications.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences 14.0 (SPSS, Chicago, Illinois, USA). Mean±SD, or median with range if not normally distributed, described continuous parameters. Student's t test, Mann–Whitney U test, or Fisher's exact test were used where appropriate, analyzing the differences in the various parameters between groups. A P value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Table 1 shows the baseline characteristics of 101 patients undergoing PBD: 90 patients underwent EBD as primary procedure and 11 patients PTBD. The median age, male–female ratio, and the extent of bile duct involvement classified according to the Bismuth staging system did not differ significantly between groups. No differences were observed in plasma bilirubin levels before drainage. The diagnosis as confirmed by histopathological assessment of the resection specimen or of biopsies in the non-resected patients was equally distributed between the EBD and PTBD group. There was a difference between both groups in the type of hospital where the initial drainage procedure was undertaken. In the PTBD group more initial procedures (6/11) were performed in a tertiary care center (P=0.01). Surgical outcome was not different between both groups in terms of morbidity and mortality (data not shown).

Technical and Therapeutic Success

Initial drainage was technically successful in 73 (81%) patients in the EBD versus 11 (100%) patients in the PTBD group (P=0.203, Table 2). In all patients in the PTBD group, internal biliary drainage was achieved by passing the catheter across the tumor site, into the duodenum. With regard to the 17 patients in the endoscopic group in whom the initial procedure failed, this was due to patient agitation (n=2), procedure-related complications (n=2, severe sphincterotomy bleeding and duodenal perforation, respectively) and difficulties in passing the stricture (n=13). In eight of these 17 patients, endoscopic stent placement succeeded at a subsequent attempt. The other nine patients were either directly switched to PTBD or after failure of subsequent endo-

Table 1 Characteristics of 101 Patients Undergoing PBD Suspicious of Resectable HCCA

	PTBD (n=11)	EBD (n=90)	P value[a]
Gender male–female	6–5	64–26	0.305
Median age (range)	61 (36–75)	61 (37–77)	0.870
Mean plasma bilirubin pre drainage	231 (±140)	177 (±112)	0.231
Bismuth classification			0.837
Type I, II	3 (27%)	22 (25%)	
Type III, IV	8 (73%)	68 (75%)	
Final pathological diagnosis			0.237
Cholangiocarcinoma	8 (73%)	80 (89%)	
Metastatic disease	–	1 (1%)	
Benign stricture	3 (27%)	9 (10%)	
Initial procedure tertiary—referring hospital	6–5	16–74	0.012

PBD preoperative biliary drainage, *EBD* endoscopic biliary drainage, *PTBD* percutaneous transhepatic biliary drainage

[a] P value is PTBD vs. EBD (Fisher's exact test or Mann–Whitney U test)

scopic attempts. Further procedure-related complications other than failure of drainage, were bile duct perforation in one patient in the EBD group and hemobilia in the PTBD group. The mean number of drains/stents in situ before surgery to achieve sufficient drainage of at least the future remnant liver was 1.4 (range 1–3) in the PTBD group and 1.7 (1–4) in the endoscopic group (P=0.134). Therapeutic success was equally effective since the plasma bilirubin levels before laparotomy were similar in both groups (Table 2).

Complications

The distribution of complications in both groups is shown in Table 2. The most frequent complication was cholangitis which occurred significantly more often in the EBD group. Forty-eight percent of the patients in the EBD group had one or more infectious complications compared to 9% in the PTBD group (P=0.021). Another infectious complication was acute cholecystitis which occurred in one patient of the EBD group. This patient was treated successfully by percutaneous drainage of the gallbladder until laparotomy. Although the rate of one or more stent dislocations per patient was similar in the EBD and PTBD groups (23% vs. 20%, P=0.701), the number of re-interventions required to manage infectious and stent-related problems was significantly increased in the EBD group compared to the PTBD group (2.8 vs. 1.4, P<0.01). The increased number of infectious complications in the EBD group resulted in a longer mean drainage period until explorative laparotomy, namely 15 weeks (min–max 4–29) in comparison to 11 weeks (3–21) in the PTBD group (P=0.033). Furthermore, other complications were recorded such as acute pancreatitis (n=7), hemobilia (n=1), and biliary perforation (n=1). Pancreatitis was only observed in the EBD group. In one patient after an endoscopic procedure, a bile duct perforation resulted in severe peritonitis, sepsis, and admission to the intensive

Table 2 Clinical Outcome of Patients After PBD via the Endoscopic or Percutaneous Approach

	PTBD (n=11)	EBD (n=90)	P value[a]
Technical success stent insertion	11 (100%)	73 (81%)	0.203
Complications			
Infectious	1 (9%)	43 (48%)	0.021
Cholangitis	1	43	
Acute cholecystitis	–	1	
Dislocation	2 (20%)	21 (23%)	0.701
Other			
Pancreatitis	–	7	
Hemobilia	1	–	
Duodenal perforation	–	1	
Biliary perforation	–	1	
Wks drainage → laparotomy (range)	11 (3–21)	15 (4–29)	0.033
Mean no. of procedures (range)	1.4 (1–3)	2.8 (1–7)	0.001
Mean no. of stents in situ (range)	1.4 (1–3)	1.7 (1–4)	0.134
Mean plasma bilirubin pre-laparotomy	18 (±14)	23 (±21)	0.995

EBD endoscopic biliary drainage, *PTBD* percutaneous transhepatic biliary drainage

[a] P value is PTBD vs. EBD (Fisher's exact test or Mann–Whitney U test)

care unit. Transient hemobilia occurred in one patient in the PTBD group, but required no blood transfusion.

Patients Treated with Both Procedures

The EBD group included patients in whom the endoscopic interventions were finally converted to PTBD. In total 30 patients were switched including the nine abovementioned patients in whom initial endoscopic drainage had failed. Conversion to PTBD was mainly due to recurrence of complications and in three patients (10%) because the endoscopic approach had failed to drain the future remnant liver. In 10 (33%) patients in whom endoscopic stent placement was eventually converted to the percutaneous approach, one single PTBD procedure sufficed until explorative laparotomy. One severe complication occurred after a PTBD procedure, namely portal vein thrombosis which rendered the patient unresectable as determined during explorative laparotomy. The rate of infectious complications in patients with mixed procedures was 67%. Sixteen (53%) of the 30 switched patients had one or more stent dislocations, resulting in a mean number of 4.2 (range 2–7) procedures per patient. Finally, the mean drainage period until explorative laparotomy was 15 weeks (min–max 5–26 weeks). The number of stent dislocations in the switched group comprised the sum of endoscopic and percutaneous migrated stents, whereas in the analysis of the EBD group (the abovementioned 90 patients) only the endoscopic-migrated stents were included. Concerning infectious complications no distinction was made because after a mix of different approaches it is difficult to assess which procedure initially caused the infection.

Discussion

The results of the present study show a more favorable outcome of PTBD than of EBD for PBD in patients with potentially resectable HCCA. EBD is associated with more infectious complications resulting in a higher number of procedures and finally a longer work-up period until explorative laparotomy. We are aware of the limitations of the present study; a retrospective analysis and unequal distribution of patient number in the treatment groups. However, to our knowledge, no other studies are available comparing endoscopic with percutaneous biliary drainage in patients with potentially resectable HCCA. As in the earlier mentioned prospective trials,[14–16] the results of a recently published retrospective study about this issue was in the setting of palliative treatment.[22]

In the diagnostic strategy of hilar lesions accuracy of computed tomography or magnetic resonance cholangiography is known to be higher when performed prior to stent placement, due to prevention of endoprosthesis scattering artifacts. Correct staging according to the Bismuth classification has shortcomings for determining resectability of tumors,[23] but is useful in deciding a proper biliary drainage strategy, i.e. the future liver remnant. Moreover, this highly improves the success of subsequent stent placement.[24,25] Interventional radiologists are more likely to perform preprocedural imaging themselves and therefore, benefit from this information. Although considered an obsolete procedure for diagnostic purposes, endoscopic retrograde cholangiography is nevertheless still regularly performed before radiological imaging in the evaluation of obstructive jaundice. This might at least in part explain the high number of EBD procedures used as initial mode in this series.

Tumors of the proximal bile ducts are rare and the varying experience of the endoscopist during the initial drainage procedure could have biased the outcome of this study. Most initial procedures in the PTBD group were performed in a tertiary referring center (i.e. AMC) with consequently, greater case load and experienced interventional radiologists. A number of surgical studies have shown a relationship between procedural volumes of an institution and patient outcomes.[26,27] This relationship has been most consistent for complex procedures and along the same lines, seems to hold true on the level of interventions for biliary drainage,[28] especially in cases of hilar bile duct tumors.

Cholangitis due to bacterial contamination originating from the duodenum is a serious clinical problem which often requires additional interventions. Cholangitis after PTBD is also possible especially when extended to internal drainage. A 48% infectious complication rate after EBD is comparable with other series in the literature,[9,29] albeit drawing a parallel between these studies is difficult depending on applied definitions of infectious complications. A 9% infectious rate after PTBD is low and could be biased by the small number of patients included in this group although comparable rates have been described after PTBD in larger series in the literature.[30] Acute pancreatitis, however uncommon, is a potentially severe complication which was only observed in the EBD group. The increased infection rate probably explains the significantly higher number of necessary re-interventions in the EBD group in comparison to the PTBD group.

Stent migration is another important complication requiring re-intervention. With self-expanding metal stents, dislodgement of the stent is exceptional,[31] but its use is generally confined to unresectable disease. In the present study, polyethylene endoprostheses were used because patients were all potentially resectable. Stent dislodgement in the endoscopic and percutaneous group occurred around 20%, which is rather high in comparison to other

studies.[32,33] Apart from the high migration incidence we can conclude that the approach, either by EBD or by PTBD, had no influence on stent patency.

Which part of the liver should be drained is an ongoing controversy.[12,32] Pre-procedural planning should involve evaluation of the exact level and extension of the stricture site, selection of the most appropriate liver segments for drainage and assessment of an appropriate access route. PTBD offers the possibility to perform selective biliary drainage (SBD) whereas EBD via both the left and right hepatic duct often implies total biliary drainage (TBD). An argument for SBD of the future remnant liver is the subsequent induction of hypertrophy on this side of the liver, and atrophy of the non-drained part of the liver to be resected.[34,35] In a retrospective cohort study in which the effect of SBD versus TBD was investigated before hepatectomy in 42 patients, SBD was not found to increase the risk of cholangitis.[36] In association with portal vein embolization, SBD proved superior to TBD in promoting hypertrophy of the future remnant liver, by which extended hemihepatectomy could be performed more safely. The only existing prospective randomized controlled trial comparing TBD versus SBD included patients with unresectable hilar bile duct tumors.[37] Unilateral drainage resulted in a higher technical success rate of stent insertion and a significantly lower incidence of complications. The above studies showed better results for SBD and therefore indirectly indicated a preference for PTBD through which segmental drainage is more easily achieved.

In our study we did not evaluate the cost-effectiveness of both procedures. From other studies in literature it is known that the number of re-interventions is an important factor influencing the final costs. In three studies for example, metallic stents were compared with plastic endoprostheses.[33,38,39] The initial high costs made in the group with metallic stents, were counterbalanced by the reduction in the need for endoscopic re-interventions and/or re-hospitalization. Therefore, the number of extra procedures needed is a significant factor in the comparison of costs and, based on our results, suggests a preference for the PTBD group. The introduction of costs into the decision-making process is of course, only justified when both procedures under consideration have equal clinical benefit.

From a surgical point of view, preoperative PTBD may have an additional advantage during exploration of the hilar area of the liver. In the authors' experience, the biliary tubes help to define the bile ducts proximal of the tumor in the operative field and to guide the parenchymal dissection at a safe distance of the tumor. Also, when the resection has taken place and the biliary ducts of the liver remnant are anastomosed to a Roux-en-Y jejunal loop, the PTBD tubes are shortened and used as transanastomotic drains to facilitate healing of the hepaticojejunostomies. After a control cholangiography via the PTBD tubes at 3–6 weeks postoperatively, the tubes are removed. In case of EBD, the stents are removed during resection and new transanastomotic biliary drains are placed, usually in a retrograde fashion.

In conclusion, our results indicate that preoperative percutaneous biliary drainage could outperform endoscopic stent placement in patients with resectable HCCA, showing fewer infectious complications resulting in significantly less procedures. These results underline the importance of further (randomized) studies to confirm this point, which should be conducted in specialized centers with experience in the preoperative work-up of this relatively rare tumor.

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ORIGINAL ARTICLE

Changes in Quality-of-Life Following Laparoscopic Cholecystectomy in Adult Patients with Cholelithiasis

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Abstract
Background The aim of this study was to evaluate changes in quality-of-life following laparoscopic cholecystectomy (LC) in adults with cholelithiasis.
Methods Patients were evaluated with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the Gastrointestinal Quality of Life Index (GIQLI) preoperatively and 12 months after LC. Outcome predictors were analyzed using correlation and regression statistics.
Results Ninety-nine patients were enrolled (male/female, 32:67, age 49.8±13.7 years old). At baseline, patients performed inferiorly to general population in all SF-36 general health dimensions ($p<0.0001$). Postoperatively, the "role-physical", "role-emotional", and "bodily pain" dimensions of health significantly improved. There were significant improvements in GIQLI "total", "physical well-being", "mental well-being", "gastrointestinal digestion", and "defecation" subscales scores. Serum direct bilirubin level and drainage tube indwelling were significant predictors for quality-of-life improvement following LC.
Conclusions LC can greatly reduce gastrointestinal symptoms to improve quality-of-life for patients with cholelithiasis. Patients with severe baseline conditions may benefit from greater quality-of-life improvement following LC.

Keywords Cholelithiasis · Laparoscopic cholecystectomy · Quality of life

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Introduction

The yearly incidence of gallstone disease may range from a low of 1 in 1,000 young men to 19 in 1,000 elderly women.[1] An Italian longitudinal population study revealed that the overall 10-year incidence of gallstone disease was 6.3%.[2] The change of dietary habit with increase intake of calories and cholesterol has led to the escalation of gallbladder disease in many countries.[3]

The development of laparoscopic cholecystectomy (LC) in the last two decades has partly led to the increase of cholecystectomy. Urbach and Stukel reported that the adjusted annual rate of elective cholecystectomy per 100,000 population in Canada increased from 201.3 in 1988–1990 to 260.8 in 1992–2000.[4] Ho et al., attributing to the improvement of nutritional status and living standard in Taiwan, reported steady increase of surgical interventions for gallstones.[5]

However, there are limited researches in the literatures that have reported LC quality-of-life outcomes.[6–10] The quality-of-life impacts of LC and the predictors of patients'

subjective outcomes remained undetermined, especially in the Asian context. The aims of this study are to use the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and Gastrointestinal Quality of Life Index (GIQLI) surveys to report subjective quality-of-life following LC and to investigate the factors that may predict LC quality-of-life outcomes in adults with cholelithiasis.

Materials and Methods

Study Population

The study was conducted in a prospective, nonrandomized manner. A total of 99 consecutive adult patients (aged 18 years or older) who underwent abdominal sonography confirming symptomatic gallstone seeking surgical treatment in a tertiary referral medical center were enrolled within a 1-year period (July 2004–June 2005). Patients with stable chronic condition or at acute exacerbation of disease were both included. Approval from institutional review board of Cathay Medical Center was obtained in advance. Patients' demographic data and health history were reviewed during initial visit. The systemic comorbidity including diabetes mellitus, hypertension, peptic ulcer, gastroesophageal reflux disease, heart disease, and hyperlipidemia were screened and documented upon entry.

Patients all received routine blood biochemistry workup, including blood cell count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total and direct bilirubin. Prior to any medical or surgical intervention, all patients were administered with the International Quality of Life Assessment SF-36 Standard Taiwan version 1.0[11–13] and the Chinese Taiwan version of GIQLI.[14] Patients were asked to fill out the surveys by themselves with the assistance from research staff if needed. Patients were evaluated with the SF-36 and GIQLI again 12 months after surgery. Standard four-port LC was performed for all patients.

Quality-of-Life Measure

SF-36

The SF-36 is a widely used generic quality-of-life measuring instrument that divides quality of life into eight dimensions, including physical functioning (PF), role-physical (RP), bodily pain (BP), general health, vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Each subscale score from 0 to 100, with 100 as the most optimal health status.[12,13]

GIQLI

The GIQLI is a 36-item survey that evaluates the physical and mental problems associated with gastrointestinal disease on a Likert scale; each survey question has five response levels (0–4, worst to best condition). The GIQLI generates a total score and four subscale scores (physical well-being 0–40, mental well-being 0–20, gastrointestinal digestion 0–40, and gastrointestinal defecation 0–24). The physical well-being (PW) subscale reflects the limitations in physical or social activities directly related to gastrointestinal conditions. The remaining subscales are reflective of a patient's mental (mental well-being, MW), digestion (gastrointestinal digestion, GDG), and defecation (gastrointestinal defecation, GDF) problems. Total and subscale scores are scaled from 0 (worst) to 124 (best).[15,16] The Taiwan version GIQLI was validated in previous study.[14]

Statistical Analysis

Results are expressed as mean±SD. Student's *t* test with unequal variance is applied to compare the SF-36 subscale scores of gallstone patients (pre- and postoperative) with 6,109 age- and sex-matched Taiwanese population norms.[12,13] Paired *t* test is used to compare preoperative and postoperative quality-of-life scores. Using the pre-/postoperative SF-36 and GIQLI score differences as dependent variables, step-wise multiple regression analyses are applied to investigate the effects of patient characteristics, operative information, and preoperative blood biochemistry on the quality-of-life changes following LC.

Results

Study Population

There are 32 males and 67 females (mean age 49.8±13.7 years; range 23 to 75) in this study cohort. Comorbidities were observed in 39% of the patients, including hypertension (18), heart disease (eight), diabetes mellitus (11), GERD (seven), and others (16). There are 76 with chronic stable (biliary colic only) condition (mean age 48.95±12.30 years, male/female 25:51) and 26 with acute exacerbation (acute cholecystitis) condition (mean age 52.0±16.92 years, male/female 8:18).

Stable chronic and acute exacerbations of gallstone disease are defined as the following: Patients of known cholelithiasis for at least 3 months prior to operation with symptoms no more than biliary colic are considered as under stable chronic condition; on the other hand, patients with acute exacerbation of gallstone may suffer from elevated inflammatory serum marker, fever, jaundice, right upper abdomen tenderness, or other gastrointestinal symp-

toms related to cholecystitis. Twenty-six patients are grouped into gallstone with acute exacerbation according to the aforementioned definition, and all have GIQLI total scores less than 80. There is no significant difference regarding age and sex distributions between chronic stable and acute exacerbation disease.

Operation

The mean operation time was 55±31 min; 15 (15.2%) patients had subhepatic close suction drainage tube (Jackson–Prett type) placed after LC. The mean total length of stay was 3 days. There was no bile leak, no wound infection, and no surgical mortality. Multiple stones were identified in 57 patients. The mean size of stone was 9.7±7.4 mm. The histopathology examination showed 30 cholesterol and 69 noncholesterol stones.

There was no conversion to open surgery in this study population. The follow-up rate was 100% at 12 months after operation.

Quality-of-Life Improvement in SF-36

All eight SF-36 subscale scores from preoperative gallstone patients were significantly lower than those form Taiwanese population norms (*t* test, $p<0.0001$). Compared with preoperative quality-of-life status, three out of eight SF subscale domain showed significant improvement (paired *t* test): RP 20.9% ($p=0.003$), BP 27.8% ($p<0.0001$), and RE 17.7% ($p=0.0069$; Fig. 1). Even after operation, gallstone patients still performed inferiorly to matched general population in seven out of eight SF-36 health dimensions except for RE (Fig. 1).

Quality-of-Life Improvement in GIQLI

Total and all GIOLI subscale scores (PW, MW, GDG, and GDF) improved significantly (paired *t* test, $p<0.0001$) following LC surgery (Fig. 2), indicating remarkable recovery of gastrointestinal symptoms or disabilities. Compared with preoperative GIQLI survey, the degrees of improvement were 19.1% for GIQLI total, 17.2% for PW, 20.4% for MW, 26% for GDG, and 7.8% for GDF scores.

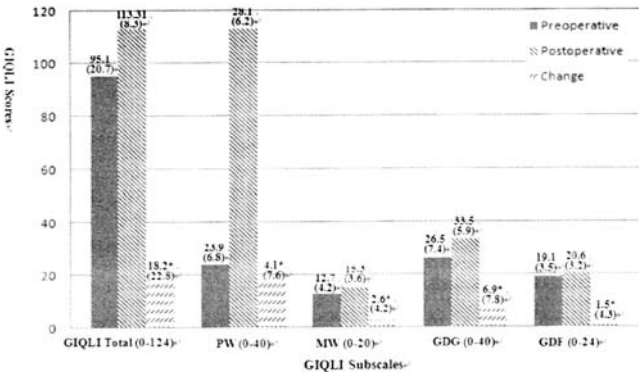

Figure 2 Preoperative and postoperative GIQLI scores ($N=99$). *PW* physical well-being, *MW* mental well-being, *GDG* gastrointestinal digestion, *GDF* gastrointestinal defecation. *$P<0.0001$: *t* test, significant difference between preoperative and postoperative scores.

Quality-of-Life Outcome Predictors

Step-wise multiple regression models revealed that patients' characteristics and serum biochemistry markers had various impacts upon postoperative quality-of-life changes as compared with preoperative baseline. Direct bilirubin was a strong predictor for SF-36 PF (adjust $R^2=0.14$, $\beta=33.4$, $p<0.01$) and BP (adjust $R^2=0.15$, $\beta=35.1$, $p<0.05$) subscale scores improvements. Postoperative drain tube indwelling was predictive of BP (adjust $R^2=0.15$, $\beta=24.1$, $p<0.01$), VT (adjust $R^2=0.10$, $\beta=16.1$, $p<0.01$), SF (adjust $R^2=0.11$, $\beta=13.8$, $p<0.05$), and MH (adjust $R^2=0.03$, $\beta=12.4$, $p<0.05$) SF-36 dimensions scores gains 1 year following LC intervention.

Direct bilirubin was also a significant predictor in the changes of total (adjust $R^2=0.13$, $\beta=32.8$, $p<0.01$), GDG (adjust $R^2=0.20$, $\beta=15.3$, $p<0.01$), and GDF (adjust $R^2=$

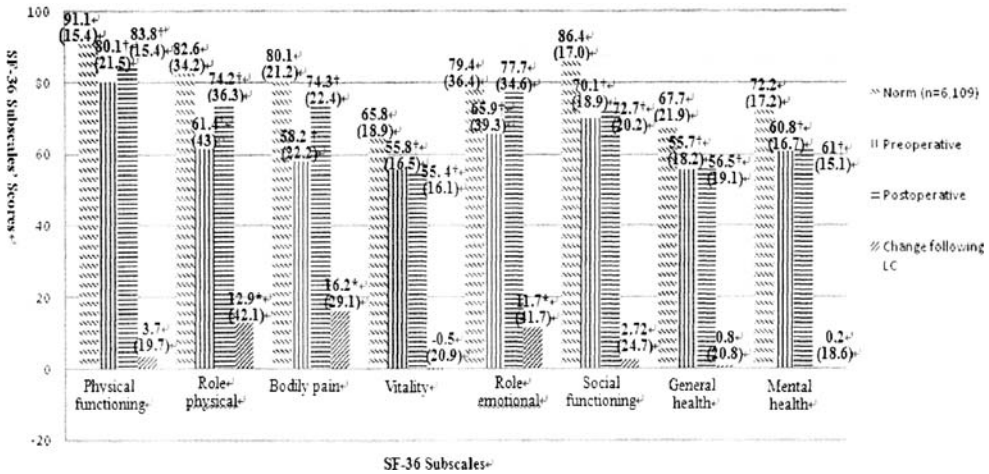

Figure 1 Norm and pre-/post-operative SF-36* subscales' scores ($N=99$). *SF-36* Medical Outcomes Study 36-Item Short-Form Health Survey. *$P<0.05$: *t* test, significant differences between preoperative and postoperative SF-36 subscale scores. †$P<0.05$: *t* test, significantly different as compared to Taiwanese population norm.

0.06, β=3.8, p<0.05) subscale scores in GIQLI questionnaire. Patients with elevated preoperative direct bilirubin level tended to have greater symptomatic improvements after LC.

Discussion

Cholelithiasis is prevalent among general population. The change of diet habit with increasing calorie intake has led to its higher occurrences among many countries. The development of LC technique has drastically changed the principle in treating gallstone and cholecystitis; complication rates have steadily declined over years.[17,18] The reduced morbidity and mortality rates have made LC a safe and standard procedure to treat benign gallbladder diseases. However, quality-of-life outcomes of LC remain undetermined. It is our interest to understand the impacts of LC to a patient's well-being and to investigate the factors that may influence the subjective quality-of-life outcomes.

There are limited studies that report the subjective patient quality-of-life outcomes following LC. Vetrhus et al. used quality-of-life and pain surveys to compare chronic gallbladder disease outcomes between observation (conservative treatment) and LC groups. The observation group had higher rate (31% vs. 19%) of gallstone-related events, but had similar quality-of-life outcomes with LC group.[9] Using GIQLI, Planells et al. detected significant and similar quality-of-life improvements following LC in both calculous and acalculous cholecystitis patients.[6] Using both GIQLI and SF-36, Quintana et al. found that patients with symptomatic cholelithiasis and low surgical risk experienced the highest quality-of-life gains; patients with asymptomatic cholelithiasis or high surgical risk experienced least improvement. The authors concluded that LC is appropriate for patients with symptomatic gallstone and low surgical risk.[7] In addition, Mentes et al. observed significant total GIQLI score improvements in both symptomatic and asymptomatic gallstone groups. The gallstone-related quality-of-life improvements are especially remarkable in symptomatic patients, indicating that gallstone patients with lower baseline GIQLI scores are more likely to benefit from LC.[8]

The normative Taiwan SF-36 population data provide important references to patients' pre- and postoperative quality-of-life status in this study. Our data showed that gallstone disease indeed incurred considerable health burdens. The preoperative SF-36 scores from gallstone patients were significantly inferior to the age- and sex-matched population norms in all dimensions. Our data, in consistent with those from others,[10] proved that LC can effectively reduce gastrointestinal symptoms, as can be seen from the improvement in GIQLI total, physical well-being, mental well-being, gastrointestinal digestion, and defecation subscale scores.

However, since patients still did not regain full GIOLI subscales scores after LC, we speculate that some residual gastrointestinal problems may continue to bother patients. This explains the persistent, measurable decrements in many of the SF-36 health dimensions at 12 months following surgery.

Many serum markers have been used to evaluate patients with gallstone. For example, erythrocyte sedimentation rate, C-reaction protein, and α-1 and α-2 globulin were elevated even in asymptomatic gallstone patients.[19] Mild to moderate hyperbilirubinemia is frequently seen in patients with cholecystitis; around one third of patients may show elevated serum bilirubin level at time of admission.[20,21] Preoperative alkaline phosphatase were reported to associate with surgical outcomes by some authors.[22–25] In current study, we found that both generic SF-36 and digestive system-specific GIQLI survey score improvements in some quality-of-life dimensions can be predicted by preoperative direct bilirubin level and by the placement of drainage tube intraoperatively. This indicates that patients with worse preoperative health condition may benefit from greater quality-of-life improvements following LC surgery.

Conclusion

LC can greatly reduce gallstone-related gastrointestinal symptoms and proves to be an effective therapy to enhance quality-of-life. Serum direct bilirubin is a good predictor for post-LC quality-of-life outcomes. This study suggests that patients with severe cholelithiasis can benefit from greater quality-of-life gains following LC.

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ORIGINAL ARTICLE

Tumor Relapse after Pancreatic Cancer Resection is Detected Earlier by 18-FDG PET than by CT

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Abstract
Introduction Pancreatic cancer recurrence is often difficult to detect by conventional imaging. Our aim was to evaluate the impact of fluorodeoxyglucose-positron emission tomography (FDG-PET) in the diagnosis of recurrent pancreatic cancer.
Methods One-hundred thirty-eight patients were followed after resection for pancreatic cancer. Sixty-six underwent only CT and were excluded. Seventy-two patients also had FDG-PET. Recurrent patients were divided in two groups: group-1, CT positive and group 2, CT non diagnostic, FDG-PET positive. Characteristics and survival curves of the two groups were compared. Significance was set at $p<0.05$.
Results Overall, tumors recurred in 63 of 72 (87.5%) patients; two patients had a second cancer resected, thanks to FDG-PET. Tumor relapse was detected by CT in 35 patients and by FDG-PET in 61. Prognostic factors were similar in groups 1 and 2. Five out of 35 group 1 patients underwent surgery (two R0, two bypass, and one exploratory). Ten out of 28 group 2 patients underwent surgery (four R0, two R2, two bypass, and two exploratory). FDG-PET influenced treatment strategies in 32 of 72 patients (44.4%). Group 2 patients survived longer ($P=0.09$), but the difference was not significant. Disease-free survival was similar in groups 1 and 2.
Conclusion Tumor relapse is detected earlier by FDG-PET than by CT. FDG-PET can help select the best candidates for surgical exploration, although the real benefit is still to be defined. It influences treatment strategies in a significant percentage of patients. An earlier diagnosis did not influence survival due to the lack of effective therapies.

Keywords Pancreas · Pancreatic cancer · Tumor relapse · PET scan · Follow-up

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Introduction

In spite of advances in the management of several of the more common cancers of the gastrointestinal tract, pancreatic cancer (PC) remains difficult to treat, with nearly as many deaths as the cases diagnosed each year. Among 34,290 estimated cancer deaths in 2008, PC ranks fourth among the leading causes of cancer death in the USA, while, it ranks tenth in terms of incidence.[1] At diagnosis, only about 32% of patients are in American Joint Committee on Cancer (AJCC) stages I and II and only about 50% of them are resected.[2] Resection, with or without adjuvant or neoadjuvant treatment, offers the only chance of long-term survival,[2,3] although patients cured of

this disease are very rare.[3,4] Most patients' tumors recur within 2 years of surgery,[5–8] and the pattern of recurrence is well known.[5–7,9–11] Patients with local recurrence and no distant metastases appear to have a better prognosis.[12–14] Although no standardized follow-up program exists, surveillance after PC resection usually includes clinical examination, CA 19-9 determination[5], and radiological studies [i.e., ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and chest X-ray).[5–7,9–11,15,16] The value of follow-up in the early detection of recurrences, and its impact on the survival of patients with PC, has yet to be clearly determined, however. Moreover, no treatment has had any strong impact on recurrent PC to date. In a series of 18 patients with local metastases after primary surgery for PC, Wilkowski et al.[17] provided the first indication that chemoradiotherapy is feasible and may be an effective option. Administering Gemcitabine afforded a longer mean survival in five patients (22.3 months) than in four untreated patients (6.6 months) with PC and liver metastases.[18] A patient resected for PC was still recurrence-free 31 months after a repeat radical resection and intraoperative irradiation and 49 months after the first operation.[19] Similar case reports have been published by others.[12,20,21] Kleef et al.[22] reported their experience with successful resection of recurrent PC in 15 of 31 patients who underwent surgical exploration. They nonetheless concluded that resection for recurrent disease was unlikely to be worthwhile.

Preliminary studies have found 18-fluorodeoxyglucose-positron emission tomography (18-FDG-PET) useful in the follow-up of patients with PC.[23–25] Ruf et al.[26] recently reviewed 31 patients with suspected recurrent disease, showing that 96% of local recurrences were detected by FDG, while only 23% were detected by CT or MRI. The impact on treatment was nil, however.

The aim of the present retrospective study was to assess the impact of 18-FDG-PET and PET/CT (FDG-PET) in detecting recurrences, and influencing their management, of patients with previously resected PC.

Methods

One hundred forty-two patients underwent resection for PC between January 1998 and July 2007. Neoplasms different from pancreatic adenocarcinoma were carefully excluded. A pancreaticoduodenectomy (PD) was performed in 101 patients [six Whipple and 95 pylorus preserving PD (PPPD)], a total pancreatectomy (TP) in six, and a distal pancreatectomy (DP) in 35. Standard lymphadenectomy was performed in all patients according to previously reported criteria.[27] Limited mesenteric or portal vein involvement was not a contraindication to resection. Cancer was staged according to the pTNM (AJCC) system.[28]

Two patients (1.5%) died after surgery (one after PD and one after DP). Further 68 patients were excluded from the study because FDG-PET was not performed (66) or were lost to follow-up (two; Fig. 1). A standardized follow-up was performed in the remaining 72 patients (Fig. 2). They were followed up with physical examination, laboratory tests, CA 19-9 (RIA, Centocor Inc., Malvern, PA, serum reference <37 U/mL) and CEA (fluorometric enzyme immunoassay, Baxter S.p.A., Milan, Italy; serum reference, <5 ng/mL) determination, abdominal US and high resolution, thin slice helical CT (CT Light Speed, GE Medical System, Milwaukee, USA), chest X-rays, and in some instances, MRI, every 3 months for the first 2 years and then every 6 months. At least one FDG-PET was also performed in all patients (Fig. 2) because of a rise in CA 19-9 levels in 51 (nine had no sign of disease on conventional imaging, and 24 were completely symptom-free), because of increased CEA levels in two, because of evidence of metastatic disease or inconclusive results on conventional imaging procedures in nine, and because of abdominal complaints with no sign of any recurrence on conventional radiology or changes in tumor markers in six. FDG-PET was also performed in further four completely symptom-free patients. The median interval between CT and FDG-PET was 7 days (range, 1–21).

Between 1998 and 2004, FDG-PET was performed using a conventional PET scanner and interpreted as described elsewhere.[29]

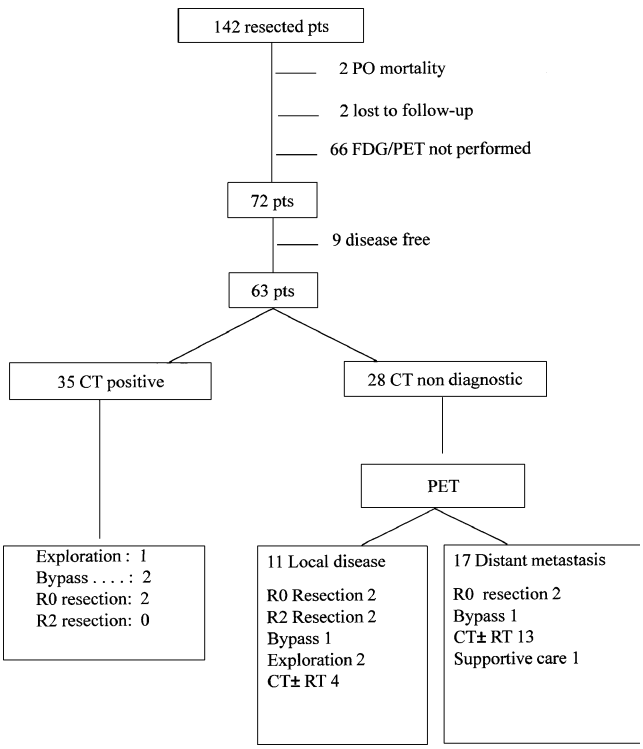

Figure 1 Flow chart of the study analysis.

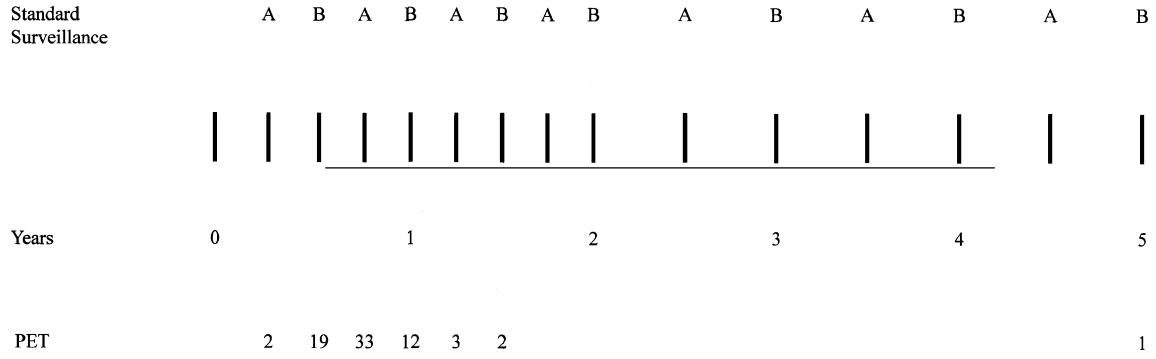

Figure 2. Standard surveillance algorithm following pancreatic resection for PC. **a** Physical examination, laboratory tests, CA 19-9, CEA, abdominal US. **b** Physical examination, laboratory tests, CA 19-9, CEA, and high resolution, thin slice helical computed tomography. *PET* number of first FDG/PETs performed during the previous 3 months.

From 2004 onwards, PET was performed with a hybrid PET/CT system (Biograph Sensation 16, Siemens SPA) equipped with a multislice (16) CT and a PET tomograph with LSO crystals. The cost of the procedure was 1.093 €.

To avoid interference due to hyperglycemia, blood glucose levels were checked just before the procedure. After an overnight fast, 185–370 MBq of FDG were injected i.v., and then a scout view was obtained an hour and 20 min later to select the field for whole body scan. CT was acquired first (120 keV, 80 mAs), followed by PET scanning, considering seven to eight beds (2–3 min per bed). After iterative reconstruction of the raw PET data and attenuation correction by CT, a radiologist and a nuclear physician (trained in CT and PET, respectively) performed a qualitative evaluation on fusion CT and PET images. Contrast-enhanced CT was not performed routinely. A semi-quantitative analysis (SUV) was also done on transaxial PET reconstructed slices.

On the basis of previous experience, a focal uptake with a SUV>2.5 was considered positive.[29] At the time of interpretation, the observers (SB and FC) were blinded to the patient's clinical status and outcome.

There was no difference in the diagnostic accuracy of FDG-PET and FDG-PET/CT. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the tumor markers, CT, and FDG-PET in detecting tumor recurrences were calculated according to the following formulas: sensitivity = TP/TP + FN; specificity = TN/TN + FP; PPV = TP/TP + FP; NPV = TN/TN+ FN; accuracy = TP + TN/TP + TN + FP + FN, where TP stands for true positive, TN for true negative, FP for false positive, and FN for false negative.

Patients were grouped according to the results of their CT into group 1 (CT positive for tumor relapse) and group 2 (CT non-diagnostic).

Tumor relapse was diagnosed by tumor resection (eight) or sampling (nine) in 17 patients and by imaging and tumor progression in 46 patients.

Tumor re-resection was attempted whenever a resectable localized tumor relapse was clearly shown at least 6 months after primary surgery. The value of SUV was also considered, avoiding reoperation in patients with a quite high focal uptake at FDG/PET.[30,31]

Overall, disease free and residual life survival was estimated using the Kaplan–Meier method and compared with the log-rank and Mann–Whitney tests. The residual life survival[32] was calculated from the time of morphological diagnosis (CT and/or FDG-PET) of tumor relapse to death or last follow-up. The χ^2 test was used for categorical variables. Significance was set at $p<0.05$.

Results

The clinicopathological features of the two groups are given in Table 1. The primary PC was located in the head of the pancreas in 53 patients, in the body–tail in 15, and diffuse in four. The initial surgical procedure was a PD in 53 patients (Whipple, 3; PPPD, 50), a DP in 15, and a TP in four. Eight patients were in AJCC stage I, nine in stage IIa, 44 in stage IIb, seven in stage III, and four in stage IV. Adjuvant treatment was given to 49 of 72 patients, i.e., 20 received chemotherapy and 29 chemoradiotherapy. No neoadjuvant therapy was used. Twenty-three only had best supportive care (BSC). Eighteen patients (90%) relapsed after adjuvant chemotherapy, 24 (82.8%) after chemoradiotherapy, and 21 (91.3%) after BSC. The mean follow-up was 28.6 months with a median of 22 months (range, 5–104 months).

Table 2 shows the sensitivity, specificity, PPV, NPV, and accuracy of CA 19-9, CT, and FDG-PET in detecting recurrences. The overall accuracy was 80% for CA 19-9, 57% for CT, and 96% for FDG-PET. The association of high CA 19-9 levels with a CT pattern of recurrence raised the specificity and PPV to 100%, but the sensitivity dropped to 50% and the accuracy to 55%. The corresponding features for CA 19-9 and FDG-PET findings showed a similar 100% specificity and PPV, with a sensitivity of 77% and an accuracy of 75%.

Table 1 Patients' Clinical and Pathological Characteristics

		Overall	Group 1[a]	Group 2[a]	*p* value
Patient's starting conditions		72	35	28	
Sex	M/F	34/38	17/18	14/14	NS
Age	Mean	63.9	64.2	63.4	NS
	Range	35–84	41–84	35–81	
Initial surgical treatment	Whipple	3	1	1	NS
	PPPD	50	25	19	
	DP	15	6	8	
	TP	4	3	0	
Radicality	R0	59	26	24	NS
	R1	11	9	2	
	R2	2	0	2	
AICC stage	I	8	3	3	
	IIa	9	5	3	
	IIb	44	21	20	
	III	7	4	2	
	IV	4	2	0	
Tumor grading	Well-diff.	10	5	3	NS
	Moderately	44	22	17	
	Poorly	18	8	8	
Vascular resection	Yes	14	5	7	NS
	No	58	30	21	
Adjuvant therapy	CT	20	12	6	NS
	RT	0	0	0	
	CT+RT	29	11	13	
	None	23	12	9	

[a] Groups 1 and 2 include only patients with documented tumor relapse

Patients with Recurrences

Sixty-three out of 72 patients (87.5%) recurred (Table 3) after a mean follow-up of 13.9 months (median, 11.0; range, 3–66). Thirty-five were included in group 1 and 28 in group 2. Only local recurrences were seen in 11 patients (five in group 1 and six in group 2), distant metastases alone in 34 patients (22 in group 1 and 12 in group 2), and local recurrences together with distant metastases in 18 patients (eight in group 1 and ten in group 2).

Tumor relapse was detected by FDG-PET in 61 of 72 (84.7%) patients and by CT in 35 of 72 (48.6%). Nine patients remained disease-free, one even after a second primary cancer was resected. CA 19-9 levels rose in 51 of 63 patients (81%) and CEA levels only in two (3.2%). Thirty patients were symptom-free, and five of them also had normal CA 19-9 levels. Overall, 15 underwent surgery (six R0 and two R2 resections, four surgical bypasses, and three exploratory procedures). Forty-three received chemotherapy, eight had radiotherapy, and 12 were given BSC. Radiofrequency ablation of a liver metastasis was performed in two patients, one on chemotherapy and one receiving BSC.

Twelve (34.3%) of 35 group 1 patients were symptom-free. Two patients had gastric or biliary bypasses after PD and TP, respectively. One patient underwent exploratory laparotomy for isolated liver metastasis, but multiple, small liver metastases were found at surgery. Two patients had lesions detected by CT with negative FDG-PET findings: A liver metastasis was resected in one, a colonic and bladder recurrence in the other; they survived 18 and 8 months, respectively (Table 4, numbers 11 and 12). Twenty-seven patients were given chemotherapy, three had radiotherapy too (one is still alive

Table 2 Diagnostic Accuracy of CA 19-9, CT, and FDG-PET in Identifying Recurrence or Second Primary Tumor

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
CA 19-9	81	77	96	37	80
CT scan	55	75	92	24	57
CA 19-9+CT	50	100	100	22	55
FDG-PET	98	90	98	89	96
CA 19-9+FDG-PET	77	100	100	30	75

PPV positive predictive value, *NPV* negative predictive value

Table 3 Follow-Up Data

		Overall	Group 1[a]	Group 2[a]	*p* value
Patients	Recurrent/total	63/72	35	28	NS
Length of follow-up	Mean	28.6	24.7	30.9	NS
	Median	22	20.0	26	
	Range	5–104	5–90	9–104	
Symptoms	Absent	30	12	18	NS
	Present	42	22	11	
CA 19-9 > 37 U/mL	No	21	7	5	NS
	Yes	51	28	23	
CEA >5 ng/mL	No	70	34	27	NS
	Yes	2	1	1	
Time to recurrence	Mean	14.0	13.5	14.4	NS
	Median	11.0	11	11	
	Range	2–66	2–66	5–38	
Site of recurrence[b]	Local	15	7	8	NS
	Pancreas	2	0	2	
	Lymph node	11	4	7	
Site of metastasis[b]	Liver	25	18	8	NS
	Peritoneum	14	7	7	
	Lung	11	7	4	
	Colon	3	1	2	
Second look surgery	None	47	30	18	NS
	Exploration	3	1	2	
	Bypass	4	2	2	
	R0 resection	6	2	4	
	R2 resection	2	0	2	
Treatment	Chemotherapy	43	27	16	NS
	Radiotherapy	8	3	5	
	BSC	12	5	7	
Overall survival	Mean	27.6	24.6	31.3	$p=0.09$[c]
	Median	22	19.5	24.5	
	Range	5–104	5–69	9–104	
Disease-free survival	Mean	13.9	13.5	13.5	NS
	Median	11	11	15	
	Range	3–66	3–66	5–38	
Residual life survival	Mean	13.1	10.3	16.4	$p<0.01$[c]
	Median	9	9	17	
	Range	2–87	2–87	3–85	

[a] Groups 1 and 2 include only patients with documented tumor relapse

[b] Twenty-four patients in group 1 and 23 in group 2 had more than one site of tumor relapse

[c] Group 1 vs group 2

13 months after chemotherapy associated with stereotactic radiotherapy), and five only had BSC (Table 3).

Eighteen (64.3%) of the 28 group 2 patients with recurrences were symptom-free: ten of them underwent surgery (four R0, two R2, one gastric bypass after PD, one gastric and biliary bypass after DP, and two exploratory laparotomy). Overall, 21 patients were given chemotherapy or radiotherapy (three had stereotactic radiotherapy and survived 8, 8, and 26 months, respectively), and seven only had BSC. A second primary cancer (of the larynx) was discovered by FDG-PET and resected in one of the 28 patients before his PC relapsed: He died of liver metastases from PC 25 months later (48 months after the first operation; Table 4, number 8).

Overall survival was longer for group 2 than for group 1 but not significantly so ($p=0.09$) (Fig. 3). Disease-free survival was similar in groups 1 and 2, while residual life survival was significantly longer ($p<0.01$) for group 2 than for group 1 (Table 3 and Fig. 3). Three group 1 and three group 2 patients are still alive 22, 31, and 56 and 27, 46, and 104 months, respectively, after primary surgery.

Patients Without Recurrence

Nine patients remained tumor relapse free.

During the follow-up, a rise in CA 19-9 levels was recorded in two patients (transient in one), and three patients had CT findings suggestive of tumor relapse in

Table 4 Details of Patients Who Underwent Surgery for Tumor Recurrence or A Second Primary Cancer

Number	Surgery	Time	Site	CT	PET	Treatment	FU (month)	Exit
1	DP	19	Lymph node	Neg.	Pos.	Excision R0	104	A, NED
2	DP	28	Lymph node	Neg.	Pos.	Excision R0	18	DOD
3	DP	17	Liver	Neg.	Pos.	Excision R0	16	DOD
4	DP	7	Lymph node+colon	Neg.	Pos.	Colectomy+partial LFN excision R2	5	DOD
5	PPPD	36	Lung	Neg.	Pos.	Lobectomy R0	14	DOD
6	PPPD	9	Pancreas+colon	Neg.	Pos.	Completion pancreatectomy R2	5	DOD
7	PD	16	Colon[a]	Neg.	Pos.	Colectomy	92	A, NED
8	PPPD	16	Larynx[b]	Neg.	Pos.	Laryngectomy	48	DOD
9	PPPD	36	Pancreas+liver	Neg.	Pos.	Laparotomy+biopsy	5	AWD
10	DP	10	Pancreas	Neg.	Pos.	Bypass	12	AWD
11	PPPD	26	Liver	Pos.	Neg.	Excision R0	18	DOD
12	DP	29	Bladder+colon	Pos.	Neg.	Colectomy+cystectomy R0	8	DOD

DP distal pancreatectomy, *PD* Whipple pancreaticoduodenectomy, *PPPD* pylorus preserving pancreaticoduodenectomy, *A, NED* alive, no evidence of disease, *DOD* died of disease, *AWD* alive with disease

[a] Second primary tumor

[b] Second primary tumor resected 8 months before tumor relapse was revealed by FDG-PET

the liver (two patients) or peritoneum (one patient). FDG-PET was negative in seven patients and positive in two: A marked tracer uptake in the right colon of the first patient was explained by endoscopy revealing inflammatory findings alone (false positive FDG-PET); the second patient had a colon cancer detected by FDG-PET, performed due to a rise in CEA levels, and a carcinoma of the left colon was resected 16 months after PD. The patient was alive and disease-free 92 months after PD (Table 4, number 7).

All nine patients were alive and disease-free at the time of writing, with a median survival of 29.6 months (range, 24–104 months).

Impact of FDG-PET on Treatment of Relapsed Patients

FDG-PET showed tumor relapse in 28 patients with negative or inconclusive CT results (group 2 patients), enabling chemo-radiotherapy to be started in 15 patients and the resection of recurrent disease in six (four R0 and two R2 resections; Table 4, numbers 1–3, and 5 and 4 and 6). It also enabled the resection of a second primary tumor in one patient (Table 4, number 8), who died of PC recurrence 25 months later, however.

FDG-PET findings prompted an exploratory laparotomy in the hope of finding a localized tumor recurrence in two patients, but resection proved unfeasible due to extensive fibrosis, with intraoperative bleeding in one case and liver metastases (not seen by CT and FDG-PET) being discovered in the other.

Negative FDG-PET findings supported the decision to perform an R0 resection of tumor relapses detected by CT (Table 4, numbers 11 and 12) in the conviction that the recurrent tumor was localized and scarcely aggressive.[30,31]

Impact on Treatment of Non-relapsing Patients

FDG-PET enabled a second primary tumor (adenocarcinoma of the descending colon) to be detected and resected in one patient, 16 months after a PPPD (Table 4, number 7). Because this patient's FDG-PET findings were negative, a gastroenteroanastomosis was performed to deal with an inflammatory stenosis of the pylorus 25 months after PPPD, and a jejunal–jejunal anastomosis was performed to deal with severe adhesions 76 months after PPPD. The patient was still alive and disease-free at the time of writing, 92 months after PPPD.

In five patients (6.9%), tumor recurrence was suggested by rising CA 19-9 levels (two cases) or CT findings (three), but FDG-PET was negative, so these patients were spared further treatment. They remained alive and disease-free during the subsequent follow-up (median, 17.0 months; range, 12–48 months).

FDG-PET findings therefore changed the clinical management for 32 of the 72 (44.4%) patients.

Discussion

The dismal prognosis for patients with PC is due to a late diagnosis,[2] aggressive tumor biology, a technically challenging surgical management, and the lack of effective, adjuvant and neoadjuvant systemic therapies.[33]

Most patients relapse within 2 years after potentially curative surgery for PC,[5–8] and the pattern of recurrence is well known.[5–7,9–11] Despite the high rate of tumor relapse

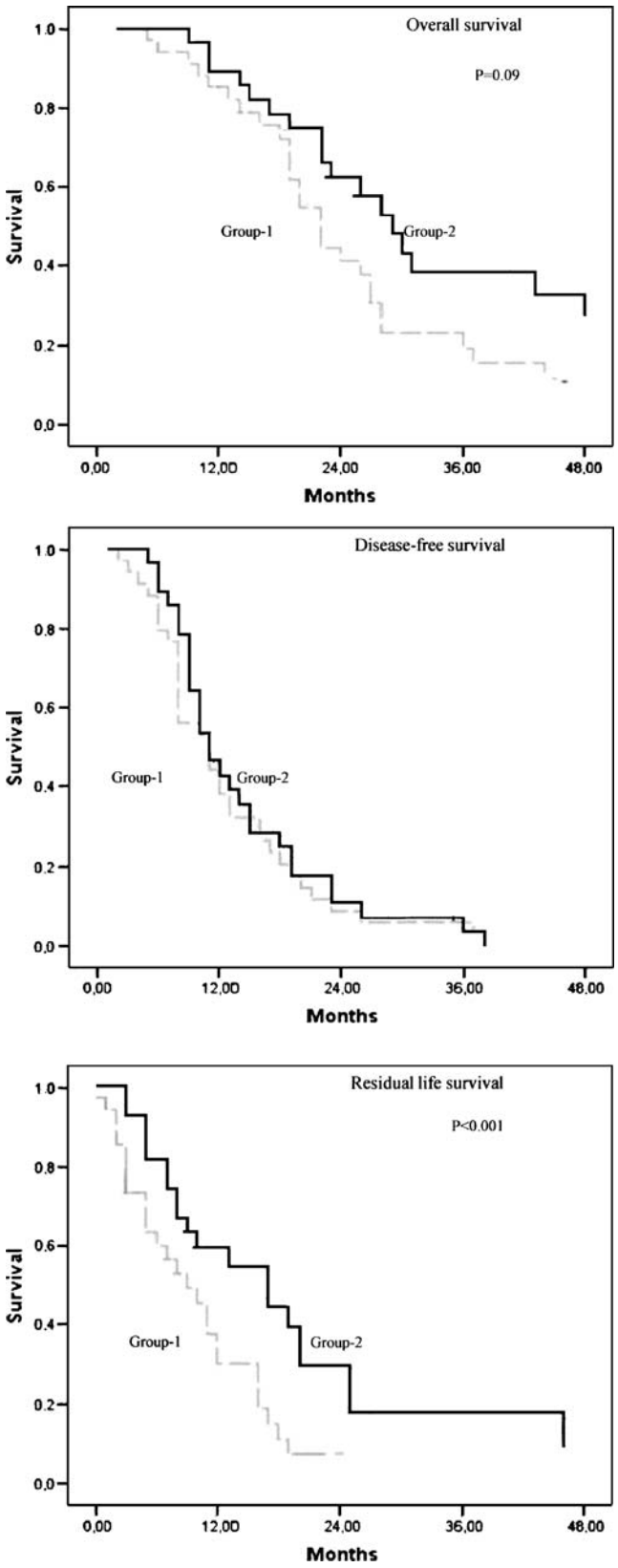

Figure 3 Overall, disease-free and residual life survival rates in groups 1 and 2 patients.

within a relatively short space of time, only a few, small studies have been conducted to find the best imaging procedure for an early detection of recurrent tumor.[6,16,23–26] This may be prompted by a nihilistic approach to relapsing PC, given the lack of effective systemic and local therapies.[33]

Contrast-enhanced CT scanning is considered the method of choice for detecting PC relapses after potentially curative resection. "However, it is sometimes very difficult, if not impossible, to differentiate local recurrence from postoperative change with only one CT examination."[6] Kim et al.[6] suggest evaluating dynamic changes in the lesion on follow-up CT scans obtained at short intervals. On the other hand, mesenteric lymphadenopathy persists even years after surgery, even in the case of benign disease, and it is impossible to differentiate reactive adenopathy from lymph node metastases.[16] Lymph node metastases can only be suggested by a progressive increase in lymph node diameter and/or the coexistence of a recurrent mass.[16]

In such patients, FDG-PET can be extremely helpful in differentiating postoperative changes and reactive adenopathy from local tumor relapse or lymph node metastases (Figs. 4 and 5).

FDG-PET is increasingly used to detect recurrence in the follow-up of patients with colorectal,[34,35] ovarian, breast, lung, head and neck, thyroid,[34] and gastric cancer.[36] Small preliminary studies have found 18-FDG-PET useful in the follow-up of patients with PC.[23–25] In the present study, we demonstrated that FDG-PET is more sensitive and specific than CT in detecting tumor relapse (Table 2). Tumor relapse was detected by FDG-PET in 28 of 63 (44.4%) patients before any clear-cut CT image of tumor relapse became available. On the other hand, CT detected tumor relapse in only two FDG-PET-negative patients that underwent an R0 resection of tumor relapses in the conviction that the recurrent tumor was localized and scarcely aggressive.[30,31] Similar results are reported by Ruf et al.,[26] who detected 36 of 44 (81.8%) malignant lesions by FDG-PET and 20 of 44 (45.5%) by CT/MRI. Jadvar[25] reported a 10/10 tumor relapse detection rate (after Whipple) for FDG-PET and 7/10 for CT. Casneuf et al.[37] reported an accuracy of 90% for PET, CT, and PET/CT in detecting recurrent or progressive cancers in a series of 12 patients: This figure may be due to the small number of patients involved and to the delayed use of PET and PET/CT to detect tumor relapses. Furthermore, the number of patients with recurrent cancer after resection was not reported. We can therefore conclude that FDG-PET enables an earlier diagnosis of tumor relapses in a significant percentage of patients.

FDG-PET also enabled a resectable second primary tumor to be detected in two patients with no recurrent PC. One of them remained disease-free (Table 4, number 7), while the other had a PC relapse 8 months later and died 48 months after PPPD (Table 4, number 8).

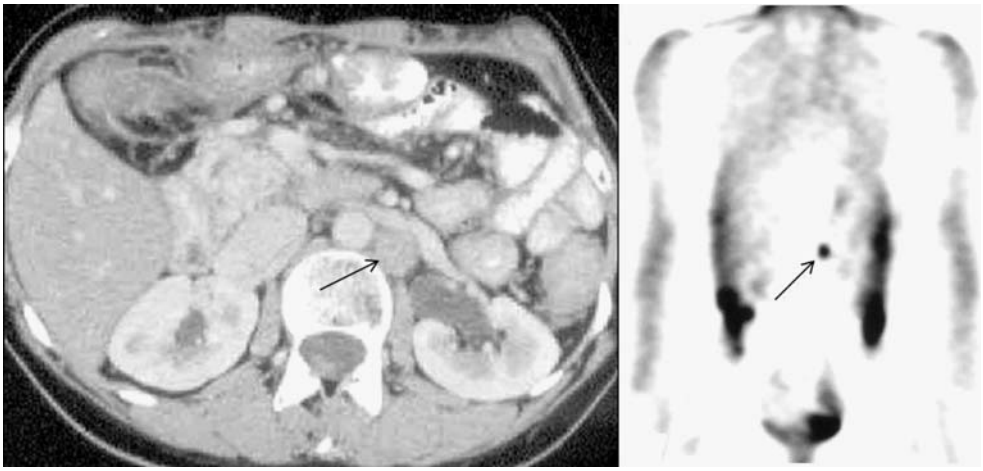

Figure 4 Patient evaluated after distal pancreatectomy for pancreatic cancer and mastectomy for right breast cancer: CT shows an enlarged lymph node behind the left renal vein (*arrow*). FDG-PET shows an area of increased uptake coinciding with the lymph node (*arrow*). The metastatic lymph node was excised, and the patient was alive and disease-free after 104 months (Table 4, patient 1).

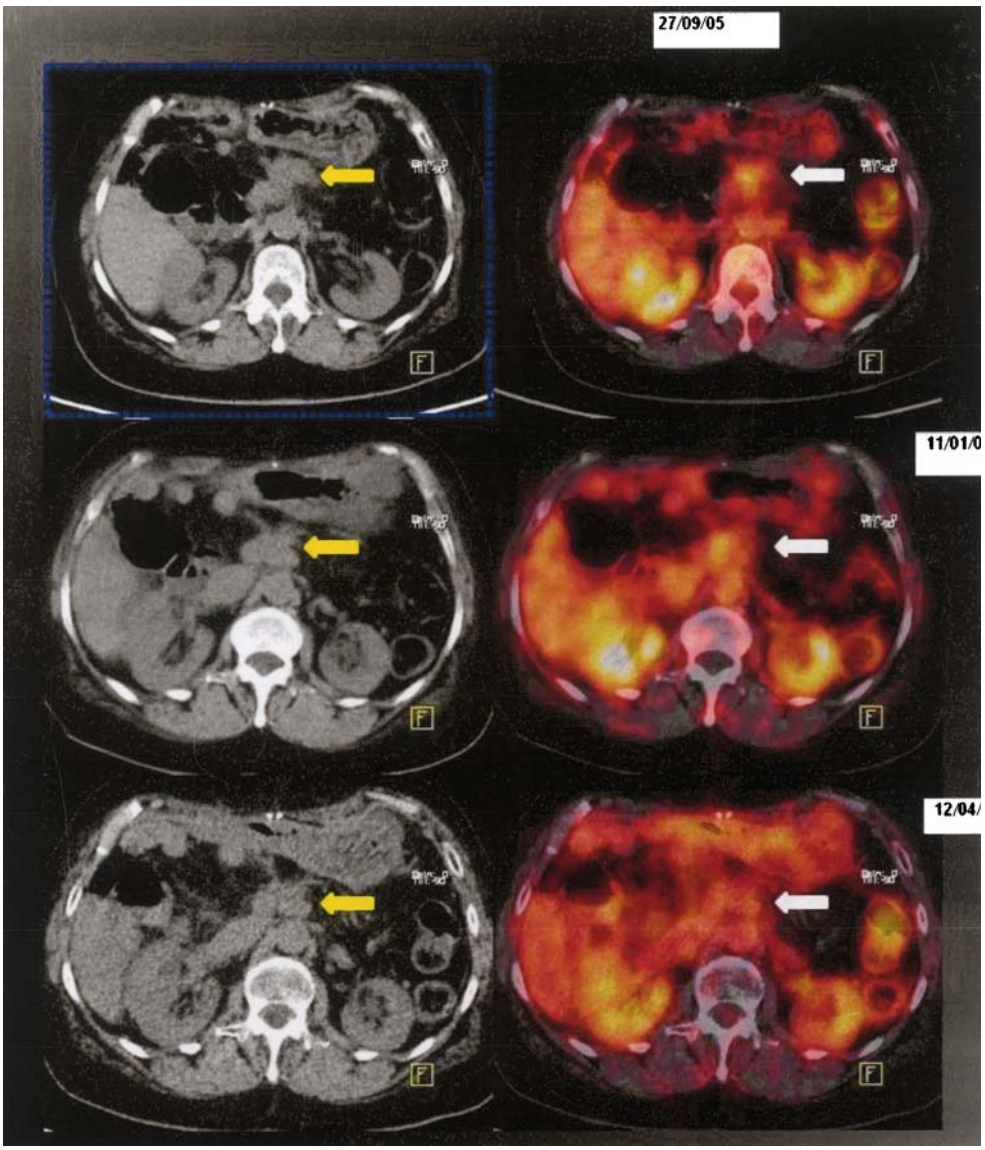

Figure 5 *Top to bottom* Tumor relapse (*white arrows*) 39 months after a PPPD detected by FDG-PET, while CT (*yellow arrows*) was unchanged with respect to previous examinations. Three months later, after completing chemoradiotherapy, CT was unchanged but FDG-PET was still positive (with decreased SUV). Stereotactic radiotherapy was performed and FDG-PET was negative 3 months later. The patient died of disseminated disease 15 months later (5 years after PPPD).

Treatment strategies were influenced by the results of FDG-PET in 32 of 72 patients (44.4%), enabling targeted local treatment (including surgery) in 23 patients, resecting a second primary cancer in two, prompting an explorative surgery in two, and preventing any unnecessary treatment in five relapse-free patients. A similar incidence (38.9%) of changes to patient treatments was reported by Hillner et al.[38] in a large prospective, nationally representative study on the impact of FDG-PET on the expected management of cancer recurrences, PC included.

But does an earlier diagnosis of tumor recurrences also mean a longer survival?

Unfortunately, the answer is probably not, as the longer survival observed in the group 2 patients was not significant ($p=0.09$), and FDG-PET probably selected a group of patients with more favorable prognosis as patients with non diagnostic CT and only small lesions seen with FDG-PET are likely to do better. Patients with locally recurrent tumor reportedly have a better prognosis than metastatic patients.[12–14] However, the incidence of local tumor relapse alone was similar in our group 1 (five of 34; 14.7%) and group 2 (six of 28; 21.4%) patients. A significantly longer residual life survival (after the demonstration of tumor relapse) of group 2 patients (Fig. 3) can be explained by the anticipation of effective local and systemic therapies or by the anticipation of the diagnosis by FDG-PET. In our opinion, the latter explanation is preferred, as three group 1 and three group 2 patients are still alive 22, 31, and 56 and 27, 46, and 104 months, respectively, after primary surgery; only one group 2 patient is alive after repeat resection, and local and systemic therapies were equally used in both groups (Table 3). It is therefore difficult to explain the longer residual life survival of group 2 patients only with treatment's anticipation.

Surgery is usually not indicated for the treatment of PC relapses. Single case reports have been published on the long-term survival of patients after repeat radical resections of tumor relapses,[12,19–21] and Kleef et al.[22] resected recurrent PC in 15 of 31 patients (five R0, three R1, and seven R2 resections) undergoing surgical exploration. However, they concluded that, "it seems unlikely that resection for recurrent disease offers a substantial overall survival advantage." Resection was attempted in 11 of our 63 relapsed patients and was successful in eight (six R0 and two R2 resections) for an overall resection rate of 12.7%, but 72.7% of the patients who underwent exploratory surgery were resected. The lack of well-defined anatomic planes and the discovery of hitherto undiagnosed liver or peritoneal metastases were the main reasons for the failure of surgery. FDG-PET can help select the best candidates for surgical exploration, although the real benefit is still to be defined.

The correct and timely identification of local–regional recurrence or of a single metastasis will affect the choice of therapy, such as surgery, innovative ablation procedures, or three-dimensional intensity-modulated radiotherapy, preceded by aggressive systemic chemotherapy regimens when indicated.[34] FDG-PET can help to pinpoint patients with localized tumor relapses and also to verify the efficacy of their treatment (Fig. 5)

The ideal timing of postoperative FDG-PET remains to be defined. We suggest that it should be done about 4–6 months after surgery and at least 1.5 months after completing any adjuvant treatment. A contrast-enhanced multidetector CT scan should be performed immediately beforehand to facilitate the interpretation of the FDG-PET and avoid any pointless FDG-PET in patients with clearly demonstrated distant metastases.

Conclusions

In conclusion, tumor relapse is detected earlier by FDG-PET than by CT in a significant percentage of patients after a potentially curative resection for PC. FDG-PET can help select the best candidates for surgical exploration, although its actual usefulness is still to be defined. It influences treatment strategies in a significant percentage of patients (44.4%). Unfortunately, an earlier diagnosis did not influence survival due to the lack of effective therapies.[33] Finally, FDG-PET is useless for patients with multiple recurrences or metastases already demonstrated by CT.

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ORIGINAL ARTICLE

Enucleation of Pancreatic Cystadenomas

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Abstract
Background Optimal surgical treatment of pancreatic cystadenomas is controversial due to the rarity of the tumors and paucity of studies regarding long-term outcomes. This is especially true for large pancreatic cystadenomas. The objective of this study was to determine the safety and effectiveness of treating pancreatic cystadenomas by enucleation.
Methods Eleven cases of pancreatic mucinous or serous cystadenomas were selected for enucleation according to the following criteria: (1) the benign nature of the tumors was ascertained preoperatively and intraoperatively, (2) small tumors or larger tumors no more than 6 cm in diameter growing outwardly with small tumor beds, and (3) the main pancreatic duct was not in jeopardy of damage by enucleation. The patients' demographics, tumor features, morbidity, and follow-up results were retrospectively reviewed and analyzed.
Results Among 11 cases, three were serous cystadenomas and eight were mucinous cystadenomas; the average size of the neoplasms was 4.8 cm (ranging from 3 to 6 cm). Two cases were complicated by the development of fistulas postoperatively and one had an incision infection. All cases were followed up from 23 to 67 months, which revealed no neoplasm recurrence or new onset of diabetes mellitus; one patient developed a pseudocyst in the body 30 months after enucleation.
Conclusions It is safe and effective to perform enucleation for well-selected benign pancreatic cystadenomas even if the tumor size is as large as 6 cm, and the endocrine or exocrine function of the pancreas is maintained as much as possible.

Keywords Pancreatic neoplasm · Cystadenoma · Enucleation

Introduction

Primary cystic neoplasms reportedly constitute 10–15% of pancreatic cysts,[1] showing all stages of cell differentiation from truly benign neoplasms to localized malignancy to advanced, invasive cancer. Due to the diagnostic uncertainty of the nature of cystic tumors, many experts routinely resect these lesions. However, although these procedures can now be performed with a low mortality rate, resection often requires a pancreatoduodenectomy or a distal pancreatectomy with or without splenectomy. Furthermore, resection of an otherwise normal pancreas can be associated with substantial morbidity and late sequelae of endocrine or exocrine insufficiency. An alternative surgical procedure is enucleation, which, when compared to resection, is associated with less operation time and blood loss,[2,3] preserves normal pancreatic parenchyma and has better long-term functional outcomes.[4] In fact, enucleation of benign tumors is a well-established surgical procedure for the pancreas. There are examples of successful enucleation of tumors such as selected insulinomas,[5] gastrinomas,[6] and pancreatic cystadenomas.[2,3] However, due to the rarity and poor understanding of the natural history of pancreatic cystadenomas, considerable

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controversy exists regarding the treatment of pancreatic cystic neoplasms. There is no consensus regarding what tumor size is considered safe and effective for enucleation. Various studies give different cut-off criteria ranging from 1.5–2 to 3–4 cm; Kiely et al. and Talamini et al. reported on enucleation of smaller tumors (which averaged 2.2 and 2.8 cm, respectively),[2,3] but for larger neoplasms (>4 cm), standard pancreatic resections were usually recommended.[7–9] However, long-term follow up of enucleation for large pancreatic cystadenomas has been lacking. In our series of 11 cases of pancreatic cystadenomas that underwent enucleation, the average size of the neoplasms was 4.8 cm (ranging from 3 to 6 cm); all cases were followed up from 23 to 67 months, which revealed no neoplasm recurrence or new onset of diabetes mellitus. We propose the indications for enucleation of pancreatic cystadenoma to be as follows: (1) benign nature is ascertained intraoperatively, (2) small tumors or larger tumors no more than 6 cm in diameter growing outwardly with small tumor beds, and (3) the main pancreatic duct not in jeopardy of damage with enucleation. We conclude that it is safe and effective to perform enucleation for well-selected benign pancreatic cystadenomas even as large as 6 cm.

Methods

Forty-one cases of pancreatic cystic neoplasms, with 32 benign cases and nine malignant cases, were treated with operation from January 2001 to December 2007 at First Affiliated Hospital of China Medical University. Of the 32 benign cases, 33% (11 patients) underwent pancreatic enucleation for either pancreatic serous cystic neoplasms or pancreatic mucinous cystic neoplasms, and the other 21 benign cases underwent routine resection procedures. All 11 patients who underwent enucleation were retrospectively reviewed. Information regarding demographics, presentation, radiological, pathology, postoperative recovery, morbidity, mortality, length of stay, and follow-up results were obtained. For comparison, clinical data of 21 cases that underwent resection were also presented. Endoscopic ultrasound with fine-needle aspiration (EUS-FNA) was not used in this study because EUS-FNA was not regularly performed in our hospital at that time. Also, all 11 cases would have required an operation, so the most accurate method of judging the nature of the tumors available to us was multiple intraoperative biopsy.

During the operation, enucleation was performed along and as close as possible to the fibrous tissues of the capsule to spare the spleen vessels and as much pancreatic tissue as possible. The average operative time was 125±33 min and the average blood loss was 80±24 ml. In the resection group, of the four cases of cystadenoma that were located in the pancreatic head, two underwent duodenum-preserving pancreatectomy and two underwent standard pancreaticoduodenectomy. For 17 cases of cystadenoma that were located in the body and tail, 11 underwent resection of the body and tail, five underwent a spleen-preserving distal pancreatectomy, and one underwent middle segment pancreatectomy. The average operative time was 210±90 min and the average blood loss was 280±110 ml. Multiple biopsies of the tumor were taken for immediate frozen section examination to establish a provisional diagnosis. For all cases in the enucleation group, the tumors were cut and extensively sampled in at least five sections of the tumor, including the area of deepest penetration of the tumor wall, the resection margins, and the body in each quadrant. Final histological examinations were regularly performed. The samples were fixed in 10% formalin, embedded in paraffin, cut, and stained with hematoxylin–eosin. The provisional diagnosis and definitive diagnosis were first obtained by histopathological examination by one of two pathologists. To assure more certainty, all histological slides were further reviewed by a supervisor to confirm the diagnosis.

A pancreatic fistula was considered to be present from intraoperatively placed drains when drainage of more than 30 ml/day of amylase-rich fluid lasting for 3 days after surgery from postoperative day 4, according to the recommendations of the International Study Group on Pancreatic Fistula. Wound infection was defined as culture-positive purulent drainage (regardless of postoperative day or amount).

Results

The demographics, tumor features, complications, and follow-up results of the 11 patients who underwent enucleation are summarized in Table 1. The demographics, tumor location, size, presentation, morbidity, blood loss, operation time, and hospital stay were compared between enucleation and resection as listed in Table 2. The mean age of the patients was 47 years, ranging from 32 to 67, in the enucleation group and 48.3 years, ranging from 22 to 65, in the resection group. Women accounted for 81.8% (9) and 85.7% (18) in the enucleation and resection groups, respectively. The average follow-up time was 40.7 months, ranging from 23 to 67 months, for the enucleation group. Of the 11 patients who underwent enucleation, eight had mucinous cystadenomas and three had serous cystadenomas, and of the 21 patients who underwent resection, 15 (71.4%) had mucinous cystadenomas and six (28.6%) had serous cystadenomas. The average size of the tumors was 4.8 cm, ranging from 3 to 6 cm in enucleation group, with an average

Table 1 Patients, Tumor Features, Complications and Follow-up Results of the Enucleation Group

No.	Sex	Age	Location	Size	Histology	Complication	Follow up time (month)	Result
1	F	51	Body	4×3×3	Mucinous	–	67	NR
2	F	34	Body	6×5×4	Mucinous	–	30	Pseudocysts in body
3	F	48	Tail	5×5×4	Mucinous	Fistula	57	NR
4	F	53	Tail	5×3×3	Serous	Incision infection	50	NR
5	F	43	Body	5×3×4	Mucinous	–	49	NR
6	F	44	Body	3×3×3	Mucinous	–	40	NR
7	F	67	Tail	4×4×3	Serous	–	36	NR
8	M	50	Body	6×6×5	Mucinous	Fistula	38	NR
9	F	32	Body	5×5×4	Mucinous	–	30	NR
10	M	54	Head	5×4×3	Serous	–	28	NR
11	F	40	Tail	5×4×4	Mucinous	–	23	NR

NR no recurrence

Table 2 A Comparison of the Clinical Data of Patients in Enucleation and Resection Groups

	Resection	Enucleation
Number of cases	21	11
Type		
Serous	6 (28.6%)	3 (27.3%)
Mucinous	15(71.4%)	8 (72.7%)
Sex		
Male	3 (14.3%)	2 (18.2%)
Female	18 (85.7%)	9 (81.8%)
Age range (mean)	22–65 (48.3)	32–67 (47.1)
Location (case number)/tumor size (cm)		
Head	4/5–13	1/5
Body	9/6–18	6/3–6
Tail	8/7–15	4/4–5
Follow-up time (month)	28–84	23–67
Morbidity		
Fistula	3 (14.3%)	2 (18.2%)
Incision infection	2 (9.6%)	1 (9.0%)
Pseudocyst	0	1 (9.0%)
New diabetes mellitus	0	0
Operation time (min)	210±90	125±33
Blood loss (ml)	280±110	80±24
Hospital stay (days)	13.6±2.4	11.4±1.5
Presentation		
Upper abdominal pain	14 (66.7%)	3 (27.3%)
Back pain	7 (33.3%)	2 (18.2%)
Upper abdominal mass	5 (23.8%)	1 (9%)
Nausea and vomit	2 (9.6%)	2 (18.2%)
Gastrointestinal tract bleeding	1 (4.8%)	0 (0%)
Jaundice	1 (4.8%)	0 (0%)
Asymptomatic	3 (14.3%)	4 (36.4%)

of 11.2 cm, and ranging from 5 to 18 cm in the resection group. In the enucleation group, four cystic tumors were located in the tail of the pancreas, one was located in the head, and six were in the body. In resection group, four were in head, nine were in the body, and eight were in the tail.

No malignancy was reported intraoperatively from histological examination of the frozen sections of all cases in enucleation and resection groups, and final histological examination gave the same results. The average hospitalization was 11.4 days in the enucleation group, compared with 13.6 days in the resection group. There was no mortality up to the last day of follow-up in either group. All cystic neoplasms were characterized before surgery by abdominal ultrasound and enhanced CT scan and diagnosed initially as benign pancreatic cystadenoma in all patients. Thoracic X-ray and liver images were all normal and no abnormal lymph nodes around the tumors were identified in any patients. There were no signs of metastases. Seven patients had blood examination of CEA, AFP, CA199, CA125, and CA153 performed, and all values were within the normal range. Two cases of the mucinous cystadenoma are shown in Fig. 1.

The major features of patient presentation in the enucleation group were pain in five patients (three with upper abdominal pain, two with back and waist pain) and nausea in two patients; four patients were asymptomatic at presentation (the tumors were discovered during a regular checkup or studies of other conditions). All 11 patients underwent enucleation due to the following reasons: first, the preoperative and intraoperative evaluation strongly suggested benign features of pancreatic cystic neoplasms. Second, tumor sizes were no more than 6 cm in diameter, none of the 11 patients had jaundice, and the preoperative CT scans identified no vascular involvement. Lastly, during the operation, we assessed the conditions of the cystic lesions including the feasibility of resection by enucleation, and confirmed that no adjacent organs were found to be involved.

Morbidity

Of all 11 patients in the enucleation group, two (18.2%) developed pancreatic fistulas and one (9.1%) developed an incision infection, which resolved in 3 weeks. For one patient (9.1%), follow-up in the 30th month after enucleation revealed a 2.5-cm-sized cystic lesion in the pancreatic body (Fig. 2), which proved to be a pseudocyst after reoperation. A resection of pancreatic body and tail was performed. No intraoperative or hospital deaths occurred. For comparison, of the 21 benign patients that underwent resection, three patients (14.3%) developed fistulas, which all resolved between 2 and 4 months, and two patients

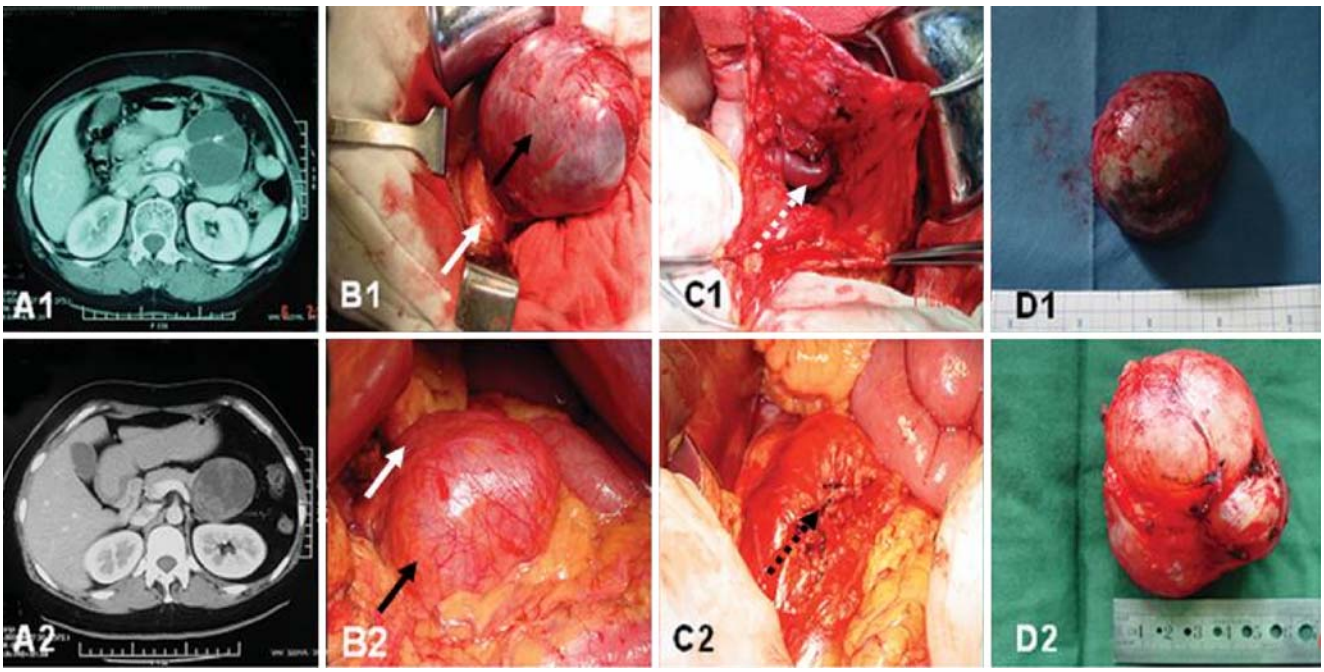

Figure 1 Demonstration of two cases of mucinous cystadenoma in the pancreatic body. **A1**–**2**, Preoperative views of the tumors in CT scan in two different cases. **B1**–**2**, Intraoperative views of the tumors of the two respective cases, pancreas (*white arrows*) and cystadenomas can be seen (*black arrows*). **C1**–**2**, Views of the corresponding regions after tumor enucleation of the two respective cases, splenic vein (*broken white arrow*) and sutured pancreas (*black broken arrow*). **D1**–**2**, Views of the resected tumors with diameters of 5 cm (**D1**) and 6 cm (**D2**) from the two respective cases.

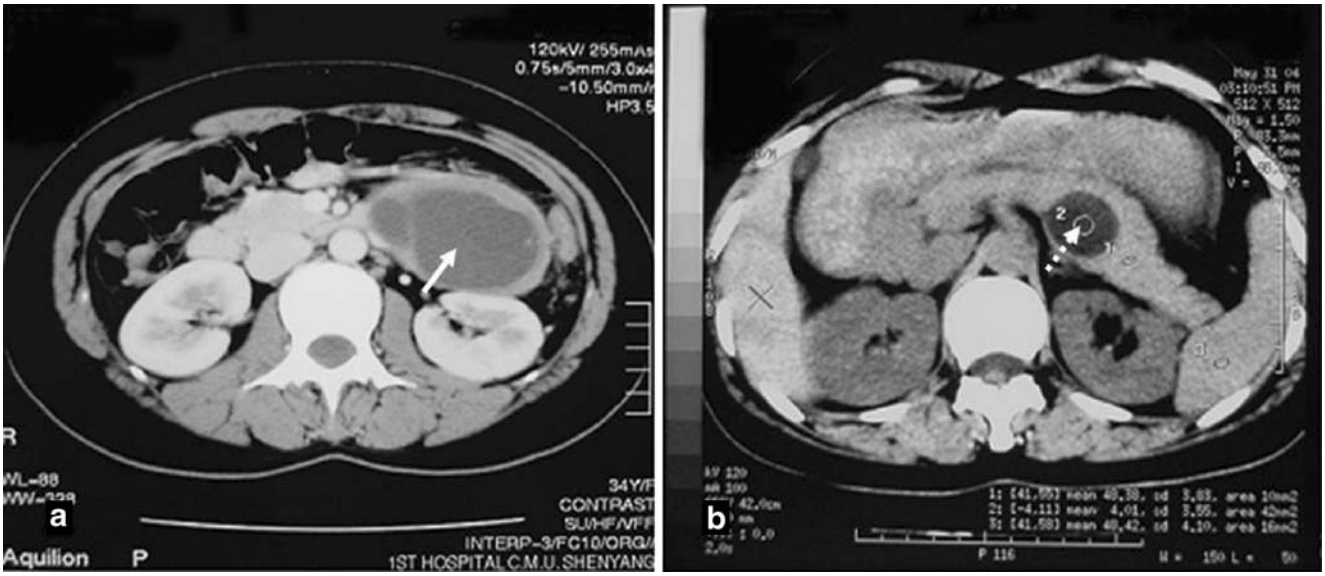

Figure 2 CT scan of a pancreatic mucinous cystadenoma before enucleation and after 30 months of follow-up. **A** Preoperative CT scan of the mucinous cystadenoma (*white arrow*) in the pancreatic body. **B** CT scan findings 30 months after enucleation. The lesion proved to be a pseudocyst (*broken white arrow*) after reoperation.

developed incision infections. No reoperation was necessary during the follow-up period.

In order to identify the causes of pancreatic fistula that might happen after enucleation, amylase assay of the cystic fluid was performed intraoperatively in eight patients, of which two patients had amylase levels higher than 1,000 U/L. It was in these two patients in the enucleation group that pancreatic fistulas occurred, which strongly suggested a communication between the cysts and pancreatic ducts. One fistula occurred on day 3 postoperatively, in which the drainage reached 500 ml/day on postoperative day 8. The fistulas were treated by endoscopic nasopancreatic drainage (ENPD), which dramatically reduced drainage, and the fistula closed 10 days later. Another case of fistula occurred on postoperative day 6, in which the initial drainage was 30–60 ml/day and increased to 200–300 ml/day in 2 weeks, then remained unchanged during the next week. After ENPD, the drainage was gradually reduced to 20–30 ml/day or less until the fistula closed 2 weeks later.

Follow-up

Follow-up was performed every 6 months after surgery and included assessment of the remission status by ultrasound and enhanced computed tomography scans and serial serum CEA, AFP, CA199, CA125, and CA153. The follow-up time for the 11 patients who underwent enucleation ranged from 23 to 67 months, with an average 40.7 months. Based on follow-up CT information, no recurrence of serous or mucinous cystadenoma occurred in the ten patients in the enucleation group and in all 21 cases in the resection group. Follow-up blood assays of CEA, AFP, CA199, CA125, and CA153 were within the normal range in all 11 patients in the enucleation group. No new-onset diabetes occurred in either group of patients.

Discussion

Since Ernesto Tricomi first reported enucleation of a pancreatic neoplasm in 1898, enucleation has become a widely accepted procedure for the treatment of pancreatic endocrine tumors. Other indications, including serous and mucinous cystadenoma,[4,3,10,11] branch duct IMPNs,[12,13] and benign conditions,[14] have also been reported. Kiely et al. reported 11 cases of pancreatic cystadenoma that underwent enucleation,[2] which proved to be safe based on 1–122 months of follow up. They proposed that enucleation should be the standard operation for small benign cystic neoplasms. We performed enucleation on 11 pancreatic cystadenomas, including eight mucinous cystadenomas and three serous cystadenomas, which, compared with the Kiely et al. series, were larger in size (4.8 vs 2.2 cm), with two tumors reaching 6 cm in one dimension. All cases were followed up from 23 to 67 months, which revealed no neoplasm recurrence or new onset of diabetes mellitus. Thus, we propose that, for pancreatic cystadenomas, if the benign nature is assured during operation, the upper limit of the tumor size for enucleation should be increased to as large as 6 cm.

Compared with conventional resection, enucleation is characterized by less operation time and blood loss[2,3] and

fast recovery and extensive preservation of parenchyma and, thus, has been widely accepted. However, the indications of pancreatic enucleation remain equivocal. The following factors need to be considered: tumor location, size, malignancy, and the relationship of the tumor to the pancreatic duct. In our series of 11 cases that underwent enucleation, only one tumor was smaller than 4 cm in all three dimensions, and the largest two tumors were as big as 6 cm in at least one dimension. The average size was 4.8 cm. Most of them (8, 72.7%) were mucinous cystadenomas, growing outwardly with a relatively small tumor bed. Two of these cases were complicated with fistula, but long-term follow up (28–67 months) showed no occurrence of exocrine or endocrine insufficiency and no tumor recurrence. We suggest that the tumor size for enucleation should be increased for the following two reasons: first, small pancreatic cystadenomas are usually asymptomatic and probably larger than 4 cm when discovered. Second, some cystadenomas are well-encapsulated and grow outwardly with a small contact surface with pancreatic parenchyma rather than being encased in the gland. The former is favorable for enucleation. The result of long-term follow up also demonstrated the safety of enucleation for pancreatic cystadenomas as large as 6 cm. So far, the largest reported mucinous pancreatic tumor successfully enucleated was 23 cm in diameter.[15] Location also needs to be considered for enucleation. Kiely et al.[2] reported much more tumors located in the pancreatic head than in our study (45% vs 9%), which actually favored enucleation; we consider that a location of tumors in the head, neck, or uncinate is favorable for enucleation.

Another important question regarding enucleation for pancreatic cystadenoma is the potential malignancy for cystadenoma, especially for mucinous neoplasms, which have a high likelihood of malignant transformation. More radical resection used to be standard practice. So far, only a couple of studies on treating mucinous pancreatic cystadenomas with enucleation have been recorded. Long-term follow up revealed no recurrence of the tumor.[12] In our series of eight cases of mucinous cystadenoma treated with enucleation, none of them recurred after a follow-up of 23–67 months, which strongly supports the safety of treating pancreatic mucinous cystadenoma with enucleation. However, a definitive evaluation demonstrating that the tumor is benign is a prerequisite for performing enucleation of cystic neoplasms. In all 11 cases, we preoperatively assessed the size, location, and growth orientation of the tumor by ultrasound and enhanced CT scan, and made a final decision on the surgical procedure intraoperatively depending on immediate histological examination of the tumor. Due to the possible existence of diverse cell differentiation within one cyst from benign to low-grade malignancy to advanced malignancy, multiple biopsies with extensive sampling are warranted, and if permanent sections suggest malignancy, reoperation for radical treatment is clearly needed. Of all 11 cases of pancreatic cystadenoma undergoing enucleation, one case developed a cystic lesion that was proven to be a pseudocyst by histological examination after reoperation during the follow-up of 30 months.

Two cases (18.2%) in our series were complicated with fistula, which is in line with other reports that fistula formation is the most common complication of enucleation and even more common than in conventional resection.[16] The reported rates of fistula formation after pancreatic enucleation have been as high as 27–50% in some studies.[3,10] The depth of the lesion in the parenchyma and its relationship to the main pancreatic duct rather than the size is considered to affect the risk of main duct damage and pancreatic leak. Crippa[17] suggested that, for enucleation to be performed safely, the lesion should be located not too deep in the parenchyma and at least 2–3 mm from the main pancreatic duct as determined by intraoperative ultrasound. However, most pancreatic enucleations performed previously were on endocrine neoplasms, which were usually located in the pancreatic parenchyma and closely related to pancreatic duct. In some operations, when resection of parenchyma was necessary, fistulas inevitably occurred. This is why pancreatic fistulas were reported frequently after enucleations. In pancreatic cystadenoma, there is usually a fibrous capsule surrounding the pancreatic cystadenoma, a layer of loose connective tissue between the capsule and adjacent pancreatic parenchyma. Stripping along the capsule is relatively easy and allows for isolation of the tumor with little damage to the main pancreatic duct intraoperatively. Thus, the rate of occurrence of postoperative fistula is low, and in our series, it was 18.2%. Communication with pancreatic main duct has been reported in 9% of the pancreatic cystadenoma,[18] which presumably contributes significantly to the postoperative fistula after enucleation of pancreatic cystadenoma. In support of this theory, in our series, the two cases that had high amylase in cystic fluid intraoperatively were the ones that were complicated with fistulas postoperatively. Strategies have been proposed to reduce the incidence of fistulas after enucleation, such as the use of octreotide preoperatively or suture of the enucleation bed or Rou-en-Y pancreatojejunostomy in selected patients. Most of the fistulas after enucleation can be resolved with conservative management, while if the drainage is rather high, ENPD has been suggested. This reduces the intraductal pressure and promotes fistula closure. Both cases of fistula in our series recovered with ENPD treatment.

The most prominent advantage of enucleation is the short operation time, less blood loss, fast recovery, and extensive preservation of the normal pancreatic tissues. The

most common complication was pancreatic leak or fistula, which can be resolved with conservative management or ENPD for stubborn cases. Our experience with 11 cases of pancreatic cystadenoma treated with enucleation indicates that enucleation is a safe, effective procedure preserving most exocrine or endocrine function of the pancreas. For patients who cannot withstand major operation or are comorbid with pancreatic endocrine or exocrine insufficiency, enucleation should be the treatment of choice.

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ORIGINAL ARTICLE

Laparoscopic Drainage of Pancreatic Pseudocysts: a Methodological Approach

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Abstract
Background This paper describes our tailored and methodological approach to laparoscopic drainage of pancreatic pseudocysts (PPs) based on an anatomical classification.
Methods We adopted the laparoscopic approach in "all comers" who had PPs requiring surgical drainage. The recipient organ for drainage (e.g., cystgastrostomy, cystjejunostomy, or cystduodenostomy) and method of access (e.g., transgastric, endogastric, exogastric or lesser sac, and infracolic) were decided based on preoperative computed tomography (CT) and intraoperative findings. The results shown represent median (range).
Results Between 2001 and 2009, 30 laparoscopic drainage procedures for PPs were performed in 28 consecutive patients. The surgical approach included transgastric (n=17) or endogastric (n=3) cystgastrostomy for large retrogastric PPs (n=20), exogastric cystgastrostomy for small perigastric PPs (n=4), cystduodenostomy (n=1) under ultrasound guidance, cystjejunostomy for infracolic PPs (n=4), and one external drainage. The operative time was 118 (25–300) min. There was one conversion to laparotomy (3.3%), low morbidity (3.3%), and no mortality. The postoperative hospital stay was 2 (1–7) days. At a follow-up of 15 (1–48) months, PPs recurred in two patients (7.1%) and were drained by laparoscopic cystgastrostomy.
Conclusion CT findings and laparoscopic exploration demonstrate the anatomical characteristics of PPs and enable successful planning and execution of their laparoscopic drainage.

Keywords Laparoscopic · Pseudocyst · Pancreatitis · Cystgastrostomy · Cystjejunostomy

Introduction

Up to 85% of pancreatic pseudocysts (PPs) that develop after acute necrotizing pancreatitis resolve spontaneously within 6 weeks and seldom require intervention.[1] However, prolonged observation of PPs in the expectation of spontaneous resolution exposes the patient to unwarranted risks such as rupture, abscess, jaundice, and hemorrhage.[2] Internal drainage is indicated in patients with symptomatic, persistent (>6 weeks), large (>6 cm), enlarging, and complicated PPs.[2–4] Internal drainage has traditionally been performed by open surgery and consistently produced good long-term results, thus considered to be the treatment of choice.[5,6]

The laparoscopic approach to internal drainage of PPs has gained popularity in recent years due to favorable results and the added advantages of the minimally invasive approach. The aim of this paper is to describe our tailored laparoscopic approach to drainage of PPs depending on their anatomical location and size and to describe its outcomes. The potential role of laparoscopic ultrasound (LUS) is evaluated and discussed.

This paper was presented at the annual meeting of the European Hepato-Pancreato-Biliary Association (EHPBA), Verona, Italy 6–9 June 2007.

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Material and Methods

Patients

The laparoscopic approach to drainage of PPs was applied to "all comers" with PPs that complicated acute pancreatitis and required drainage and to selected patients with PPs that complicated chronic pancreatitis and failed to be drained or recurred after attempts at endoscopic drainage but clinically still required effective drainage. We have favored surgical (laparoscopic) drainage of acute persistent PPs that complicated necrotizing pancreatitis as the initial mode of therapy over the endoscopic approach whenever possible, while the latter approach was routinely adopted as first choice.

The PPs were confirmed on preoperative ultrasound (US) and contrast-enhanced (intravenous and oral) computed tomography (CT). The exact location of the PP (especially in relation to the stomach), the PP size, and the presence or absence of pseudoaneurysm was ascertained on careful evaluation of the CT imaging preoperatively. Disruption of the pancreatic duct or communication between the PP and the pancreatic duct was evident in some patients on endoscopic retrograde cholangiopancreatography (ERCP). Acute PPs were defined according to the Atlanta criteria of 1992 international symposium[7] and therefore represented fluid collections that arose in association with an episode of acute pancreatitis, were of more than 4 weeks' duration, and were surrounded by a definite wall on imaging. All acute PPs were persistent (>6 weeks duration) and were large (>6 cm in diameter) and symptomatic thus requiring surgery.

Anatomic Classification of Pseudocysts

The operative approach depended on the anatomical location of the pseudocyst, its size, and ease of detection at laparoscopy. The following describes a surgically oriented and practical approach to the description and classification of PPs.

Retrogastric Pseudocysts

These could be classified as either large or small. Large retrogastric PPs are readily visible and palpable on laparoscopy (Fig. 1a, b) and do not require LUS for their detection. We have intentionally not attached a size limit to their description as the approach we adopt depended largely on ease of visible and palpable laparoscopic detection of the retrogastric pseudocyst. Large retrogastric PPs were drained via endogastric or transgastric approach without the need for LUS. We adopted an endogastric approach (see description below) in the early part of our experience[8] and thereafter moved to a transgastric approach (see description below) as a more favorable option.[9]

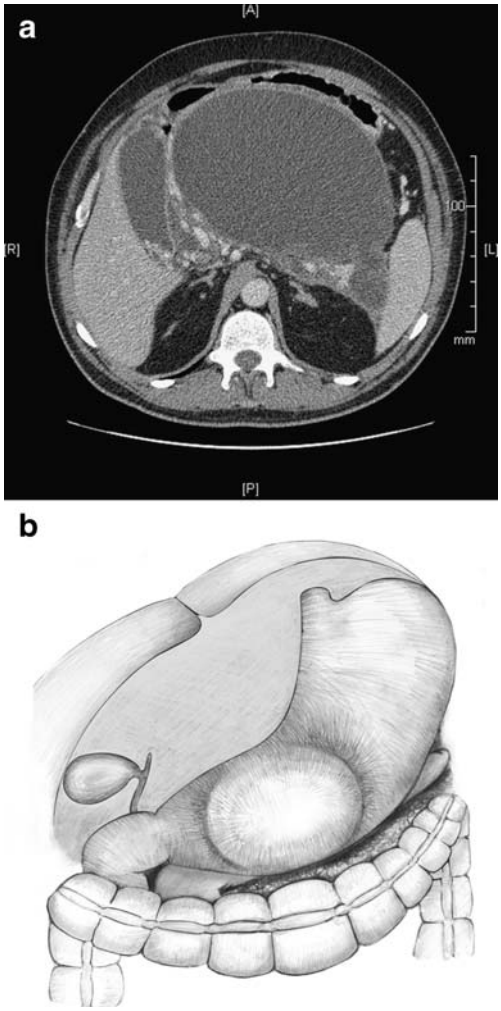

Figure 1 **a**, **b** CT scan section (**a**) and schematic drawing (**b**) of a large retrogastric PP displacing the stomach; this was readily visible and palpable at initial laparoscopy and was drained (cystgastrostomy) through a transgastric approach. Note the gallstone etiology (**a**).

While LUS may aid the detection of smaller retrogastric PPs (Fig. 2a) for a potential transgastric drainage approach, we feel that these not readily palpable PPs are best drained via an exogastric approach (see description below). A transgastric approach for such small PPs will only achieve a small communication as the area of contact between the stomach and the pseudocyst is relatively small. Small retrogastric PPs were readily identified through a lesser sac approach (Fig. 2b); exogastric drainage enabled the construction of a much larger anastomosis across the entire width of the pseudocyst.

Pseudocysts in the Splenic Hilum

There are no large PPs in the splenic hilum as these would have been described as large retrogastric PPs. Small splenic

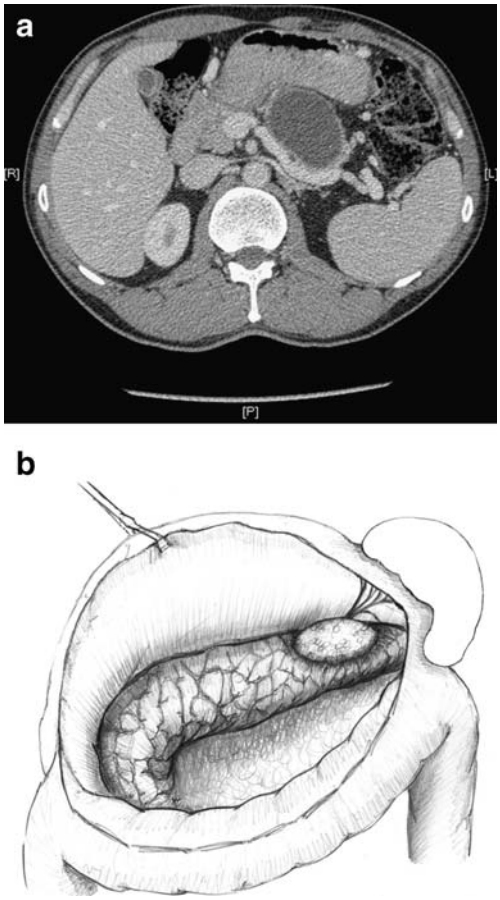

Figure 2 **a**, **b** This CT scan section (**a**) shows a small retrogastric PP that was drained (cystgastrostomy) via an exogastric approach. Division of the gastrocolic omentum (lesser sac approach) readily identifies small retrogastric PPs (**b**) and facilitates exogastric drainage.

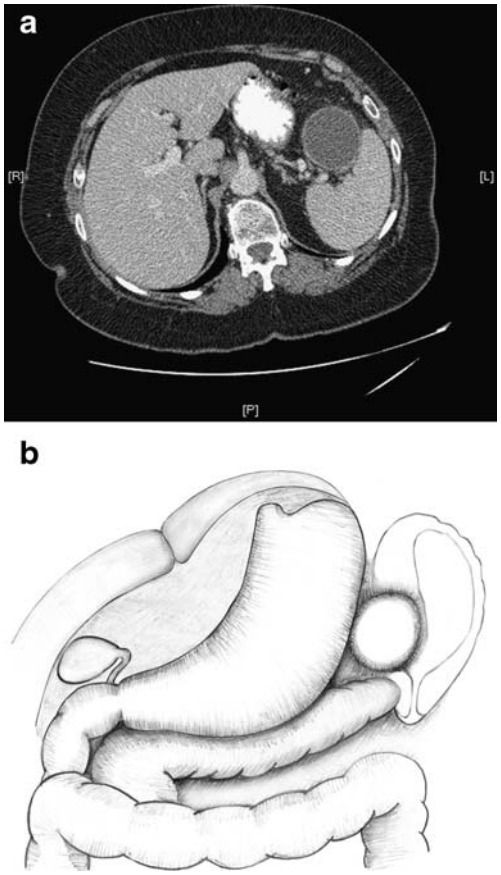

Figure 3 **a**, **b** This CT section (**a**) shows a small (6 cm) PP in the splenic hilum that was accessed via the lesser sac approach after division of the gastrocolic omentum (**b**) and was drained (cystgastrostomy) via an exogastric approach.

hilum PPs (Fig. 3a) were accessed by the lesser sac approach with division of the gastrocolic ligament. This approach rendered the pseudocyst readily visible (Fig. 3b) and allowed for an adequate anastomosis to be created with the posterior wall of the stomach. A transgastric approach is inappropriate for these PPs.

Pseudocysts in the Gastrohepatic Ligament

There are no large PPs at this location as these would have been classified as large retrogastric PPs. A small pseudocyst in the gastrohepatic ligament is readily visible at laparoscopy (Fig. 4) and the exogastric approach is the only available route to its drainage.

Infracolic Pseudocysts

Small PPs do not extend into the infracolic compartment as by their size and relation to the pancreas they will lie in a retrogastric position. Infracolic PPs describes large PPs that bulge predominantly into the infracolic compartment (Fig. 5a, b); these were readily seen at laparoscopy and were drained by Roux-en-Y cystjejunostomy. For these cysts, dependent drainage is unachievable by cystgastrostomy.

Figure 4 A schematic representation of a PP lying in the gastrohepatic ligament; this is readily drained (cystgastrostomy) by the exogastric approach.

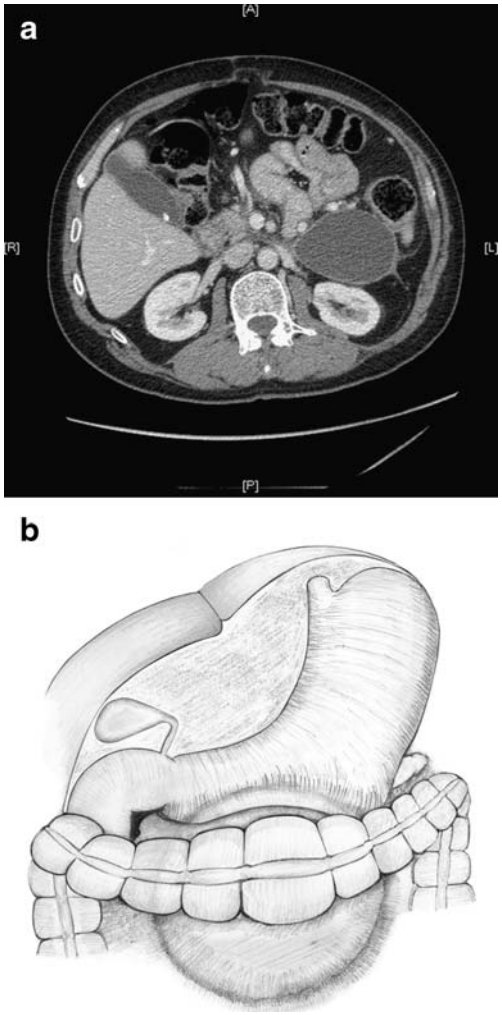

Figure 5 **a**, **b** This patient had a large PP that extended well into the infracolic compartment as shown in this CT section (**a**). The PP was readily visible within the infracolic compartment at laparoscopy (**b**) and was drained by cystjejunostomy.

Pancreatic Head Pseudocysts

These are small PPs that lie predominantly within the head of the gland and are largely associated with chronic pancreatitis. These are best managed endoscopically using either endoscopic ultrasound-guided aspiration/drainage or pancreatic duct stenting. Failure to achieve lasting resolution via the endoscopic approach, either due to PP being inaccessible or due to symptomatic recurrence, necessitates surgical drainage. Their proximity to the medial wall of the second or third parts of the duodenum renders cystduodenostomy, the surgical option of choice. LUS aids their accurate localization when not readily visible upon exposure of the head of the pancreas.

Surgical Approach

All procedures were performed by the senior author (BJA) or under his direct supervision, under general anesthesia, with broad-spectrum antibiotic cover and prophylaxis against deep vein thrombosis. The patients were placed in either supine position with the surgeon and assistant standing on the left of the patient and the monitor and scrub nurse on the right of the patient or in a French position with the surgeon standing between the legs and the assistant and scrub nurse to either side of the patient with the monitor over the patient's head. The 10-mm 30° laparoscope was employed routinely.

Endogastric Approach

This technique has been described previously[8] and employed four ports (one 10 mm and three 5 mm). In brief, under laparoscopic vision, three purse string sutures were placed in the anterior gastric wall through which three additional ports were introduced into the gastric lumen. Carbon dioxide insufflation and the laparoscope were then transferred to one of these ports for endogastric surgery. A needle was introduced through the posterior gastric wall into the pseudocyst to sample its fluid content for amylase and microbiological assay. A posterior, approximately 5-cm, gastrotomy that extended deep into the PP lumen was then created using the ultrasonically activated scalpel (UAS; Ethicon EndoSurgery, Cincinnati, OH, USA), and any necrotic pancreatic tissue was debrided. Suturing of the cystgastrostomy was only undertaken if the pseudocyst wall spontaneously detached from the posterior gastric wall upon drainage of its fluid contents or if there was bleeding from the gastrotomy. After completion of the cystgastrostomy, the CO_2 insufflation and the laparoscope were returned to the initial port, the gastric ports were withdrawn into the peritoneal cavity, and the purse string sutures were tied.

Transgastric Approach

We described this approach previously.[9] In brief, this approach employed three ports: one 10 mm and two 5 mm. An additional port may be used if exposure of the anterior gastric wall necessitated retraction of the left lobe of the liver. An anterior longitudinal gastrotomy of approximately 7–8 cm was made using an UAS to provide access for a *distal* internal drainage of the pseudocyst into the gastric lumen. The cystgastrostomy was fashioned in a similar manner as described for the endogastric approach, and necrotic pancreatic tissue was debrided. The necrotic tissue was placed in a water-impervious bag (Lapsac surgical tissue pouch, Cook Incorporated, Bloomington, IN, USA) and was removed at completion of surgery. After completion of the cystgastrostomy, the anterior gastrotomy was closed with a continuous Vicryl 2/0 (Ethicon Inc., Somerville, NJ, USA) running suture in one layer.

Abdominal drains and nasogastric decompression of the stomach were not employed routinely.

Exogastric Approach

The ports' access for this approach is similar to that of the transgastric approach. For small retrogastric PPs and for small PPs in the splenic hilum, the gastrocolic omentum was opened with the UAS and the pseudocyst was identified and its fluid sampled with a needle introduced percutaneously. Small PPs in the gastrohepatic ligament were readily accessible upon laparoscopic division of the gastrohepatic ligament. Two adjacent 3–4-cm transverse openings were made into the stomach and the PP, and an anastomosis was fashioned with continuous Vicryl 2–0 suture in one layer.

Roux-en-Y Cystjejunostomy

All cystjejunostomies were constructed in a Roux-en-Y manner rather than a simple loop for fear of consequences of anastomotic leak. Inflammatory adhesions between the omentum and the PP wall were divided to enhance exposure and the omentum and transverse colon were rolled upward. The proximal jejunum was divided some 50–75 cm from the duodenojejunal flexure with the endostapler (ATB45 45 mm articulating, Ethicon Endo-Surgery, Cincinnati, OH, USA), and a Roux loop of approximately 50–60 cm was constructed. A side-to-side jejunojejunal anastomosis was fashioned in one layer using Vicryl 2–0 continuous suture. The mesenteric defect was closed with Vicryl 2–0 continuous suture, and the Roux loop was approximated to the pseudocyst with 1–4 interrupted Vicryl 2–0 sutures. After sampling its fluid contents with a needle, the pseudocyst was opened for approximately 3–4 cm, and its contents were thoroughly debrided. The jejunum was similarly opened longitudinally for 3–4 cm and a side-to-side cystjejunostomy was fashioned with a running Vicryl 2–0 suture in one layer. Reinforcement second layer interrupted sutures may be placed if judged necessary. Abdominal drains were not employed.

Postoperative Care

Parenteral prophylactic antibiotic cover was not continued after surgery. Patients were commenced on oral fluid on the evening of surgery and received liquid diet on the first or second postoperative day depending on their clinical progress. Abdominal drain and nasogastric tube, if employed, were removed on the first postoperative day. Patients were discharged from hospital when adequately mobile and tolerating liquid diet. They were advised to continue with liquid diet for 10 days after surgery and to resume solid diet thereafter.

Follow-up

Patients were followed up in outpatient clinic and underwent abdominal US at 6 months and annually thereafter or earlier if symptoms indicated possible recurrence.

Data Management

Data were prospectively collected on specifically designed audit sheets and were entered into a computer-based data file. The digital records were updated regularly with follow-up information.

Results

Patients and Pseudocysts

Between 2001 and 2009, 30 laparoscopic drainage procedures for PPs were carried out on 28 patients with complicated acute (n=27) or chronic (n=3) pancreatitis; two of these procedures were for recurrent PPs. All procedures were performed electively some 2–58 (median, 7) months after the index attack of acute pancreatitis. The patient details are listed in Table 1. The etiology of the attacks of acute pancreatitis included gallstones (n=13 patients), alcohol (n=8), ERCP (n=1), drug-induced (n=1), and idiopathic (n=2). Alcohol was the etiology in all three patients with chronic pancreatitis.

Table 1 Details of Patient and Characteristics of the Pseudocysts

Total no. of patients	28
Age (years)[a]	53 (19–75)
Sex: F/M	10/18
Pancreatic pseudocyst largest diameter (cm)[a]	11.5 (4–23)
ASA score[a]	2 (1–3)
No. of patients with pancreatic necrosis (%)	21 (75%)
Extent of necrosis (%)[a]	70 (30 to more than 80)
Interval between index attack of acute pancreatitis and surgery (months)[a]	7 (2–58)

ASA American Society of Anesthesiology

[a] Data shown represent median (range)

Procedures and Outcomes

The 30 drainage procedures that were performed included 29 internal drainage procedures (cystgastrostomy, $n=24$; cystjejunostomy, $n=4$; and cystduodenostomy, $n=1$). One patient underwent an unplanned external drainage due to extensive and dense inflammatory intestinal adhesions to a large infracolic pseudocyst; these were related to a previous subtotal colectomy and subsequent relaparotomy for anastomotic dehiscence and later an acute pancreatitis and rendered cystjejunostomy unsafe. LUS was required in one patient to accurately locate a small pseudocyst that lied entirely within the head of the pancreas; the pseudocyst was drained by cystduodenostomy.

The endogastric approach was adopted in the initial part of our experience in three patients with large retrogastric PPs measuring 8.5, 10, and 12 cm, while the transgastric approach was adopted in a subsequent 17 patients with retrogastric PPs that measured 6.5–18 cm (median, 14 cm). In three patients who underwent transgastric cystgastrostomy, the pseudocyst wall fell away from the posterior gastric wall upon drainage of their contents (transgastric $n=2$, endogastric $n=1$) and required a sutured cystgastrostomy. The exogastric approach was adopted in five patients with PPs that measured 4–8 cm (median, 6 cm) and lied in a retrogastric position ($n=3$), within the hilum of the spleen ($n=1$) or within the gastrohepatic ligament ($n=1$).

Pancreatic necrosis was present in 21 patients; 14 patients underwent debridement at the same time as the laparoscopic drainage of the pseudocyst. Two patients who underwent cystgastrostomy and one patient who underwent cystjejunostomy had a concomitant laparoscopic cholecystectomy. All fluid samples obtained from the pseudocyst were sterile and had a high amylase concentration. Conversion to a minilaparotomy was required in one patient with a pseudocyst in the gastrohepatic ligament that bled during suturing of the anterior layer of the cystgastrostomy from an adherent left gastric artery; the patient received two units of blood transfusion and was discharged from hospital 7 days later after an uneventful recovery. Blood loss in the remaining patients was minimal (less than 100 ml per procedure) and none required blood transfusion.

The main overall outcomes of surgery are summarized in Table 2, while Table 3 lists the specific outcomes of the various approaches to cystgastrostomy and that of cystjejunostomy. One patient was readmitted 8 days after laparoscopic cystgastrostomy with pyrexia; a CT scan of abdomen showed no complications and the fever resolved with a course of antibiotics. The pseudocyst recurred in two patients (7.1%) 43 and 54 months after transgastric drainage; these were redrained laparoscopically through the exogastric and transgastric approaches, respectively, and have not recurred on follow-up US at 14 and 6 months, respectively.

Table 2 Procedures ($n=30$) and Outcomes

Operative time (min)[a]	118 (25–300)
Conversion	1 (3.3%)
Blood transfusion	1 (3.3%)
Postoperative morbidity/mortality (%)	3.3/0
Postoperative hospital stay (day)[a]	2 (1–7)
Follow-up period (months)[a]	15 (1–48)
Recurrence rate: no. (%)	2 (6.7%)

[a] Data shown represent median (range)

Interestingly, the single patient who had external drainage of a large infracolic pseudocyst has not had a recurrence at 31 months follow-up. Another patient developed gastric outlet obstruction 6 weeks after laparoscopic cystgastrostomy secondary to duodenal stenosis in association with a further attack of acute pancreatitis within the head of the gland and underwent laparoscopic gastrojejunostomy.

Discussion

Patients requiring surgical internal drainage of PPs, particularly those that complicate acute necrotizing pancreatitis, could be managed laparoscopically. This approach offers adequate stoma between the pseudocyst and the gastrointestinal tract with effective drainage. Laparoscopic drainage also enables concomitant pancreatic necrosectomy; pancreatic necrosis is a common cause for failure with the endoscopic transmural approach[10] where stents are used as necrotic debris may lead to stent occlusion with subsequent secondary infection of the pseudocyst and necrotic tissue, sepsis, and recurrence.[11] In a systematic review of the literature, laparoscopic drainage was associated with low morbidity, rapid recovery, and recurrence rates comparable to those reported by open surgery.[11] The current series of 28 patients illustrates these observations with very low morbidity (3.3%) of the drainage procedures carried out, a median postoperative hospital stay of 2 days, and a recurrence rate of 6.7% at a median of 15 months follow-up.

The principle of surgical treatment is to create a wide stoma between the pseudocyst and the gastrointestinal tract choosing a site that would achieve dependent drainage. In addition, the necrotic pancreas could be debrided thus reducing the potential risks of secondary infection; significant pancreatic necrosis (30% or more of the gland) was present in nearly three quarters of our patients. In order to achieve the above, it is essential to study carefully cross-sectional images of the pseudocyst obtained preoperatively to determine size and location of the pseudocyst and to rule out or pretreat with embolization a pseudoaneurysm within its wall. This will enable the surgeon to plan the optimal

Table 3 Outcomes of the Three Approaches to Cystgastrostomy and That of Cystjejunostomy

	Cystgastrostomy approaches			Cystjejunostomy
	Endogastric	Transgastric	Exogastric	
No. of procedures	3	17	5	4
Operative time (min)[a]	165 (125–200)	70 (25–140)	120 (50–180)	135 (85–240)
Conversion	0	0	1	0
Postoperative morbidity/mortality: no.	0/0	1/0	0/0	0/0
Postoperative hospital stay (day)[a]	4 (3–4)	1 (1–2)	2 (2–7)	1.5 (1–2)
Follow-up period (months)[a]	17 (15–21)	15 (1–48)	3.5 (1–14)	17 (8–26)
Recurrence rate: No. (%)	0	2 (11.8)	0	0

[a] Data shown represent median (range)

laparoscopic approach to internal drainage of the pseudocyst. Also, a review of the CT scan obtained after onset of acute pancreatitis is essential to establish the presence and extent of necrosis; the surgeon can then predict the need for concomitant pancreatic necrosectomy and its extent.

Most pseudocysts lie in a retrogastric location and could be drained into the stomach.[12] Drainage of large retrogastric PPs into the posterior wall of the stomach may be readily accomplished with an endogastric approach where the surgery is carried out within the CO_2 distended gastric lumen[8,13] or via a transgastric approach through an anterior gastrotomy.[9,14] We have found the latter approach more favorable as it was associated with better exposure and shorter operative time (median, 165 and 70 min, respectively).[9] Park and Heniford[15] reported similar observations with longer operating time when the endogastric approach to cystgastrostomy was applied. Although some advocate routine suturing of the cystgastrostomy to prevent postoperative bleeding,[15] we have not found this to be routinely necessary and have not encountered postoperative bleeding. Occasionally, however, the pseudocyst wall might not be adherent to the posterior gastric wall and rather separates away from it once the fluid content of the pseudocyst has been drained; suturing the pseudocyst wall to the posterior gastric wall is then more readily achievable with the transgastric compared with the endogastric approach. While some adopted the use of LUS routinely,[16] we have found its use unnecessary as these large PPs are readily identifiable both visibly and palpably at laparoscopy by virtue of their size.

Small PPs in a retrogastric location or those situated within the hilum of the spleen are more precisely drained by a direct exposure of the pseudocyst through a lesser sac approach with division of the gastrocolic ligament,[16] an approach that renders the use of LUS for their localization[17] immaterial. A sizable cystgastrostomy can then be fashioned spanning most of the width of the pseudocyst. Attempts at transgastric drainage of such PPs may be quite difficult as the area of contact between the pseudocyst and the posterior gastric wall is relatively small with a tendency for the ultrasonically activated scalpel to slip outside the lumen of the pseudocyst (even if LUS is employed for precise localization). Moreover, the anastomosis achievable with the transgastric approach is likely to be rather small too and perhaps inadequate. The exogastric approach is the only option available for PPs that lie within the gastrohepatic ligament abutting the lesser curvature of the stomach. Whilst the lesser sac approach avoids the anterior gastrotomy while preserving the ability to fashion a generous cystgastrostomy, some[15] have found that severe inflammation had obliterated the lesser sac and therefore precluded the exogastric approach.

In our reported experience as well as that of others,[15] PPs are most commonly situated in a retrogastric location with laparoscopic cystgastrostomy therefore being the most common procedure. Among 108 laparoscopically treated patients with PPs, Palanivelu et al.[12] employed transgastric cystgastrostomy in 90 patients, cystjejunostomy in eight patients, and external drainage techniques in eight patients, while open surgery (cystgastrostomy) was resorted to in two patients. Park and Heniford[15] treated 29 patients with PPs using laparoscopic intragastric (n=16) or exogastric (lesser sac approach; n=9) cystgastrostomy, cystjejunostomy (n=3), and external drainage techniques (n=1); the procedure was aborted in one patient due to extensive gastric varices.

Large PPs that extend well into the infracolic compartment are better drained dependently by cystjejunostomy.[5] Though some surgeons have employed a simple jejunal loop in continuity to establish a cystjejunostomy,[18] the consequences of a leak from this anastomosis, albeit a rare occurrence, may be considerably more serious than if a leak occurred from a Roux loop; we have therefore adopted the latter approach favoring its enhanced safety despite the longer operating time.

While some surgeons advocated the routine use of LUS during drainage procedures of PPs in order to confirm their location and exclude pseudoaneurysms,[5,19,20] we have found the routine use of LUS unnecessary if preoperative CT images were carefully evaluated and the methodological

approach described above to access and drain the PPs is adopted. An exception to this has been a patient with 4-cm chronic pseudocyst that lied entirely beneath the anterior surface of the head of the pancreas and required a planned LUS for its intraoperative localization and drainage by cystduodenostomy. We have adopted the laparoscopic approach in "all comers" with acute PPs that required surgical drainage with very low morbidity and have not encountered a situation where the application of LUS would have altered the operative decision making or its outcome. There is no convincing evidence in the literature to support the routine use of LUS during drainage procedures for *acute* PPs with the premise that its use would avoid complications, reduce conversion rate, or alter surgery. Palanivelu et al.[12] successfully treated over a hundred patients with PPs using the laparoscopic approach without the use of LUS, while Hindmarsh et al.[17] found LUS helpful in identifying smaller PPs that were not visually detectable (six of 15 patients), we argue that these would have been readily identified and drained using an exogastric (lesser sac) approach. In the context of chronic pancreatitis, however, we agree that the use of LUS has its applications in some patients, and we employed it in one of the three patients with chronic PPs as described above. Performing open surgery in patients with chronic pancreatitis, Machi et al.[21] have shown that the findings of intraoperative ultrasound altered the surgical procedure for PPs (drainage versus resection, or drainage sites) in 20% of operations.

Conclusion

Laparoscopic drainage of PPs is highly successful, carries very low morbidity and mortality, and is associated with rapid recovery and recurrence rates comparable to those observed after open surgery. Careful preoperative planning facilitates a methodological laparoscopic approach to internal drainage of PPs and renders the routine use of LUS unwarranted. The surgical approach adopted is dependent on the location and size of the pseudocyst.

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ORIGINAL ARTICLE

Reporting on Quality of Life in Randomised Controlled Trials in Gastrointestinal Surgery

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Abstract
Background Although health-related quality of life (HRQOL) has become an important outcome measure in surgical trials, questions still remain about the quality of its reporting. The aim of this study was to evaluate HRQOL assessment methodology of randomised clinical trials concerning gastrointestinal surgery.
Methods All articles published in the calendar years 2006 and 2007 that purported to assess quality of life as end points or make some conclusion about quality of life were chosen for review from eight general surgical journals and four medical journals. Identified eligible studies were selected and then evaluated on a broad set of predetermined criteria.
Results Twenty-four published randomised controlled clinical trials (RCTs)s with an HRQOL component were identified. Although most trials exhibited good-quality research, some methodological limitations were identified: Only 21% of the studies gave a rationale for selecting a specific HRQOL measure, 46% of the studies failed to report information about the administration of the HRQOL measure, and 37% did not give details on missing data.
Conclusions Although it is clear that HRQOL is an important end point in surgical RCTs because the information helps to influence treatment recommendations, a number of methodological shortcomings have to be further addressed in future studies.

Keywords Quality of life · Randomised controlled trial · Surgery

Introduction

This century, we have witnessed significant progress in the diagnosis and treatment of disease. The effects of disease and its treatment on patients have traditionally been assessed in terms of pain scores, duration of hospital stay and return to normal activities. These outcomes, however, are dependent much on external factors, such as on local habits and social security matters. Thus, the application of quality-of-life instruments, which measure recovery in a patient-centered manner, has become more popular in recent times and has been accepted more and more as a solid primary outcome measure in scientific studies.[1]

At the present time, there is no single definition of health-related quality of life (HRQOL). Nevertheless, there is a broad consensus that it refers to the physical, psychologic, and social functioning of patients and the impact of disease and treatment on their abilities and daily functioning.[2–5]

There are several valid measures of HRQOL that are suitable to use in surgical research. Generic measures (such as the short form health survey SF-36[6]) broadly assess physical, mental and social health and can be used to compare conditions and treatments. Measures specific to illnesses (such as the Gastro-Intestinal Quality of Life Index GIQLI[7]) can supplement generic measures or can be used independently.[8]

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Although these instruments are widely available, careful application of the tools in clinical studies is needed to produce reliable and clinically useful results. These range from the accurate selection of the most appropriate instrument for the particular trial objective to the handling of missing data and accurate interpretation of outcomes.[9–11] Unless standards for measuring HRQOL are adhered to in clinical trials, the data that are collected will be difficult to interpret and unlikely to make clinical sense.[11]

Previous review on randomised controlled clinical trials (RCTs) including an HRQOL evaluation in oncology have shown overall a number of methodological shortcomings.[12–19]

However, to date, no detailed systematic methodological review of the quality of the conduct and reporting of quality of life (QOL) results from RCTs for gastrointestinal surgery has appeared. Therefore, the aim of this study was to evaluate the quality of HRQOL methodologic assessment in randomised controlled clinical trials involving the gastrointestinal surgery and determine how improvements can be made.

Because they are considered the optimal study design for evaluating the effects of different surgical interventions,[20] we limited our search to "randomised controlled trials" and to recent articles published between January 2006 and December 2007.

Methods

Search Strategy for Identification of Studies

Twelve journals were chosen for review: eight English-language surgical journals (*American Journal of Surgery*, *Annals of Surgery*, *Archives of Surgery*, *Journal of the American College of Surgeons*, *Surgery*, *British Journal of Surgery* and *European Journal of Surgical Oncology*) and four English-language medical journals (*New England Journal of Medicine*, *Lancet*, *British Medical Journal* and *Journal of the American Medical Association*).

To identify eligible articles, all issues of these journals were hand-searched.

Studies included for review had to be randomised-controlled gastro-intestinal surgical trials, phases III published between 01 January 2006 and 31 December 2007.

All randomised-controlled trials comparing different treatment were eligible regardless of the intervention type. No restrictions were performed on trial location, number of patients enrolled in the trial, treatment modalities and sponsor of trial.

The exclusion criteria were: (a) trials published as a letter, abstract or short article; (b) randomised phase II trials; and (c) non-experimental (observational) studies.

The search was restricted to RCTs as they represent the gold standard by which health care professionals make decisions about treatment effectiveness.[20]

Characteristics Assessed

Two reviewers (V.B. and JJ.T.), who were not involved in any of the identified studies, analysed the identified RCTs independently. Any disagreement was resolved through discussion between the two reviewers.

As quality of life was the main outcome measure sought, any studies including assessing quality of life as an end point or making some conclusion about quality of life were considered.

The standardised protocol was based on a checklist (available from the authors). The items to be included were: country of origin, industry funded (yes versus no), number of patients randomised, multicenter studies (yes versus no), informed consent reported (yes versus no), approval of a research ethics committee reported (yes versus no) and health-related quality of life difference between treatment arms (yes versus no). The latter was defined as any statistical difference between treatment arms at any given time point assessment during the trial (even if this only occurred in one HRQOL domain).

The selected articles were evaluated for trial quality and quality of reporting on HRQOL.

Trial quality was evaluated with the Jadad scale.[21] The maximum possible score was 13 points using an 11-item instrument. This was considered to be good when the score was more than nine points and poor when the score was equal to or less than nine points. Items related directly to the control of bias using the Jadad scale are:

1. Was the study designed as randomised?
2. Was the study designed as double blind?
3. Was there a description of withdrawals and dropouts?

Other markers not related directly to the control of bias:

1. Were the objectives of the study defined?
2. Were the outcome measures defined clearly?
3. Was there a clear description of the inclusion and exclusion criteria?
4. Was the sample size justified (for example, power calculation)?
5. Was there a clear description of the interventions?
6. Was there at least one control (comparison) group?
7. Was the method used to assess adverse effects described?
8. Were the methods of statistical analysis described?

Items are scored as follows:

Give either a score of 1 point for each "yes" or 0 point for each "no". There are no in-between marks.

Give 1 additional point if, for question 1, the method to generate the sequence of randomisation was described and was appropriate (table of random numbers, computer generated, etc.) and/or if, for question 2, the method of double blinding was described and was appropriate (identical placebo, active placebo, dummy, etc.).

Deduct 1 point if, for question 1, the method to generate the sequence of randomisation was described and was inappropriate (patients were allocated alternately or according to date of birth, hospital number, etc.) and/or if, for question 2, the study was described as double blind but the method of blinding was inappropriate (for example, comparison of tablet versus injection with no double dummy).

The criteria used to evaluate quality of reporting on HRQOL were based on those proposed by Efficace et al.[11] (Table 1).

This 11-item checklist was developed on the basis of good practice in conducting a HRQOL evaluation, and it was specifically aimed at evaluating the reported *quality* of the HRQOL assessment methodology in a clinical trial setting. The checklist items were devised to have a dichotomous answer; these can be scored as "yes" (giving a score of 1) or "no" (giving a score of 0); the higher the score, the higher the considered robustness of the outcomes. This checklist addresses the basic and essential issues that a given trial should report to have methodologically sound outcomes.

The original checklist also included whether the measure covered, at least, the main HRQOL dimensions relevant for a generic cancer population. This criterion has been built into this review automatically.

Studies scoring at least *7* on this checklist, including three mandatory items (i.e. baseline compliance, missing data and psychometric properties reported), could be considered as probably robust. Hence, all studies were classified into "probably robust" (as defined above), limited (scoring higher than *3* but either lower than *7* or not including all three mandatory items) and very limited (all other studies, i.e. scoring *3* or lower on the checklist score).

When an article provided explicit reference to a related paper reporting additional data, this was retrieved as well. When more than one paper reported HRQOL data of the same trial, information was pooled to be reported in the tables.

Ethical Aspects

In accordance with French regulations, this study was exempted from Institutional Review Board approval.

Results

The Appendix lists all articles reviewed.

According to the eligibility criteria, a total of 26 citations were identified that included HRQOL outcomes in 24 randomised clinical trials (Appendix). Besides these, three other studies were also retrieved but excluded from trial analyses (with the consensus of all authors). One of these studies met our criteria but did not report any details about the methodology used to assess HRQOL, and the remaining two were excluded because it was impossible to check for the HRQOL measure used.

Demographics and Trial Design Characteristics

The studies were conducted across a variety of countries: 16 (66.6%) in European countries, two (8.3%) in the USA, two (8.3%) in Asia, one (4.2%) in Australia and one (4.2%) in Burkina Faso, and two (8.3%) were conducted on an international setting.

Eight (33.3%) of the 24 studies were industry sponsored, as identified by author affiliation with a company or by a statement regarding commercial funding.

Half of the trials were multi-centre studies.

The number of patients enrolled into the trials varied considerably, ranging from 27 to 700 patients, with a total of 3,476 patients.

A total of 23 trial reports (95.8%) stated that a research ethics committee had approved the research and reported that informed consent from patients had been requested from the participants.

Methodological Quality

The methodological quality score (Jadad scale) ranged from 8 to 13, with a mean of 10.6±1.07. Only five articles, in which the study was described as double blind and could therefore score an extra 2 points, were eligible for the maximum possible score of 13, and just two achieved this score.

The methodological quality was insufficient (score <9) for only one trial (Table 2). All trials were randomised, but three trials (12.5%) were randomised without the method of randomization being specified. All but one trial detailed trial inclusion and exclusion criteria.

HRQOL Assessment

The 24 RCTs identified were classified according to the predefined checklist. One of these could be considered as *very limited* in terms of methodological design according to previously defined criteria (4%).Twelve trials (50%) were considered *limited*, while 11 (45.8%) were evaluated as

Table 1 Minimum Standard Checklist for Evaluating HRQOL Outcomes in Cancer Clinical Trials[11]

HRQOL issue	Answer			Description
Conceptual				
A priori hypothesis stated	Yes	No	N/A[a]	Assessed whether authors had a predefined HRQOL end point and/or stated expected changes because of the specific treatment
Rationale for instrument reported	Yes	No		Assessed whether authors gave a rationale for using a specific HRQOL measure
Measurement				
Psychometric properties reported	Yes	No		Assessed whether a previously validated measure was used or psychometric properties were reported or referenced in the article
Cultural validity verified	Yes	No	N/A[b]	Assessed whether the measure was validated for the specific study population
Adequacy of domains covered	Yes	No		Assessed whether the measure covered, at least, the main HRQOL dimensions relevant for a generic cancer population and/or according to the specific research question
Methodology				
Instrument administration reported	Yes	No		Assessed whether authors specified who and/or in which clinical setting the HRQOL instrument was administered
Baseline compliance reported	Yes	No		Assessed whether authors reported the number of patients providing an HRQOL assessment before the start of treatment
Timing of assessments documented	Yes	No		Assessed whether authors specified the HRQOL timing of assessment during the trial
Missing data documented	Yes	No		Assessed whether authors gave some details on HRQOL missing data during the trial
Interpretation				
Clinical significance addressed	Yes	No		This refers to the discussion of HRQOL data being clinically significant from a patient's perspective and not simply statistically significant
Presentation of results in general	Yes	No		Assessed whether authors discussed the HRQOL outcomes, giving any comments regardless of the results (either expected or not)

HRQOL health-related quality of life

[a] If a study explicitly states an exploratory HRQOL evaluation

[b] If the HRQOL measure is validated in the same population as the one of the trial

being *probably robust*. The overall level of reporting is provided in Table 3.

Fourteen distinct QOL questionnaires (five generic, nine specific) were used in the 24 studies analyzed. The most frequently used instrument (in conjunction or not with other tools) was the Short Form 36-item questionnaire in 13 trials and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 in four trials.

In two studies, SF-36 was administered in a modified version, attempting to give a more comprehensive HRQOL assessment but altering the psychometric properties of the original tool.

Table 2 Numbers of Trials According to the Jadad Score[21] (n=24)

Score	≤7	8	9	10	11	12	13
Number of trials	0	1	2	7	12	0	2

Forty-five percent (11 of 24) of the reports described the questionnaires, i.e. the number of dimensions and their contents, such as the number of items per dimension, and the minimal and maximal scores. Only the name of the questionnaire was given in 13 others.

QOL was a primary endpoint in only six (25%) studies. QOL was a secondary endpoint in 75% (18 of 24) of the analyzed reports. In two of them, trial results were published in several different articles, one relating the QOL findings and the other(s) the clinical outcomes. Only five (20.8%) studies reported the use of power calculations for HRQOL aspects.

Only ten studies (41.6%) reported a priori hypotheses, and only five studies (20.8%) provided a rationale for selecting a HRQOL measure.

Information about the administration of the HRQOL questionnaire was mentioned in 13 (54.1%) reports.

Three RCTs (12.5%) did not provide the absolute number or the percentage of patients who completed the questionnaire before commencing the trial.

Table 3 Level of Reporting According to the Minimum Standard Checklist for Evaluating HRQOL Outcomes in Cancer Clinical Trials

HRQOL Issue	Number[a]	Percent
Conceptual		
A priori hypothesis stated	10/24	41.6
Rationale for instrument reported	5/24	20.8
Measurement		
Psychometric properties reported	22/24	91.6
Cultural validity verified	22/24	91.6
Methodology		
Instrument administration reported	13/24	54.1
Baseline compliance reported	21/24	87.5
Timing of assessments documented	24/24	100
Missing data documented	15/24	62.5
Interpretation		
Clinical significance addressed	8/24	33.3
Presentation of results in general	23/24	95.8

HRQOL health-related quality of life.

[a] Number of articles reporting item/number of articles to which item is applicable

Methods of Health-Related Quality of Life Analysis and Results

The response rate for quality of life end points was given in 19 of the studies, with response rates ranging from 14.2% to 100%.

Nine RCTs (37.5%) did not provide any details about HRQOL missing data during the course of the trial. Furthermore, in those trials where an indication of HRQOL missing data was provided, only one trial undertook a detailed statistical exploration of the biases due to missing data. The remaining studies did not investigate this issue.

Reporting the level of missing data and the reasons why the data are missing (i.e. random or systematic) are factors critical to understanding any possible source of bias in determining HRQOL significance.

However, all studies provided details about the timing of HRQOL assessment, and 14 (58.3%) discussed somehow the HRQOL outcomes in the paper.

All RCTs, with the exception of one, applied a statistical test for determining a HRQOL difference between treatment arms.

Of the 23 eligible studies, 11 (47.8%) found some significant difference on HRQOL scales between arms.

Obtaining a statistical difference in terms of HRQOL outcome does not necessarily imply a clinically meaningful difference from a patients' perspective.[22] But only six (25%) discussed the related HRQOL outcomes in terms of clinical significance from a patient's perspective. This issue is closely related to the difficulty in interpreting the HRQOL data from a given measure.

Discussion

Inadequate reporting of randomised controlled trials is common and hampers the appraisal of the validity and generalisability of results.[22,23] To overcome such problems, the Consolidated Standards for reporting of Trials (CONSORT) Group developed the CONSORT statement[24] in 1996, which was followed by a revised version in 2001.[25]

This can explain the high level of the mean Jadad score found in our study.

The main objective of this article was to evaluate the methodological quality of RCTs with a HRQOL component in gastrointestinal surgery.

Using the stated selection and eligibility criteria, we found 24 RCTs with HRQOL assessment which included some 3,476 patients. HRQOL was a secondary end point in most trials (75%).

The aim of our study was not to compare results with other medical or surgical specialities but to describe how digestive surgeons use HRQOL in their trials and to find ways on how to improve.

However, compared with other HRQOL studies in other disease sites and treatments,[12–19,26,27] (Table 4) the overall quality of the reported trials is good, although there are a number of shortcomings with regard to the reporting of the HRQOL design and results.

Among the studies reviewed, there are, generally, poor details about the rationale for selecting a specific measure and instrument administration.

A justification for selecting the HRQOL measure was given in only five studies (20.8%). In other reviews, this justification was given in 9.7% to 90% of the trials (Table 4).This point has to be improved as well in surgery as for others specialities.

This is regarded as important because instrument selection is critical for reliability, validity and reproducibility of results.

It is also important to standardise the instructions and completion procedures of assessment material administered to patients, particularly in RCTs, because often many researchers and institutions are involved in collecting HRQOL data. Thus, standard procedures help to ensure adequate data quality and minimise any possible bias in data collection (for example, will patients answer the questionnaire at a clinic visit, by telephone, by mail? Is it to be done by the investigator, his colleagues or a research nurse?).

Our study was in accordance with previous studies (Table 4) where instrument administration was reported in 0% to 66.6%.

Table 4 Results of Previous Review on RCTs Reporting HRQOL Evaluation by the Efficace's Checklist

			Conceptual		Measurement		Methodology				Interpretation	
		Number	A priori hypothesis stated (%)	Rationale for instrument reported (%)	Psychometric properties reported (%)	Cultural validity verified (%)	Instrument administration reported (%)	Baseline compliance reported (%)	Timing of assessments documented (%)	Missing data documented (%)	Clinical significance addressed (%)	Presentation of results in general (%)
Our study	Gastrointestinal surgery (2006–2007)	24	41.6	20.8	91.6	91.6	54.1	87.5	100	62.5	33.3	95.8
Efficace[11]	Prostate cancer (1980–2001)	24	13	29	87	81	25	46	96	54	12	67
Efficace[12]	Brain cancer (1980–2001)	5	20	80	NA	50	0	100	100	60	40	80
Bottomley[14]	Non-small-cell-lung cancer (1980–2002)	29	31	34.5	NA	100	34.5	13.8	100	62	20.7	58.6
Efficace[17]	Colorectal cancer (1980–2003)	31	25.8	9.7	100	94.7	9.7	61.3	100	48.4	12.9	93.5
Efficace[18]	Leukaemia (1980–2007)	9	22.2	55.5	100	100	66.6	83.3	100	66.6	44.4	100
Gujral[19]	Surgery for colorectal cancer (1980–2006)	8	50	87.5	NA	NA	25	20	8/8	50	66.6	62.5
Blazeby[26]	Surgical oncology (1985–2005)	33	72.7	90.9	NA	NA	63.6	45.4	90.9	54.5	NA	NA
Efficace[27]	Cancer clinical trials (1990–2004)	159	28.9	47.8	94.3	96.6	30.8	75.5	99.4	74.8	24.5	93.1

NA not available

A major methodological drawback was a lack of a priori hypothesis about possible HRQOL changes before commencing the trial. Only ten RCTs (41.6%) explicitly stated an a priori hypothesis, thus limiting spurious HRQOL results due to multiple significance testing. These results were similar to and even better than the majority of previous studies where the a priori hypothesis was stated in 13% to 72.7% of the trials (Table 4).

A key consideration for future studies is the selection of a limited number of HRQOL indicators before commencing the trial, possibly basing this selection on previous related trials, or on a specific a priori research hypothesis about the impact of a given therapy.

One major issue is the reporting of compliance at baseline and the documentation of missing data. Three RCTs (12.5%) did not provide the absolute number or the percentage of patients who completed the questionnaire before commencing the trial, and nine (37.5%) did not provide any details about HRQOL missing data during the course of the trial.

This result was similar to previous studies where missing data were documented in only 48.4% to 74.8% (Table 4).

Although the majority of trials started with reasonable sample sizes, many were plagued with problems of patient dropout. Such attrition often limits the general robustness of the results and reduces confidence in the HRQOL conclusions. Data are generally not missing at random, and therefore bias can be introduced.[17,28–30] The benefit of an intervention may be overestimated by comparison of group means as only individuals who remain well enough to fill in questionnaires provide data. The unreported details of missing data are a frequent problem in studies where HRQOL is measured,[31] and previous works already proposed procedures to address this issue.[32,33] More attention to improving compliance and reporting in future studies would be valuable.

Of the 23 eligible studies, 11 (47.8%) found some significant difference on HRQOL scales between arms. This would indicate that the HRQOL measures are valuable in providing additional data.

However, although HRQOL differences were observed, it is necessary to remember that, whereas many subscales are often used and compared over treatments and time, not all subscales will show a significant difference.

This underlines the need to declare in advance the HRQOL hypotheses and the importance of careful interpretation of multiple repeated statistical analyses.

A further trap in analysis of HRQOL data is the difference between statistical and clinical significance in changes of scores. It is acknowledged that, although analysis of large samples may reveal small changes that seem to be statistically significant, these changes may not be clinically meaningful to the patient and are, therefore, of limited value to the improvement of patient care.

An effort to determine if such small numerical differences have a clinical meaning from a patient's perspective has been highlighted as an important aspect for determining the impact of a given treatment.[28,34]

Unfortunately, only six of these studies (26%) examined the clinical significance of apparent differences. It is highly desirable that future studies will routinely include the concept of clinical significance to help evaluate the value of HRQOL results.

Furthermore, in several RCTs, the HRQOL results were not formally presented, but the main results were described in the text.

It is possible that this occurred because most trials used HRQOL as a secondary end point. In such trials, it is frequently observed that limited space is given to HRQOL data, with priority given to the primary clinical end point.

Two authors have overcome this difficulty by separately reporting clinical and HRQOL trial outcomes.

This is an opportunity for adequate explanation and presentation of what may often be complex results.

However, the disadvantage of splitting the HRQOL data from the main trial paper is that surgeons are unlikely to read the HRQOL paper once the main clinical message of a particularly trial has been published. If this occurs, then during the process of clinical decision making, the HRQOL impacts of treatment may be overlooked.[19] It is therefore recommended that clinical and HRQOL outcomes are published together so that clinical decision making is based upon relevant patient-centred endpoints.

Whilst we identified the above reported methodological limitations, it was impressive that nearly all the studies used HRQOL valid measures and provided details on the HRQOL timing of assessment during the trial.

There were 11 trials (45.8%) with robust HRQOL design, and statistically significant differences in HRQOL were reported in six of these trials. Only one trial "very limited" (4%) could be invalidated by its lack of rigor in presenting HRQOL data.

Pertinently, the strict methodological approach to the assessment of the patient-based QOL criteria in the evaluation of therapeutic strategies can help patients and their doctors in medical decision making.

The Efficace's checklist can be considered as a minimum standard; however, HRQOL design also greatly depends on the context and the specific research question of the trial; hence, good reports may have different emphases, and some issues might have different relevance according to the specific study questions.[11]

If HRQOL is considered to be a relevant outcome in a clinical trial and if HRQOL is assessed robustly, then it will always contribute to clinical decision making regardless of the direction of the outcomes.[11,26] Only if HRQOL assessments are flawed (underpowered study, too many missing

data items, invalid questionnaires) may they not contribute to clinical decision making.

Our study showed some limitations. We selected randomised controlled trials from 12 journals. This restrictive choice was led by the recognised quality of the four medical journals selected (leading journals that publish research reports in all fields and have a broad readership) and because the eight surgical journals comprised a good sample of surgery around the world. The purpose of this choice was to create a homogeneous group of publications and conditions that allowed standardised analysis. This arbitrary choice may have introduced a bias causing overestimation of the quality of the RCTs analysed. In addition, authors of original articles were not pursued for additional data or for clarification of points that were unclear about trial methodology.

We recognise also that our review is limited by its restriction to RCTs, but the checklist developed by Efficace et al.[11] was originally devised only for this type of design.

It could be interesting to develop an applicable and useful checklist for not randomised studies.

Despite these potential limitations, this paper suggests that surgeons are interested in HRQOL outcomes and that HRQOL assessment in RCT settings has the potential to provide invaluable data for developing new treatments in gastrointestinal surgery.

Conclusion

Despite the emphasis on quality of life outcomes, there are still deficiencies in the execution of these studies.

In attempt to improve in the future the use of QOL as an endpoint in RCTs, researchers should include prior statement of hypotheses, better reporting, improved compliance, detailed methods of analysis and reporting of missing data.

Such improvements will enhance the reliability of future HRQOL investigations with the ultimate aim of giving a comprehensive picture of a given treatment and also facilitate clinical decision-making

Appendix

The Appendix shows a list of 24 RCTs that were included in the present study:

1. Maartense S, Dunker MS, Slors JF, Cuesta MA, Pierik EG, Gouma DJ, Hommes DW, Sprangers MA, Bemelman WA. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. *Ann Surg* 2006;243:143–149; discussion 150–143.

2. Puzziferri N, Austrheim-Smith IT, Wolfe BM, Wilson SE, Nguyen NT. Three-year follow-up of a prospective randomized trial comparing laparoscopic versus open gastric bypass. *Ann Surg* 2006;243:181–188.

3. Tang CL, Jayne DG, Seow-Choen F, Ng YY, Eu KW, Mustapha N. A randomized controlled trial of 0.5% ferric hyaluronate gel (Intergel) in the prevention of adhesions following abdominal surgery. *Ann Surg* 2006;243:449–455.

4. Mui WL, Ng CS, Fung TM, Cheung FK, Wong CM, Ma TH, Bn MY, Ng EK. Prophylactic ilioinguinal neurectomy in open inguinal hernia repair: a double-blind randomized controlled trial. *Ann Surg* 2006;244:27–33.

5. Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006;244:34–41.

6. Draaisma WA, Buskens E, Bais JE, Simmermacher RK, Rijnhart-de Jong HG, Broeders IA, Gooszen HG. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic versus conventional Nissen fundoplication. *Br J Surg* 2006;93:690–697.

7. O'Dwyer PJ, Norrie J, Alani A, Walker A, Duffy F, Horgan P. Observation or operation for patients with an asymptomatic inguinal hernia: a randomized clinical trial. *Ann Surg* 2006;244:167–173.

8. Oelschlager BK, Pellegrini CA, Hunter J, Soper N, Brunt M, Sheppard B, Jobe B, Polissar N, Mitsumori L, Nelson J, Swanstrom L. Biologic prosthesis reduces recurrence after laparoscopic paraesophageal hernia repair: a multicenter, prospective, randomized trial. *Ann Surg* 2006;244:481–490.

9. Johansson M, Thune A, Nelvin L, Lundell L. Randomized clinical trial of day-care versus overnight-stay laparoscopic cholecystectomy. *Br J Surg* 2006;93:40–45.

10. King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, Kipling RM, Kennedy RH. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg* 2006;93:300–308.

11. Morino M, Pellegrino L, Giaccone C, Garrone C, Rebecchi F. Randomized clinical trial of robot-assisted versus laparoscopic Nissen fundoplication. *Br J Surg* 2006;93:553–558.

12. Mehta S, Hindmarsh A, Cheong E, Cockburn J, Saada J, Tighe R, Lewis MP, Rhodes M. Prospective randomized trial of laparoscopic gastrojejunostomy versus duodenal stenting for malignant gastric outflow obstruction. *Surg Endosc* 2006;20:239–242.

13. Langenbach MR, Schmidt J, Zirngibl H. Comparison of biomaterials: three meshes and TAPP for inguinal hernia. *Surg Endosc* 2006;20:1511–1517.

14. Freudenberg S, Sano D, Ouangre E, Weiss C, Wilhelm TJ. Commercial mesh versus Nylon mosquito net for hernia repair. A randomized double-blind study in Burkina Faso. *World J Surg* 2006;30:1784–1789; discussion 1790.

15. Woodcock SA, Watson DI, Lally C, Archer S, Bessell JR, Booth M, Cade R, Cullingford GL, Devitt PG, Fletcher DR, Hurley J, Jamieson GG, Kiroff G, Martin CJ, Martin IJ, Nathanson LK, Windsor JA. Quality of life following laparoscopic anterior 90 degrees versus Nissen fundoplication: results from a multicenter randomized trial. *World J Surg* 2006;30:1856–1863.

16. Fazio VW, Zutshi M, Remzi FH, Parc Y, Ruppert R, Furst A, Celebrezze J, Jr., Galanduik S, Orangio G, Hyman N, Bokey L, Tiret E, Kirchdorfer B, Medich D, Tietze M, Hull T, Hammel J. A randomized multicenter trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers. *Ann Surg* 2007;246:481–488; discussion 488–490.

17. Braga M, Frasson M, Vignali A, Zuliani W, Di Carlo V. Open right colectomy is still effective compared to laparoscopy: results of a randomized trial. *Ann Surg* 2007;246:1010–1014; discussion 1014–1015.

18. Han-Geurts IJ, Hop WC, Kok NF, Lim A, Brouwer KJ, Jeekel J. Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. *Br J Surg* 2007;94:555–561.

19. Janson M, Lindholm E, Anderberg B, Haglind E. Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer. *Surg Endosc* 2007;21:747–753.

20. Kostic S, Kjellin A, Ruth M, Lonroth H, Johnsson E, Andersson M, Lundell L. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. Results of a randomized controlled trial. *World J Surg* 2007;31:470–478.

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CASE REPORT

Common Bile Duct Injury following Laparoscopic Cholecystectomy in the Setting of Sinistroposition of the Galladder and Biliary Confluence: A Case Report

Tricia A. Moo-Young · Daniel D. Picus · Sherry Teefey · Steven M. Strasberg

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Abstract
Introduction A bile duct injury occurred to a 64-year-old female with highly aberrant bile ducts due to sinistroposition. Methods of potential injury avoidance are discussed.
Materials and Methods A patient underwent elective laparoscopic cholecystectomy for symptomatic cholelithiasis. A left-sided gallbladder was diagnosed intraoperatively. Three days later, the patient presented with jaundice and rising liver function tests. The patient was referred to our institution for suspected bile duct injury. Endoscopic retrograde cholangiopancreatography showed complete occlusion of the common bile duct. A percutaneous transhepatic tube was placed in the bile ducts for decompression. During later operative exploration, a left-sided common hepatic duct was discovered. Review of preoperative imaging confirmed that the right hepatic duct crossed superior to the umbilical portion of the left portal vein and that segment 4 ducts drained into the right anterior sectional bile duct.
Conclusion This case describes an extremely rare anomaly associated with an injury to the common bile duct during laparoscopic cholecystectomy. Knowledge of the complex and unusual alterations in biliary anatomy, which may accompany sinistroposition of the gallbladder, should aid in avoidance of such injuries in the future.

Keywords Sinistroposition · Gallbladder · Bile ducts · Bile duct injury

Case Report

A 64-year-old woman presented with typical biliary colic. Ultrasound demonstrated cholecystolithiasis with no evidence of cholecystitis or choledocholithiasis. Past medical history was notable for hypothyroidism, chronic obstructive lung disease, hypertension, and gastroesophageal reflux disease. Her only prior surgical procedure was cataract removal. She was seen in consultation and scheduled for laparoscopic cholecystectomy. The operative report noted that, after insufflation and insertion of the laparoscope, the gallbladder was located "to the left of the falciform." A cholangiogram was performed; it showed normal filling of the common bile duct and duodenum but the intrahepatic ducts were not opacified. The procedure was completed without recognition of a bile duct injury.

The patient was discharged on postoperative day 1. Two days later, she noted jaundice. A computed tomography scan (not shown) demonstrated dilated intra- and extrahepatic bile ducts extending to the level of metal clips. A hepatobiliary iminodiacetic acid scan showed no filling of the common bile duct at 60 min. Endoscopic retrograde cholangiopancreatography (ERCP) was attempted but the bile duct could not be cannulated. The patient was transferred to our hospital 6 days after cholecystectomy for further care.

On admission, the patient was stable and afebrile, but jaundiced. Abdominal examination was unremarkable. Hepatic function panel revealed total bilirubin 17.4 mg/dL, alkaline phosphatase 562 IU/L, serum aspartate transaminase 414 IU/L,

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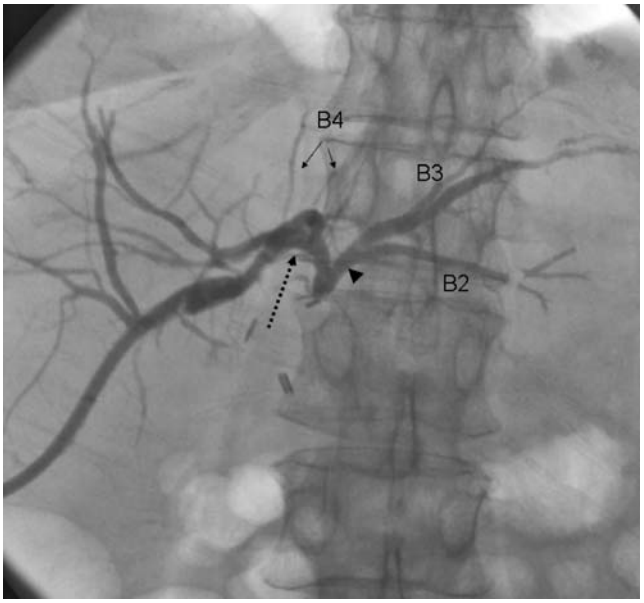

Figure 1 Preoperative percutaneous transhepatic cholangiogram (PTC). The PTC catheter is in a branch of the right posterior sectional bile duct. The confluence of the right sectional ducts to form the right hepatic duct is at edge of the vertebral body. Preoperatively, we believed that the duct indicated by the *arrowhead* was the left hepatic duct. Based on operative findings, we appreciated that there was no left hepatic duct and that that duct was actually the left lateral sectional duct (B2, B3). Note that the ducts from the left medial section (segment 4) enter the right ducts. Note also the bowing of the right hepatic duct as it curls around the upper border of the umbilical portion of the left portal vein (*large dashed arrow*). This was also not appreciated preoperatively.

alanine transaminase 575 IU/L, and albumin 3.1 g/dL. Blood cell counts were within normal limits. An ERCP performed on hospital day 2 demonstrated complete obstruction of the bile duct. A percutaneous cholangiogram performed through the right liver showed moderate to severe dilation of intrahepatic ducts with approximately 1 cm of common hepatic bile duct visible before abruptly tapering at the level of the metal clips (Fig. 1). Post-procedure the serum bilirubin and transaminase levels returned toward normal. An MRI showed resolution of intrahepatic biliary duct dilation and no evidence of vascular injury. Over the ensuing months, the patient required two biliary catheter exchanges but otherwise her clinical course was uneventful. The unusual positional anomalies to be described, which were present on the cholangiogram and MRI (see below), were not appreciated prior to bile duct reconstruction.

The bile duct repair was performed 5 months later. Upon opening the abdomen, there were dense adhesions between the viscera and the underside of the liver. The operative plan was to employ a standard Hepp–Couinaud[1] approach by taking down adhesions to segment 4, lowering the hilar plate, and exposing the left hepatic duct at the base of segment 4. The exact position of the gallbladder fossa was unclear because of the extensive chronic inflammation, but it was definitely not between segments 4 and 5, an area that was relatively free of adhesions. This was in keeping with the original surgeon's description of the position of the gallbladder to the left of the round ligament. With further dissection, surgical clips were located along a densely inflamed area adjacent the umbilical fissure, although it was unclear why there should be clips in this location, since it was not yet appreciated that this was the position of the common hepatic duct (CHD). The hilar plate was lowered as usual with the expectation of finding the left hepatic duct in its normal position (Fig. 2), but the left hepatic duct could not be seen nor could the stent be palpated at this site. Segment 4 seemed to be of normal size.

Intraoperative ultrasound was then used in an attempt to locate the bile ducts and a sonographer was called to the operating room to help with interpretation. Saline was flushed into the percutaneous transhepatic cholangiogram (PTC) catheter under pressure to distend the bile ducts and further facilitate identification. The only extrahepatic bile duct that could be detected on ultrasound was a short segment of duct located at the base of segment 3 to the left of the umbilical fissure near the aforementioned densely inflamed area containing clips. Flushing the PTC catheter with saline resulted in fluid emanating from this site. Under ultrasound guidance, a needle was advanced into that duct and the duct was opened by cutting down onto the needle. A catheter was inserted into the proximal bile ducts (Fig. 2). Note that it enters the liver to the left of the umbilical fissure at the base of segment 3. A sound could be passed to the left and right confirming that the short segment of common hepatic duct seen on the preoperative cholangiogram had been entered. As the sound was passed into the right hepatic duct, it was clear that the right duct passed superior to and around all the structures in the

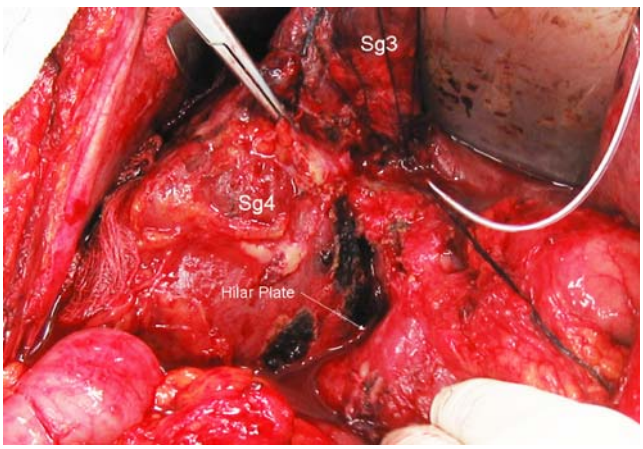

Figure 2 Operative photograph. Catheter has been advanced into stump of the common hepatic duct. Note that it is emanating from the liver between segments 3 and 4 to the left of the position of the umbilical portion of the left portal vein.

umbilical fissure. It was at this point that we first appreciated the unusual anomalies that were present. There was no left hepatic duct at the base of segment 4. In fact, there was no left hepatic duct. What had been taken to be the left hepatic duct on the preoperative cholangiogram was the left lateral sectional duct (B2, B3), which was located completely to the left of the umbilical fissure. The confluence of right hepatic duct and left lateral sectional duct was also in this location and the right hepatic duct had to pass superior to and around the structures in the umbilical fissure to get to the confluence with the left lateral sectional duct. In doing so, it was joined by ducts from segment 4. The cholangiogram and the MRI were reviewed and the unusual bowing of the right duct on the cholangiogram (Fig. 1) and the MRI (Fig. 3) was appreciated to be due to the duct passing around the umbilical portion of the left portal vein in the umbilical fissure. A schematic of the anatomical findings described above are shown in Fig. 4. An additional anomaly which was discovered on the MRI was that a branch off the right side of the umbilical portion of the left portal vein crossed the midplane of the liver to supply the right anterior section (not shown).

The common hepatic duct was opened longitudinally on its anterior surface and the incision was carried onto the right hepatic duct as far as possible, the limitation being that the right duct disappeared behind the structures in the umbilical fissure. The length of the opening was 1.5 cm. A Roux-en-Y hepaticojejunostomy was performed in a side-to-side manner as we have advocated.[2] Postoperatively, a cholangiogram was obtained (Fig. 5) and the PTC drain was removed. The patient is well 6 months later.

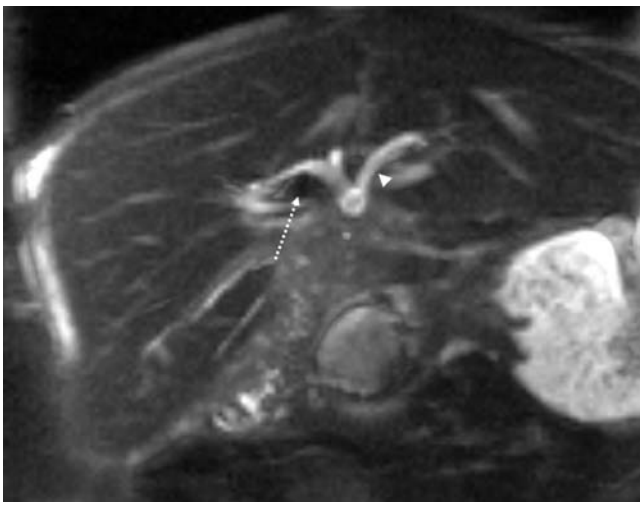

Figure 3 Coronal MRI section corresponding in position to the PTC. *Dashed arrow* points to the umbilical portion of the left portal vein and *arrowhead* to the left lateral sectional duct. Note again the bowing of the right hepatic duct as it curls around the vein. This was not appreciated before the reconstruction was performed.

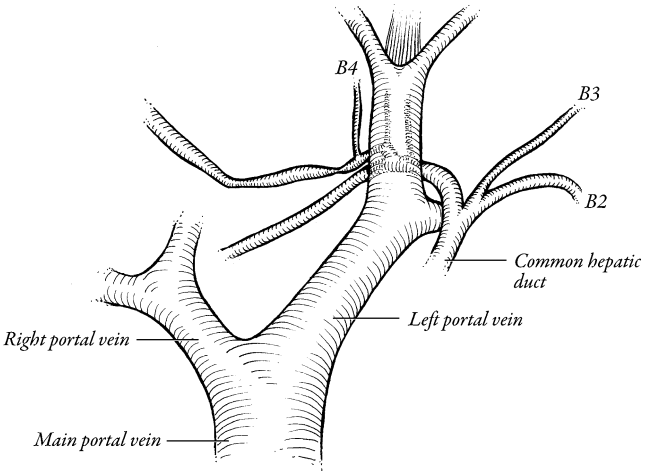

Figure 4 Schematic diagram corresponding to the anatomical features described in Figs. 1 and 2.

Discussion

Anomalies of the biliary tree are very common;[3–5] however, sinistroposition of the gallbladder is quite rare. Situs inversus totalis, i.e., when all abdomino-thoracic organs are transposed, has an incidence of one in 10,000. Left-sided gallbladder in a right-sided liver[6,7] is also quite rare but exact incidence is unclear. Rozoz et al. reported four cases in 2,500 patients having cholecystectomy.[8] Characteristically, in these patients segment 4 is underdeveloped[9] and portal vein abnormalities, such as those described in our patient, are frequently present.[10,11]

Two types of gallbladder malposition have been described: medioposition and transposition.[12] Medioposition is present when the gallbladder is shifted medially to the base of segment 4 but still is located to the right of the round ligament. In sinistroposition, the gallbladder is

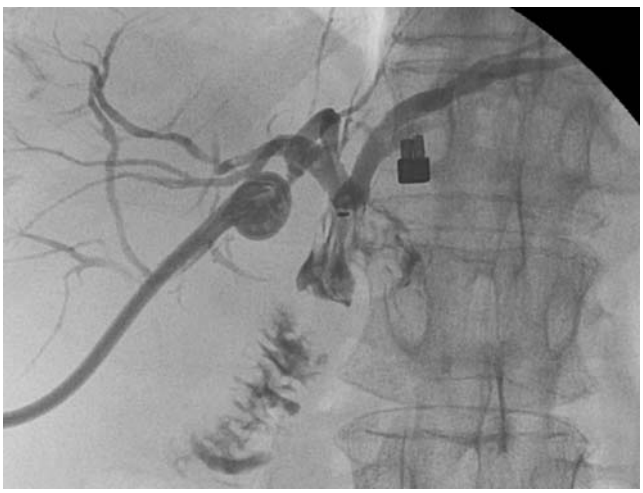

Figure 5 Postoperative cholangiogram prior to removing stent.

located to the left of the round ligament and either at the base of segment 3 or between segments 3 and 4. In our case, intraoperative dissection suggested that the gallbladder fossa had most likely been located along the umbilical fissure between segments III and IV, i.e., sinistroposition. Case reports describing a left-sided gallbladder date back more than 60 years.[13,14] To date, roughly 100 case reports have been made in the medical literature and in few instances has the left-sided gallbladder been diagnosed preoperatively.

Left-sided gallbladders are also associated with anomalies of the cystic duct and artery.[15–17] The cystic artery originates from the right hepatic artery, which lies to the right of the common hepatic duct. The cystic artery then *always* crosses from right to left *in front* of the CHD to insert on the gallbladder.[15] The cystic *duct* may enter the CHD either directly on its left side; however, more commonly, it curls around the CHD to join it on its right side. We are unable to describe the position of the cystic structures in our patient because the gallbladder was removed prior to coming to our institution and the intraoperative cholangiogram only shows the lower biliary tree.

While associated abnormalities of the portal vein, size of segment 4, and position of the cystic elements are well described, there are very few descriptions of associated bile duct abnormalities with left-sided gallbladders. Bender et al. described a case of duplication of the bile duct in association with left-sided gallbladder.[18] Regimbeau described a patient with a left-sided gallbladder and an underdeveloped segment 4 who suffered a biliary injury in the course of a left lateral sectionectomy for tumor.[9] Although cholangiograms were not provided, a line drawing suggests that the biliary abnormalities in their patient were very similar to those in ours. Therefore, we consider our case to be the second in the literature to describe a patient in whom the bile duct confluence was situated in the umbilical fissure to the left of the umbilical portion of the portal vein. The fact that both cases were associated with a biliary injury, ours with a laparoscopic cholecystectomy, speaks to the danger of this anomaly in patients having surgical procedures in this area. To identify the anomaly, we suggest that surgeons and radiologists look on cholangiograms for a confluence that is unusually far to the left over the spine, and for the unusual upward concavity of the right duct as it passes around the umbilical fissure. Surgeons should consider the possibility that the anomaly of the bile ducts is present whenever a left-sided gallbladder is encountered.

Several reports have stated that cholecystectomy in sinistroposition can be performed safely through a laparoscopic approach.[15,19–21] Yet, most of these studies were in patients with sinistroposition in the setting of situs inversus where there is transposition of the entire abdominal viscera. In reports in which patients have pure sinistroposition, the addition of a retracting port has been advocated with placement of the subxiphoid port to the left of the midline.[11] Others have described using the falciform lift maneuver to lift the liver and falciform ligament and allow better visualization of the critical structures.[22]

Based on the injury that occurred in this case and the report of Reginbeau et al.,[9] we believe that surgeons should be alerted to the dangers of sinistroposition especially in performing laparoscopic cholecystectomy. We estimate that if sinistroposition is very conservatively estimated at 1/10,000, between 70 and 100 cases will be seen in the USA annually during laparoscopic cholecystectomy. Our recommended approach in this anomaly depends on the type of sinistroposition. In the case of situs inversus totalis or when the whole liver is transposed, the hepatobiliary anatomy is mirror imaged but otherwise normal. In these types of sinistroposition, the umbilical fissure will be on the right side of the organ. A cautious laparoscopic approach is reasonable, of course taking into account other local conditions especially inflammation. In the type of sinistroposition illustrated by this case and that of Reginbeau et al., the anatomical variants are much more treacherous. As a result, biliary injury is much more likely to occur especially in the presence of even moderate inflammation. It would seem prudent to lean strongly to performing this surgery as an open procedure when the diagnosis is made preoperatively or converting to an open surgery early when the diagnosis is made intraoperatively. This is particularly important when anatomical uncertainty engendered by the anomalies or inflammation is encountered. Cholangiography may lead to the diagnosis of injury intraoperatively, as it might have in this case, but is probably less likely than usual to prevent injury. Finally, in encountering this type of sinistroposition, it would also be acceptable practice to insert a cholecystostomy tube and refer the patient to a tertiary hepatobiliary center for later cholecystectomy, especially in the face of moderate to severe inflammation.

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MULTIMEDIA ARTICLE

Completely Laparoscopic Subtotal Pancreatectomy with Splenic Artery Preservation

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Abstract
Introduction Laparoscopic distal pancreatectomy has emerged as an attractive minimally invasive alternative for selected patients. Although technically challenging, distal pancreatectomy with splenic artery preservation has consistently been correlated with reduced blood loss and perioperative morbidity in multiple studies. Herein presented is our technique for completely laparoscopic (non-hand-assisted) subtotal pancreatectomy with splenic artery preservation (LSP-SAP).
Methods An 87-year-old woman with an incidentally identified 3-cm cystic lesion in the pancreatic body–tail interface underwent EUS, which supported side-branch intraductal papillary mucinous neoplasm. The patient subsequently underwent laparoscopic resection. A completely laparoscopic procedure was performed using a four-trochar technique. The tail and body of the pancreas were dissected off of the retroperitoneum along the embryologic plane and separated from the colonic splenic flexure. Next, the splenic artery was dissected, isolated, and preserved, while the splenic vein was dissected off the ventral pancreas up to the level of the splenic–portal vein confluence. The technique employed a bipolar cutter-sealing device for dissection and hemostasis. Pancreatic parenchymal transection was performed with a standard vascular load endomechanical stapling device.
Results Total procedure time was 210 min, and the estimated blood loss was 200 mL. Postoperatively, the patient was admitted, advanced to regular diet the next day, and discharged home on postoperative day 3. The pathological review of the specimen revealed high-grade dysplasia with a non-invasive malignant component, classified as intraductal carcinoma. Foci of PanIN 1–3 were identified with no high grade dysplasia at the surgical margin. Five lymph nodes were included in the specimen and were negative for malignancy.
Conclusion Completely LSP-SAP can be safely performed in selected patients. This procedure may be an optimal alternative to open surgery.

Keywords Laparoscopy · Pancreatectomy · Splenic artery preservation · Outcome

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Introduction

The scope of pancreatic surgery has recently been expanded by the addition of laparoscopic surgical techniques.[1] Traditional benefits of the laparoscopic approach include decreased blood loss and postoperative pain and early recovery. These observations are also applicable to pancreatic operations; however, the oncological outcomes and credentialing for this approach remain controversial. Herein reported is our technique for completely laparoscopic subtotal pancreatectomy with splenic artery preservation (LSP-SAP).

Methods

The attached media file was developed at Roger Williams Medical Center by the Division of Hepatobiliary and Surgical Oncology. The movie represents a case of completely LSP-SAP. This procedure was performed by a team of formally trained surgical oncologists with advanced laparoscopic hepatopancreatobiliary surgical experience. Patient consent was obtained for recording and using this material for educational purposes.

The patient is an 87-year-old Caucasian woman who presented after a follow-up CT scan for a stable thoracic aneurysm measuring 3.6 cm and the incidental discovery of a cystic pancreatic lesion measuring 3 cm at the level of the pancreatic body–tail interface. These findings prompted an endoscopic ultrasound examination (EUS), which supported the diagnosis of side-branch intraductal papillary mucinous neoplasm. EUS-guided cyst aspiration revealed 15 cc of mucinous material with a CA 19-9 level of 7,065.7 U/mL and carcinoembryonic antigen level of 313 U/mL. Pathological examination of the cyst content further suggested a mucinous pancreatic lesion. A laparoscopic approach for subtotal pancreatectomy was offered to the patient.

The patient was positioned in supine position on a bean bag with arms tucked to the sides. Four 5-mm trocars were placed as shown on the media file. The infra-umbilical port was used for camera device and was extended for specimen retrieval at the end of the procedure, the epigastric port was used for stomach retraction, and the two upper quadrant ports were used as working ports. With the stomach retracted, the lesser sac was entered by dividing the gastrocolic ligament using a bipolar cutter-sealing device. The dissection was continued toward the spleen with preservation of the short gastric vessels. The tail and body of the pancreas were dissected off of the retroperitoneum along the embryologic plane and separated from the colonic splenic flexure. Next, the splenic artery, now exposed in the lesser sac, was dissected from the pancreas using a combination of blunt dissection and bipolar energy dissection. Once a segment of the artery was freed, it was elevated and held to facilitate further dissection. The pancreas was held up using a standard suction cannula, and a tunnel was bluntly created between the pancreas and splenic vein separate from the splenic artery. Next, further dissection of the splenic artery was carried distally toward the splenic hilum. After this was completed, a second plane of dissection between the pancreas and the splenic vein was developed using a combination of blunt dissection and bipolar energy dissection. The dissection was pursued distally, freeing the pancreatic tail from the splenic hilum. At the level of the splenic hilum, the pancreatic tail was now completely freed form the splenic vessels and was transected using a standard vascular load endomechanical stapling device. The stapling device was introduced through the infra-umbilical port, which was converted to a 12-mm trocar for this purpose. The camera position was changed to the right or left upper quadrant trocar site(s) as appropriate, while the stapler was used.

The pancreas was then retracted medially. Using intra-operative ultrasound, the location of the pancreatic lesion was confirmed; in order to achieve an adequate tumor margin from the resection, further medial dissection beyond the splenic–portal vein confluence was necessary. Once this was completed, the pancreas was divided using a standard vascular load endomechanical stapling device. The specimen was placed in an endo-bag and extracted through an extended (about 4 cm total length) umbilical port site. A JP drain was placed through the left upper quadrant port site to drain the pancreatic bed. Total procedure time was 210 min, and the estimated blood loss was 200 mL.

The patient was extubated on the table and admitted to the surgical floor. Oral diet was allowed on the first postoperative day. Our postoperative protocol after pancreatic resection consists of blood glucose monitoring every 4 h and covering hyperglycemia with insulin sliding scale as needed. For the case reported herein, the patient developed transient hyperglycemia in the immediate post-operative period with blood sugar ranging between 150 and 200 mg/dL while receiving intravenous fluid containing dextrose 5%. Postoperative hyperglycemia resolved over the course of admission with normoglycemia on a regular diet. The patient did not develop any symptoms of indigestion or steatorrhea after the procedure. We do not routinely check stool content in patients if they remain asymptomatic. The patient is followed on our surgical clinic, and on her 3-month postoperative follow-up, the patient reported complete return to her daily activity. Additionally, her weight and blood sugar are within normal limits. As others, we believe that pancreatic insufficiency after partial pancreatic resection is multifactorial and is an underinvestigated topic; further discussion is beyond the scope of this media file manuscript.

The patient was discharged home on the third postoperative day after JP drain removal. The drain output was about 50 mL/24 h; amylase level of the output was measured and was found to be within serum value prior to removal. Our protocol is to measure the amylase content of the drain output before its removal. Although pancreatic duct leak can still occur at a later period, in our experience, a late onset leak is usually associated with a proximal pancreatic duct flow issue (i.e., mild to moderate stricture at the genu, more commonly seen in pancreatitis). Furthermore, delayed onset fistulae are frequently not adequately drained by intraoperatively placed drains and have generally required a well-localized interventional radiology placed drainage catheter.

The pathological review of the specimen revealed high-grade dysplasia with a non-invasive malignant component classified as intraductal carcinoma. Foci of PanIN 1–3 were identified with no high-grade dysplasia at the surgical margin. Five lymph nodes were included in the specimen, and they were negative for malignancy.

Discussion

Although elective distal pancreatectomy in high volume center is associated with a mortality rate of <1%[2], older patients are more likely than younger to require an ICU stay, suffer a cardiac complication, and experience compromised nutritional and functional status after major pancreatic resection.[3]

Multiple studies comparing the laparoscopic and open approach for distal pancreatectomy report decreased blood loss, morbidity, and hospital stay for patients treated laparoscopically.[4] Although no studies have investigated the role of laparoscopic distal pancreatectomy (LDP) in elderly patients, the beneficial effects inherent to the minimally invasive approach may be of special interest in this population.

Prior studies of LDP report a fistula rate of 0–17%, splenic preservation ranging from 50 to 80%, and mean length of stay of 5–7 days.[5–9] The attached media file illustrates the technique employed for LDP.

Besides the universal limitations of the laparoscopic approach, including anatomic limitations precluding appropriate visualization and physiological limitations mainly due to poor cardiorespiratory status, the authors would like to emphasize a specific limitation for this technique: occlusion or invasion of the splenic vessels by a pancreatic tumor or distortion of the normal anatomic course of the splenic vessels prohibiting safe dissection. This finding should, in our opinion, be a contraindication for the preservation of the splenic vessels. On the other hand, age alone should not, in our opinion, be considered contraindication if the patient's general condition allows such a procedure. In our opinion, the minimally invasive approach with a potential earlier return to activity may be of benefit for elderly patients requiring this procedure.

Several studies have reported that splenic preservation, when possible, carries multiple benefits apart from preventing postsplenectomy sepsis. Govil et al.[10] reported, in a series of patients with chronic pancreatitis, that the incidence of diabetes mellitus was less after spleen-preserving distal pancreatectomy than after en bloc distal pancreatectomy. Similarly, Hutchins et al.,[11] in a series of chronic pancreatitis patients, reported that splenic conservation was associated with a reduced incidence of postoperative diabetes. In a series of patients with pancreatic adenocarcinoma, Schwarz et al.[12] reported that splenectomy had a negative influence on long-term survival independent of disease-related factors and suggested that, unless required because of tumor proximity or invasion, splenectomy should be avoided in the operative treatment of exocrine pancreatic cancer at any location.

A laparoscopic modification to the Warshaw technique for spleen-preserving distal pancreatectomy with division of the splenic vessels was previously described.[13] Unlike the Warshaw procedure, where splenic blood supply is maintained by the short gastric vessels that are left intact during the dissection, our approach preserves both splenic and short gastric vessels to avoid the risk of postoperative splenic infarct or abscess as reported following the Warshaw procedure, specially in the case of an enlarged spleen when the preserved short gastric vessels are insufficient.[9,14] On the other hand, in the setting of preoperative splenic vein thrombosis or arterial occlusion, the Warshaw technique can be applied if splenic preservation is deemed necessary.

The authors would like to emphasize the crucial role of the state of art, high-definition laparoscopic video technology, which provides sharp and magnified visualization compared to open techniques, as well as the new generation of energy sealing devices, used in this case to attain minimally invasive hemostasis. It is clear that advances in minimally invasive surgery are dependent on advances in surgical technology, providing us the tools necessary for complex laparoscopic procedures.

This technique consists of a completely laparoscopic approach to minimize surgical stress, splenic vein, and artery preservation to minimize blood loss and postoperative pain, direct admission to the floor to minimize ICU utilization, and finally, early feeding and ambulation to minimize the hospital stay.

While minimally invasive surgery may be appealing for younger aged patients for aesthetics and potential earlier return to work, its role in elderly patients may have clinical importance. The value of early mobilization for elderly patients cannot be overemphasized. After a laparoscopic procedure, the lessened potential for postoperative pain compared to a traditional open procedure is crucial. At the same time, avoiding larger abdominal incisions in older patients should correlate with lessened wound complications, i.e., wound dehiscence and incisional hernias, which, in this group of patients, are know to have higher than average rates of compromised nutritional status and lessened physiological reserve for wound healing.

Conclusion

LSP-SAP can be performed safely in centers with both laparoscopic and hepatopancreatobiliary expertise. The

potential benefit of the minimally invasive approach especially in elderly patients should be further defined.

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HOW I DO IT

Repair of Abdominal Wall Hernias with Restoration of Abdominal Wall Function

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Our operative approach to the repair of abdominal wall hernias has changed tremendously over the last two decades based on our ongoing insight into the etiopathogenesis of their development. For instance, 20 years ago, use of alloplastic prosthetic material in the repair of direct inguinal hernias was rare, but currently, the accepted standard of care involves routine use of prosthetic material to "repair" the defective inguinal floor.

Repair of incisional hernias of the anterior abdominal wall is undergoing a similar transition with our appreciation of recurrence rates of >50% in long-term follow-up studies of autogenous tissue repairs.[1–4] Moreover, research into the inherent metabolic abnormalities in wound healing in the majority of patients developing incisional hernias in the absence of technical errors or tissue loss had led to evidence-based support for the use of prosthetic material in the repair of incisional hernias.[5–6] Indeed, most herniologists today believe that prosthetic material to repair or reinforce the repair of incisional hernias is imperative in these patients to assure the best results. In addition, interest in the biomechanics of the abdominal wall and its musculature has altered the operative approaches as well. For instance, the technique of components separation offers restoration of medialization of the rectus muscles, *but* this repair is an autologous repair despite the concept of it being a "tension-free" repair.

With these considerations in mind, this technique-based manuscript will describe the open and laparoscopic techniques we utilize for repair of incisional hernia. While we have our own parochial beliefs, we believe strongly that the literature supports the concepts of (1) a sublay repair (versus an onlay or inlay repair), (2) wide lateral overlap of prosthesis to maximize surface ingrowth and/or sublay support, and (3) restoration of reapproximation of the rectus musculature whenever possible. With these approaches and employing the above concepts, recurrence rates should be about 5%.[7]

Preoperative Evaluation

Determination of the width and rostral/caudal extent of the hernia defect is important as well as determining other associated defects (Swiss cheese defects) or lateral defects where, for instance, a stoma had been located. Abdominal computed tomography, although not imperative, may help in recognizing associated defects and in delineating the status of the remnant abdominal wall musculature.

Two other concerns require discussion. First, can/should the operation be performed laparoscopically or via an open approach? Factors supporting a laparoscopic approach include smaller defects, lack of severe adhesions, a history of previous prosthetic infection, and lack of need for restoration of muscular reapproximation (e.g., the elderly patient). Factors supporting an open approach include known severe adhesions, defects extending up to the bony

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confines of the abdomen (pubis, costal margin), and the need for complete restoration of muscular reapproximation because of the occupation of the patient (e.g., younger patients and laborers). Second is the presence of obesity. With a BMI>35 kg/m^2 (or even >30), the primary discussion with the patient should not be directed at the hernia but rather at their obesity; strong consideration should be given to obligating substantive weight loss or an initial bariatric operation *before* any definitive operative repair of the abdominal wall hernia.

Open Ventral Hernia Repair

Concepts of Repair

Our approach involves a modification of the original, prosthetic-based, Rives-Stoppa repair. The guiding principles involve a repair that is (a) largely extraperitoneal, (b) a sublay with wide 5- to 10-cm overlap of the prosthesis laterally, and, whenever possible, with intramural placement of the prosthetic material posterior to the rectus muscles and anterior to the posterior rectus fascia, (c) use of a meshed, alloplastic prosthetic to allow tissue transgrowth as the form of permanent fixation, (d) coverage of the anterior surface of the prosthetic material with autogenous, musculofascial tissues which restores muscular reapproximation, and (e) fixation transabdominally to a solid anterior fascia rather than limited fixation using a short tacker.

Creation of Retrorectus Plane

An incision is made directly over the defect usually excising the previous incision (Fig. 1a, b). Skin and subcutaneous scar should be excised back to healthy tissue

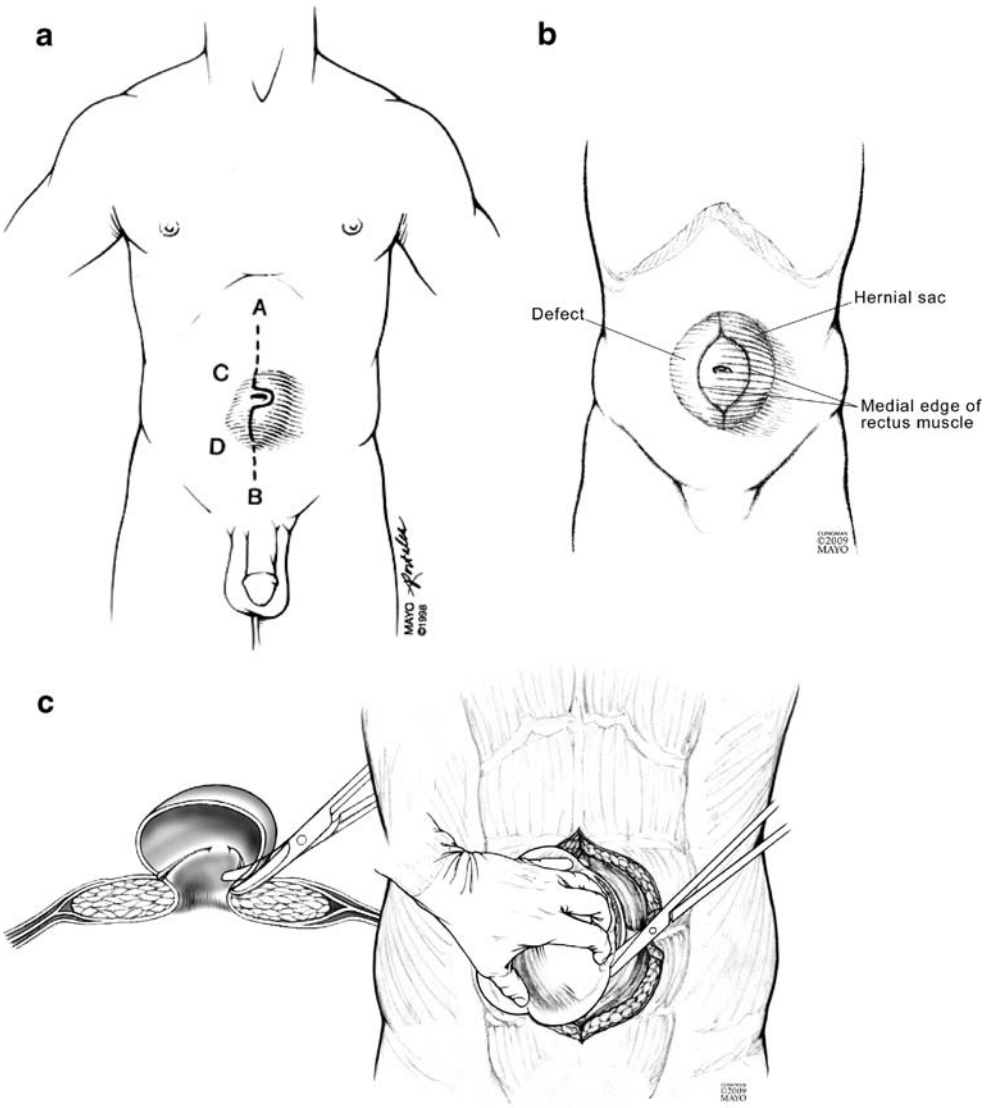

Figure 1 The incision **a** usually lies directly over the defect excising the previous scar. **b**, **c** The sac is dissected from the subcutaneous tissue back to the fascial edge of the defect. Copyrighted and reproduced with permission of Mayo Foundation for Medical Education and Research.

whenever possible. The length of the incision should be long enough to develop the appropriate planes and take down any adhesions safely but most often does not require reopening of the entire incision. The initial maneuver involves freeing the hernia sac entirely both laterally and rostrocaudally down to the edges of the fascial defect (Fig. 1c). *But* this peritoneal sac is *not* excised but rather is bunched up, if necessary, and is positioned posterior to the prosthetic material to serve as autogenous tissue between the intraperitoneal viscera and the prosthetic material in an attempt to prevent complications related to adherence of intraperitoneal viscera to the prosthesis (adhesions, fistulas) (Fig. 2a).

Next, an anterior fasciotomy is made at the medial-most edge of the anterior rectus fascia (Fig. 2a), the rectus muscle is identified, and a plane is developed posterior to the muscle (Fig. 2b) but anterior to the posterior rectus fascia (rostral to the semicircular line) and anterior to the peritoneum (caudal to the semicircular line) in the preperitoneal plane (Fig. 2c). This essentially avascular plane is freed up bluntly, being careful to preserve the superior epigastric vessels rostrally and the inferior epigastric vessels caudally. The plane is developed to the lateral extent of the rectus muscles, often up to and over the costal margin rostrally (the rectus muscles do not insert on the costal margin but rather about 5 cm rostral to the costal margin; Fig. 3a) and down to the pubis and Coopers ligament (if necessary) caudally. This plane should be developed 5–10 cm beyond the edges of the fascial defect for eventual placement of the prosthesis (Fig. 3b) at the same time being careful to look for smaller "Swiss cheese" defects in any other part of the fascia that was incised previously and also to look for an associated umbilical hernia. Be careful to look for a potential knuckle of bowel that may potentially herniate through *only* the posterior rectus fascia at the site of any prior transrectus stoma (e.g., ileostomy, colostomy).

Xiphoid Many/most upper midline hernias extend up to or near the xiphoid. It is important to develop the plane rostral and posterior to the xiphoid. This maneuver requires dissection anterior to the triangular fat pad (which can be excised) but posterior to the xiphoid/lower sternum (Fig. 4a). And, when placing the prosthesis, it will be necessary to disconnect the insertion of the posterior rectus fascia rostrally near the xiphoid to allow a smooth transition

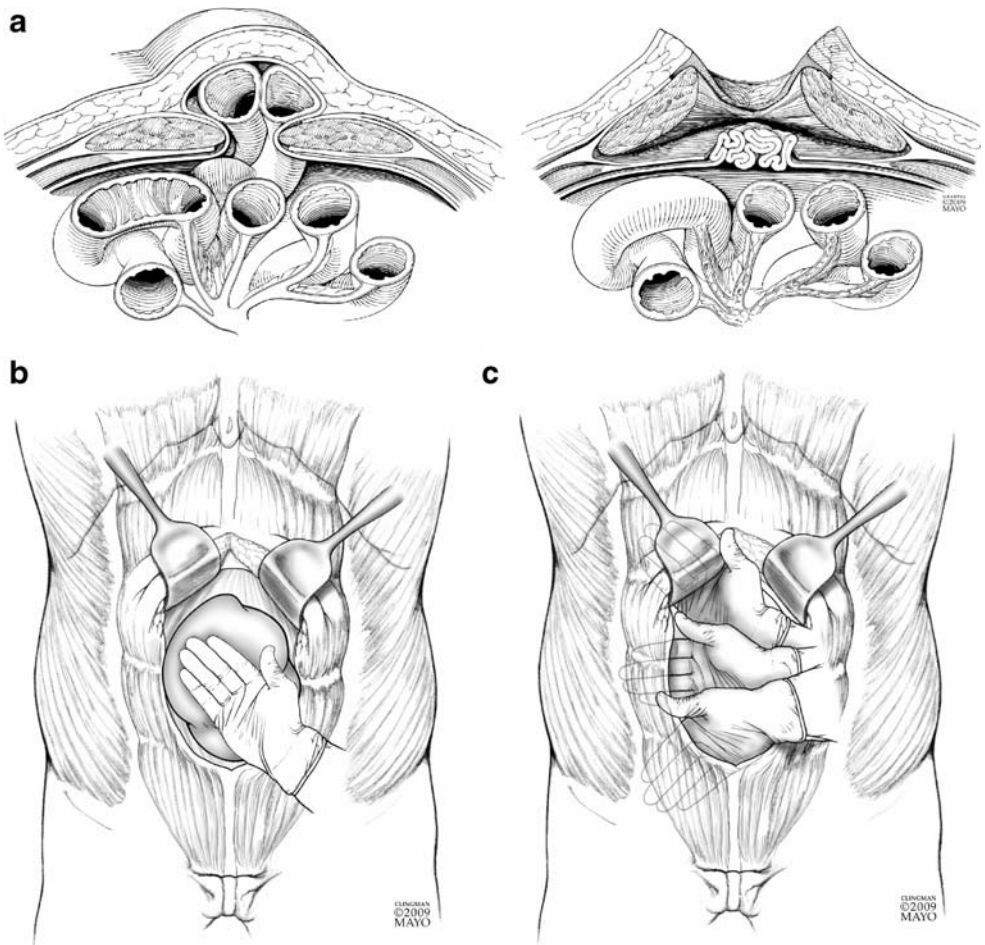

Figure 2 Development of retrorectus plan. **a** Transverse depiction of retrorectus plane; **b** preserving the hernia sac, the retrorectus plane is developed bluntly; **c** note the extent of rectorectus plane to 5–7 cm lateral, rostral, and caudal to the fascial defect. Copyrighted and reproduced with permission of Mayo Foundation for Medical Education and Research.

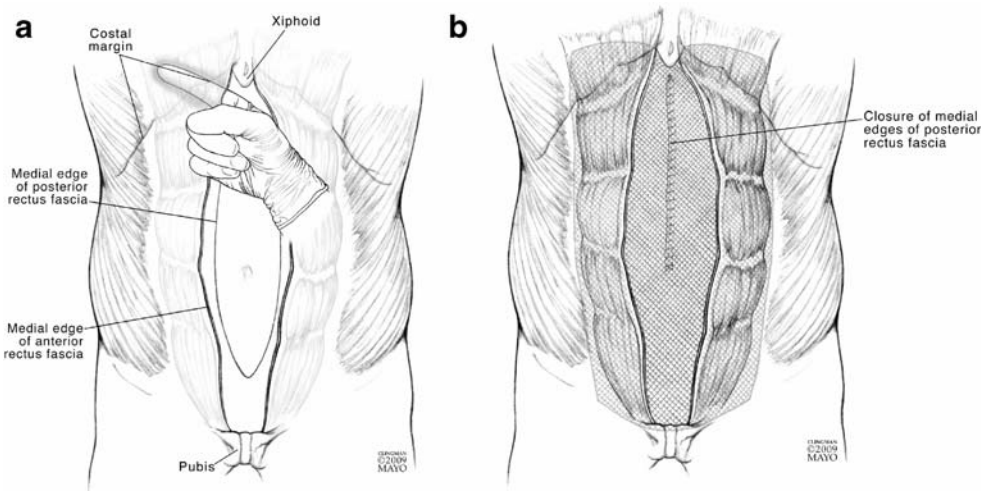

Figure 3 Placement of prosthesis. **a** Note rostral extent of retrorectus space anterior and rostral to costal margin; **b** the posterior rectus fascia is approximated posterior to the prosthesis; caudally, the posterior rectus sheath ends at the semicircular line. Copyrighted and reproduced with permission of Mayo Foundation for Medical Education and Research.

of the prosthesis from behind the xiphoid and into the retrorectus plane laterally (Fig. 4b). A similar disconnection is necessary caudal to the extent of the defect to allow the rectorectus planes bilaterally to communicate posterior to the otherwise intact lower midline fascia. At this point, prior to placing the prosthesis, the surgeon should try to reapproximate the medial edges of the posterior rectus fascia if at all possible (Fig. 3b). This maneuver will not only add another barrier of autogenous tissue between the intraperitoneal viscera and the prosthesis but will also help to reapproximate the rectus muscle in the midline.

Insertion/Fixation of Prosthesis

A large sheet of prosthesis is then positioned in this rectorectus plane. We prefer to use the large-pore, low-weight polypropylene mesh prosthesis (e.g., Ultrapro, Ethicon, Inc., Somerville, NJ, USA), but we will also use Prolene® mesh (Ethicon, Inc.) or Parietex Tet (Covidien). We usually do not use expanded polytetrafluorethylene (ePTFE) or some of the mesh prostheses with the one-sided non-adhesive barriers because we want to promote tissue transgrowth both anteriorly and posteriorly.

Fixation of the prosthesis to the anterior fascia is performed by making a small stab wound in the anterior abdominal wall like the numbers of a clock at the lateral-most extent of the retrorectus plane (Fig. 5a). We use the more blunt-tipped laparoscopic suture passer (Endoclose, Covidien, Norwalk, CT, USA) that facilitates this maneuver markedly. The suture is passed through the anterior rectus fascia and full thickness of the rectus muscle at its lateral extent, through the prosthetic mesh, and then back out through the muscle and fascia. We use an absorbable #1 polydioxanone for the initial fixation; we are consciously

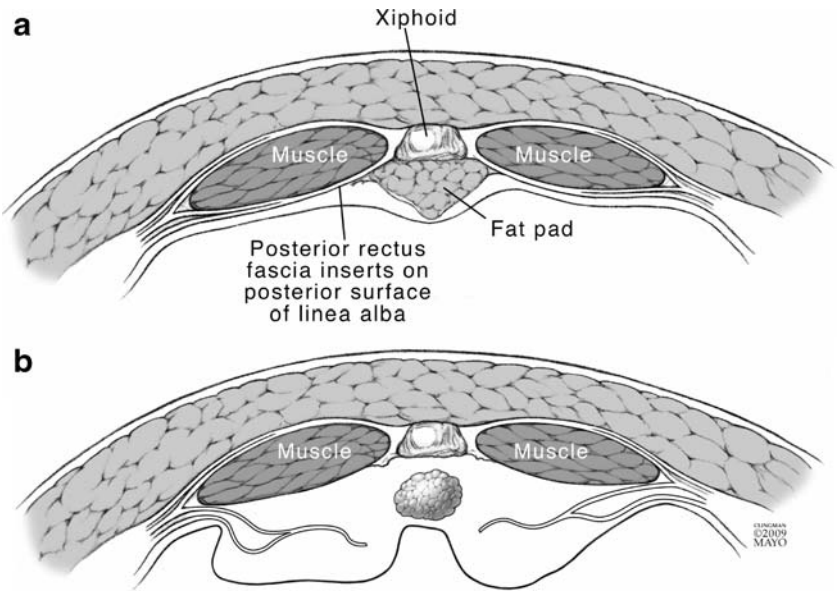

Figure 4 (**a**) Rostral dissection; when the fascial defect extends near the xiphoid, the retrorectus plane should extend rostral and posterior to the xiphoid. This dissection requires mobilization of the retrorectus fat pad and transection of the insertion of the posterior rectus fascia from its anterior insertion medially (**b**). Copyrighted and reproduced with permission of Mayo Foundation for Medical Education and Research.

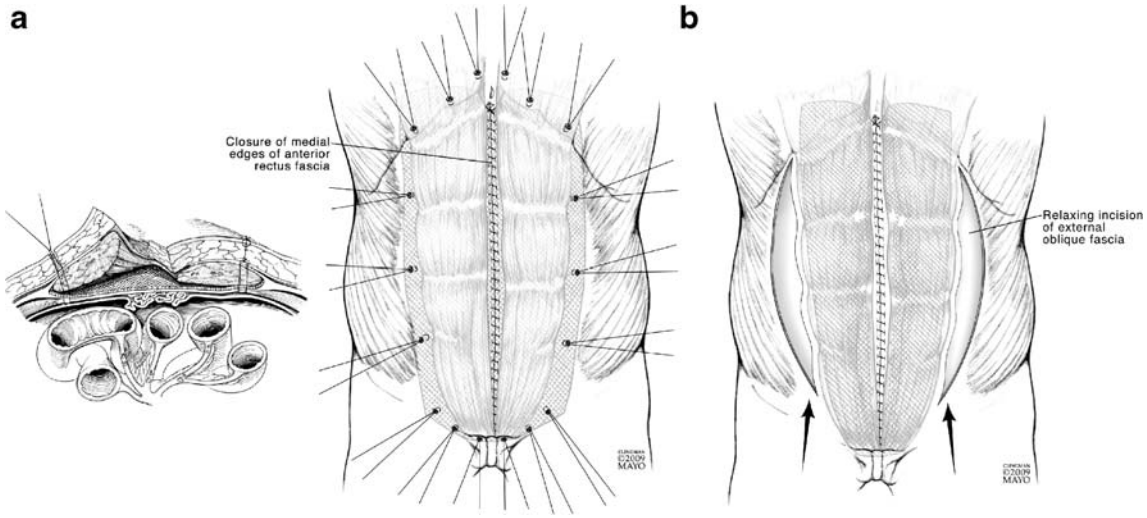

Figure 5 Fixation of prosthesis. **a** Lateral, rostral, and caudal fixation at the edges of the prosthesis; note closure of the anterior rectus fascia medially. **b** Use of a lateral relaxing incision through external oblique aponeurosis (components separation) if necessary to approximate the medial edges of the anterior rectus fascia. Copyrighted and reproduced with permission of Mayo Foundation for Medical Education and Research.

relying on future tissue transgrowth to anchor the meshed prosthesis in place permanently. Rostrally, we place two #1 polypropylene sutures either through the sternum when possible or on either side of the sternum rostral to the xiphoid; these sutures are attached to the prosthesis behind the xiphoid and lower sternum to assure a solid fixation and then passed back anteriorly through the same stab wound. Caudally, if the hernia defect extends to ≤5 cm from the pubis, we sew the prosthesis in three or more places to the pubis; this maneuver requires mobilizing the peritoneal sac off the posterior aspect of the pubis and exposing Cooper's ligament bilaterally (Fig. 6). We also sew the prosthesis to the medial aspect of Cooper's ligament using at least three individual polypropylene sutures; the needle is forced through the bony part of these structures and not just the periosteum. This maneuver requires a heavy needle and a bit of force; we have had no success with use of the laparoscopic tacker for a secure bony fixation. On occasion, fixation laterally in the lower abdominal wall is less reliable, and on occasion, we will also fix the prosthesis to the bony aspect of the anterior superior iliac spine if deemed necessary; a drill may be required for this fixation. Again, the fixation is not solely to the periosteum but rather a more solid fixation to the bone itself. Similarly, in the rostral aspect, the prosthesis can be sewn directly to the costal margin (in addition to extending the prosthesis rostrally over the costal margin). We keep the prosthesis unfolded but do not pull it tight because we fully expect some shrinkage of the surface area of the prosthetic material.

After irrigating the prosthesis with a topical antibiotic (in which the prosthesis was soaked during mobilization of the rectorectus plane), we usually place two closed-suction drains on top of the prosthesis which exit the abdominal wall rostrally (not in the groin where the skin may have more bacteria); these drains are removed usually the first or second postoperative day (for fear of a hospital-acquired bacterial infection). Then, every attempt is made to reapproximate the anterior rectus fascia in the midline (Fig. 5a) for two reasons: first, this maneuver brings another layer of autogenous tissue between the prosthesis and the bacteria-laden skin, and second, this reapproximation of the rectus muscles medially restores the biomechanics of the abdominal wall.

Special Situations

Prior Incision Extending Up to Xiphoid or Down to Pubis In these situations, it will be more difficult to develop the retrorectus plane; also, to allow the prosthesis to cross the midline will require transecting the attachment of the posterior rectus fascia to the resutured midline fascial closure.

Loss of Abdominal Musculature When parts of the rectus muscle have been lost and the retrorectus space is not wide enough, this space can be extended lateral to the lateral border of the rectus muscle by transecting the fascia lateral to the rectus muscle and remaining anterior to the internal oblique muscle but posterior to the external oblique muscle/fascia. This space can be mobilized out to the posterior axillary line if necessary with fixation of the prosthesis to the anterior fascia of the back musculature.

Large, but Not Huge Fascial Defects When reapproximation of the midline fascial edges is not possible without addition of a components separation, strong consideration

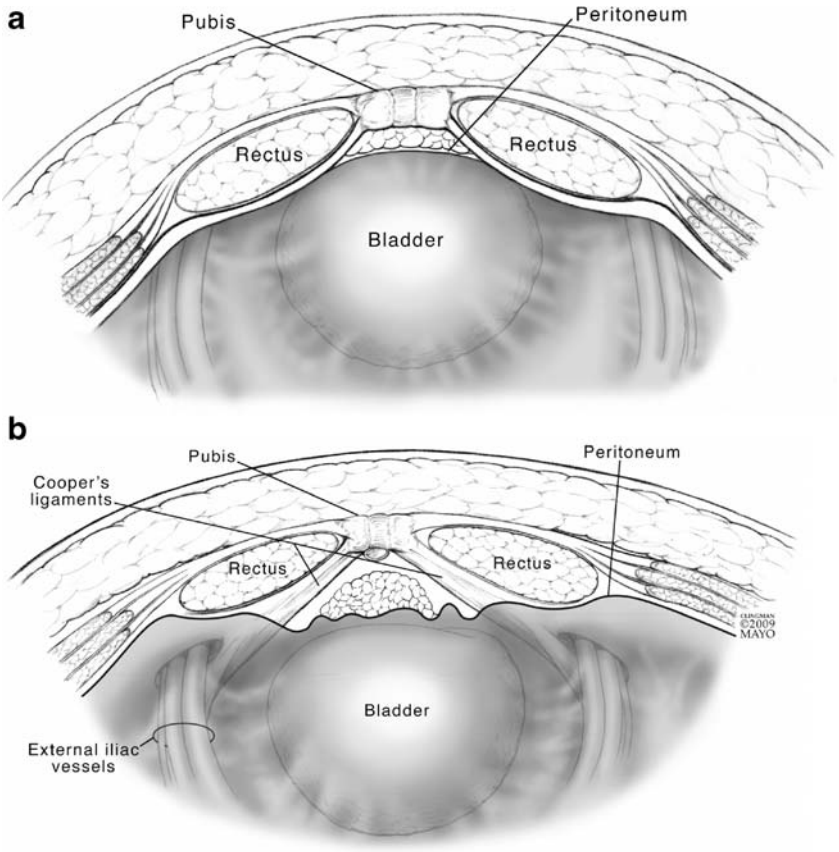

Figure 6 Caudal dissection. When necessary, the peritoneum and/or hernia sac is dissected from the posterior surface of the pubis to expose the pubis and Cooper's ligaments bilaterally. Note absence of the posterior rectus fascia caudal to semicircular line. Copyrighted and reproduced with permission of Mayo Foundation for Medical Education and Research.

should be given to performing this type of lateral fascia release (Fig. 5b), *provided the medial advance obtained will allow reapproximation of the fascia* (see below—minimal access approach). This medialization of the rectus muscles will not only help to restore the biomechanics of the abdominal wall but will also prevent a large surface area of prosthesis from being exposed in the subcutaneous space. Covering the mesh with another layer of autogenous tissue should decrease seromas and the possibility of infection of the prosthesis.

Huge Fascial Defect When the fascial defect is too large to allow midline fascial reapproximation, we do not use the rectorectus repair but rather proceed to a wide, intraperitoneal sublay repair. In this situation, we enter the peritoneum directly and do not mobilize the hernia sac laterally for several reasons; the lateral freeing up of the hernia sac will create a large subcutaneous dead space, the hernia sac will be devascularized, and the prosthesis will still be placed posterior to this sac.

When placing the prosthesis intraperitoneally, there are two choices of fixation. One is to place the prosthetic fully intraperitoneal and use a similar technique of transabdominal suture fixation using the laparoscopic suture passer. Unlike in the retrorectus space, all the lateral edges of the intraperitoneal prosthesis need to be fixed to the peritoneum so that no bowel can become entrapped between fixation sutures. We tend to place many more fixation sutures than the usual four fixation sutures used for a primary laparoscopic repair; we place these fixation sutures every 3 cm or so, and before tying down the rostral fixation sutures, we obliterate the spaces between these lateral and caudal areas of suture fixation using a laparoscopic tacker (Stryker, Kalamazoo, MI, USA) passed behind the prosthesis and fired totally under vision at the lateral extents of the prosthetic material. Although the risk of bowel entrapment rostrally is less, we still use the laparoscopic tacker rostrally but tend to place the tacks anterior to the prosthesis. For intraperitoneal repairs, two of the authors (JF and MGS) prefer a composite prosthesis with ePTFE facing the bowel and polypropylene anteriorly (Bard Composix, E/X mesh, Davol, Cranston, RI, USA). Our reasoning for choosing this prosthesis is that ePTFE has *no* ingrowth, while the other prosthetics bonded with an absorbable adhesion barrier always have the risk of visceral adherence. In contrast, the other author (MJR) prefers the Parietex™ composite graft (Covidien).

The second option of fixation is to develop the retrorectus space from a posterior approach by incising the medial edge of the posterior rectus fascia bilaterally. The prosthesis that will be placed intramurally can be a mesh (without a non-adhesive barrier) which should lead to

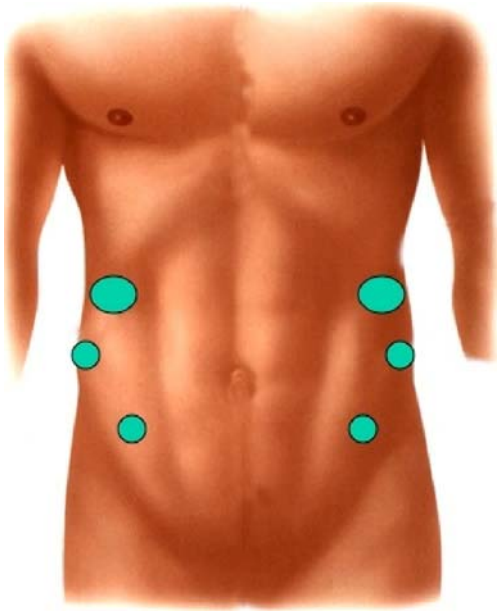

Figure 7 Trocar location for bilateral endoscopic component separation.

a more stable fixation with a lesser risk of seroma. After lateral fixation, the medial edge of the posterior rectus fascia can then be sewn to the posterior aspect of the prosthesis. We tend to use this more extensive approach for younger patients who are laborers.

The abdominal wall is then closed over two to three suction drains by approximating first the hernia sac over the prosthesis, then the subcutaneous tissue whenever possible, and then the skin. The drains are left in for only 1 or 2 days, but quite frankly, we have no idea how long they should be left in place; again, the worry is infection.

Laparoscopic Approach to Ventral Hernia Repair

After being first described in 1993, laparoscopic ventral hernia repair was accepted rapidly as an approach to ventral hernia repair.[8] The laparoscopic repair provides the advantage of placing a large prosthetic as a sublay in the intraperitoneal position. The major advantage of the laparoscopic approach is that it avoids the need for an anterior incision and the requisite extensive subcutaneous soft-tissue dissection, thereby bringing a predictably lesser rate of wound complications and mesh infections compared to open approaches.[9] The classic laparoscopic approach of bridging the defect from behind with the prosthesis prevents bowel herniation but does not reconstruct a functional, dynamic abdominal wall. The prosthesis in essence patches the hernia defect from behind. In an active, thin patient, some form of a bulge or paradoxic motion will remain and may result in patient dissatisfaction with the repair. In our practice, we reserve this approach typically for patients who are obese or are elderly and less active; the slight bulge is often imperceptible, and the risk of wound complications outweighs those issues.

Laparoscopic Ventral Herniorrhaphy with Abdominal Wall Reconstruction An entirely minimally invasive hernia repair but combined with abdominal wall reconstruction is suited particularly well for those patients with either an active lifestyle or a physically demanding profession and for thin active patients who would otherwise note a bulge (and be unhappy) after a standard laparoscopic ventral hernia repair with a prosthesis which bridges the defect. Appropriate patient selection is crucial; defects of >8–12 cm or lateral abdominal walls with repeated scarring from multiple prior stomas, drains, or infection may not be able to be reapproximated in the midline, and adding a minimally invasive component separation will not be advantageous and may lead ultimately to less abdominal wall stability.

In 1990, Ramirez et al.[10] described techniques of components separation designed to provide a tension-free, musculofascial advancement. This technique has undergone several technical modifications but essentially involves

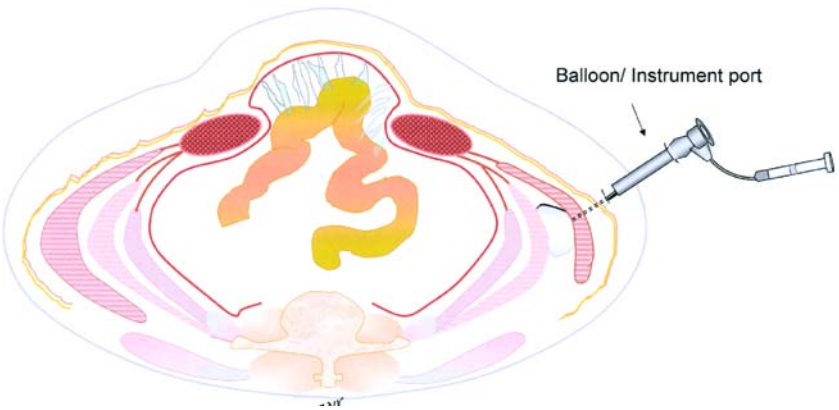

Figure 8 Initial placement of laparoscopic balloon dissector in between internal and external oblique muscles.

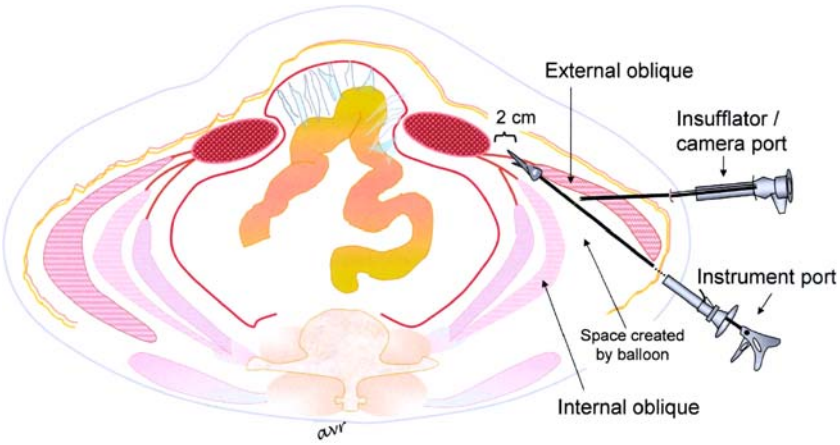

Figure 9 The external oblique muscle is released using the lateral laparoscopic port 2 cm lateral to the linea semilunaris.

gaining access to the lateral abdominal muscular compartment bilaterally typically by raising large lipocutaneous flaps, incising the external oblique fascia 2 cm lateral to the linea semilunaris, and separating the external and internal oblique in their avascular plane, allowing medialization of the rectus muscles. Some have claimed that this technique has been able to approximate defects up to 20 cm wide at the umbilicus; we believe these claims to be a generous overestimation of realistic medial advancement of the rectus muscles. The technique of component separation does, however, accomplish the goals of preventing bowel eventration but also reconstructs a mechanically more functional abdominal wall by restoring the muscular aponeurosis to the midline. Despite these seemingly important advantages, most surgeons reserve this technique for very complicated repairs because of reluctance to perform this lateral fascial release due to the high rate of associated wound complications.

Concepts of Repair

The ideal abdominal wall reconstruction for a ventral hernia would provide a minimally invasive technique to release the rectus abdominal wall musculature, enable laparoscopic adhesiolysis, reapproximate the midline, and reinforce the repair with permanent prosthetic material.[11] Ideally, this goal could be performed without creation of the large, lipocutaneous tissue flaps. Our approach to performing an endoscopic component separation can be combined with a midline incision and retrorectus mesh placement (as described above) or via a laparoscopic approach as described below.

Totally Laparoscopic Approach

Patients are positioned supine on the operating table with the arms out on arm boards. Placing the arms out is important because the lateral port for the component separation must be in the posterior axillary line which otherwise would be obscured. Placement of two laparoscopic towers at the patient's head facilitates everyone's view of the operation. The procedure is begun first by performing bilateral, endoscopic component separations;[12,13] performing this maneuver part first prevents potential problems with air leak into the abdomen if the ports were placed initially into the peritoneal cavity. The

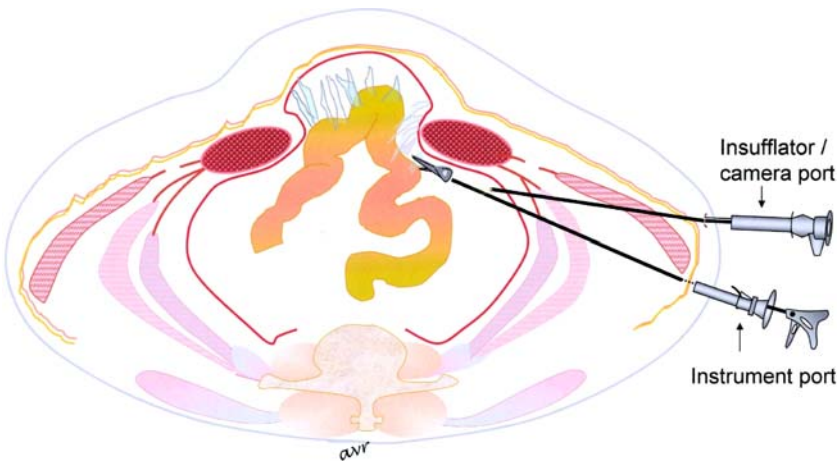

Figure 10 The laparoscopic ports are placed intraperitoneally, and adhesiolysis is performed.

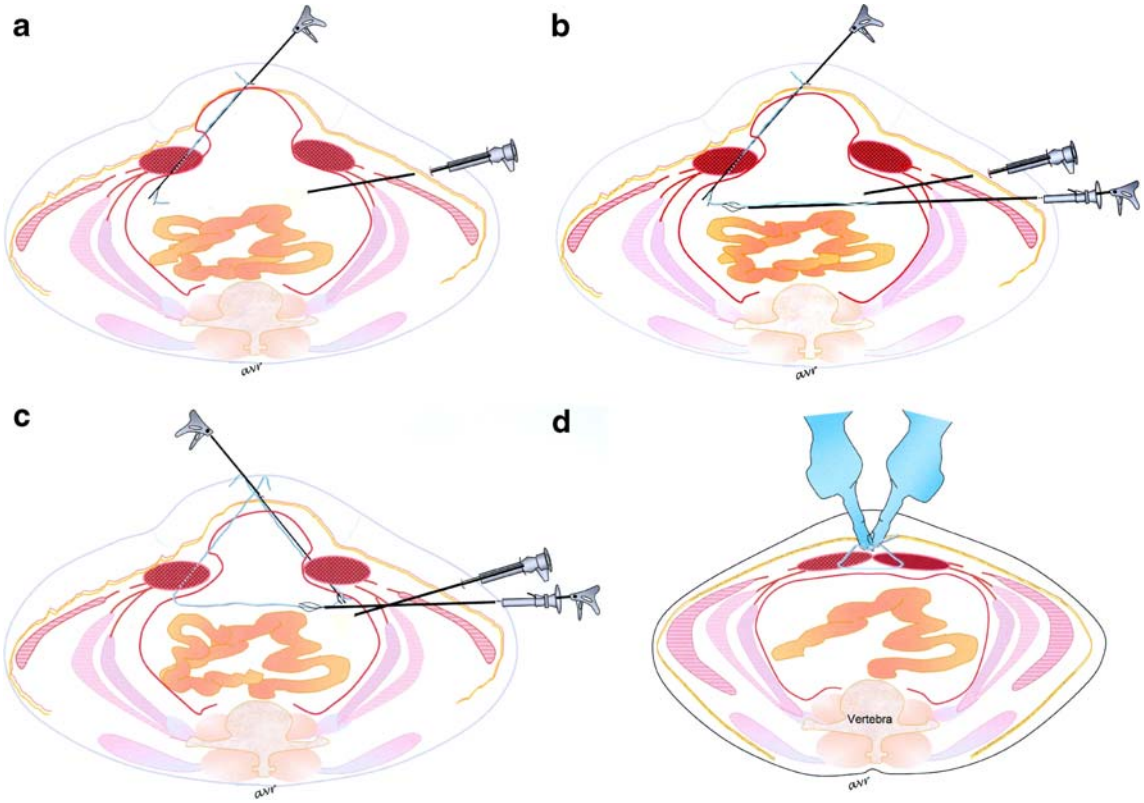

Figure 11 Reapproximation of the midline fascial defect. **a** Via a stab wound, a suture passer with a #1 polypropylene suture is passed through one fascial edge into the peritoneum, **b** retrieved by a forceps, **c** the suture passer now passed through the edge of the other fascial edge and removed through the stab wound, and **d** the suture tied with the knot subcutaneously.

costal margins and inguinal ligaments are identified and marked. The linea semilunaris representing the lateral edge of the rectus muscle is typically 8–10 cm from the midline and is then drawn on the patient's abdomen bilaterally. It is quite important to confirm this landmark because placing the port too far medially or in the rectus muscle may prevent the accomplishment of the procedure endoscopically and require conversion to an open procedure. To insure lateral placement, we place the initial port just off the tip of the 11th rib (Fig. 7). Using a 1-cm incision, the external oblique fascia is localized with Kocher clamps, incised sharply, and spread in the line of its fibers. The internal oblique muscle with its filmy anterior fascia is identified underneath, and the avascular plane between the external and internal oblique fascias is created with retractors. A bilateral, laparoscopic inguinal hernia balloon dissector (Covidien) is passed into this plane and advanced caudally down to the inguinal ligament. Because this is an entirely avascular plane, the balloon should meet little or no resistance. Inflation of the balloon separates the external oblique fascia from the underlying internal oblique fascia covering the internal oblique muscles (Fig. 8). This

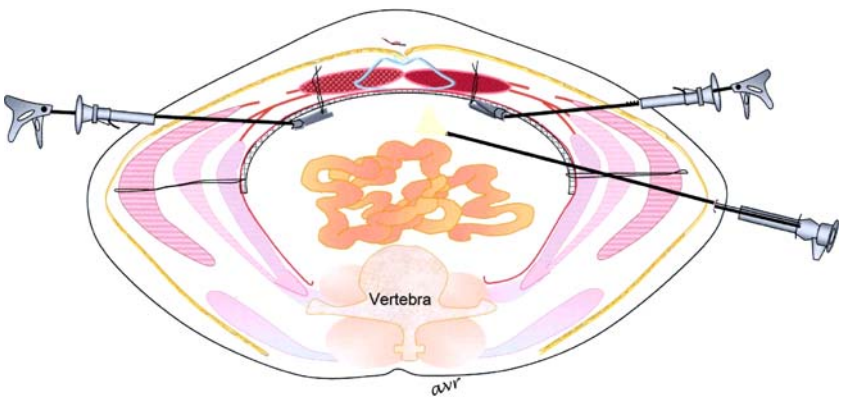

Figure 12 An appropriately sized piece of mesh is placed intraperitoneally to reinforce the fascial closure.

maneuver is performed under direct visualization from within the balloon to confirm the appropriate orientation of the respective muscle fibers. The balloon is removed, and a 30-ml, balloon-tipped port is placed. Insufflation pressures of only 10–12 mmHg will allow adequate visualization but prevent subcutaneous emphysema. The tip of the camera can be used to complete the posterior lateral dissection bluntly. A 5-mm port is then placed as far laterally as possible to provide an adequate angle to incise the external oblique fascia 2 cm lateral to the linea semilunaris. Using scissors and cautery, the external oblique fascia is transected in a caudal direction down to the inguinal ligament (Fig. 9). The surgeon must identify the linea semilunaris carefully during this dissection and avoid dividing it which would result in a full thickness defect and a lateral hernia, which is very difficult to repair and would require changing the operative approach. Maintaining a lateral distance of at least 2 cm from the linea semilunaris for the fascial release will prevent this complication. Once the fascia is released caudally, another 5 mm port is placed through the area of the fascial release medial to the initial camera port to provide adequate visualization of the fascial transection rostrally. The camera is then repositioned in the posterior axillary line, and the scissors are placed in the inferior port. Transection of the external oblique fascia in the other direction is then continued for at least 3–5 cm rostral to and above the costal margin. Meticulous hemostasis should be maintained during this maneuver because the external oblique muscle in this region can bleed postoperatively.

After completing the bilateral components separation, the ports for the intraperitoneal hernia repair are then placed into the abdominal cavity (Fig. 10). The posterior surface of the entire anterior abdominal wall is freed of adhesions. The hernia defect is measured internally using spinal needles in conjunction with a 15-cm ruler in a rostrocaudal and medial-lateral orientation. At this point, the fascial defect is reapproximated as follows. A small stab wound is made just above the hernia, and a suture passer is placed with a #1 polypropylene suture through the skin and through the fascial edge of the hernia defect (Fig. 11a) and retrieved with a laparoscopic grasper (Fig. 11b); the suture passer is then removed and passed through the same skin incision to the contralateral side of the hernia defect, and the suture is retrieved (Fig. 11c). A series of these interrupted sutures are placed throughout the length of the hernia defect to allow a secure, musculofascial approximation, the insufflation pressure is decreased, and the sutures are tied with the knots below the skin on the fascia (Fig. 11d). An appropriately sized piece of prosthesis based on the measurements required is placed intraperitoneally and secured with transfascial fixation sutures (Fig. 12). A laparoscopic tacker then obliterates the lateral defects of the prosthesis. We prefer the use of Parietex™ Composite (Covidien) for intraperitoneal placement and Parietex™ TET (Covidien) for intramurally placed prosthetic.

Combined Open and Endoscopic Repair

This combined approach is utilized either when an open herniorrhaphy is needed (as described above—"Open Ventral Hernia Repair") or when the anterior abdominal wall is contaminated or there has been a prior mesh infection—in these latter situations, once the infectious source has been removed and gastrointestinal continuity restored. After assessing the size of the defect, if the defect is too large to close primarily, we perform the endoscopic component separation. The lateral border of the rectus muscle is assessed easily by compressing the lateral abdominal wall bimanually and identifying the ridge of the rectus muscle. The initial port is placed at least 2 cm lateral to this landmark, and the procedure is performed as above.

We try not to repair an incisional hernia with a permanent prosthesis whenever the bowel is opened electively (clean contaminated) or with local contamination. On occasion, we will carry out such a combined repair when taking down a relatively simple enterocutaneous fistula, an ileostomy, or a colostomy, but both we as the surgeons and the patient must acknowledge the increased risk of infection and weigh the risk/benefit ratio.

Conclusion

The hernia surgeon has many available options to choose from when repairing abdominal wall defects. Understanding the physiology and biomechanics of the abdominal wall and the need to recreate a functional dynamic platform may result in increased postoperative patient functional recovery and satisfaction with the repair.

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REVIEW ARTICLE

Gastrointestinal and Retroperitoneal Manifestations of Type 1 Neurofibromatosis

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Abstract
Background Type 1 neurofibromatosis (NF1) is a genetic disease characterized by neoplastic and not neoplastic disorders, involving tissues of neuroectodermal or mesenchymal origin. The mainly involved districts are skin, central nervous system, and eye, and there is a wide range of severity of clinical presentations.
Data sources Abdominal manifestations of NF1 comprehend five categories of tumors: neurogenic with neurofibromas, malignant peripheral nerve sheath tumors and ganglioneuromas, neuroendocrine with pheochromocytomas and carcinoids, non-neurogenic gastrointestinal stromal tumors, i.e., GISTs, and embryonal tumors and miscellaneous.
Conclusions Early diagnosis of these abdominal manifestations is very important given the risk of malignancy, organic complications such as in the case of pheochromocytomas or hemorrhagic-obstructive complications such as in the case of the tumors of the gastrointestinal tract (GISTs and neurofibromas). The importance of an annual clinical evaluation on the part of a multidisciplinary pool of clinicians in highly specialized centers allows early detection of complications and of neoplastic transformation.

Keywords Von Recklinghausen's disease · Neurofibromatosis · GIST · MPNST

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Introduction

Neurofibromatosis type I (NF1), known as von Recklinghausen disease, is one of the most common inheritable disorders with an autosomal dominant transmission, an incidence of 1:3,000, and a prevalence of 1:4–5,000.[1,2] The clinical expression is extremely variable, including neoplastic or not neoplastic disorders, mainly involving tissues of neuroectodermal or mesenchymal origin in different districts, such as skin, central nervous system, and eye. Pathogenesis is based on mutations of the NF1 gene, a tumor suppressor, encoding the cytoplasmic protein neurofibromin which controls cellular proliferation by inactivating the p21 RAS and the MAP kinase pathway.[3,4] Only 50% of patients have a first-degree relative with NF1; the others have a sporadic mutation since the locus is highly mutagenous.[5,6] Variety in clinical expression is a characteristic of the NF1 depending on the nature, timing, location and extension of mutations, the association of mutations in modifying genes, and the eventual somatic mosaicism (in which the mutation occurs in somatic cells, thus involving only a district of the body).[7]

The diagnosis is generally based on clinical criteria established by the National Institutes of Health Consensus Development Conference (Table 1) in 1988.[8] Two or more criteria are needed.

Cafè au lait spots (ubiquitary pigmented cutaneous macular),[9] freckling of the intertriginous areas,[10] and Lisch nodules (melanocytic amartomas of the iris),[11] are the earliest clinical manifestations and are present in 95% of patients. Nevertheless, the hallmark lesion of NF1 (more than 95%of patients) is represented by neurofibromas, benign nerve sheath tumors which can appear as soft dermal or subcutaneous masses or in 30% of patients as plexiform lesions, thus involving a nervous plexus or many nerve fascicles inside a large-sized nerve. Neurofibromas can remain asymptomatic or can manifest with pain along the distribution of the involved nerve or with symptoms due to compression of surrounding structures.[12] About 10% of them can develop malignant transformation in malignant peripheral nerve sheath tumors (MPNST).

Optic glioma, a benign tumor of the optic pathways, presents in 15% of patients with NF1 usually before age 10 years. It is often asymptomatic, but in 2–5% of cases, it is progressive up to visual impairment or hypothalamic dysfunction, and in this case, it is treated with vincristine and cisplatinum.[13,14]

A distinctive osseous lesion such as dysplasia of the sphenoid or thinning of long bone cortex (tibia and fibula) with a radiological aspect of pseudoarthrosis occurs on 2–5% of patients.[15,16]

Besides the diagnostic criteria, there are a lot of clinical disorders strictly associated with NF1. The most common of which is cognitive impairment, with learning disability and behavioral difficulties in 50% of patients even if only 2% of patients present low IQ.[17] RAS hyperactivation and following GABA inhibition in the hippocampus are the molecular bases of cognitive disorders.[18] A radiological mark is represented by the unidentified bright objects (UBOs), focal areas of high signal intensity in T2-weighted MR, which may be due to a delayed myelination or gliosis.[19,20]

Orthopedic disorders include macrocephaly, short stature, and scoliosis which, in 10%, can be progressive.

Cardiovascular disorders include hypertension and high frequency of congenital heart and vascular disease (valvular pulmonary stenosis, aneurismas).[21]

Neoplastic lesions are frequent in patients with NF1 because of the pathogenetic role of mutated neurofibromin; an association is recognized for gliomas, ependymomas, lymphomas, myeloid leukemia, Wilms tumor, pheochromocytomas, MPNST, gastrointestinal stromal tumor (GIST), and carcinoids.

Because of the variety of clinical manifestations of NF1, the severity of this disorder ranges from benign (75%) to very aggressive conditions (25%).

Mutation testing attains the diagnosis of neurofibromatosis in over 95% of patients; however, it is still unable to predict disease severity.[22,23] Recent studies have discovered an association between microdeletions and higher risk of developing MPNST.[24] The importance of severity prediction is evident in order to program a closer follow-up and moreover to obtain prenatal and preimplantation diagnosis.[25]

The association between NF1 and neoplasms may involve the abdominal district. There are five categories of abdominal neoplasms occurring in patients with NF1: neurogenic tumors, neuroendocrine tumors, non-neurogenic gastrointestinal stromal tumors, embryonal tumors, and miscellanea[26] (Table 2).

Table 1 National Institutes of Health Consensus Development Conference 1988

Diagnostic criteria of neurofibromatosis type 1
>2 criteria are needed
1 Six or more cafè au lait macules
>0.5 cm large in pre-puberal age
>1.5 cm large in post-puberal age
2 Two or more neurofibromas of any type/1 plexiform neurofibroma
3 Freckling in the axillary or inguinal regions (Crowe's sign)
4 Optic glioma
5 Two or more Lisch nodules (iris hamartomas)
6 Peculiar osseous lesions
Sphenoid dysplasia
Thinning of long bone cortex with or without pseudoarthrosis
7 A first-degree relative with NF1

Neurogenic Tumors

Neurofibromas and Plexiform Neurofibromas

Neurofibromas (Fig. 1) represent the most common neoplasm occurring within the abdominal cavity (and retroperitoneum) and the gastrointestinal tract of NF-1 patients. Frequently, they present paraspinal, sacral, or mesenterial localization. They are often asymptomatic (65%) but may present with pain, palpable abdominal mass, and symptoms secondary to obstruction when originated in the GI tract or in the mesentery and bleeding when the mucosa is involved.[27,28] Rarely, neurofibromas involve other structures such as liver and the genitourinary tract.[29]

Plexiform neurofibromas growing in retroperitoneum are typically symmetric, bilateral lesions originating from paraspinal spaces (Fig. 2).

Table 2 Five Categories of Abdominal Neoplasms

Neurogenic tumors
Neurofibroma
Plexiform neurofibroma
MPNST
Ganglioneuroma
Neuroendocrine tumors
Carcinoid
Pheochromocytoma
Paraganglioma
Non-neurogenic gastrointestinal stromal tumors
Gist
Embryonal tumors
Neuroblastoma
Wilms tumor
Rhabdomyosarcoma
Miscellanea
Adenocarcinomas
Extra-abdominal tumors (leukemia, lymphomas)

Both localized and plexiform neurofibromas are composed of Schwann cells, fibroblasts, and myxoid matrix, but while the former are well-defined lesions confined to the affected nerve, the latter are complex and disordered masses involving an entire plexus or multiple fascicles of a large size nerve totally altered in its architecture.[30] Moreover, plexiform neurofibromas are exclusive of NF1 and may develop into MPNST. Neurofibromas of the GI tract originate from the myenteric plexus, often present as multiple, polypoid lesions.[31] As the clinical manifestation, radiological diagnosis depends on the localization of the tumor. On computed tomography (CT) scan, neurofibromas appear as smooth, round, or tubular masses homogenously hypoattenuating;[32] on magnetic resonance imaging (MRI), they characteristically present low signal intensity on T1-weighted images and in T2-weighted images a high signal of the cystic or myxoid areas and a low signal of the collagenous and fibrotic tissue that enhances with gadolinium administration. Plexiform neurofibromas appear with the characteristic "ring-like" pattern due to their fascicular architecture.[33] Neurofibromas affecting the gastrointestinal tract (Fig. 3) often appear as thickening of bowel wall or multiple nodules recognized at conventional barium examination as mural rigidity, external mass effect, or scalloping of the mucosa. Surgical treatment aims to resolve pain, bleeding, obstruction, and symptoms due to compression of other structures; moreover, surgical removal prevents local infiltration and malignant transformation of plexiform neurofibromas.[34] These kinds of neurofibromas are often difficult to remove because of their origin in the entire nervous plexus and the involvement of surrounding structures. Due to increased risk of malignant transformation, radiotherapy is not currently indicated. A potential role of antiprogesterone therapy is suggested by the high presence of progesterone receptors in neurofibroma (75%),[35] while a randomized control trial is in progress to establish the role of therapy with farnesyltransferase inhibitor and pirfenidone.[36]

Malignant Peripheral Nerve Sheath Tumor

MPNSTs are the most common malignant neoplasm in NF1 (Fig. 4). The lifetime risk of developing an MPNST for patients with NF1 is 7–12%. In these patients, diagnosis is

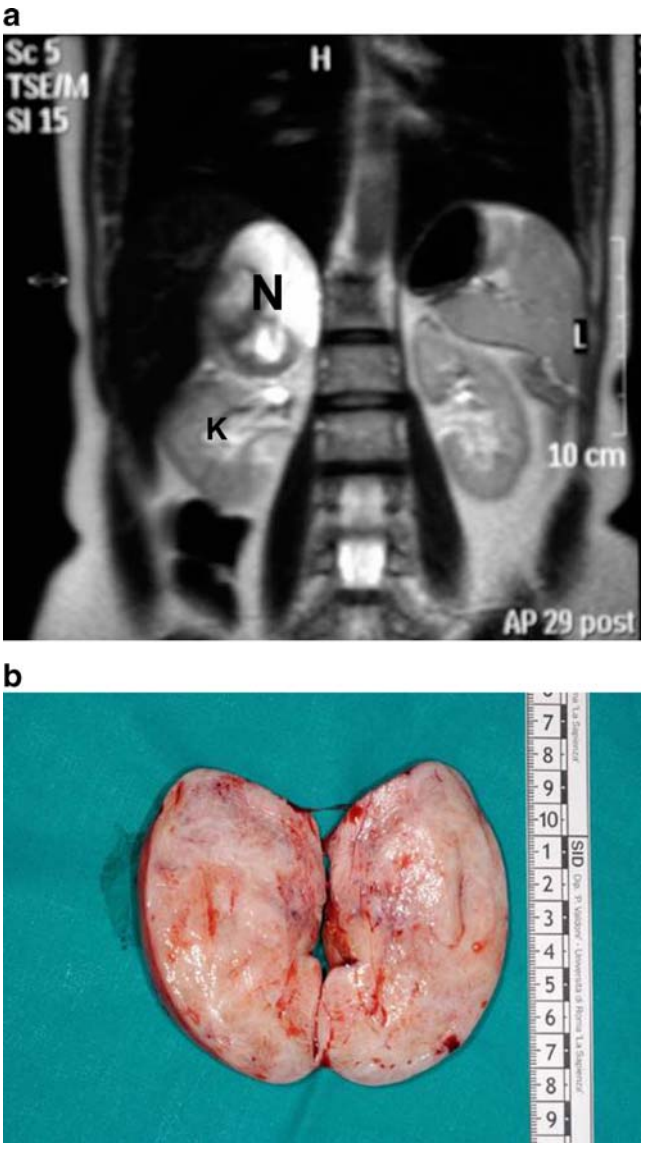

Figure 1 **a** Voluminous retroperitoneal neurofibroma (*N*), in suprarenal position, displacing and compressing the right kidney (*K*). **b** Voluminous retroperitoneal neurofibroma: the opened specimen shows the typical features of benign neurofibromas.

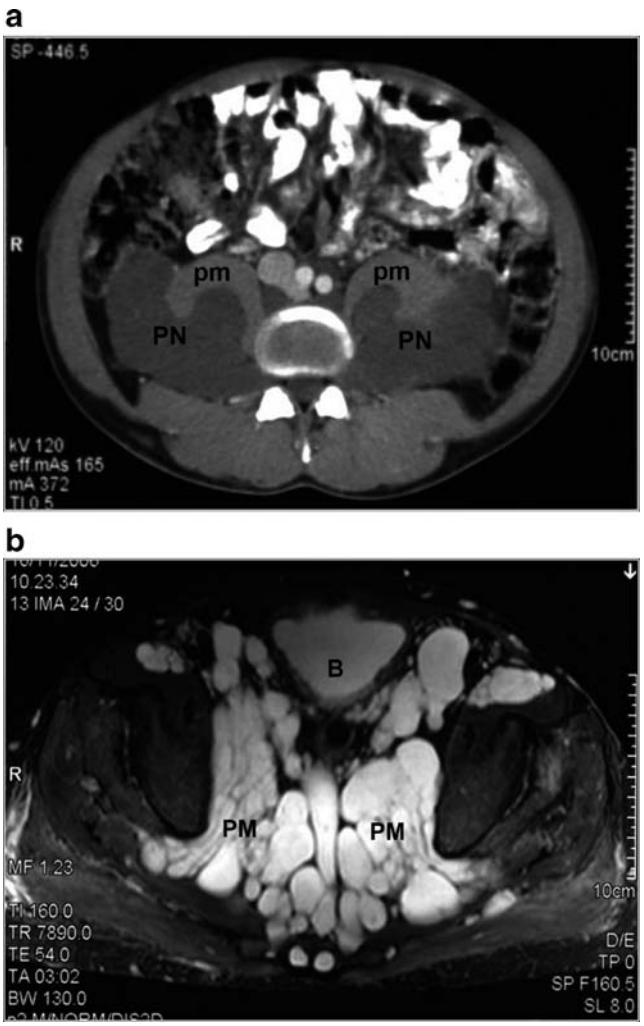

Figure 2 **a** CT scan view of bilateral retroperitoneal paraspinal bilateral plexiform neurofibromas (*PN*), compressing and displacing anteriorly the psoas muscle (*pm*). **b** MRI view of pelvic retroperitoneal plexiform neurofibromas (*PN*), hyperintense on T1-weighted images, involving the entire pelvic space. *B* bladder.

more precocious than in the general population, but the tumors are usually more aggressive.[37,38]

MPNSTs located within the abdominal cavity give usually late symptoms (due to compression or infiltration of surrounding structures, thus presenting worst prognosis, higher rate of metastasization, and recurrence because of the delayed diagnosis.[39] Within the abdomen, they mostly arise in the retroperitoneum and remain silent until they increase in volume, involving surrounding structures producing pain, obstruction, neurological deficits, and bone erosion. They are capsulated globular or fusiform masses often larger than 5 cm with signs of infiltration of surrounding structures. At histological analysis, they are composed of spindle cells organized in fascicles or completely lacking of any pattern. Necrotic tissue and vascular infiltration are frequent and a high mitotic rate is characteristic. Diagnosis is based on radiological aspects even if it is not so easy to distinguish MPNST from neurofibromas since both of them present irregular borders, heterogeneous enhancement, and infiltration of adjacent structures up to bone erosion.[40] 67-Gallium citrate scintigraphy may support differential diagnosis showing an uptake only in malignant tumors, although this is helpful in a low percentage of MPNST since the majority of them are Ga-citrate-negative.[41] MPNST often derives from preexisting plexiform neurofibromas. It is important to recognize any signs of malignant transformation of neurofibromas such as rapid increase in size and sudden appearance of neurological deficit or pain. The treatment of choice is radical excision of the tumor, even if the role of surgery is often limited to a palliative debulking.[42] In these cases, radiotherapy plays an important role in improving local control, and chemotherapy with ifosfamide and doxorubicin instead is helpful in metastatic disease and before surgery in order to reduce tumor size.

Ganglioneuromas and Ganglioneuromatosis

Ganglioneuromas are benign tumors originating from sympathetic ganglia and appearing as well-defined masses along the paravertebral sympathetic plexus, in the adrenal gland, and rarely in polypoid form in the gastrointestinal tract. In this last case, they may present as focal polypoid lesions (ganglioneuromas), multifocal polyps (ganglioneuromatous polyposis), or diffuse infiltrating lesions leading to a thickening of the intestinal wall (ganglioneuromatosis). These last conditions usually are associated to multiple endocrine neoplasia syndromes and NF1 and involve colon and rectum. Depending on their location, they can be silent or present with

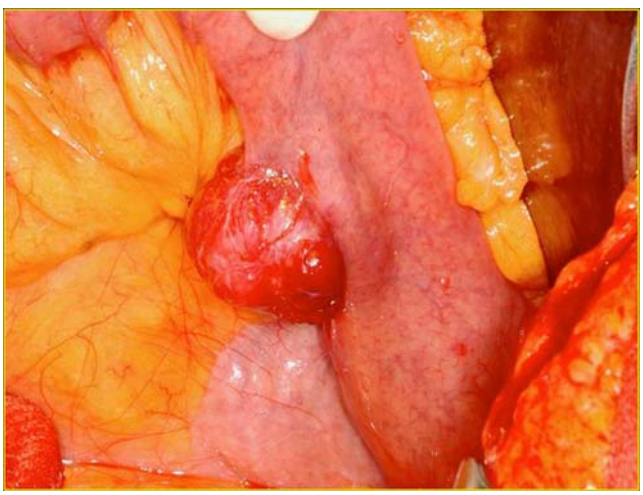

Figure 3 Intraoperative view of jejunal neurofibroma requiring bowel resection.

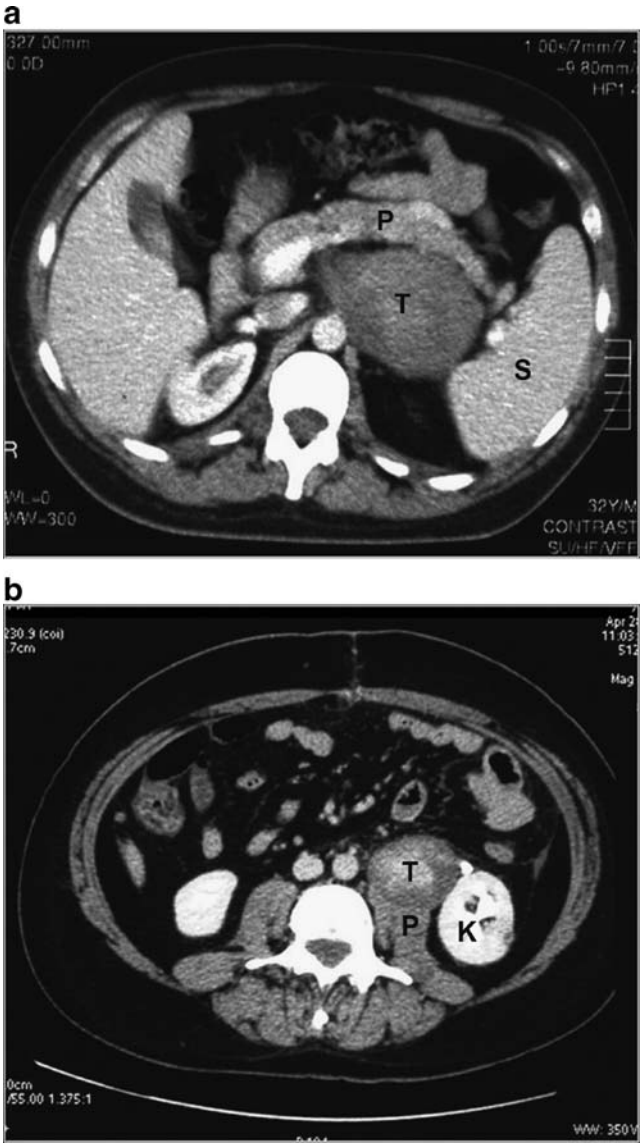

Figure 4 **a** MPNST: voluminous malignant peripheral nerve sheath tumor (*T*) in retroperitoneal position, displacing anteriorly the body and tail of the pancreas (*P*). *S* spleen. **b** Recurrent retroperitoneal MPNST (*T*), infiltrating the left psoas muscle (*P*), and lying adjacent to the left kidney (*K*).

neurological deficits or pain along the distribution of the affected nerve, or when situated in the gastrointestinal tract, they may present with bleeding or symptoms of intestinal obstruction up to a Hirschprung-like condition and megacolon in the case of most severe ganglioneuromatosis. At histology, they are composed of autonomic ganglionar cells and axonal fibers with Schwann cells and satellite cells. On radiological images, they appear as well-defined hypoattenuating oval masses, and in the gastrointestinal localization, barium examination can be useful to detect them. Their treatment follows the management of benign neurofibromas.[43]

Tumors of Neuroendocrine Origin

Carcinoids

These tumors originate from the enterochromaffin cells of Kulchitsky in the bowel wall. Their incidence increases in patients with NF1, but the prognosis is the same of the general population. The most common localizations are the ampulla of Vater and the appendix, but they can involve the whole gastrointestinal tract.[44] Although they may produce somatostatin, they rarely present with signs and symptoms such as diarrhea and flushing. More frequently, they present with jaundice fever, vomiting, abdominal pain, and intestinal bleeding or obstruction. Carcinoid tumors are usually solid polypoid or infiltrative lesions composed of little eosinophilic cells with salt-and-pepper nuclei organized in trabecular or tubuloglandular patterns. At CT scan, it is difficult to distinguish carcinoids from periampullary adenocarcinomas; therefore, somatostatin analogues scintigraphy may be helpful in providing the differential diagnosis. Histological examination is based on immunohistochemical reactivity for synaptophysin, chromogranin, and somatostatin.[45]

NF-1-related carcinoids present slow growth, with a 5-year survival rate of 95% and low metastasization rate for tumors smaller than 2 cm.

Their management does not differ from the management of sporadic neuroendocrine tumors, depending on the site of occurrence and being based on surgical resection (when feasible), even in the presence of distant metastases and/or specific targeted therapies alone or in association with conventional chemotherapy (streptozotocin).[46]

Pheochromocytomas

Pheochromocytomas arise from the chromaffin cells of the adrenal medulla, catecholamine-secreting. They are unilateral in 85% of cases, bilateral in 9.6% of patients and extra-adrenal in 10% of patients. In these cases, they arise from the organ of Zuckerkandl and within the paraganglias (paragangliomas). Pheochromocytoma has an incidence of 1–2:100,000 and occurs in 0.01–0.1% of patients with hypertension.[47] This prevalence really increases in NF1 patients; in fact, up to 0.1–5.7% and 20–30% of NF-1 patients having high blood pressure are affected by pheochromocytoma. In 60% of patient, pheochromocytoma becomes symptomatic, presenting with hypertension, palpitations, flushing, and headache. It is more common in adults since hypertension in children is mostly due to renal artery stenosis, aneurisma, or aortic coarctation.[48] Pheochromocytomas usually are well-defined, spherical capsulated masses involving the adrenal medulla and well separated from the cortical tissue. At histology, they are

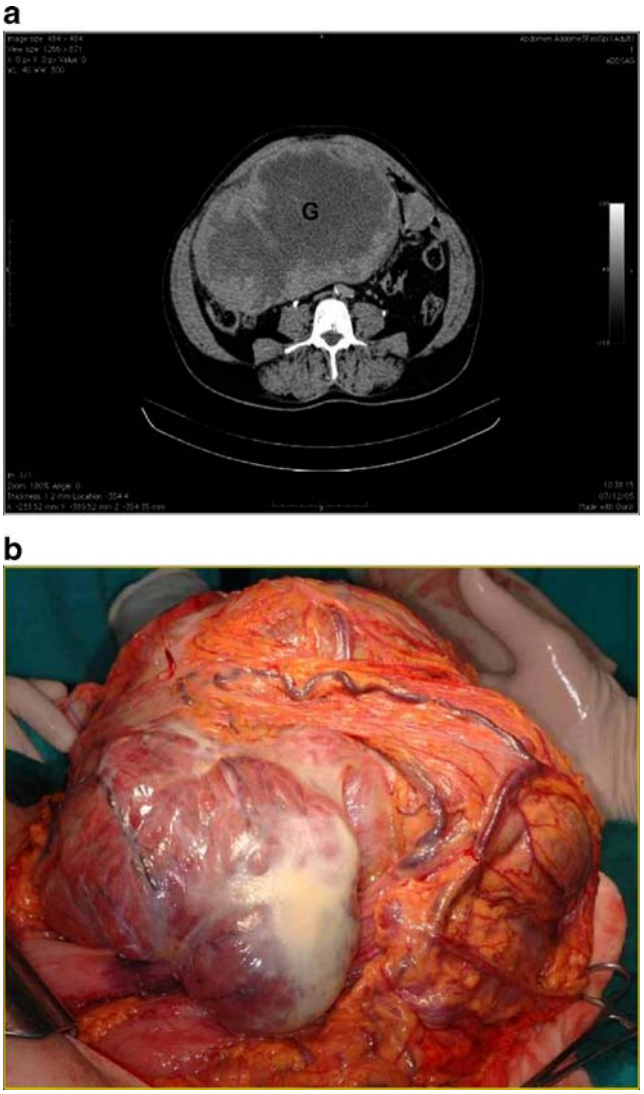

Figure 5 **a** Giant gastric GIST (*G*) in NF-1 patient, involving the entire abdominal cavity, and displacing the bowel. **b** Same case: intraoperative view of the giant gastric GIST.

composed of polygonal chromaffin cells organized in trabecular or round pattern (Zellballen). Immunohistochemical diagnosis is based on reactivity for neurono-specific-enolase, chromogranin-A, and S-100 protein.

CT scan has a high sensibility in detecting pheochromocytomas, showing them as homogeneous, defined, and contrast-enhanced masses of the adrenal gland. MRI presents high specificity in distinguishing pheochromocytomas from cortical tumors due to the typical hyperintensity on T2-weighted images. 123-I-MIBG scintigraphy allows recognizing functioning lesions with high specificity and sensibility.

Surgical excision of the tumor is the treatment of choice (as for sporadic pheochromocytomas) in order to normalize blood pressure values and prevent any possible malignant evolution.

Since the first experience in 1992 by Gagner, mini-invasive techniques are considered the gold standard in the management of these tumors even in the case of larger lesions (up to 10 cm), with the absolute contraindication represented by evidence of malignancy with infiltration of surrounding structures. In case of suspicion of extra-adrenal localization, exploration of the whole abdomen is important to identify multiple localizations.

In NF1 patients, because of the possible presence of other neurofibromatosis-related tumors, exploration of the abdominal cavity becomes mandatory to detect eventual associated GISTs, carcinoids, neurofibromas, and ganglioneuromas.[49,50]

Non-Neurogenic Tumors

Gastrointestinal Stromal Tumors

GISTs are mesenchymal neoplasms which occur in the gastrointestinal tract, arising from the interstitial cells of Cajal of the myenteric plexus.

Their feature, which distinguished them as a nosological entity, is the immunohistochemical positivity for KIT or PDGFRA, transmembrane receptors regulating cellular proliferation.[51] Their incidence is of 1.5:100,000 persons per year. The median age of presentation is 55–65 years and the most frequent localizations are the stomach (60%), the ileum (30%), rarely the duodenum (5%), colon–rectum (5%), and esophagus. In NF1 patients, GISTs (Fig. 5) are more common, with an incidence of 3.9–25%; they can be diagnosed at younger age (median age 50 years), usually originating in the bowel and are often multiple.[52] At histology, they are composed of spindle cells organized in interlacing fascicles with a collagenous matrix.[53] NF1-associated GISTs differ from sporadic GIST in that they do not present the peculiar immunohistochemical pattern since they result negative for KIT (exons 9, 11, 13, 17) and PDGFRA (exons 12 and 18) mutations.[54] Those mutations are the principal pathogenetic events in sporadic GIST, as indicated by their detection in the earlier steps of malignant transformation (tumors <1 cm).[55] The different pathogenesis probably derives from the lack of inactivation of the MAP kinase pathway–RAS controlled, as it happens in the genesis of neurofibromas.[56] This alternative mechanism seems to lead to a better prognosis with respect to sporadic GIST. The most important prognostic factors are the mitotic index and tumor diameter (10 cm). The diagnosis can be incidental during radiological examinations and surgical exploration (due to a synchronic tumor) or can be guided by clinical suspicion.[57] They are better detected on echoendoscopy, CT, MR, and positron emission tomography.[58]

Surgical R0 resection (with or without visceral resection) is still the gold standard for localized disease, even if

several authors consider acceptable R1 resections in cases of low-risk tumors and/or particular localization (duodenum, esophagus) that would require extensive resection (with high morbidity and mortality rates) to achieve R0 resection.[59]

In cases of diffuse or metastatic disease, tyrosine kinase inhibitors (such as imatinib mesilate) are considered the gold standard treatment, having up to 80% response rate. A new drug which acts at the same time as a tyrosine kinase inhibitor and as an antiangiogenic factor has just been validated (sunitinib).[60]

The use of selective KIT inhibitors is now being evaluated even in preoperative settings, in case of localized disease, in order to avoid extensive surgical resections.

Embryonal Tumors

Associations between neurofibromatosis and Wilms tumor or neuroblastoma are reported, though they are not confirmed from a genetic and molecular point of view.[61] Instead, a common pathogenetic mechanism is more evident in the association between NF1 and rhabdomyosarcoma due to the accepted role of NF1 gene in the differentiation of muscular cells.

Miscellanea

Adenocarcinomas involving the whole gastrointestinal tract have been detected in patients with NF1. Colic, esophageal, gastric, biliary, and pancreatic localization may be considered casual because of their high incidence in the general population. Adenocarcinomas of the small bowel instead seem to be associated to NF1 given the increase incidence in NF1 patients, particularly in the periampullary site.[62] Actually, some hesitations about this association depend on the difficulty in distinguishing, at histological examination, adenocarcinomas from carcinoids for which it is universally accepted. Other extra-abdominal tumors NF1-associated are leukemias and non-Hodgkin lymphomas.

Conclusions

Clinical manifestations of neurofibromatosis type 1 present a wide range of severity depending on timing, extension, and number of mutations of the Nf1 gene.

Abdominal localizations involve five categories of tumors out of which we find in our experience: neurofibromas, MPNST, pheochromocytomas, and GIST.

Early diagnosis of these abdominal manifestations is very important given the risk of malignancy, organic complications such as in the case of pheochromocytomas or hemorrhagic-obstructive complications such as in the case of the tumors of the gastrointestinal tract (GIST and neurofibromas).

The importance of an annual clinical evaluation on the part of a multidisciplinary pool of clinicians in a highly specialized center allows early detection of complications and of neoplastic transformation.

Genetic screening allows preclinical diagnosis with a sensibility of 95%. Further studies are necessary to detect predictive factors of malignant tumor development of severe clinical conditions.

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GI IMAGE

Inflammatory Pseudotumor of the Esophagus—GI Image

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Clinical data

A 45-year-old woman presented with a 7-month history of dysphagia. Four months ago, chest pain was found and deteriorated after swallow. She also had vomiting or regurgitation, occasionally with a dry cough. In the recent 2 months, the status got worse, accompanied with stuffy chest. No hoarseness was found. About 5-kg weight had been lost in the recent 7 months. A barium meal examination of upper digestive tract revealed a 10-cm smooth filling defect in the level to aorta arch with minimal mucosal irregularity. Barium was obstructed above the level of T7 (Fig. 1a). Gastric mucosa is thickened, without significant niche or filling defect. Computed tomography (CT) of the thorax revealed a soft tissue mass in the wall of the esophagus projecting into the lumen. Enhanced CT showed the mass was enhanced with the lumen stenosis and the trachea compressed (Fig. 1b). The gastroscopy showed that there was an irregular mass 18–30 cm away from the incisor. The surface was rough with erosive mucosa and some papillae. The mucosa 30 cm away from incisor to the cardiac esophagus, body, and antrum of stomach were all smooth. There is no stenosis for cardia of stomach. Biopsy revealed chronic mucosal inflammation and mild to moderate squamous epithelial dysplasia. The preoperative diagnosis was esophageal space-occupying lesion. After discussion among the Departments of Digestive Diseases, Medical Imaging, and Digestive Endoscopy, a diagnosis of esophageal tumor was rendered, with more possibilities to be benign or low-grade malignant cancer. Surgery was a better choice.

Surgery

Exploration was undertaken using a right anterolateral fourth intercostal incision with a preoperative plan of enucleating the tumor. After incision of esophageal bed, the mass was exposed, located in the upper-middle part of the lumen. It was movable, 12×5 cm×3 cm in size (Fig. 2a). In the esophageal bed, the mass could be touched and be pushed to the cervical segment of the esophagus. On account of the stalk near the inlet of the thorax, it was concluded that the mass hung to the thoracic segment of

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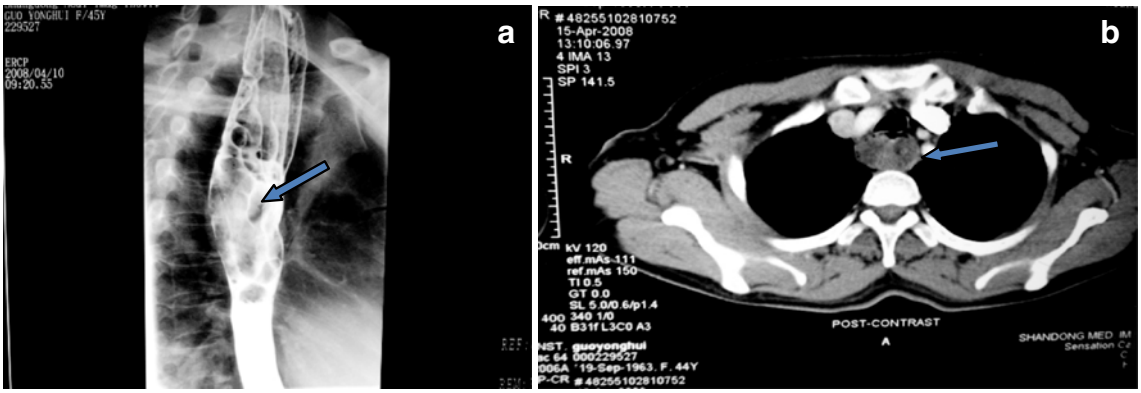

Figure 1 Images of esophageal inflammatory myofibroblastic tumor. **a** Barium X-ray image of esophageal IMT. The esophageal lumen of the upper segment was dilated, with a filling defect (*arrow* shows) and irregular mucosa. **b** Thoracic enhanced CT images of IMT. The *arrow* shows the mass in heterogeneous density extruding to the dilated lumen, with part liquefaction and necrosis.

esophagus. Therefore, another left cervical anterior sternocleidomastoid muscle incision was undertaken. After exposure of esophageal bed, esophagus was incised and the mass was pulled out (Fig. 2b). The stalk lay 3 cm near the inlet of thorax, with a 2-cm base. After resection of the mass from base, the biopsy was sent for pathology.

Pathology

Gross pathology demonstrated a gray to white ovoid mass with a complete capsule. Bleedings could be found in the cross sections. An admixture of inflammatory infiltrate with spindle-shaped fibroblasts, plasma cells, and lymphocytes was shown in microscopy. Some fibroblasts underwent hyaline degeneration. Immunohistochemically, fibroblastic cells were positive for vimentin, epithelial membrane antigen, and Ki-67 >5%, while negative for CD117, cytokeratin, leukocyte common antigen, CD34, HMB45, S-100, and Des (Fig. 2c–g). The final diagnosis were made as inflammatory pseudotumor (IPT) of the esophagus.

The patient had an uneventful postoperative recovery except a little voice hoarseness. Inflammatory symptoms resolved and preoperative chest pain also resolved rapidly. Postoperatively, the patient tolerated a regular diet and was discharged home on postoperative day 12. At month 10, the patient denied pain and had relieved the voice hoarseness.

Discussion

Inflammatory myofibroblastic tumor (IMT) is a rare neoplasm that can occur in various anatomic locations, most commonly in the lungs and mesentery or omentum, and it is equally distributed across gender. Though not uncommon in the rest of the gut, they are rare in the esophagus and constitute a major diagnostic and therapeutic dilemma. The proposed etiologies included Epstein Barr virus, human herpes virus 8, and overexpression of interleukin 6.[1,2] The recent reports suggested that IMT was probably a neoplasm rather than a postinflammatory process because of cytogenetic clonality, aberrant expression of anaplastic lymphoma kinase gene,[3] recurrent involvement of chromosomal region 2p23, occasional aggressive local behavior, and metastasis of the tumor.[1,4–6] Immunohistochemical analysis could contribute to distinguish the fibroblastic histological characterization of IMT from other soft tissue tumors. IMT exhibits immunopositivity for vimentin, partly for desmin, actin, and cytokeratin and immunonegativity for S-100, CD34, CD117, and CD68.[1,7,8]

The most commonly reported primary therapy is surgical resection (i.e., enucleation and partial or total esophagectomy).[7–10] The use of enucleation versus esophagectomy must be balanced between the recurrence risk and operative morbidity. It was reported that esophagectomy (whether partial or total) should be the procedure of choice for large (>2.5 cm) or obstructing esophageal IMTs or any tumor with muscularis propria involvement. Enucleation should be reserved for small (<2.5 cm) tumors without evidence of muscularis involvement on endoscopic ultrasound.[11] Such therapy appears to be associated with less than a 10% risk of local recurrence.[1] Total recurrences after surgery have been reported in up to 25% of cases, some due to incomplete resection.[1] In this case, the stalk located near the neck and the base of the tumor was 2 cm, though the mass was large with normal esophageal mucosa. For this reason, we underwent enucleation of tumor.

If complete resection is not possible, due to anatomic location or comorbidities, then adjuvant chemotherapy in conjunction with radiation therapy should be considered. The unpredictability of the clinical course, the potential for local recurrence, and the rare phenomenon of metastases, combined with the challenges of surgical management of large lesions or unresectable sites, have led to a variety of alternative or adjunctive treatments, mainly reported as

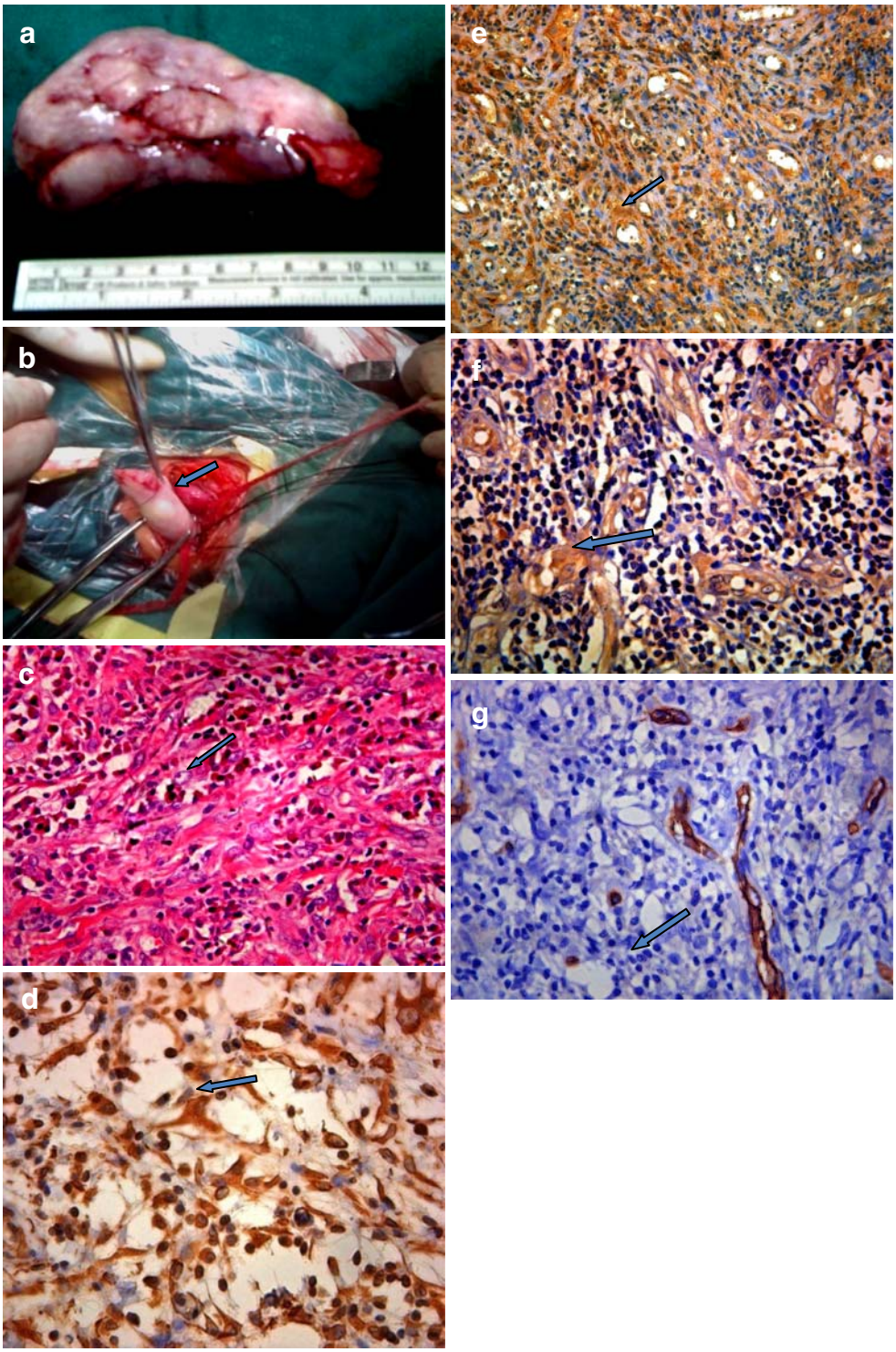

Figure 2 Clinical findings of the specimen. **a** Gross pathological findings. **b** The mass was resected (*arrow* shows the mass was removed via the left cervical incision). **c** HE staining. *Arrow* shows the irregularly arranged spindle-shaped fibroblasts, with some infiltrated lymphocytes (×400). **d** IHC vimentin staining (positive, S-P, ×400). *Arrow* shows the spindle-shaped fibroblast was in brown. **e** IHC desmin staining (positive, S-P, ×200). *Arrow* shows the spindle-shaped fibroblast was in brown, with some infiltrated lymphocytes. **f** IHC cytokeratin staining (positive, S-P, ×400). *Arrow* shows the spindle-shaped fibroblast was in brown, with some infiltrated lymphocytes. **g** IHC CD34 staining (negative, S-P, ×400). *Arrow* shows the spindle-shaped fibroblast was negatively stained, and the vascular epithelial cell was positive.

individual cases or small series. There has been variable success with chemotherapy,[12,13] steroids,[14] nonsteroidal anti-inflammatory drugs,[15] and imatinib.[16] The choice of chemotherapeutic regimen and radiation treatment should be guided by the particular tumor biology with more aggressive regimens reserved for those patients with clonal abnormalities and evidence of local invasion.[1]

Conclusion

Esophageal IPT is rare and should be included in the differential diagnosis of dysphagia associated with submucosal or pedunculated esophageal neoplasms. For patients with suspected IPT of the esophagus, a surgical excision is a better choice.

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GI IMAGE

Duodenal Duplication Cyst (DDC) Communicating with the Pancreatobiliary Duct—A Rare Cause of Recurrent Acute Pancreatitis in Adults

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Abstract
Introduction Duodenal duplication cysts (DDC) are rare congenital anomalies that usually present in infancy and childhood. Acute presentation in adults is even rarer.
Case History We report a case of a 34-year-old man who presented with recurrent acute pancreatitis and was found to have a cystic lesion in the second part of his duodenum. Further investigations revealed communication between the cystic lesion and the distal common bile duct. We describe the details of the operative approach taken to resect the DDC.
Discussion We describe the differential diagnoses and the criteria for diagnosing DDC. Management options for DDC are discussed along with our recommendations.

Keywords Duodenal diseases · Congenital cyst · Choledochol cyst · Pancreatic cyst · Pancreatitis

Introduction

Duodenal duplication cysts (DDC) are rare congenital malformations that are usually found in infants and children. DDC rarely present in adulthood, although a late presentation in a 75-year-old man has been reported.[1] We report a case of recurrent pancreatitis caused by a DDC in an adult.

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Case History

A 34-year-old Caucasian male presented to a local hospital with a 3-day history of epigastric pain and nausea. Although he suffered two episodes of acute pancreatitis in the past, no etiology was ascertained. Abdominal examination was unremarkable except for mild epigastric tenderness. Serum amylase was elevated at 1,711 IU/L, and the liver function tests were normal. A diagnosis of mild acute pancreatitis was made (Ranson's score of one). He denied alcohol intake, and an ultrasound scan showed no evidence of gallstones within the gallbladder or bile duct. Computer tomography (CT) scan revealed a 48×20-mm cystic lesion adjacent to the intrapancreatic portion of the distal common-bile duct (CBD; Fig. 1). The patient was referred to our institute for further management for what was originally thought to be a type III choledochal cyst (choledochocele).

A large cyst was found within the second part of duodenum on magnetic resonance cholangio-pancreatography and appeared to communicate with the CBD (Fig. 2). No focal lesion or pancreatic divisum was found. On endoscopy, the major papilla was found to be distorted, and retrograde biliary cannulation was unsuccessful. However, endoscopic retrograde pancreatogram did reveal a mildly dilated pancreatic duct within the head of the pancreas. Further evaluation

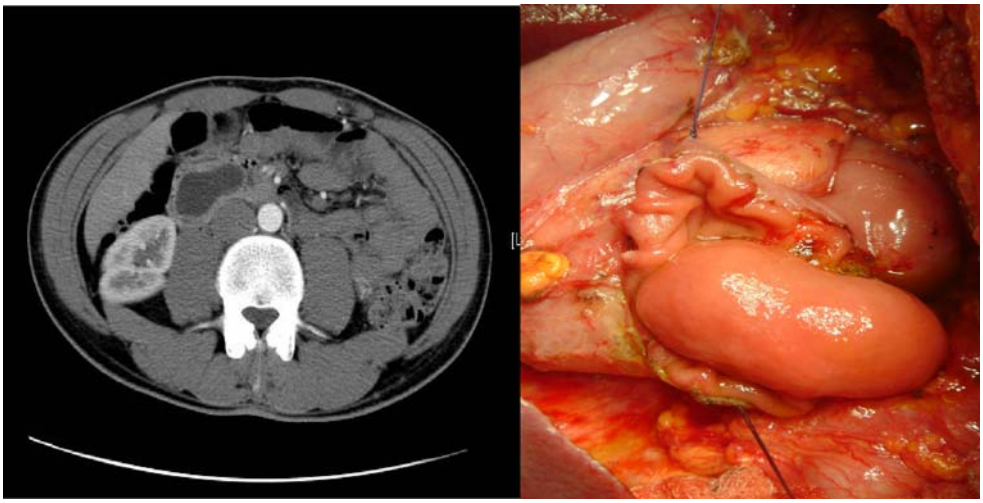

Fig. 1 Abdominal CT scan showing a large cystic lesion adjacent to the intrapancreatic portion of the distal common bile duct (CBD) corresponding with the intraoperative findings.

by endoscopic ultrasound showed a three-layered cystic lesion compatible with either a DDC or a choledochal cyst.

At laparotomy, a cystic duodenal lesion was found in the second part of the duodenum. We excised the gallbladder and performed an intraoperative cholangiography, which failed to demonstrate a communication between the cystic lesion and the bile duct. Next, a duodenotomy was made, and the cystic lesion was found in close proximity to the ampulla (Fig. 3). The duodenal mucosa adjacent to the ampulla was incised longitudinally along the cystic lesion and the lesion carefully dissected from the submucosa. Separately, the CBD and main pancreatic duct were identified and cannulated with plastic catheters. On completion of the dissection, the lesion was confirmed to communicate with the distal CBD (Fig. 4), and this communication was transected and then oversewn. The divided duodenal mucosa was closed, followed by the closure of duodenotomy. Postoperative recovery was uneventful, and the patient has remained well and asymptomatic since discharge.

Histology of the cystic lesion revealed small bowel mucosa and a layer of smooth muscle. These findings were consistent with the diagnosis of a DDC. No dysplasia and malignancy was seen.

Discussion

Alimentary tract duplications are rare congenital anomalies that can occur anywhere along the alimentary tract from the mouth to anus. The most commonly affected sites were the small bowel (47%), colon (20%), esophagus (17%), stomach (8%), and duodenum (5%).[2] DDCs are observed in less than 1 per 100,000 live births.[3] Review of the English literature reveals that the first case of a DDC was reported in 1967,[4] and subsequently over 120 cases have been reported, mostly as anecdotal case reports.

Although it is possible to diagnose DDC antenatally,[5] most patients normally present in infancy or childhood with recurrent pancreatitis and duodeno-jejunal intussusception leading to subsequent bowel obstruction.[6] External compression or distortion of the distal CBD may lead to jaundice.[7] Ectopic gastric epithelium is present in about

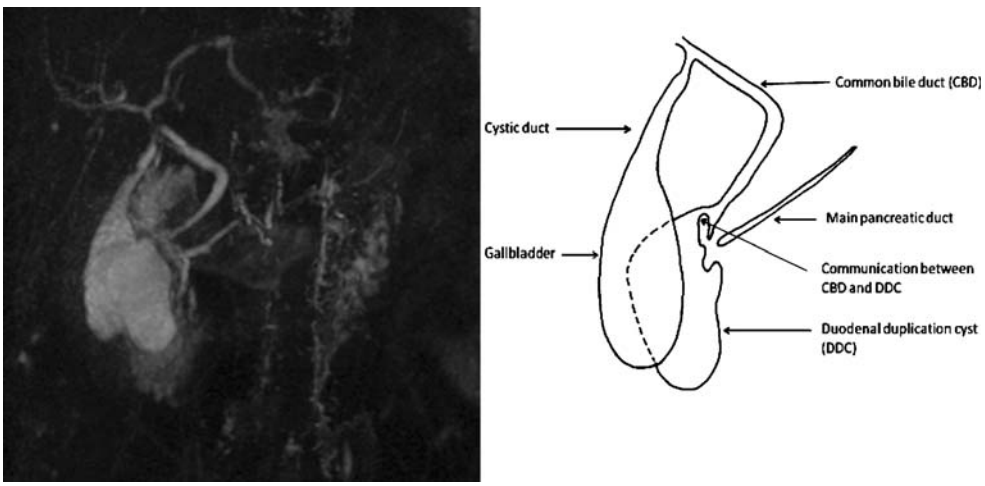

Fig. 2 Magnetic resonance cholangio-pancreatography demonstrating a communication between the cystic lesion (DDC) and the distal CBD.

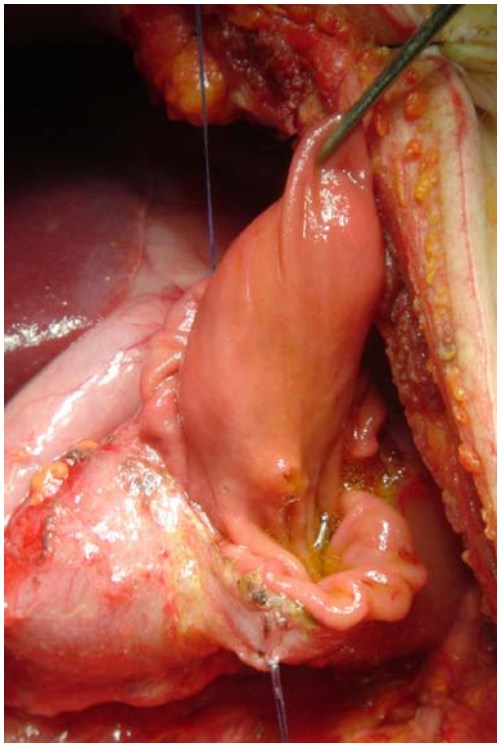

Fig. 3 Intraoperative photograph. The cystic lesion was found to be in close proximity to the ampulla. A longitudinal incision was made to begin the dissection.

15% of DDC, predisposing the patient to peptic ulceration, hemorrhage,[8] and perforation.[9] Rare complications such as stone formation within the cyst,[10] infection,[11] infarction,[12] perforation,[13] transdiaphragmatic communication with the cervical intraspinal,[14] or malignant transformation[15–17] have all been reported.

To make a diagnosis of DDC, the duplication cyst must be adherent to a portion of the duodenum, contain a smooth muscle layer, and be lined by alimentary epithelium, which may be that of the adjacent bowel, ectopic gastric,[9] squamous, transitional, ciliated mucosa, or pancreatic tissue. The cyst may be spherical or tubular and infrequently communicates with the pancreato-biliary ductal system. Cysts communicating with the pancreatic duct are extremely rare and only 21 cases have been described in the English literature between 1958–1998.[18] Our patient presented with recurrent episodes of pancreatitis that could be explained by the intermittent occlusion of the pancreatic duct by debris and sludge found within the cyst.[19] This theory is supported by the successful long-term outcomes in patients treated by endoscopic fenestration of duplication cysts in order to improve drainage.[20]

Since some DDC communicate with both the common bile duct and the main pancreatic duct, clinical differentiation between the DDC and choledochocele (type III choledochol cyst) can be difficult preoperatively. Antaki and colleagues have suggested that a normal-looking papilla is always found on the proximal side of the protrusion of a DDC into the duodenum at endoscopy, whereas, the papilla is found to be on the distal side in choledochoceles.[20] Ultimately, the histological appearance of the resected specimen is the only way to distinguish between a DDC and choledochocele. The three diagnostic criteria for the diagnosis of a duplication cyst on histology are the presence of an intimate attachment to the gastrointestinal tract, a smooth muscle coat, and an alimentary mucosal lining; in contrast, choledochoceles are lined by either a biliary or gallbladder mucosa and lack a smooth muscle layer. DDC can also be confused with post-inflammatory pseudocysts[21] or cystic neoplasms of the pancreas,[22] particularly in the adult population. Cystic fluid aspirated by endoscopic ultrasound has been reported to show profoundly increased tumor markers (CA19-9 and CEA). This finding led to the misdiagnosis of a cystic neoplasm in a patient who subsequently underwent a pancreaticoduodenectomy.[22]

The management options for DDC include endoscopic fenestration and open surgical excision. Endoscopic incision and marsupialization of the DDC have been performed by using a variety of endoscopic tools (needle-knife and regular sphincterotomes, cystotomes, and polypectomy snares). In a series reported by Antaki and colleagues, it

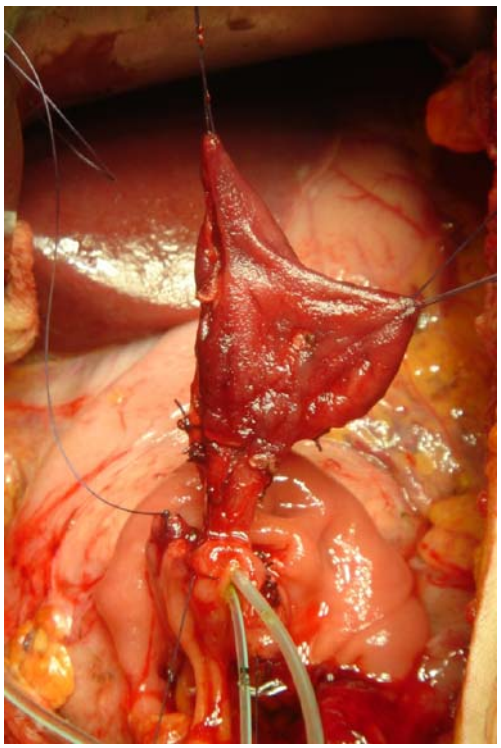

Fig. 4 Intraoperative photograph. Careful dissections confirmed a communication between the cystic lesion and the distal common bile duct. The large catheter cannulated the common bile duct whilst the smaller catheter cannulated the main pancreatic duct.

appears to be a safe and effective technique resulting in excellent long-term outcomes (all eight patients remained asymptomatic at a median follow-up of 7.3 years).[20] However, the natural history of DDC remains uncertain in the long term. Three cases of malignancy have been reported in the literature;[15–17] therefore, a repeat endoscopy plus biopsies is recommended 6 to 12 months after treatment.[20] In addition, the presence of ectopic gastric epithelium in 15% of patients exposes the patient to the risk of subsequent hemorrhage. For these reasons, we recommend surgical excision of the DDC rather than endoscopic treatment, particularly if the patient is young. Not only will the histology provide confirmation of the diagnosis but it will also remove the risk of potential complications associated with DDC.

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