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2011 SSAT POSTER PRESENTATION

Utilization and Morbidity Associated with Placement of a Feeding Jejunostomy at the Time of Gastroesophageal Resection

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Abstract
Background The purpose of the study was to evaluate the utilization and morbidity associated with feeding jejunostomy tubes (JT) placed at the time of gastroesophageal resection (GER).
Methods Under institutional review board approval, a prospective database of patients undergoing GER from January 2004 to September 2010 was reviewed. Data analyzed included patient demographics, postoperative complications, JT use, and JT specific complications. Fisher's exact tests explored associations with utilization of a JT following resection.
Results Seventy-three patients (51 men, 22 women, median age of 59) underwent placement of a JT at the time of GER (total gastrectomy=28, Ivor–Lewis=28, subtotal gastrectomy=8, proximal gastrectomy=6, and transhiatal esophagectomy=3) of both malignant (97%) and benign (3%) disease processes. Twenty-one JT specific complications (11 minor and 10 major) were identified. Reoperation was required in the management of two complications (small bowel obstructions), while all other complications were easily managed by an interventional radiologist (n=8), bedside procedure (n=5), or did not require intervention (n=6). Eighty-six percent of patients were discharged tolerating a postgastrectomy diet, 10% nothing per orem, and 4% a liquid diet. Inpatient enteral nutrition (EN) was initiated in 68%, but continued on discharge in only 54% secondary to failure to thrive (54%), dysphagia (21%), anastomic leak (15%), chyle leak (3%), esophagostomy (3%), and duodenal stump leak (3%). The mean time to discontinuance of EN and removal of the JT was 44 days (range, 4–203) and 71 days (range, 15–337) respectively. Although only 13% (n=5) of patients requiring adjuvant therapy were utilizing their JT at the commencement of therapy, 75% (n=21) required EN during its course. The median time to adjuvant therapy was found to be slightly longer in those who required outpatient EN versus those who did not (61 vs. 90 days, p=0.08). However, the median time to adjuvant therapy did not differ between those who were and were not receiving EN at the time of adjuvant therapy commencement (80 vs. 92 days, p=0.2). Age (p=0.4), number of co-morbidities (p=0.2), preoperative percent body weight loss (p=0.9), and clinical stage (p=0.8) were not significantly associated with outpatient JT use. Patients who suffered a postoperative complication were most likely to require EN (p=0.002), an association that strengthened as the number of complications increased (p=0.0008). Although not statistically significant, a trend towards increased outpatient EN was noted in patients who underwent transhiatal esophagectomy and total gastrectomy (p=0.06).
Conclusions JT placement carries a considerable morbidity in patients undergoing GER. However, because it is difficult to preoperatively ascertain who will need prolonged EN, the routine placement of a JT is recommended, particularly in those who will likely require adjuvant therapy or are at high risk for postoperative complications. Despite patient desires for early removal of an unused JT, caution should be taken if adjuvant therapy is being considered.

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Keywords Feeding jejunostomy · Gastroesophageal resection

Background

Poor nutritional status negatively impacts postoperative outcomes, a relationship recognized as early as 1936 when Studley reported increased post-operative mortality (3.5% versus 33%) in patients undergoing gastric resection for chronic peptic ulcer disease when the preoperative weight loss was >20%, a finding independent of age, cardiopulmonary function, and type of surgery.[1] This association between malnutrition and poor clinical outcomes has subsequently been validated by others and is attributed to both impaired wound healing and immune function.[2,3] Interestingly, method of caloric replacement appears to play a significant role in curtailing malnutrition-related impaired healing and immune function, with enteral nutrition (EN) providing greater improvement in gastrointestinal flora, mucosal immunity, and diminished acute phase response when compared to parenteral nutrition.[4,5]

Patients undergoing gastroesophageal resection (GER) best exemplify a concern for the deleterious effect of malnutrition and its consequences on clinical outcomes. At present, the primary indication for GER is esophageal and gastric malignancy, disease processes often presenting at advanced stage and heralded by significant dysphagia and weight loss. Although extent of resection and surgical approach vary based on pathology, location of disease, and surgeon preference, all methods carry significant morbidity (dysphagia, aspiration pneumonia, poor gastric emptying, anastomotic leak, and chyle leak), which may further preclude substantial postoperative oral caloric intake.[6] Additionally, the side effects of increasingly used multimodality neo-adjuvant and adjuvant therapies (anorexia, oral mucositis, nausea, and diarrhea) may further exacerbate malnutrition. Taken together, these place patients at higher risk for therapeutic failure, postoperative infections, re-hospitalization, intolerance of adjuvant therapy, and poor overall survival.[7–11]

Since its first description by Busch in 1858, the delivery of EN via a feeding jejunostomy tube (JT) has gained acceptance as an effective method of providing postoperative nutrition to patients incapable of maintaining adequate oral caloric intake.[12] Although the placement of a JT at the time of elective GER is thought to be with low morbidity, the potential for postoperative complications exist and is probably underappreciated and underreported by clinicians. Given this, speculation revolves around the need for routine placement of JT following elective GER. The purpose of this study was to evaluate the utilization and morbidity associated with feeding jejunostomy tubes placed at the time of gastroesophageal resection.

Methods

Patient Population

Under institutional review board approval, a prospective database of patients undergoing elective GER with routine placement of a JT from January 2004 to September 2010 was reviewed. During this time period, a JT was utilized in all patients undergoing a total gastrectomy or any type of esophagectomy. For those undergoing a subtotal gastrectomy, a JT was utilized selectively at the discretion of the surgeon. Several JTs were utilized during this time period. These included 12 and 14-Fr balloon retention MIC jejunal feeding tubes (Kimberbly-Clark, Roswell, GA, USA, stock no. 0200-12LV and 0200-14, respectively) and a 14-Fr MIC jejunostomy feeding tube with a Dacron cuff (Kimberbly-Clark, Roswell, GA, USA, stock no. 0301-14). Tubes were placed in a conventional manner in the proximal jejunum. In patients undergoing a Roux-en-Y reconstruction, tubes were placed distal to the enteroenterostomy. Data analyzed included patient demographics, postoperative complications, inpatient and outpatient JT use, and JT specific complications. JT-related complications were classified as minor or major according to the Clavien Complication Grading System.[13] Trophic EN were defined as small volumes (10–20 ml/h) of nutrients administered via the JT and were not designed to serve as a significant source of caloric intake. Therapeutic EN was defined as ideal body weight-based volumes administered via the JT and meant to serve as the primary source of caloric intake in patients unable to maintain adequate oral intake.

Statistical Analysis

Frequencies and descriptive statistics are provided for patient and treatment characteristics. Fisher's exact tests explored associations with utilization of a JT following resection for categorical variables, and Wilcoxon rank sum tests compared associations for continuous variables. Analyses were performed using SAS v9.2 statistical software.

Results

Seventy-three patients [51 men, 22 women, median age 59 years (range, 21–90)] underwent placement of a JT at the time of elective GER. Primary procedures performed included total gastrectomy (n=28), Ivor–Lewis esophagectomy (n=28), subtotal gastrectomy (n=8), proximal gastrectomy (n=6), and transhiatal esophagectomy (n=3) for both malignant (97%) and benign (3%) disease processes (Table 1). Fifty patients (69%) had multiple baseline co-

Table 1 Patient and treatment characteristics

Variables	73 patients (%)
Gender	
Male	51 (70)
Female	22 (30)
Median age (range), years	59 (21–90)
Patient comorbidities	
Median comorbidities (range)	2 (0–7)
No comorbidity	14 (19)
Single comorbidity	9 (12)
Multiple comorbidities	50 (69)
Comorbidities	
Hypertension	46 (63)
History of tobacco dependence	44 (60)
History of alcohol dependence	20 (27)
Coronary artery disease	17 (23)
Diabetes	14 (19)
Mental health disorder	11 (15)
Chronic obstructive pulmonary disease	10 (14)
Cerebral vascular accident	8 (11)
Peripheral vascular disease	8 (11)
Patient weight (kg, median)	
Normal weight	79 (48–142)
Preoperative weight	74 (48–142)
Preoperative percent weight loss	3 (0–30)
Procedures	
Total gastrectomy	28 (38)
Ivor–Lewis esophagectomy	28 (38)
Sub-total gastrectomy	8 (11)
Proximal gastrectomy	6 (8)
Transhiatal esophagectomy	3 (4)
Postoperative complications	38 (52)
Reoperation	7 (10)
Non-JT-related complication	5 (71)
JT-related complication	2 (29)
Pathology	
Adenocarcinoma	66 (90)
Other (malignancy)	5 (7)
Other (benign)	2 (3)
Systemic and radiation therapy	
Neo-adjuvant chemotherapy	1 (1)
Neo-adjuvant chemo-radiotherapy	16 (22)
Adjuvant chemotherapy	6 (8)
Adjuvant chemo-radiotherapy	22 (30)
Median length of stay (range)	12 (7–93)

JT feeding jejunostomy tube

morbid conditions, the most common being hypertension (63%), history of tobacco dependence (60%), history of alcohol dependence (27%), coronary artery disease (23%), and diabetes (19%). The median normal weight, preoperative weight, and percent weight loss was 79 kg (range, 48–142), 74 kg (range, 48–142), and 3% (range, 0–30), respectively. Seventeen patients (23%) had completed a course of neo-adjuvant therapy (chemotherapy=1%, chemo-radiotherapy=22%), and 28 patients (38%) went on to receive adjuvant therapy (chemotherapy=8%, chemo-radiotherapy=30%). The median length of stay was 12 days (range, 7–93).

Forty-nine percent (n=38) of the cohort experienced a non-JT-related complication. Complications included pneumonia (19%), anastomotic complication (18%), intra-abdominal abscess (12%), atrial fibrillation (11%), surgical site infection (8%), and small bowel obstruction (7%). Twenty-four percent (n=18) experienced a major (n=10) or minor (n=11) JT-specific complication (Table 2). Seven patients (10%) required reoperation for five non-JT-related (three anastomotic leaks, one fascial dehiscence, and one intra-abdominal abscess) and two JT-related (two small bowel obstructions) inpatient postoperative complications (Table 1). All remaining JT-related complications were

Table 2 Jejunostomy-tube-associated complications

Variables	*N* (%)
Number of patient with JT complication	18 (25)
Number of JT complications	21
Complication grade[a]	
Minor (grade≤2)	11 (52)
Major (grade≥3)	10 (48)
Types of JT complications	
Dislodgement	
Inpatient	2
Outpatient	5
Leak (outpatient)	5
Small bowel obstruction (inpatient)	3
Unable to unclog (outpatient)	1
Site infection (outpatient)	2
Pain requiring removal (outpatient)	1
Broken catheter (inpatient)	1
Non-functional (inpatient)	1
Management of major complications	
Interventional radiology procedure	8 (80)
Laparotomy	2 (20)
Management of minor complication	
No intervention	6 (55)
Removal of JT	3 (27)
Topical medicine application	1 (9)
Balloon deflation	1 (9)

JT Feeding jejunostomy tube

[a] Clavien complication grading system

managed by an interventional radiologist (n=8), bedside procedure (n=5), or did not require intervention (n=6). Of the six minor outpatient complications identified which did not require intervention, two were minor leaking around the base of the JT, which were managed with frequent dressing changes, and the remaining four were accidental JT dislodgement in four patients all nearing the end of their adjuvant therapy, only two of whom were using supplemental EN.

Sixty-three patients (86%) were discharged tolerating a postgastrectomy diet, seven (10%) nil per os, and three (4%) restricted to a liquid diet (Table 3). Inpatient EN was initiated in 50 patients (68%) primarily in the form of trophic EN (84%), but continued on discharge with therapeutic intent in 40 patients (54%). Indications for outpatient therapeutic EN included failure to thrive (54%), dysphagia (21%), anastomotic leak (15%), chyle leak (3%), esophagostomy (3%), and duodenal stump leak (3%). For the entire cohort, the median time to discontinuance of outpatient EN and removal of the JT was 44 days (range, 4–203) and 71 days (range, 15–337), respectively. The median time to removal of the JT was significantly shorter in patients who did not require outpatient EN [52 days (range, 15–337) versus 127 days (range, 25–254), p=0.01].

When the adjuvant therapy cohort (n=28) was analyzed, whereas five patients (13%) utilized their JT at the commencement of therapy for caloric supplementation, 21 patients (75%) required therapeutic EN during its course secondary to failure to thrive. Although not statistically significant, the median time to adjuvant therapy was found to be slightly longer in those who required outpatient EN versus those who did not (61 versus 90 days, p=0.08). However, the median time to adjuvant therapy did not differ between those who were and were not receiving EN at the time of adjuvant therapy commencement (80 versus 92 days, p=0.2). Median time to removal of the JT in the adjuvant therapy cohort was 173 days (range, 25–254; Table 3).

Univariable analyses explored the association of demographic, clinical, and pathological variables with outpatient JT utilization (Table 4). Patients who suffered a postoperative complication were more likely to require outpatient therapeutic EN (69% versus 32%, p=0.002), an association that strengthened as the number of complications increased (p=0.0008). Twenty-six percent of patients requiring outpatient therapeutic EN had three or more

Table 3 Post-operative diet and jejunostomy tube utilization

Variables	73 patients (%)
Discharge diet	
Postgastrectomy	63 (86)
Nil per os	7 (10)
Liquid	3 (4)
Inpatient JT utilization	50 (68)
Trophic EN	42 (82)
Therapeutic EN	9 (18)
Outpatient JT utilization	39 (53)
Trophic EN	0 (0)
Therapeutic EN	39 (100)
Indication	
Failure to thrive	22 (54)
Dysphagia	8 (21)
Anastomotic leak	6 (15)
Chyle leak	1 (3)
Duodenal stump leak	1 (3)
Esophagostomy	1 (3)
Adjuvant therapy cohort (n=28)	
EN dependence at initiation of therapy	5 (13)
EN dependence during therapy	21 (75)
Median time to EN discontinuance (range), days	44 (4–203)
Median time to JT removal (range)	
Entire cohort, days	71 (15–337)
Therapeutic EN cohort, days	127 (25–254)
No therapeutic EN cohort	52 (15–337)
Adjuvant therapy cohort	173 (25–254)

EN enteral nutrition, *JT* feeding jejunostomy tube

Table 4 Univariable analysis of factors associated utilization of routinely placed feeding jejunostomy following elective gastroesophageal resection

	N	Outpatient JT Use (%)	*p* value
Gender			
Male	51	29 (57)	0.4
Female	22	10 (45)	
Procedure			
Total gastrectomy	28	19 (66)	0.06
Ivor-Lewis esophagectomy	28	13 (46)	
Subtotal gastrectomy	8	2 (25)	
Proximal gastrectomy	6	2 (33)	
Transhiatal esophagectomy	3	3 (100)	
Pathologic stage			
Stage 1	24	13 (54)	0.5
Stage 2	33	21 (64)	
Stage 3	8	3 (38)	
Stage 4	3	1 (33)	
Post-operative complications			
Yes	38	27 (71)	0.002
No	35	12 (34)	
Adjuvant therapy			
Yes	28	16 (57)	0.9
No	40	22 (55)	

JT feeding jejunostomy tube

complications compared to only 5% of patients who did not require outpatient EN. When the relationship between the type of procedure performed and JT utilization was analyzed, a trend toward increased JT utilization was noted in patients undergoing transhiatal esophagectomy, and total gastrectomy ($p=0.06$). Gender ($p=0.4$), pathological stage ($p=0.5$), and adjuvant therapy ($p=0.9$) were not significantly associated with outpatient JT use. Similarly, age ($p=0.5$), number of co-morbidities ($p=0.2$), and preoperative percent body weight loss ($p=0.9$) were not significantly associated with outpatient JT use.

Discussion

Few authors have sought to report the utilization and morbidity associated with placement of a JT at the time of elective GER. Given this, conflicting opinions exist regarding the overall safety of routine JT placement, the extent to which JT are used after gastroesophageal resection and, more interestingly, the influence of adjuvant therapy on JT utilization. Han-Geurts et al.[14] investigated the incidence of JT-related complication requiring reoperation following esophageal resection ($n=1,166$). Thirteen complications (1.1%) were identified that required reoperation for intraperitoneal leakage ($n=5$), JT dislodgement ($n=4$), herniation ($n=3$), and torsion ($n=1$). Mortality rate was 0.4% ($n=4$) despite reoperation. The authors concluded that complications of leakage necessitating reoperation are associated with a high mortality rate and that other means of enteral access should be considered. No data were provided regarding perioperative JT utilization. Gupta et al.[15] similarly reviewed his institution's experience of 203 consecutive patients who underwent esophagectomy for both malignant (82%) and benign (18%) disease with placement of a JT at the time of laparotomy. EN was initiated in all patients within 72 h of surgery. Fifty-two percent ($n=106$) continued to require EN by the tenth postoperative day, and only 13% ($n=27$) required EN beyond 30 days to maintain caloric requirements. The mean length of JT use was 16.6±22 days. Sixty-four percent of patients with an anastomotic leak versus 50% of the patients with any other postoperative complication required EN beyond 30 days. The mean duration for JT utilization was significantly higher for patients who developed an anastomotic leak (33 versus 15 days, $p=0.000$) and other postoperative complications (27 versus 15 days, $p=0.000$) when compared to those without anastomotic leak or postoperative complications. No JT-related complications required surgical intervention or were associated with death. Wani et al.[16] reported a series of 463 patients who underwent GER for carcinoma with routine placement of a JT and routine initiation of EN within the first 24 h of the postoperative period. EN was continued for a mean of 19±8.4 days, with 54% of patients requiring supplemental EN at 2 weeks. Catheter blockage was the most commonly reported complication (7.3%), 79% of which were managed with saline flush and 21% required reoperation for jejunojejunal intussusception ($n=3$) and *Ascaris*-associated JT blockage ($n=4$). Seven patients (1.5%) reported skin excoriation at the site of the JT, and no catheter dislodgements were identified. No JT-related deaths were reported. The authors of this series concluded that the JT use is effective and safe following GER, and it should be placed routinely. Influence of postoperative adjuvant therapy on outpatient utilization of JT was not explored in any of the aforementioned series

Our analysis of 73 patients who underwent GER with placement of a JT demonstrates that JT placement is not without significant morbidity. Twenty-five percent ($n=18$) of the cohort suffered a JT-related complication, half of which were considered major complications defined as requiring surgical, endoscopic, or radiological intervention. Although most of the major complications ($n=8$) were managed via an interventional radiologic procedure with minimal additional morbidity, two required reoperation. The observed major complication rate and resulting reoperative rate begs the question of whether a more selective approach should be taken to JT placement at the time of GER and whether specific clinical factors may help predict who will likely require postoperative EN. Despite the potential for morbidity, we continue to believe that the placement of a JT following GER is justified by the observed pattern of outpatient JT utilization in our patients. While postoperative complication was found to be statistically associated with increased outpatient JT utilization ($p=0.002$), the overwhelming majority of patients who required EN at discharge were secondary to failure to thrive (54%) and dysphagia (21%). Similarly, in a patient population where 90% of the cohort underwent surgery for gastroesophageal malignancy, it was noted that a significant number of patients (75%) who went on to receive systemic adjuvant therapy became JT dependent during the course of adjuvant therapy secondary to failure to thrive related to chemotherapy and/or radiotherapy associated side effects, despite only 13% of the cohort initially requiring EN at the commencement of therapy. Not surprisingly, univariable analysis found a strong association between postoperative complications and outpatient JT utilization ($p=0.002$). Albeit non-statistically significant, the type of procedure performed (transhiatal esophagectomy>total gastrectomy>Ivor–Lewis esophagectomy) was also found to be associated with increased postoperative JT utilization ($p=0.06$). Despite these findings, it remains difficult to preoperatively ascertain who will most likely benefit from

routine JT placement secondary to risk of postoperative complication or type of procedure performed. GER is commonly attended by postoperative morbidity, regardless of the type of resection, our series showing a 52% non-JT-related complication rate and 10% overall reoperative rate. One could argue that it is feasible to selectively place a JT only in those patients who experience a postoperative complication or in those in whom the risk of a postoperative complication is predictably high. However, the postoperative placement if a JT is likely to be associated with higher morbidity than that of routine placement and early removal if not utilized. Furthermore, when patient characteristics routinely used by physicians to help stratify risk of postoperative complications, such as advanced age, advanced pathological stage, number of co-morbidities, and preoperative percent body weight loss, were analyzed, no significant association was found with outpatient JT use, underscoring our inability to accurately predict who will experience a postoperative complication necessitating prolonged EN. Lastly, a significant number of patients appear to require EN for reasons other than postoperative complications, as well as following a prolonged period of JT disuse, as noted above.

The observed complication rate has prompted us to take additional measures in hopes of diminishing JT-associated morbidity. Several technical considerations are worth mentioning based on our experience. The most serious of these complications were JT-related bowel obstruction. One technical consideration is to bring the tube in through the abdominal wall as laterally as comfortably possible such that the loop of jejunum that the tube enters lies laterally as opposed to anteriorly in the abdomen making small bowel volvulus less likely. Additionally, we Witzel the proximal JT and affix the small bowel to the posterior abdominal wall in at least three points (enterotomy site, 2 cm proximal and 2 cm distal to enterotomy) in hopes of preventing torsion. In our early experience, we routinely used a 14-Fr tube with a 7–10 cc retention balloon. This balloon is large enough that in some patients with small caliber jejunum, it has the potential to obstruct the small bowel. One of the postoperative bowel obstructions was clearly related to the size of the balloon on this tube, and it should be used with caution in our opinion. As such, we began to sabotage the balloon on the 14-Fr tubes to prevent this problem. However, doing this increased the likelihood that the tube would become dislodged, and a number of patients with this complication were during this time period. We then began using a 14-Fr tube with a Dacron cuff that is designed to become incorporated into the subcutaneous tissue and prevent dislodgement. However, the design of this tube is not patient friendly, and on at least one occasion, there was a tube-associated subcutaneous infection that we deemed potentially associated with the Dacron cuff. We currently use a 12-Fr tube with a 3–5 cc balloon that does not have the potential to obstruct the small bowel, and since routine use of this tube, we have not had a that problem. However, use of the 12-Fr tube has increased the likelihood of JT clogging. To try and prevent this, we educated patients and their family with regard to this problem, and patients receive JT care teaching by the nursing staff prior to discharge and are advised to flush the JT three times daily with carbonated water regardless of its use.

In conclusion, placement of JT at the time of GER is associated with significant morbidity, most of which can be managed non-invasively or via the use of an interventional radiological procedure. The reoperation rate for JT-related complications is not insignificant accounting for one third of the 10% reoperative rate in this patient cohort. Because it is difficult to preoperatively ascertain who will need prolonged EN, the routine placement of a JT is recommended, particularly in those who will likely require adjuvant therapy or who are at high risk for postoperative complications. Despite patient desires for early removal of unused JT, caution should be taken if adjuvant therapy is being considered.

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Systemic Inflammation with Multiorgan Dysfunction Is the Cause of Death in Murine Ligation-Induced Acute Pancreatitis

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Abstract
Background We have previously shown that distal pancreatic duct ligation-induced acute pancreatitis in mice is associated with substantial mortality.
Methods We examined the cause of death in duct ligation-induced acute pancreatitis in mice by serial examination of multiple parameters in three experimental groups: distal pancreatic duct ligation (PD), bile duct ligation alone (BD), and sham operation (S).
Results BD and S had no mortality, while PD had 94% mortality with most deaths between days 2 and 4. Characteristics of mice with acute pancreatitis included (ANOVA; $p<0.05$): extracellular regulated kinase activation in the pancreas and lung; pancreatic neutrophil infiltration and acinar cell necrosis maximal on day 2; increased plasma cytokine and aspartate aminotransferase levels and bronchoalveolar lavage fluid neutrophil count and cytokine levels, peaked on day 3; hypotension and bradycardia were worst on day 4; pulmonary neutrophil infiltration and plasma creatinine level peaked on day 4. Liver injury evidenced by raised aspartate serum transaminase after hepatic obstruction was exacerbated by PD.
Conclusions Systemic inflammation with multiorgan dysfunction causes death in pancreatic duct ligation-induced acute pancreatitis in mice. This experimental model is a suitable experimental analogy of "early severe gallstone pancreatitis" to investigate disease pathogenesis and to evaluate novel therapeutic strategies.

Keywords Acute pancreatitis · Systemic inflammatory response syndrome · Multiple organ dysfunction syndrome · Mouse · Extracellular signal-regulated kinase

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Introduction

We recently established a novel murine model of pancreatic duct ligation-induced acute pancreatitis that is associated with substantial mortality within a few days.[1] As mortality following murine pancreatic duct ligation has not been described previously by other investigators prior to our original description,[1] we performed the present study to identify the possible factors that may contribute to the mortality associated with this model. Our strategy was to determine the time course of death in ligation-induced acute pancreatitis in mice and to correlate our findings with other important observations such as systemic cytokine release and distant organ injury. We found that the onset and progression of the systemic inflammatory response syndrome and the multiple organ dysfunction syndrome

paralleled the period of maximum mortality observed between postoperative days 2 to 4. Hypercytokininemia and hypotension along with acute lung injury seemed to be the major pathogenetic mechanisms leading to death in ligation-induced acute pancreatitis in mice. Our findings indicate that this new experimental model of early severe gallstone pancreatitis resembles the human disease sufficiently to be used as a suitable analogy to investigate disease pathogenesis and to test new therapeutic options. Although there are fundamental species differences between mice and humans with respect to specific pathophysiologic events, the limitations in investigating early stages of disease pathogenesis in humans necessitates the search for new experimental models to perform preliminary investigations. Taking into perspective advances such as increased availability of transgenic mice and progress made with in vivo gene modulation techniques, a new mouse model of acute pancreatitis has the potential to serve as a convenient experimental setting for a wide variety of preliminary investigative studies to be performed.

Materials and Methods

Materials

We used C57BL/6, male, retired breeder mice (≥9 months of age) weighing 30–50 g in these studies (National Cancer Institute, Frederick, MD, USA). Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay was performed using a commercial kit and following the manufacturer's instructions (cat. no. S7101, Milipore, Billerica, MA, USA). Antibodies against phosphorylated extracellular regulated kinase (ERK) and total ERK (cat. no. 7641 and 9101, Cell Signaling, Danvers, MA, USA), and β-actin (cat. no. A-5316, Sigma-Aldrich, St. Louis, MO, USA) were used for immunoblotting.

Animal Surgery

Experimental protocols were approved by the Institutional Animal Care and Use Committees at the University of Iowa and the VA Medical Center. Midline laparotomy was performed on mice under general anesthesia with isoflurane.[1] Postoperatively, mice were allowed access to food and water ad libitum and were given buprenorphine analgesia and 1 cm^3 sterile normal saline s.c. hydration twice daily. The mice were monitored for physical activity, grooming, alertness, response to stimulation, and other signs of stress at least two times daily.

In mice, the duct that drains the splenic portion of the pancreas unites with the common bile duct to form a long common bile-pancreatic duct that drains the duodenal portion of the pancreas prior to entry into the duodenum (Fig. 1). The mice were studied in three experimental groups: (1) sham operation (S): the distal bile-pancreatic duct was dissected but not ligated, (2) bile duct ligation (BD): only the common bile duct was ligated prior to its junction with the splenic portion of the pancreatic duct, and (3) distal common bile-pancreatic duct ligation (PD): the common bile-pancreatic duct was ligated near its junction with the duodenum. In our previous study,[1] we have already shown that acute pancreatitis induced by PD alone results in similar mortality and morphological pancreatic changes as PD+BD, and therefore we limited our studies to PD in the present study. It must be noted that PD will cause biliary obstruction in addition to obstructing outflow from the pancreatic ductal system and that BD alone for 2 weeks is not associated with mortality in our model.[1] Therefore, BD is a useful control group to compare and contrast the influence of biliary obstruction alone with biliary obstruction in relation to acute pancreatitis induced by PD. For time-course studies, sham-operated and BD controls were electively euthanized on days 2, 3, or 4, to serve as controls

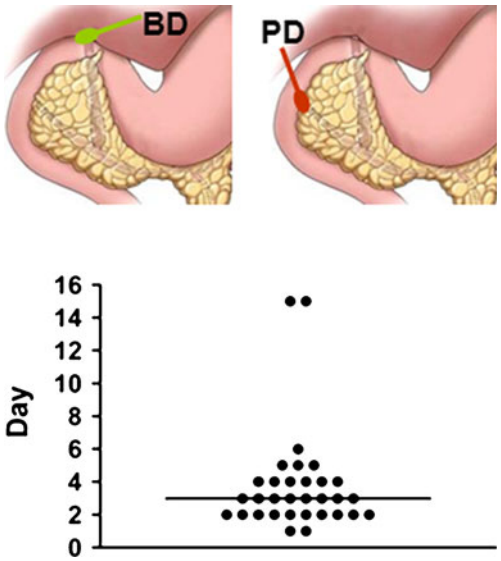

Fig. 1 *Upper panels*, surgical anatomy of bile duct ligation (*BD*) and pancreatic duct ligation (*PD*). In a control group with BD, the common bile duct was ligated before its junction with the splenic portion of the pancreatic duct. In the diseased group with PD, the distal common bile-pancreatic duct was ligated near its junction with the duodenum. Note that PD also results in biliary obstruction in addition to pancreatic duct obstruction. *Lower panel*, scatter plot of mortality in mice with ligation-induced acute pancreatitis. Thirty out of 32 mice died between days 1 and 6 after pancreatic duct ligation. The *y*-axis depicts the number of days after surgery. The *solid line* depicts the median mortality (3 days). All sham-operated controls and bile duct-ligated controls (n=10/control group, respectively; mortality data not shown for controls), and two mice with pancreatic duct ligation, survived the entire 15 days of observation and were euthanized electively

for the mice with PD that were euthanized in the premortal state.

Survival Studies

For survival studies (n=32 in the PD group), when mice began to show signs of severe disease, they were euthanized to prevent suffering. The decision to euthanize mice in the premorbid state was based on twice daily monitoring using criteria such as visibly reduced physical movement, diminished grooming activity, blunting of alertness, and poor reflex response to sound (e.g., gently tapping on the cage). Mice that were active and survived were observed for 15 days prior to elective euthanasia.

Morphological Studies

Paraffin-embedded portions of pancreas and lung that were fixed in neutral-buffered formaldehyde were sectioned and stained with hematoxylin and eosin (H&E). Prior to harvesting the lung for histology, a tracheotomy was performed to inflate the lobe with fixative. Selected specimens were subjected to immunohistochemistry for TUNEL assay. Dr. Meyerholz (Director, Comparative Pathology Laboratory, University of Iowa) independently conducted the morphological and morphometric analyses, as described previously.[1,2]

Bronchoalveolar Lavage

Under general anesthesia, immediately prior to euthanasia, a tracheotomy tube was inserted and the lungs were filled with 1 ml of sterile saline that was then siphoned out and the process was repeated 3 times. The bronchoalveolar lavage (BAL) fluid was centrifuged at 290×g for 10 min at 4°C, and the cell pellet was re-suspended in phosphate-buffered saline. A total white blood cell (WBC) count was performed using a hemocytometer, a smear was prepared using a Shandon cytospin-2 cytocentrifuge (Shandon Inc., Pittsburgh, PA, USA), and a neutrophil count was performed after staining with a Hema-3 Stain Set (cat. no. 122-911, Fisher Scientific Company LLC, Kalamazoo, MI, USA) using a light microscope (Olympus IX51, Olympus, Tokyo, Japan) under a ×60 oil immersion objective lens. The concentration of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in BAL fluid was measured using a commercial ELISA kit (cat. no. CMC3013 and CMC0813, Invitrogen, Carlsbad, CA, USA).

Blood Pressure Measurement

Tail cuff-blood pressure was measured using a rodent Blood pressure analysis system (Visitech System, Inc. Apex, AC). Briefly, the animal was placed on platform maintained at 37°C, and the tail was fed through a cuff. The animal was restrained using a magnetic rectangular box designed to calm the animal. After a 5-min calming period, pressure recordings were begun using a software system that automates the procedure where the blood pressure is averaged over ten consecutive readings and the mean pulse rate is also recorded.

Systemic Studies

Plasma creatinine and aspartate serum transaminase (AST) levels were measured on a Vitros Chemistry Analyzer (Vitros 350, Ortho Clinical Diagnostics, Raritan, NJ, USA). Plasma TNF-α and IL-1β concentrations were measured using ELISA as for BAL.

Immunoblotting

Immunoblotting to evaluate phosphorylation of the mitogen activated protein (MAP) kinase ERK was performed as previously described.[2] Briefly, frozen portions of pancreas or lung were homogenized, and 20 μg protein was electrophoresed with a 12% SDS-polyacrylamide gel. After transfer to a PVDF membrane, incubation with the respective primary antibody was performed, and the blots were developed. Densitometry was performed using ImageJ software (Research Services Branch, National Institute of Mental Health, Bethesda, MD, USA).

Statistics

Parametric data were analyzed with one-way ANOVA, while nonparametric data were compared using the Kruskal–Wallis one-way ANOVA (p<0.05), with post hoc tests for confirmation of significance.

Results

Survival Studies

For determination of the time course of mortality, day 1 was defined as 0 to <24 h, day 2 as 24 to <48 h, day 3 as 48 to <72 h (and so on and so forth), after surgery. The vast majority of mice from the PD group were euthanized in a premorbid state or died (24/32 mice or 75%) on days 2, 3, and 4 (ten, eight, and six mice, respectively), with a median survival time of 3 days (Fig. 1). Therefore, for detailed characterization studies, we selected days 2, 3, and 4 to evaluate the possible mechanisms contributing to death in this experimental model. Seven mice from the PD group died even before euthanasia could be performed (two on

day 1 and five on day 2), and no investigations were done on the carcasses. The range of death was 1 to 6 days while only two (6.25%) mice survived the entire 15 days to be euthanized electively; a small percentage of rodents may have an accessory pancreatic duct that partially decompresses the ductal system that may possibly explain this deviation from the norm.[3] Sham-operated controls and BD controls had no mortality within the 15 days of observation. For the time-course study, additional sham-operated controls and BD controls were prepared and electively euthanized on days 2, 3, or 4, even though they were active and not premorbid, to serve as comparisons for the mice with acute pancreatitis that were euthanized.

Pancreatic Morphology

Mice in the PD group, but not those in the sham or BD control groups, developed morphological changes diagnostic of acute pancreatitis as evidenced by interacinar and interlobular edema, polymorphonuclear (PMN or neutrophils) infiltration and acinar necrosis (Fig. 2). Morphometric analysis of edema (range of score, 0–3), acinar cell necrosis (range of score, 0–3), and neutrophilic infiltration showed significant increases in pancreata of diseased mice on days 2, 3, and 4. The necrosis score and neutrophil infiltration were highest on day 2. Interestingly, apoptosis was a relatively late finding with significant changes in the diseased pancreas only on day 4 (Fig. 2; TUNEL).

Acute Lung Injury

Morphometric analysis of lung morphology showed increased neutrophil infiltration that peaked on day 4 in both the BD and PD groups (Fig. 3). To clarify why mice with PD died while those with BD did not, although significant pulmonary neutrophil infiltration occurred in both groups, we extended our investigations to determine the characteristics of BAL fluid so that we may distinguish the extent of acute lung injury in these groups. BAL neutrophil count was significantly increased only in the PD group but not the

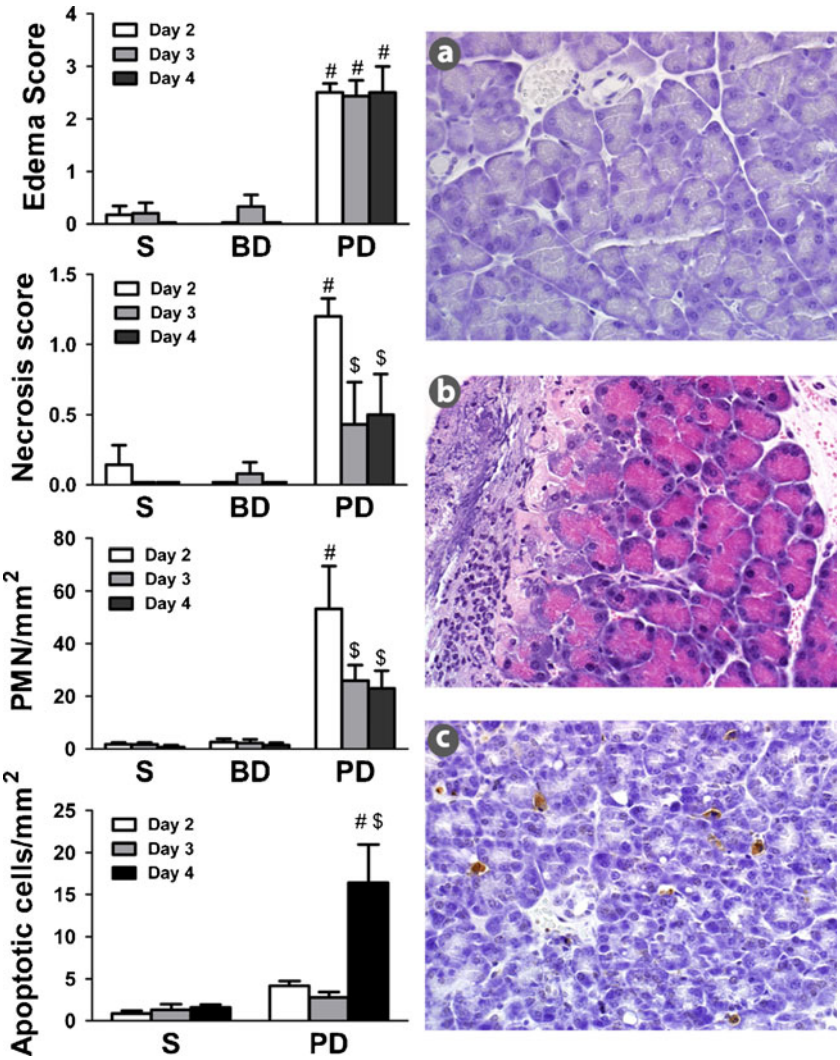

Fig. 2 Pancreatic morphological studies. *Left panels*, morphometric analysis of H&E-stained sections of pancreas show the time course of edema, acinar necrosis, and PMN infiltration in sham (*S*), bile duct ligation (*BD*), and pancreatic duct ligation (*PD*) groups. Morphometric analysis of TUNEL-stained sections of pancreas show significant apoptosis only on day 4 after PD. Data are mean±SEM, $p<0.05$; *pound sign*, significance vs. S and BD of the same day, *dollar sign*, significance vs. PD of day 2. *Right panels*, photomicrographs of pancreas show representative areas of *a* sham-operated pancreas, *b* acinar cell necrosis and neutrophil infiltration after PD, and *c* apoptotic cells in pancreas after PD by TUNEL staining (*brown stain*)

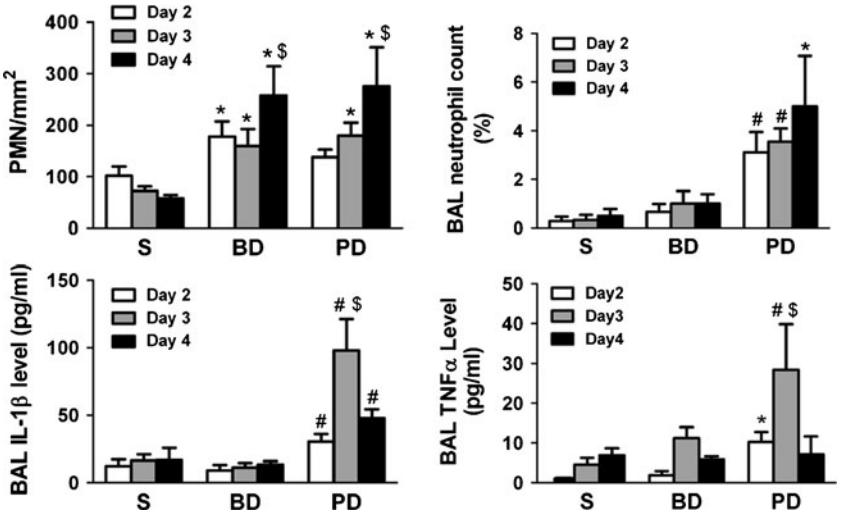

Fig. 3 Acute lung injury. Morphometric evaluation of H&E-stained slides show that neutrophil (*PMN*) infiltration in the lung of bile duct ligation (*BD*) and pancreatic duct ligation (*PD*) groups was elevated in comparison to sham operation controls (*S*), reaching maximum on day 4 (n=3–10/group). Neutrophil count of bronchoalveolar lavage (*BAL*) fluid showed an elevated number only in the PD group (n=3–8/group). Level of IL-1β and TNF-α in BAL fluid was elevated only in the PD group, with a peak on day 3 which corresponded to median mortality (n=4–11/group for IL-1β and 3–13/group for TNF-α). Data are mean±SEM, n=3–10/group, $p<0.05$; *asterisk*, significance vs. S; *pound sign*, significance vs. S and BD of the same day; and *dollar sign*, significance vs. PD of day 2

BD group (Fig. 3); there was no significant difference in total WBC count between the groups (S=1.79±0.29, BD=1.39±0.13, PD=1.92±0.14; mean±SEM, $\times 10^2$ cells/μl; ANOVA, $p>0.05$). Similarly, BAL concentrations of IL-1β and TNF-α were not higher in the BD group compared with sham controls while they were elevated in the PD group with a peak on day 3. The increased inflammatory characteristics of BAL fluid in the PD group, but not in both controls, indicates that acute lung injury is of greater pathophysiologic severity in pancreatitic mice compared with hepatic obstruction alone.

Cardiovascular Dysfunction

As cardiovascular dysfunction resulting from the effects of inflammatory mediators in the systemic circulation may contribute to mortality, we evaluated changes in blood pressure and pulse rate in mice with acute pancreatitis. Compared with sham controls, both systolic and diastolic blood pressures decreased in the PD group over time and were undetectable by day 4 (Fig. 4). The pulse-rate measurements showed a similar pattern with progressive bradycardia that was worst on day 4. Neither blood pressure nor pulse rate showed significant changes in the sham group over time.

Renal and Hepatic Dysfunction

Increased plasma creatinine concentration, which peaked on day 4, is functional evidence of renal injury in mice with PD (Fig. 5). During the same period, BD was not associated

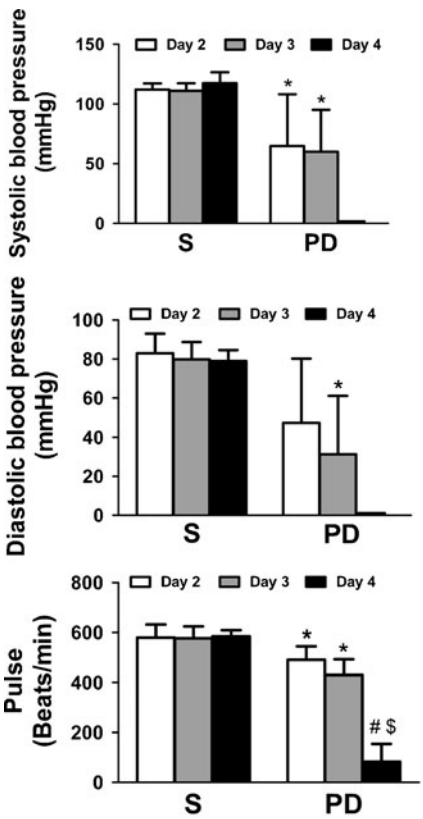

Fig. 4 Cardiovascular dysfunction. Mean systolic blood pressure (*BP*), diastolic BP, and pulse rate of mice after sham operation (*S*) or pancreatic duct ligation (*PD*) are shown. Both BPs decreased in the PD group over time and were undetectable on day 4. Tail pulse rate showed a similar pattern of change to that of blood pressure. Data are mean±SEM, n=4–5/group, $p<0.05$; *asterisk*, significance vs. S; *pound sign*, significance vs. S and BD of the same day; *dollar sign*, significance vs. PD of day 2

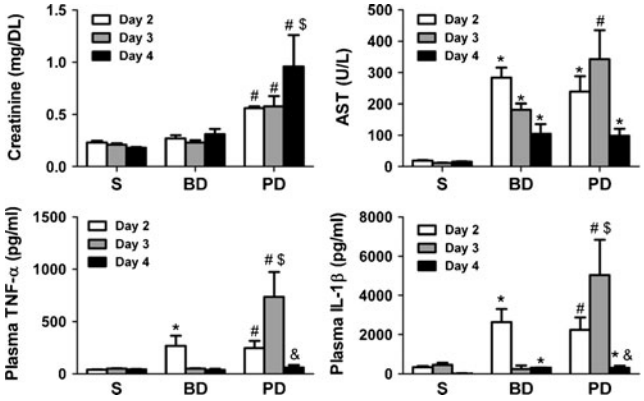

Fig. 5 Renal, hepatic, and systemic changes. Renal injury, evidenced by increased plasma creatinine levels, was seen only in the pancreatic duct-ligated (*PD*) group with a peak on day 4. Liver injury, detected by elevated plasma aspartate aminotransferase (*AST*) levels, occurred in the PD and bile duct-ligated (*BD*) groups but was higher in the PD group than in the BD group on day 3 (suggesting that acute pancreatitis exacerbates liver injury following biliary obstruction; n= 3–8/group). Systemic inflammation, evidenced by elevated plasma levels of TNF-α and IL-1β, was seen to be higher in the PD group than the BD group on day 3 (BD ligation led to a moderate systemic inflammation on day 2 that dissipated thereafter; n=3–10/group). Data are mean±SEM, $p<0.05$; *asterisk*, significance vs. S; *pound sign*, significance vs. S and BD of the same day; *dollar sign*, significance vs. PD of day 2; and *ampersand sign*, significance vs. PD of day 3

with significant elevation of plasma creatinine concentration, compared with sham controls. Therefore, renal dysfunction following PD is attributable to acute pancreatitis rather than hepatic obstruction. Not surprisingly, BD was associated with increased plasma AST that trended downwards after day 2 (Fig. 5). On the other hand, increased plasma AST after PD was significantly higher than after BD on day 3, suggesting that acute pancreatitis exacerbates hepatic obstruction-induced hepatocellular injury.

Systemic Cytokine Release

After pancreatic duct ligation, plasma levels of the cytokines TNF-α and IL-1β were significantly increased on days 2 and 3 and trended downwards thereafter (Fig. 5). Following bile duct ligation, plasma TNF-α and IL-1β levels showed an early increase on day 2 that returned to the baseline soon after, while in contrast, pancreatic duct ligation was associated with a dramatic escalation of both cytokine levels on day 3 compared to day 2.

ERK Activation

MAP kinases such as p38 and ERK are upstream of nuclear transcription factors such as nuclear factor kappa B (NF-κB), while NF-κB is implicated in acute pancreatitis pathogenesis in several experimental models.[4] Our in vitro studies have suggested that ERK inhibition subdues NF-κB activation to a greater extent than p38 MAP kinase in exocrine pancreatic cells.[5,6] Therefore, we developed an interest in ERK as a potential target for inhibition in our experimental model. In our previous study, we showed early activation of ERK in the pancreas within 1 h and the lung within 5 h of PD.[1] In the present study, we evaluated ERK activation at time points beyond the early phase. In mice with acute pancreatitis, ERK activation was apparent in the pancreas and lung on day 3 and increased further in the pancreas on day 4 (Fig. 6). On day 2, pancreatic and pulmonary ERK phosphorylation was prominent even in sham-operated and bile duct-ligated controls, suggesting an influence of the surgical procedure on baseline kinase levels. On day 3, ERK activation in the lung of bile duct-ligated mice was higher than sham controls, consistent with the morphological evidence of acute lung injury associated with hepatic obstruction.

Discussion

In the present report, we have characterized in detail various aspects of our novel experimental model of severe acute pancreatitis and have shown several parallels with

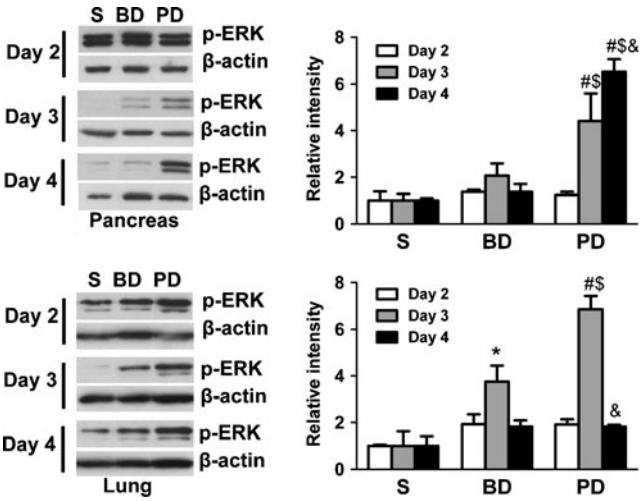

Fig. 6 ERK activation in the pancreas and lung. In the pancreas, ERK was more strongly activated in the pancreatic duct ligation (*PD*) group in comparison to the sham (*S*) and bile duct ligation (*BD*) groups on days 3 and 4, with the maximum difference on day 4. ERK activation in the lung showed a different pattern however, with the maximum difference in activation in the PD group occurring on day 3. Also in the lung, ERK showed higher activation in the BD group in comparison to sham controls on days 3 and 4. β-Actin protein expression in each sample was used as a normalizing control. Relative intensity data from densitometry of blots are presented as comparison of sham of day 2. Data are mean±SEM, $p<0.05$; *asterisk*, significance vs. S; *pound sign*, significance vs. S and BD of the same day; *dollar sign*, significance vs. PD of day 2, *ampersand sign* significance vs. PD of day 3

clinical disease such as increased circulating cytokines, acute lung injury, renal dysfunction, cardiovascular instability, and exacerbation of hepatocellular injury. These similarities with clinical disease will provide the groundwork for detailed investigations into disease pathogenesis and a testing ground for new therapeutic initiatives. We have systematically depicted the time course of salient events related to the systemic inflammatory response syndrome and multiple organ dysfunction syndrome in an original murine model that serves as an experimental analogy of severe gallstone pancreatitis. As "early severe acute pancreatitis" has recently been defined as a new subgroup of patients with a high mortality rate associated with the failure of one or more organ systems, our novel murine model assumes special relevance.[7]

Our results show that the preponderance of mortality (75%) from pancreatic duct ligation-induced acute pancreatitis in mice occurs within 2 to 4 days. The median mortality of 3 days in this model is paralleled by a peak on day 3 of circulating cytokines, BAL fluid neutrophil count, BAL cytokine levels, and liver injury and by a peak on day 4 of hypotension, bradycardia, pulmonary neutrophil infiltration, and renal injury. This pattern of early organ dysfunction and high mortality within a few days is very reminiscent of the "early severe acute pancreatitis" subgroup identified clinically and may, therefore, provide insights into the pathogenesis of this high risk population of acute pancreatitis patients. Clinical studies have shown that 40–60% of deaths related to severe acute pancreatitis occur within 7 days of admission and that early organ failure plays an important role in fatal outcomes in severe acute pancreatitis.[7–11] These studies have concluded that once early organ failure is present at admission, the risk of progressive organ failure leading to death is high. One of these studies showed that organ failure developed or progressed in nearly 80% of the early severe acute pancreatitis patients even though they were admitted within 3 days of symptoms and in spite of intensive care treatment.[7] Therefore, if novel therapeutic protocols can be applied based on a better understanding of the pathophysiology of the early stages of the disease, in addition to non-specific intensive care treatment, there could potentially be improvements in mortality in this subgroup of patients.

In our murine model of ligation-induced acute pancreatitis, we see that ten out of 32 (31%) mice died by postoperative day 2. On day 2, we also see that: (1) the pancreas has interstitial edema, neutrophil infiltration, and acinar cell necrosis; (2) circulating cytokines are elevated; (3) BAL fluid cytokines and neutrophils have increased; (4) renal function is affected; and (4) bradycardia and hypotension are noticeable. Therefore, within 24–48 h of pancreatic duct ligation, acute pancreatitis has progressed to systemic inflammation, multiorgan failure has ensued, and almost a third of the mice have died. Therefore, detailed investigations of the first 24 h could elucidate salient pathogenic events and provide a road map for further examination of the key premortal events that follow in this experimental model.

Systemic inflammation leading to acute lung injury is the major determinant of death from acute pancreatitis irrespective of the etiology of pancreatitis.[12,13] In the present study, we have demonstrated that in contrast to hepatic obstruction, pancreatic duct obstruction is associated with a substantially greater degree of acute lung injury as evidenced by the inflammatory characteristics of the BAL fluid. Although bile duct ligation alone was also associated with pulmonary neutrophil infiltration it was not associated with increased neutrophils, IL-1β or TNF-α in BAL fluid, as seen in mice with acute pancreatitis. Interestingly, patients with evidence of renal dysfunction in addition to acute lung injury have a higher mortality rate than those with lung injury alone.[12] We have found that mice with pancreatic duct ligation show biochemical evidence of renal injury that increases from days 2 to 4, while mice with hepatic obstruction alone did not show changes in renal function compared with the sham control group although we previously showed that morphological evidence of renal tubular injury was similar after pancreatic or bile duct ligation.[1]

In our study, BD alone did not cause mortality during the 2 weeks of observation. Reports from other investigators have shown that BD alone in C57BL/6 mice can result in mortality within 2 weeks.[14,15] We attribute this difference to the more mature (older) mice used in our study, as the mortality following BD alone in C57BL/6 mice reported by other investigators was seen in mice that were less than 8 weeks of age in contrast to the C57BL/6 mice that were at least 9 months old in our study. Although BD alone did not cause mortality in our study, it is possible that hepatic obstruction contributes to disease pathogenesis in murine ligation-induced acute pancreatitis as PD was associated with higher serum AST levels compared with BD alone, suggesting that ligation-induced acute pancreatitis exacerbates hepatocellular injury seen with hepatic obstruction. In this regard, hepatic inflammation in acute pancreatitis is implicated in disease pathogenesis in other experimental models.[16,17] For future studies, it will be interesting to introduce an additional experimental group where the splenic portion of the pancreatic duct is ligated before its union with the common bile duct, to compare proximal pancreatic duct ligation with and without bile duct ligation. The PD group in the present study represents patients with persistent gallstone impaction of the ampulla of Vater where the biliary tract, in addition to the pancreatic duct, is obstructed.

The pathogenic mechanisms of acute pancreatitis are not well understood, partly due to difficulties related to timely or anatomical access to clinical specimens. Patients with acute pancreatitis typically present to the hospital a day or more after onset of abdominal pain and the deep anatomical location of the pancreas makes it difficult to access. Furthermore, there are insufficient animal models that recapitulate the early stages of the disease. New experimental models that reproduce the natural history of severe acute pancreatitis are evidently required to advance our understanding of the pathophysiology of the disease and its complications. Existing animal models of acute pancreatitis are either not analogous to known etiologies of acute pancreatitis or are not severe enough to cause mortality.[18] For example, choline-deficient ethionine-supplemented diet-induced acute pancreatitis in mice is fatal but the diet does not cause pancreatitis in humans. On the other hand, pancreatic duct ligation in rats causes transient inflammation of the pancreas but the rats survive for several months with atrophy of the pancreas.[3,19] Compared with these models, distal pancreatic duct ligation in mice more closely resembles impaction of the ampulla of Vater seen in gallstone pancreatitis.

A potential role for the MAP kinases JNK, p38, and ERK in the pathogenesis of acute pancreatitis was suggested in view of their regulation of nuclear transcription factors such as NF-κB and activator protein-1 (AP-1), as these transcription factors were shown to be involved in the pathogenesis of acute pancreatitis in experimental models.[4,5,20–26] We have previously shown that ERK, NF-κB, and AP-1 are activated in the mouse pancreas within 1 h of pancreatic duct ligation,[1] while here we have shown that pancreatic ERK activation is sustained and also progresses until the premortal state in acute pancreatitis; also, pulmonary ERK activation peaks on day 3. As we have observed that ERK inhibition reverses agonist-stimulated increases in NF-κB-dependent gene transcription in an exocrine pancreatic malignant cell line (AR42J cells)[5] while p38 inhibition only partially reduces it,[6] we are currently focusing on the role of ERK in disease pathogenesis in ligation-induced acute pancreatitis in mice.

In summary, we have shown in the present study that sequential events in murine ligation-induced acute pancreatitis include pancreatic inflammation with ERK activation, increased plasma cytokines, and distant organ inflammation and dysfunction. Also, liver injury evidenced by raised AST after hepatic obstruction is exacerbated by acute pancreatitis. Additionally, morphological evidence of lung and renal injury after hepatic obstruction alone is not associated with death within the 2-week period of observation. Our findings indicate that the high mortality rate seen in ligation-induced acute pancreatitis in mice is associated with progressive systemic cytokine increase, cardiovascular instability, acute lung injury, liver injury, and renal dysfunction, suggesting that systemic inflammation with multiorgan failure is the proximate cause of death in this experimental model. The mouse is the most commonly used laboratory animal, transgenic mice are constantly being produced to evaluate specific signaling pathways, and in vivo gene modulation techniques have made commendable progress in recent years. Hence, our novel model of ligation-induced acute pancreatitis in mice potentially has wide experimental applications for future studies in the field.

Conclusions

Systemic inflammation with multiorgan dysfunction causes death in ligation-induced acute pancreatitis in mice. This experimental model is a suitable experimental analogy of severe gallstone pancreatitis to investigate disease pathogenesis and to perform preliminary studies of novel therapeutic strategies.

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Ischemic Preconditioning-Like Effect of Polyunsaturated Fatty Acid-Rich Diet on Hepatic Ischemia/Reperfusion Injury

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Abstract
Aim The aim of this study was to investigate a possible preconditioning effect of oral diet enriched with polyunsaturated fatty acids (PUFAs) on liver ischemia/reperfusion (I/R) injuries.
Methods Wistar male rats were fed a standard diet or polyunsaturated fatty acid-rich diet (PRD) enriched with (GII) or without (GIII) ω-3 PUFA. Rats were submitted to partial liver ischemia during 1 h and evaluated in pre- and post-I/R conditions. In pre-I/R condition, livers were collected for determination of fatty acid composition, liver mitochondrial function, malondialdehyde (MDA) content, and histological analysis. Four hours after liver reperfusion serum activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), serum levels of tumor necrosis factor-alpha, interleukin-6, interleukin-10, and prostaglandin-E2, liver mitochondrial function, MDA content, and histology were evaluated.
Results In the pre-I/R condition, GII and GIII groups had an increase on PUFA content and exhibited slight increased macrosteatosis and microsteatosis in the liver. After 4 h of reperfusion, PRD-fed rats showed a marked decrease on steatosis, diminished necrosis, an increase in MDA formation, and mitochondrial uncoupling. We also observed a marked decrease in plasma levels of cytokines and ALT and AST activities in post-I/R condition in PRD groups.
Conclusion In this experimental model in the rat, PRD has a preconditioning effect protecting the liver from I/R injury and should be object of future clinical studies.

Keywords Liver ischemic/reperfusion lesion · Preconditioning · Polyunsaturated fatty acid-rich diet · Hepatic mitochondrial dysfunction

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Introduction

Ischemia is a condition caused by partial or absolute blockage of blood flow through an organ, which results in relative deficiency of oxygen supply. Reperfusion and restoration of oxygen supply, paradoxically, aggravate this condition, causing ischemia/reperfusion (I/R) injury.[1–3]

Liver I/R injury occurs in several clinical situations such as hemorrhagic shock, hepatic resection, liver transplantation, and in multiple organ failure. Injury in liver arises as a result of multiple pathophysiological processes.[4,5] Oxygen deprivation in liver leads to metabolic imbalance with mitochondrial dysfunction and energy deficiency. Hepatocyte and endothelial cells swelling after reperfusion contribute to narrowing sinusoidal blood vessels, leukocyte entrapment, and platelet aggregation, resulting in occlusion and failure of hepatic microcirculation. The subsequent inflammatory response with activation of macrophages,

neutrophils, and Kupffer cells, which produce several mediators such as reactive oxygen species (ROS), proteases, and cytokines, causes further cell damage.[6] Thus, mitochondrial dysfunction and energy deficiency early in the ischemic phase trigger a chain of deleterious pathophysiological responses, ultimately causing hepatocyte death and liver dysfunction.[7]

Some studies have suggested the ischemic preconditioning may ameliorate hepatic I/R.[8–11] The concept of preconditioning was introduced in 1961 to describe a pathological stimulus that occurs below the threshold of definitive lesion that leads to a protective effect.[12] Previous studies have demonstrated that in heart and in brain, preconditioning is associated with a moderate uncoupling of mitochondria respiratory chain.[13,14] Previous study reported that a lipid emulsion (Intralipid) raises hepatocyte uncoupling protein 2 productions that may have a protective effect on hepatocyte by inhibiting mitochondrial production of ROS.[15]

In spite of the information above, the effect of polyunsaturated fatty acid (PUFA)-rich diets on liver I/R injury has not been extensively investigated. The aim of this study was to investigate the preconditioning effect of a PUFA-rich diet on liver injury of rats submitted to ischemia/reperfusion. Mitochondrial function was evaluated by mitochondrial oxidation and phosphorylation activities in rat liver under ischemia/reperfusion injury. The degree of the liver lesion was estimated by measuring serum activities of aspartate aminotransferase and alanine aminotransferase and by tissue histological analysis. The inflammation state of the rats was evaluated by measuring the serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), and prostaglandin-E2 (PGE_2).

Material and Methods

Treatment of Animals

Male Wistar rats weighing 180–200 g were housed in cages with a controlled 12 h-light/dark cycle with free access to a standard chow and water for 1 week. Rats were then randomly divided into three groups: GI (n=20) that received standard diet (SD) containing 4% soybean oil, 23% protein, and 62% carbohydrate (Nuvital, Brazil); GII (n=20) rats were fed a polyunsaturated fatty acid-rich diet (PRD) containing 27% soybean oil enriched with 1% codfish liver oil, 23% protein, and 38% carbohydrate; and GIII (n=20) rats were fed a PRD without codfish liver oil for 4 weeks.

Animal weights were not different among the groups after 4 weeks, ranging from 250 to 280 g. This study was designed in accordance with the Guidelines for the Care and Use of Laboratory Animals.[16] The experimental protocol was approved by the Ethics Committee of the University of São Paulo.

Surgical Procedure and Sample Collection

The rats were submitted to the following experimental protocols:

Pre-ischemia/reperfusion condition (pre-I/R): ten rats from each group were killed without being submitted to surgery. Rats were anesthetized for blood sampling through cardiac puncture and killed by exsanguination. Liver tissue was collected for biochemical and histological examination.

Ischemia/reperfusion condition (post-I/R): ten rats from each group were submitted to partial liver ischemia. Animals underwent 1 h of warm liver ischemia followed by reperfusion (I/R). The animals were anesthetized with intraperitoneal ketamine (30 mg/kg) and xylazine (30 mg/kg) and submitted to orotracheal intubation, and ventilated with a tidal volume of 0.08 ml/g body weight, at a respiratory rate of 60/min, and FiO2 of 0.21 (Small Animal Ventilator model 683, Harvard Apparatus, Holliston, MA, USA). During the surgical procedure, body temperature was monitored using a rectal digital thermometer (YSI Precision 4000A Thermometer, USA), being maintained at 37°C. Median laparotomy was performed and the hepatic pedicle of median and left anterolateral segments were dissected, exposed, and clamped with a nontraumatic microvascular bulldog clamp during 1 h that induces ischemia to 70% of the total liver volume. In this model, intestinal congestion is avoided allowing the possibility to study the effects of isolated liver ischemia. The incision was closed, and after a 60-min ischemic period, the abdomen was reopened allowing clamp removal and liver reperfusion.[17,18]

At 4 h after liver reperfusion, rats were re-anesthetized for blood sampling through cardiac puncture and killed by exsanguination. The liver tissue for post-ischemic analysis was obtained from median and left anterolateral segments previously submitted to I/R injury and collected for biochemical and histological examination. No mortality is observed in this model of partial liver ischemia.

Determination of Liver Fatty Acid Composition

Total lipids from the liver of pre-ischemia/reperfused rats were extracted as previously described by Folch et al.[19] The lipids were saponified using 2 ml of an alkaline methanol solution (1 mol per ml NaOH solution in 90% methanol), at 37°C, for 2 h, in a shaking water bath. Afterwards, the solution was acidified to pH 3 with HCl (1 mol/ml). Fatty

acids were then extracted three times with 2 ml hexane. After extraction procedure and saponification, the fatty acids were derivatized with 4-bromomethyl-7 coumarin,[20] and the analysis carried out in a liquid chromatographer (Shimadzu model LC-10A, Shimadzu, Kyoto, Japan). The samples were eluted using a C8 column (25 cm×4.6 i.d., 5 μm of particles) with C8 pre-column (2.5 cm×4.6 i.d., 5 μm of particles), 1 ml per minute of acetonitrile/water (77:23 *v*/*v*) flow and fluorescence detector (325 nm excitation and 395 emission).

Liver Mitochondrial Oxidation and Phosphorylation Activities

Liver mitochondria were prepared as previously described.[21] Briefly, rat livers were rapidly excised and placed in medium containing 250 mM sucrose, 10 mM Tris–HCl, and 1 mM EGTA, pH 7.3, at 4°C. The tissue was scissor-minced and homogenized in ice using a Teflon Potter homogenizer. The homogenate was centrifuged at 600×*g* for 10 min. The supernatant was centrifuged for 10 min at 10,000×*g* to obtain the mitochondrial pellet. Mitochondrial suspension containing 30–40 mg/ml of mitochondrial protein was prepared and stored on ice before the assay of mitochondrial respiration.

The mitochondrial oxygen consumption was polarographically[22] measured using a Gilson 5/6H Oxygraph (Gilson Medical Electronics, Inc., Middleton, WI) in a closed reaction vessel fitted with a Clark oxygen electrode (Yellow Springs Instruments Co., Yellow Springs, OH) at 28°C. The incubation medium consisted of 120 mM KCl, 2 mM sodium phosphate, 10 μM rotenone, and 1 mM EGTA (Ethylene glycol-bis(2-aminoethylether)-N,N,N′,N′-tetraacetic acid) and was buffered at pH 7.3 with 5 mM Tris–HCl. Mitochondria were energized with potassium succinate as substrate at a final concentration of 10 mM. After a brief equilibration period, state 3 (activated state, S3) respiration was induced by the addition of 280 nmol adenosine diphosphate (ADP). The added ADP was phosphorylated to adenosine triphosphate (ATP), and the state 4 (basal state, S4) respiration was then measured. The oxygen consumption ratio in the presence of ADP to that in absence (respiratory control rate, RCR) and the ADP/O ratio were calculated as indices of mitochondrial oxidation and phosphorylation activities.[23]

RCR oxygen consumption in the S3/oxygen consumption in the S4

ADP/O moles of ATP formed from ADP per atom of oxygen consumed

S3 and S4 were measured and reported as nmol oxygen per milligram mitochondrial protein per minute. Mitochondria protein content was determined by the method of Lowry et al.[24]

Serum Activities of Aspartate Aminotransferase and Alanine Aminotransferase

The extension of hepatocellular injury was assessed by measuring serum activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The enzyme activities were assayed by using the optimized ultraviolet method (COBAS MIRA) from Roche (Roche Diagnostics, Rotkrenz, Switzerland). Results are expressed as units per liter (U/l).

Lipid Peroxidation Analysis

Malondialdehyde (MDA) formation was used as indicative of the occurrence of lipid peroxidation in the tissues and was estimated as thiobarbituric acid-reactive substances (TBARS). Liver tissues (100 mg/ml) were homogenized in 1.15% KCl buffer and centrifuged at 14,000×*g* for 20 min. An aliquot of the supernatant was then added to a reaction mixture consisting of 1.5 ml 0.8% thiobarbituric acid, 200 μl 8.1% (*v*/*v*) sodium dodecyl sulfate, 1.5 ml 20% acetic acid (pH 3.5), and 600 μl distilled water. The mixture was then heated at 90°C for 45 min. After cooling to room temperature, the samples were cleared by centrifugation (10,000×*g* for 10 min), and the absorbance was measured at 532 nm using malondialdehyde bis (dimethyl acetal) as external standard. The content of lipid peroxides was expressed as nmol MDA per mg of protein.[25]

Determination of Inflammatory Mediators

Serum levels of TNF-α, IL-6, and IL-10 from both pre- and post-I/R conditions were determined by ELISA using commercial kits (Biosource International Cytoscreen, Camarillo, CA, USA). PGE_2 was also determined by ELISA using Cayman Chemical kit (MI, USA).

Histological Analysis of the Liver from Pre- and Post-I/R Conditions

Liver samples were fixed in 10% buffered formalin for standard hematoxylin and eosin staining. Histological evaluation of the liver sections was performed by the same pathologist in a blinded manner. The severity of histological injury was analyzed according to the scoring system proposed by Quireze et al.[26] The following features were considered: hepatocellular steatosis (micro- and macro-steatosis), cellular necrosis, and tumefaction. Each feature was assigned with score from 0 to 3 based on its absence (0) or presence to a mild (1), moderate (2), or severe (3)

degrees. The intensity of steatosis was semiquantitatively evaluated: absence (0); low steatosis, 5% to 15% (1); mild steatosis, 16% to 30% (2); moderate steatosis, 31% to 60% (3); and severe steatosis, > 60% (4).[27]

Determination of Glucose-6-Phosphate Content

Liver samples were homogenized in 0.6 N perchloric acid and the glucose-6-phosphate content was analyzed as described by Lang and Michal.[28]

Determination of Glycogen Content

For determination of glycogen content, liver samples were digested for 1 h in 1M-KOH at 70°C. The digest was acidified with glacial acetic acid to pH 4.8. Amyloglucosidase (in acetate buffer, pH 4.8) was added, and the samples were incubated at 40°C for 2 h to allow complete degradation of glycogen to glucose. The glucose concentration was measured enzymatically using a Bioclin's Glucose Reagent Kit (Bioclin, São Paulo, Brazil)

Statistical Analysis

Continuous variables (fatty acid composition, liver mitochondrial function, MDA content, activities of AST and ALT, TNF-α, IL-6, IL-10, and PGE_2, glucose-6-phosphate, and glycogen content) were compared using Student's t test, and results were presented as mean values±SEM. Histological analysis was performed by the Mann–Whitney test, and results were presented as median and range. The level of $p<0.05$ was considered statistically significant. The GraphPad Prism Software (GraphPad Software, San Diego, CA) was used for statistical analysis.

Results

Effect of the PRD Diet on Liver Fatty Acid Composition in Pre-I/R Condition

GII and GIII groups showed a significant increase of liver unsaturated fatty acid content when compared to the GI group (Table 1). The unsaturation index shows that GII and GIII groups have an increase of 32% and 9.1%, respectively, when compared to SD group. The n-3/n-6 ratio showed that the GII group, as expected, had the highest value (0.20). The GIII group showed the lowest value of the n-3/n-6 ratio (0.09) due to the increase of soybean oil which has a high content of n-6 fatty acids, especially linoleic acid.

Effect of PRD Diet on Mitochondrial Uncoupling in Pre- and Post-I/R Conditions

Pre-I/R Results

GII and GIII groups showed increased oxygen consumption rate by the liver mitochondria in S4 (Fig. 1b) and a decrease

Table 1 Fatty acid composition (percentage) in liver from rats fed the standard and HFD (PUFA-rich) diets

	GI	GII	GIII
Fatty acids			
Monounsaturated			
Palmitoleic (16:1, n-7)	0.60±0.09	0.70±0.15	0.46±0.07
Oleic (18:1, n-9)	7.18±0.43	8.83±0.67	8.00±0.58
PUFA			
n-6			
Linoleic (18:2, n-6)	21.72±1.58*	24.99±2.22	24.66±0.76
γ-linnoleic (18:3, n-6)	1.73±0.27	1.69±0.23	1.51±0.11
Arachidonic (20:4, n-6)	15.58±1.30*	20.16±1.23	19.92±1.59
n-3			
Eicosapentaenoic (20:5, n-3)	0.61±0.06	0.96±0.14**	0.49±0.05
Docosahexaenoic (22:6, n-3)	4.94±0.64	8.29±0.58**	3.46±0.33
Saturated fatty acids			
Lauric (10:0)	0.56±0.09	0.59±0.09	0.59±0.13
Myristic (12:0)	2.82±0.45	2.52±0.56	1.75±0.06
Palmitic (16:0)	24.21±1.16	19.15±2.17	21.23±1.03
Stearic (18:0)	19.54±1.57	12.11±2.85	19.10±1.42
Unsaturation index	151.42	199.76**	165.20
n-3/n-6 ratio	0.14	0.20**	0.09

GI refers to the standard diet, GII refers to PRD enriched with ω-6 and ω-3 PUFA, and GIII refers to PRD enriched with ω-6 PUFA. Data are expressed as mean±SEM of seven animals per group

*$p<0.05$ comparing GI with GII and GIII groups

**$p<0.05$ comparing GII with GI and GIII groups

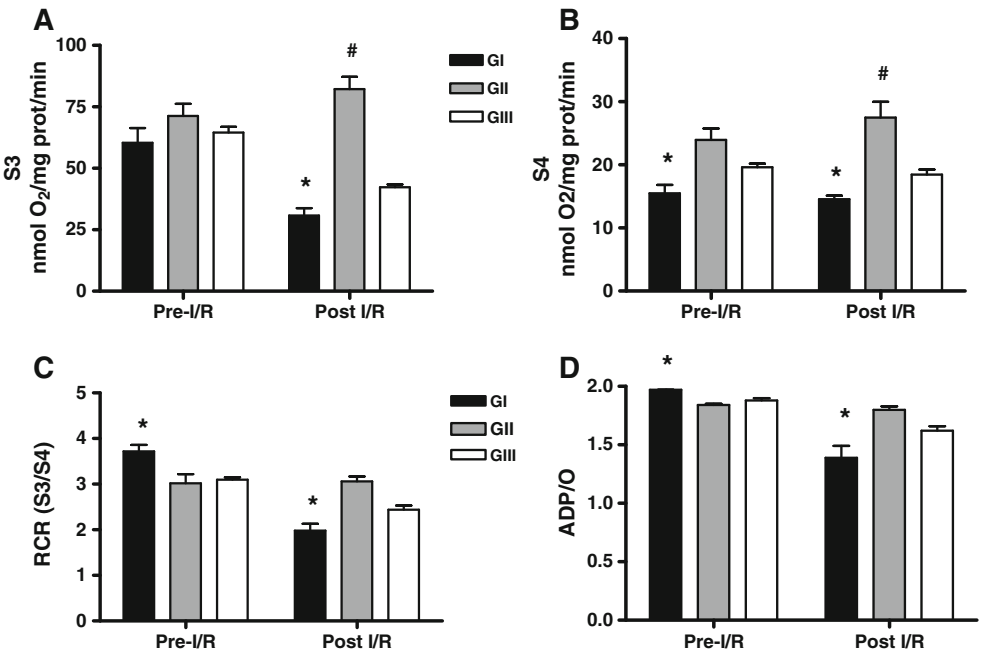

Fig. 1 Effects of a PUFA-rich diet on liver mitochondria oxidation and phosphorylation activities in pre- and post-ischemia/reperfusion conditions. *GI* standard diet, *GII* PRD enriched with ω-6 and ω-3 PUFA, *GIII* PRD enriched with ω-6 PUFA. **a** State 3 respiration (*S3*), **b** State 4 respiration (*S4*), **c** respiratory control rate (RCR), and **d** ADP/O ratio. Data are presented as mean±SEM of ten animals per group. *$p<0.05$ comparing GI with GII and GIII groups; #$p<0.05$ comparing GII with GI and GIII groups

in both RCR and ADP/oxygen ratio (Fig. 1c, d) when compared to the SD group. The S3 respiration results did not show significant differences between the groups (Fig. 1a).

Post-I/R Results

After I/R, SD and GIII groups presented a decrease in the S3 value when compared to the pre-I/R results. The GII group, however, showed a significant increase in S3 after I/R when compared to the pre-I/R values. Among the groups studied, only the GII group had a significant increase of S3 in the post-I/R condition (Fig. 1a). Results from S4 showed a decrease in the GI group when compared to the PRD-fed rats. No differences were observed between the GII and GIII groups when compared to the pre-I/R results. GI group exhibited a decrease in RCR and ADP/oxygen when compared to the PRD-fed groups after I/R. No differences were found between GII and GIII groups in both parameters (Fig. 1c, d). When compared to the pre-I/R condition, GI group had a significant decrease in both RCR and ADP/oxygen results. No differences were found in between GII and GIII.

Effect of PRD Diet on Lipid Peroxidation in Pre- and Post-I/R Conditions

In the pre-I/R condition, both GII and GIII had an increased content of TBARS. There was no significant difference between GII and GIII groups (Fig. 2). In the post-I/R condition, an increase of TBARS levels was found in the GII and GIII groups when compared to its pre-I/R results (Fig. 2).

Effect of PRD Diet on Serum Activities of ALT and AST in the Pre- and Post-I/R Conditions

Serum activities of AST and ALT were not different among the groups in the pre-I/R condition. However, in the post-I/R condition, a significant decrease in the plasma activities of both AST and ALT was observed in the GII and GIII groups when compared to the SD rats (Fig. 3). No differences for both enzymes were observed between GII and GIII.

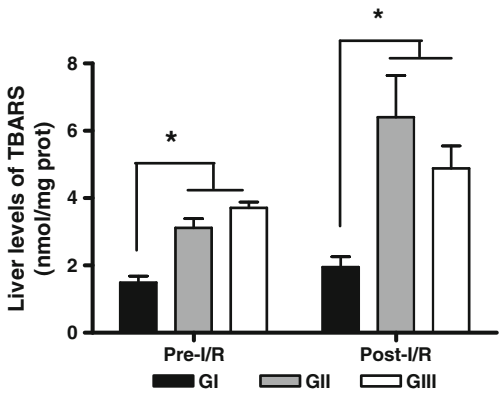

Fig. 2 Effects of a PUFA-rich diet on liver MDA content in pre- and post-ischemia/reperfusion conditions. *GI* standard diet, *GII* PRD enriched with ω-6 and ω-3 PUFA, *GIII* PRD enriched with ω-6 PUFA. Data are presented as mean±SEM of ten animals per group. *$p<0.05$

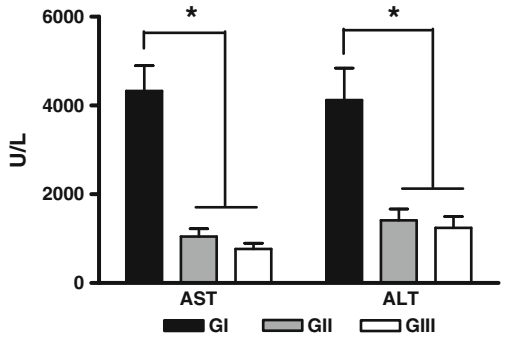

Fig. 3 Effects of a PUFA-rich diet on serum activities of aspartate aminotransaminase (AST) and alanine aminotransferase (ALT) in post-ischemia/reperfusion condition. *GI* standard diet, *GII* PRD enriched with ω-6 and ω-3 PUFA, *GIII* PRD enriched with ω-6 PUFA. Data are presented as mean±SEM of ten animals per group. *$p<0.05$

Effect of PRD Diet on Production of Cytokines and PGE_2 in the Pre- and Post-I/R Conditions

TNF-α, IL-6, IL-10, and PGE_2 could not be detected in serum from rats under pre-I/R condition in all groups. In the post-I/R condition, the PRD-fed groups exhibited a marked decreased in the levels of TNF-α, IL-6, and IL-10 when compared with the SD group (Fig. 4a, b). However, the plasma PGE_2 levels of PRD-fed rats were increased when compared to the SD-fed rats (Fig. 4c).

Effect of PRD Diet on Histological Evaluation in the Pre- and Post-I/R Conditions

In the pre-I/R condition, there were no differences in cellular necrosis. However, a decrease in cell tumefaction was found in the GII and GIII groups when compared to the SD group (GI, 1.7±0.5; GII, 1.0±1.0; and GIII, 1.3±0.8, mean±SEM of ten rats). An increase of microsteatosis and macrosteatosis was observed in the PRD-fed groups. Nevertheless, the GII group had a twofold increase in macrosteatosis occurrence when compared to the GIII group. Microsteatosis, on the other side, was significantly less frequent in the GII group when compared to the GIII group. Macrosteatosis was not observed in the SD group. However, PRD diet does not induce steatohepatitis.

In the post-I/R condition, cell necrosis was observed revealing liver injury. However, the PRD-fed groups showed diminished degree of liver injury when compared to the SD group (GI, 3.0±1.1; GII, 1.4±0.5; and GIII, 1.5±0.9). Cell tumefaction was diminished in the PRD-fed groups when compared to the SD group (GI, 1.5±0.8; GII, 0.6±0.5; and GIII, 0.3±0.2) and with the results from the pre-I/R condition. The GII group had a slight but significant increase in cell tumefaction when compared to the GIII group. Macrosteatosis was not found after the post-I/R condition in all groups. The occurrence of microsteatosis was also decreased in the PRD-fed groups when compared to the pre-I/R results. In contrast, the SD group revealed an

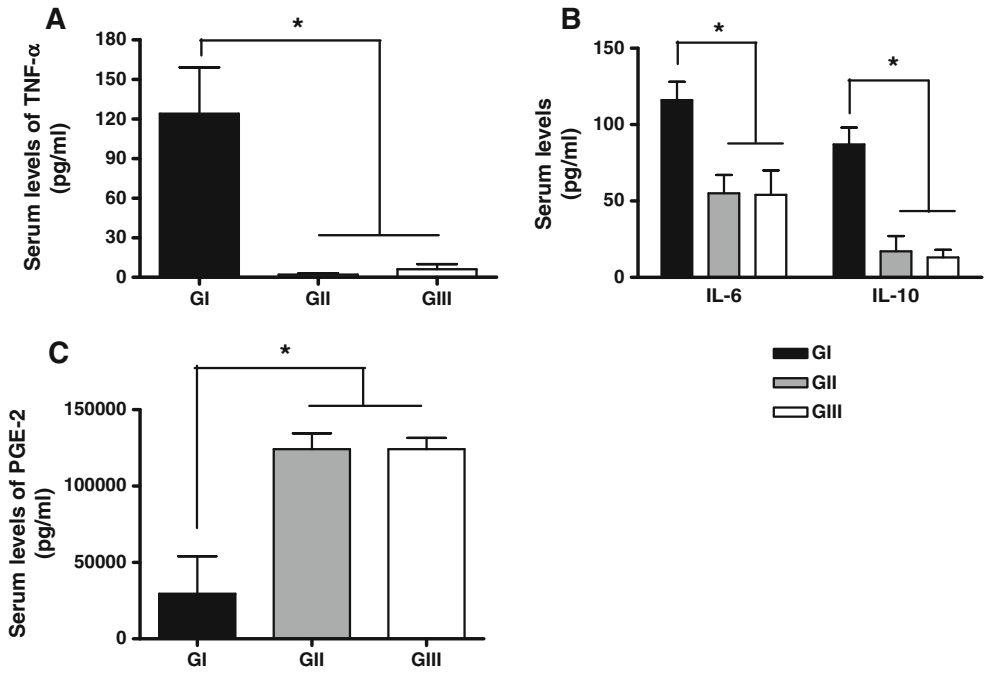

Fig. 4 Effects of a PUFA-rich diet on serum levels of inflammatory mediators in post-ischemia/reperfusion condition. *GI* standard diet, *GII* PRD enriched with ω-6 and ω-3 PUFA, *GIII* PRD enriched with ω-6 PUFA. **a** Serum levels of TNF-α, **b** Serum levels of IL-6 and IL-10, and **c** Serum levels of PGE_2. Data are presented as mean±SEM of ten animals per group. *$p<0.05$

increase of microsteatosis when compared to the results obtained in the pre-I/R condition and to the PRD groups in the post-I/R condition (Table 2).

Effect of PRD Diet on Liver Content of Glycogen and Glucose-6-Phosphate Content in the Pre- and Post-I/R Conditions

In the pre-I/R condition, a decrease of the glycogen content was found in the PRD groups when compared to SD rats. No differences were found in the glucose-6-phosphate content. In the post-I/R condition, a decrease of glycogen content was observed as compared to the pre-I/R condition. However, the glycogen content was lower in the SD groups as compared to the GII and GIII groups. The glucose-6-phosphate content was increased in all groups. Nevertheless, the glycogen/glucose-6-phosphate ratio was higher in the GII and GIII groups as compared to the SD group, indicating a preservation of the glycogen storage in the liver of the PRD groups (Fig. 5).

Discussion

In the present study, liver I/R injury was reduced in rats fed a PRD when compared to animals fed a SD. This observation was confirmed by reduction of cellular necrosis and tumefaction, transaminase activity, and levels of inflammatory markers in serum. Before ischemia, the liver from PRD groups exhibited macro- and microsteatosis, accumulation of fatty acids and uncoupling of mitochondrial oxidative phosphorylation. After I/R, these animals exhibited a severe reduction of steatosis, increase of TBARS levels, and mitochondrial uncoupling. Also, the PRD groups showed a lower reduction of liver glycogen content when compared to the SD group after I/R. These results show that ω-6 or ω-6 plus ω-3 PUFA supplementation may consist a preconditioning strategy that can protect the liver from I/R injuries.

Table 2 Liver histological analysis

	GI	GII	GIII
Pre-I/R			
Microsteatosis	1.0±0.6	1.4±0.8	1.7±0.5
Macrosteatosis	0	2.6±1.1 *	1.3±1.0
Cell necrosis	0	0	0
Cell tumefaction	1.7±0.5	1.0±1.0	1.3±0.8
Post-I/R			
Microsteatosis	2.0±1.0*	0.4±0.3	0.8±0.4
Macrosteatosis	0	0	0
Cell necrosis	3.0±1.1*	1.4±0.5	1.5±0.9
Cell tumefaction	1.5±0.8*	0.6±0.5	0.3±0.2

GI refers to the standard diet, GII refers to PRD enriched with ω-6 and ω-3 PUFA, and GIII refers to PRD enriched with ω-6 PUFA. Data are expressed as median and range of ten animals per group

*$p<0.05$

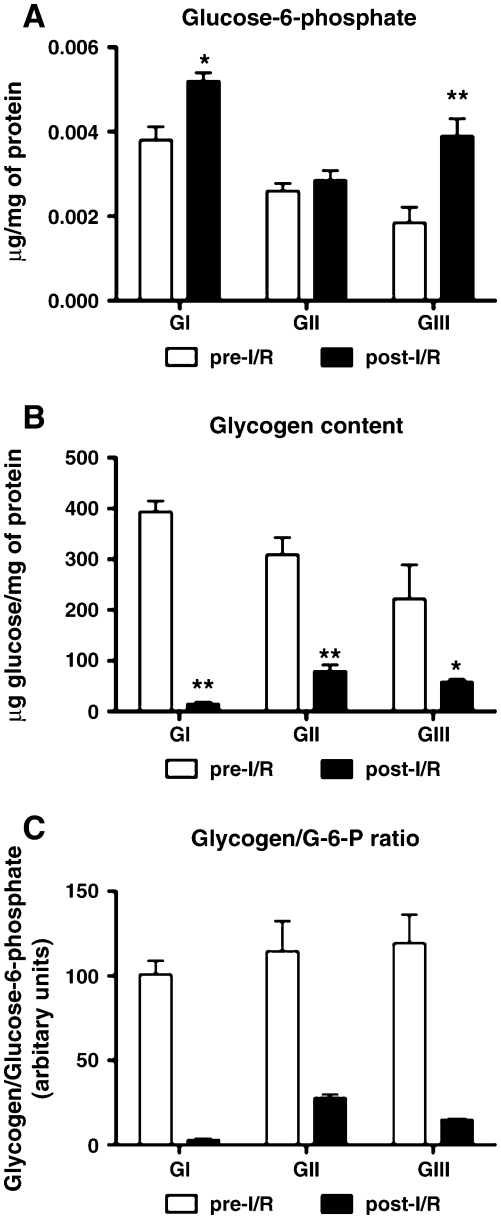

Fig. 5 Effects of a PUFA-rich diet on liver glycogen and glucose-6 phosphate content in pre- and post-ischemia/reperfusion condition. *GI* standard diet, *GII* PRD enriched with ω-6 and ω-3 PUFA, *GIII* PRD enriched with ω-6 PUFA. **a** Glucose-6-phosphate content. **b**, **c** Glycogen/glucose-6-phosphate ratio Data are presented as mean± SEM of ten animal per group. *$p<0.05$; **$p<0.001$

Although mitochondria are the main intracellular source of ROS, there is no study addressing the effects of polyunsaturated fat acid-rich diet on mitochondrial function before and after ischemia/reperfusion liver injury. The novel finding of the present study is that diets enriched with ω-6 or ω-6 plus ω-3 PUFA induced the uncoupling of mitochondrial oxidative phosphorylation and this condition remains even after I/R injury (Fig. 1b). In spite of these mitochondrial alterations, hepatic tissue was protected from I/R injury. On the other hand, animals fed a standard diet had no alteration on mitochondrial function in the pre-ischemia period. However, I/R injury induced in these animals a significant alteration in liver mitochondrial function with decreased RCR, state 3 respiration, and ADP/O ratio (Fig. 1a, c, d), suggesting a degenerative and necrotizing process that is characteristic of cellular ischemia. Due to its role in the production of cellular ATP, intracellular calcium regulation, redox signaling, and apoptosis, mitochondria have been considered to actively participate in the preconditioning phenomenon and organ protection.[29] Moderate mitochondrial uncoupling has been associated with preconditioning state in brain and heart.[13,14] Thus, the uncoupling of mitochondrial oxidative phosphorylation observed in animals fed PUFA-rich diet is probably involved in the protective effect on liver I/R injury observed in the present study.

The uncoupling of mitochondrial oxidative phosphorylation observed in the present study may be related to dissipation of the electrochemical proton gradient between the intermembrane space and the mitochondrial matrix. Therefore, uncoupling electron transport from ATP synthesis probably is related to the increase of PUFAs content in the liver (Table 1).

After I/R procedure, an increase of TBARS levels was observed in the PRD groups that correlates with the reduction of steatosis mass in the liver. A moderate increase in lipid peroxidation concentration was found to reduce cultured neuron injury induced by several agents.[30] This preconditioning effect was abolished by the use of radical scavengers.[31] The mechanism underlying the protection induced by moderate ROS formation is not completely understood. Recently, a relationship between mitoK (ATP) channel and ROS production was postulated. Protection induced by moderate levels of ROS was abolished by a mitoK (ATP) channel antagonist. In addition, an antioxidant agent (*N*-acetyl-cystein) abolished the tissue protection induced by a mitoK (ATP) channel opener agent.[32] These results demonstrate the critical role of mitochondria and mitochondrial ROS levels in the mechanism of the protection induced by preconditioning.

The consumption of the steatotic mass by the PRD groups after I/R condition might also be a preconditioning effect of PUFAs by preserving liver glycogen content. Before ischemia, there were no significant differences in glycogen and glucose-6-phosphate content in both fat fed groups. After I/R, a reduction in glycogen content was observed in all groups; however, the glycogen/glucose-6-phosphate was lower in the SD group when compared to PRD groups. Several studies have demonstrated that maintenance of glycogen storage is important for the improvement of injuries related to I/R in the liver.[33,34]

Several reports indicate that Kupffer cells are activated during ischemia/reperfusion injury increasing the production of cytokines and ROS.[35–37] In the present study, a significant decrease of serum levels of cytokines in the PRD groups that may reflect the reduction of hepatic lesion after ischemia/reperfusion injury was observed (Figs. 4 and 5a, b). The increase in IL-10/TNF-α ratio by tenfold in the PRD groups indicates the prevalence of an anti-inflammatory activity when compared to the SD group. Previous study demonstrated a modified response to LPS in mice fed a coconut-rich diet with low TNF-α production and increased IL-10 generation.[38]

Administration of ω-3 PUFA reduced hepatic reperfusion injury in a low flow and reflow perfusion model in rat with marked attenuation of portal vein pressure increase observed after reperfusion.[39] Recently, El-Bachy et al.[40] demonstrated that dietary supplementation of ob/ob mice diet with ω-3 PUFA in a liver I/R model resulted in reduction of microcirculatory lesions and an improvement after reperfusion. However, there was no study on the preconditioning effect of the administration of PUFAs to normal rats on hepatic I/R injury.

In the present study, an increase of PUFA content in the liver from PRD rats was observed (Table 1). Alterations in liver fatty acid composition may also affect production of prostaglandins and thromboxanes. Prostaglandins confer protection after reperfusion through several mechanisms including improvement of liver perfusion[41,42] and inhibition of leukocyte adhesion by reducing intracellular adhesion molecules 1 in the vascular endothelium,[43] and therefore decreasing microcirculatory disturbances. In the present study, serum PGE_2 levels were increased after I/R in rats fed with PUFA-enriched diets (Fig. 5c). Recently, the protective effect of ω-3 enriched diet on liver I/R injury was associated to a decreased production of 2-series prostanoids and proinflammatory cytokines.[44] However, in the present study, in spite of an increase in PGE_2 levels, a similar reduction in plasma levels of proinflammatory cytokines was found (Fig. 4). Similar results were observed in a pig model of liver I/R injury.[45] The protective effect of the diet enriched with PUFA was probably related to a liver preconditioning condition that involves changes in prostaglandin production.

In conclusion, diet enriched with ω-6 or ω-3 plus ω-6 PUFA has a preconditioning effect reducing the liver

ischemia/reperfusion injury and has to be investigated aiming its therapeutical use in situations where hepatic ischemia/reperfusion injury is anticipated as in enlarged hepatic resections and live donor liver transplantation.

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2011 SSAT POSTER PRESENTATION

Magnetic Resonance Enterography for Crohn's Disease: What the Surgeon Can Take Home

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Abstract
Background Crohn's disease (CD) is a life-long, chronic, relapsing condition requiring often morphological assessment. MR enterography (MRE) offers advantages of not using ionizing radiation and yielding intraluminal and intra-abdominal informations. The aim of our study was to identify how MRE can be useful in planning surgical procedures.
Patients and Methods In this retrospective study, 35 patients who underwent MRE and then surgery for CD were enrolled from 2006 to 2010. MRE findings were compared to intraoperative findings. Histology of operative specimens, systemic inflammatory parameters, and fecal lactoferrin were also evaluated. Cohen's κ agreement test, sensitivity and sensibility, uni-/multivariate logistic regression, and non-parametric statistics were performed.
Results MRE identified bowel stenosis with a sensitivity of 0.95 (95% CI 0.76–0.99) and a specificity of 0.72 (95% CI 0.39–0.92). The concordance of MRE findings with intraoperative findings was high [Cohen's κ=0.72 (0.16)]. Abscesses were detected at MRE with a sensitivity of 0.92 (95% CI 0.62–0.99) and a specificity of 0.90 (95% CI 0.69–0.98) with a Cohen's κ=0.82 (0.16). The grade of proximal bowel dilatation resulted to be a significant predictor of the possibility of using strictureplasty instead of/associated to bowel resection either at univariate or at multivariate analysis.
Conclusion Our study confirmed that MRE findings correlate significantly with disease activity. Detailed information about abscess could suggest percutaneous drainage that could ease the following surgery or avoid emergency laparotomy. Proximal bowel dilatation can suggest the possibility to perform bowel sparing surgery such as strictureplasty.

Keywords Crohn's disease · Magnetic resonance enterography

Introduction

Crohn's disease (CD) is a life-long, chronic, relapsing condition that affects the whole alimentary tract. Although

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the recent advances in the medical therapy, intra-abdominal surgery is often required to treat CD complication or in case of failure of medical therapy and about 80% of patients with CD have at least a surgical procedure and quite often more during their lifetime.[1,2] Therefore, surgical management of CD includes different peculiar procedures that aim to be as conservative as possible. In fact, minimally invasive surgery and strictureplasty may reduce the negative impact of surgery in these patients limiting scars and bowel loss.[3] In fact, body image and cosmesis after intestinal surgery for CD is better preserved in patients who have laparoscopic surgery.[3–5] Stenosis can be treated with resection but strictureplasty can preserve as much bowel length as possible and can reduce the risk of short bowel syndrome.[6,7]

For these reasons, it is important to plan as carefully as possible the surgical procedure in advance to tailor it to each single patient. Knowing the morphological situation before operation appears essential for such planning. Although conventional small bowel enterography and enteroclysis may still have a good reliability to evaluate stenosis and can also be useful to study internal fistula,[8] conventional imaging techniques appear inadequate for a comprehensive morphologic study of small bowel for the detection of typical CD radiological lesions (sensitivity 23–80%).[9–11] In fact, these imaging techniques as well as endoscopy (enteroscopy with double balloon or wireless capsule enteroscopy) can yield only intraluminal information and they cannot identify any extraluminal complications of CD such as abscess or fistulae. Moreover, these exams retain a sort of invasiveness and they often are not well tolerated by patients. CT enterography can overtake this problem with a good sensitivity (71–95%), remarkable specificity (90–98%), and with limited costs.[12] However, it utilizes ionizing radiation and patients with CD should undergo such exams several times during their lives. A recent study has highlighted the high cumulative radiation dosages imparted to patients with CD, mainly due to the increased use of CT. In this study, CT accounted for up to 84.7% of the cumulative dose imparted to patients and 15.5% of patients had cumulative dosage in excess of 75 mSv.[13] The carcinogenic effect of radiation can be particularly significant in patients with CD who already have an increased risk of developing gastrointestinal, hepatobiliary cancer, and small bowel lymphoma as reported by Sinha et al.[14]

MRI enterography (MRE) can be an important instrument of evaluation to establish the best surgical approach for each patient. In fact, it is not invasive, does not use ionizing radiation, and can give more information about bowel morphology, CD phenotype, and presence of possible extraluminal complications. In a study of active CD in the terminal ileum with endoscopy and histology results as standard criteria, MRE had a sensitivity of 89% compared with 72% for conventional enteroclysis.[15] MRE distinguishes between bowel inflammation, and so susceptible to medical therapy, and fibrosis that requires surgical therapy. Moreover, MRE is a good exam for staging disease activity in patients with frank disease and so susceptible of a surgical therapy; on the other hand, its use is limited in remission or mild disease.[16] However, most of the previous studies were mainly focused on the comparison of endoscopical and MRE findings and on the decision between medical therapy and surgery.[16]

Therefore, the aim of our study was to assess the specificity and sensitivity of MRE findings in CD in comparison with intraoperative findings. The secondary endpoint was to evaluate the role of MRE findings in planning abdominal surgery in CD.

Patients and Methods

Study Design

In this retrospective study, all the consecutive patients with Crohn's disease who underwent MRE and subsequent abdominal surgery from October 2006 to April 2010 were enrolled. MRE reports, surgical descriptions, and histological reports of each patient were collected. MRE findings were compared with intraoperative findings. Radiologic images were evaluated by two radiologists who described presence of stenosis, fistulas, bowel thickening, dilatation, inflammatory contrast enhancement, fat wrapping, wall and fat edema, and lymph nodes. Presence of fistulas, abscess, stenosis, dilatation, and the length of ileum involved were recorded during surgical procedure. Montreal classification system was used to stratify patients.

MRI Enterography Technique

All patients drank only clear fluids for 6 h prior to their MRE and were nil by mouth for 2 h. Patients who underwent MRE drank 1,000–1,500 mL of the bowel contrast agent over 20 min. The bowel contrast agent used was a polyethylene glycol–water solution (Glycoprep-C; Pharmatel Fresenius Kabi, Australia). A total of 1,000–1,500 mL was usually required to distend the small bowel to the terminal ileum. This varied depending on previous bowel resections. Patients were scanned supine using a 1.5-T MRI system (Avanto SQ; Siemens Medical Solutions, Erlangen, Germany) with a phased-array coil providing compression. In patients with an ileostomy, the stoma bag was emptied and a sponge placed between the surface coil and stoma. Small bowel filling was dynamically assessed using a coronal 150-mm-thick single slab T2-weighted

(HASTE) sequence to monitor small bowel distension. To reduce bowel peristalsis and prolong SB distension, 10 mg intravenous hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Australia) or 0.5 mg of glucagone intravenous was given. Once there was adequate small bowel filling, the following protocol was used: haste coronal and axial (TR/TE 1,500:90; matrix size 256×320; slice thickness 5 mm; GAP 0 mm), TrueFISP coronal and axial (matrix 256×256; slice thickness 6 mm; GAP 0 mm), and TIRM axial (TR/TE 2,000:55; matrix 320×160; slice thickness 3 mm; GAP 0 mm), after the administration of 0.2 mmol/kg of gadodiamide (Omniscan; Amersham, Australia) with post-contrast imaging commencing at 30–45–60–120 s. For assessment of stenosis, cine TrueFISP were performed. Parallel imaging was used for all sequences. All sequences were performed during breath-holding.

Interpretation of MRE Findings

Each MRE was evaluated by two radiologists (C.L. and F. C.) with experience in both gastrointestinal and MR imaging blinded to clinical findings. Image analysis was performed using a standardized worksheet. Diseased bowel was identified as abnormal bowel wall thickening and abnormal transmural or mucosal enhancement. Bowel wall thickness was assessed as normal (<3 mm), mildly abnormal (3–6 mm), or markedly abnormal (>6 mm).[17] Mucosal enhancement was contrast enhancement localized to the inner layer of the intestinal wall and transmural enhancement was homogenous contrast enhancement of the whole wall (Fig. 1a). The degree of pathological bowel wall contrast enhancement was assessed as none, mild (less than renal cortical enhancement), or marked (more than renal cortical enhancement) and classified as mucosal, transmural enhancement, or both. The degree of enhancement was measured relative to the renal cortex on the coronal acquisition, and axial views were used for problem solving and cross-referencing of bowel loops. Mesenteric hyperemia, fibro-fatty proliferation, enlarged local lymph nodes, and/or abnormally enhancing lymph nodes were assessed. Mesenteric nodes <5 mm in short axis were considered physiological. Larger nodes, especially if clustered and contrast enhancing, were considered pathological.[18] The number of regional nodes and length of diseased segment were noted. Disease complications, including fistulas or abscesses, were recorded, as was free fluid, and stenoses with or without functional obstruction. Signs of functional obstruction were prestenotic dilatation and delayed contrast progression on the cine TrueFISP series. Stenoses were classified as "fibrosis" if there was bowel wall thickening without contrast enhancement and without wall edema (Fig. 1b, c). The diagnostic confidence of this was increased if the wall thickening had reduced signal intensity on TIRM images and if this region remained of constant caliber on cine trueFISP. "Marked segmental transmural hyper-enhancement" was diagnosed if there was marked transmural enhancement with increased bowel wall thickness. "Mild segmental hyper-enhancement and mild wall thickening" was present if mucosal and/or transmural contrast enhancement was mild with only mild bowel wall thickening (3–6 mm). "Mild segmental hyper-enhancement and marked wall thickening" was present if there was mild mucosal and/or transmural contrast enhancement, but the bowel wall was >6 mm. CT criteria for bowel obstruction were used to define and classify bowel dilation.[19,20] MRE criteria for bowel dilation are the presence of dilated small bowel loops (diameter >2.5 cm from outer wall to outer wall) proximally to normal-caliber or collapsed loops distally (Fig. 1d).[19] Mild bowel dilation was defined as a slight discrepancy (25–50%) between the calibers of the proximal and the distal small-bowel loops; moderate bowel dilation was defined as a discrepancy of 50% or greater between the proximal and the distal small-bowel luminal calibers with residual gas or contrast material in the distal small bowel; and severe bowel dilation was considered to be present if there was a discrepancy of 50% or greater between the proximal and distal small-bowel luminal calibers and if the distal small bowel and the colon were collapsed.[20]

Surgical Technique

The surgical procedures were performed by only one surgeon (I.A.) with experience in inflammatory bowel disease surgery. During the operating time, the surgeon reported presence and localization of fistulae, abscess, stenosis, dilatation, and the length of ileum involved. Stenosis was diagnosed in the presence of reduction of lumen diameter and of dilatation of the proximal bowel. In some cases, the presence of stenosis was investigated with a Foley catheter balloon inflated with 10 cc of physiologic solution.

Bowel resection was performed removing all grossly involved bowel through a standard midline laparotomy or with laparoscopic assistance. In the laparoscopic-assisted ileo-colonic resection, a three-trocar approach was used (sub-umbilical, 10 mm; left iliac fossa, 10 mm; suprapubic, 5 mm). The distal ileum and the right colon were fully mobilized and exteriorized by a 4–6-cm vertical incision through the umbilicus. In case of entero-sigmoid fistula or large inflammatory mass, a small Pfannestiel incision (8 cm) was used instead of the transumbilical incision.[3] Vascular ligation, bowel division, and anastomosis were performed extracorporeally. Stapled anastomoses were constructed in a side-to-side fashion using an 80-mm linear stapler (GIA75; US Surgical Corporation, Norwalk, CT,

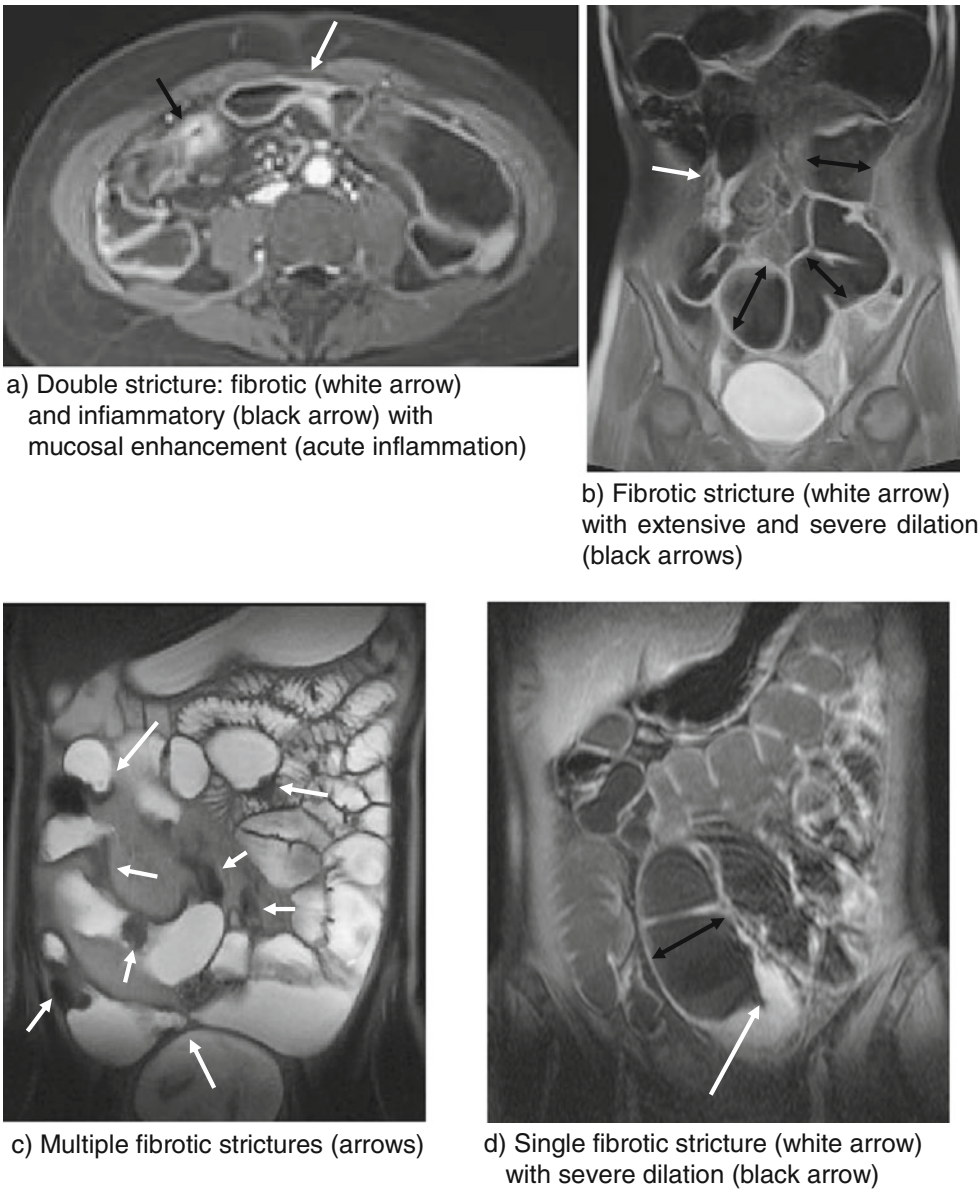

Fig. 1 **a** Double stricture: fibrotic (*white arrow*) and inflammatory (*black arrow*) with mucosal enhancement (acute inflammation). **b** Fibrotic stricture (*white arrow*) with extensive and severe dilation (*black arrows*). **c** Multiple fibrotic strictures (*arrows*). **d** Single fibrotic stricture (*white arrow*) with severe dilation (*black arrow*)

USA). Hand-sewn anastomoses were created in a side-to-side orientation using a running suture of 3-0 Vicryl for the inner layer (mucosal) (Ethicon, Inc., Somerville, NJ, USA) and a running 3-0 TiCron (US Surgical Corporation) for the outer layer (sero-muscolar). End ileostomy was typically used in cases of extensive colonic CD with macroscopic rectal disease, not responding to medical therapy. The ileal loop was delivered through a trephine in the abdominal wall. After closure of the laparotomy, the ileostomy was opened and the proximal component of loop was everted and then fixed to the skin with muco-cutaneous absorbable 3-0 Vicryl (Ethicon) sutures. No stitches were placed to fix the ileostomy to the inner layer of the abdominal wall. Strictureplasty was constructed in case of ileal or jejunal skip lesions in order to minimize the extent of small bowel resected. The main site of disease (i.e., the ileo-colonic junction) was usually resected and in case of multiple disease sites, standard strictureplasty was performed. Strictureplasty were performed according to Miculickz, Finney, or Michelassi techniques. The bowel was incised along its main axis on the anti-mesenteric side on a Crohn's stenosis and sutured transversally with absorbable 3-0 Vicryl (Ethicon) stitches.[3]

Histology

After fixation in 10% neutral-buffered formalin at room temperature for 24/48 h, the resected specimens were dehydrated and embedded in paraffin wax. Sections (3-μm thick) were then cut and standard hematoxylin/eosin stain applied was evaluated by pathologists specialized in gastrointestinal pathology and in inflammatory bowel

disease (C.M. and M.R.). Macroscopic and microscopic characteristics were described. Macroscopic findings included the length of the resected bowel, the presence of thickening, strictures, ulcers, and/or peri-intestinal adipose tissue hypertrophy. Microscopic features included the presence and the degree of inflammation based on the presence of inflammatory cells infiltration, ulcers, granulomas, villi atrophy, loss of globet cells, crypt abscesses, and architectural distortion were assessed in at least five different fields. The inflammation was graded in none (0), mild (1), moderate (2), and severe (3).

Statistical Analysis

Statistical analysis was performed using both Microsoft Excel and STATISTICA 7.1 software (Statsoft, Tulsa, OK, USA). Continuous data are expressed as medians and interquartile ranges, while dichotomic data are expressed as frequencies and proportions. Vassarstat online calculator was used to calculate specificity and sensitivity of MRE. Agreement of MRE findings with surgical and histopathologic findings as well as inter-observer agreement were analyzed by Cohen's κ statistic, intraclass correlation test, and Fischer test. Univariate logistic regression was calculated to identify possible predictors of outcome among MRE findings. Only predictors that resulted significant at univariate analysis were included in multivariate logistic regression models. Two-tailed p values <0.05 were considered significant.

Results

Patients

The consecutive 35 patients with CD who underwent MRE and subsequent abdominal surgery from October 2006 to April 2010 were enrolled. The interval between MRE and surgery was less than 6 months (median 1.4 months, range 0.3–6). Twenty patients were males (57.15%) and 15 were female (42.85%) and the median age was 39 (range 16–88 years). One patient was <16 years old, 21 patients were between 17 and 39 years old (60%), and 13 patients were more than 40 years old. CD localization was ileal in 13 patients (37.15%), colic in five patients (14.28%), and ileocolonic in 17 patients (48.57%); perianal localization (8.58%) was also present in three patients. Ten patients presented a inflammatory phenotype (28.58%), 11 stricturing phenotype (31.42%), and 11 penetrating phenotype (31.42%). Nineteen patients had previous surgery. The indication for surgery was obstruction or sub-obstruction in 13 patients (37.14%), presence of fistula or abscess in 18 patients (51.42%), presence of colitis unresponsive to medical treatment in two patients (5.7%), and inflammatory disease with failure to medical treatment in other three patients (8.57%). In 18 patients, surgery was performed with a video-laparoscopic access; in only one a conversion with a median access was necessary for difficulty to identify anatomic structures. Twenty-four patients underwent bowel resection, two patients underwent strictureplasty, and four patients underwent resection plus strictureplasty. In only one patient, in whom MRE resulted negative for active disease, only adherences were found at surgery. Postoperative complications included obstruction in six patients who did not need any further operation, diarrhea in two patients, rectal bleeding in a patient who required transfusion, and minor complications in three patients (wound infection, fever, and urinary infection). No anastomotic leak was observed. The characteristics of patients are reported in Table 1.

MRI Findings

MRE described bowel stenosis in 26 patients and in eight of them the stenosis was frankly fibrotic. Wall thickness was described in 26 patients and bowel dilatations proximal the stenosis were observed in 24 patients. Bowel dilatation was graded as mild in nine patients, moderate in nine, and severe in six. MRE reports described active inflammation within the bowel wall in 30 patients with overt abscess and fistulas in 15 patients and 15 patients, respectively. Fibro-adipose proliferation was observed in eight patients and peri-intestinal adipose tissue edema in six patients. Vasa recta were recognizable in 11 patients while lymph nodes were evident in 19 patients. Neoplastic findings were only described in one patient (small-bowel polyp). The inter-observed agreement was complete (Cohen's κ=1) for presence stenosis, fistulas, bowel thickening, dilatation, inflammatory contrast enhancement, fat wrapping, wall and fat edema, and lymph nodes. The inter-observed agreement for the number of stenosis was high (ICC=0.95). The frequency of MRE findings in this cohort of patients are reported in Fig. 2.

Sensitivity and Specificity of MRI Enterography

MRE identified bowel stenosis with a sensitivity of 0.95 (95% CI 0.76–0.99) and a specificity of 0.72 (95% CI 0.39–0.92). The concordance of MRE findings with intraoperative findings was high [Cohen's κ=0.72 (0.16)]. On the other hand, MRE identified simply fibrotic stenosis with a sensitivity of 0.41 (95% CI 0.19–0.66) and a specificity of 0.94 (95% CI 0.70–0.99). In this case, the concordance of MRE findings with intraoperative findings was only acceptable [Cohen's κ=0.33 (0.14)].

Abscesses were detected at MRE with a sensitivity of 0.92 (95% CI 0.62–0.99) and a specificity of 0.90 (95% CI 0.69–0.98). The concordance of MRE findings with intraoperative findings was high [Cohen's κ=0.82 (0.16)]. On

Table 1 Patients' characteristics

		Number	Percent
Sex	Male	20	57.15
	Female	15	42.85
Age	A1 ≤16	1	2.85
	A2 17–39	21	60
	A3 ≥40	13	37.15
Localization	L1 small bowel	13	37.15
	L2 colon	5	14.28
	L3 ileo-colonic	17	48.57
Phenotype	B1 inflammatory	10	28.58
	B2 stricturing	11	31.42
	B3 fistulizing	11	31.42
	B1+perianal disease	0	0
	B2+perianal disease	0	0
	B3+perianal disease	3	8.58
Indications	Fistula/abscess	18	51.42
	Obstruction	13	37.14
	Severe colitis	2	5.7
	CD unresponsive to medical therapy	3	8.57
Type of surgery	Resection	24	68.57
	Strictureplasty	2	5.71
	Resection+strictureplasty	4	11.42
	Explorative laparotomy or stoma creation	5	14.28
Access	Laparoscopy (conversion)	17 (1)	48.57 (2.85)
	Open	8	22.85
Incision	Midline incision	17	48.57
	Peri-umbilical	4	11.42
	Pfannestiel	10	28.57
Complication	Obstruction	6	17.14
	Rectal bleeding	1	2.85
	Diarrhea	2	5.71
	Anastomotic leak	0	0
	Other	3	8.57

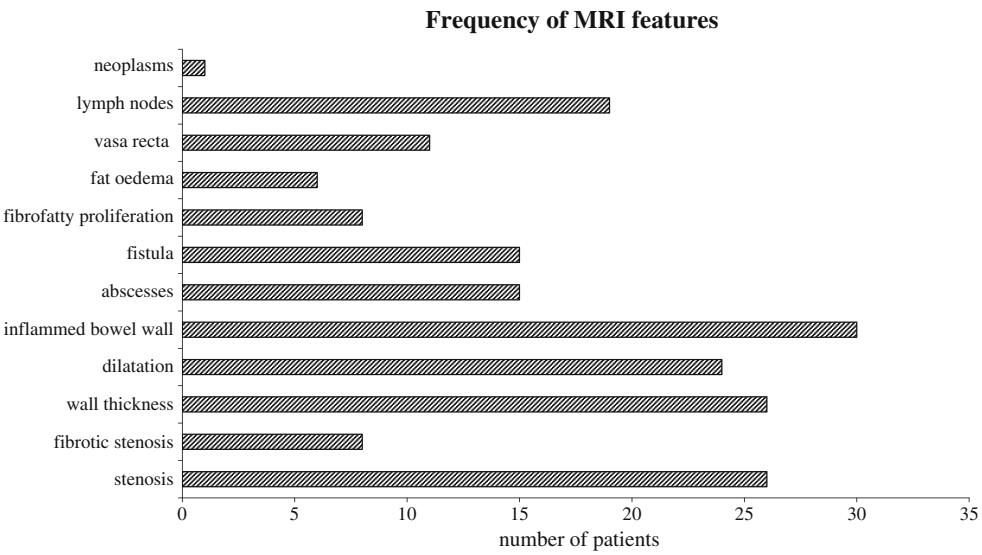

Fig. 2 Frequency of MRI features

the other hand, MRE identified bowel fistulae with a sensitivity of 0.71 (95% CI 0.42–0.90) and a specificity of 0.76 (95% CI 0.52–0.90). In this case, the concordance of MRE findings with intraoperative findings was lower but still good [Cohen's κ=0.47 (0.17)].

Finally, MRE identified preoperatively only one out three neoplasms (two leiomyomas and one lymphoma) with a sensitivity of 0.33 (95% CI 0.01–0.87) and a specificity of 1.00 (95% CI 0.86–1.00). The concordance of MRE findings with intraoperative findings was high [Cohen's κ=0.48 (0.14)]. Sensitivity and specificity of MRE are shown in Table 2.

MRI Findings as Predictors of Outcome of Surgery

Bowel stenosis, fibrotic stenosis, wall thickness, proximal bowel dilatations, active inflammation within the bowel wall, abscess, fistulas, fibro-adipose proliferation, peri-intestinal adipose tissue edema, vasa recta lymph nodes, and neoplastic findings observed at MRE were tested as possible predictors of the type of surgical procedure used and of surgical outcome at univariate and multivariate logistic regression analysis. The grade of proximal bowel dilatation resulted to be a significant predictor of the possibility of using strictureplasty instead of/associated to bowel resection either at univariate or at multivariate analysis. The type of abdominal incision (suprapubic transverse incision vs midline paraumbilical incision) seemed to be predicted by CD colonic localization, fibro-adipose proliferation, and the number of fistulas at univariate analysis, but these associations were not confirmed at multivariate analysis. Univariate and multivariate logistic regression analysis is shown in Table 3.

Discussion

CD is a life-long, chronic, relapsing condition that involves the whole digestive tract. Patients affected by this disease require several and repeated radiological and instrumental exams to identify localization and relapsing of inflammation during their lifetime. For this reason, minimally invasive exams which also expose them to a minimal quantity of ionizing radiations should be preferred. MRE can respond to these requirements since it does not use radiation and it can yield adequate morphological images. A good preoperative morphological assessment is essential to plan the best surgical procedure. Surgical procedures can be different in relation to the different localization and the different presentation of the disease. In fact, the different phenotypes of CD (inflammatory, stricturing, or fistulizing) require different approaches.

In our study, MRE findings and intraoperative findings of 35 consecutive patients with CD who underwent MRE and subsequent abdominal surgery were compared. In a recent systematic review, Horsthuis et al. evaluated seven studies about the use of MRE for evaluation of disease activity in confirmed or suspected CD.[16] In this meta-analysis, 140 patients from seven studies were analyzed.[21–27] In all these studies but one,[21] the sample size was lower[22–25] or comparable[26,27] to our study group. Furthermore, only few studies compared MRE findings and intraoperative findings.[24,27–29] However, all these studies were focused on the evaluation of disease activity in CD as a key point in the decision making between medical and surgical treatment. As far as we know, no study was focused on surgical details that could be useful in the further step of planning surgical procedures.

Prospective comparative studies between MRE and conventional enteroclysis have reported sensitivity and specificity ranges for MRE of 100 and 88–92.9% in the detection of stenosis and 75–100 and 97.8–100% in the detection of fistulas, respectively.[30–34] However, in our series, MR enterography identified bowel stenosis with a sensitivity of and a specificity of 95% and 72% and fistulae with a sensitivity of 71% and a specificity of 76%. The lower sensitivity and specificity observed in our series may be due to the different gold standard adopted. In the abovementioned studies, MRE findings were compared to

Table 2 Sensitivity and specificity of MRE compared to intraoperative findings

MRE findings	Fibrosis	Stenoses	Abscesses	Fistulas	Neoplasms
True positive	7	23	12	10	1
False positive	1	3	2	5	0
True negative	17	8	20	16	32
False negative	10	1	1	4	2
Sensitivity (95% CI)	0.41 (0.19–0.66)	0.95 (0.76–0.99)	0.92 (0.62–0.99)	0.71 (0.42–0.90)	0.33 (0.01–0.87)
Specificity (95% CI)	0.94 (0.70–0.99)	0.72 (0.39–0.92)	0.90 (0.69–0.98)	0.76 (0.52–0.90)	1 (0.86–1)
Positive predictive value (95% CI)	0.60 (0.46–0.99)	0.88 (0.68–0.96)	0.85 (0.56–0.97)	0.66 (0.38–0.87)	1 (0.05–1)
Negative predictive vaue (95% CI)	0.62 (0.42–0.79)	0.88 (0.50–0.99)	0.95 (0.74–0.99)	0.08 (0.55–0.93)	0.94 (0.78–0.98)
Cohen's κ (SE)	0.33 (0.14)	0.72 (0.16)	0.82 (0.17)	0.47 (0.17)	0.48 (0.14)

Table 3 MRE findings as predictors of type of surgical procedure

	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*p* level	OR (95% CI)	*p* level
Predictors of strictureplasty (vs. resection)				
Number of fibrotic stenosis at MRI	4.8 (0.69–33.36)	0.09	2.71 (0.30–24.30)	0.35
Score of dilatation at MRI	3.70 (1.13–12.15)	0.02	3.31 (0.99–11.04)	0.04
Predictors of Pfannestiel incision (vs. midline incision)				
Colonic localization	11.45 (1.15–113.79)	0.03	10.17 (0.80–129.27)	0.06
Fat hypertrophy at MRI	7 (1.15–42.35)	0.02	2.02 (0.19–20.83)	0.53
Number of fistulae at MRI	4.95 (0.94–25.89)	0.04	4.58 (0.57–36.84)	0.13

conventional enteroclysis findings while in our series they were compared to intraoperative findings. The difference may be equivalent to the difference between shadows projected on the wall and real person in the Plato "Myth of the cave".[35]

On the other hand, the sensitivity and specificity of MRE for intra-abdominal abscesses was 92% and 90%, respectively, and this result showed the reliability of MRE in the diagnosis of this CD complication. An adequate preoperative assessment of intra-abdominal abscess is crucial since small abscesses may be treated with antibiotics or drained percutaneously under CT or ultrasound guidance.[14] Percutaneous, image-guided drainage may obviate the need for surgery or permit a minimally invasive approach that would be difficult otherwise.[14,36]

CD is associated with an increased risk of developing intestinal cancer compared to the general population, and late diagnosis of cancer often occurs since misdiagnosis due to overlapping symptoms that are often typical of active CD is frequent.[37] Moreover, at radiology, neoplasms may present as a stricturing lesion that can be difficult to differentiate from benign strictures related to CD.[14] In fact, lymphomas have been reported to present as multifocal areas of increased nodularity and strictures on barium examinations.[38] In our series, the sensitivity and specificity MRE for neoplasms were 33% and 100%, respectively. However, the small number and the heterogeneity of the neoplasms observed in our series made these data not conclusive.

Minimally invasive surgery and strictureplasty may reduce the negative impact of surgery in patients affected by CD.[3] Specific MRE findings were tested as possible predictors of the type of surgical procedure that could be used at univariate and multivariate logistic regression analysis. A high grade of proximal bowel dilatation resulted to be a predictor of the possibility of using strictureplasty instead of associated to bowel resection. This information might be useful for patients in those strictureplasty could be indicated such as those who have already had small bowel resection and are at risk of short bowel syndrome. In fact, although in surgical management of CD bowel resection is usually preferred as first operation, strictureplasty remains an effective means of alleviating obstructive CD while conserving bowel length. However, it requires a specific expertise to be done[3,7] and a high grade of proximal bowel dilatation may preoperatively suggest the possibility to perform this bowel sparing technique and to refer the patients to expert and dedicated surgeons.

On the other hand, although the type of abdominal incision (suprapubic transverse incision vs. midline peri-umbilical incision) seemed to be predicted by CD colonic localization, fibro-adipose proliferation, and the number of fistulas at univariate analysis, this result was not confirmed at multivariate analysis. The importance of cosmetic results of surgery in CD patients was described by Dunkers et al.[4,5] It would have been useful to predict the site of the most convenient service incision since Pfannestiel incision is the most unapparent. However, the retrospective setting of this study may have masked the exact role of MRE in the decision of the best site of the service incision. In fact, at the beginning of our experience of video-assisted laparoscopic surgery for CD, the peri-umbilical incision was preferred independently from the intra-abdominal findings.

A limitation of this study is its observational retrospective design. A randomized controlled trial that compared CT enterography and MRE findings to operative ones would have provided important information about the best preoperative work-up. However, in our opinion, the detailed sensitivity and sensibility results of this study can provide the basis of such a study. A further limitation of the study was that the surgeon was not blinded to MRE findings. In this retrospective setting, this was not possible and the awareness of the MRE results has surely influenced the decision about the following operative procedures. On the other hand, the same retrospective setting preserved the intraoperative assessment of the disease activity, complication, and localization from any influence of the preoperative work up. In fact, the intraoperative assessment was

routinely performed at the moment of filling the preformatted operative records, and this is a standard procedure in our department that is usually done for every patient.

In conclusion, our study confirmed that MRE findings correlate significantly with disease activity. Once decided that the patient should undergo surgical treatment, MRE can provide the surgeon useful and adequate information about abscess, stenosis, and fistulas. Detailed information about abscess could suggest percutaneous drainage that could facilitate the following surgery or avoid emergency laparotomy. Proximal bowel dilatation can suggest the possibility to perform bowel sparing surgery such as strictureplasty.

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2011 SSAT QUICK SHOT PRESENTATION

Adult Intussusception in the Last 25 Years of Modern Imaging: Is Surgery Still Indicated?

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Abstract
Background Because most adult intussusceptions are reportedly due to malignancy, operative treatment is recommended. With current availability of computed tomography, we questioned the role of mandatory operative exploration for all adult intussusceptions.
Methods This study is a retrospective review of all adults treated from 1983 to 2008 at a large tertiary referral center for intussusception.
Results One hundred ninety-six patients had intussusception over the 25-year study period. Computed tomography was obtained in 60% of patients. Neoplasms [malignant, (21%); benign, (24%)] were the commonest etiology; 30% cases were idiopathic. One hundred twenty (61%) patients underwent operative treatment for intussusception. Six of the 58 idiopathic or asymptomatic cases were operated on with negative findings in all. Palpable mass (OR 4.56, $p<0.035$), obstructive symptoms (OR 9.13, $p<0.001$) or obstruction (OR 9.67, $p<0.001$), GI bleeding (OR 14.41, $p<0.001$), and a lead point on computed tomography (OR 10.08, $p<0.001$) were associated with the need for operation.
Conclusion In the current era of computed tomography, idiopathic or asymptomatic intussusception is being seen more commonly; however, the majority of adult intussusceptions still have pathologic lead points. From our experience, all patients with palpable mass, obstructive symptoms or obstruction, gastrointestinal bleeding, or a lead point on computed tomography should undergo operative exploration.

Keywords Intestinal obstruction · Intussusception · Computed tomography · Gastrointestinal surgical procedure · Celiac disease

Introduction

Intussusception involves the telescoping of one segment of bowel into an adjacent segment of bowel. This pathologic process often results in obstruction. Because intussusception in children is usually idiopathic and lacks a lead point, most cases are treated with attempts at nonoperative reduction. Intussusception in adults is much less common comprising only 5% of all intussusceptions.[1–3] In contrast, adult intussusception is often secondary to a malignancy. Adult colonic intussusception is associated with primary carcinoma in 65–70% of cases, while adult small bowel intussusceptions are secondary to a malignancy in only 30–35% of cases.[3–7] As a result, most authors recommend operative exploration to prevent or treat the resultant bowel obstruction and to diagnose or exclude an underlying malignancy.[7]

This study was presented at the annual meeting of the Society for Surgery of the Alimentary Tract during the Digestive Disease Week on May 7–10, 2011 in Chicago, IL, USA.

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Over recent years, computed tomography (CT) has become the preferred imaging modality for the evaluation of acute abdominal pain. Evidence of intussusception on CT includes a target sign, a sausage-shaped mass with different layers of attenuation, and intraluminal fat, and as the obstruction progresses, proximal dilation and distal decompression with increasing bowel wall edema and vascular compromise. Older studies of CT suggested that intussusceptions are often due to malignant lead points, while more recent studies have noted a pathologic lead point is increasingly less common in adult intussusception.[8] In one study, only 39% of patients with intussusception required an operation.[7,9] Others have suggested that small bowel inflammation, as it occurs in celiac disease and inflammatory bowel disease, causes bowel wall edema and dysmotility that leads to intussusception (Table 1).[10–12] As the resolution of CT scanners has improved, increasing amounts of data are available from the images including the possible etiology or lack of a lead point of the intussusception. Several studies with current CT scanners have found a sensitivity of 58–100% and a specificity of 57–71% in determining the underlying etiology of intussusception.[13–15] Therefore, we questioned the validity of mandatory operative exploration of adults with intussusception (Table 2). We reviewed our experience with adult intussusception over the past 25 years to: (1) determine the frequency of malignancy as a lead point for intussusception in the era of modern imaging and (2) the clinical criteria that mandate exploration.

Table 1 Etiologic causes of adult intussusception

1. Primary malignancy	24 (14%)
Colon adenocarcinoma	10 (42%)
Small bowel lymphoma	7 (29%)
Small bowel adenocarcinoma	4 (17%)
Small bowel GIST	2 (8%)
Small bowel leiomyosarcoma	1 (4%)
2. Metastatic malignancy	19 (10%)
Malignant melanoma	9 (47%)
Leukemia/lymphoma	3 (16%)
Small cell lung cancer	3 (16%)
Others [MFH (1), osteosarcoma (1), metastatic peripheral, nerve sheath tumor (1), unknown primary (1)]	4 (21%)
3. Benign neoplasms	47 (24%)
Polyp	23 (49%)
Lipoma	10 (21%)
Peutz-Jeghers syndrome	6 (13%)
Leiomyoma	4 (9%)
Appendiceal cystadenoma	1 (2%)
Submucosal hematoma	1 (2%)
GIST	1 (2%)
Inflammatory fibroid polyp	1 (2%)
4. Others	48 (24%)
Adhesions	12 (25%)
Crohn's disease	9 (19%)
Celiac sprue	8 (17%)
Infection/appendicitis/abscess	7 (15%)
Meckel's diverticulum	5 (10%)
Pneumatosis cystoides intestinalis	2 (4%)
Congenital malrotation	1 (2%)
Amorphous inspissated mucous	1 (2%)
Gallstone	1 (2%)
Submucosal hematoma	1 (2%)
Focal vasculitis/ischemia	1 (2%)
5. Idiopathic	58 30%)
Total	196

MFH malignant fibrous histiocytoma, *FB* foreign body, *IBD* inflammatory bowel disease, *SB* small bowel, *GIST* gastrointestinal stroma tumor

Materials and Methods

With the approval of the Mayo Clinic Institutional Review Board, we reviewed retrospectively the records of all patients aged >18 years, who were diagnosed with intussusception on imaging or at time of operation at Mayo Clinic, Rochester from 1983 to 2008. CT was available throughout this time period for the evaluation of patients with abdominal pain. Patients with rectal, stomal, or anastomotic intussusceptions were excluded, as were those related to intestinal intubation. We specifically included asymptomatic patients with incidentally discovered intussusceptions. A total of 196 patients who met all inclusion and exclusion criteria were identified over the 25-year time period. Specific data elements collected when available for each of these patients included age, sex, the clinical presentations of abdominal pain, abdominal mass, partial or complete bowel obstruction or gastrointestinal bleeding, duration of symptoms, and results on all forms of imaging (CT, ultrasonography, small bowel radiologic contrast studies, endoscopy, and laparoscopy). Operative and pathologic records were reviewed to identify the type of intussusception, intraoperative findings, operative procedure performed, and pathologic findings.

The 196 patients were subclassified into four categories based on the site of the lead point of the intussusception.

1. Enteroenteric intussusception in which the lead point and intussusception are confined to the small bowel
2. Ileocolic intussusception where the ileum intussuscepts through a stationary ileocecal valve

Table 2 Operative treatment of adult intussusception

Type of intussusception	Primary resection	Reduction then resection	Reduction only	Endoscopic reduction and resection
Colocolonic				
Benign	11	3	0	5
Malignant	3	0	0	0
Other	0	0	1	1
Total	14	3	1	6
5 patients with idiopathic intussusception and 1 patient with terminal advanced cecal cancer were nonoperative				
Enteroenteric				
Benign	16	3	1[a]	2
Malignant	28	1	0	0
Malrotation	0	1	0	0
Meckel's	5	0	0	0
Crohn's disease	2	0	0	0
Gallstone	0	0	1	0
Infection	0	2	0	0
Adhesions	3	0	0	0
Idiopathic	11	0	4	2
Total	69	7	6	4
32 patients with idiopathic, 7 with celiac disease, 3 with infection, 2 patients with terminal cancer were nonoperative				
Ileocecal				
Benign	3	1	0	0
Malignant	3	0	0	0
Idiopathic	2	0	0	2
Total	8	1	0	2
1 patient with celiac disease-associated intussusception was observed, 1 patient had lymphoma treated with chemotherapy				
Ileocolic				
Benign	1	1	0	1
Malignant	5	0	0	0
Idiopathic	2	0	1	0
Infection	0	1	0	0
Crohn's disease	1	0	0	0
Total	8	2	1	1
1 patient with lymphoma-associated intussusception was treated with chemotherapy				

[a] Peutz-Jeghers polyps-associated intussusception

3. Ileocecal intussusception where the ileocecal valve is part of the lead point, and
4. Colocolonic intussusception where the lead point and intussusception are confined to the colon.

Incidental intussusception was defined as intussusception detected on CT in patients with no symptoms attributable to the intussusception.[16] They are often transient and asymptomatic and usually do not appear on subsequent imaging.[17]

Idiopathic (primary) intussusception was defined as an intussusception for which no etiology or lead point could be identified by imaging, exploration, and/or pathologic evaluation regardless of symptoms.[18] The need for operative intervention was defined as the presence of a benign or malignant neoplasm or clinical and radiologic evidence of bowel obstruction. Symptom variables were analyzed using a univariate logistic regression model. All significant variables in the univariate analysis were included in the multivariate analysis. A p value<0.05 was considered significant for the multivariate logistic regression analysis. The presence of a lead point or mass associated with intussusception on CT was analyzed separately in a univariate model. Sensitivity, specificity, and negative and positive predictive values for each of the symptom variables were calculated. A chi-square test was performed

to analyze the relationship of primary malignancies to location of intussusception.

Results

Demographics

A total of 196 adult patients were identified with intussusception over the 25-year study period. In contrast to the slight male preponderance reported in our earlier study on 1955–1978,[7] this patient cohort demonstrated a slight female preponderance with 109 (56%) women and 87 (44%) men. The median age at diagnosis was 51 years (range 18–90), with 45% older than 50 years of age; 11% were younger than 30 years old. The majority of patients had enteroenteric intussusception, $n=138$ (70%), followed by colocolonic intussusception in 30 (16%), ileocecal intussusception in 16 (8%), and ileocolic intussusception in 12 (6%).

Clinical Presentation

Most patients presented with chronic symptoms over a mean duration of 69 days (range 1 day to 3 years). Only 38% of patients presented with a symptom duration of less than 2 weeks. The most common finding on presentation was abdominal pain which occurred in 143 (73%) patients. Partial bowel obstruction was apparent in 93 (48%), a palpable mass in 30 (15%) patients, heme-positive stools in 27 (14%), and complete bowel obstruction in 11 (6%). Thirty-seven (19%) patients were asymptomatic at presentation with the intussusception found incidentally on imaging. The classic triad of abdominal pain, mass, and heme-positive stool was present in only four (2%) patients. Potentially important, however, was the association of a malignant etiology of the intussusception with the presence of palpable mass (OR 4.56, 95% CI 1.11–18.68, $p<0.035$), hemorrhage (OR 14.41, 95% CI 3.01–68.9, $p<0.001$), and obstructive symptoms (OR 9.13, 95% CI 4.54–18.36, $p<0.001$) on multivariate analysis (Table 3). Pain, while very sensitive (97%), was not a specific (50%) predictor of the need for operative intervention. In contrast, although a palpable mass or bleeding occurred relatively infrequently, (sensitivity of 18% and 24%, respectively, for need for operative intervention), these findings were very specific (100% and 97%, respectively) for the need for operative intervention (Table 4).

Etiology of Intussusception

A discrete pathologic process was present in 138 patients (70% of all intussusceptions) (Table 1). The etiopathogenesis for intussusception in the remaining 58 patients (30%) was idiopathic including incidental cases. Primary and metastatic neoplasms were the causes of intussusception in only 43 (22%) patients. Idiopathic adult intussusception was the most common etiology with imaging; the majority of these (52%) were incidental asymptomatic intussusceptions. When these patients are excluded, benign neoplasms were as likely a cause of intussusception as a malignancy. Benign tumors accounted for 24% ($n=47$) of all intussusceptions. Adhesions ($n=12$), Crohn's disease ($n=9$), celiac sprue ($n=8$), infection/appendicitis-associated ($n=7$), Meckel's diverticulum ($n=5$), pneumatosis cystoides intestinalis ($n=2$), and other common causes accounted for the remaining 48 (24%) cases of intussusception (Table 1).

Primary malignancy was present in 24 patients (14%) with nearly half (ten) of these colonic adenocarcinomas. For the rare ileocolic intussusceptions, a malignant lead point was the most common mechanism at this site ($p=0.002$). The majority of the small bowel primary malignancies were lymphomas (53%), while small bowel adenocarcinomas accounted for (31%) (see Table 1). The small bowel, however, was the least likely location of a primary malignancy accounting for only 9% of all enteric intussusceptions compared to 21% of all other types of intussusception ($p=0.018$). Metastatic malignancy to the small bowel was the lead point in 19 patients (10%); only one metastatic tumor caused a colonic intussusception. Metastatic melanoma accounted for 47% of all metastatic intussusceptions.

Imaging

CT imaging was obtained in 117 (60%) patients. A lead point was identified in 28 (32%) of the 88 scans available for review. Of these, 12 (43%) were benign neoplasms, 7 (25%) were malignant neoplasms, 4 (14%) were idiopathic, 3

Table 3 Univariate analysis of predictors of malignant neoplasms ($N=196$)

Predictor variable	Odds ratio	95% CI for OR	p value
Pain	9.75	2.27–41.93	0.002
Palpable mass	11.04	4.08–29.87	<0.001
Obstructive symptoms	10.08	3.75–27.08	<0.001
Bleeding	3.21	1.35–7.61	0.008

Table 4 Univariate analysis of predictors of the need for surgery ($N=196$)

Predictor variable	Odds ratio	95% CI for OR	p value
Pain	5.69	2.79–11.59	<0.001
Palpable mass	6.14	1.75–21.57	0.005
Obstructive symptoms	9.67	5.03–18.57	<0.001
Bleeding	14.06	3.23–61.24	<0.001

Table 5 CT lead point as a predictor of etiology (N=88)

Etiologies	Odds ratio	95% CI for OR	p value
Malignant primary neoplasms	4.13	0.91–18.72	0.066
Malignant metastatic neoplasms	1.68	0.35–8.07	0.517
Malignant neoplasm	3.00	0.90–9.97	0.073
Benign neoplasms	10.50	2.98–37.04	<0.001
Any neoplasm	10.56	3.72–29.98	<0.001
Need for surgery	10.08	3.46–29.36	<0.001

(10%) were associated with adhesions, and 2 (7%) were associated with Crohn's disease. The identification of a lead point on CT was highly associated with the presence of a neoplasm (OR 10.56, 95% CI 3.72–29.98, $p<0.001$) and the need for an operation (OR 10.08, 95% CI 3.46–29.36, $p<0.001$) (Table 5). A small bowel contrast study was done in 50 (25%) patients, often as a follow-up study in patients with a clinical suspicion of intussusception or for an asymptomatic intussusception seen on CT; the study detected intussusception with a lead point in only seven patients, five of whom had intussusception on CT. Thirty-one patients were diagnosed with intussusception only at the time of operative exploration without preoperative imaging and 48 were diagnosed on endoscopy. Abdominal ultrasonography was obtained in only two patients and the intussusception was visualized in only one.

Treatment

One hundred and 20 (61%) patients underwent operative treatment (Table 2). Thirteen patients were managed by colonoscopic reduction of intussusception with concomitant polypectomy. Three patients had advanced metastatic cancer and were treated nonoperatively. Two patients with asymptomatic intussusception associated with lymphoma were treated with chemotherapy. Fifty-two of the remaining 58 patients with idiopathic intussusception reduced spontaneously on CT or subsequent imaging and were observed. These included 37 (64%) patients with incidental intussusceptions, all of which were managed nonoperatively because they were asymptomatic (Table 6). The six patients with idiopathic intussusceptions who were explored operatively had negative explorations (three open and three laparoscopic).

Of the 120 patients who underwent operative treatment, primary resection without reduction was performed in 99 (82%) patients. Thirteen (11%) patients had an operative reduction of their intussusception followed by resection; eight patients (7%) underwent reduction only.

Recurrence

Mean follow-up was 64 months (range 0.1–305.2 months) for the entire cohort. Only 2 of the 21 patients with idiopathic intussusception not detected incidentally experienced a subsequent recurrence, and both resolved spontaneously. None of the patients with idiopathic or incidental intussusceptions were found subsequently to harbor gastrointestinal malignancies. For patients with intussusceptions associated with malignancy, only one patient had a recurrence secondary to another metastatic leiomyosarcoma in the small bowel. For the benign intussusceptions, there were five recurrences involving one patient with vasculitis, one with Peutz-Jeghers, one with pneumatosis intestinalis, and two with no obvious etiology; only two of these five recurrences were treated by resection.

Discussion

Much of the older surgical literature, including our own published in 1981, cautioned that adult intussusception is associated with a discrete pathologic process in more than 75% of patients[1,7,19] with malignant neoplasms accounting for the majority of adult intussusceptions.[7] As a result, operative exploration was considered mandatory for the management of an adult intussusception. In the more current era of use of advanced techniques of imaging especially CT, to evaluate patients with abdominal symptoms, there has been a twofold increase in the incidence of recognized intussusceptions secondary to idiopathic and incidentally detected intussusception. Whereas in the pre-CT era, idiopathic intussusception accounted for less than 15% of adult intussusception, in our series, idiopathic intussusception accounted for 30% of all adult intussusceptions. Although increased from our pre-CT experience, several recent reports have found idiopathic intussuscep-

Table 6 Distribution of incidental intussusceptions

Type of intussusception	n (%)
Enteroenteric	28 (76%)
Ileocecal	3 (8%)
Ileocolic	1 (2%)
Colocolonic	5 (14%)

tion to account for 48–94% of cases.[13,20,21] This discordance is likely the result of the routine use of CT identifying a new subset of patients with incidental intussusception. The clinical significance of an asymptomatic radiographic finding of intussusception is uncertain. This study demonstrated the safety of observation in the setting of asymptomatic incidental intussusception without an identified lead point; indeed only one patient had a recurrence, and none required operative intervention. The one patient with recurrent symptoms had no further problems on follow-up at 2 years. Operative exploration for asymptomatic incidental intussusception was routinely negative in our experience (n=6), suggesting that in the absence of clinical signs, symptoms, or specific radiographic findings of a lead point, incidental intussusception seen on CT may represent a transient clinically unimportant event that may be more common than previously thought. The use of CT in the diagnosis of intussusceptions helps to differentiate between nonpathologic and pathologic intussusceptions. The presence of a mass imaged as a lead on CT was highly associated with the presence of a neoplasm and the need for operative treatment. In addition, CT findings of a bowel obstruction are significantly associated with malignant neoplasms and the need for an operation. Other authors have found an increased length and diameter of the intussusceptum on CT to warrant exploration.[22,23] Previous studies and our current review suggest that intussusceptions that lack a pathologic cause of obstruction on CT are likely self-limiting and do not require operation.

Despite the increase in the number of idiopathic and incidental cases of intussusception over the last three decades, we found that the majority of cases (at least 70%) in our practice are still associated with a pathologic lead point, either cancer, a benign neoplasm, or a non-neoplastic pathology involving the wall of the bowel. About half of the lead points are either primary malignancies or metastases and the other half are benign neoplasms. Primary malignant neoplasms are more commonly found in colocolonic and ileocolic intussusceptions, and hence, resection is well-advised. Malignant enteroenteric intussusceptions are more frequently due to metastatic tumors and may require resection depending on symptoms and stage of the underlying malignancy. Palliative bypass or palliative chemotherapy is an option in selected individuals. Benign neoplasms comprised a significant number of the adult intussusceptions in our study. Most of these patients required intervention to relieve symptoms or to exclude malignancy. Several authors have suggested other nonneoplastic etiologies such as celiac sprue[12,24] and Crohn's disease[25,26] as causes of intussusception in adults as in our series.

Conclusion

The incidence of recognized intussusception in adults has increased with advanced techniques of imaging, thereby changing the clinicians' approach to their management. Although incidental intussusceptions have become much more common, the majority of adult intussusception cases are still associated with a pathologic lead point which, in many patients, is malignant. Most small bowel intussusceptions discovered incidentally on CT are transient processes of no clinical significance provided a lead point is not identified. In contrast, if clinical symptoms are present, such as obstructive symptoms, gastrointestinal bleeding, or a palpable mass, these patients should undergo exploration. Together, our data suggest that the majority of adult intussusceptions are still clinically relevant and require further investigations to define the underlying etiology.

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2011 SSAT POSTER PRESENTATION

Management and Outcomes of Primary Coloduodenal Fistulas

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Abstract
Purpose Primary coloduodenal fistula (CDF) is a rare entity. We review our experience with the management and outcomes of CDF.
Methods This is a retrospective review from 1975 to 2005 of patients with primary CDF. Patients were followed through clinic visits and mail correspondence with a mean (±SE) follow-up of 56±14 months.
Results Twenty-two patients were diagnosed at a mean age of 54±3 years with primary CDF: benign (n=14) or malignant (n=8). Benign CDF were due to Crohn's disease (n=9) or peptic ulcer disease (n=5); malignant CDF was primarily due to colon cancer (n=7) plus 1 patient with lymphoma. Indications for operative intervention included intractable symptoms (n=15), gastrointestinal bleeding (n=14), and to rule out malignancy (n=8). Complete resection of malignant CDF with negative margins was achieved in half of patients after en bloc resection. Palliative bypass was performed in those patients with unresectable disease. Thirteen patients with benign CDF had resection of the fistula—2 of these patients required a duodenal bypass. There were no perioperative deaths, and the morbidity rate was 38%. Median survival for patients with malignant CDF was 20 months (range 1–150 months). Two patients with malignant CDF had >5-year survival. All patients with benign CDF who underwent fistula resection had resolution of fistula-related symptoms with one recurrence.
Conclusion Benign CDF is amenable to operative therapy with resolution of symptoms and a low recurrence rate. Complete resection of malignant CDF can impart survival benefit.

Keywords Coloduodenal fistula · Duodenocolonic fistula · Duodenum · Colon · Enteroenteric fistula

Introduction

Coloduodenal fistulae (CDF) can be classified as either primary or secondary. A primary fistula is de novo occurrence of CDF in patients without a relevant surgical history and is seen secondary to infectious, inflammatory, or neoplastic processes. A secondary CDF is typically a complication of an invasive gastrointestinal procedure. The literature on primary coloduodenal fistulae is limited to case series.[1–6,8–10,12–15,17,19–21,23–26] Consequently, the clinical presentations, optimal diagnostic and management strategies, and outcomes of CDF are poorly described. The effectiveness of current treatment strategies for fistula treatment and patient survival outcomes are unknown for both benign and malignant CDF.

We reviewed our 30-year experience with the management of CDF. Herein, we summarize the clinical presentations, review the diagnostic strategy and surgical management, and compare perioperative and long-term outcomes of benign and malignant CDF.

Methods

With IRB approval, we conducted a retrospective review of the Mayo Clinic Rochester medical and surgical database to

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identify patients who were treated at our institution for a primary coloduodenal or duodenocolonic fistulae from 1975 to 2007. Patients with secondary CDF were excluded. Clinical presentation, diagnostic evaluation, indication for and type of surgical procedure, pathology, and treatment outcomes were collected during a detailed chart review. Follow-up was accomplished through recent clinic visits or mail correspondence. Follow-up data was available for all patients until death or as of December 2007 with mean (±SE) duration of 56±14 months. The primary outcome measures included: fistula recurrence, completeness of resection for malignant fistulas, and overall survival. The secondary outcome measures were perioperative mortality and morbidity.

Statistical analyses were performed using the JMP statistical package (JMP software, Cary, NC, USA). Student's *t* test or ANOVA were used to evaluate for statistical differences between fistulas from benign vs. neoplastic etiologies, where $p<0.05$ was considered statistically significant. The Kaplan–Meier method was used to analyze survival outcomes, and the log-rank test was used to assess survival differences between groups. Means and standard error of the mean (±SE) are used to express value uncertainty, unless specified otherwise.

Table 1 Patient and fistula features

Age	
Mean±SE	54±3 year
Gender	Number of patients (%)
Male	12 (55)
Female	10 (45)
Total	22 (100)
Main presenting symptoms and signs[a]	Number of patients (%)
Obstruction	16 (73)
GI bleeding, anemia	14 (64)
Abdominal pain	14 (64)
Weight loss	3 (9)
Abdominal bloating	1 (5)
Etiology of coloduodenal fistulas	Number of patients (%)
Malignant	8 (36)
Benign	14 (64)
Portion of Duodenum Involved[b]	Number of Patients (%)
First	4 (18)
Second	14 (64)
Third	11 (50)

[a] A patient may present with multiple symptoms or signs. Other symptoms and signs were small bowel obstruction[b] and jaundice[a]

[b] Multiple portions of the duodenum were involved in seven patients

Results

Twenty-two patients with the diagnosis of primary CDF were identified. Table 1 summarizes the clinical presentation and features of CDF. The mean age at presentation was 54±3 years. Eight patients (36%) had a malignant CDF, while 14 (64%) had a benign CDF due to either Crohn's disease ($n=9$) or peptic ulcer disease ($n=5$).

Patients with malignant CDF were more likely to present with acute gastrointestinal hemorrhage compared to those patients with benign CDF (87% vs. 50%, $p=0.07$). Patients with benign CDF more commonly presented with intractable nausea, vomiting and diarrhea (86% vs. 50%, $p=0.073$), and abdominal pain (86% vs. 25%, $p=0.004$). The diagnosis of CDF was confirmed preoperatively in 16 patients on radiologic imaging and/or endoscopy (see Fig. 1), and intra-operatively in 6 patients (see Table 2).

Twenty-one patients underwent an operative procedure, and the indications are listed in Table 2. A single patient with benign CDF was medically unfit for a procedure. Complete resection was achieved in four patients with colon carcinoma via an en bloc right hemicolectomy and limited duodenectomy with primary duodenal repair in three patients and en bloc right hemicolectomy and pylorus-preserving pancreaticoduodenectomy in one patient (see Table 2). Two patients who had a primary repair of the lateral duodenotomy also required a gastrojejunostomy because of significant duodenal narrowing. Palliative bypass for impending duodenal and/or colonic obstruction was performed in four patients with locally advanced (involving the mesenteric root) or metastatic colon cancer. All malignant CDF were due to colon adenocarcinoma except for a single patient with a primary intestinal lymphoma (see Table 3).

Resection of benign CDF was achieved with primary duodenal closure without a duodenal bypass in 11 patients (85%). Two patients with benign CDF had a bypass. Bypass was necessary in one patient found to have a duodenal stricture which was managed with a loop gastrojejunostomy; the other patient was bypassed as part of a definitive ulcer operation (Billroth II with Roux-En-Y reconstruction). Altogether, 6 patients (of the 22) underwent procedures that included a duodenal bypass (four malignant and two benign).

Overall morbidity was 38% and was similar regardless of malignant or benign CDF (see Table 4). There were no perioperative deaths and most of the post-operative complications were self-limiting. One patient with a benign CDF developed a recurrent CDF due to Crohn's disease at the anastomotic site. Patients with malignant CDF had poorer overall survival as compared to those with benign CDF (20 vs. 232 months median survival, $p=0.009$; see Fig. 2).

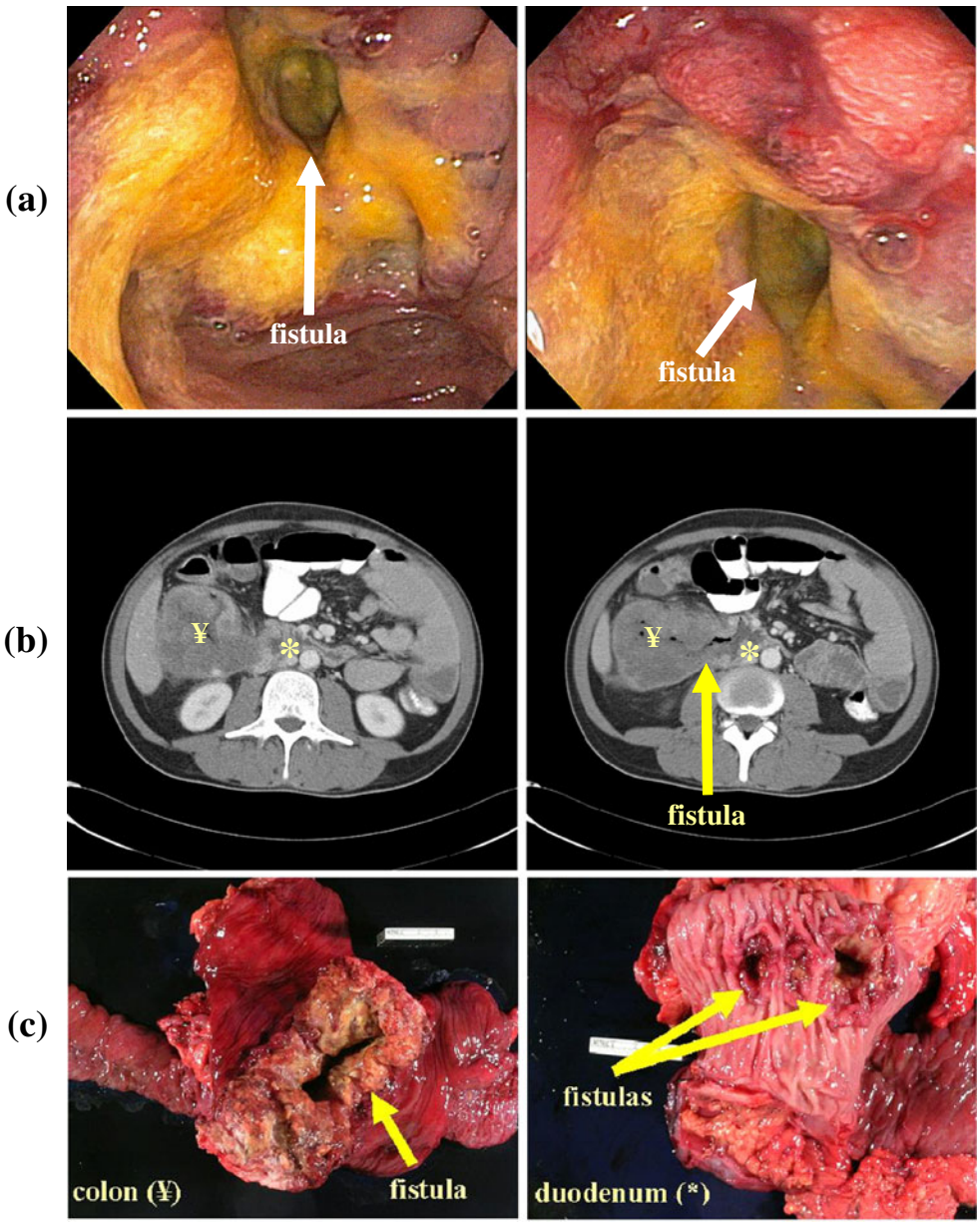

Fig. 1 Example of endoscopic (**a**), computer tomography (**b**), and gross pathology (**c**) images of coloduodenal fistula from colon cancer. *Asterisk* indicates colon, while *yen sign* indicates the duodenum. *Arrows* indicate the fistula

Discussion

Primary CDF is a rare complication of Crohn's disease, peptic ulcer disease, infection (such as bacterial, syphilis, or tuberculosis), or cancer (primarily colon adenocarcinoma but also duodenal, peri-ampullary, or pancreatic adenocarcinoma and lymphoma).[1,3,6,7,9,11,16,18,19,26] In this study, we summarize our institutional experience over three decades with the management of benign and malignant CDF.

Patients with malignant CDF (which are most frequently due to primary colon adenocarcinoma) were more likely to present with gastrointestinal hemorrhage necessitating blood transfusion. Patients with a benign CDF tend to present with intractable gastrointestinal symptoms consisting of nausea, vomiting, diarrhea, and abdominal pain. We have found that a combination of radiologic imaging and endoscopy are complimentary in evaluating the location and etiology of CDF when suspected.

Surgical management of the colonic component of the CDF is straightforward through a segmental colectomy. For the duodenal component of the fistula, however, the management decisions are more complex because of the implications for the biliary and pancreatic drainage through the ampulla, as well as the intimate relationship between the duodenum and the pancreas. In the case of malignant CDF, the goal is an oncologic en bloc resection with negative microscopic margins. This was achieved in half of the patients with malignant CDF in this series. Complete resection requires a right hemicolectomy for colon cancer and a duodenal resection. When a duodenoduodenostomy

Table 2 Treatment and pathology summary

Preoperative diagnosis of coloduodenal fistula	Number of patients (%)
Radiologic imaging	12 (55)
Endoscopy (esophagogastroduodenoscopy, colonoscopy)[a]	4 (18)
Indications for coloduodenal fistula resection[b]	Number of patients (%)
Intractable symptoms (diarrhea, vomiting, pain, unable to eat)	16 (73)
Gastrointestinal bleeding	10 (45)
Malignancy or rule out malignancy	9 (41)
Peritonitis (free perforation)	2 (9)
Surgical procedure for malignant fistulas	Number of patients (%)
En bloc right hemicolectomy and lateral (partial) duodenectomy	3 (38)
Above procedure with duodenal bypass	2
En bloc right hemicolectomy with Whipple procedure	1 (12)
Palliative bypass (duodenal and/or colonic side)	4 (50)
Surgical procedure for benign fistulas	Number of patients (%)
Coloduodenal fistula resection without duodenal bypass	11 (85)
Coloduodenal fistula resection with duodenal bypass	2 (15)
Pathology of malignant fistulas[c]	Number of patients (%)
Colon adenocarcinoma (stage II: T_4, N_0, M_0)	4 (50)
Colon adenocarcinoma (stage III: T_4, N_1, M_0)	1 (13)
Colon adenocarcinoma (stage IV: T_4, N_x, M_1)	2 (25)
Lymphoma	1 (13)
Pathology of benign fistulas[c]	Number of patients (%)
Inflammatory bowel (Crohn's disease)	9 (64)
Peptic ulcer disease	5 (36)

[a] Also identified radiographically

[b] Each patient may have multiple indications for surgery. GI bleeding only included patients with documented GI bleed and required transfusion in the preoperatively

[c] Percent relatives to the proportion of patients within the malignant or benign fistula group

cannot be safely performed in the setting of malignancy due to involvement of the ampulla, a long gap with tension between the ends, or resultant narrowing of the duodenum we recommend undertaking complete duodenal resection via a pancreaticoduodenectomy. Another option we have used in the setting of a narrowed duodenum is a bypass using a gastrojejunostomy (either loop or Roux-en-Y). Other options include a Roux-en-Y duodenojejunostomy or a serosal patch.

Another consideration in the patient with a malignant CDF is a palliative bypass when complete resection is not feasible. Four patients in this group underwent a palliative bypass, and while it did not impart any survival benefit, the patients experienced symptomatic relief from their symptoms.

Benign CDF most commonly arises from either Crohn's disease or peptic ulcer disease, although other etiologies for a benign CDF have been reported. Whether to perform a

Table 3 Characteristics of malignant CDF

Patient	Neoadjuvant	Adjuvant chemotherapy	Adjuvant radiation	Stage	Complete resection	Survival (months)
1	−	+	−	II	+	52
2	−	+	−	IV	−	83
3	−	+	+	II	+	155
4	−	+	+	II	+	13
5	−	+	+	II	−	26
6	−	+	+	IV	−	14
7	−	+	−	IIIB	+	40[a]
8[b]	−	+	−	−	−	8
Total	0	8	4	−	4	20[c]

[a] Still alive at time of study

[b] Patient diagnosed with lymphoma, all other patients with primary colon adenocarcinoma

[c] Median survival 26 months for patients with colon adenocarcinoma

Table 4 Post-operative complications

Complication	Malignant (n=8) no. (%)	Benign (n=13) no. (%)
Delayed gastric emptying	3 (38)	0
Deep venous thrombosis	1 (13)	0
Ileus	0	1 (8)
Pneumonia	0	1 (8)
Reoperation (for stricture)	0	1 (8)
Recurrence	0	1 (8)
Total	4 (51)	4 (32%)

bypass procedure with a gastrojejunostomy after fistula takedown, in the setting of benign CDF, is an important consideration. In this series, duodenal bypass was deemed necessary in only 15% of patients undergoing resection of a benign CDF. This is in contrast to a recent report on 30 patients with duodenal Crohn's where most patients were managed with bypass. However, only four of the patients in that series had a duodenoenteric fistula, one of which was managed with a bypass.[22] The indications for duodenal bypass included duodenal narrowing after primary duodenal closure, concern for a duodenal leak because of poor tissue quality, or a need, in the setting of ulcer disease, for a definitive ulcer operation such as an antrectomy with Billroth II reconstruction.

The perioperative mortality (0%) and morbidity (33%) of patients with malignant vs. benign CDF were comparable. As expected, long-term survival was determined by the underlying disease. Of the four patients with malignant CDF in whom complete resection with negative margins was achieved, two patients achieved long-term survival (>5 years). Therefore, we feel that CDF, benign or malignant, does not contraindicate resection or appear to portend a worse prognosis for patients when complete resection is feasible.

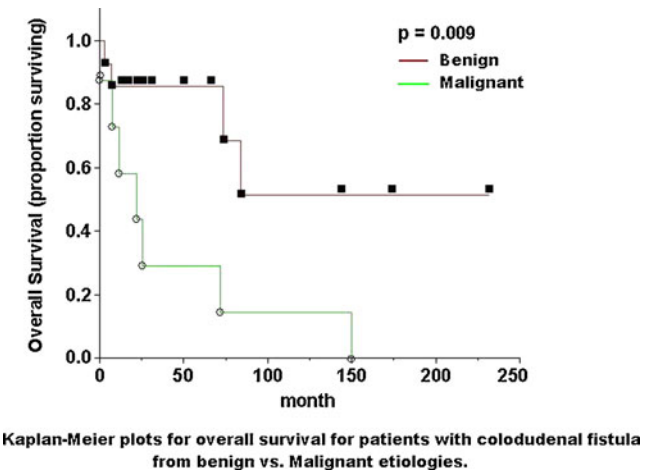

Fig. 2 Kaplan–Meier plots of the overall survival for patients with coloduodenal fistulas from benign vs. malignant etiologies

Conclusion

Malignant CDF are distinct from benign CDF in presentation, surgical management, and outcome. CDF from both etiologies can cause symptoms that are mostly amenable to surgical intervention. Resection can achieve long-term survival in malignant CDF, while it will resolve debilitating symptoms in benign CDF with a low recurrence rate. Resection can be performed safely with low perioperative mortality. Operative morbidity was not negligible but most complications resolve with conservative management. Surgical resection of CDF should be aggressively pursued in patients with both malignant and benign etiologies who can tolerate a complex resection.

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2011 SSAT QUICK SHOT PRESENTATION

Depression Is Associated with Prolonged and Complicated Recovery Following Colorectal Surgery

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Abstract
Background There are little data regarding the impact of depression on outcomes after gastrointestinal surgery. We hypothesize that depression would be associated with prolonged hospital stay and changes in discharge disposition for patients undergoing colon and rectal surgery.
Methods We identified 292,191 patients undergoing colon and rectal surgery using the 2008 Nationwide Inpatient Sample. We used multivariate regression to evaluate the effect of depression on length of stay and discharge disposition.
Results A preoperative diagnosis of depression was present in 20,039 (6.9%) patients. Mean length of stay for those with depression (10.4 days, 95% confidence interval (CI) 10.04–10.76) was significantly longer than for patients without depression (9.64 days, 95% CI 9.48–9.81). After adjusting for cofounders, depression still predicted an increase in length of stay. Additionally, depressed patients were less likely to resume normal function at discharge, as 40% required either home health or time in a skilled facility following discharge from the acute care hospital.
Conclusions Among patients undergoing colorectal surgery, depression is associated with a significantly prolonged hospital stay and higher likelihood of requiring skilled nursing assistance after discharge. Further research into the mechanism underlying these differences and potential treatment strategies among depressed patients is warranted.

Keywords Colorectal surgery · Depression · Outcomes

Introduction

Depression is a highly prevalent disease, with reports from international surveys indicating a prevalence of 8–12%.[1] Depression has a significant economic impact, with the total economic cost of depression in the USA estimated at US $83.1 billion in the year 2000.[2] It is also a common co-morbidity associated with poor outcomes. Patients with heart disease and co-morbid depression demonstrate decreased medication adherence,[3] poorer perception of health status,[4] and increased mortality[5] to such an extent that the American Heart Association recommends universal screening for depression in patients with coronary artery disease.[6] Depression has also been linked with central adiposity[7] and non-insulin dependent diabetes,[8–11] as well as diminished adherence to treatment[12,13] and greater risk of diabetes-related complications.[14] Similar findings have been published for patients with stroke,[15–17] end-stage renal disease,[18,19] and patients admitted to general medicine inpatient wards.[20,21] Al-

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though the adverse impact of co-morbid depression on medical illness has been extensively documented, the effect of depression on surgical outcomes has received relatively little attention.

Co-morbid depression has been associated with increased risk of surgical complications, greater in-hospital mortality, prolonged length of stay, diminished physical and mental function, and a greater incidence of cardiovascular events in patients undergoing coronary artery bypass graft (CABG) surgery.[22–28] However, the impact of depression on other surgical procedures has not been examined. In this study, our aim was to evaluate the effect of depression on hospital length of stay and site of discharge in colorectal surgery patients. We hypothesized that co-morbid depression would be associated with prolonged hospital stay and an increased need for post-discharge care including home health and utilization of skilled facilities for recovery.

Methods

Patient Selection

The Nationwide Inpatient Sample (NIS) is part of the Healthcare Cost and Utilization Project and represents the largest all-payer inpatient care database in the USA.[29] The NIS consists of data from over 1,000 hospitals representing a 20% stratified sample of all US community hospitals with the exception of Veterans Affairs Hospitals and Federal Facilities (Department of Defense and Indian Health Service). All patients in the 2008 NIS who were at least 18 years old and underwent colorectal resections for benign or malignant disease were identified using ICD-9 codes and included in the study. The 2008 NIS was selected because this was the first year with a distinct ICD-9 code for laparoscopic colorectal surgery and it was felt that surgical approach would be an important covariate in subsequent analysis.

Independent Variable

The main variable of interest is co-morbid depression identified by ICD-9 codes (300.4, 301.12, 309.0, 309.1, and 311 as previously described).[30]

Outcomes

The primary outcome of interest was length of inpatient hospital stay. For purposes of analysis, the natural logarithm of length of stay was analyzed as the dependent variable to correct for right skew. Secondary endpoints included discharge disposition defined as home, with home health, or to a skilled facility. Patients were considered discharged home if the uniform disposition indicator was coded as routine or against medical advice. Discharge was categorized as with home health if disposition was coded as home health care. Discharge to skilled facilities included skilled nursing homes, short-term recovery hospitals, rehabilitation hospitals, or other facilities.

Covariates

Co-morbidities were modeled using the Deyo modification of the Charlson co-morbidity index.[31] All co-morbidities from the NIS Severity File were included unless cross-tabulations indicated less than 1% prevalence. Data indicating race/ethnicity is not reported by several states in the NIS so this field is not missing at random. In order to avoid selection bias from excluding these cases, two modeling strategies were pursued. First, a separate category was created for missing values so these cases could be included in the analysis. Second, the analysis was repeated with race omitted from the model. None of the subsequent findings differed between these two approaches so results from the first approach are presented. Indication for surgery was classified as benign or malignant, and procedure approach was defined as laparoscopic versus open based on ICD-9 diagnosis and procedure codes, respectively. Presence or absence of an ileostomy or colostomy was also determined using ICD-9 codes. Hospital location (urban or rural) was based on Core Based Statistical Area Codes from the 2000 US Census with metropolitan areas classified as urban while micropolitan or non-core areas were considered rural. Hospital volume was defined as the total number of weighted colorectal resections performed during 2008 in the NIS. The high volume category represents hospitals in the top 1/3 of volume for 2008 while the low volume category represents hospitals in the lowest 1/3 of volume. A hospital was considered a teaching institution if it had an AMA-approved residency program, was a member of the Council of Teaching Hospitals, or had a ratio of full-time equivalent interns and residents to beds of 0.25 or higher.

Statistical Analysis

Multiple linear regression was utilized to evaluate the association between volume and discharge status after adjusting for potential confounders. All analysis took into account the clustered nature of the data by utilizing robust standard errors. Tests for main effects and interactions were considered significant at an $\alpha<0.05$, and the finite population correction was not employed. All analysis was conducted using the Complex Samples Module of SPSS version 18 © SPSS Inc (Chicago, IL, USA).

Results

Patient Population

A total of 292,191 patients underwent colon or rectal resections in the 2008 NIS, and 20,039 had a diagnosis of co-morbid depression. Patients with depression were slightly younger with a mean age of 62.1 years compared to 63.2 years for those without a diagnosis of depression ($p<0.001$, Table 1). Patients with depression were also more likely to be female, white, and to have experienced significant weight loss prior to admission. Depressed patients were also more likely to be admitted for benign disease and to have received an ostomy prior to discharge.

Length of Hospital Stay and Discharge Disposition

Length of inpatient stay was compared between patients with co-morbid depression and those without a diagnosis of depression. Mean length of stay for patients with a diagnosis of depression was 10.4 days compared to 9.6 days for patients without depression ($p<0.001$, Table 1). The percentage of patients having a prolonged length of stay (greater than 14 days) was also increased in patients with depression compared to individuals with no history of depression (19% versus 16%, $p<0.001$). Additionally, discharge disposition differed significantly between the two groups with depressed patients being less likely to return home and more likely to be discharged to a skilled facility. Overall, 59% of patients with depression were discharged home compared to 65% of those with no diagnosis of depression. Although 20% of both depressed and non-depressed patients were discharged with home health, 20% of depressed patients were discharged to skilled facilities versus 15% of individuals without co-morbid depression.

In order to adjust for potential confounding factors due to differences between depressed and non-depressed patients, multiple linear regression was used to assess the independent effect of depression on length of hospital stay. After controlling for patient, surgical, and hospital factors, co-morbid depression remained a significant predictor of the length of inpatient stay. As shown in table 2, having co-morbid depression predicted a 6% increase in length of hospital stay even controlling for the above factors.

Discussion

Our findings suggest that having a diagnosis of depression before surgery is associated with prolonged length of stay in patients undergoing colorectal surgery. Although the absolute magnitude of the effect is a relatively modest 6% increase in length of stay, the fact that depression is an eminently treatable illness indicates that even this small effect may be an unnecessary and avoidable delay in recovery time. Additionally, the actual recovery time for patients with co-morbid depression is likely to be considerably longer as length of stay is artificially shortened by an increased rate of discharge to skilled facilities.

The increased likelihood of discharging depressed patients to skilled facilities is particularly relevant given recent studies looking at the long-term implications of failing to discharge patients home after surgery. Davidson et al. examined differences in mortality for trauma patients discharged home versus to either home health or skilled facilities.[32] The authors found that during their study period, the length of hospital stay for trauma patients diminished as more patients were discharged with home health or to skilled facilities in recent years. Notably, while the in-hospital mortality rate diminished along with decreased length of stay, the overall mortality at 1 year remained essentially static. In essence, efforts to reduce hospital stay and move patients to skilled facilities resulted in the same risk of death, but the venue shifted from inside the hospital to inside skilled facilities. Consequently, it is important to consider not only how long patients remain in the hospital but also their discharge destination following surgery.

Screening for depression in the preoperative setting might help identify which patient will have a more difficult recovery. Rapid screening tools for depression including the Patient Health Questionnaire (PHQ)-2[33] and PHQ-9 are readily available and have been evaluated in CABG surgery patients.[34] Additionally, risk factors for preoperative depression have been identified in patients undergoing this procedure, and these findings may also apply to patients undergoing other operations.[35]

Identifying patients at risk for depression or those with a current diagnosis of depression is important given the availability of pharmacological and behavioral treatments that could be initiated prior to surgery. For example, selective serotonin reuptake inhibitors could potentially be used to treat depression before surgery, and the safety of these medications has been established in patients undergoing CABG surgery.[36] However, whether this medication can reduce the post-operative consequences of depression is unknown. Future research is needed to definitively evaluate the potential effectiveness of depression treatment in this population. Preoperative nurse-led interventions like health education and motivational interviews have been shown to reduce depression and anxiety and improve physical functioning preoperatively in cardiac surgery patients,[37,38] although one study did not show any differences in length of hospitalization.[38] More studies are needed to examine these possibilities.

Table 1 Characteristics of the study population

	Depression (*N*=20,039)	No depression (*N*=272,152)	
Patient factors			
Age	62.1 (0.3)	63.2 (0.2)	0.001
Gender			0.001
Male	6,068 (30)	130,969 (48)	
Female	13,965 (70)	140,716 (52)	
Race/ethnicity			0.001
White	14,508 (87)	174,905 (80)	
Black	866 (5)	18,576 (9)	
Hispanic	972 (6)	14,456 (7)	
Other	422 (1)	10,776 (4)	
Income			0.56
Quartile 1	4,477 (23)	60,182 (23)	
Quartile 2	5,114 (28)	73,471 (28)	
Quartile 3	4,992 (25)	65,570 (25)	
Quartile 4	4,844 (25)	67,812 (25)	
Primary insurance			0.02
Medicare	9,767 (49)	130,026 (48)	
Medicaid	1,162 (6)	12,731 (5)	
Private	8,073 (40)	113,273 (42)	
Self-pay	407 (2)	7,243 (3)	
No charge	66 (0.3)	1,269 (0.5)	
Charlson co-morbidity index	2.08 (0.05)	2.06 (0.02)	0.47
Number of chronic conditions	6 (0.08)	4 (0.05)	0.001
Drug abuse	352 (2)	1,766 (1)	0.001
Psychoses	454 (2)	5,432 (2)	0.19
Weight loss	2,129 (11)	22,241 (8)	0.001
Surgical factors			
Elective surgery	11,414 (57)	163,610 (60)	0.001
Indication for surgery			0.001
Cancer	4,548 (23)	74,756 (28)	
Benign disease	15,490 (77)	197,396 (73)	
Surgical approach			0.31
Laparoscopic	1,281 (6)	18,612 (7)	
Open	18,758 (94)	253,540 (93)	
Ostomy	4,400 (22)	53,881 (20)	0.003
Hospital factors			
Hospital bed size			0.96
Small	2,219 (11)	29,959 (11)	
Medium	4,645 (23)	63,715 (23)	
Large	13,150 (66)	178,131 (66)	
Hospital location			0.75
Urban	17,797 (89)	241,995 (89)	
Rural	2,217 (11)	29,810 (11)	
Hospital region			0.001
Northeast	4,133 (21)	55,770 (21)	
Midwest	5,100 (26)	64,032 (24)	
South	6,785 (34)	100,140 (37)	
West	4,020 (20)	52,210 (19)	
Volume of colorectal surgery			0.01
Low	6,143 (31)	90,502 (33)	
Medium	6,770 (34)	90,728 (33)	
High	7,126 (36)	90,922 (33)	
Hospital status			0.73
Teaching	9,348 (47)	126,588 (47)	
Non-teaching	10,665 (53)	145,217 (53)	
Outcomes			
Discharge disposition			0.001
Home	9,643 (59)	144,949 (65)	
Home health	3,439 (20)	43,228 (20)	
Skilled facility	3,358 (20)	34,012 (15)	
LOS	10.4 (0.19)	9.6 (0.08)	0.001
LOS>14 days	3,781 (19)	43,208 (16)	0.001

Values represent number (percent) or mean (standard error). Percentages may add to greater than 100% due to rounding

Our study is limited by the fact that patients were identified by ICD-9 codes. This may lead to misclassification bias; therefore, we cannot distinguish between incident and prevalent depression. However, the diagnostic codes developed by Elixhauser et al.[30] were specifically validated to identify prevalent rather than incident co-morbidity. Additionally, prior treatments for depression are unavailable in the NIS so it is unclear whether these patients have tried and failed different regimens and whether they would truly benefit from additional therapy.

In conclusion, among patients undergoing colorectal surgery, depression is associated with a significantly prolonged hospital stay. At the same time, patients with depression are more likely to require assistance after discharge in the form of skilled rehabilitation facilities. The need for assistance after discharge adds to an already protracted recovery and can significantly increase cost of

Table 2 Depression is associated with prolonged length of hospital stay

	Beta	Standard error	95% CI	*p*
Depression (unadjusted)	0.10	0.01	0.07–0.12	0.001
Depression (adjusted[a])	0.06	0.01	(0.04–0.08)	0.001

Dependent variable is natural logarithm of the length of hospital stay

[a] Adjusted for characteristics in Table 1

care. When operating on individuals with a diagnosis of depression, efforts should be made to engage a multidisciplinary care team to focus on optimizing factors which promote a more rapid recovery in order to reduce these disparities. Further research is needed to evaluate if early detection and treatment of depression can improve surgical outcomes.

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The Current Role of Simulators in Teaching Surgical Techniques

Daniel B. Jones

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Keywords Surgery · Simulation · Training · Education

As the trainees' work week is abbreviated, simulators have been hailed by proponents as an efficient and effective way to assure technical skills, exposure to uncommon procedures, and decision-making with complex operations (Table 1). Probably more importantly, simulation can also hone team work, communication, and nontechnical skills.

Naysayers of simulation sought data that the time spent in the skills lab was better than the traditional apprentice training model. Scott et al. demonstrated that residents practicing tasks in the skills lab as little as 30 min per day for 2 weeks resulted in improved operative performance of a laparoscopic cholecystectomy compared to controls.[1] Tasks included moving lead numbers, dropping a bean, triangle transfer, running rope, and endostitch (Fig. 1).

While practicing tasks in the skills lab was beneficial, few tasks provided feedback to the learner. Computer-based simulators such as the MIST-VR could assess both right and left hand and record errors. Hamilton et al. compared videotrainer and MIST-VR training modalities.[2] While trainees preferred the videotrainer for realism, the computer-based system resulted in more intraoperative improvement. Seymour et al. then demonstrated that training in an MIST-VR in the skills lab resulted in fewer errors by residents during a laparoscopic cholecystectomy in the operating room (Fig. 2).[3]

While global assessment of performance repeatedly demonstrated improved overall operative performance by intraoperative raters blinded to training status, these initial studies failed to show improved knowledge of the procedure (e.g., laparoscopic cholecystectomy). This made sense, as the training to date focused on skills only. Hamilton et al. then created a laparoscopic hernia model molded from a cadaver.[4] During the 2-week training in the skills lab, senior residents were also provided videotapes of the operation performed by experts and a commercially available interactive CD. Compared to controls, residents who participated in the skill-based curriculum improved operative performance and, importantly, knowledge of the procedure (Fig. 3).

As more and more residency programs embraced technical skills training, the American College of Surgeons (ACS) established formal accreditation of education insti-

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Table 1 Forces driving support of surgical skills training and simulation[6]

•Patient safety concerns
•Work-hour restrictions
•Financial constraints
•Emerging technology

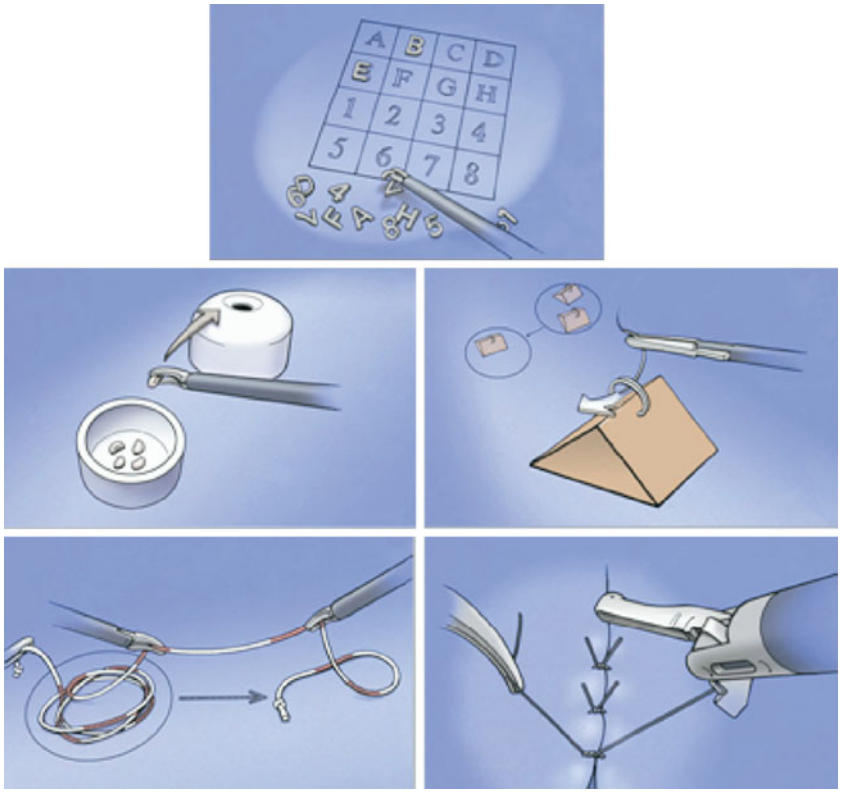

Fig. 1 Tasks: checkerboard, bean drop, triangle block transfer, running rope, and endostitch[1]

tutes. The ACS-APDS has released a national curriculum for training resident skills (phase I), essential operations (phase II), and teamwork (phase III). These modules outline learning objectives, materials, selected readings, and benchmarks for assessment. Educational materials include video clips to demonstrate skills. A second edition expanded version of ACS-APDS curriculum is currently under development (Tables 2, 3, and 4).

Arguably, the most important development in advancement of skills training has been the ACS/SAGES Fundamentals of Laparoscopy (FLS). In addition to online CME, the FLS tasks include peg transfer, circle cut, loop ligature, and suturing (Fig. 4). While FLS began as a validated self-

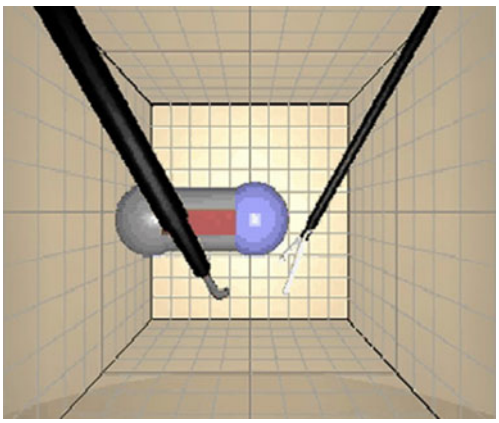

Fig. 2 MIST-VR task

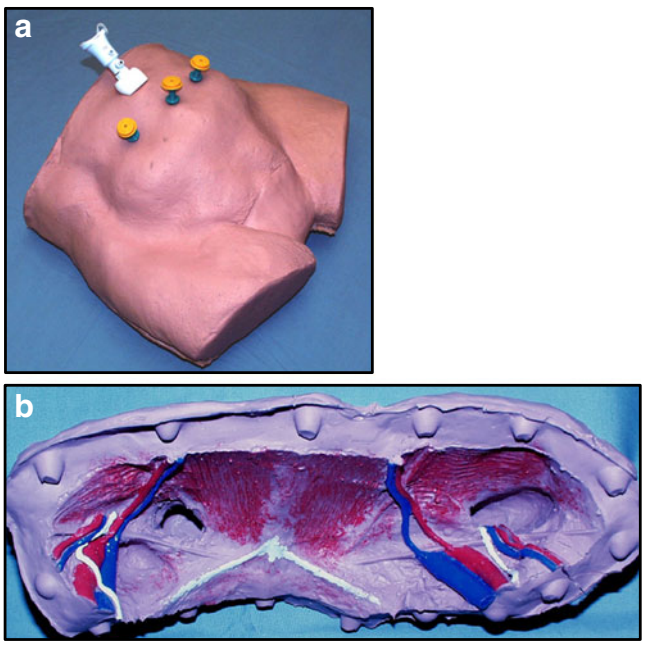

Fig. 3 Laparoscopic hernia model with external of various port placements (**a**) and internal view of direct, indirect, and femoral hernia (**b**)

Table 2 ACS-APDS phase I skill modules

●Basic laparoscopy
●Advanced laparoscopy
●Stapled anastomosis
●Vascular control
●Advanced vascular control
●Bone fixation
●Endoscopy
●Surgical biopsy
●Asepsis
●Suturing
●Knot tying
●Catheterization
●Airway management
●Thoracentesis
●Central line insertion
●Arterial lines

assessment of cognitive and hands-on skills, it has become a national standard required of all residents prior to sitting for ABS National Board Examinations. Furthermore, malpractice carriers have begun to incentivize surgeons to successfully complete FLS with the hope of promoting patient safety.[5] Recently, SAGES released Fundamentals of Endoscopy (FES) certificate. Like FLS, FES has a cognitive MCE and simulator-based assessment.

While surgeons have focused on skills acquisition, communication and team work skills are probably equally as important when performing complex operations. Lord Darzi at Imperial College was the first to bring a team into the mock operating room. The scenario used a model of a bleeding femoral vessel. Both technical and nontechnical skills were assessed.[6] Powers et al. created a mock MIS endosuite and studied teams confronted with a laparoscopic crisis.[7] Trainees would greet the patient in the holding area and review the chart. Next the learners and confederates would gown, glove, and begin the operation. From behind a one-way mirror, other faculty could adjust the scenario and manipulate vital signs. Afterwards, the team would debrief. In addition to technical skills, Powers et al. studied leadership, communication, and situational awareness and this scenario is now part of the ACS-APDS phase III curriculum (Fig. 5).

Table 3 ACS-APDS phase II advanced procedures

●Laparoscopic ventral hernia
●Laparoscopic colon resection
●Laparoscopic/open bile duct exploration
●Abdominal wall stomas
●Laparoscopic appendectomy
●Laparoscopic Nissen fundoplication
●Sentinel node biopsy and axillary lymph node dissection
●Open inguinal/femoral hernia repair
●Laparoscopic inguinal hernia
●Laparoscopic/open splenectomy
●Laparoscopic/open cholecystectomy
●Thyroidectomy
●Parathyroidectomy
●Gastrectomy
●Distal/total pancreatectomy

Table 4 ACS-APDS phase III modules

●Teamwork in the trauma bay
●Postoperative pneumonia (hypoxia, septic shock)
●Postoperative hypotension
●Laparoscopic crisis
●The preoperative briefing
●Laparoscopic troubleshooting
●Postoperative pulmonary embolus
●Postoperative MI (cardiogenic shock)
●Latex allergy anaphylaxis
●Abdominal compartment syndrome (hypotension)
●Patient handoff
●Retained sponge on postoperative chest radiograph

While there is no substitute for the patient in learning patient care, simulators are an effective way for trainees to hone their technical skills before arriving to the operating theater. Furthermore, safe practices and teamwork such as use of preoperative time out, checklists, closed loop communication, and assertiveness can be taught with simulation scenarios. Today, surgeons can demonstrate skills on simulators and judgment within simulated, safe environments.

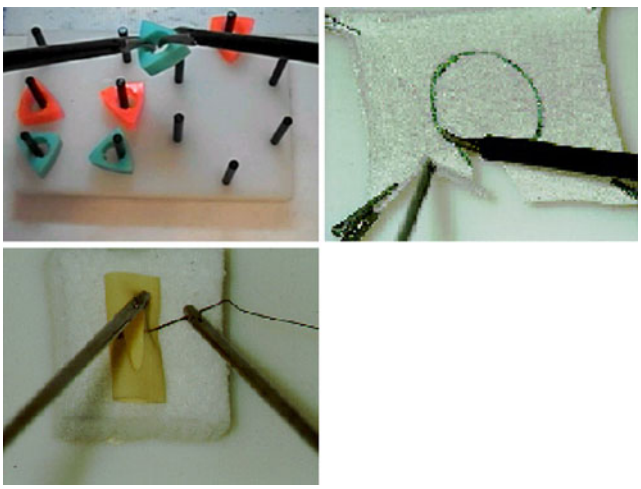

Fig. 4 FLS tasks: peg transfer, circle cut, and intracorporeal suture

Fig. 5 Simulation. Preoperative holding area, mock MIS endosuite, control room, and debrief room

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2010 SSAT EDUCATION PANEL

What Are The Complex Operations and Why?

Keith D. Lillemoe

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Abstract
Introduction Surgeons are often judged by their ability to perform complex surgical procedures.
Discussion Data show the number of these procedures as defined by the number of procedures performed during surgical training may be significantly more common than would be expected by their program directors.

Keywords Complex surgical procedures · Surgical training

The objective of surgical training in North America is to train surgeons who have the knowledge, experience, judgment, personal qualities, and technical ability to serve the various populations of our continent. Although to be an excellent surgeon requires the proper combination of all of these qualities, the major focus of many of the metrics on which surgeons are judged is the outcomes of surgical procedures. That is, in most cases, people do not talk about how smart or what kind of person a surgeon is, but rather can he or she operate. Performing an operation is far more than cutting and sewing, and certainly a successful outcome for any operation requires knowledge, experience, and judgment. Yet in the end, what is recorded as the measure of the surgeon's training, experience, and ability with respect to board certification and often for privileges, referrals, and outcome reporting is the actual number and the results of operative procedures performed.

Surgeons often judge themselves, not the total number of operations, but how many complex operations that one performs. Therefore, defining complex with respect to an operative procedure is important. A dictionary defines complex as "not simple, involved, or complicated, or that which is made up of many elaborately inter-related or interconnected parts, so that much study or knowledge is needed to understand or operate".[1] Although those who write the dictionary are not surgeons, that definition fits closely to my personal definition of a complex operation as a "surgical procedure that is technically challenging and involves intricate surgical techniques for resection and/or reconstruction usually performed infrequently in training/practice".

To better define what operations are common and an important part of surgical training and practice, The American Board of Surgery and the Association of Program Directors in Surgery conducted a survey of the 254 program directors of surgical residences in the USA in the spring of 2006.[2] The program directors were asked of their opinions as to whether surgical trainees should be competent or familiar with over 300 surgical procedures. The program directors classified 121 procedures (40%) as being "A procedures" in which they would expect a graduating chief resident should be competent to perform (Table 1). Furthermore, over half of the program, directors felt that these procedures were "essential" to general surgery practice. The program directors also listed 171 procedures (57%) as being B procedures, in which a chief resident should be familiar (Table 2). Finally, only eight procedures (3%) were considered such that a chief resident neither be familiar or competent. This C list included no gastrointestinal or hepatopancreatobiliary procedures. It can be concluded from this survey that roughly 40% of surgical procedures are essential and therefore should not be considered complex. One might conclude that roughly

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Table 1 Examples of alimentary tract/HPB A procedures

Includes	
Lap chole	CBDE (open)
Splenectomy (lap/open)	Inguinal hernia (lap/open)
Appendectomy (lap/open)	Ventral hernia
Colectomy (lap/open)	Antireflux procedure (lap/open)
Upper and lower endoscopy	Gastric resection (open)
Hemorrhoidectomy	Drainage of pancreatic abscess/ pseudocyst
Wedge resection of liver	Distal pancreatectomy
Choledochoenteric anastomosis	

Procedures felt to be essential to general surgical practice by US program directors[1]

HPB hepatopancreatobiliary, *CBDE* common bile duct exploration

Table 3 Reported operative experience for B procedures

	Chief residents		Recertifying surgeons	
	Mean	Median	Mean	Median
Esophagectomy	1.2	1	0.1	0
Total gastrectomy	1.0	1	0.3	0
Whipple procedure	5.6	4	0.8	0
Hepatic lobectomy	5.5	4	0.9	0
Colectomy with ileoanal pull through	0.1	0	0.1	0

Data provided by American Board of Surgery for graduating chief residents (2009) and general surgery recertification candidates (2008). The data for chief residents represent the experience for their entire 5 years of training. The experience for recertifying surgeons represents their last 12-month operative log as required for recertification

57% of procedures could be considered complex by those individuals who have the primary responsibility for training US surgical residents.

Unfortunately, data generated from the operative logs of graduating chief residents in 2005 show a disturbing finding that the expectations of the program directors with respect to operative competency or familiarity based on reported case numbers falls far short. Of the 121 procedures of the A list, only one procedure, laparoscopic cholecystectomy, was performed at a mean of more than 50 times by graduating chief residents. Even more concerning was that 83 of the 121 A procedures were performed on average less than five times during residency training. Most of these low-volume exposure procedures were abdominal (n=15) or alimentary tract (n=25) procedures. Forty-seven procedures on the A list were performed on average less than two times with a mode of 0 including common bile duct exploration, anorectal procedures, laparoscopic splenectomy, and vagotomy and drainage procedures. The data with respect to type B operations are even more discouraging with respect to the familiarity of graduating chief residents or even recertifying general surgeons based on data provided by the American Board of Surgery (Table 3). Furthermore, many of these operations are associated with significant perioperative mortality. In a report by Dimick and colleagues, the Medicare mortality rate for pancreatic resection was 10.3%, gastric resection was 11.5%, and esophagectomy was 15%.[3]

The reasons for the failure to achieve adequate experience are likely multifactorial and include regionalization of cases in tertiary care specialty centers and an increase in advanced surgical fellowships and fundamental problems in surgical training.[4] The solutions are complex and likely will require major changes in residency training, perhaps with a tracking mechanism established.

In conclusion, there is an ever increasing number of complex operations in general and alimentary tract surgery. In many cases, the lack of proper exposure during residency to such procedures, rather than the technical difficulty of the procedure itself, is accounting for this increase. American surgical leadership must address these issues at both levels of surgical training and practice.

Table 2 Examples of alimentary tract/HPB B procedures

Includes
Whipple procedure
Hepatic lobectomy
Esophagectomy/esophagogastrectomy
Colectomy with ileoanal pull through
Biliary sphincteroplasty

Procedures with which chief residents should be familiar by US program directors[1]

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2010 SSAT EDUCATION PANEL

Teaching Uncommon and Highly Complex Operations: Maximizing The Teaching and Learning

Sarah E. Peyre · Stanley W. Ashley

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Abstract Teaching complex and uncommon operative procedures require instruction on technical skill and cognitive decision-making frameworks. To understand this dynamic process, several adult learning theories are discussed including the Fitts-Posner's three stage theory, transfer learning theory, and expert performance theory. By understanding how trainees can deconstruct complex task and transfer learning from more basic operative cases, surgical educators can reflect on how they structure and stratify operative and simulation experiences to maximize learning.

Keywords Operative teaching · Learning theory · Technical skill · Cognition · Simulation · Assessment

Understanding how we teach uncommon and complex operations requires examination of adult learning theory, current best practices, and the context in which surgical residency programs are required to train operative skill to competency. The American Board of Surgery has now categorized required operations, but uncommon and complex teaching and learning are largely dependent on the culture of each training program. Most surgeons learned how to teach surgery in the same way that they learned how to perform it. Using Halsted's model, a graduated apprenticeship with senior surgeons, trainees learned a variety of ways of teaching; incorporating some into an evolving skill set and rejecting others. Most surgeons would say that they came out of their general surgery training well skilled to both perform and teach surgery. However, there are clearly a lot of moving parts that might make us want to rethink how we have traditionally approached teaching and learning, especially for the uncommon and complex operations.

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There are two central parts of learning how to do any operative procedure. The first is motor skill acquisition which is best described in a review of the Fitts–Posner Three Stage Theory from Toronto.[1] Acquisition of technical skills includes first understanding the task, then integrating its mechanics, and finally doing it enough that it becomes automatic. There is a growing body of literature about technical skills acquisition that argues we can and should teach technical skills using simulation to support this automation process. However, the simulation market lacks comprehensive models for many of the advanced, complex, and uncommon procedures. The animal lab may work for some of these procedures, such as common bile duct exploration, but this option is becoming increasingly difficult for multiple reasons. Considering these limitations, training for complex procedures is still predominantly going to occur in the operating room.

The second part of learning to operate, and arguably the most pertinent component of learning complex and uncommon procedures, is the cognitive decision-making framework associated with each procedure. As surgeons become experts in performing complex procedures, they become automated in their technical skill and decision making. Often this automation of the cognitive process means they are less able to teach essential decision-making elements such as critical cues during the procedure, continual assessments that are made during the operation, and maybe most importantly how to avoid errors.[2] The automation of cognitive processes changes how expert surgeons store information and makes it

less likely for them to recall incremental tasks and decisions even while performing the task.[2,3]

Understanding that each complex and uncommon operation requires teaching technical skill and cognitive decision making, it is important to also understand how our adult trainees learn. There is extensive educational literature that addresses the topic of complex learning and cognition including metacognition, self-regulated learning, social processes in knowledge construction, expertise and expert performance, and transfer learning theory. [4] The most relevant framework for considering complex and uncommon operative procedures is the transfer learning theory which is defined as the process of applying information and skills learned in one situation to learning or performance in another situation. Surgical trainees will transfer skills and/or problem solving if they can connect previous task learning to the new situation. The development of a mental set can aid trainees in retrieving this information. Trainees should approach basic operative procedures with the idea that the skill and knowledge they acquire will be able to apply to future procedures. Therefore, learning uncommon and complex procedures begins prior to participating in that case. Their mental set is created during teaching on basic cases by setting the expectations that they should connect skills to the more complex procedures they will experience later in training. Ericson connects this to the development of expertise by demonstrating that transfer of training from existing knowledge to new knowledge is more effective than novel learning.[3]

This framework leads to part–whole training where complex tasks can be deconstructed into distinct subtasks that are integrated when performing the whole task. For complex tasks, educational learning theory argues that there is benefit in practicing the subcomponents, mastering each before performing the whole task.[4] This takes us back to the role of simulation. Perhaps the absence of complex simulators is not a limitation, that mastery of the subtasks is what is essential for any operation, common, or complex.

Moving forward, we can look at some of the best practices from around the country. Dunnington's group at Southern Illinois University has proposed that, rather than trying to do it all with each operation, we focus the teaching and learning for each operation with a specific learning objective chosen during a preoperative briefing.[5] For instance,"…Today I am going to focus on the portal dissection". Teaching intraoperatively is concentrated on this learning objective and then additional teaching is focused during the postoperative debrief. The faculty asks the trainees to reflect on their performance providing self assessment, reinforce positive aspects, and set rules for the next time operative procedure.

An additional component of teaching and learning is the mechanism of assessment. The assessment of performance for each operative procedure is needed to measure learning and identify areas for growth. A current initiative by SCORE and the ABS is to create a psychometrically sound assessment tools for operative cases. This should eventually be applicable to the complex procedures as well.

Effective teaching, skill acquisition and automation, and measuring trainee performance in the operating room all play a role in the dynamic process that occurs over the operating room table. As our trainees are encouraged to specialize at an earlier stage in their training and as we continue to deconstruct the common and uncommon procedures required for general surgery competency, we need to be mindful of our own influences in our teaching and the expectations that our learners bring into the operating room. Lawrence Way, MD suggests that we already have a model that works, "…Halsted had it figured out 100 years ago, and in my opinion, the formula has not changed much since. The program, which nowadays is called a cognitive apprenticeship, would consist of operating together and gradually shifting the responsibility to the learner as the learner progresses. At the end, the learner would be independent of the mentor, and the latter would be available, but not scrubbed unless needed…The learner must work his way through enough cases that he will have encountered the full spectrum of contextual variety."[6]

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2010 SSAT EDUCATION PANEL

How to Teach Uncommon and Highly Complex Operations

Richard H. Bell Jr

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Abstract The Surgical Council on Resident Education (SCORE) was officially formed by six surgical organizations in 2006 with the goal of improving general surgery residency training through the development of an explicit curriculum. As a result, SCORE has identified a group of "essential" operations which believes that residents should be competent to perform by the end of training. Other "complex" operations require additional training beyond residency. Currently, operative data submitted by residents suggest that there are significant gaps between ideal and actual operative experience. A particularly difficult challenge is to train residents to perform procedures that are rarely encountered.

Keywords Surgery · Graduate medical education · residency · curriculum

Part I. SCORE: How Will It Change the Training of Residents in the Operating Room?

The Surgical Council on Resident Education (SCORE) was officially formed by six surgical organizations in November 2006[1]. It is a voluntary consortium with the mission of improving resident education in surgery. The charter members were the American Board of Surgery, American College of Surgeons, American Surgical Association, Association for Surgical Education, Association of Program Directors in Surgery, and Residency Review Committee for Surgery of the Accreditation Council on Graduate Medical Education (ACGME). The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) later became a member of the consortium. SCORE was formed in response to increasing concerns about deficiencies in the training of general surgeons and the waning attractiveness of the field of general surgery as a career choice for US medical students.

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SCORE believed that general surgery suffered from a lack of definition of the field, and the sense that general surgery was becoming defined as the residual left behind as increasing numbers of subspecialty fields grew out of traditional general surgery. SCORE made a decision to proactively define general surgery and create a competency-based curriculum for the training of general surgeons (Fig. 1). The traditional surgical "curriculum" assumed that a resident would encounter enough opportunities to master procedures in the course of 5 years of training that he/she could be assumed to be competent on the basis of time spent. However, work done at the beginning of the SCORE curriculum project indicated clearly that there was a large gap between our expectations about resident operative experience and reality. In 2005, we began a study to determine the frequency with which residents performed various operations[2]. Our starting point for the study was the ACGME operative case log, which lists over 300 procedures. We then surveyed all US program directors and asked them to choose the procedures that they believed residents should be competent to perform at the end of training. One hundred twenty-one procedures were chosen by a majority of program directors. An additional 171 procedures were characterized by the program directors as ones for which competency would not be expected at the end of the training. Typically, these procedures were more complex than the 121 procedures, for which competency was expected by the end of the training.

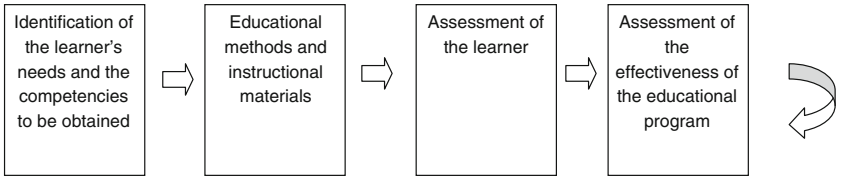

Fig. 1 The steps in the creation of a competency-based curriculum. Modified from Prideaux D: ABC of learning and teaching in medicine. Curriculum design. BMJ. 326(7383):268–70, 2003, with permission

As the SCORE curriculum was developed, we re-examined the operative survey data with several stakeholder groups and ultimately chose to define 124 procedures as "essential" to the practice of general surgery and 156 as "complex", procedures not ordinarily performed by general surgeons and which typically are learned in advanced subspecialty fellowships.[1] SCORE adopted the position that a graduating general surgery resident should be able to competently perform any of the "essential" procedures. We proposed that general surgery residents should be exposed to "complex" operations and perform some during residency under supervision, but that we would not expect graduating residents to be competent to perform these procedures.

When we looked at the actual operative experience of residents as reported to the ACGME at the conclusion of their training, we found tremendous gaps in experience. For about half of the "essential" operations, the most commonly reported experience was zero cases. These findings led SCORE to divide the "essential" operations into two groups—"essential–common" (63 procedures) and "essential–uncommon" (61 procedures). The "essential–uncommon" procedures are generally operations that are rarely performed in practice, but may need to be performed on an urgent basis by any general surgeon. The "essential–uncommon" operations include several trauma procedures, for example, as well as operations like open common bile duct exploration or superior mesenteric artery embolectomy. Most residents never perform these procedures during their training, so trying to prepare residents to be able to perform these procedures if called upon to do so in practice is a substantial educational challenge. The same is true for all of the "complex" operations. A few residency programs may offer a significant experience in some of the complex operations like pancreaticoduodenectomy or hepatic lobectomy, but the average resident graduates having performed these procedures once or twice.

From SCORE's point of view, the teaching of complex operations can begin in residency by exposing residents to a set of complex procedures so that they begin to understand some of the advanced skills required for these procedures. However, SCORE has taken the position that mastery of these "complex" procedures requires additional training beyond a 5-year general surgery residency.

The challenge for the SCORE general surgery residency curriculum is the group of "essential–uncommon" operations which may well be required of a general surgeon in practice, but which are rarely if ever performed by residents. Interestingly, most of our simulation efforts have gone into operations that are done relatively frequently, and we have almost no tools for teaching the uncommon operations. The Advanced Trauma Operative Management[3] course using live animals is an example of a good effort to provide training in areas where real-life experience is very limited. However, live animal models are expensive and are not applicable for many operations, so other modalities will need to be adopted. A systematic effort to develop tools to teach uncommon operations would be a very worthwhile undertaking.

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[1] A full listing of the SCORE operations can be found at www.surgicalcore.org.

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SSAT POSTER PRESENTATION

Endoscopic Management of Early Esophageal Neoplasia: an Emerging Standard

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Abstract
Introduction Endoscopic mucosal resection (EMR) and ablation technologies have markedly changed the treatment of early esophageal neoplasia. We analyzed treatment and outcomes of patients undergoing multimodal endoscopic treatment of early esophageal neoplasia at our institution.
Methods Records of patients undergoing endoscopic treatment for esophageal low-grade intraepithelial neoplasia (LGIN, $n=11$), high-grade intraepithelial neoplasia (HGIN, $n=24$), or T1N0M0 neoplasia ($n=10$), presenting between 2007 and 2009, were reviewed. Outcomes included eradication of neoplasia/intestinal metaplasia, development of metachronous neoplasia, and progression to surgical resection.
Results There were 45 patients, 96% male, with a mean age 67 years. The degree of neoplasia prior to intervention was intramucosal (8) or submucosal (2) carcinoma in 10, HGIN in 24, and LGIN in 11. Patients underwent a total of 166 procedures (median 3/patient, range 1–9). These included 120 radiofrequency ablation sessions, 38 EMRs, and 8 cryoablations. Mean follow-up was 21.3 months. Neoplasia and intestinal metaplasia were eradicated in 87.2% and 56.4% of patients, respectively, while 15.4% developed metachronous neoplasia. Three patients underwent esophagectomy. No patient developed unresectable disease or died.
Conclusion Endoscopic treatment of early esophageal neoplasia is safe and effective in the short term. A minority of treated patients developed recurrent neoplasia, which is usually amenable to further endoscopic therapy. Complications are relatively minor and uncommon. Endoscopic therapy as the initial treatment for early esophageal neoplasia is an emerging standard of care.

Keywords Barrett's esophagus · Ablation techniques · Mucosal resection · Endoluminal therapies · Dysplasia · Esophageal cancer · Adenocarcinoma

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Introduction

The identification of high-grade intraepithelial neoplasia (HGIN) or intramucosal carcinoma (IMC) in a patient with Barrett's esophagus (BE) has resulted in referral for esophageal resection for much of the nearly 60 years since Mr. Barrett's original description of the disease. Although esophagectomy is curative, reasonably safe in modern high-volume centers,[1] and allows good if not excellent long-term alimentary function,[2] alternative treatment options sparing the native esophagus and surgical morbidity have obvious benefit. Three major advances over the past decade are

changing the long-standing paradigm of esophagectomy as the standard of care: (1) the introduction of high-resolution video endoscopy, (2) techniques of endoscopic mucosal resection (EMR),[3] and (3) safe and efficacious widespread availability of endoluminal mucosal ablation.[4] Reports over the past 5–6 years from focused centers in Wiesbaden,[5] Amsterdam,[6] and Minnesota[7] clearly document the ability to safely eradicate early esophageal neoplasia using endoscopic methods. Much of the current data, however, come from these uniquely high-volume centers and are generated from complex and high-intensity prospective study protocols. There is relative paucity of data outside of such protocols and from other esophageal centers.

Once uncommon, early esophageal neoplasia limited to areas of HGIN or IMC now encompasses a significant proportion of a growing incidence of esophageal epithelial neoplasia. The incidence of BE has grown exponentially over the past 15–20 years such that it is now estimated that 1–2% of the population (2–3 million Americans) harbor the disease. While experience suggests that endoscopic therapy can be used safely and effectively outside of protocols in everyday clinical care, the combinations and order of these newer therapeutic options have yet to be determined, and long-term outcomes are only sparsely available. As such, the aim of this study is to assess the course of the patients treated at the University of Rochester Medical Center between January 2007 and December 2009 who underwent ablative (radiofrequency or cryoablation) or EMR therapy for early esophageal neoplasia.

Methods

Patients and Treatment

The study population consisted of 51 consecutive patients with BE with low- or high-grade intraepithelial neoplasia (LGIN, HGIN) or early esophageal adenocarcinoma undergoing endoscopic ablative or resective therapy at the University of Rochester Medical Center between January 1, 2007, and December 31, 2009. Three patients were unable to give informed consent due to dementia, two declined to participate, and one was lost to follow-up leaving 45 evaluable patients. The University of Rochester's Research Study Review Board approved this study.

Clinical and demographic data were obtained retrospectively via review of paper and electronic medical records. Pre-treatment demographics included body mass index, clinical history, endoscopic findings, and histological results. Details, including endoscopic treatment modality, number of interventions, endoscopic findings, and complications were recorded. Post-treatment data included complications, progression/regression/eradication of neoplasia/dysplasia/intestinal metaplasia (IM), and any surgical interventions.

Patients underwent confirmatory high-definition endoscopy, narrow band imaging, four-quadrant biopsies for every 1 cm of visible columnar-lined esophagus (CLE), and biopsy of any visible lesions prior to the initiation of therapy. Endoscopic ablation consisted of radiofrequency ablation (RFA) (HALO^{360} and HALO^{90}, BÂRRX, Inc., Sunnyvale, CA), cryoablation (CryoSpray, CSA Medical, Baltimore, MD), or a combination of these technologies. The details of these therapies have been published elsewhere.[4,8,9]

Cryoablation dosimetry typically included two cycles of 20 s each for HGIN and three cycles of 20 s each for adenocarcinoma, at each site. Visible lesions, including nodules or abnormal mucosal patterns, were resected via EMR, and this was repeated, if necessary, every 6 weeks to 3 months until all visible lesions were absent. EMR was performed using a variceal banding device and electrocautery snare without submucosal injection (Duette™ Multi-band Mucosectomy device; Cook Medical, Inc.; Bloomington, IN). Endoscopic ultrasonography was used liberally, at the discretion of the endoscopist, to rule out tumor involvement of the submucosa or deeper layers for larger visible lesions. Computed tomography scans were obtained for all cases of confirmed neoplasia. Positron emission tomography scans were not routinely obtained except for confirmed submucosal tumor infiltration. Visible non-nodular CLE was ablated using RFA or cryoablation, although occasionally EMR was used to further remove residual CLE. Patients returned for repeat ablations every 6–8 weeks until endoscopically visible CLE or histologic IM was absent.

Treatment Algorithm

All patients with LGIN, HGIN, or IMC were considered candidates for primary endoscopic management. Upon referral, initial "mapping" biopsies were obtained to outline the extent of neoplasia. This included four-quadrant biopsies every 1 cm of the BE segment and focused biopsy of any endoscopically visible lesion. High-definition endoscopes with both white light and narrow band imaging were routinely used for mucosal examination. Visible lesions, particularly those harboring HGIN or IMC, were removed via EMR and pathologically staged prior to beginning RFA treatment. Patients with submucosal tumor infiltration were treated with esophagectomy unless prohibitive comorbidity existed. RFA using either the Halo^{360} and/or the Halo^{90} device was repeated until all IM was eradicated. Patients with HGIN or IMC intermittently underwent further mapping biopsy protocols during RFA ablation.

Definitions

BE was defined as any endoscopically visible esophageal columnar mucosa that had IM on histology (goblet cells). Patients were assigned the worst pathological grade found by biopsy or EMR. All biopsies underwent review by two or more pathologists with special expertise in GI pathology including BE. Biopsies interpreted as two different grades were assigned the more advanced grade. Biopsies identified as "indefinite" for dysplasia were considered to reflect inflammation rather than neoplasia. Complete eradication of neoplasia/metaplasia was considered present if two consecutive biopsy sessions, at least 4–6 weeks apart, demonstrated the absence of neoplasia or IM. The time to complete eradication was calculated as the time from the beginning of the first therapy to the first biopsy demonstrating absence of neoplasia or IM. Patients with subsequent biopsies demonstrating HGIN or adenocarcinoma after two consecutive biopsies without neoplasia were defined as having metachronous lesions, as previously described by Pech et al.[5]

Results

Forty-five patients underwent endoscopic therapy during the study period, of which 96% were male, with a mean age of 67 years. Eleven patients had LGIN, 24 had HGIN, 8 had IMC, and 2 had submucosal carcinoma. The mean BE segment length was 5.0 cm (SD 3.5, median 4.0 cm) and ranged from 1–13 cm. Endoscopic nodularity was present in 29% of patients prior to treatment. Mean and median follow-up were 21.3 and 17.4 months, respectively (range 8.5–42.6 months).

The 45 patients underwent a total of 166 endoscopic procedures with a median of three per patient (range 1–9). Treatments included 120 RFA sessions, 38 EMRs, and 8 cryoablation sessions. Twenty-four patients underwent RFA alone, 14 had both EMR and RFA, and 4 had EMR alone. Two patients had EMR and cryoablation, and one patient had EMR, cryoablation, and RFA. Complications occurred in four patients and 2.4% (4 out of 166) of procedures. These included one patient with symptomatic stricture, requiring dilation, and three patients requiring hospital admission post-endoluminal therapy: one for observation following a mucosal tear resulting from RFA and two for post-procedure chest pain. Complete treatment and biopsy results of each patient organized by presenting pathology are shown in Figs. 1 (LGIN), 2 (HGIN), and 3 (T1 cancer).

Over the same time period, 18 patients underwent primary esophagectomy for HGIN or IMC. The majority of these were performed in the earlier part of our endoscopic management experience, particularly for those who had invasive adenocarcinoma on biopsy. As our experience progressed, these patients were considered for EMR if possible and subsequent RFA. There were no esophagectomies for HGIN in 2009.

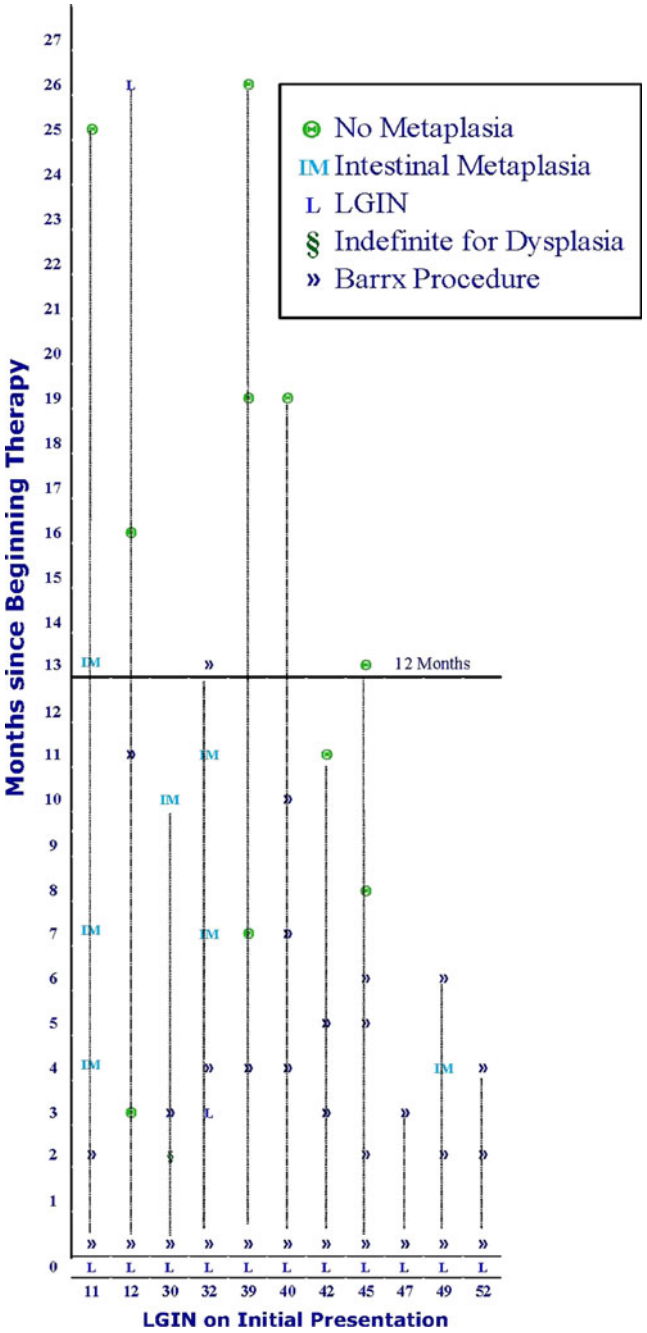

Fig. 1 Complete treatment and biopsy results of each patient with LGIN on initial presentation

Treatment Efficacy

Using two consecutive negative biopsy sessions at least 4–6 weeks apart as the definition of successful treatment, 87.2%

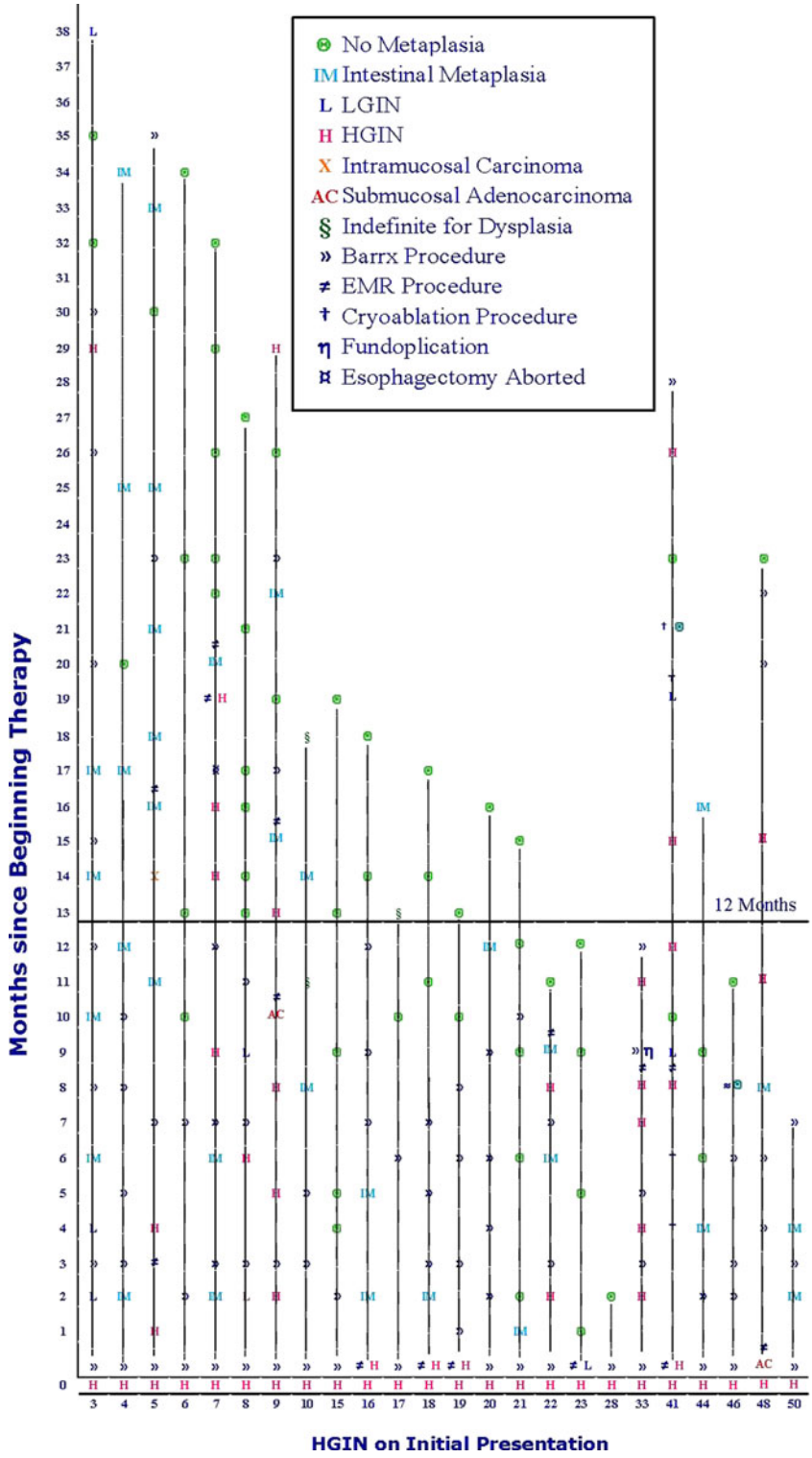

Fig. 2 Complete treatment and biopsy results of each patient with HGIN on initial presentation

(34 out of 39) of patients had complete endoscopic eradication of early neoplasia/dysplasia. Using less strict criteria of one biopsy session, 90.7% (39 out of 43) of neoplasia/dysplasia was successfully eradicated. Efficacy data are shown stratified by initial biopsy pathology in Table 1.

Using two consecutive negative biopsy sessions at least 4–6 weeks apart as the definition of successful treatment, 56.4% (22 out of 39) achieved complete eradication of IM. Using the less strict criteria of one biopsy session, 65.1% (28 out of 43) of IM was successfully eradicated. Surveying

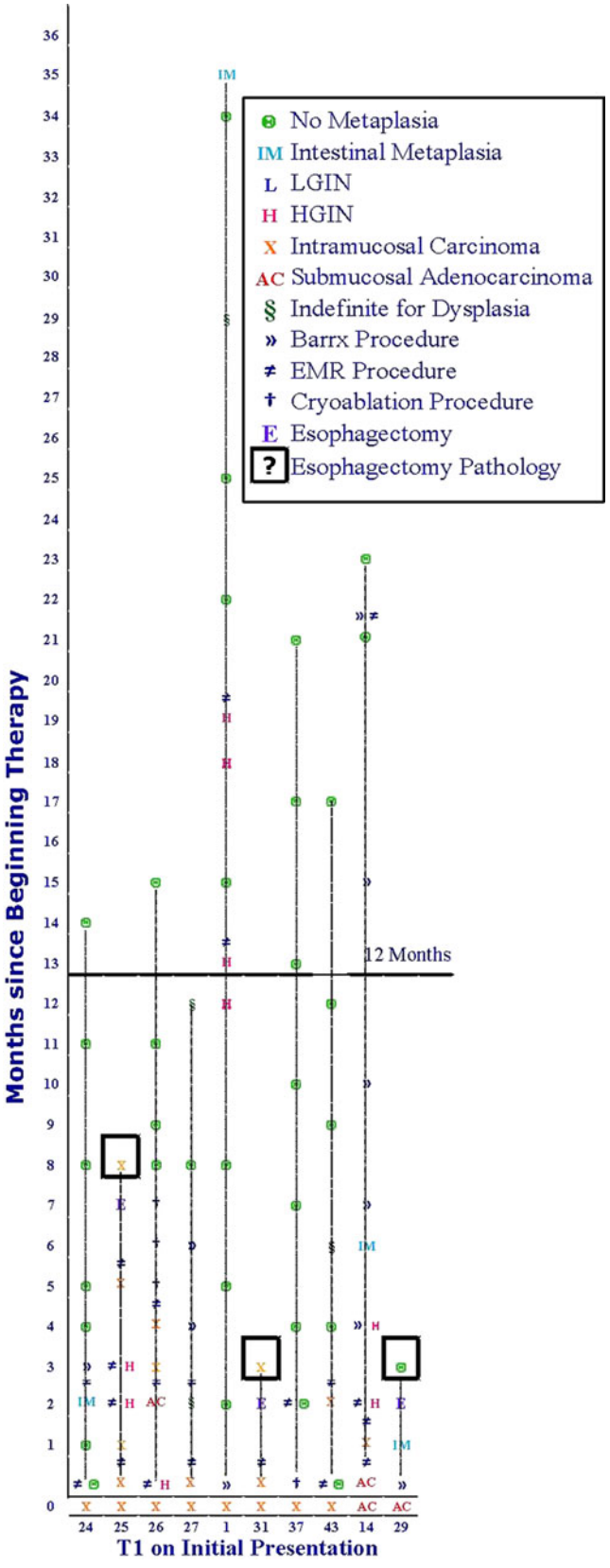

Fig. 3 Complete treatment and biopsy results of each patient with T1 on initial presentation

the outcomes of biopsies taken 12 months from the beginning of therapy, 86.2% (25 out of 29) had eradication of neoplasia, and 65.5% (19 out of 29) had eradication of metaplasia.

There were four endoscopic treatment failures (10%). Attesting to the severity of disease in these patients, their average BE segment was 6.3 cm (SD 3.5), and all had nodular disease. One patient had EMR margins positive for adenocarcinoma and went on to esophagectomy (pTr1aN0M0; r: post-endoscopic resection). The second patient had IMC and persistent multifocal disease prompting esophagectomy which demonstrated node-negative adenosquamous cancer with a small focus of invasion of the lamina propria. A third patient with initial biopsies suspicious for invasion prior to beginning therapy had an EMR specimen demonstrating superficial submucosal disease and positive deep margins, although the submucosa was not present at the involved margins. The final pathology report demonstrated no residual tumor within the esophagectomy specimen (pTr0N0M0). The fourth patient had an 8-cm BE segment with multifocal HGIN and a large hiatal hernia with severe reflux. Because of persistent HGIN despite three ablations and one EMR, along with continued reflux symptoms on proton-pump inhibitors, he underwent a laparoscopic Nissen fundoplication. His reflux-related symptoms completely resolved, and at last biopsy, he had >50% neo-squamous replacement with persistent multifocal HGIN in the columnar epithelium. He is currently undergoing stepwise EMR.

We advised patients with submucosal disease to undergo esophagectomy. However, in addition to the above-mentioned patient who underwent esophagectomy (for positive deep margin at EMR), another patient with a positive deep margin on EMR declined esophagectomy. After three more EMRs and five RFAs, he has had eradication of metaplasia with no residual CLE on continued surveillance endoscopies.

Five patients were found to progress to higher grades of neoplasia at some point during the study period. One patient, initially thought to have intramucosal disease, had submucosal disease later identified, including a positive deep EMR margin, and underwent esophagectomy as was discussed above. A second patient who presented with IMC had an EMR specimen that could not exclude submucosal involvement, but following two EMRs and three cryoablation sessions, he has had eradication of neoplasia and metaplasia. Two patients diagnosed with HGIN later had submucosal invasion demonstrated by EMR. Both of these patients who had superficial submucosal invasion in the setting of significant comorbidities were successfully treated endoscopically. Lastly, a patient with multiple comorbidities and previous gastric surgery progressed from HGIN to IMC (found on follow-up biopsy). He continues to have RFAs due to persistent metaplasia but has had eradication of neoplasia.

Table 1 Efficacy data stratified by initial biopsy pathology

	LGIN (*n*=11)	HGIN (*n*=24)	T1 (*n*=10)
Mean length of follow-up (SD), months	15.1 (9.8)	23.3 (9.8)	20.5 (8.9)
Median length of BE (range), cm	5.0 (1–13)	5.0 (1–13)	3.9 (1–10)
Patients w/ eradication of dysplasia (%), *n*/number of patients with 2 consecutive biopsies following initiation of therapy	6/6 (100%)	21/23 (91%)	7/10 (70%)
Mean time (SD) to eradication of dysplasia, months	5.0 (2.6)	7.7 (5.7)	6.5 (7.6)
Mean # of procedures/patient with eradication of dysplasia	2.5 (15/6)	4.2 (88/21)	4.1 (29/7)
Patients w/ eradication of metaplasia (%), *n*/number of patients with two consecutive biopsies following initiation of therapy	3/6 (50%)	13/23 (57%)	6/10 (60%)
Mean time (SD) to eradication of metaplasia, months	6.1 (2.8)	11.7 (8.9)	7.1 (7.5)
Mean # of procedures/patient with eradication of metaplasia	2.7 (8/3)	4.2 (54/13)	4.2 (25/6)
Patients w/ metachronous lesion (%), *n*/number of patients with two consecutive b iopsies following initiation of therapy	1/6 (17%)	4/23 (17%)	1/10 (10%)
Mean time (SD) to metachronous lesion, months	25.6 (NA)	23.5 (9.5)	11.8 (NA)
Mean # of RFAs/patient (SD)	2.8 (0.9)	3.3 (1.6)	0.9 (1.6)
Mean # of EMRs/patient (SD)	0 (0)	0.7 (0.9)	2.2 (1.1)
Mean # of cryoablations/patient (SD)	0 (0)	0.2 (0.8)	0.4 (1.0)

Recurrent Dysplasia/Neoplasia

Six patients (15.4%) developed metachronous neoplasia/dysplasia at a mean follow-up of 33.9 months (Table 1). The mean time to eradication of neoplasia in this group was 8.6 months (SD 7.6, median 5.6), and to metachronous neoplasia, it was 21.9 months (SD 8.9; median 26.0, range 9.3–29.4). Five of the six had long-segment (≥3 cm) BE or multifocal HGIN prior to ablation. No patient with a metachronous lesion had a more advanced pathology than on original presentation. No deaths resulted from treatment or during the follow-up interval, and no patient developed node-positive or distant metastatic cancer.

Discussion

As recently as 3–4 years ago, the majority of patients in this report would have undergone esophagectomy at our institution. Endoscopic ablative and resective techniques have now evolved to the point that, as this and other studies have shown, endoscopic treatment of early esophageal neoplasia is safe and effective in the majority of patients. Nearly 90% of patients were successfully treated endoscopically with complications that were relatively minor and uncommon. Although the reported stricture rate varies,[10–12] the largest randomized controlled trial reported a rate of 6%.[4] Our symptomatic stricture rate was 2%.

Three patients required esophagectomy for endoscopic treatment failure. All had node-negative early neoplasia on final pathology: two with pT1aN0MX and one with pTr0N0Mx disease. Recurrent neoplasia occurred in six out of 39 patients (15.4%), consistent with previously published reports. These lesions were not more advanced than at initial presentation and were generally amenable to repeat endoscopic therapy. Three of the six had multifocal, nodular HGIN, a recognized risk factor for recurrent neoplasia. The mean time to metachronous neoplasia was 21.9 months, although half of the patients have been followed for 17 months or less, and metachronous neoplasia may increase as the population matures.

The development of RFA utilizing a balloon-based endoscopically guided technique, coupled with EMR, is clearly among the most significant advances in the treatment of BE and associated dysplasia/neoplasia over the past decade. Studies of the efficacy of RFA are evolving rapidly as the frequency of its use in patients with early esophageal neoplasia is increasing. The high rate of complete response coupled with an excellent safety profile and reasonable cost makes RFA a nearly ideal treatment for patients with dysplastic Barrett's epithelium. Furthermore, recent data indicate that eradication of all intestinal metaplasia is associated with a lower prevalence of metachronous dysplasia.[5] While ablation is an effective therapy, it is not a diagnostic modality. Because even minor bleeding from biopsies may make ablation uneven, biopsies are best done at separate endoscopy sessions. As such, current recommendations include EMR of any visible lesion prior to RFA.

Pech and Ell reported the initial experience with EMR in a group of 100 patients selected from a cohort of 667 referred with suspected intraepithelial neoplasia.[13] Complete ablation was achieved in 99 out of the 100 patients with a maximum of three resections at a mean of 1.9 months. Metachronous or recurrent disease occurred in 11% of patients during an average follow-up of

36.7 months. In a follow-up report published in 2008[5] with 349 patients (follow-up of 63.6 months), metachronous lesions were noted in 21.5%, and esophagectomy for failed endoscopic control of neoplasia was necessary in 3.7%. Risk factors for recurrent disease were identified including piecemeal resections, long-segment BE, lack of ablative therapy after EMR, and multifocal neoplasia.

Bergman and colleagues assessed outcomes of combined EMR and radiofrequency ablation in 44 patients with dysplastic BE or early IMC.[6] Thirty-one patients underwent EMR as initial therapy, 16 with IMC, 12 with HGIN, and 3 with low-grade dysplasia (LGIN). Eradication of all dysplasia, as well as complete endoscopic and histologic clearance of BE, was achieved in 98% after a median of one circumferential ablation session, two focal ablation sessions, and rescue EMR in three patients. At a median follow-up of 21 months, no dysplasia had recurred.

A multicenter randomized (2:1) sham-controlled trial assessing the efficacy of RFA in patients with either HGIN or LGIN with both circumferential ($HALO^{360}$) and focal ($HALO^{90}$) ablation was carried out every 3 (HGIN) or 6 months (LGIN). Four-quadrant biopsies every centimeter were taken at a 12-month endpoint and interpreted by a single reference center (Cleveland Clinic). Of 117 of 127 subjects reaching the primary endpoint by the time of reporting, 58 had HGIN, and 59 had LGIN; 39 served as sham controls. By intention to treat analysis, 86% (72 out of 84) had complete eradication of dysplasia (81% in HGIN and 90% in LGIN), and 77% (65 out of 84) of RFA subjects had complete ablation of IM. Three patients progressed (4%): two to HGIN and one to adenocarcinoma. Only one of the sham patients had eradication of IM; 9 out of 43 had eradication of dysplasia, and seven progressed (16%); three to HGIN and four to adenocarcinoma. The authors concluded that RFA is superior to sham for the treatment of dysplasia and BE.[4] These data underscore the feasibility and efficacy of endoscopic ablation in patients referred with HGIN or LGIN and treated at a specialty center. Given these circumstances, the outcomes at 5 years are excellent, with cure rates approximating those obtained by esophagectomy.

The Mayo group retrospectively compared outcomes in 178 patients with IMC seen between 1998 and 2007.[14] One hundred thirty two of these patients were treated with endoscopic ablation and 46 with surgical resection. At an average follow-up of 3.5 years, 12% of the patients in the endoscopic treatment group (16 out of 132 patients) developed recurrent adenocarcinoma: nearly ten times the prevalence after surgical resection (one patient). Although all recurrences were IMC and all but one was managed endoscopically, this emphasizes the need to define risk factors for recurrences.

EMR is an important additional method for diagnosis, staging, and treatment of visible mucosal abnormalities suspicious for dysplasia or early esophageal carcinoma. With increasing experience, EMR is now offered as a potentially curative treatment either alone or in conjunction with RFA or cryotherapy. First utilized in Japan,[3] EMR was found to be a safe and potentially curable technique for squamous cell carcinomas with low risk of intramural spread as defined by the following criteria: tumor size ≤2 cm, infiltration to lamina propria, ≤1/2 esophageal circumference, and absence of lymphatic or vascular invasion. Following the Japanese experience, EMR was adopted in the USA and Europe as an excisional biopsy of visible mucosal irregularities in two applications: (1) as a large biopsy guiding further tailored therapy or (2) as a curative procedure for tumors with low risk of nodal spread. A significant advantage of EMR over ablative therapies for treatment of dysplasia or early neoplasia is the preservation of specimen for histopathological examination and staging; it also allows for the assessment of the completeness of resection. Current criteria for the use of EMR include focal HGIN or IMC in the presence of a visible lesion. While EMR does have significant advantages over ablative therapy, its use in achieving complete eradication of BE has been associated with a high symptomatic stricture rate.[15]

In recent years, endoluminal cryotherapy has also emerged as a safe and effective ablation modality. IM and dysplasia eradication rates are comparable to RFA in recent studies.[17] Cryoablation can be used as a primary modality or in conjunction with EMR and/or RFA to achieve IM/neoplasia eradication, as reflected in our study.

Indications for endoscopic therapy have rapidly increased, and the evolution of our experience and diagnostic improvements continue to keep guidelines in flux. For example, the risk of LGIN progressing varies widely within the literature and likely has been overestimated in prevalence. Inversely, because of this overdiagnosis, true LGIN, as confirmed by an expert pathologist, has a significant risk of progression to HGIN or IMC: 13.4% per year.[16] This significant rate of progression warrants the small risk associated with the discussed endoscopic therapies.

Endoscopic therapy for early esophageal neoplasia is indeed an emerging standard of care. While the long-term outcome following endoscopic therapy remains to be seen, we have demonstrated that this therapy can be performed safely outside of rigorous protocol with appropriate patient selection and available expertise. The applicability of endoscopic treatment for the overall population of patients referred with esophageal neoplasia remains to be defined, as does the issue of whether similar results can be obtained in the general community by non-specialty physicians and centers. It will be essential to closely follow patients over the next several years as the biology that led to the development of dysplasia and cancer remains in place.

The latter fact has led to data that make it increasingly clear that eradication of all metaplastic epithelium is the ultimate goal and that the importance of close follow-up cannot be overemphasized. While the advantages of a less invasive approach are intuitive, less obvious is the anxiety that comes with the slow and/or incomplete eradication of neoplasia, the need for serial endoscopic interventions, and surveillance over a prolonged time period. Surgical resection remains a viable option, particularly for those with refractory neoplasia and the young in which the possibility of new tumors arising beyond 5 years must be considered.

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Endoscopic Management of Gastrogastric Fistulae Does Not Increase Complications at Bariatric Revision Surgery

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Abstract
Background Gastrogastric fistula (GGF) is a challenging complication of primary obesity surgery that often leads to revision surgery. The impact of prior endoscopic intervention on subsequent surgical revisional outcomes remains unknown. We present the largest series of Roux-en-Y gastric bypass GGF with subsequent surgical revision of fistulae to date.
Methods A database of bariatric surgical revisions performed at a single institution was collected. The cohort was divided between patients with and without attempted endoscopic fistula closure prior to surgical revision. Thirty-day morbidity and mortality was the primary outcome.
Results Thirty-five cases of revision were performed for GGF. Of the 35 cases, 22 patients had attempted endoscopic closure prior to surgical revision while 13 patients went directly to surgical revision. In the endoscopy group, two minor complications and seven major complications occurred (total 9 of 22; 40.9%). In the surgery only group, three minor complications and three major complications occurred (total 6 of 13; 46.1%). No deaths occurred.
Conclusion Prior attempts at endoscopic fistula closure do not lead to increased surgical complications at the time of surgical revision.

Keywords Gastrogastric fistulae · Revision · Bariatric · Complications

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Introduction

Rates of obesity continue to rise globally posing increasing risk to individual and societal health.[1–4] As of 2005, the WHO projected that approximately 1.6 billion individuals over the age of 15 were overweight. The WHO further projects that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million will be obese (body mass index ≥30 kg/m^2).[5] To address this epidemic, the demand for bariatric surgery grows.[6–13] An estimated 220,000 bariatric surgeries were performed in 2008.[14]

Roux-en-Y gastric bypass (RYGB) remains the most frequently performed bariatric surgical procedure. Gastrogastric fistulae (GGF) contribute significantly to morbidity following gastric bypass surgery. The term GGF refers to an abnormal communication between the surgically created functional gastric pouch and the excluded gastric remnant after RYGB. A noted complication in up to 46% of cases

when the gastric pouch is created in continuity with the remnant stomach or only partially transected, recent data from the laparoscopic era report this complication in less than 6% of cases.[15–23] Patients with GGF may present clinically with suboptimal weight loss, acid reflux, abdominal pain, and/or nausea.[24–26] While some cases can be managed conservatively, most fistulae will require endoscopic or surgical management for complete closure. Less-invasive, endoscopic technologies are evolving to address GGF and other bariatric postoperative complications. Suturing, injectable agents, and clips have been used with varying success.[27–38] In patients with GGF, durable endoscopic fistula closure is possible with low morbidity.[39]

Despite important advances in the endoscopic techniques for the management of GGF, surgical revision remains the standard of care. These operations are technically demanding and carry an associated high morbidity and mortality.[40–43] Recent literature reports a complication rate of approximately 5–35% for bariatric surgical revision.[44–52] While endoscopic GGF management carries less morbidity, many patients will ultimately require surgical revision. The effect of early endoscopic intervention on subsequent surgical complications remains unknown. Our aim is to evaluate the impact of endoscopic gastrogastric fistula closure on 30-day morbidity and mortality for subsequent revisional bariatric surgery.

Materials and Methods

This research project was IRB approved by the Partners Healthcare Human Research Committee. We performed a retrospective cohort study of subjects selected from a prospectively collected database of consecutive patients undergoing surgical revision of a prior RYGB between May 2004 and June 2009 at a single, tertiary academic center. Subjects undergoing surgical revision for GGF were identified. Subjects with less than 6 months of follow-up, a history of malignancy, or significant psychiatric illness (severe, refractory depression, psychosis, or suicide attempt) were excluded. Patients with prior endoscopic intervention to the gastric pouch, including endoscopic management of a dilated gastrojejunostomy, were included. All patients had upper gastrointestinal series or computed tomography imaging on postoperative day 1 to evaluate for leak. Methodical review of operative record, electronic medical records, and clinic charts was performed. Subjects were divided into two groups—those receiving endoscopic attempt at GGF closure prior to surgical revision (endoscopy group) and those who did not undergo an endoscopic attempt at GGF repair prior to surgical revision (surgery group). A single surgeon performed all revision surgeries, and a single gastroenterologist performed all endoscopies. At our institution, each patient with a known or suspected GGF is referred to the bariatric surgical center for consultation and discussion of management options, including endoscopic attempt at fistula closure and surgical revision. Allocation into each study group was a result of this consultation between surgeon and patient.

Pre-procedural variables were recorded including age, sex, BMI at initial surgery, BMI at revision surgery, presence of diabetes, presence of thyroid disease, psychiatric medication use, smoking status, type of initial surgery and revision surgery (open or laparoscopic), and number of prior abdominal surgeries. Procedural variables were recorded including number of endoscopic GGF closure attempts prior to revision surgery, size of fistula (millimeters), number of clips and sutures placed at GGF, presence of dilated gastrojejunostomy, prior intervention at the gastrojejunostomy, and operation room time at revision surgery. The presence of ulceration or friability of the gastrojejunostomy on prior endoscopy was recorded. The primary outcome of interest was 30-day complications following surgical revision. Each event was categorized as a minor or major complication with inter-author event review and agreement.

Median and interquartile range were calculated for continuous and categorical variables. Wilcoxon signed-rank test was used to analyze continuous data. Fisher's exact test was used to analyze categorical data.

Table 1 Pre-procedural and preoperative variables

	Endoscopy (N=22)	Surgery only (N=13)	P value
Age	47.5 [40.0, 54.0]	42.0 [39.0, 46.0]	0.166
BMI at initial surgery	48.2 [43.3, 54.9]	50.5 [41.5, 54.1]	0.771
BMI at revision surgery	41.4 [36.5, 42.4]	34.9 [31.8, 41.7]	0.253
Diabetes	4 (18.2)	1 (7.7)	0.630
Thyroid disease	6 (27.3)	1 (7.7)	0.220
Psychiatric medication use	13 (59.1)	10 (76.9)	0.463
Current smoker	3 (13.6)	4 (30.8)	0.383
Type of revision (lap)	16 (72.7)	12 (92.3)	0.220
Type of initial surgery (open)	21 (95.4)	11 (84.6)	0.541
Prior abdominal surgeries	2.0 [1, 3]	3.0 [3, 4]	0.034

Categorical variables are presented as numbers (percentage). Continuous variables are presented as median [interquartile range]

Table 2 Endoscopic interventions

	Endoscopy (*N*=22)	Surgery only (*N*=13)	*P* value
Endoscopic closure attempts	2.0 [1, 2]	0	<0.0001
Fistula clips placed	1.0 [0, 4]	0	0.003
Fistula sutures placed	3.5 [2, 8]	0	<0.0001
Presence of dilated GJ	11 (50.0)	6 (46.2)	0.999
Prior intervention to GJ	6 (27.3)	3 (23.0)	0.999
Operation room time at revision (min)	243.5 [188, 295]	273.0 [182, 307]	0.864

Categorical variables are presented as numbers (percentage). Continuous variables are presented as median [interquartile range]

GJ gastrojejunostomy

Results

Thirty-five patients underwent surgical revision of primary Roux-en-Y gastric bypass for an indication of gastrogastric fistula repair. Of these 35 patients, 22 patients (62.9%) had at least one attempt at endoscopic fistula closure prior to revision surgery. Thirteen patients (37.1%) went directly to revision surgery without an attempted endoscopic fistula closure. All patients in the study were female. Patient characteristics are reported in Table 1. Pre-procedural variables including age, BMI at initial and revision surgery, smoking status, presence of diabetes or thyroid disease, type of revision performed, and psychiatric medication use demonstrated no statistical difference between the two groups. The endoscopy group had less prior abdominal operations compared with the surgery group. Operation room time at revision surgery, a surrogate marker for the degree of complexity for a given surgery, demonstrated no statistical difference between the two groups.

In the endoscopy group, 8 of 22 patients had evidence of ulceration on prior endoscopy, of which seven out of eight were described as marginal ulceration. All identified ulcers were treated with proton-pump inhibitor and/or sucralfate. Eight of the remaining 14 cases were noted to have a friable gastrojejunostomy or gastritis. In the surgery alone group, 9 of 13 patients had previous ulceration, of which five were described as marginal. Three of the remaining four patients were treated empirically with proton-pump inhibitors for upper intestinal symptoms.

Procedural or operative variables were analyzed and reported in Table 2. Fistula size was measured in 22 of 22 (100%) subjects in the endoscopy group and 3 of 13 (23%) subjects in the surgery group. In 38.4% of patients in the surgery group, the GGF could not be visualized on endoscopy or appeared closed at the time of endoscopy. Data for fistula size are presented in Table 3.

Our primary end-point was incidence of 30-day minor and major complication. In the endoscopy group, 2 of 22 patients (9.1%) had a minor complication. In the surgery group, 3 of 13 patients (23.1%) had a minor complication. No statistical difference existed between the two groups for minor complication (p=0.337). In the endoscopy group, 7 of 22 patients (31.8%) had a major complication. In the surgery group, 3 of 13 patients (23.1%) had a major complication. No statistical difference existed between the two groups for major complication (p=0.709). These results are presented in Table 4. No deaths occurred in either group. Complications are presented in Table 5.

Discussion

With obesity rising to epidemic proportions, surgical management will continue to play an important role in the management of refractory obesity and its associated co-morbidities. Consequent to this, the role of endoscopy in the bariatric patient continues to evolve. While the endoscopic management of surgical complications including GGF and weight regain has demonstrated efficacy, the impact of endoscopic bariatric intervention on subsequent surgical revision has not been previously studied. With the increased technical difficulty and associated complication rates of bariatric revisional surgery, prior endoscopic GGF closure attempts were thought to be relevant as they could impact these outcomes. Our study sought to evaluate the bariatric revision surgery 30-day minor and major complication rate in patients with and without prior endoscopic fistula

Table 3 Fistula size

	Endoscopy (*N*=22)	Surgery only (*N*=13)
Average measured size in mm	15.3 (*N*=22; 100%)	20.0 (*N*=3; 23.1%)
GGF not visualized or appeared closed on endoscopy		5 (38.4%)
Deemed not amenable to endoscopic closure due to position of GGF		2 (15.4%)
Patient selected surgery without prior endoscopy		2 (15.4%)
Multiple small fistulae		1 (7.6%)

GGF gastrogastric fistula

Table 4 Thirty-day minor and major complications

	Endoscopy (N=22)	Surgery only (N=13)	P value
Minor complication	2 (9.1)	3 (23.1)	0.337
Major complication	7 (31.8)	3 (23.1)	0.709

Presented as number (percentage)

closure attempt. It is the largest study of surgical revision for GGF to date.

Multiple factors can lead a patient to require surgical revision including pain, weight regain, intractable nausea/emesis, and GGF. At our bariatric center, surgical and endoscopic modalities are discussed with each patient. Endoscopy management is offered for both weight regain caused by dilated gastrojejunostomy and for symptoms and complications associated with GGF. Both entities can be addressed by the use of sutures, clipping, and/or sclerosants at the gastrojejunostomy and fistula, respectively. In this study, patients with prior endoscopic attempt at gastric outlet reduction were included.

Stomal or marginal ulceration is a well-described risk factor in the formation of gastrogastric fistulae. Many factors are believed to be associated with ulcer development including ischemia, increased acid exposure, smoking, nonsteroidal anti-inflammatory drugs, and pouch size.[24] In our study, 12 of 35 patients (34.3%) were noted to have marginal ulceration on previous endoscopy, and an additional 8 of 35 (22.8%) had a friable gastrojejunostomy. All patients with these risk factors or upper intestinal symptoms were treated with proton-pump inhibitor and/or sucralfate prior to revision surgery.

We found no statistical difference between the number of 30-day minor and major complications in those receiving endoscopic GGF closure attempt prior to revision surgery and those who went directly to surgery. In the endoscopy group, minor complications included one patient with chest pain, admission to the ICU for cardiac monitoring and a localized wound infection and a second patient with postoperative fever and extended hospitalization. In the surgery group, minor complications included one patient with hematoma requiring transfusion and extended hospitalization, a second patient with localized wound infection, and a third patient with postoperative fever and extended hospitalization for evaluation. Major complications in the endoscopy group (following surgical revision) included pulmonary embolism, re-admission for wound infection requiring intravenous antibiotics, re-admission for abscess with reoperative debridement, two cases of postoperative leak, abdominal pain requiring diagnostic exploratory laparotomy, and an exploratory laparotomy for high-grade obstruction. Major complications in the surgery group included two cases of intra-abdominal abscess and one case of splenic abscess requiring operative drainage and splenectomy. Recent literature has suggested a standardized classification system for surgical complications.[53] Our minor and major complications correlate well with grades I–II and grades III–V proposed "Clavien–Dindo" complications, respectively.

Anastomotic leak occurred in two cases of revision surgery with previous endoscopic fistula closure attempt. In the first case, the patient had a normal upper gastrointestinal series and computed tomography scan of the abdomen and pelvis on postoperative day 1. The patient presented to the hospital on postoperative day 12 with abdominal pain and was found to have a leak on repeat imaging. The patient had a history of prior ventriculoperitoneal shunt, two prior exploratory laparotomies for adhesions, a total of four prior intra-abdominal surgeries, and a single prior endoscopic fistula closure attempt with suturing. In the second case, a leak was identified on abdominal imaging on postoperative day 10 when the patient presented with abdominal pain. Prior imaging in the postoperative course had not demonstrated leak. The patient had three prior intra-abdominal surgeries, and two previous endoscopic fistula closure attempts with suturing. Given the limited data, it is difficult to draw conclusions whether the number of prior endoscopic attempts at fistula

Table 5 Frequency of complications

		Endoscopy (N=22)	Surgery only (N=13)
Minor complication	Localized wound infection/extended hospitalization	1	1
	Postoperative fever/extended hospitalization	1	1
	Hematoma/extended hospitalization		1
Major complication	Wound infection/intravenous antibiotics/re-admission	1	
	Intra-abdominal abscess	1	3
	Postoperative leak	2	
	Pain requiring exploratory laparotomy	1	
	Pulmonary embolism	1	
	Exploratory laparotomy for high-grade bowel obstruction	1	

closure increases the risk of leak; however, the placement of additional foreign material within the gastric pouch represents a nidus for inflammation and a potential pathophysiologic mechanism for increased risk of leak. More importantly in these two cases, as described in previous literature, the number of previous operations is a noted risk factor for anastomotic leak.[54,55]

In our multidisciplinary practice, patients with complications related to Roux-en-Y gastric bypass surgery are offered endoscopic and surgical options. Our tertiary referral center often receives patients with a history of prior surgery at other institutions. More than 30% of patients in the study had an initial open RYGB at an outside facility. Of the remaining patients who had initial open RYGB, 21 of 32 RYGB operations (65.6%) were performed at our hospital, all prior to 2003. In our study, all patients were female which likely reflects the relatively low sample size of patients undergoing surgical revision for GGF. Recent studies also demonstrate a high female preponderance up to 95%.[13,52]

As many patients will experience weight regain after surgery, endoscopy following bariatric surgery may present a less morbid option to revisional surgery. Recent data suggest that complete initial endoscopic GGF closure can be achieved in 95% of patients, but reopening will occur in more than half by around 1 year.[39] Many of these patients are likely to require revision surgery for persistent symptoms or weight regain, though temporary fistula closure brings the added benefit of lowered pre-surgical morbidity achieved through weight loss. Techniques involving suturing, clipping as well as the use of injectable sclerosant have been evaluated.[56] Studying the impact of these additional modalities on surgical outcomes remains an important area of future investigation.

Results must be evaluated in the context of the study design. Nearly all pre-intervention variables showed no statistical difference between the groups; however, patient preference and the ability to detect a GGF at endoscopy influence group allocation. Out of 35 total cases, only two patients (5.7%) chose to go directly to revision surgery without endoscopic evaluation for possible closure. Those who ultimately did not have attempted endoscopic closure prior to surgery (13 of 35) tended to have GGF that were not visualized on endoscopy, GGF in technically challenging positions within the pouch, or larger fistulae (15, 20, 25 mm). Recent data from our institution suggest that endoscopic attempt at GGF closure for fistula >10 mm is unlikely to be successful.[39] From our data, it is difficult to draw conclusions regarding the effect of fistula size on 30-day complications.

The potential for missing data in the database must be considered as well as the accuracy of patient records. The selected study design limits the ability to account for all potential variables. Information regarding patient diet, exercise, and psychosocial status may be present, but incomplete. Despite a low sample size, our study demonstrates power to detect a difference when measured across the historical complication rate of gastrogastric fistula in up to 46% of patients. To detect a 40% difference in morbidity with one group set at a 5% morbidity rate consistent with the laparoscopic era, a study would require a total sample of 34 patients to detect the difference with 80% power and an alpha of 5%. To detect a 15% difference, which may better represent the laparoscopic era, a total sample of 118 patients would be required for similar power. While the low total number of subjects must be factored into the interpretation of significance and generalizability of results, our study is currently the largest study of the surgical management of GGF.

Conclusion

The role of endoscopic and surgical management continues to be redefined as technological advances and new methods develop to meet the challenges of a global obesity epidemic. While endoscopic management of bariatric complications demonstrates success with low complication, surgical revision provides definitive therapy for the majority of patients but with higher morbidity. In the first study of its kind, we sought to assess the impact on endoscopic management of gastrogastric fistula on future operative risk as defined by 30-day complication rate. Endoscopic attempt at gastrogastric fistula closure does not increase 30-day complications at future RYGB revisional surgery. This interplay of endoscopic management and revisional surgery will likely be of growing importance and warrants future study.

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ORIGINAL ARTICLE

Paraesophageal Hernia Repair with Biomesh Does Not Increase Postoperative Dysphagia

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Abstract
Introduction Laparoscopic techniques have led to hiatal procedures being performed with less morbidity but higher failure rates. Biologic mesh (biomesh) has been proposed as an alternative to plastic mesh to achieve durable repairs while minimizing stricturing and erosion. This paper documents the lack of significant dysphagia after the placement of biomesh during hiatal hernia repair.
Methods A retrospective chart review of patients who underwent paraesophageal hiatal hernia repairs with and without biomesh was performed. Hernias were diagnosed with esophagogastroscopy and esophageal manometry. Demographic, procedural, and pre- and post-surgery symptom data were recorded.
Results Fifty-six patients underwent biomesh repair while 33 patients underwent non-mesh repairs. The procedure time for mesh repairs was significantly longer ($p=0.004$). Hospital stays, resting lower esophageal sphincter pressure, and mean contraction amplitudes were similar between groups. Residual pressure was measured to be significantly higher in patients who had mesh repairs ($p=0.0001$). Normal esophageal peristalsis was maintained in both groups. At first follow-up, mesh patients complained of more dysphagia and bloating, but non-mesh patients had more heartburn. At second follow-up, non-mesh patients had more symptom complaints than mesh patients.
Conclusion The addition of biomesh for hiatal hernia repair does not result in significantly increased patient dysphagia rates postoperatively compared with patients who underwent primary repair.

Keywords Hiatal hernia · Mesh · Biologic mesh · Dysphagia · Laparoscopic · Esophageal · PEH

Introduction

Since the beginning of the twentieth century, surgical management of hiatal hernia has been and continues to be in evolution. With improved understanding of the physiology of the gastroesophageal junction and diaphragmatic hiatus, great strides were made with transthoracic and open transabominal procedures to restore effective anatomy in this complex and difficult area. Most recently, the development of minimally invasive surgical techniques has led to a dramatic increase in the number of hiatal procedures performed and has lessened surgery-related morbidity.[1–9] However, the well-documented advantages of laparoscopic hiatal hernia repair—less pain, shorter hospital stays, and faster overall recovery—are partly lost by the reported rates of failure that are higher than in patients who had had open repairs.[10–13] Based on the advances made in the fields of body wall reconstruction and inguinal hernia repair, the addition of prosthetic material at the hiatus has been proposed to minimize recurrence in laparoscopic repairs.[14–17] Synthetic meshes, however, have been associated with serious complications at the hiatus, such as fibrosis, esophageal stricturing, erosion, and gastric fibrosis.[18–22]

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Biologic mesh materials have been proposed as an alternative to plastic mesh in hopes of avoiding these potentially catastrophic complications while achieving a robust permanent repair. In theory, these materials cause less foreign body reaction and instead act as a temporary matrix for native tissue ingrowth and remodeling. Several investigators have found that hiatal hernia reinforcement with biologic mesh is associated with low objective recurrence rates of 0–11%.[23–26] This has led to a rapid adoption of biologic mesh reinforcement for giant hiatal hernias. Although it is an ideal solution in principle, as with any foreign material, the body is able to recognize biologic mesh and respond to its presence. The same studies that show a decrease in recurrence rates with their use also report morbidity rates ranging from 0% to 24%, with the most common complication being dysphagia related to fibrosis and contraction of the mesh.[23–26]

We hypothesize that patients who have biologic mesh placed during laparoscopic hiatal hernia repair will have higher rates of dysphagia related to mesh hiatal inflammation than patients who have hiatal procedures without mesh placement.

Methods

Patients

All patients provided consent to participate in the retrospective review of the prospectively collected data. Queries were performed on an institutional review board-approved database containing prospectively collected data of patients who underwent type II, III, or IV paraesophageal hiatal hernia (PEH) repairs between 2004 and 2008. Patients having a Collis gastroplasty or partial fundoplication for severe dysphagia where excluded. All patients who were noted at operative exploration to have more than 30% of their stomach in the thoracic cavity, along with a widened hiatus with thinning of hiatal pillars, underwent repair using a standardized biomesh placement technique (Fig. 1). During the same time frame, a comparable cohort of type III hiatal hernia patients underwent standardized non-mesh PEH repairs either because they were felt to have healthy crura or biological mesh was unavailable. Patient demographics [age, sex, body mass index (BMI), history of prior abdominal surgery] and pre- and post-surgery symptom scores were collected at the time of enrollment. Procedural data including estimated blood loss and intraoperative complications were collected at the time of the procedure and entered into the database. Postoperative complication data and length of stay were recorded at the time of the first postoperative visit. Patients were objectively diagnosed with esophagogastroscopy and high-resolution esophageal manometry before surgery and manometry and pH testing after surgery (6 months and 3 years).

Manometry

All patients underwent high-resolution esophageal manometry in our swallowing lab using a solid-state esophageal manometry catheter incorporating 36 individual pressure sensors along the catheter, with 1-cm spacing (Sierra Scientific Corporation, Los Angeles, CA). The catheter was placed transnasally until respiratory inversion indicated that the catheter had reached the stomach. Intragastric pressure was recorded. Measurement of pressure across the lower esophageal sphincter (LES) at rest was performed to determine a mean LES baseline pressure. Peristalsis, upper esophageal, body, and LES residual pressures were recorded during ten liquid swallows. In normal anatomy, the LES and the diaphragmatic crura overlie one another and the manometric depiction is a single high-pressure zone (Fig. 2a). The presence of a hiatal hernia was inferred by the finding of a "dual high-pressure zone" (DPZ; Fig. 2b). Postoperative development of a DPZ is presumed to indicate wrap herniation.

Symptom Assessment

All data were prospectively collected on standardized data collection forms and maintained in an electronic database system (Microsoft Access; Microsoft Corp, Redmond, WA). Demographics and preoperative clinical data were obtained at the time of the initial office visit. Symptom assessment was performed at each visit using a standardized validated assessment tool that grades reflux, heartburn, and dysphagia on a scale of 0 to 4, with higher ordinal values representing greater frequency or severity of symptoms. Initial follow-up was performed between 3 and 4 weeks after surgery. Similarly, at 6 months following surgery, patients were recalled with a letter or a phone call for

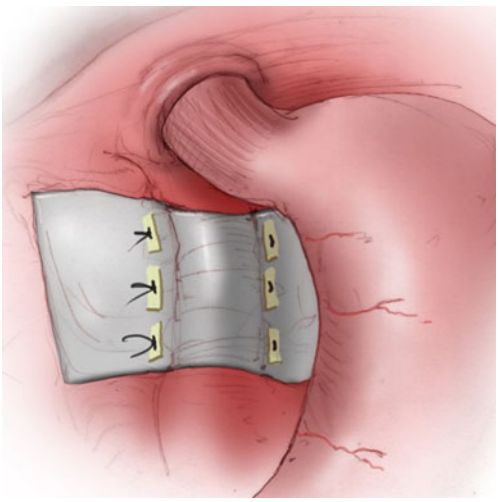

Fig. 1 Standardized hiatal repair with horizontal mattress sutures incorporating biologic mesh

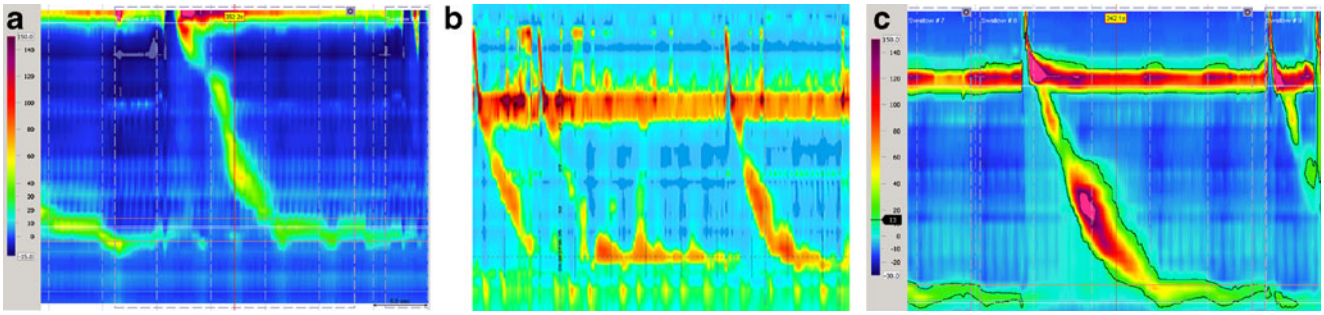

Fig. 2 **a** Normal manometry including single HPZ. **b** Manometry with PEH, dual HPZ. **c** Manometry status post-repair of hiatal hernia with mesh, single HPZ

clinical assessment, esophageal manometry, upper endoscopy or barium swallow, and 24-h pH testing.

Surgical Technique

A five-port technique is used with the patient positioned supine. The phrenoesophageal ligament is incised around the periphery of the hiatus and the hernia sac is completely dissected from the mediastinum. Mediastinal mobilization of the esophagus is continued until 2.5 to 3 cm of the distal esophagus rests without tension within the abdominal cavity. Posterior closure of the hiatus is performed with the assistant gently retracting the esophagus anterior and to the patient's left. Primary repair of the hiatus is done in all cases using pledgeted, double-armed, 0-polyester sutures placed in a horizontal mattress fashion. Closure usually proceeds from posterior to anterior ending at the posterior aspect of the esophagus. For mesh repairs, a rectangular piece of biomesh is incorporated into the horizontal mattress suture closure to assure the close apposition of the mesh to the diaphragm. The remainder of the fundoplication is then performed as previously described.[11]

Statistics

Independent samples t test and Fisher's exact test were performed to determine significance between groups. Values of $p<0.05$ were considered statistically significant. Statistical analysis was performed using PASW (version 18.0, SPSS, Inc., Chicago, IL, USA).

Results

Patients

One hundred and sixty-two patients who underwent type II, III, or IV PEH repairs between 2004 and 2008 were identified through a prospectively collected database. Fifty-six patients underwent PEH repair with bioprosthetic mesh, and 33 patients who underwent hiatal hernia repair without mesh and had complete follow-up data were included in the analysis. Seventy-three patients either did not meet the inclusion criteria (had a Collis procedure, severe dysmotility, preoperative dysphagia, or were reoperative) or did not return for follow-up ($n=21$) and were not included in the analysis.

Of the patients who underwent PEH repair with bioprosthetic mesh, 40 patients completed the second postoperative evaluation and manometric studies. Sixteen patients had either not yet returned for manometry or were lost to follow-up ($n=6$). Of those who underwent hiatal hernia repair without mesh, 32 completed the manometry and symptomatic studies at their second postoperative visit. One patient was lost to follow-up.

Demographics

Overall, both cohorts of patients were the same in terms of age, BMI, and gender distribution (Table 1).

Procedural and Hospital Data

The cases in which mesh was placed at the hiatus took longer than cases where the hiatus was closed primarily. On average, the mesh cases took more than 50 min longer than non-mesh cases (190±84.7 vs. 132.9±40.4 min, $p=0.004$). Despite the higher complexity of cases and longer operative times, patients in the mesh group had uncomplicated initial postoperative courses and were discharged from the

Table 1 Demographic and operative procedure data

	Mesh ($n=56$)	No mesh ($n=33$)	p value
Age (years)	64.5±11.8	61.8±11.0	0.29
BMI	30.4±5.9	31.7±5.6	0.51
% male	35.7	45.5	0.38
Surgery length (min)	190.1±84.7	132.9±40.4	0.004
Discharge day	2.26±0.94	2.24±0.90	0.94

hospital at similar times to their non-mesh counterparts (day 2.26±0.94 vs. 2.24±0.90, p=0.94).

Postoperative Symptom Assessment

The first postoperative symptomatic assessment was completed in the office 3 weeks after surgery. Mesh patients were seen on postoperative day 24.9±10.7 and the non-mesh patients followed up on day 23.0±17.0 (p=0.57). As is seen in Fig. 3, non-mesh patients had higher heartburn scores than patients who had had their hiatal hernias repaired with mesh. Mesh patients also tended to complain more of solid food dysphagia and bloating, but the differences did not reach significance. Otherwise, symptom scores were the same for both groups.

A second structured interview regarding patient wellness and symptom profiling was performed 6 months following surgery. However, patient compliance with the timing of this visit was variable. The mesh patients returned for follow-up on day 195±80.1, while the non-mesh cohort returned, on average, nearly 3 months later (287.8±173.1 days postoperatively). Overall, during this second visit, non-mesh patients had more symptom complaints (Fig. 4). They had significantly more chest pain, abdominal pain, and complaints of inability to belch to relieve discomfort. An initial trend at the first 3- to 4-week visit of non-mesh patients having more heartburn complaints continued at the second assessment, but did not reach significance.

Manometry

Esophageal manometric testing was routinely performed at the 6-month visit. While the resting LES pressure was the same for both hernia repair groups (Table 2), the residual pressure was significantly higher in the patients who had a mesh repair (13.7±6.6 vs. 1.7±5.8 mmHg, p=0.0001).

Mean contraction wave amplitudes were significantly higher in the mesh patients compared with the non-mesh patients; however, both were still considered to possess amplitudes within the acceptable normal limits (Fig. 2c and Table 2). Similarly, normal esophageal peristalsis was maintained in both patient groups. There were no postoperative studies that showed a double PIP, which would have indicated failure of the repair.

Discussion

Hiatal hernia surgery has changed significantly since the first repair was reported by Soresi in 1926.[27] Perhaps the biggest change was the introduction of laparoscopic antireflux surgery in the 1990s which demonstrated significant patient advantages and quickly became the "gold standard" of treatment. Treatment of giant paraesophageal hernias, however, was more controversial as they were both more technically difficult and have always had a substantial recurrence rate.[10,17,25] Most surgeons still feel that the decreased morbidity of the laparoscopic approach justifies its use. There has been substantial research focused on techniques to reduce recurrence including hernia sac resection, different suturing techniques for primary closure, and the use of mesh to either close or reinforce the hiatal closure. Reinforcement of the repair with synthetic mesh has the lowest reported recurrence rates in the literature.[3,15] Synthetic mesh repairs of the hiatus have, however, been shown to have the potential for serious late complications due to mesh erosion into the stomach or esophagus or dysphagia from mesh contraction.[28] To avoid these complications, many have advocated the use of

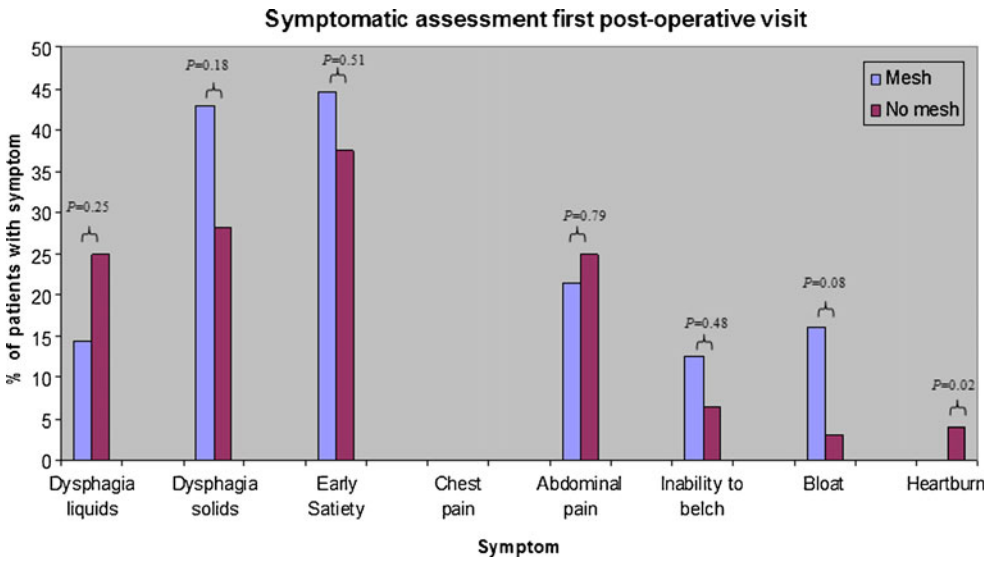

Fig. 3 First postoperative visit assessment of symptoms in patients who underwent primary and mesh hiatal hernia repairs (mean follow-up day: mesh patients (n=55), day 24.9±10.7; non-mesh patients (n=32), day 23.0±17.0, p=0.57)

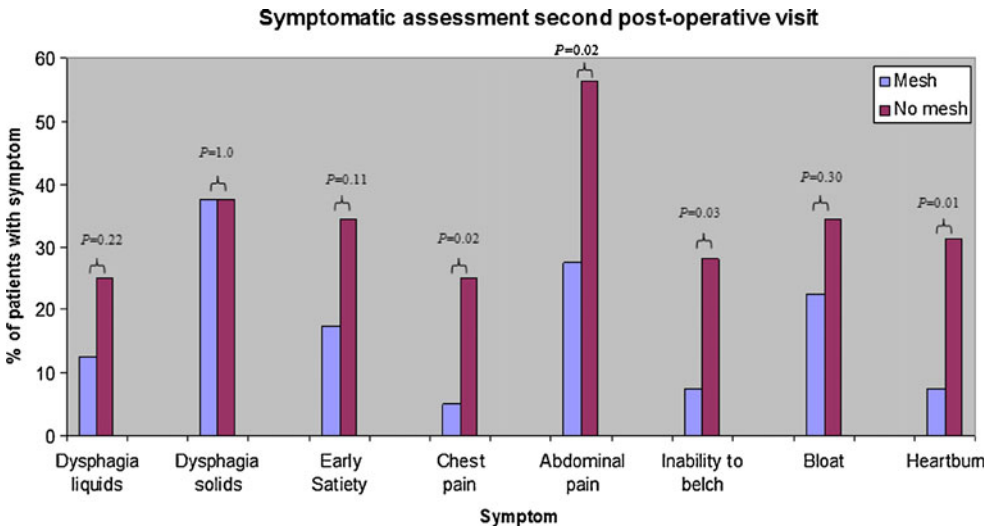

Fig. 4 Second postoperative visit assessment of symptoms in patients who underwent primary and mesh hiatal hernia repairs (mean follow-up day: mesh patients (n=40), day 195.7±80.1; non-mesh patients (n=32), day 287.8±173.1, p=0.01)

biologic mesh which act as scaffolding for native tissue ingrowth and theoretically would present less risk of mesh erosion. In 2006, our group, along with three other centers, presented the results of a prospective randomized comparison of PEH repair with and without a biologic mesh reinforcement. This study showed a clear benefit in recurrence rates with the use of biomesh.[25] However, this study did not report in detail on the symptomatic results such as dysphagia that might result from the use of the mesh.

Patients with giant hiatal hernias can present with insidious anemia or acute incarceration and strangulation, but the vast majority of patients who present for elective repair have complaints of dysphagia, post-prandial pain, early satiety, and sometimes weight loss. Therefore, repair should focus on the restoration of normal anatomy, symptom alleviation, and lifestyle improvement. Outcomes studies have often defined failure as any recurrence even if asymptomatic, which in fact the vast majority of recurrences are. This may be beside the point if the prevention of minor asymptomatic recurrences occurs at the cost of introducing disruptive symptoms like dysphagia. The objective of our study was specifically to report on the occurrence of dysphagia in patients who had hiatal hernia repairs with biologic mesh reinforcement compared with those with primary repairs alone.

The patients in this study who underwent primary repairs had more postoperative complaints at both their first and second office visits than patients who had biomesh placed. This was an unexpected result as we had predicted that inflammation and scar contraction of the biomesh would result in hiatal stricturing from contraction and resulting dysphagia, as had been described in animal studies.[29] The fact that this was not seen may be due to several reasons. It may be that the inflammation and fibrosis that is associated with synthetic mesh does not happen to the same extent with biologic materials. This in fact has been shown in biologic mesh repair of other body hernias.[30–33] Less inflammation and fibrotic tissue changes at the hiatus might predictably lead to less overall symptoms, specifically dysphagia. Desai et al.[29] reported no dysphagia in a canine study where paraesophageal hernias were repaired using biologic mesh. Similarly, in short-term human studies, patients who underwent biomesh repairs have done well clinically.[23,32,34]

Primary repair failure results from the poor quality of the crus and the diaphragm, which means that the tissue does not hold suture well and tears easily. Also, the defects are usually long-standing and large, and the primary closure of the hernia is always under tension. These factors make the recurrence of the hernia more likely and may be associated with symptom recurrence including dysphagia. While we

Table 2 Postoperative manometric evaluation

	Mesh	No mesh	p value
LESP resting (mmHg)	17.6±8.6	20.2±7.2	0.33
LESP residual (mmHg)	13.7±6.5	1.7±5.8	0.0001
Mean amplitude (mmHg)	82.4±36.6	56.2±22.0	0.02
% peristalsis	93.3±7.3	98.0±0.8	0.49
Intraabdominal length of LES (cm)	1.6±0.5	1.8±0.8	0.29

did not specifically report hernia recurrence in this study, we know from previous reports that a 6-month recurrence of up to 25% can be expected.[25] It is possible that the symptomatic patients who had primary repairs were herniating their wraps, causing distal esophageal compression and dysphagia. Conversely, the biomesh-repaired patients may have not recurred, and therefore, their lower rate of symptomatic dysphagia is a result of an intact repair.

Of note is that patients who underwent repairs with mesh had significantly longer operative times. This large difference is more than we expected. While the added time is mostly accounted for by the added complexity of incorporating a mesh into the repair, it may also imply that these patients were more complex. Certainly, as noted in the selection criteria, patients who had mesh placed generally had both large hernias and thinned diaphragmatic crura. In the majority of patients with these findings, the hernias have been present for a long period of time. The incidence of hiatal inflammatory changes may be higher in these types of hernias and patients and result in a more difficult and lengthy dissection. Also, in the vast majority of these cases, the dissection and the suturing of mesh is done by trainees, adding to the operative time.

A weakness of this study is that it was not randomized. The two groups were well matched demographically, but the surgeon chose whether or not to use mesh based on a subjective appraisal of the hiatus at surgery or the availability of mesh. If anything, this should have biased against the mesh patients at least for recurrence, but probably had little impact on dysphasia rates. Another problem is the duration of follow-up with the patient cohort. It is possible that the development of strictures from biomesh may become apparent with longer periods of observation. However, studies of biomaterials used in various hernia repairs in the literature have shown that the material is degraded and has ingrowth of surrounding native tissue within weeks of placement. Considering that the gradual mesh replacement would be occurring during the course of our study's duration, we should have seen most of the effects of inflammation or mesh contraction.

Conclusion

This study demonstrated that the addition of biomesh at the esophageal hiatus for hiatal hernia repair does not result in significantly increased patient dysphagia during the postoperative period when compared with patients who underwent primary repair alone. More frequent symptom complaints were seen following surgery in the patients who did not have mesh placed, possibly due to a higher hernia recurrence rate. The relationship between dysphagia symptoms and foreign body reaction or hernia recurrence needs to be elucidated in further studies that include a longer follow-up period.

While the biomesh reinforcement of hiatal hernia repairs seems to be a logical step to reduce problematic hernia recurrence, further studies to differentiate optimal biomesh types and the best fixation techniques are needed. Also, the use of biomaterials has an unfavorable healthcare cost component in terms of hospital charges and longer operative times. However, if quality studies can be performed that document long-term cost savings in terms of patient recovery, symptom-free postoperative courses, and lower rates of recurrences requiring treatment, this cost differential could be justified.

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ORIGINAL ARTICLE

The Amount of Neoadjuvant Chemotherapy for Barrett's Carcinoma Does Not Correlate with Long-Term Survival

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Abstract
Introduction Several studies have proven an ameliorated prognosis after a neoadjuvant therapy for locally advanced Barrett's carcinoma in case of response. The necessary amount of neoadjuvant chemotherapy within a multimodal therapy concept with following oesophageal resection has never been evaluated so far.
Methods The clinical course of 122 patients with Barrett's carcinoma, who all underwent a neoadjuvant chemotherapy with cisplatin, five fluorouracil and leucovorin and following oesophagectomy, was reviewed. The pretherapeutic clinical and postoperative histopathological staging, histopathological response, clinical course, recurrence rates and long-term survival were retrospectively analysed and compared to the data of 30 patients, who were included in the same multimodal therapy concept, but who had to cease the chemotherapy early because of toxicity.
Results Postoperative pathological staging showed that the response rate correlates with the N and R status. The responding patients benefit from longer survival. Comparing the two subgroups, we could not find a significant difference in response rate, tumour staging, resection rate, long-term survival or pattern of recurrent disease. However, postoperative morbidity and mortality did not correlate with severe chemotherapy-induced toxicity.
Conclusions This is the first study on the necessary number of chemotherapy cycles in terms of a neoadjuvant therapy for Barrett's carcinoma. We could show a similar downstaging effect, a good histopathological response and a comparable ameliorated long-term survival of patients with one compared to patients with three chemotherapy cycles. A biological selection seems to determine the course of the disease already at this early stage.

Keywords Oesophageal surgery · Barrett's carcinoma · Neoadjuvant therapy · Prognostic factors

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Introduction

The majority of patients with an oesophageal adenocarcinoma present with an at least locally advanced or even a metastatic tumour stage at the time of diagnosis.[1–5] In patients with stage IV disease, survival rates remain dismal and only palliative treatments are recommended, whereas in patients with locally advanced tumours, several studies could show a survival advantage after a multimodal therapy consisting of a neoadjuvant chemotherapy and following resection in case of chemotherapy response.[6–10] The used chemotherapy consists of 3 cycles of cisplatin, five fluorouracil (5 FU) and leucovorin over a period of 6 weeks per cycle. A good response rate with less than 50% viable tumour cells in the postoperative specimen can histopathologically be proven in almost 50% of

patients. In up to 10% of patients, even a complete response without any residual tumour (pT0N0) can be achieved.[10–12] In several studies, responding patients were demonstrated to have even a 5-year survival time of 70%.[7,8,10–12] Up until now, the necessary amount of neoadjuvant chemotherapy for this effect is unknown in patients with oesophageal cancer.

Methods

From January 1997 until December 2006 in the Klinikum rechts der Isar, Munich, 152 patients with locally advanced adenocarcinoma of the distal oesophagus (Barrett's carcinoma) underwent a multimodal therapy consisting of a neoadjuvant polychemotherapy and following oesophageal resection and reconstruction with a gastric tube. One hundred twenty-two patients received three full cycles of chemotherapy. Thirty patients had to cease the neoadjuvant treatment after 6 weeks because of toxicity. The clinical profiles of all patients are detailed in Table 1.

Initial tumour staging included gastroscopy with the histologic proof of an adenocarcinoma, endosonography for the local tumour staging (depth of invasion, lymph node status), a CT scan to exclude distant metastases and a risk assessment concerning the operability and the chemotherapy.

For polychemotherapy, patients received 1 to 3 cycles of PLF over a period of 6 weeks per cycle (5-fluorouracil 2,000 mg/body surface area (BSA) continuously over 24 h for 6 weeks, 500 mg leucovorin for 2 h every 7 days, cisplatin 50 mg/BSA for 1 h every 14 days). After 4 to 6 weeks of recovery, the clinical response was evaluated by the comparison of the pre- and posttherapeutic endoscopy, endosonography and CT scan. Thirty patients interrupted their chemotherapy already after their first cycle and consequently underwent the restaging 9 weeks after primary staging.

All 152 patients underwent an abdominothoracic resection and reconstruction with a gastric tube (Ivor-Lewis) 4 weeks after the last day of chemotherapy. A D2 lymph node dissection was routinely performed. In addition, the perioesophageal and infracarinal lymph nodes were resected. In selected patients, a lymph node dissection extended to the right apex of the right chest.

The tumours were staged according to the guidelines of the International Union Against Cancer 1997. The histopathological response was assessed according to Becker in the postoperative specimen. Tumours with

Table 1 Clinical and histopathological data of all patients and divided into two subgroups comparing patients receiving 1 versus 3 cycles of neoadjuvant polychemotherapy with cisplatin, five fluorouracil and leucovorin

	All patients $n=152$	3 cycles chemotherapy $n=122$	1 cycle chemotherapy $n=30$
Patient age, median (interquartile range)	57 (49–64)	56 (48–63)	59 (52–66)
Mean follow-up (range)	31.74 (1–95)	32.6 (1–94)	28.2 (1–83)
Gender (M/F)	116/36	99/23	17/13
pT category:			
T_0	11 (7.2%)	10 (8.1%)	1 (3.3%)
T_1	8 (5.2%)	7 (5.7%)	1 (3.3%)
T_2	65 (42.7%)	54 (44.2%)	11 (36.6%)
T_3	55 (36.1%)	43 (35.2%)	12 (40%)
T_4	13 (8.5%)	8 (6.6%)	5 (16.6%)
			$p=0.274$
pN category:			
N_0	62 (40.8%)	50 (41%)	12 (40%)
N_1	90 (59.2%)	72 (59%)	18 (60%)
			$p=1.0$
R category:			
R_0	117 (77%)	96 (78%)	21 (70%)
R_1	35 (23%)	26 (22%)	9 (30%)
			$p=0.68$
Regression rate:			
Reg 1	65 (42.8%)	54 (44.3%)	11 (36.6%)
Reg 2	87 (57.2%)	68 (55.7%)	19 (63.3%)
			$p=0.539$

M male, *F* female, *Reg* regression rate according to Becker,[13] *Reg 1* regression rate with less than 50% viable tumour cells, *Reg 2* regression rate with more than 50% viable cells

less than 50% viable tumour cells of the primary Barrett's carcinoma accounted to responding cancers, whereas more than 50% viable tumour cells signified a non-response.[13]

The medical records of all patients were reviewed, and demographic information, clinical features and tumour characteristics were recorded. The patients were seen every 3 months for the first year after surgery and every 6 months thereafter until death or 5 years after surgery. Follow-up included physical examination, endoscopy and CT scan. Survival data and pattern of recurrent disease were collected from hospital or follow-up records.

Statistics

Pretherapeutic and histopathologic staging, response rate and survival time were correlated. Comparison between groups was performed with the Mann–Whitney *U* test, Kruskall–Wallis test, Student's *t* test or .2-test. Overall survival rates were calculated by the method of Kaplan and Meier, and included operative mortality. Differences in survival between groups were shown with the log rank test. The significance level was set at $p<0.005$. Analyses were performed using SPSS® 14.5 for windows (SPSS, Chicago, IL, USA).

Results

Demographic data of the study population are summarized in Table 1. Mean age of all our patients was 55.6± 10.8 years. One hundred sixteen patients were male, and 36 were female. One hundred twenty-two patients completed the multimodal therapy with three courses of chemotherapy and following resection. Thirty patients did not complete the neoadjuvant chemotherapy, but were eventually resected.

On primary staging, all patients presented with tumours located in the distal third of the oesophagus within areas of specialized intestinal-type columnar epithelium (Barrett's oesophagus). Endoscopy and endosonography showed an invasion of all wall layers in all included patients. Eighty-one percent of patients had a perioesophageal or truncular lymphadenopathy on endosonography or CT scan. A significant difference in primary staging between both groups could not be detected.

Since a pretherapeutic risk assessment did not give any contraindications, all 152 patients started with the neoadjuvant polychemotherapy. Thirty patients ceased their therapy because of toxic side effects with regard to the pending operation. The chemotherapy-induced complications are listed in Table 2. All patients recovered under a conservative therapy without any residual symptoms or organ failure. Since a restaging of all patients did not show distant metastases and resectability of the primary tumour seemed to be possible, the 30 patients were resected like the 122 patients of the other group as described above.

Table 2 The amount of received chemotherapy and the incidence of the different toxicities

Toxicity	Number of patients (*n*)	Received chemotherapy (weeks)
Haematoxicity	3	7
Neurotoxicity	2	7
Cardiac	4	5
Renal	6	6
Mucositis	15	6

Chemotherapy-induced toxicities are the reasons for an interruption of the chemotherapy after 5 to 7 weeks in 30 patients

Postoperative morbidity and mortality did not show a significant difference in patients with 1 versus 3 cycles of chemotherapy. Mortality rate in the short chemotherapy group was 3% (one patient) because of anastomosis insufficiency, mediastinitis and consequently sepsis with multiorgan failure. In the regular chemotherapy group, mortality was 1.6% (two patients) because of pneumogen sepsis and anastomosis insufficiency, respectively. The median length of postoperative clinical stay was 17 days in both groups. There was not a significant association to the postoperative course or complications.

A summary of the pathological features of the tumours is outlined in Table 1. There is no significant difference between both groups concerning the depth of invasion, lymph node status, resection rate or response rate (Table 1). Patients receiving the full chemotherapy protocol showed a relatively higher response rate with a lower T and N category. Complete resection was possible in 78.5% of cases after 3 cycles versus 70% of cases with 1 cycle. However, these differences did not reach the level of significance. Overall, a significant correlation could be found for the response rate compared to resection rate and postoperative lymph node status ($p<0.001$, respectively). In both subgroups (3 cycles versus 1 cycle), this significant correlation between response and resection rate can also be detected ($p<0.001$, $p=0.004$, respectively). Even the relative number of recurrent tumour within the follow-up does not differ ($p=0.872$). Table 3 shows that the pattern of the recurrence is actually very similar between both subgroups. Interestingly, the number of local recurrence is even lower in the subgroup with a short neoadjuvant therapy, and the relative number of organ metastases is in both subgroups identical.

Survival is significantly correlated with the response rate of all 152 patients (Fig. 1). In responding patients, 5-year

Table 3 Recurrence rates and localisation according to number of chemotherapy cycles do not show a significant difference between the subgroups with 1 versus 3 cycles of neoadjuvant chemotherapy

Localisation of recurrent tumour	All patients, $n=152$	3 cycles chemotherapy $n=122$	1 cycle chemotherapy $n=30$
No recurrence	78 (51.3%)	63 (51.6%)	15 (50%)
Local recurrence	6 (3.9%)	6 (4.9%)	0 (0%)
Lymph node	19 (12.5%)	14 (11.5%)	5 (16.6%)
Organ metastases	49 (32.2%)	39 (32%)	10 (33.3%)

Even the incidence of distant metastases cannot be influenced by a higher preoperative dose of chemotherapy
$p=0.586$

survival can be detected in almost 70% of patients, whereas nonresponding patients show a 5-year survival rate of about 30%. In comparison of our two subgroups of patients, 5-year survival does not show a significant difference (Fig. 2) ($p=0.681$).

Discussion

Locoregional advanced Barrett's carcinoma has a poor overall survival rate with surgery alone.[14,15] A multimodal concept has to be discussed in these patients.[9,13] Several studies have shown that a multimodal therapy concept consisting of a neoadjuvant polychemotherapy and following resection in the treatment of Barrett's carcinoma can ameliorate long-term survival in responding patients.[7,9,10] Polychemotherapy in these studies follows the PLF protocol (cisplatin, 5FU, leucovorin) as also used in our study. However, the multimodal therapy is still under discussion because the behaviour of the adenocarcinoma of the oesophagus towards polychemotherapy is very heterogenous, and not even 50% of patients respond and therefore benefit from this treatment.[16] The other 50% of patients suffer from the time lag of 3 cycles of chemotherapy and the chemotherapy-induced side effects without any profit.

Responding patients benefit from a downsizing and a downstaging of the tumour, which result in higher complete resection rates and significantly longer survival rates, as shown in our study. In 8% of patients, we could detect a complete response without any residual tumour (pT0N0). We could see a downstaging of initially a clinical T3 category with invasion of all wall layers to a pT1 category in additional 6%. As also indicated by previous studies, the lymph node involvement, one of the strongest predictive values, also showed a downstaging from initially 81% of cases with clinical lymphadenopathy to 59% of cases with histopathologically involved lymph nodes.[4,15]

In fact, an initial cT_3 category is usually associated with a lymph node involvement in 80% of cases.[10] The downstaging of the T and the N category (Table 1) both shows

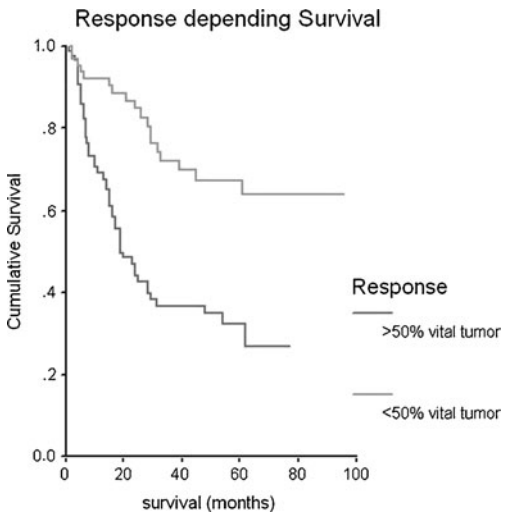

Fig. 1 Impact of tumour response after neoadjuvant chemotherapy on survival. In 65 out of 152 patients, a good response rate with less than 50% vital tumour cells in the postoperative pathological specimen could be found. These patients benefit from a significantly better 5-year survival rate. $p<0.001$

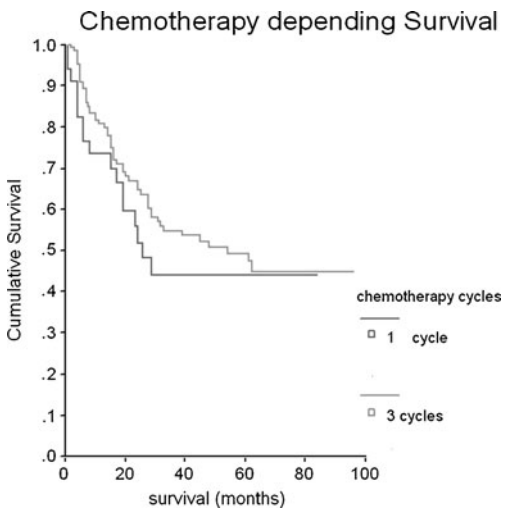

Fig. 2 The number of chemotherapy cycles is not significantly correlated with survival. $p=0.681$

the effectivity of the neoadjuvant chemotherapy similarly in both study groups.

With this study, we could show for the first time for solid tumours that the number of neoadjuvant chemotherapy cycles has to be newly discussed. In the literature, different chemotherapy agents were compared for chemotherapy response and long-term survival in terms of a neoadjuvant treatment. Thus, it could be shown that cisplatin can be replaced by oxaliplatin with the same outcome.[17–19]

In a French study, patients with gastric, cardia or oesophageal cancer were treated with 2–3 cycles of cisplatin and 5 FU in a neoadjuvant intention. There was a significant positive effect of the therapy on resection rate, lymph node involvement and long-term survival compared to patients without a neoadjuvant therapy.[20] However, a comparison of 2 versus 3 cycles of chemotherapy was not performed.

Up until now, we do not know when this prognostic positive effect is generated within the polychemotherapy and if 3 cycles of chemotherapy are necessary in the neoadjuvant setting. Concerning the time frame for generating a prognostic effect, the studies by Ott and Weber may give a hint. Their group analysed the possibility of an early response evaluation with a baseline PET scan within the initial staging and a second PET 2 weeks after starting the polychemotherapy. Comparing these two PET scans, an early metabolic evaluation of the tumour response seems to be possible. Tumours that present a metabolic reduction of at least 35% SUV rank among the responding tumours. A significant correlation with the downstaging, resection rate, histopathologic response and even long-term survival could be shown.[21,22] These results confirm our hypothesis that the effect of chemotherapy on long-term survival and the selection of a favourable biologic behaviour of the tumour is already generated very early during chemotherapy.

Our results suggest that 1 cycle of chemotherapy is sufficient in terms of neoadjuvant chemotherapy. Further preoperative chemotherapeutic treatment did not significantly influence histopathologic response, resection rate or long-term survival in our patients. Long-term survival was not superior in the long chemotherapy group compared to the other subgroup. Even the recurrence rate and the pattern of tumour recurrence did not change under higher doses of preoperative chemotherapy. Interestingly, local tumour control had a better outcome in the short chemotherapy group. Distant metastases occurred in both groups with the same incidence.

On the basis of these results, it would be possible to halve the time lag between initial diagnosis and surgical resection without passing on the prognostic advantages of a multimodal therapy. Time for recovery would presumably be shorter, and patients enter the surgical procedure in a better general condition. Severe toxic side effects of the chemotherapy did not induce a higher morbidity or mortality rate in our patients, but went along with a massive psychological and physical stress. A shorter chemotherapy has a positive psychological effect on the patient and improves the patients' quality of life within the treatment of this disease.

Our results do not prove that one chemotherapy cycle is sufficient for the neoadjuvant treatment of Barrett's carcinoma. In our opinion, further clinical data have to be collected on this subject for a definite answer to this question. However, we would recommend discussing the number of chemotherapy cycles with the patient especially if severe chemotherapy-induced toxic side effects occur, and the operability of the patient is at risk, because a profit of the second and third chemotherapy cycle could not be proven with our data.

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ORIGINAL ARTICLE

Is There an Association Between Hiatal Hernia and Ineffective Esophageal Motility in Patients with Gastroesophageal Reflux Disease?

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Abstract

Introduction The pathophysiology of gastroesophageal reflux disease is multifactorial, where esophageal motility is one of the factors implicated in its genesis. However, there is still no consensus on the existence of an association between esophageal dysmotility and hiatal hernia in patients with gastroesophageal reflux disease. The objective of this study was to establish the prevalence of esophageal dysmotility in patients with hiatal hernia and to determine if herniation is a factor related to esophageal dysmotility in patients with gastroesophageal reflux disease.

Methods The study included 356 patients with a clinical diagnosis of gastroesophageal reflux disease submitted to upper digestive endoscopy and esophageal functional diagnostics. Hiatal hernia was defined endoscopically by a distance equal to or greater than 2 cm between the diaphragmatic constriction and the squamocolumnar junction and esophageal dysmotility when the esophageal manometry identified the amplitude of the peristaltic waves in the distal esophagus as <30 mmHg and/or less than 80% of effective contractions. For univariate statistical analysis, the patients were divided into two groups: with and without hiatal hernia. Poisson regression models were used to estimate crude and adjusted prevalence ratios (PR) of esophageal dysmotility according to hiatal hernia.

Results Gastroesophageal reflux disease patients with hiatal hernia had a prevalence of esophageal dysmotility equal to 14.8% and those without hiatal hernia, a prevalence of 7.7% ($p=0.041$). Patients with hiatal hernia also showed a higher frequency of erosive esophagitis (47.5% versus 24.2%, $p<0.001$), lower low esophageal sphincter pressure (10.4 versus 13.10; $p<0.001$), and higher frequency of individuals with abnormal pH-metry values ($p<0.001$). The crude PR for esophageal dysmotility, according to the presence of hiatal hernia, was 1.92 (confidence interval (CI), 1.04–3.53; $p=0.037$), but this association did not persist when controlled for age, esophagitis, altered pH-metry, and altered low esophageal sphincter (adjusted PR, 1.69; CI, 0.68–4.15; $p=0.257$).

Conclusion Despite the prevalence of esophageal dysmotility in the hiatal hernia group being higher than that in the group without hiatal hernia, the association between these variables in individuals with gastroesophageal reflux disease disappeared when controlling for age, esophagitis, altered pH-metry, and altered low esophageal sphincter, leading us to believe that in these patients, hiatal hernia is not an independent risk factor for dysmotility.

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Keywords Hiatal hernia · Esophageal dysmotility · Gastroesophageal reflux disease · Erosive esophagitis · Risk factor

Introduction

Various factors contribute to the pathophysiology of gastroesophageal reflux disease including delayed gastric emptying, nature of the refluxed contents, incompetence of the lower esophageal sphincter, abnormality in the motor profile of the esophageal body—esophageal dysmotility or ineffective motility—and the presence of hiatal hernia.[1]

Various authors suggested that the presence of hiatal hernia has a limited role in etiopathogenesis of gastroesophageal reflux disease, even that it is not essential in the development of the disease.[2] However, the prevalence of hiatal hernia in patients with gastroesophageal reflux disease is high, varying between 50% and 94%,[2–5] while the frequency is substantial in individuals with erosive esophagitis and Barrett's esophagus.[2,5] Moreover, a positive correlation of hiatal hernia size with decrease in resting pressure of lower esophageal sphincter has been demonstrated in several publications.[6,7]

Another aspect related to the presence of hiatal hernia is the relationship with esophageal dysmotility, signifying that there is a peristaltic wave amplitude decrease in the distal esophagus in patients with hiatal hernia.[8,9] Contrary to this widely accepted idea, Cuomo et al. identified an increase in the amplitude of the peristaltic waves, stirring up even more controversy.[10]

Therefore, hiatal hernia has a proven influence on lower esophageal sphincter, suggesting that its presence affects the decrease of peristaltic wave amplitudes in the distal esophagus, but there are no studies that directly relate hiatal herniation with esophageal dysmotility. The aim of this study was to determine the prevalence of esophageal dysmotility in patients with gastroesophageal reflux disease and hiatal hernia, and to analyze the presence of hiatal hernia as an independent factor in the genesis of the motor alterations of the esophageal body in patients with gastroesophageal reflux disease.

Patients and Methods

Patients

In the period from January 2006 to May 2010, a cross-sectional study was conducted in the Laboratory of Esophageal Motility in our Department. The study involved 356 patients with a clinical diagnosis of gastroesophageal reflux disease (GERD)[11,12] submitted to upper digestive endoscopy and esophageal manometry. The sample of patients was divided into two groups: with hiatal hernia and without hiatal hernia. In 280 (78.65%) patients, 24-h esophageal pH-metry was additionally performed.

Exclusion Criteria

The patients excluded from the study were those previously submitted to surgical procedures of the esophagus and stomach, and those with known motor alterations of the esophagus (primary and secondary), peptic stenosis, and esophageal and/or gastric neoplasms. Medications that were known to alter gastric secretion and/or function were suspended for 7 days before esophageal manometry and esophageal pH-metry.

Upper Digestive Endoscopy

All patients were submitted to upper digestive endoscopy prior to esophageal manometry. At each endoscopy, location of the gastroesophageal junction was defined as the point where the proximal extent of the gastric rugal folds met with the tubular esophagus. The length of Barrett's epithelium was measured from this point to the highest point of the squamocolumnar junction.

A hiatal hernia was diagnosed when the crural impression was separated from the top of the gastric rugal folds by 2 or more centimeters.[13] Erosive esophagitis was classified according to the criteria of the Los Angeles classification,[14] and its presence or absence was taken into account for statistical analysis.

Esophageal Manometry

The pressure and the length of the lower esophageal sphincter, the amplitudes of the peristaltic waves in the distal esophagus, the percentage of effective contractions, and the profile of these waves were determined by EM. We utilized a Dynapack MPX816 manometry apparatus (Dynamed, São Paulo, Brazil) with an eight-channel water perfusion catheter, graduated in centimeters. The manual retrograde traction technique was utilized with the patient positioned in the supine position. Resting lower esophageal sphincter pressure was evaluated at the pressure inversion point, at the height of the mean expiratory point. Lower esophageal sphincter was considered structurally defective in case of one of the following manometric findings: resting pressure <6 mmHg, total length <2 cm, and abdominal segment <1 cm.[15] The esophageal body was evaluated with the sensors positioned at 3, 8, 13, and 18 cm above the proximal border of the lower esophageal sphincter, in ten swallowing of 5 ml of water and with an interval of 30 s between them. Esophageal dysmotility was considered

when the amplitude of the peristaltic waves of the distal esophagus was equal to or <30 mmHg and/or the percentage of these effective waves was <80%.[16]

24-h Esophageal pH-Metry

The examinations were performed with a portable pH meter (Sigma Instruments, Belo Horizonte, Brazil), which was connected to a catheter with an antimony electrode. Another external sensor, used for reference, was connected to the patient's chest. After calibration in solutions of pH 4 and 7, the catheter was introduced through one of the nostrils and positioned 5 cm above the proximal border of the lower esophageal sphincter, previously defined by stationary manometry, and left there for at least 18 h. The patients made daily notes about meals, postural changes, and symptoms during the examination period. The DeMeester score was used to quantify the exposure to esophageal acid during 24-h pH-metry, where pathologic reflux was considered as DeMeester score of >14.7.

Statistical Analysis

The comparison between the groups with and without hiatal hernia was performed using the *t* or Wilcoxon–Mann–Whitney tests for quantitative variables and the chi-squared test for qualitative variables. The association between hiatal hernia and esophageal dysmotility was evaluated by the prevalence ratio of esophageal dysmotility according to the presence or not of hiatal hernia, estimated by Poisson regression and using age, erosive esophagitis, altered pH-metry, and altered lower esophageal sphincter as co-variables. The results are expressed as mean±standard deviation and range for the continuous variables. Absolute frequency and percentage are given for categorical variables, and prevalence ratios (PR) are accompanied by the respective 95% confidence interval. Our samples sizes have a 0.56 power to detect a difference of 7.1% in the frequency of dysmotility of the populations with and without hiatal hernia. Values of $p<0.05$ were considered statistically significant. The study was approved by the Ethical Committee of Hospital de Clinicas de Porto Alegre and registered in Brazilian National Board of Education and Research.

Results

In the sample of 356 patients enrolled in the study, age varied between 14 and 86 years (overall mean, 48.6 years) and 201 (56.5%) were women. Thirty-nine patients (11.0%) showed esophageal dysmotility, and hiatal hernia was diagnosed in 162 patients (45.5%). Esophageal dysmotility diagnosed by stationary manometry was present in 24 (14.8%) patients out of 162 with hiatal hernia and 15 (7.7%) out of 192 patients without hiatal hernia ($p=0.041$).

Table 1 shows other characteristics of the patients with hiatal hernia (group 1, $n=162$) and without hiatal hernia (group 2, $n=194$). There was no statistically significant difference between group 1 and group 2 with regard to sex ($p=0.283$) or age, whether considered as continuous

Table 1 Description of individuals with and without HH, with respect to demographic variables and clinical characteristics

	With HH	Without HH	Comparison between the two groups	
Variable	($n=162$)	($n=194$)	Test	p*
Esophageal dysmotility	24 (14.8%)	15 (7.7%)	χ^2	0.041
Females	86 (53.1%)	115 (59.3%)	χ^2	0.283
Age[a]	48.9±14.5 (17–86)	46.6±14.0 (14–82)	*t*	0.134
Elderly (60 and older)	40 (24.7%)	37 (19.1%)	χ^2	0.245
Erosive esophagitis	77 (47.5%)	47 (24.2%)	χ^2	<0.001
LES (pressure in mmHg)[a]	10.41±6.56 (−2.6–45.4)	13.10±6.7 (2.4–33.8)	WMW	<0.001
LES (total length in cm)[a]	3.42±1.9 (1.0–6.6)	3.27±0.94 (1.0–5.8)	WMW	0.375
LES (abdominal length in cm)[a]	1.91±1.12 (0.0–5.0)	2.03±0.86 (0.0–4.2)	WMW	0.092
Altered LES	87 (53.7%)	85 (43.8%)	χ^2	0.071
Amplitude of waves (mmHg)[a]	78.44±36.6 (0–188)	89.74±36.77 (5.8–231.9)	WMW	0.003
No. of effective contractions[a]	9.5±1.2 (3–10)	9.5±1.5 (0–10)	WMW	0.578
DeMeester[b]	23.52±25.79 (0–194.7)	18.03±23.73 (0–154.1)	WMW	0.005
Abnormal pH-metry[b]	72 (59%)	57 (36.1%)	χ^2	<0.001

*$p<0.05$, statistically significant

[a] Mean±standard deviation and range

[b] One hundred fifty-eight individuals without HH, 122 with HH, with a total of 280 patients

variables (p=0.134) or using the classes "elderly" (60 years or older) and "non-elderly" (p=0.245). Erosive esophagitis was observed more often in individuals with hiatal herina (47.5%) than in those without hiatal hernia (24.2%) (p<0.001).

When comparing individuals with and without hiatal hernia in relation to lower esophageal sphincter, no difference was observed in total length of the sphincter (p=0.375) and length of the abdominal segment (p=0.092), but patients with hiatal hernia showed a significantly lower baseline pressure than individuals without hiatal hernia (p<0.001). The proportion of patients with altered lower esophageal sphincter did not differ between the patients with hiatal hernia (53.7%) or without hiatal hernia (43.8%; p=0.071). In the study of the esophageal body, there was a difference between the groups in amplitude (p=0.003), but not in number of effective contractions of peristaltic waves in the distal esophagus (p=0.578).

In relation to 24-h esophageal pH-metry, there was a difference in DeMeester score, which showed higher values in the group with hiatal hernia (p=0.005); the frequency of individuals with abnormal results was also greater in patients with hiatal hernia (p=0.001).

Various Poisson regression models were used to test the association of hiatal hernia with esophageal dysmotility. When a simple association was estimated, a statistically significant crude prevalence ratio of 1.92 (confidence interval (CI), 1.04–3.53; p=0.037) was found. Next, various models were used to estimate the adjusted prevalence ratio, taking into account confounding factors in the evaluation of hiatal hernia as a risk factor of esophageal dysmotility. The inclusion criteria for the selection of the co-variables were: co-variables not being in the casual path between hiatal hernia and esophageal dysmotility and a p value of less than 0.20 in the association tests with hiatal hernia and with esophageal dysmotility. By these criteria, the following potential confounding variables were considered: age (as continuous variable), erosive esophagitis (yes or not), altered pH-metry, and altered lower esophageal sphincter. The various models tested, combining sequentially hiatal hernia with co-variables, are shown in Table 2. The use of co-variables changed the estimate of the effect of hiatal hernia, which became statistically nonsignificant when adjusted for age, esophagitis, and alterations in pH-metry and lower esophageal sphincter (PR, 1.69; CI, 0.68–4.15; p=0.257).

Table 3 presents the detailed results of the more complete model, containing hiatal hernia, age, esophagitis, altered pH-metry, and altered lower esophageal sphincter as predictors for esophageal dysmotility. When controlling for the other variables present in this model, only alteration in pH-metry showed a statistically significant association with esophageal dysmotility. The adjusted risk of developing esophageal dysmotility was almost four times higher for gastroesophageal reflux disease patients with altered pH-metry than those patients without this characteristic (PR, 3.57; CI, 1.36–9.36; p=0.010). No interactions between hiatal hernia and the other co-variables were observed (p>0.35).

Discussion

Gastroesophageal reflux disease is a clinical condition caused by the presence of gastroduodenal contents in the esophagus and/or adjacent organs, which is responsible for the appearance of symptoms with or without tissue damage.[11,12] For a complete understanding of its physiopathology, an adequate clinical investigation is indispensable to attain specific knowledge of its etiology and to determine an effective treatment for each patient.

Hiatal hernia has been widely studied since the recognition of its association with gastroesophageal reflux disease. Initially, its presence was considered essential for the development of gastroesophageal reflux disease.[17] However,

Table 2 Effect of HH on the risk of developing ED in patients with GERD, estimated by prevalence ratios obtained in different Poisson regression models

Variables in the model	PR	95% CI	p*
HH	1.92	1.04–3.53	0.037
HH, age	1.86	1.01–3.44	0.047
HH, esophagitis	1.72	0.97–3.23	0.090
HH, age, esophagitis	1.64	0.88–3.08	0.120
HH, age, esophagitis	1.55	0.83–2.91	0.171
HH, altered pH-metry[a]	1.96	0.85–4.53	0.114
HH, age, altered pH-metry[a]	1.95	0.85–4.48	0.116
HH, age, altered pH-metry, altered LES[a]	1.81	0.77–4.25	0.173
HH, age, esophagitis, altered pH-metry[a]	1.82	0.76–4.34	0.178
HH, age, esophagitis, altered pH-metry, altered LES[a]	1.69	0.68–4.15	0.257

PR prevalence ratio

*p<0.05, statistically significant

[a] n=280

Table 3 Results of Poisson multiple regression analysis that considered age, HH, esophagitis, altered pH-metry, and ineffective LES together as predictors of ED

Predictor	PR	95% CI	p*
HH	1.69	0.68–4.15	0.257
Age	1.01	0.98–1.03	0.608
Esophagitis	1.27	0.58–2.78	0.544
Abnormal pH-metry	3.57	1.36–9.36	0.010
Altered LES	2.24	0.95–5.26	0.065

PR prevalence ratio

*$p<0.05$ statistically significant

current studies demonstrate that in patients with gastroesophageal reflux disease, the incidence of hiatal hernia can vary from 50% to 94%.[2–5] In the present study, of 356 patients with gastroesophageal reflux disease, only 45.5% had hiatal hernia. On the other hand, another important relation of hiatal hernia, since the appearance of pressure studies of the esophagus, is its positive association with a defective lower esophageal sphincter.[6,7,18]

The relation of esophageal dysmotility with gastroesophageal reflux disease and erosive esophagitis is well known,[5,19–21] but there is no consensus on the true etiology of esophageal dysmotility and if it is the cause or the consequence of gastroesophageal reflux disease. Defenders of the notion that the esophageal dysmotility represents a consequence of gastroesophageal reflux disease base their argument on the fact that ineffective esophageal motility improves after surgery.[22–24] In opposition to this idea, Xu et al. concluded that drug treatment with proton pump inhibitors does not show the same results on esophageal dysmotility,[25] suggesting that improvement provided by surgery would be secondary to the barrier effect caused by the antireflux valve, tending to the conclusion that this motor alteration is one of the causes of gastroesophageal reflux disease.

The objective of our study was to determine if the presence of hiatal hernia constitutes a predictive factor for esophageal dysmotility, independent of the above-mentioned ones. For this, the prevalence of esophageal dysmotility was evaluated in gastroesophageal reflux disease patients with hiatal hernia (HH+) and without hiatal hernia (HH−). The prevalence of esophageal dysmotility was significantly higher in the HH+ group (14.8%) than in the HH− group (7.7%; $p=0.041$). In this univariate analysis, the groups were similar with respect to age and sex, not taking the other variables into consideration. Still, in the group of patients with hiatal hernia, there were no patients with paraesophageal hernia, and only six patients had large hernias and just two of them had esophageal dysmotility. Because of this small number of patients, we did not perform the stratification of paraesophageal or large hernias, even though these patients have a higher incidence of esophageal dysmotility.[6]

The literature results are contradictory in relation to the association between HH and esophageal dysmotility. Ping et al. studied esophageal motility in patients with hiatal hernia (two groups) and in a control group, but the two groups with hiatal hernia included individuals with the presence of erosive esophagitis. The results showed a statistical difference with respect to amplitude of the waves in the distal esophagus and their frequency and duration between the groups with hiatal hernia and the control group.[8] Kasapidis et al. also studied groups with and without HH with regard to the esophageal body motility and, like Ping et al., compared only the absolute values of wave amplitudes, allowing the determination of the presence or absence of dysmotility of the esophageal body. In these studies, it is not possible to evaluate or estimate if hiatal hernia is an independent predictive factor for esophageal dysmotility. In our study, we carried out Poisson regression analyses to estimate the crude effect of hiatal hernia (only HH as predictor) and controlling for the confounding factors age, presence of erosive esophagitis, altered pH-metry, and ineffective lower esophageal sphincter.

The crude prevalence ratio of esophageal dysmotility for hiatal hernia was 1.92 (CI, 1.04–3.53; p, 0.037). After the including of age in the model, the prevalence ratio presented a small reduction (PR, 1.86; CI, 1.01–3.44; p, 0.047), still confirming the association obtained. However, when esophagitis, altered pH-metry, and altered lower esophageal sphincter were considered as well in the Poisson regression model, the association between hiatal hernia and esophageal dysmotility was not confirmed. In this model, the only statistically significant association with esophageal dysmotility was that of altered pH-metry. In other words, when controlling for other variables, the main factor that determines esophageal dysmotility is alteration in pH and not the presence of hiatal hernia.

It is important to remember that pH monitoring with the Bravo system is able to measure the pathological acid reflux for 48 h and thus is more sensitive in diagnosis. It is likely that with its use, the statistical difference in favor of pH monitoring, as the only single factor of risk for the presence of esophageal dysmotility, would be even greater. Because our service does not have this technology, we could not use it in our study.

Our results allow us to conclude that although the prevalence of esophageal dysmotility in patients with hiatal hernia is important and significantly greater than in patients without hiatal hernia, the effect of hiatal hernia on esophageal dysmotility disappears if other relevant factors such as age, esophagitis, altered pH-metry, and ineffective lower esophageal sphincter are taken into account.

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ORIGINAL ARTICLE

Sentinel Lymph Node Biopsy in Esophageal Cancer: Should It Be Standard of Care?

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Abstract
Introduction Sentinel node mapping is established in some superficial cancers but remains controversial in harder-to-access solid tumors. There are an increasing number of recent studies suggesting that isolated tumor cells have prognostic significance in predicting poor survival, in breast cancer, esophageal cancer, and others. It is for this reason that we have persevered with the sentinel lymph node concept in our esophagectomy cancer patients, and we report our results since 2008.
Methods Thirty-one of 32 consecutive patients underwent resection for invasive esophageal cancer along with sentinel lymph node retrieval (resection rate, 97%). Peritumoral injection of ^{99m}Tc antimony colloid was performed by upper endoscopy prior to the operation. A two-surgeon synchronous approach via a right thoracotomy and laparotomy was performed with a conservative lymphadenectomy. Sentinel lymph nodes were identified with a gamma probe both in and ex vivo, and sent off separately for three serial sections and immunohistochemistry with AE1/AE3.
Results The median patient age was 63.4 years (range, 45–75 years). Most patients (81%) had an adenocarcinoma, and 61% had received neoadjuvant therapy. At least one sentinel lymph node (median, 3) was identified in 29 of 31 patients (success rate, 94%). Sentinel nodes were present in more than one nodal station in 16 patients (55%). One false negative case led to a sensitivity of 90%. In 28 of 29 patients, the sentinel lymph node accurately predicted findings in non-sentinel nodes (accuracy, 96%).
Conclusions Sentinel lymph node biopsy is both feasible and accurate in esophageal resections with conservative lymphadenectomy. It allows targeted serial sectioning and immunohistochemical studies of those nodes and should become standard of care in patients undergoing esophagectomy for esophageal cancer.

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Introduction

The sentinel lymph node (SLN) concept describes the preferential lymphatic drainage of a primary tumor to a regional lymph node(s).[1] Since its inception by Morton in 1992, sentinel lymph node biopsy has become the gold standard for patients with melanoma and breast cancer. However, its use in other solid tumors has been more controversial with continued debate regarding its role, if any, in staging and treatment algorithms.[2–4]

Perhaps recent studies have strengthened the case for the routine use of sentinel lymph node biopsy in the treatment of esophageal cancer patients. First, we (and others) have

recently shown that occult tumor deposits in lymph nodes have prognostic significance for decreased survival.[5,6] These results have been replicated in larger studies in other solid tumor types such as breast cancer.[7] The smallest of the occult tumor deposits, isolated tumor cells, are on average 10 to 30 μm in size (0.01–0.03 mm), making their detection virtually impossible without the use of serial sections and immunohistochemistry. Sentinel lymph node biopsy is the only practical method in today's economic climate to identify the most important lymph nodes for more detailed histopathological analysis.

The second reason to establish this technique in esophageal cancer is to promote the introduction of improved sentinel lymph node tracers that may lead to better diagnostic and staging investigations. We do not agree that other imaging techniques "may be as accurate (as SLN biopsy) in detecting esophageal cancer metastases", as written by Zhang and colleagues in 2010.[8] Positron emission tomography/computed tomography (PET/CT) cannot distinguish positive lymph nodes in close proximity to the primary tumor due to the shine-through effect (a strong overlapping signal from the tumor),[9] nor can it detect positive lymph nodes less than 7 to 8 mm in size. It most certainly does not have the sensitivity required to detect lymph nodes containing only micrometastatic disease.[10] Similarly, endoscopic ultrasound is not able to identify occult tumor deposits within a lymph node from a fine needle aspirate.

We recently published our initial experience with sentinel lymph node biopsy with conservative lymphadenectomy in esophageal cancer and we showed that it was feasible to identify the SLN in 88% of cases, and it was accurate 92% of the time.[11] We have persevered with this approach because we do not believe the current pathological analysis for non-sentinel lymph nodes is sufficient. In this prospective study, our aims included evaluating the accuracy of the sentinel node in predicting the status of non-sentinel lymph nodes with a larger sample size, and determining the frequency of skip metastases in esophageal cancer.

Materials and Methods

Patient Selection and Preparation for Surgery

Thirty-two consecutive patients undergoing a surgical resection for invasive squamous cell carcinoma or adenocarcinoma of the esophagus were selected for the study. These patients were recruited between June 2008 and March 2011, and include 17 patients from our prior publication.[11] All operations were performed or closely supervised by one of five surgeons who are involved with our unit. The study was approved by the Research Ethics Committee at the Royal Adelaide Hospital, Adelaide, South Australia.

Preoperative clinical staging included upper gastrointestinal endoscopy, computed tomography scans (chest, abdomen, and pelvis), PET/CT scans, endoscopic ultrasonography (if minimal stricturing), and diagnostic laparoscopy (for gastroesophageal junction tumors). Selected patients (T2 or greater) were treated with neoadjuvant therapy according to protocol.[12] This consisted of two cycles of cisplatin (80 mg/m^2 on day 1) and 5-FU (800 mg/m^2 continuous infusion for 5 days) during weeks 1 and 5 of radiotherapy, plus 25 fractions of radiotherapy (over 5 weeks) to a total of 45 Gy. Patients underwent surgical resection 5 to 6 weeks after completion of neoadjuvant therapy.

Lymphoscintigraphy and Surgery

As previously described, peritumoral injection of four 1-ml aliquots of 10 MBq ^{99m}Tc antimony colloid (Lymphflo), maximum dose 40 MBq, were undertaken once the patient was under general anesthetia immediately before surgery. At endoscopy, injections were performed into the submucosal layer at both the proximal and distal margins (if possible) of the tumor.[13] In accordance with our Ethics Review Board, a licensed nuclear medicine physician (D.B.) transported and injected the radioactive tracer.

Esophagectomy was usually performed by a two-surgeon synchronous Ivor-Lewis technique via a right antero-lateral thoracotomy and an upper midline laparotomy, as described previously.[14] A gamma probe (gammasonics MK2) was used to identify any sentinel lymph node(s) in both the upper abdomen and thorax after mobilization of the esophagus and stomach. Readings were taken with the probe tip directed away from the tumor to minimize background interference. A sentinel node was defined in vivo as any node with an activity twice that of surrounding tissue.[1,13] Readings were also taken after esophageal and gastric resection to identify any residual sentinel node(s) because it is our practice to perform a conservative lymph node dissection (removal of all nodes adjacent to the tumor) rather than a two-field radical lymphadenectomy.[15] Continuity of the gastrointestinal tract was restored by either a handsewn or stapled end-to-side esophago-gastrostomy, depending on surgeon preference.

Specimen Handling and Pathology

Each specimen was dissected on the back table in the operating room by S.K.T. Lymph node stations were removed sequentially from the specimen. Using the

EANM-EORTC guidelines for sentinel node diagnosis in melanoma, a sentinel node was defined ex vivo as the hottest node plus any other hot nodes containing more than 10% of the activity in the hottest node in the lymphatic basin.[1] In our feasibility study, we had found that all sentinel nodes contained 20% or more of the activity of the hottest node.[11] Each lymph node station and sentinel node was sent separately for pathological analysis.

Non-sentinel lymph nodes were bisected once, fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E) according to standard procedures. Sentinel lymph nodes were bisected along their longitudinal axis, or cut into 2- or 3-mm slices if thicker than 5 mm. On the first section, one slide was stained with H&E, and the other with the monoclonal epithelial antibody AE1/AE3 (DAKO, Carpinteria, CA) for immunohistochemistry (IHC).[16] Sections of primary tumors were used as positive controls with each run, and a negative control (primary antibody omitted) was also included.

Sentinel lymph nodes that remained tumor free by both H&E and IHC on the first section had a minimum of two further serial step sections performed.[17–19] A lymph node metastasis was defined as a metastasis >2 mm in size (pN1). A micrometastasis was defined as a metastasis >0.2 mm and ≤2 mm [pN1mi(sn)], while isolated tumor cells were defined as single tumor cell(s) or cluster(s) of tumor cells ≤0.2 mm in size [pN0(i+)(sn)].[20–22] Strict criteria were used to designate a positive cell(s) as an isolated tumor cell(s), including increased cell size, enlarged nuclear size, and increased nuclear/cytoplasmic ratio.[21]

Statistical Analysis

Data were collected prospectively. Calculations were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA). The Chi-square test was used to compare groups, if applicable. The sensitivity, specificity, and accuracy of sentinel lymph node biopsy were calculated by the standard definitions.[23] Statistical significance was set at the 5% level.

Results

Patient and Tumor Characteristics

One patient who had undergone neoadjuvant therapy was deemed unresectable at the time of operation because his tumor was invading the right atrium (resection rate, 97%). The median patient age of the remaining patients was 63.4 years (range, 45–75 years), and 28 of 31 patients were male. The average body mass index in our patient population was 28 kg/m^2, with eight patients above 30 kg/m^2 and two above 40 kg/m^2. Tumor characteristics are listed in Table 1. Twenty-five of 31 patients (81%) had an adenocarcinoma, and the majority of these (64%) were lower esophageal tumors (Siewert type I). Nineteen patients (61%) underwent neoadjuvant therapy. Of these, six (32%) had a complete pathological response with no residual viable tumor cells on final conventional pathology (i.e., without taking into account the results of immunohistochemistry).

Table 1 Patient and tumor characteristics (n=31)

Variable	No. patients (%)
Histology	
Adenocarcinoma	25 (81)
Squamous cell carcinoma	6 (19)
Neoadjuvant therapy	
No	12 (39)
Yes	19 (61)
Tumor location	
Middle 1/3 esophagus	3 (10)
Lower 1/3 esophagus	22 (71)
GOJ[a]	6 (19)
Grade of differentiation	
Well/moderate (G1+G2)	15 (48)
Poor/undifferentiated (G3+G4)	14 (45)
Not assessable	2 (7)
pT-stage	
T0[b]	6 (19)
T1a	6 (19)
T1b	6 (19)
T2	4 (13)
T3	9 (30)
pN-stage	
N0	24 (77)
N1	4 (13)
N2	3 (10)
Vascular invasion	
No	25 (81)
Yes	6 (19)
Perineural invasion	
No	24 (77)
Yes	3 (10)
Not reported	4 (13)
Barrett's esophagus	
No	9 (29)
Yes	22 (71)

[a] GOJ = gastroesophageal junction

[b] T0=no residual viable tumor cells

Sentinel Node Identification

The sentinel lymph node detection rate using lymphoscintigraphy was 94% (29 of 31 patients). One of the two patients (both Siewert type I adenocarcinomas) in whom we could not identify a sentinel lymph node had had extensive prior upper gastrointestinal surgery. The second patient was morbidly obese with a body mass index of 42. In the remaining 29 patients, there were 92 sentinel lymph nodes, with a median of three lymph nodes per patient (range, 1–8 lymph nodes). A total of 438 lymph nodes were resected (as identified by the pathologist) with a median of 14 per patient (range, 4–31 lymph nodes).

The majority of sentinel lymph nodes were located in one of the following lymph node stations (in conjunction with a conservative lymphadenectomy): lower para-esophageal, left paracardial, and left gastric artery (Fig. 1). In patients with a Siewert type I tumor, the sentinel lymph nodes were mostly located in the para-esophageal tissue (75%) although in 31% of patients, sentinel nodes were found on both sides of the diaphragm. In Siewert type II tumors, the sentinel nodes were located more often in the peri-gastric tissue (83%). Sixteen patients (55%) had sentinel nodes present in more than one lymph node station. Nine of 29 patients (31%) had sentinel lymph nodes identified in the tumor basin once the esophageal cancer and adjacent lymph nodes had been removed (in the para-esophageal, celiac artery, and carinal lymph node locations). These were all negative for metastasis except for one celiac artery sentinel node.

Accuracy of Sentinel Lymph Node(s)

Overall, sentinel lymph nodes were significantly more likely to contain tumor than non-sentinel nodes: 13 of 92 (14%) positive sentinel nodes versus 11 of 346 (3%) positive non-sentinel nodes ($P<0.001$). A total of 13 sentinel lymph nodes were positive in nine patients (9/29, 31%). Eight of these nodes contained overt metastases, three had micrometastatic disease, and two had isolated tumor cells.

The accuracy of the sentinel lymph node procedure in predicting the status of non-sentinel nodes is shown in Table 2. Six patients (21%) had overt metastases in the sentinel lymph node(s), and four of these had corresponding positive non-sentinel nodes on routine H&E staining. Three patients had positive sentinel nodes on IHC staining, two of whom had micrometastatic deposits, and one with isolated tumor cells only. The non-sentinel nodes for all three of these patients were negative on routine lymph node analysis. We had one false negative result in our series. This particular patient had an advanced long 10-cm esophageal tumor with overt metastases in four non-sentinel nodes, but no metastatic deposits in two identified sentinel nodes. The sensitivity of sentinel lymph node biopsy in our series was therefore 90% (9/10). The overall accuracy of sentinel lymph node biopsy was 96% (28/29) using immunohistochemistry and a minimum of three serial sections for all sentinel lymph nodes.

Discussion

Sentinel lymph node biopsy was performed successfully in 29 of 31 (94%) consecutive esophageal cancer patients. A median of 3 sentinel nodes per patient were removed, and the diagnostic accuracy based on SLN status was 96%. SLN mapping was successful even with a *conservative* lymphadenectomy, an average body mass index of 28, and the addition of neoadjuvant therapy in 61% of patients.

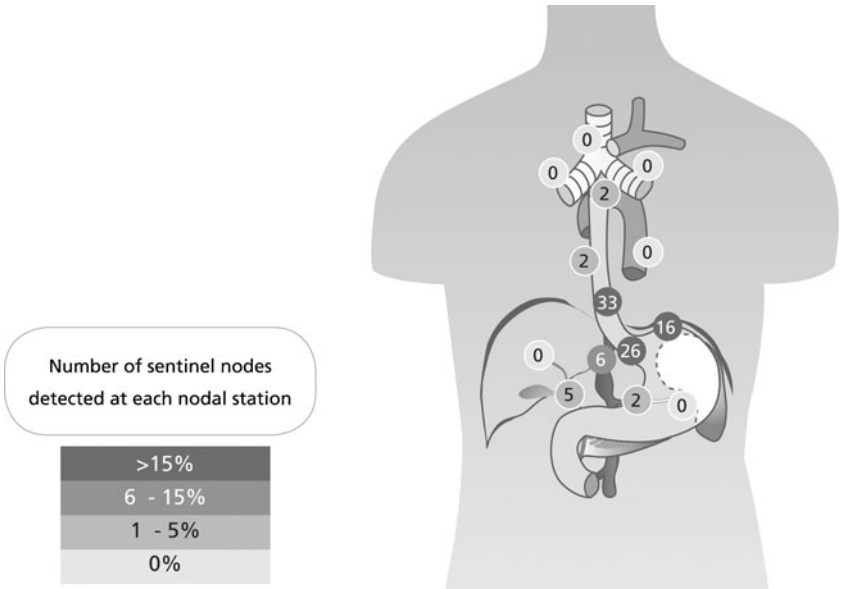

Fig. 1 Graphical depiction of 92 sentinel lymph nodes in 29 esophageal cancer patients. Sentinel nodes were most commonly located in the lower para-esophageal, left paracardial, and left gastric artery lymph node stations

Table 2 Accuracy of the sentinel node in predicting the status of non-sentinel nodes (n=29)

	Overall nodal pathology	
	H&E[a] positive	Negative
Sentinel lymph node		
H&E positive	4	2
IHC[b] positive		3
Negative	1	19

[a] H&E = hematoxylin and eosin stain (routine pathology)

[b] IHC=immunohistochemistry (with epithelial antibody AE1/AE3)

Four studies (with a sample size of at least 20 patients) using a radio-guided approach to find sentinel lymph nodes in esophageal cancer have reported success rates of 85% to 100%, and accuracy rates of 88% to 96%.[13,24–26] These results are superior to the two existing studies in the literature which used the blue dye method in esophageal cancer patients.[27,28] Grotenhuis et al. identified a sentinel lymph node in 98% of patients, but they had an unacceptably high false negative rate of 15% and an overall accuracy rate of only 85%.[27] Similarly, Bhat et al. detected a SLN in 81% of patients with an accuracy rate of only 75%.[28] Both studies had a high number of pT3 tumors (65% and 72%, respectively) but radiocolloid tracer is uniformly regarded as superior to the dye method for SLN biopsy in most solid tumor types.[4,13,29]

There is no doubt that obesity contributed to increased difficulty in our patients with surgical resection and identification of sentinel lymph nodes. It is also noteworthy that, despite some reports to the contrary, the addition of neoadjuvant therapy prior to surgical resection did not affect our results. In fact, all nine patients with overt or occult tumor in their sentinel nodes had undergone neo-adjuvant therapy. Several authors have found a significant correlation between a higher metastatic area within the node, and lower radioisotope counts.[30,31] However, these studies have used the 100 nm ^{99m}Tc-tin colloid particles. We believe that smaller particles, such as 10±3 nm ^{99m}Tc-antimony trisulfide colloid, are able to penetrate metastatic lymph nodes, contributing to our high accuracy rate in the setting of advanced esophageal cancer.

With the use of three serial sections and immunohisto-chemistry on negative sentinel lymph nodes, 14% (3/22) of patients were upstaged: two from pN0 to pN1mi(sn), and one from pN0 to pN0(i+)(sn). Lamb et al. also found that 12% (3/25) of pN0 patients were upstaged following IHC analysis in their landmark study.[13] We recently published results showing that node-negative patients with either isolated tumor cells or micrometastases detected by IHC have a significantly decreased 5-year survival compared to those who remain node negative following additional analysis of their lymph nodes (33% and 40% versus 60%, respectively).[5] These patients may benefit from adjuvant therapy. A further patient in our series was up-graded from pN1 (two positive lymph nodes) to pN2 (three or more positive lymph nodes) with the identification of a micro-metastasis within a sentinel lymph node. This patient went on to receive adjuvant chemoradiotherapy and is currently well with no evidence of tumor recurrence 21 months later.

Much of the lack of enthusiasm surrounding the routine use of sentinel lymph node biopsy in esophageal cancer is because, at present, it cannot alter or limit the extent of lymphadenectomy in the same way as is seen in breast cancer and melanoma. Most hospitals, like ours, do not have a dedicated pathologist who is willing to perform *intraoperative* rapid immunohistochemical analysis on the sentinel nodes. And in esophageal cancer, preoperative access to sentinel nodes may be as invasive, and as morbid, as the operation itself. But, if one agrees that isolated tumor cells have prognostic significance in esophageal cancer and, as shown above, are detected in 12–14% of node-negative patients using serial sections and immunohistochemistry, then the sentinel lymph node concept becomes the only practical method of improving pathological staging. So, although sentinel node biopsy has not yet been shown to minimize the extent of lymphadenectomy, it may influence postoperative therapy for a significant number of patients.

Another criticism in the literature regarding sentinel lymph node biopsy in esophageal cancer is the reported high incidence of skip metastases, although most of these findings have been in patients with squamous cell carcinomas. It is well-known that lower esophageal cancers and junctional tumors (albeit, mostly adenocarcinomas) disseminate in a longitudinal fashion (rather than segmental) to lower mediastinal and abdominal lymph nodes.[32–34] And, sentinel lymph nodes in esophageal cancer are often multiple and found in more than one nodal station (range, 21% to 55%).[13,27] However, it is important not to confuse multiple sentinel nodes with true "skip metastases". Tumor cells in esophageal cancer follow a predictable linear drainage pattern to "first tier" nodal stations, and over 90% of them seem to be within 3 cm of the primary tumor.[35] Similar to Lamb's study,[13] every one of our 29 patients had a sentinel node in one of the "first tier" lymph node groups: lower para-esophageal, right or left paracardial, or left gastric artery. One patient in our study was found to have a positive celiac lymph node in conjunction with a negative left gastric artery sentinel node. But, as celiac lymph nodes are now considered regional nodes according to the 7th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging manual,[22] not even this can be called a skip metastasis.

Probably the biggest limitation with sentinel lymph node biopsy in esophageal cancer is the variable type of sentinel lymph node tracer legislated for clinical use in each country.[30] The vastly different particle sizes hinder wide application of the concept and creation of a uniform protocol. For example, Japan's ^{99m}Tc-tin colloid (100 nm in size) allows for lymphoscintigraphy 24 h prior to surgical resection,[26] while other smaller radiocolloids (like Australia's ^{99m}Tc-antimony trisulfide colloid) have much shorter transit times in the sentinel nodes.[1,30] Facilitating preoperative lymphoscintigraphy in between endoscopic peritumoral injection and same-day surgery is often not practical. Future efforts should be made to design better sentinel lymph node tracers with dual imaging capabilities and, ultimately, the ability to differentiate a positive node (containing only micrometastatic tumor deposits) from a negative one prior to the initiation of any treatment.

Conclusion

Sentinel lymph node biopsy is both feasible and accurate in esophageal resections with conservative lymphadenectomy. There is no doubt that SLN biopsy improves pathological staging and may then influence postoperative treatment decisions. Further work is needed to optimize sentinel node tracer type particularly with recent advances in imaging technology, but it is our opinion that SLN biopsy should become standard of care in patients with esophageal cancer. Whether it will ever be useful as a tool for tailoring a lymphadenectomy is a question for the future.

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ORIGINAL ARTICLE

Prognostic Implications of Lymphadenectomy in Esophageal Cancer After Neo-adjuvant Therapy: a Single Center Experience

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Abstract
Introduction The objective of this study is to explore the prognostic implications of lymphadenectomy in esophageal cancer patients after neo-adjuvant therapy.
Methods Retrospective review of a prospectively maintained database identified esophageal cancer patients with locoregional disease who received neo-adjuvant therapy and surgery. Patients were grouped based on the number of nodes resected, pathological lymph node status, and percentage of positive nodes. Kaplan–Meier curves were used to analyze overall survival (OS) and disease-free survival (DFS). Log-rank test was used to compare survival between groups.
Results Eighty-four patients formed the study group. Patients with ≥18 nodes resected had a significantly longer median OS than those with <18 nodes resected (68.6 vs. 29.6 months; $p=0.014$). Lymph node-negative patients had significantly longer median OS (51.4 vs. 27.4 months; $p=0.025$) and DFS (45.3 vs. 12.9 months; $p=0.03$) when compared to lymph node-positive patients. Patients with a percentage of positive nodes <0.25 had a significantly longer median OS (31.1 vs. 17.8 months; $p=0.015$) and DFS (21.7 vs. 8.9 months; $p=0.021$) than patients with ≥0.25% positive.
Conclusion Extent of lymphadenectomy, percentage of positive nodes, and pathological lymph node status are significant prognostic markers in patients who undergo esophagectomy after neo-adjuvant therapy.

Keywords Lymph nodes · Survival · Chemoradiation

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Introduction

Esophageal cancer is a leading cause of cancer death and accounted for 406,800 deaths worldwide in 2008.[1] The current 5-year survival rate is 17%.[2] Surgery is the mainstay of treatment for locoregional disease; however, adjuvant and neo-adjuvant therapy have been recommended to improve outcomes. Despite conflicting evidence from randomized controlled clinical trials, many patients with locally advanced esophageal cancer are currently treated with neo-adjuvant therapy followed by surgical resection.[3]

Recently, a survival benefit has been demonstrated in patients receiving primary surgery with extended lymph node resection.[4–6] The role of lymphadenectomy after neo-adjuvant therapy has not been extensively studied. Addi-

tionally, studies have shown that pathological lymph node status and percentage of positive nodes, commonly described as the lymph node ratio, are significant prognostic indicators.[7–11] The aim of this study is to examine the impact of pathological lymph node status, extent of lymphadenectomy, and lymph node ratio on survival in patients who received neo-adjuvant therapy.

Methods

A prospective database of patients undergoing esophagectomy is maintained at Creighton University Medical Center. After institutional review board approval, the database was queried to identify patients who underwent elective resection for esophageal cancers following neo-adjuvant therapy between June 1, 2004 and December 31, 2010. Patients with stage IV disease were excluded.

The cohort was divided according to lymph node status and extent of lymphadenectomy. Among lymph node-positive patients (LNP), a lymph node ratio (LNR) was calculated by dividing the number of positive nodes by the total number of nodes resected. From these groups, the data were analyzed sequentially to examine the role of nodal status, extent of lymphadenectomy, and LNR on overall survival (OS) and disease-free survival (DFS). Points for analysis were determined after a review of the literature. OS was defined as the period between diagnosis and death/follow-up, and DFS was defined as the period between surgery and recurrence/death/follow-up.

Preoperative staging was established by endoscopic ultrasound, esophagogastroduodenoscopy with biopsies, CT, and/or PET scans. Patients were re-evaluated with CT or PET scans after neo-adjuvant therapy to rule out metastatic progression. The choice of operative technique was based on tumor location and patient co-morbidities with the objective of obtaining clear surgical margins. Emphasis was placed on maximizing lymph node harvest. The lymphadenectomy performed adheres to published techniques of nodal dissection for transhiatal, transthoracic, and thoracoscopic laparoscopic minimally invasive esophagectomies, respectively.[12–14] The specimen was assessed for margins with frozen sections. Lymph nodes were histologically examined in adherence to guidelines that have been previously described.[15] Briefly, nodes were carefully identified and sectioned if larger than 3 mm. All nodes were fixed in formalin and stained with hematoxylin and eosin for histological analysis. Postoperative follow-up included clinical visits and CT scans at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months after surgery. Additionally, a registered nurse corresponded with the patient, patient's family, or oncologist to complete survival and recurrence data.

Statistical Methods

SPSS version 17 (SPSS Inc., Chicago, IL, USA) was utilized for statistical analyses. OS and DFS were analyzed using Kaplan–Meier curves. The log-rank test was used to compare survival between groups. Chi-square analysis was used to compare categorical variables while the Mann–Whitney and ANOVA tests were employed for continuous variables. Preoperative, intraoperative, and postoperative variables were included in a Cox regression model to identify independent predictors of survival. *P* values less than 0.05 were considered statistically significant.

Results

Study Subjects

One hundred and twenty-five patients underwent esophagectomy for adenocarcinoma or squamous cell carcinoma during the study period. All surgeries were performed by the senior author (SKM). After excluding emergent procedures (two), no neo-adjuvant therapy (35), and stage IV disease (four), 84 patients formed the study cohort (Fig. 1). Table 1 depicts the type of surgical technique and associated lymph node harvest.

Lymph Node Status

Significant differences were found in both OS ($p=0.025$) and DFS ($p=0.03$). Median OS for lymph node-negative (LNN) patients was 51.4 months (39.1–63.7 months) compared to 27.4 months (12.8–41.9 months) for LNP patients (Fig. 2). Median DFS for LNN was 45.3 months (quartiles not

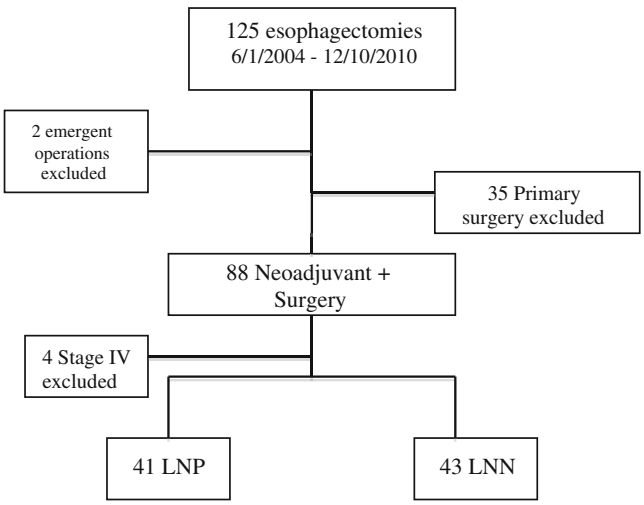

Fig. 1 Eighty-four patients formed the study cohort

Table 1 Nodal harvest with surgical technique

Surgical Technique	Mean number of nodes resected
Open transhiatal (n=20)	14.4
Open transthoracic (n=24)	22.0
Thoracoscopic laparoscopic minimally invasive (n=35)	19.0
Laparoscopic transhiatal (n=5)	16.6

Nodal harvest for surgical technique was compared. The only significant difference was between open transhiatal and open transthoracic esophagectomy (p=0.019)

available) compared to 12.9 months (0.9–24.9 months) in LNP (Fig. 3). As expected, LNP patients had more extensive disease (p=<0.001) and consequently a greater proportion received adjuvant therapy (p=0.002) (Table 2).

Extent of Lymphadenectomy

The mean number of nodes removed was 18.6 (range 5–53). Survival between groups was compared at ≥10, ≥15, and ≥18 nodes resected. There was a trend toward improved OS when ≥10 (p=0.203) and ≥15 (p=0.098) were resected. This difference became significant (p=0.014) when ≥18 nodes were resected. Median OS for patients with <18 nodes resected was 29.6 months (23.1–36.0) compared to 68.6 months (quartiles not available) for patients with ≥18 nodes removed (Fig. 4). DFS did not reach significance at any point of analysis. There were no significant differences in perioperative variables between the groups (Table 3).

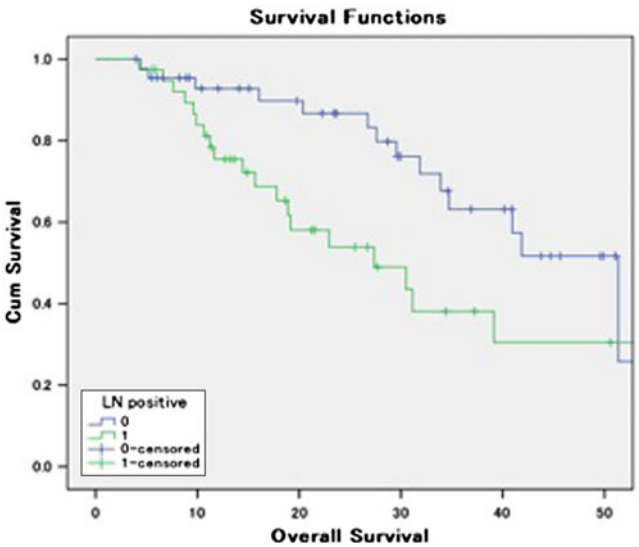

Fig. 2 Kaplan–Meier overall survival—lymph node status (0 = LNN; 1 = LNP; p=0.025). 0=51.4 months (median survival). 1=27.4 months (median survival)

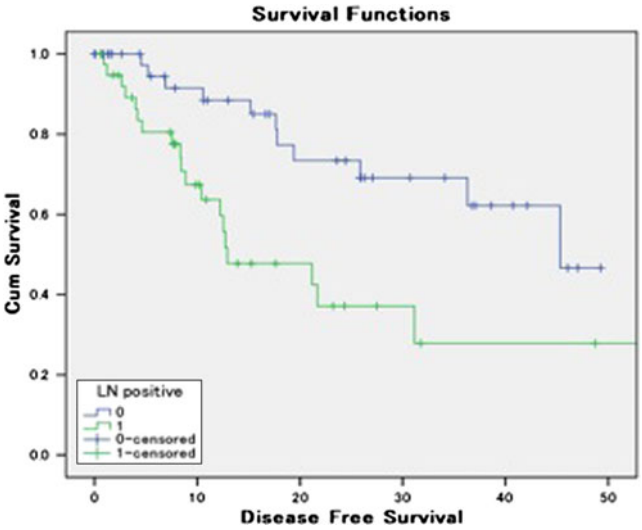

Fig. 3 Kaplan–Meier disease-free survival—lymph node status (0 = LNN; 1 = LNP; p=0.03). 0=45.3 months (median survival). 1=12.9 months (median survival)

Lymph Node Ratio

The LNP group was arranged by LNR. The mean number of positive nodes and total nodes resected were 3.8 and 18.4, respectively. OS and DFS were examined at ratios of ≥0.2 and ≥0.25. A significant difference in OS (p=0.015) and DFS (p=0.021) was found at LNR ≥0.25. Median OS was 31.1 months (17.7–44.6 months) in the <0.25 group compared to 17.8 months (8.7–26.7 months) in the ≥0.25 group (Fig. 5). Median DFS was 21.7 months (2.2–41.2 months) in the <0.25 group compared to 8.9 months (2.1–15.6 months) in the ≥0.25 group (Fig. 6). There was a trend toward significance at an LNR of ≥0.2 in both OS (p=0.054) and DFS (p=0.089). Median OS was 31.1 months (16.1–46.1 months) in the <0.20 group compared to 17.8 months (11.8–23.8 months) in the ≥0.20 group. Median DFS was 21.2 months (4.9–37.5 months) in the <0.20 group against 10.4 months (6.1–14.7 months) in the ≥0.20 group. RO resection (p=0.033) and coronary artery disease (p=0.048) were significantly different between the groups (Table 4).

Independent Predictors of Survival

A Cox regression analysis of preoperative, intraoperative, and postoperative factors demonstrated that the total number of nodes resected (p=0.004) and positive lymph node status (p=<0.001) were significant predictors of survival.

Table 2 Lymph node status

Variable	Lymph node positive (*N*=41)	Lymph node negative (*N*=43)	*p* value
Age (median)	63.0 years	61.6 years	0.460
Gender	Male—37 (90%) Female—4 (10%)	Male—35 (81%) Female—8 (19%)	0.247
Smokers	29 (71%)	28 (65%)	0.582
Diabetes mellitus	11 (27%)	7 (16%)	0.239
Hypertension	21 (51%)	21 (49%)	0.827
Coronary artery disease	7 (17%)	6 (15%)	0.693
Pathology	EAC—36 (88%)[a] SCC—5 (12%)[b]	EAC—36 (84%) SCC—7 (16%)	0.593
Type of surgery	TTE—12 (29%)[c] THE—11 (27%)[d] MIE—16 (39%)[e] Lap THE—2 (5%)[f]	TTE—12 (28%) THE—9 (21%) MIE—19 (44%) Lap THE—3 (7%)	0.679
Number of nodes resected (median)	18.4	18.8	0.554
RO resection	39 (95%)	42 (98%)	0.529
Postoperative stage	0–0 I—0 II—18 (44%) III—23 (56%)	0–17 (40%) I—10 (23%) II—16 (37%) III—0	**<0.001**
Adjuvant therapy	21 (51%)	8 (19%)	**0.002**
Intraoperative morbidity	8 (20%)	9 (21%)	0.872
Postoperative morbidity	24 (59%)	27 (63%)	0.690
Perioperative mortality	1 (2%)	2 (5%)	0.585

[a] Adenocarcinoma

[b] Squamous cell carcinoma

[c] Open transthoracic esophagectomy

[d] Open transhiatal esophagectomy

[e] Thoracoscopic laparoscopic esophagectomy

[f] Laparoscopic transhiatal esophagectomy

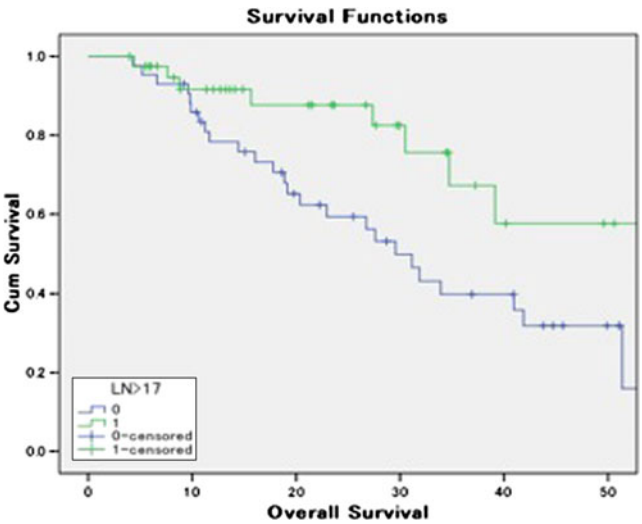

Fig. 4 Kaplan–Meier overall survival—extent of lymphadenectomy (0=<18; 1=≥18; p=0.014). 0=29.6 months (median survival). 1=68.6 months (median survival)

Discussion

The incidence of adenocarcinoma in white males in the USA has increased by more than 450% since 1975.[16] The current 5-year survival of 17.0% (SEER) is only slightly better than the 5% reported in 1977.[2,17] In the USA, an estimated 14,500 deaths were attributed to esophageal cancer in 2010.[2]

Surgical resection remains the most definitive treatment for locoregional esophageal cancer. Although historically associated with high morbidity and mortality, high volume centers now report an operative mortality of less than 5%.[18] The high recurrence rates with surgery alone have led to increasing use of adjuvant and neoadjuvant therapy. Despite conflicting results from several randomized trials comparing surgery alone with neoadjuvant therapy followed by surgery,[19–23] the latter has been accepted as the standard of care for locoregional esophageal adenocarcinoma.[3]

Table 3 Extent of resection

Variable	Lymph nodes resected <18 (N=43)	Lymph nodes resected ≥18 (N=41)	p value
Age (median)	63.0 years	61.5 years	0.570
Gender	Male—37 (86%) Female—6 (14%)	Male—35 (85%) Female—6 (15%)	0.929
Smokers	31 (72%)	26 (63%)	0.395
Diabetes mellitus	9 (21%)	9 (22%)	0.909
Hypertension	23 (53%)	19 (46%)	0.513
Coronary artery disease	8 (19%)	5 (12)	0.417
Pathology	EAC—37 (86%)[a] SCC—6 (14%)[b]	EAC—35 (85%) SCC—6 (15%)	0.929
Type of surgery	TTE—11 (26%)[c] THE—15 (35%)[d]	TTE—13 (32%) THE—5 (12%)	0.081
	MIE—14 (33%)[e]	MIE—21 (51%)	
	Lap THE—3 (6%)[f]	Lap THE—2 (5%)	
Positive nodes on resection	17 (40%)	22 (54%)	0.194
RO resection	42 (97%)	39 (95%)	0.529
Postoperative stage	0–11 (26%) I—7 (16%)	0–7 (17%) I—4 (10%)	0.281
	II—14 (32%)	II—18 (44%)	
	III—11 (26%)	III—12 (29%)	
Adjuvant therapy	16 (37%)	13 (32%)	0.653
Intraoperative morbidity	8 (19%)	9 (22%)	0.703
Postoperative morbidity	28 (65%)	23 (56%)	0.398
Perioperative mortality	2 (5%)	1 (2%)	0.585

[a] Adenocarcinoma

[b] Squamous cell carcinoma

[c] Open transthoracic esophagectomy

[d] Open transhiatal esophagectomy

[e] Thoracoscopic laparoscopic esophagectomy

[f] Laparoscopic transhiatal esophagectomy

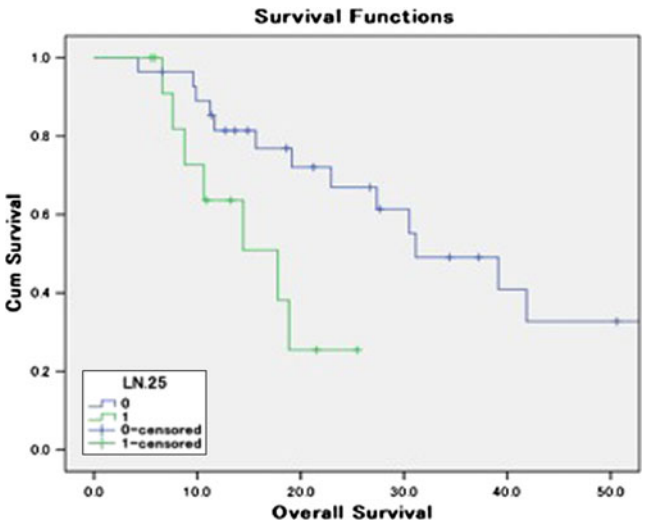

Fig. 5 Kaplan–Meier overall survival—lymph node ratio (0=<0.25; 1=≥0.25; p=0.015). 0=31.1 months (median survival). 1=17.8 months (median survival)

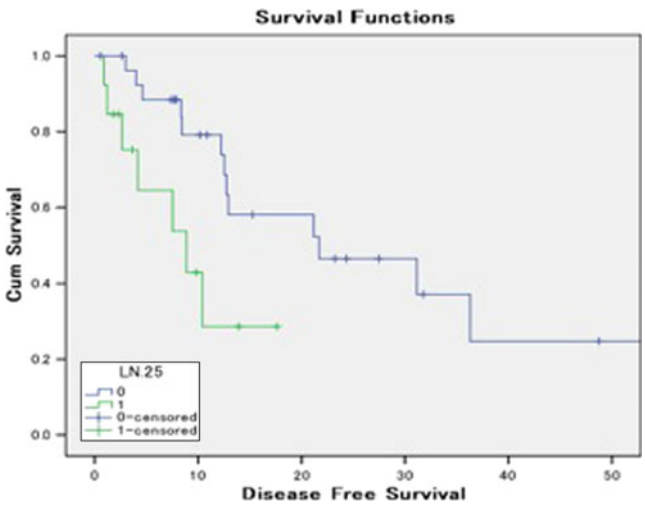

Fig. 6 Kaplan–Meier disease-free survival—lymph node ratio (0=<0.25; 1=≥0.25; p=0.021). 0=21.7 months (median survival). 1=8.9 months (median survival)

Table 4 Lymph node ratio

Variable	LNR<0.25 (*N*=28)	LNR≥0.25 (*N*=13)	*p* value
Age (median)	61.8 years	65.4 years	0.251
Gender	Male—24 (86%) Female—4 (14%)	Male—13 (100%) Female—0 (0%)	0.151
Smokers	19 (67%)	10 (76%)	0.553
Diabetes mellitus	7 (25%)	4 (31%)	0.698
Hypertension	14 (50%)	7 (54%)	0.819
Coronary artery disease	7 (25%)	0 (0%)	**0.048**
Pathology	EAC—25 (89%)[a] SCC—3 (11%)[b]	EAC—11 (85%) SCC—2 (15%)	0.671
Type of surgery	TTE—8 (29%)[c] THE—8 (29%)[d]	TTE—4 (31%) THE—3 (23%)	0.935
	MIE—11 (39%)[e]	MIE—5 (38%)	
	Lap THE—1 (3%)[f]	Lap THE—1 (8%)	
Number of lymph nodes resected (median)	19.5	16.0	0.157
R0 resection	28 (100%)	11 (85%)	**0.033**
Postoperative stage	I—0 (0%) II—14 (50%)	I—0 (0%) II—4 (31%)	0.211
	III—14 (50%)	III—9 (69%)	
Adjuvant therapy	13 (46%)	8 (62%)	0.368
Intraoperative morbidity	4 (14%)	4 (31%)	0.215
Postoperative morbidity	15 (54%)	9 (69%)	0.344
Perioperative mortality	1 (4%)	0 (0%)	0.490

[a] Adenocarcinoma

[b] Squamous cell carcinoma

[c] Open transthoracic esophagectomy

[d] Open transhiatal esophagectomy

[e] Thoracoscopic laparoscopic esophagectomy

[f] Laparoscopic transhiatal esophagectomy

The decision to proceed with neo-adjuvant therapy was typically made in conjunction with the medical oncologist. Most of the patients in this study received neo-adjuvant therapy at outside facilities. Approximately three quarters (74%) of the patients received chemoradiation while the remaining quarter (26%) were treated only with chemotherapy. Ninety percent of the cohort received 5-FU and platinum-based chemotherapy regimens. Additionally, the majority of the patients received 5,040 cGy of radiation.

Lymph node status has been shown to impact survival. Patients with positive nodes have a worse prognosis than node-negative patients.[24] We also found a significant difference in overall (p=0.025) and disease-free survival (p=0.03) between node-positive and node-negative patients that confirms the prognostic importance of nodal status in patients receiving neo-adjuvant therapy.

An extended lymphadenectomy has been shown to improve survival in patients treated with primary surgery.[4–6] These studies define optimal lymph node resection between 10 and 40 lymph nodes. Extensive lymphadenectomy potentially confers a survival benefit due to increased clearance of micrometastatic disease and more accurate pathological staging leading to appropriate administration of adjuvant treatment. The 2010 NCCN guidelines state that at least 15 nodes should be resected in patients receiving primary surgery for locally advanced disease; however, there is no recommendation for lymphadenectomy in patients receiving neo-adjuvant therapy.[25] Our results indicate that in patients treated with neo-adjuvant chemotherapy or chemoradiation followed by surgery, a significant survival benefit exists with the resection of 18 or more lymph nodes (p=0.014). Median overall survival increased from 29.6 to 68.6 months at this threshold. Importantly, there was no difference in perioperative morbidity or mortality with more extensive dissection. To the best of our knowledge, this is the first study showing therapeutic benefit of an extended lymphadenectomy in patients undergoing esophagectomy after neo-adjuvant therapy.

The lymph node ratio, or the ratio of positive nodes to total number of nodes resected, has been considered as a prognostic indicator.[7–9,11] The lymph node ratio takes both the extent of resection and the number of positive nodes into consideration. As mentioned above, these factors have

been independently shown to effect prognosis in esophageal cancer. A recent study demonstrated that the majority of primary surgery patients with three or more positive lymph nodes have systemic failure in follow-up.[10] An extended lymphadenectomy would not be beneficial in these patients. We did not find a significant difference in survival in patients treated with neo-adjuvant therapy with three or more positive nodes (p=>0.05). This could either be due to eradication of systemic disease with neo-adjuvant therapy or a type I error due to small sample size.

The lymph node ratios most commonly cited as conferring a survival benefit range from 0.2 to 0.4.[8] We found a significant difference in overall and disease-free survival at a ratio of 0.25 (p=0.015 and 0.021, respectively). Overall survival increased from 17.8 to 31.1 months with disease-free survival from 8.9 to 21.7 months. Of note, RO resection rates and coronary artery disease were significantly different between the groups. Two patients (15%) had an R1 resection in the ≥0.25 group (which most likely is a marker of more extensive disease). Given our small sample size, it is impossible to exclude this as a source of bias.

The response to neo-adjuvant therapy has been clearly shown to impact survival. Rice et al. demonstrated that patients who are downstaged to node-negative status following neo-adjuvant therapy have a survival between those without clinical or pathologic evidence of nodal involvement and those with positive nodes on pathology.[24] This suggests that the response to chemoradiation should be incorporated into the staging of patients treated with neo-adjuvant therapy. Rizk et al. demonstrated that the American Joint Committee on Cancer (AJCC) system is heavily reliant on tumor depth and fails to adequately differentiate survival between concurrent stages.[26] Additionally, they showed that pathologic complete response and estimated treatment response have significant limitations in their ability to independently predict outcomes in patients treated with neo-adjuvant therapy.[26] Swisher et al. found that combining the degree of response to chemoradiation with pathologic nodal status was most predictive of outcome in patients treated with neo-adjuvant therapy.[27] The authors recommended revising the AJCC staging to include degree of pathologic response. Our study suggests that the lymph node ratio deserves further consideration as a prognostic indicator in patients receiving neo-adjuvant therapy. Additionally, our findings indicate that the resection of 18 or more lymph nodes is a significant prognostic factor. This is important as the extent of lymphadenectomy is under the surgeon's control.

This study is limited by its small sample size. Neo-adjuvant treatment regimens were not standardized. Although different surgical approaches were utilized, a single surgeon (SKM) performed all operations. A greater number of minimally invasive operations were performed later in the study period. Lymph node harvests varied according to the method of resection. Follow-up was short but complete. Finally, the role of adjuvant therapy in node-positive patients was not explored.

Conclusion

Extent of lymphadenectomy, lymph node ratio, and pathological lymph node status are important prognostic markers in patients who undergo esophagectomy after neo-adjuvant therapy. Our results suggest that negative nodes on pathology, lymph node ratio of <0.25, and resection of ≥18 nodes improve survival. An extensive lymphadenectomy should be advocated for patients receiving neo-adjuvant therapy as long as it does not increase operative morbidity and mortality. Larger studies with longer follow-up are needed to validate these findings.

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ORIGINAL ARTICLE

Optimal Size of Jejunal Pouch as a Reservoir after Total Gastrectomy: A Single-Center Prospective Randomized Study

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Abstract
Background In order to improve a patient's quality of life after total gastrectomy, jejunal pouch reconstruction has been employed. However, little information exists regarding the optimal size of the jejunal pouch after total gastrectomy.
Methods The study was designed as a single-center randomized trial in which the results of double-tract reconstruction with pouches of two different sizes were compared, i.e., short and long pouch double tract (SPDT and LPDT, respectively). We conducted a clinical assessment with standard questionnaire after surgery. The amount of residual food in the jejunal pouch was determined by endoscopy.
Results No demographic differences were noted between the two groups. The eating capacity per meal was higher in the SPDT group than in the LPDT group. The postoperative weight loss 24 months after surgery was lower in SPDT group than that in the LPDT group. Although the incidence of early dumping symptoms was higher in the SPDT group, no difference was noted in the other postprandial abdominal symptoms between the two groups.
Conclusions We conclude that the optimal pouch should be relatively short, as a short pouch improves the eating capacity per meal and the weight loss ratio to the preoperative value.

Keywords Gastric cancer · Jejunal pouch · Quality of life · Pouch volume

Introduction

Total or subtotal radical gastrectomy with D2 lymphadenectomy has been widely adopted for cases of both early and advanced gastric cancer in order to improve mortality rates in Japan. However, such surgical procedures can sometimes lead to serious postgastrectomy symptoms and reduce a patient's quality of life (QOL), especially in the case of total gastrectomy. Various reconstruction methods exist, including interposition for maintaining duodenal transit and pouch reconstruction for reservoir function; however, no optimal reconstruction method has been established thus far.[1,2]

In order to improve a patient's QOL after total gastrectomy, jejunal pouch reconstruction has been employed by many surgeons, and the short- and long-term effects of pouch reconstruction in terms of reservoir function were shown to be satisfactory in several randomized controlled trials (RCTs) and by meta analysis.[3–8] However, little information exists regarding the optimal size of the jejunal pouch after total gastrectomy with curative intent.[9,10] To address this issue, we conducted a prospective randomized trial to evaluate the difference in long-term QOL with double-tract reconstruction using pouches of two different sizes, i.e., the short or long pouch size.

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Materials and Methods

Study Design

In this single-center randomized trial, we compared the results with double-tract reconstruction using pouches of two different sizes after potentially curative total gastrectomy. The inclusion criteria for the trial were as follow: age less than 80 years, no previous bowel resection, and normal kidney and liver function tests. Patients who met these criteria and in whom a potentially curative resection could be achieved were enrolled in the trial. This trial was planned to be performed for 5 years. During the period from 2002 to 2007, a total of 27 patients with gastric cancer who underwent a total gastrectomy were included in this prospective randomized trial. Patients were assigned intraoperatively to either the short or long pouch double-tract reconstruction (SPDT or LPDT, respectively) after the surgeon completed the gastric resection with curative intent. Randomization was carried out using sealed envelopes. SPDT and LPDT were performed with the two and three stapler firings from a 60-mm linear stapler device (Endo-GIA blue 60 mm, Covidien, Tokyo), respectively. A jejunal pouch was made by side-to-side anastomosis of both limbs of the jejunum folded into an inverted U, leaving a jejunal bridge at the top of the jejunal pouch (apical bridge). The apical bridge was cut near the oral end and an esophagojejunostomy was conducted using a circular stapler (CEEA 25 mm, Covidien), leaving the isoperistaltic jejunum approximately 6–8 cm long between the esophagus and jejunal pouch and approximately 10 cm long between the jejunal pouch and duodenojejunostomy performed with a circular stapler (CEEA 28 mm, Covidien; Fig. 1).[11] All surgeries were performed by two experts who had more than 10 years of experience in performing gastrectomies (TI and SO). The laparoscopic gastrectomy had not been performed in this period.

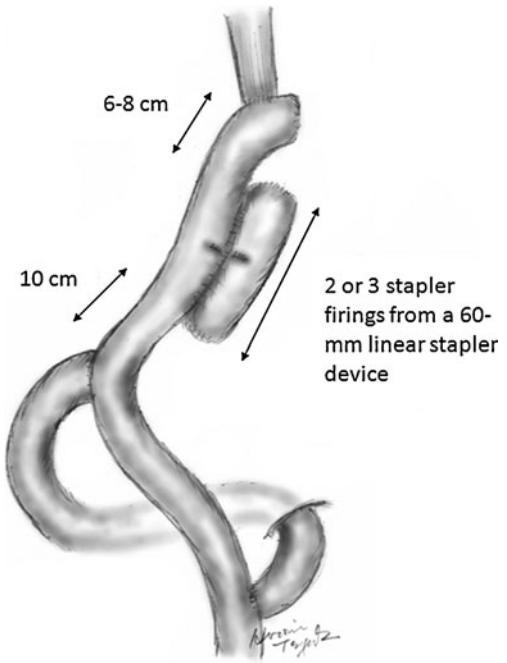

Fig. 1 Reconstruction methods after total gastrectomy

The clinical and pathological findings of the patients were described according to the second English edition of the Japanese Classification of Gastric Carcinoma, which was edited by the Japanese Gastric Cancer Association.[12]

All patients were followed up at our hospital at 3–4-month intervals during the first 2 years of the study and every 6 or 12 months thereafter for 3 years. We performed a clinical assessment with a standard questionnaire regarding the body weight, eating capacity, abdominal conditions, incidence of early dumping symptoms, and overall satisfaction levels 12 and 24 months after surgery (Table 1). Each postoperative clinical symptom including dumping symptoms, reflux, dysphagia, heart burn, vomiting, diarrhea, and appetite loss was considered to be occurred if it presented twice a week or more frequently. All questionnaires were collected when the patient visits our hospital. An endoscopic examination was performed 12 months after surgery and the amount of residual food in the jejunal pouch was evaluated and classified as previously proposed by Sasako et al.[13] All patients were prohibited from eating and drinking 12 h before the endoscopy.

Ethics

This prospective randomized study was reviewed and approved by the Institutional Review Board at the National Defense Medical College. Written informed consent was obtained from every patient before they underwent gastrectomy.

Statistical Analysis

Data are expressed as mean±standard deviation. Statistical analyses were performed using either the Mann–Whitney *U* test or chis-quare test. A p value <0.05 was considered statistically significant. All analyses were performed using the StatView version 5.0 software program (SAS Institute Inc., Cary, NC, USA).

Results

Thirteen patients were assigned as SPDT and 14 patients as LPDT. There was no difference in the demographic data between the two groups (Table 2). The average length of the

Table 1 Demographic data and surgical outcome in patients with jejunal pouch reconstruction

Number	SPDT 13	LPDT 14	*P* value
Age (years)	54.6±10.0	61.7±8.2	0.06
Sex			
Male	7 (53.8%)	12 (85.7%)	0.07
Female	6 (46.2%)	2 (14.3%)	
Tumor depth			
T1	4 (30.8%)	6 (42.9%)	0.78
T2	5 (38.5%)	5 (35.7%)	
T3	4 (30.8%)	3 (21.4%)	
Nodal status			
N0	8 (61.5%)	8 (57.1%)	0.35
N1	5 (38.5%)	4 (28.6%)	
N2	0 (0%)	2 (14.3%)	
Stage			
IA	4 (30.8%)	6 (42.9%)	0.68
IB	3 (23.1%)	1 (7.1%)	
II	3 (23.1%)	3 (21.4%)	
IIIA	3 (23.1%)	4 (28.6%)	
Cholecystectomy			
Yes	11 (84.6%)	9 (64.3%)	0.23
No	2 (15.4%)	5 (35.7%)	
Splenectomy			
Yes	3 (23.1%)	3 (21.4%)	0.92
No	10 (76.9%)	11 (78.6%)	
Pouch length (cm)	9.2±1.1	12.5±1.5	<0.0001
Operation time (min.)	331.8±34.4	343.8±36.7	0.40
Intraoperative blood loss (g)	568.7±245.5	802.8±399.8	0.09
Postoperative complication			
Yes	2 (15.4%)	2 (14.3%)	0.94
No	11 (84.6%)	12 (85.7%)	

jejunal pouch in SPDT was 9.2±1.1 cm and that in LPDT was 12.5±1.5 cm ($p<0.0001$). In addition, no difference was noted in the operation time and intraoperative blood loss. Two patients in the SPDT group developed minor anastomotic leakages, while one patient in the LPDT group had a urinary tract infection and one had pneumonia; there was no difference in the occurrence of postoperative complications between the two groups.

Of 27 patients, the outcomes of these 24 patients (SPDT=11 and LPDT=13) were evaluated in this study because two patients received adjuvant chemotherapy and one patient failed in follow up. There was significant difference of the percentage of the amount of the single oral intake to the preoperative value, which was evaluated by the patients' questionnaires, between the two groups 12 months after surgery (Table 3). However, there was no difference in the frequency of daily meals both 12 and 24 months after surgery between the two groups. The weight ratio to the

Table 2 Eating capacity and frequency of daily meals in patients with jejunal pouch reconstruction

	SPDT (n=11)	LPDT (n=13)	*P* value
Eating capacity per meal (compared with that in pre-illness state)			
12 months	69.1±19.7%	52.3±16.9%	0.03
24 months	78.6±6.9%	61.4±23.4%	0.09
Frequency of daily meals			
12 months			
3 Times	10	9	0.39
4 Times	1	3	
5 Times	0	1	
24 months			
3 Times	10	8	
4 Times	1	5	0.10
5 Times	0	0	

Table 3 Clinical outcome and residual food in the jejunal pouch

	12 months		*P* value	24 months		*P* value
	SPDT	LPDT		SPDT	LPDT	
Early dumping						
Yes	3	0	0.04	3	2	0.47
No	8	13		8	11	
Late dumping						
Yes	1	2	0.64	1	4	0.19
No	10	11		10	9	
Reflux						
Yes	2	5	0.28	0	0	>0.99
No	9	8		11	13	
Dysphagia						
Yes	7	8	0.92	0	1	>0.99
No	4	5		11	12	
Heart burn						
Yes	2	4	0.48	0	0	>0.99
No	9	9		11	13	
Vomiting						
Yes	1	3	0.36	0	1	>0.99
No	10	10		11	12	
Diarrhea						
Yes	7	5	0.22	0	1	>0.99
No	4	8		11	12	
Appetite loss						
Yes	5	9	0.24	0	3	0.09
No	6	4		11	10	
Overall satisfaction levels						
Very good	1	3	0.50	2	2	0.42
Good	6	4		8	7	
No opinion	4	5		0	0	
Bad	0	1		1	4	
Very bad	0	0		0	0	
Residual food in the jejunal pouch						
Grade 0	5	8	0.43			
Grade 1, 2	4	3				
Grade 3, 4	2	2				

Each postoperative clinical symptom was considered to be occurred when the symptom occurred twice a week or more frequently according to the standard questionnaire

preoperative value (SPDT vs. LPDT) was 88.4±7.4% vs. 85.9±4.3% and 90.2±6.4% vs. 80.9±7.1% at 12 and 24 months after surgery, respectively (Fig. 2). There were significant differences between the two groups at 24 months after surgery (P=0.03). There were significant correlation between the weight ratio to the preoperative value and eating capacity to the preoperative value 24 months after surgery but not 12 months (Fig. 3).

Although the incidence of early dumping symptoms was higher in the SPDT group than in the LPDT group 12 months after surgery, there was no difference in the incidence of the other abdominal symptoms 12 months after surgery, such as late dumping symptoms, reflux, dysphagia, heart burn, vomiting, diarrhea, and appetite loss was noted. In addition, there were no differences in the incidence of the abdominal symptoms 24 months after surgery and we could not find any difference in the overall satisfaction levels between the two groups. Furthermore, no difference in the amount of residual food in the jejunal pouch was noted between the two groups by an endoscopic examination 12 months after gastrectomy, although the endoscopic evaluation of residual food in the pouch had many potential confounding variables.

Discussion

In the present prospective randomized trial, we observed no merits with double-tract reconstruction using a long jejunal pouch after total gastrectomy. However, SPDT was superior to

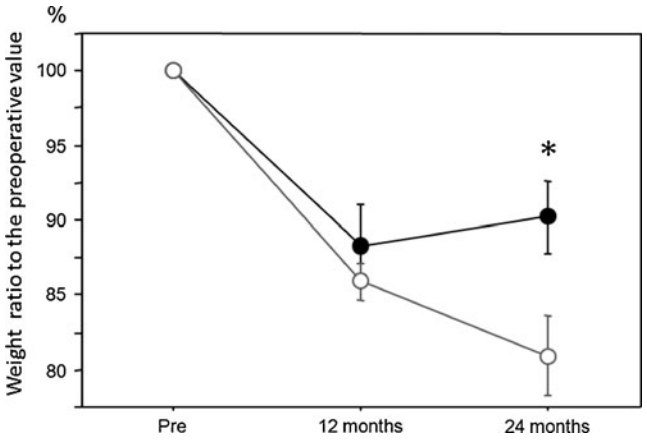

Fig. 2 Body weight rate change after surgery. The weight ratio to the preoperative value (SPDT vs. LPDT) was 88.4±7.4% vs. 85.9±4.3% and 90.2±6.4% vs. 80.9±7.1% at 12 and 24 months after surgery, respectively. There were significant differences between the two groups at 24 months after surgery. *Filled circle* patients with a short jejunal pouch, *empty circle* patients with a long jejunal pouch; **P*=0.03, SPDT vs. LPDT

LPDT in terms of improved eating capacity of the patients per meal and the recovery of body weight rate change after surgery; although the incidence of early dumping syndrome was higher 12 months after surgery in the SPDT group.

Until recently, more than 10 RCTs have been published related to the usefulness of pouch reconstruction or interposition after total gastrectomy;[2,3,10,14–20] most of these studies indicate that jejunal pouch reconstruction provides better postoperative weight gain and QOL;[2,21,22] however, some authors failed to find any difference.[18,23] It is necessary to conduct the multicenter prospective randomized study with enough sample size in order to verify the merit of the jejunal pouch reconstruction after total gastrectomy.

Among the reports on the merits of jejunal pouch reconstruction, few studies report the ideal jejunal pouch volume. It is easy to assume that a long pouch is superior in terms of reservoir function but the emptying time is longer in the case of long pouch, leading to vomiting, reflux, and appetite loss. Therefore, we conducted this randomized study to compare the results with jejunal pouchs of two different sizes. By using a radioisotope, Tono et al. revealed that a significant positive correlation existed between pouch length and half-emptying time, and they concluded that the ideal pouch length was 12–15 cm on the basis of the half-emptying time.[24] Hoksch et al. did not find any difference between the postoperative outcomes after Longmire's reconstruction with a short pouch (7 cm) and long pouch (15 cm), and they emphasized that the most important point for improving QOL is preserving the duodenal passage but not the pouch size.[9] Schwarz et al. also demonstrated that that pouch volume itself did not affect the postoperative QOL and nutritional status by using the Ulm pouch.[2] On the other hand, Tanaka et al. conducted an RCT comparing different pouch sizes after total gastrectomy (short pouch, 15 cm; long pouch, 20 cm) and demonstrated less frequent reflux symptoms, improved serum albumin and total cholesterol levels, and reduced glucose tolerance in patients with a short pouch, although no difference was noted in the amount of food intake, body weight change, and the incidence of dumping symptoms.[10,19]

Many surgeons employ a Roux limb length of approximately 40 cm to prevent biliary reflux, but our reconstruction methods had relatively short in both reconstruction groups. However, no patients with jejunal pouch had reflux symptoms 24 months after surgery and additional pouch construction may prevent a biliary reflux.

In this study, patients with a short jejunal pouch had a higher eating capacity per meal than those with a long jejunal pouch. Furthermore, patients with a short jejunal pouch had significantly greater weight ratio to the preoperative value 24 months after surgery. There were significant correlation

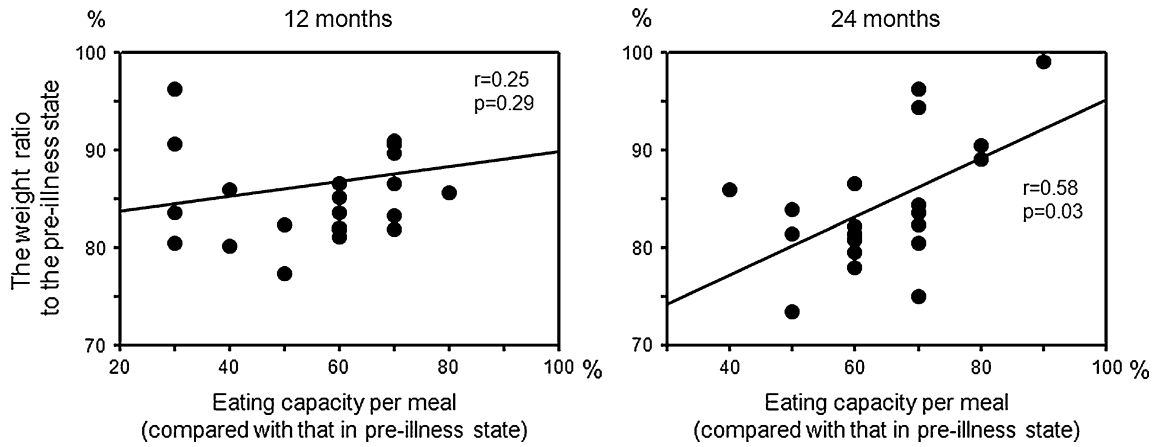

Fig. 3 Correlation between the weight ratio and eating capacity to the preoperative values after surgery

between the weight ratio and eating capacity to the preoperative value 24 months after surgery. Thus, we believe that greater eating capacity leads to the upswing in the weight ratio in SPDT group 24 months after surgery. Although the incidence of early dumping symptoms was higher in patients with a short jejunal pouch, none of them required any medications or interventions. On the basis of the results of our prospective study, we conclude that the optimal pouch size should be approximately 9 cm of jejunal pouch, which can be achieved by two stapler firings of 60 mm linear stapler device in terms of the high eating capacity per meal and the weight ratio to the preoperative value, as well as the cost reduction.

In this study, we did not have enough sample size in each arm, which is the limitation of this study and it is necessary to conduct the multicenter prospective randomized study in order to verify our current results.

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ORIGINAL ARTICLE

Predictable Factors for Lymph Node Metastasis in Early Gastric Cancer—Analysis of Single Institutional Experience

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Abstract
Introduction Prediction of lymph node metastasis in early gastric cancer (EGC) is very important to decide treatment strategies preoperatively. The aim of this study was to evaluate factors that predict the presence of lymph node metastasis and to indentify the differences between mucosal and submucosal gastric cancers.
Methods A total of 376 patients with EGC who underwent gastrectomy from March 1999 through December 2007 were retrospectively identified. The clinopathological factors and biological markers (p53, Ki67) were analyzed.
Results The rate of lymph node metastasis was 9.6% (mucosal cancer 2.8%, submucosal cancer 18.4%). Tumor size, depth of invasion, macroscopic type, and lymphovascular invasion were related to lymph node metastasis in EGC. When the carcinomas were confined to the mucosal layer, tumor size and lymphovascular invasion showed significant correlation with lymph node metastasis. On the other side, macroscopic type and lymphovascular invasion were association with lymph node metastasis in submucosal carcinoma.
Conclusion The risk factors for lymph node metastasis in EGC are quite different depending on depth of tumor invasion. To predict lymph node metastasis in EGC, it is recommended that distinct assessment according to individual situation should be clearly established.

Keywords Early gastric cancer · Lymph node metastasis · p53 · KI67

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Introduction

Early gastric cancer (EGC) is defined as when the tumor invasion is confined to the mucosa and submucosa, irrespective of the presence of a lymph node metastasis.[1] The rate of EGC has been increasing worldwide with advanced diagnostic techniques and mass screening programs. The presence of lymph node metastasis is the most important prognostic factor for patients with EGC. Lymph node metastases are present in only 3–5% of patients with mucosal cancer versus 10–25% of those with submucosal cancer.[2–6] Several clinocopathological factors, such as the tumor size, depth of invasion, histological type, and lymphatic and vascular invasion, are known to correlate with lymph node metastasis.[6–8] Recently, several biological markers have been reported as useful predictors for lymph

node metastases in gastric cancer. The p53 tumor-suppressor gene acts by modulating cell proliferation via G1 arrest checkpoint cell cycle.[9] Mutation of p53 gene is one of the most frequent genetic lesions associated with gastric cancer and correlated with lymph node metastases in early gastric cancer.[10] Ki67 is a nuclear non-histone protein and universally expressed among proliferating cells and absent in quiescent cells. Although little is known about the exact function of protein in cell division, Ki67 expression is evaluated as a marker of proliferation.[11] Ki67 expression may be useful predictor for lymph node metastases in gastric cancer with submucosa invasion.[12]

Because the prognosis of patients with EGC has improved with radical gastrectomy, the treatment strategies for EGC have been focused on the improvement of quality of life.[13] Although radical gastrectomy including lymph node dissection has been recognized as the standard surgical operation for EGC, unnecessary extended surgery could be avoided in patients with EGC without lymph node metastasis. Many retrospective studies on EGC have established an indication for minimal invasive surgery without lymph node dissection, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

The purpose of this study was to evaluate the factors that can be predicted the presence of lymph node metastasis and to identify the difference between mucosal and submucosal gastric cancers in point of lymph node metastasis. Although this process is retrospective study, authors focused on the factors that could be evaluated preoperatively.

Material and Methods

Patients

This study enrolled 376 early gastric cancer cases; those were pathologically proven after gastrectomy with lymph node dissection at Hallym University Sacred Heart Hospital between March 1999 and December 2007. The standard operative procedures were performed for EGC: distal subtotal or total gastrectomy depending on the location of gastric cancer with D2 or more extended lymphadenectomy. Patient characteristics including age and sex were collected, and information on tumor size, depth of invasion, gross appearance, histological type, and lymphovascular invasion was also retrieved from medical records.

The depth of tumor invasion was classified as mucosa and submucosa carcinoma. The maximum diameter of tumor was recorded as tumor size. The carcinomas were classified into four macroscopic types: elevated (type I or IIa), flat (IIb), depressed (IIc or III), and mixed type which include both elevated and depressed. Tumor histology was classified into two groups: the differentiated group, which included papillary adenocarcinoma and well- or moderately differentiated adenocarcinoma, and the undifferentiated group, which included poorly or undifferentiated adenocarcinoma, mucinous, and signet ring cell carcinoma. This study was approved by the Institutional Review Board of the Hallym University Sacred Heart Hospital, and informed consent was obtained from all individuals.

Immunohistochemistry

For immunohistochemistry, the avidin–biotin complex method was performed on 4-μm-thick tissue sections. The sections were deparaffinized with xylene for 15 min and treated in a microwave oven using 0.01 mol/l citrate buffer (pH 6.0) for 30 min and incubated with monoclonal antibody against recombinant human p53 (Zymed, San Francisco, CA, USA) and Ki67 (Zymed, San Francisco, CA, USA). In each experiment, both positive and negative controls were used. For the staining of p53 and Ki67, only nuclear expression was recognized as specific immunostaining. The immunohistochemical score was estimated by the percentage of the immunoreactive cells: A score of 0 indicates no positive cells or essentially none (0 or lesser than 1%); a score of 1 indicates some positive cells (1–10%); a score of 2 indicates well-defined area of positive cells (11–25%); a score of 3 indicates extensive area of positive cells (26–50%); a score of 4 indicates almost every cell stained (>50%). Slides were examined by one investigator who was blinded to clinicopathological data.

Statistical Analysis

Associations between lymph node metastasis and clinicopathological parameters were analyzed using the chi-square test (or Fisher's exact test when appropriate). Multivariate logistic regression analyses were used to assess the associated factors for lymph node metastasis. All statistical analyses were conducted using R (version 2.12.1; R foundation for Statistical Computing, Vienna, Austria). Statistical significance was established at $p<0.05$.

Results

Relationship Between Clinicopathological Findings and Lymph Node Metastasis in All Patients with EGC

The study includes 238 men and 138 women and involved 213 mucosal carcinomas and 163 submucosal carcinomas. The mean age was 59.2 years (range, 29–81 years). The mean number of retrieved lymph nodes was 26.0. Among the 376 patients with EGC, 36 (9.6%) were histologically shown to have lymph node metastasis and 340 (90.4%) had

no lymph node metastasis. Lymph node metastasis was associated with tumor size, depth of invasion, macroscopic type, and lymphovascular invasion (Table 1). A tumor larger than 2 cm and submucosal invasion were association with lymph node metastasis (p=0.0002, p<0.0001). In elevated type of carcinoma, the rate of lymph node metastasis was higher (p=0.0018). In the presence of lymphatic or vascular invasion, the rate of lymph node metastasis was also higher (p<0.0001). There was no significant difference in gender, age, tumor location, histology, and immunoreactivity for p53 or Ki67.

Table 1 Relationship between clinicopathological findings and lymph node metastasis in patients with early gastric cancer (376 patients)

Variables	Lymph node metastasis		p value
	Negative (n=340)	Positive (n=36)	
Gender			0.169
Male	219 (92.0)	19 (8.0)	
Female	121 (87.7)	17 (12.3)	
Age (years)			0.727
<60	154 (91.1)	15 (8.9)	
≥60	186 (89.9)	21 (10.1)	
Tumor location			0.518
Upper 1/3	26 (92.9)	7 (7.1)	
Middle 1/3	121 (92.4)	10 (7.6)	
Lower 1/3	193 (88.9)	24 (11.1)	
Tumor size (cm)			0.0002
<2	115 (98.2)	2 (1.7)	
≥2	225 (86.9)	34 (13.1)	
Depth of invasion			<0.0001
Mucosa	207 (97.2)	6 (2.8)	
Submucosa	133 (81.6)	30 (18.4)	
Macroscopic type			0.0018
Elevated	19 (70.4)	8 (29.6)	
Flat	100 (94.3)	6 (5.7)	
Depressed	201 (90.5)	21 (9.5)	
Mixed	20 (95.2)	1 (4.8)	
Histology			0.500
Differentiated	190 (91.3)	18 (8.7)	
Undifferentiated	150 (89.3)	18 (10.7)	
Lymphovascular invasion			<0.0001
Absent	320 (93.8)	21 (6.2)	
Present	20 (57.1)	15 (42.9)	
P53			0.275
0–2 weak	148 (91.4)	14 (8.6)	
3–4 strong	99 (83.2)	20 (16.8)	
Ki67			0.397
0–2	96 (90.6)	10 (9.4)	
3–4	165 (86.8)	25 (13.2)	

Relationship Between Clinicopathological Findings and Lymph Node Metastasis in Mucosal Gastric Carcinoma

Among the 213 patients with mucosal gastric cancer, only six (2.8%) were histologically shown to have lymph node metastasis. When the carcinomas were confined to the mucosal layer, tumor size and lymphovascular invasion showed significant correlation with lymph node metastasis (p=0.039, p=0.002) (Table 2). However, there was no significant difference in gender, age, tumor location, macroscopic type, histology, and immunoreactivity for p53 or Ki67.

Table 2 Relationship between clinicopathological findings and lymph node metastasis in patients with mucosal gastric carcinomas (213 patients)

Variables	Lymph node metastasis		p value
	Negative (n=207)	Positive (n=6)	
Gender			0.560
Male	128 (97.7)	3 (2.3)	
Female	79 (96.3)	3 (3.7)	
Age (years)			0.106
<60	97 (95.1)	5 (4.9)	
≥60	110 (99.1)	1 (0.9)	
Tumor location			0.577
Upper 1/3	12 (92.3)	1 (7.7)	
Middle 1/3	71 (97.3)	2 (2.7)	
Lower 1/3	124 (97.6)	3 (2.4)	
Tumor size (cm)			0.039
<2	91 (100)	0 (0)	
≥2	116 (95.1)	6 (4.9)	
Macroscopic type			0.982
Elevated	10 (100)	0 (0)	
Flat	79 (96.3)	3 (3.7)	
Depressed	111 (97.4)	3 (2.6)	
Mixed	7 (100)	0 (0)	
Histology			0.204
Differentiated	125 (98.4)	2 (1.6)	
Undifferentiated	82 (95.4)	4 (4.6)	
Lymphovascular invasion			0.002
Absent	206	4	
Present	1	2	
P53			0.159
0–2 weak	87 (94.6)	5 (5.4)	
3–4 strong	52 (100)	0 (0)	
Ki67			0.605
0–1	38 (95.0)	2 (5.0)	
2–4	111 (97.4)	3 (2.6)	

Relationship Between Clinicopathological Findings and Lymph Node Metastasis in Submucosal Gastric Carcinoma

Among the 163 patients with submucosal gastric cancer, 30 (18.4%) were histologically shown to have lymph node metastasis. When the carcinomas were confined to the submucosal layer, macroscopic type and lymphovascular invasion were association with lymph node metastasis (Table 3). In the elevated type of submucosal carcinoma, the rate of lymph node metastasis was higher than that of others groups (p=0.022). In the presence of lymphatic or vascular invasion, the rate of lymph node metastasis was higher (p=0.0008). However, no significant association was found between tumor size and lymph node metastasis in submucosal carcinoma.

Table 3 Relationship between clinicopathological findings and lymph node metastasis in patients with submucosal gastric carcinomas (163 patients)

Variables	Lymph node metastasis		p value
	Negative (n=133)	Positive (n=30)	
Gender			0.119
Male	91 (85.1)	16 (14.9)	
Female	42 (75.0)	14 (25.0)	
Age (years)			0.413
<60	57 (85.1)	10 (14.9)	
≥60	76 (79.2)	20 (20.8)	
Tumor location			0.182
Upper 1/3	14 (93.3)	1 (6.7)	
Middle 1/3	50 (86.2)	8 (13.8)	
Lower 1/3	69 (76.7)	21 (23.3)	
Tumor size (cm)			0.170
<2	24 (92.3)	2 (7.7)	
≥2	109 (79.6)	28 (20.4)	
Macroscopic type			0.022
Elevated	9 (52.9)	8 (47.1)	
Flat	21 (87.5)	3 (12.5)	
Depressed	90 (83.3)	18 (16.7)	
Mixed	13 (92.9)	1 (7.1)	
Histology			0.659
Differentiated	65 (80.3)	16 (19.7)	
Undifferentiated	68 (82.9)	14 (17.1)	
Lymphovascular invasion			0.0008
Absent	114 (87.0)	17 (13.0)	
Present	19 (59.4)	13 (40.6)	
P53			0.208
0–2 weak	61 (83.6)	12 (16.4)	
3–4 strong	47 (73.4)	17 (26.6)	
Ki67			0.381
0–2	34 (73.9)	12 (26.1)	
3–4	78 (81.2)	18 (18.8)	

Multivariate Analysis of Risk Factors

Multivariate logistic regression analyses were used to assess the associated factors for lymph node metastasis. In multivariate logistic regression for lymph node metastasis, the independent factors were age (dichotomized as <60, ≥60), tumor size (<2 cm, ≥2 cm), lymphovascular invasion (absent, present), and macroscopic type (categorized as elevated, flat, depressed, mixed). In mucosal gastric carcinoma group, the multivariate logistic regression could not be performed appropriately because of the small number of patients with lymph node metastasis (n=6). On the other hand, lymphovascular invasion (relative risk 4.57, 95% confidence interval (CI) 1.74–12.24, p=0.0021) and macroscopic type were independently associated with lymph node metastasis in submucosal gastric carcinoma (Table 4).

Discussion

Gastric cancer is the most prevalent cancer in Korea, which accounted for 18.3% of the whole cancer cases.[14] According to a report issued by the Korean Gastric Cancer Association, the proportion of patients with early stage gastric cancer has increased from 28.6% in 1995 to 32.8% in 1999 and 47.4% in 2004.[15] Lymph node metastasis is known to be one of the major negative prognostic factors for gastric cancer. The average 5-year survival rate in patients with EGC is over 90%, and it is up to 94.2% in patients without lymph node metastasis.[16] In this study, the rate of lymph node metastasis in EGC was 9.6%, and the risk factors of lymph node metastasis were tumor size, depth of invasion, macroscopic type, and lymphovascular invasion. When EGC was subdivided into mucosal and submucosal carcinomas, the risk factors of lymph node metastasis were quite different from each other. When the carcinomas were confined to the mucosal layer, the incidence of lymph node metastasis is 2.8%. It is similar to other reports.[6,17] Tumor size and lymphovascular invasion showed significant correlation with lymph node metastasis in mucosal carcinoma. On the other side, the incidence of lymph node metastasis is higher in submucosal carcinoma (18.4% vs. 2.8%). It is also similar to other reports.[18] In submucosal carcinoma, macroscopic type and lymphovascular invasion showed significant correlation with lymph node metastasis. Tumor size was not risk factor of lymph node metastasis in submucosal carcinoma.

Many studies have been carried out to evaluate the risk of lymph node metastasis in gastric cancer. Tumor size, depth of

Table 4 Multivariate analysis of risk factors for lymph node metastasis

Variables	Mucosal gastric carcinoma		Submucosal gastric carcinoma	
	Adjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Age (<60, ≥60)	0.15 (0.01–1.25)	0.1282	1.07 (0.42–2.75)	0.8923
Tumor size (<2 cm, ≥2 cm)	8.63×10^{7} (0–∞)	0.9950	3.31 (0.78–23.68)	0.1510
LVI (absent, present)	72.2 (4.08–3493.97)	0.0077	4.57 (1.74–12.24)	0.0021
Macroscopic type (elevated)				
Flat	7.44×10^{7} (0–∞)	0.9983	0.11 (0.02–0.57)	0.0122
Depressed	2.61×10^{7} (0–∞)	0.9984	0.17 (0.05–0.59)	0.0054
Mixed	0.58	0.9999	0.05 (0.00–0.37)	0.0119

This table demonstrates risk factors for lymph node metastasis in early gastric cancer. As shown, multivariate analysis in patients with mucosal gastric carcinoma is not fully appropriate because the cases with lymph node metastasis were too small

LVI lymphovascular invasion

invasion, histological type, gross appearance, and presence of lymphatic or vascular invasion were related to lymph node metastasis in EGC.[6,19,20] When early gastric cancer was subdivided into mucosal and submucosal carcinomas, the risk factors of lymph node metastasis were different each other. Li et al. reported that the tumor size and lymphovascular invasion were independent risk factors for lymph node metastasis in case of intramucosal undifferentiated EGC.[21] Song et al. reported that histological differentiation, increased submucosal vascularity, and invasion of tumor cells into the muscularis mucosae were correlated with the lymph node status of intramucosal gastric carcinoma.[22] Park et al. reported that tumor size and depth of invasion were significantly correlated with lymph node metastasis,[7] and An et al. also reported that tumor size and lymphatic involvement were independent risk factors for lymph node metastasis in EGC with submucosal invasion.[8] Shen et al. reported that histological classification, macroscopic type, tumor size, depth of gastric carcinoma infiltration, and the presence of vascular or lymphatic invasion were significantly and independently related to lymph node metastasis. For intramucosal cancer, tumor size was the unique risk factor for lymph node metastasis. For submucosal cancer, histological classification and tumor size were independent risk factors for lymph node metastasis.[20]

In addition to these clinicopathological factors, many studies have been carried out to evaluate the role of biological markers in lymph node metastasis. p53 is a tumor-suppressor gene that plays an important role in the cell cycle and mediates the induction of apoptosis or recovery from DNA. Because of such a crucial role in the controlling of genome integrity, p53 has earned the name "guardian of the genome." When mutant p53 protein is expressed, these functions are often blocked. It has been reported that p53 acts as a tumor growth regulator, and a correlation between p53 positivity and the presence of regional lymph node metastasis has been noted.[12,23–25] Ki67 is a nuclear antigen that is detected in proliferating but not resting cells. A high Ki67 labeling index (LI) at the deepest site of tumor penetration indicates an environment that promotes invasion and metastasis.[12,26,27] Overexpression of p53 has been demonstrated to be related to lymph node metastasis in EGC.[10,28] Goishi et al. reported that low Ki67 LI meant the low possibility of lymph node metastasis in EGC.[12] However, Ohashi et al. reported that both p53 and Ki67 did not correlate to lymph node metastases in EGC.[23] In this study, we concluded that both p53 and Ki67 did not correlate to lymph node metastasis in EGC.

Prior to operation, many investigators want to find the factors that associate with lymph node metastasis in EGC because the treatment strategies are different depending on whether lymph node metastasis is present or not. These treatments affect preservation of body function and maintenance of quality of life. It is reasonable to expect that useful information could be obtained by comparing the clinicopathological features and immunohistochemical expression of biological markers.

This research was retrospective and with small cases in single institution; furthermore, only two biological markers among a lot of immunohistochemical markers were evaluated. The value of these factors for lymph node metastasis needs to be verified by large-scale prospective studies.

In summary, prediction of lymph node metastasis in EGC is very important to decide the treatment strategies preoperatively. It is also important to estimate lymph node metastasis after EMR or ESD. The risk factors for lymph node metastasis in EGC are quite different depending on the state of things, such as depth of tumor invasion. To predict lymph node metastasis in EGC, it is recommended that distinct assessment according to individual situation must be clearly established.

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ORIGINAL ARTICLE

Analysis of Risk Factors for Delayed Gastric Emptying (DGE) after 387 Pancreaticoduodenectomies with Usage of 70 Stapled Reconstructions

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Abstract
Background Delayed gastric emptying (DGE) is one of the most troublesome complications after pancreaticoduodenectomy (PD).
Methods Between 2004 and 2009, 387 patients underwent PD and of these, 302 patients (78%) underwent pylorus-preserving PD. The stapled reconstruction of duodeno- or gastrojejunostomy was introduced in 2006, and 70 patients (18%) underwent stapled Roux-en-Y reconstruction. Postoperative DGE was defined based on the International Study Group on Pancreatic Surgery classification, and grade B or C DGE was considered to be clinically relevant. Risk factors for DGE were evaluated using univariate and multivariate analyses.
Results Four patients died in the hospital (1.0%). Postoperative DGE was found in 70 patients (18%). DGE was less frequently seen in stapled reconstruction than in hand-sewn reconstruction (7.2% vs. 21%, $P<0.001$), and in single-layer anastomosis than in double-layer anastomosis (12% vs. 24%, $P=0.02$). The multivariate logistic regression analysis revealed that the independent risk factors for DGE were postoperative pancreatic fistula (risk ratio [RR] 2.4, $P=0.002$), hand-sewn reconstruction (RR 2.9, $P=0.03$) and male (RR 2.2, $P=0.02$).
Conclusion The method of alimentary reconstruction affected the occurrence of DGE. The incidence of DGE was less in stapled reconstruction than in hand-sewn reconstruction.

Keywords Pancreaticoduodenectomy · Delayed gastric emptying · Stapled reconstruction · Hand-sewn reconstruction

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Introduction

The recent advances in imaging studies, surgical techniques, and perioperative management have decreased the mortality rate of pancreaticoduodenectomy (PD) to less than 2% in high-volume centers.[1,2] However, the morbidity rate still remains high, and postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) have been the leading complications.[3,4]

DGE after PD, otherwise known as "gastroparesis,"[5] was originally noted by Warshaw et al. in 1985.[6] DGE is not a fatal complication, but sometimes results in a significant prolongation of hospital stay and increase in hospital costs. The reported incidence of DGE has a wide range (7–45%),[7–10] partly because there was no standard definition of this complication. Very recently, the International Study Group of Pancreatic Surgery defined DGE[11] and the

incidence of DGE is now widely evaluated using the universal criteria.[12]

We previously reported the preliminary results of stapled reconstruction during PD.[13] Alimentary reconstruction using staplers during gastric and colorectal surgery is a widely accepted technique.[14,15] The use of circular staplers in esophagojejunostomy is more convenient and safer than hand-sewn suturing. Colorectal anastomoses using the double stapling technique have also become popular, especially since the advent of laparoscopic surgery.[16] Recent advances in laparoscopic surgery allow PD to be performed under laparoscopic guidance[17]; thus, it has become necessary to establish the feasibility of stapled alimentary reconstruction. To our knowledge, the clinical efficacy of stapled reconstruction using staplers during PD has not been elucidated.

The primary objective of this study is to analyze the risk factors for relevant DGE among 387 patients who underwent PD in 2004–2009 in a Japanese high-volume center. In this study, we defined DGE on the basis of the international definition and analyzed the clinicopathological variables that influenced the occurrence of grade B or C DGE. The secondary objective is to study the clinical impact of stapled reconstruction on the occurrence of DGE.

Methods

From 2004 to 2009, 387 patients underwent PD at our institute. Diseases included invasive pancreatic cancer in 202 patients, bile duct cancer in 50 patients, intraductal papillary mucinous neoplasm in 37 patients, ampullary or duodenal cancer in 53 patients, neuroendocrine tumor in eight patients, gallbladder or cystic duct cancer in seven patients, solid pseudopapillary tumor or gastrointestinal tumor in six patients, metastatic cancers in four patients, pancreatitis or autoimmune disease in seven patients, and other diseases in 13 patients. Six attending surgeons (TK, KS, TS, YS, ME, and SN) performed or controlled all the surgeries; of these six surgeons, three had more than 20 years of surgical experience, while the remaining three surgeons had less than 20 years of experience. One chief resident and four residents attended the surgical management in turn.

Surgical Procedures of PD

The details of our standard surgical procedure of PD have been described elsewhere.[18] Preoperative biliary drainage in 187 patients (48%) was performed either in the previous hospital or in our institute: only percutaneous biliary drainage (PTBD) in 103 patients, only endoscopic retrograde biliary drainage in 63 patients, and both PTBD and retrograde biliary drainage in 21 patients. The remaining 200 patients underwent PD without biliary drainage. PD was performed when the serum bilirubin concentration decreased less than 5 mg/dL. Patients received preoperative intravenous antibiotic prophylaxis, using a second-generation cephalosporin. After the removal of the pancreatic head, we routinely wrapped the stump of the gastroduodenal artery using the falciform ligament to prevent the bleeding caused by the pancreatic leakage.[19] Surgical procedures included pylorus-preserving PD (PPPD) in 296 patients, classical Whipple procedure (CW) or subtotal stomach-preserving PD (SSPPD) in 83 patients, PPPD plus limited hepatic resection in one patient, CW plus limited hepatic resection in two patients, and PPPD plus extended right hemihepatectomy in five patients. CW and SSPPD were not strictly distinguished, and the resection of the pyloric ring and antrum was performed according to the tumor extension or to the preference of the attending surgeon. The combined portal vein resection was performed in 83 patients (21%) out of 387 patients. In 382 patients, pancreaticojejunostomy was performed by duct-to-mucosa anastomosis in 342 patients, dunking method in 36 patients, and other methods in four patients. The pancreatic parenchyma was sewn to the jejunal wall by two-layer anastomosis in 324 patients, by Kakita's method[20] in 39 patients, and by other methods in 19 patients. In five patients, pancreaticojejunostomy was not performed.

Stomach Reconstruction by Conventional Hand-Sewn Method

Duodenojejunostomy was performed in PPPD in 249 patients, gastrojejunostomy in 67 patients undergoing CW or SSPPD, and jejunojejunostomy in one patient who had previously undergone total gastrectomy. Duodenojejunostomy and gastrojejunostomy were performed by the Gambee anastomosis in 84 patients, Albert–Lembert anastomosis in 198 patients, and layer-to-layer anastomosis in 31 patients. A Braun jejunojejunostomy was performed to prevent direct exposure of bile and pancreatic juice to the anastomotic site.

Stapled Roux-en-Y Reconstruction

All of the stapled reconstruction was performed by one of the authors (YS) since August 2006, and YS performed all of the alimentary reconstruction using staplers since then. The details of stapled Roux-en-Y reconstruction have been described elsewhere.[13] Briefly, an antecolic duodenojejunostomy was performed by Roux-en-Y reconstruction

using a circular stapler in 53 PPPDs (Proximate ILS™ 25 or 29 mm, Ethicon Endo-Surgery, Cincinnati, OH [n=19], EEA circular stapler, 25 or 28 mm, US Surgical, Norwalk, CT [n=34]). An antecolic gastrojejunostomy was performed by Roux-en-Y reconstruction using a linear stapler (ENDO-GIA ROTICULATOR™ 60, US Surgical, Norwalk, CT) in six CWs. A circular stapler was used to perform a gastrojejunostomy on the posterior wall of the stomach in 10 SSPPDs. In the remaining one patient who underwent total gastrectomy and PD, an esophagojejunostomy was performed using a circular stapler.

Postoperative Management

Two closed drains (8 or 10 mm in diameter) were inserted beside the pancreatojejunostomy and the drainage fluid was intermittent suctioned. The nasogastric tube was removed on postoperative day (POD) 1. The reinsertion of the gastric tube or opening of the gastrostomy was performed if the patient complained of nausea or vomiting and/or if severe distention of the stomach was observed on abdominal radiography. No patient was administered erythromycin or octreotide postoperatively. Patients were discharged from the hospital when they could eat almost half of their regular diet and had one abdominal drain left with minimal output.

Definition of Outcome Measures

POPF was defined according to the definition proposed by the International Study Group on Pancreatic Fistula,[21] i.e., when the amylase concentration of the drain fluid obtained on or after POD 3 was greater than three times the upper range of serum amylase concentration. POPF was classified into grades A, B, and C according to severity: briefly, grade A, fistula was a "transient fistula" not associated with a delay in hospital discharge; grade B, fistula led to a delay in discharge, with persistent drainage for more than 3 weeks; and grade C, fistula was usually associated with major complications. Grade B or C fistulae were considered to constitute clinically relevant POPF.

An upper gastrointestinal (UGI) study using an oral contrast medium was conducted between POD 4 and 7 at the discretion of the attending surgeon. A UGI score was calculated according to the degree of passage of the contrast medium grade A, good passage of the medium without stasis in the stomach; grade B, mild dilatation of the remnant stomach or formation of niveau in the stomach and passage of the medium maintained when the patient changes the position; and grade C, severe dilatation of the remnant stomach or no passage of the contrast medium to the jejunum.

DGE was classified into grades A, B, and C according to the definition proposed by the International Study Group of Pancreatic Surgery[11]: grade A, unable to tolerate solid oral intake by POD 7 and usually no vomiting; grade B, unable to tolerate solid oral intake by POD 14 with/without vomiting; and grade C, unable to tolerate solid oral intake by POD 21 with/without vomiting. Reinsertion of the gastric tube or opening of the gastrostomy on or after POD 7 was considered to be indicative of DGE. Because the timing of serving food was influenced by the preference of each attending surgeon, grade A was not considered to be a clinically relevant complication, but grade B and C DGE were. The complications other than POPF and DGE were classified according to the criteria proposed by Clavien and Dindo,[22] and only the complications related grade 2 above were recorded.

Univariate and Multivariate Analysis of Risk Factors for DGE

The univariate analysis of risk factors for DGE (grade B or C) was performed in relation to the following clinicopathological variables: operative period (2004–2006 vs. 2007–2009), age (≥65, <65 years), gender, body mass index (≥25, < 25 kg/m^2), presence of diabetes mellitus, performance of preoperative biliary drainage, disease (pancreatic cancer vs. others), presence of background pancreatitis, size of the main pancreatic duct (≥3 mm, <3 mm), surgical procedures (PPPD vs. CW or SSPPD), combined portal vein resection, intraoperative radiation therapy, method of pancreaticojejunostomy (duct-to-mucosa anastomosis vs. dunking method), method of duodeno-/gastrojejunostomy (stapled vs. hand-sewn reconstruction), surgical experience of the attending surgeons (≥20 years, <20 years), operative time (≥500 min, <500 min), blood loss (≥750 ml, <750 ml), results of bile juice culture on day 1, and POPF (absent or grade A vs. grade B or C). The thresholds of age, operative time, and blood loss were determined on the basis of the median value of each parameter. Multivariate analysis was performed using the significant factors in the univariate analysis.

Statistical Analysis

Analysis was performed using SPSS for Windows statistical software (SPSS Inc., Chicago, IL). The chi-square test or Fisher's exact test was used for univariate analysis, and the Mann–Whitney U test was used to compare the variables between the two groups. A multivariate analysis of the risk factors for DGE was performed using logistic regression analysis. Data were expressed as median and range. A P value of less than .05 was considered statistically significant.

Results

Four patients (1.0%) died in the hospital as a result of the surgery: massive bleeding caused by POPF in two patients, Guillain–Barre syndrome in one patient, and congestion of the portal venous system in one patient. The overall surgical complications are summarized in Table 1. Reoperation was performed in eight patients (2%). Other than the complications in Table 1, one patient who underwent hand-sewn reconstruction developed anastomotic leak, and four patients who underwent stapled reconstruction developed anastomotic bleeding on POD 1 in one, POD 9 in two, and POD 16 in one. No anastomotic leakage was found in the group of stapled reconstruction. All four patients underwent endoscopic clipping of the bleeding points, and they recovered conservatively.

Table 1 Summary of postoperative complications of 387 patients who underwent pancreaticoduodenectomy

	Grade	*n*	(%)
POPF (*n*=197, 51%)	A	56	15
	B	129	33
	C	12	3
DGE (*n*=188, 49%)	A	118	31
	B	38	9.8
	C	32	8.3
Wound infection (*n*=38, 9.8%)	2	32	8.3
	3a	1	0.3
	3b	1	0.3
Pneumonia (*n*=15, 3.9%)	2	10	2.6
	3a	2	0.3
	4a	2	0.3
	5	1	0.3
Intra-abdominal bleeding (*n*=11, 2.8%)	3a	1	0.3
	3b	2	0.5
	4a	5	0.3
	4b	1	0.3
	5	2	0.5
Intra-abdominal abscess (*n*=62, 16%)	2	31	8
	3a	22	1.3
	3b	2	0.3
	4a	4	0.3
	4b	1	0.3
	5	2	0.5
Diarrhea (*n*=17, 4.4%)	2	17	4.4

Other complications are defined according to the classification of Clavien and Dindo[22]

POPF postoperative pancreatic fistula—graded according to the definition proposed by an International Study Group on Pancreatic Fistula (ISGPF)[21], *DGE* delayed gastric emptying—defined by the International Study Group of Pancreatic Surgery (ISPGS)[11]

Risk Factors for Grade B or C DGE

DGE was found in 188 patients (49%): grade A in 118 (31%) patients, grade B in 38 (9.8%), and grade C in 32 (8.3%), excluding four patients who died as a result of surgery and one patient who did not undergo alimentary reconstruction. In univariate analysis, male sex, hand-sewn reconstruction, blood loss (≥750 mL), and POPF (grade B or C) were identified as significant risk factors for grade B or C DGE (Table 2). Median hospital stay of patients without relevant DGE (*n*=312) and with relevant DGE (*n*=70) was 22 (9–84) days and 43 (20–324) days, respectively ($P<0.001$). Multivariate analysis also revealed hand-sewn reconstruction, male sex, and grade B or C POPF as independent risk factors (Table 3).

Comparison of the Results According to Methods of Alimentary Reconstruction

There was a significant difference between stapled and hand-sewn reconstructions in blood loss, incidence of re-gastric drainage, days until regular diet, incidence of DGE, and hospital stay (Table 4). Operative time was significantly shorter in the group of double-layer anastomosis than in the group of single-layer anastomosis. In hand-sewn reconstruction, the incidences of DGE and re-gastric drainage were significantly lower in single-layer anastomosis (Gambee anastomosis, *n*=84) than in double-layer anastomosis (Albert–Lembert or layer-to-layer anastomosis, *n*=229; 12% vs. 24%, $P=0.02$). Days until regular diet and hospital stay were significantly shorter in single-layer anastomosis than those in double-layer anastomosis, although there were no differences in sex, disease, operative procedure, results of UGI study, and POPF between the 2 groups.

Discussion

DGE after PD is a unique complication, which is rarely seen after distal pancreatectomy or distal gastrectomy. DGE has been reported to be affected by several factors including gastric dysrhythmias due to intra-abdominal complications,[10,23] gastric atony after duodenal resection in response to reduction in motilin levels,[7,24,25] pylorospasm secondary to vagotomy,[26] angulation of the reconstructed alimentary tract[27] and continuous enteral nutrition.[3,28] Several comparative retrospective studies have revealed that antemesenteric reconstruction,[10] vertical reconstruction,[29] and antecolic reconstruction[30,31] were associated with a decreased risk for DGE. Furthermore, some prospective randomized trials have reported that erythromycin,[7,24] cyclic enteral feeding, rather than continuous enteral

Table 2 Summary of clinicopathological factors of patients with and without delayed gastric emptying

		Without DGE (n=312)	With DGE (n=70)	P value
Patient characteristics				
Operative period	2004–2006	157	28	0.12
	2007–2009	155	42	
Age	<65	147	28	0.28
	≥65	165	42	
Sex	Male	176	55	0.001*
	Female	136	15	
Body mass index	<25	294	63	0.20
	≥25	18	7	
Diabetes mellitus	Absent	221	45	0.28
	Present	91	25	
Preoperative biliary drainage	Not performed	160	35	0.85
	Performed	152	35	
Diseases	Pancreatic cancer	165	35	0.66
	Others	147	35	
Background pancreatitis	Absent	189	36	0.16
	Present	123	34	
Size of main pancreatic duct	<3 mm	127	36	0.10
	≥3 mm	185	34	
Surgical parameters				
Operative procedure	CW or SSPPD[a]	64	19	0.22
	PPPD	248	51	
Portal vein resection	Not performed	244	55	0.95
	Performed	68	15	
IORT	Not performed	276	60	0.67
	Performed	35	9	
Pancreaticojejunostomy	Duct-to-mucosa	281	58	0.21
	Dunking	28	11	
Braun anastomosis	Braun or Roux-en-Y	244	62	0.054
	No Braun	67	8	
Duodeno/gastrojejunostomy	Hand-sewn	248	65	0.009*
	Stapled	64	5	
Experience of the attending surgeons	<20 years	163	28	0.06
	≥20 years	149	28	
Operative time	<500 min	159	30	0.22
	≥500 min	153	40	
Blood loss	<750 mL	165	24	0.005*
	≥750 mL	147	46	
Postoperative factors				
Bile juice culture on day 1	Negative	132	29	0.31
	Positive	94	28	
POPF	Absent or grade A	214	30	<0.001*
	Grade B or C	98	40	

[a] Including two patients undergoing total gastrectomy for gastric cancer

*P<0.05

DGE delayed gastric emptying, *CW* classical Whipple procedure, *SSPPD* subtotal stomach preserving pancreaticoduodenectomy, *PPPD* pylorus-preserving pancreaticoduodenectomy, *IORT* intraoperative radiation therapy, *POPF* postoperative pancreatic fistula—graded according to the definition proposed by an international study group on pancreatic fistula (ISGPF)[21]

feeding,[32] and antecolic reconstruction[33] were effective for reducing the incidence of DGE. The present study is the first to highlight the anastomotic method and show through multivariate analysis that the method of alimentary reconstruction of duodenojejunostomy or gastrojejunostomy strongly influences the occurrence of DGE. The present result implied that DGE could be initiated by anastomotic edema or stenosis following a disturbance in blood supply,

Table 3 Multivariate logistic regression of risk factors for delayed gastric emptying (grade B or C)

Variables	Risk ratio	95% CI	*P* value
Hand-sewn reconstruction	2.888	1.094–7.623	0.03*
Sex (male)	2.189	1.145–4.183	0.02*
POPF (grade B or C)	2.371	1.365–4.117	0.002*

*$P<0.05$

POPF postoperative pancreatic fistula—graded according to the definition proposed by an international study group on pancreatic fistula (ISGPF)[21]

which in turn may accelerate the progression of gastroparesis. Stapled reconstruction rather than hand-sewn reconstruction and single-layer anastomosis rather than double-layer anastomosis were associated with decreased risks for DGE and shorter hospital stay.

In this study, the definitions of POPF and DGE were determined on the basis of the international definition recently proposed by the International Study Group of Pancreatic Surgery[11,21] to avoid detection bias resulting from the previously unclear definition. We regard grade A DGE as a non-relevant complication because the slight delay in starting a regular diet can be attributed to the discretion of the attending staff. When a patient has a high fever with relevant POPF in an early postoperative period, the patient may be prohibited from oral feeding irrespective of the presence of DGE, but this secondary fasting could not be clearly distinguished from real DGE in a retrospective analysis. Therefore, we considered only grade B or C DGE as a relevant complication.

Stapled alimentary reconstruction is now widely used in gastric, colorectal, or esophageal surgery.[14–16] The possible advantages of stapled reconstruction are: standardized approach irrespective of the operating surgeon, institution, or surgical approach (open vs. laparoscopic); easy in performing the reconstruction; and possible avoidance of anastomotic edema and subsequent stricture formation. On the other hand, its disadvantages include: high cost, risk of bleeding at the anastomotic site, and mass-production of industrial waste.[13] Notably, in our previous study, the operative costs were higher in the stapled group, but the overall hospital costs were higher in the hand-sewn group.[13] Recent advances in laparoscopic surgery have made it possible to perform PD for lower grade malignancies and invasive cancer.[17] Reconstruction of the stomach using circular a stapler can become an indispensable step of laparoscopic PD, and it is therefore mandatory to have a clear grasp of the results of employing stapled alimentary reconstruction during open PD.

Several authors have reported that some reconstructive procedures, such as antecolic reconstruction,[30,31,33] antemesenteric reconstruction,[10] and vertical reconstruction[29,30,] reduce the incidence of DGE. In some historical studies, the incidence of DGE was lower in the CW or SSPPD group than in the PPPD group.[34,35] A possible reason for a higher incidence of DGE in the PPPD group is that duodenojejunostomy is narrower than gastrojejunostomy, while the remnant stomach is larger in the PPPD group than in the CW group, which might disturb the passage of the food. However, three prospective randomized trials and a meta-analysis have negated the advantage of the CW over PPPD groups.[8,9,36,37] In our study, the incidence of DGE was comparable between CW (or SSPPD) and PPPD groups (23% vs. 17%, $P=0.22$). Based on a review of the literature and present results, it seems that PPPD is not inferior to CW or SSPPD, and that the operative procedure itself is not an essential factor for the occurrence of DGE.

In the multivariate analysis, POPF was an independent risk factor for DGE. Numerous researchers have reported that DGE develops more frequently in patients with POPF or peritonitis compared to those without such inflammatory complications.[3,5,10,12,23,39] POPF remains the leading lethal complication after PD. The incidence of POPF (grade B or C, 36%) in our series is much higher than those of the previously reported series. This may be partly because the amylase concentration in the drain fluid was measured repeatedly until it decreased, and the decision to remove the drain was made carefully and gradually. Such prolonged drain placement may evoke retrograde infection in the surgical site and may increase the risk for POPF. The hospital stay of patients in this study was longer than that of patients in the United States and Europe, which may be attributed to the difference in insurance systems. However, the mortality rate in our 387 cases of PD was 1%, which is an acceptable rate and supports the safety of our perioperative management.

In the multivariate analysis, sex was also an independent risk factor for DGE; DGE was found more often in men than in women. This finding is supported by those of other reports,[31,39] but the underling pathogenesis remains unclear. In our institute, POPF was more frequent in men than in women,[38] which could be attributed to the increased incidence of DGE in men.

There is an argument that not stapled anastomosis, but Roux-en-Y limb reconstruction or Braun reconstruction might influence on the incidence of DGE. In patients with Braun anastomosis or Roux-en-Y limbs, pancreatic and the bile juice are diverted through the jejunal limb away from the stomach. However, no significant difference was found in the incidence of DGE between Braun or Roux-en-Y group and no-Braun group (Table 2). It is difficult to speculate the clinical impact of jejunal limb reconstruction on the occurrence of DGE in this study.

Table 4 Methods of duodenojejunostomy or gastrojejunostomy and surgical outcomes of pancreaticoduodenectomy

	Stapled reconstruction (n=69)	Hand-sewn reconstruction (n=313)	P value (stapled vs. hand-sewn)	Hand-sewn reconstruction (n=313)			
				Single-layer anastomosis (n=84)	Double-layer anastomosis (n=229)		P value (Single-layer vs. two-layer)
				Gambee anastomosis (n=84)	Albert–Lembert anastomosis (n=198)	Layer-to-layer anastomosis (n=31)	
Gender, male	43 (62%)	188 (60%)	0.73	51 (61%)	116 (59%)	21 (68%)	0.89
Disease, pancreatic cancer	28 (41%)	154 (49%)	0.19	40 (48%)	97 (49%)	17 (55%)	0.74
Operative procedure							
PPPD	52	247	0.52	68	151	28	0.59
CW or SSPPD	17	66		16	47	3	
Operative time (min)	510 (240–990)	480 (210–1000)	0.82	540 (240–790)	510 (300–990)	360 (300–680)	0.04*
Blood loss, ≥750 mL	26 (38%)	167 (53%)	0.02*	47 (56%)	106 (54%)	14 (45%)	0.58
Re-gastric drainage	2 (2.9%)	45 (14%)	0.009*	3 (9.7%)	35 (17.7%)	7 (22.6%)	0.001*
POPF (grade B or C)	19 (27.5%)	119 (38%)	0.10	36 (42.9%)	72 (36.3%)	11 (35.5%)	0.29
Results of UGI study							
Grade A	38	47	0.95	23	10	14	0.35
Grade B	10	12		3	6	3	
Grade C	5	5		2	1	2	
Days until regular diet (days)	5 (4–35)	8 (4–59)	<0.001*	6 (4–34)	8 (5–59)	7 (5–40)	<0.001*
DGE (grade B or C)	5 (7.2%)	65 (21%)	0.009*	10 (11.9%)	48 (24.2%)	7 (22.6%)	0.02*
Hospital stay (days)	18 (10–60)	25 (9–324)	<0.001*	21 (10–84)	26 (9–324)	25 (14–60)	0.001*

*P<0.05

CW classical Whipple procedure, *SSPPD* subtotal stomach preserving pancreaticoduodenectomy, *PPPD* pylorus-preserving pancreaticoduodenectomy, *POPF* postoperative pancreatic fistula—graded according to the definition proposed by an international study group on pancreatic fistula (ISGPF)[21], *Re-gastric drainage* reinsertion of nasogastric tube or opening the gastrostomy tube, *UGI study* upper gastrointestinal study using oral contrast medium, *DGE* delayed gastric emptying—defined by the International Study Group of Pancreatic Surgery (ISPGS)[11]

This is a single institutional, retrospective cohort study of DGE in 387 patients who had undergone PD. We performed a multivariate analysis using logistic regression model and found that hand-sewn reconstruction was an independent risk factor of the occurrence of DGE. But we must concede that the large variability regarding the surgical procedures and techniques in our institute might make it difficult to detect the influence of a single variation on the occurrence of DGE. A multi-institutional, prospective randomized trial is necessary to objectively evaluate the clinical significance of stapled reconstruction during PD.

We experienced 5.7% anastomotic bleeding in four out of 70 patients who underwent stapled reconstruction, while 0% in 317 patients who underwent hand-sewn reconstruction, which should be a significant complication. Since the initial four bleeding events, we routinely performed intraoperative hemostasis on the anastomotic site via the jejunal loop, and thereafter, we experienced no bleeding in the subsequent 50 patients. Stapled reconstruction would be beneficial not only for patients by reducing DGE, but also for surgeons because it is a simple and easy method.

In conclusion, POPF, hand-sewn reconstruction, and sex (male) were independent risk factors for DGE in the present study on the cohort of 387 patients who had undergone PD. The method of alimentary reconstruction affected the occurrence of DGE. The incidence of DGE was more frequent in patients with hand-sewn reconstruction than in those with stapled reconstruction in our setting. A multi-institutional, prospective randomized trial is necessary to objectively evaluate the clinical significance of stapled reconstruction during PD.

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ORIGINAL ARTICLE

Liver Abscess After Liver Metastasectomy is a Poor Prognostic Factor in Patients with Colorectal Cancer

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Abstract
Purpose More and more complications of extensive hepatic resection are being encountered in patients treated for liver metastases from colorectal cancer. This study aimed to determine the impact of liver abscess after hepatic resection on overall survival (OS) and the role of adjuvant chemotherapy.
Methods This is a retrospective study of 252 patients treated by liver metastasectomy between 2001 and 2010.
Results The 5-year survival rate was 55.8%. Twenty-one (8.3%) patients developed liver abscess after liver metastasectomy. Multivariate analysis identified the size of liver metastasis, surgical margin, and the presence of liver abscess as significant prognostic factors. Patients (whether or not they developed liver abscess after hepatic resection) had similar progression-free survival (median, 9.8 vs. 12.4 months, P=0.476), but patients who developed liver abscess had significantly shorter OS (26.6 vs. 76.0 months, P=0.004). Subsequent adjuvant therapy significantly improved OS in these patients (16.9 vs. 38.5 months, P=0.032).
Conclusions Liver abscess after liver metastasectomy is an independent prognostic factor, and adjuvant chemotherapy is warranted in those patients who develop liver abscess.

Keywords Chemotherapy adjuvant · Colorectal neoplasms · Hepatectomy · Liver abscess

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Introduction

Colorectal cancer is a common cause of cancer death worldwide, and over half of all patients either have metastatic disease at the time of diagnosis or develop metastases later, usually in the liver. If left untreated, patients rarely survive beyond 5 years.[1,2] In the last decade, most surgeons only performed liver metastasectomy when the number of liver metastases was “”one to four.[3] However, the surgical criteria for resectability became more extensive as conversion therapy improved. The addition of target drugs to conventional chemotherapy {i.e., the addition of cetuximab or bevacizumab combined with FOLFOX [oxaliplatin/infusional 5-fluorouracil (5-FU)/leucovorin (LV)] or FOLFIRI [irinotecan/infusional 5-FU/LV]; FOLFOXIRI [oxaliplatin/irinotecan/infusional 5-FU/LV]; bevacizumab/oxaliplatin/irinotecan/infusional 5-FU/LV}[4–9] increased the rate of resectability so that, now, hepatic resection with clear surgical margins[10] and adequate residual liver function[11] is the standard treatment for patients with liver metastases with or without limited lung metastases. The 5-year survival rate after hepatic resection has increased in the past 10 years to 12–58%.[3,10,12,13] Unfortunately, the rate of complications (bile leak, biliary fistula, peritonitis, intestinal bleeding, pleural effusion, wound infection, hemoperitoneum, impairment of liver function, liver failure, and liver abscess) resulting from extensive hepatic resection has also increased.[14–17]

The rate of liver abscess (a common cause of morbidity after hepatic resection) is 1.1–6.9%.[4,5,14,16,17] Many studies report this complication of hepatic resection, but none have examined its association with liver abscess, survival, and efficacy of adjuvant chemotherapy in these patients.

Herein, we retrospectively obtained data from a single institution to examine the impact of liver abscess after hepatic resection on survival and the efficacy of adjuvant chemotherapy in patients with colorectal cancer metastatic to the liver.

Methods

From January 2001 to January 2010, a total of 252 consecutive patients with colorectal cancer and liver metastases received hepatic resection at Taipei Veteran General Hospital, Taiwan. Patients with histologically proven non-carcinoma were excluded. Disease stage was based on the American Joint Committee on Cancer staging system, 6th edition. Clinicopathological staging and clinical course were determined from computer database records, and recurrence and death after hepatic resection were obtained from hospital records and the National Cancer Registry.

Left colon cancer was defined as malignancy in the splenic flexure, descending colon, sigmoid, and/or rectosigmoid colon, and right colon cancer was defined as that occurring in the cecum, ascending colon, hepatic flexure, and/or transverse colon. The decision for hepatic resection was made by clinical physicians after considering the extent of the metastatic lesions and condition of the individual patient. Limited lung metastasis was defined as one to five metastases in the bilateral peripheral lung field. Also, resectability was assessed by thoracic surgeons.

Death from any cause was regarded as an event. Patients who remained alive at the end of the follow-up period were censored. Overall survival (OS) was defined as the time from hepatic resection to death from any cause. Progression-free survival (PFS) was measured from the date of hepatic resection to the date of confirmation of recurrence. Surgical mortality was defined as death within 30 days after hepatic resection.

The criteria for liver abscess were clinical signs of infection (leukocytosis, fever, bacteremia, or sepsis) and images showing liver abscess on either ultrasound or computerized tomography (CT). The treatment of liver abscess included antibiotics with or without percutaneous drainage. Microbiological findings, whether or not adjuvant therapy was given, liver abscess characteristics, and time of abscess onset were evaluated before prescribing antibiotic treatment. After hepatic resection, the attending physician decided whether to administer adjuvant chemotherapy.

The follow-up period ended either on July 2010 or on the death of the patient. Patients were followed up at least every 3 months from time of hepatic resection for the first 2 years, thereafter every 6 months for 5 years, and then annually until death. Follow-up visits included physical examination, rectal digital examination, assay of carcinoembryonic antigen (CEA) level, chest X-ray, abdominal sonogram, and/or abdominal CT scanning. If recurrence was suspected, further examinations (such as chest CT scanning, whole body bone scanning, or whole body positron emission tomography scanning) were performed.

The correlations between clinicopathological variables and liver abscess were analyzed by χ^2 test or Fisher’s exact test. The Cox proportional hazards model was applied for univariate and multivariate analyses. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used for the comparison of survival curves. Variables with P values<0.05 in univariate analyses were entered into multivariate analysis models. A two-sided P value <0.05 was regarded as statistically significant. SPSS software (version 16.00, SPSS, Chicago, IL) was used for all statistical analyses.

Results

Patient Characteristics and 5-Year OS and PFS

A total of 252 patients [160 men (63.5%) and 92 women (36.5%); mean age at diagnosis, 61.9 years; range, 28–87] were included in the analysis. Their characteristics are presented in Table 1. In most cases, adenocarcinoma (96.8%) was histopathologically diagnosed. The percentage of patients with initial stage I, II, III, and IV disease was 1.6%, 9.9%, 26.2%, and 62.3%, respectively. The median interval between initial diagnosis and the development of liver metastasis in patients of initial stage I to III was 12.9 months (range, 1.6–68.5 months). Fifteen patients had more than five liver metastases and 21 patients had limited lung metastasis. The incidence of liver abscess after hepatic resection was 8.3%. The surgical mortality rate was only 0.4%. The 5-year survival rate for the entire cohort was 55.8%. The 5-year PFS rate was 21.0% (Fig. 1a, b).

Liver Abscess After Hepatic Resection Was an Independent Prognostic Factor

Univariate analysis was used to evaluate the impact of primary tumor location, tumor stage, lobe distribution, tumor size, number of tumors, resection margin, presence of extra liver or limited lung metastases, serum CEA level, adjuvant chemotherapy, and presence of liver abscess on survival (Table 2). In our series, 10 out of 21 patients with limited lung metastasis underwent lung metastasectomy. The majority of the lung metastasectomies (seven out of ten) in our series were performed following adjuvant chemotherapy after liver metastasectomy, and three of the patients received liver and lung metastasectomies simultaneously. Metastasis to both lobes of the liver, tumor size more than 5 cm, more than five metastases, resection margin not free of tumor, extra liver and limited lung metastasis, as well as liver abscess were significant poor prognostic factors.

Table 1 Characteristics of 252 patients with liver metastases of colorectal cancer after hepatic resection

		N	Percentage
Age (years old)	Median (range)	61.9	28–87
Sex	Female	92	36.5
	Male	160	63.5
Location	Left	101	40.1
	Right	76	30.2
	Rectum	75	29.8
Pathology	Adenocarcinoma	244	96.8
	Mucinous adenocarcinoma	7	2.8
	Undifferentiated carcinoma	1	0.4
AJCC 6th	I	4	1.6
	II	25	9.9
	III	66	26.2
	IV	157	62.3
Lobe	Unilateral	217	86.2
	Bilateral	35	13.8
Size (cm)	≤5	210	83.3
	>5	42	16.7
Number	≤5	237	94.0
	>5	15	6.0
Margin	Free	229	90.9
	Not free	23	9.1
Extra liver and/or limited lung metastases	None	197	78.2
	Limited lung metastasis	21	8.3
	Others	34	13.5
CEA (ng/ml)	≤20	159	63.1
	>20	93	36.9
Abscess	No	231	91.7
	Yes	21	8.3
Surgical mortality	Yes	1	0.4

AJCC American Joint Committee on Cancer

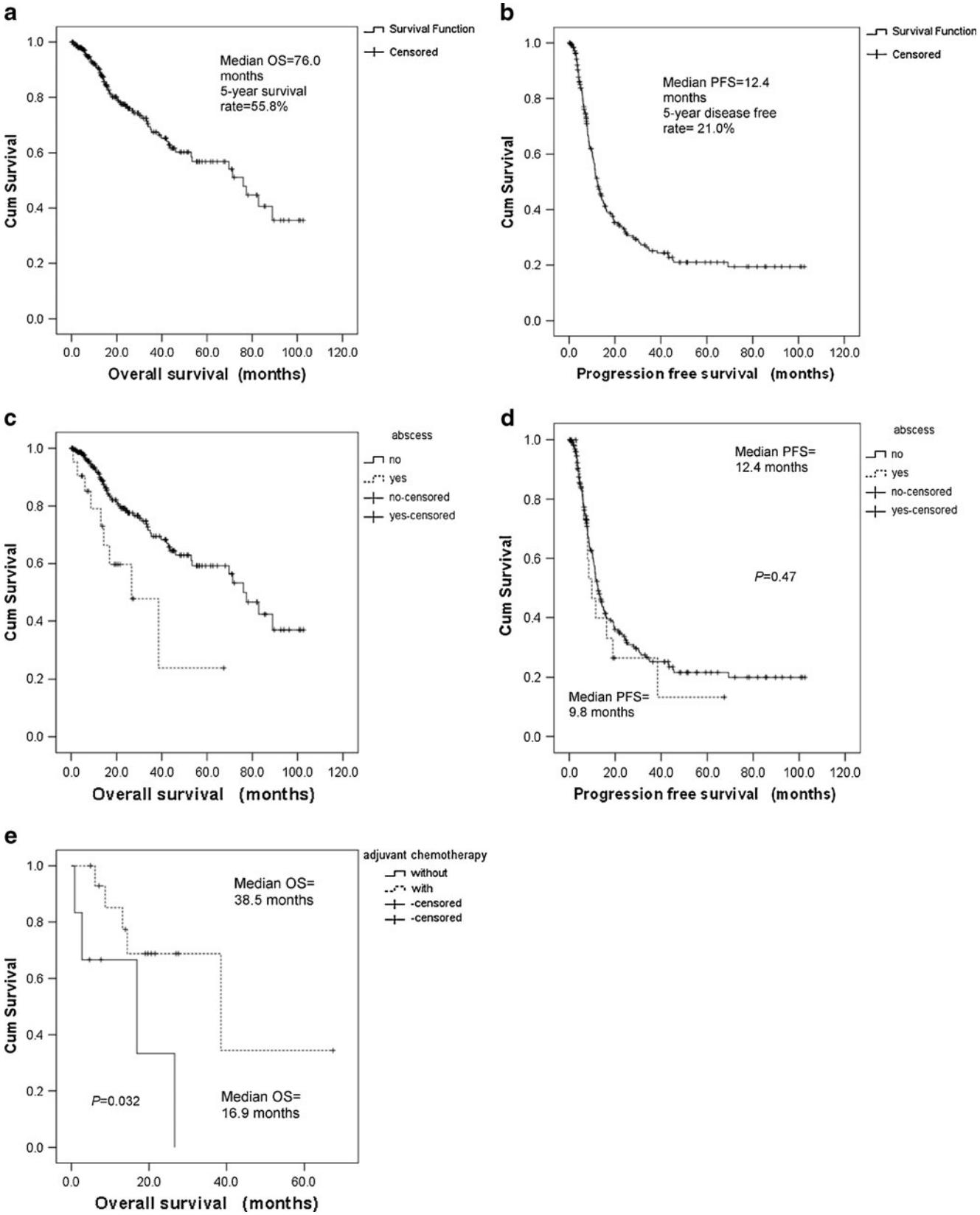

Fig. 1 Overall survival (*OS*) and progression-free survival (*PFS*) of all patients receiving hepatic resection and those patients who developed or failed to develop liver abscess. The OS of patients who developed liver abscess and received or did not receive adjuvant chemotherapy: **a** OS after liver metastasectomy. **b** PFS after liver metastasectomy. **c** OS after liver metastasectomy with and without liver abscess. **d** PFS after liver metastasectomy with and without liver abscess. **e** OS of patients with liver abscess and given or not given adjuvant chemotherapy

Table 2 Prognostic factors for overall survival of patients receiving liver metastasectomy

		Univariate analysis			Multivariate analysis		
		P value	HR	95% CI	*P* value	HR	95% CI
Location	Rectum vs. colon	0.372	0.861	0.620–1.196			
Stage	III, IV vs. I, II	0.062	1.739	0.973–3.108			
Lobe	Bilateral vs. unilateral	0.014*	2.359	1.191–4.674	0.314	1.493	0.685–3.255
Size (cm)	>5 vs. ≤5	0.010*	2.094	1.191–3.684	0.011*	2.143	1.187–3.870
Number	>5 vs. ≤5	0.008*	4.170	1.454–11.958	0.054	3.282	0.979–11.009
Margin	Not free vs. free	<0.001*	3.417	1.715–6.809	0.012*	2.624	1.239–5.559
Extrahepatic and/or limited lung metastases	Others and limited lung vs. none	0.018*	1.434	1.064–1.931	0.152	1.271	0.916–1.765
CEA	>20 vs. ≤20	0.081	1.556	0.946–2.558			
Adjuvant chemotherapy	With vs. without	0.784	1.115	0.505–2.463			
Abscess	With vs. without	0.006*	2.736	1.339–5.594	0.033*	2.303	1.072–4.947

HR hazard ratio, *CEA* carcinoembryonic antigen

*$P<0.05$

Liver abscess was identified as an independent prognostic factor by multivariate analysis after adjustment for lobe, tumor size, number, margin, and extrahepatic and/or limited lung metastasis (hazard ratio=2.303, $P=0.033$).

Characteristics of Patients Who Developed or Failed to Develop Liver Abscess After Liver Resection

Table 3 shows the characteristics of patients with or without liver abscesses after hepatic resection. Four patients developed

Table 3 Characteristics of patients with and without liver abscess before hepatic resection

		Without abscess		With abscess		*P* value
		n	%	*n*	%	
AJCC stage	I/II	25	9.9	0	0.0	0.107
	III/IV	190	75.4	21	7.9	
Hepatic lobes	Unilateral	202	80.2	15	6.0	0.042*
	Bilateral	29	11.5	6	2.4	
Size (cm)	≤5	193	76.6	17	6.7	0.760
	>5	38	15.1	4	1.6	
No. of metastases	≤5	218	86.5	19	7.5	0.470
	>5	13	5.2	2	0.8	
Extra liver and/or limited lung metastases	No or limited lung	203	80.6	15	6.0	0.035*
	Others	28	11.1	6	2.4	
Margin	Free	211	83.7	18	7.1	0.391
	Not free	20	7.9	3	1.2	
Progression site	No	84	33.3	8	3.2	0.641
	Liver	94	37.3	10	4.0	
	Not liver	53	21.0	3	1.2	
CEA (ng/ml)	≤20	147	58.3	12	4.8	0.555
	>20	84	33.3	9	3.6	
Adjuvant chemotherapy	None given	32	12.8	6	2.4	0.075
	With	197	78.8	15	6.0	

AJCC American Joint Committee on Cancer, *HR* hazard ratio, *CEA* carcinoembryonic antigen

*$P<0.05$

abscess after starting adjuvant chemotherapy, and the intervals between the start of chemotherapy and the diagnosis of liver abscess were 10, 10, 6, and 4 months each. The incidence of liver abscess formation was significantly higher in patients with extrahepatic and/or limited lung metastasis or treated by bilobar liver resection. The OS and PFS in patients with and without abscess are shown in Fig. 1c, d. These patients had similar PFS (9.8 vs. 12.4 months, P=0.476) whether or not they had liver abscesses, and the OS of patients who developed liver abscesses after hepatic resection was definitely shorter than that of patients without abscess formation (26.6 vs. 76.0 months, P=0.004). With respect to induction chemotherapy, of 252 patients who underwent liver metastasectomy, 50 patients (19.8%) received induction chemotherapy prior to liver metastasectomy, among whom seven patients (14%) developed liver abscess. Compared with patients who did not receive induction chemotherapy, they did not have a significantly increased risk of developing liver abscess (P=0.357).

Characteristics of the Liver Abscess

Table 4 presents the characteristics of liver abscesses in the 21 patients (median age, 60 years; range, 27–86). Most abscesses were diagnosed by CT imaging (71.2%) and were larger than 5 cm (85.7%). There were multiple pathogens found in the pus culture, leading to the administration of a variety of antibiotics. Liver abscesses due to the most common pathogen—*Escherichia coli* (23.8%)—developed within 3 months after hepatic resection. Most patients with abscesses were treated by percutaneous drainage (82.7%), and 43.8% of the patients needed antibiotic treatment for more than 1 month. After antibiotic treatment, the abscesses were no longer apparent on the images of 15 (71.4%) patients. The six patients who did not receive adjuvant chemotherapy had significantly shorter survival (16.9 vs. 38.5 months, P=0.032) than the patients who did (Fig. 1e). Of those treated with adjuvant chemotherapy, 80% (12 out of 15) received adjuvant chemotherapy after completing antibiotic therapy. Of 15 patients with liver abscess who received adjuvant chemotherapy, 12 were administered oxaliplatin/5-FU-based chemotherapy (one patient in combination with cetuximab) and three received irinotecan/5-FU-based chemotherapy. The median duration to the development of liver abscess after liver metastasectomy was 21 days (range, 8–610 days). Of the five patients who developed liver abscess 3 months after liver metastasectomy, four received induction chemotherapy prior to abscess formation, three being administered oxaliplatin/5-FU-based chemotherapy and one receiving irinotecan/5-FU-based chemotherapy, similar to the general population, which meant that there were no particular regimens associated with late abscess development.

Discussion

The 5-year survival rate after hepatic resection in patients with liver metastases of colorectal cancer was 55.8%, which was similar to the rates reported in a recent surgical series.[11,18] In all, 21 (8.3%) of our patients developed liver abscess after hepatic resection. These patients had significantly poorer OS than those without liver abscess (median OS, 26.6 vs. 76.0 months, P=0.004; Fig. 1c), although there was no difference in PFS between the patients who did or did not develop abscess (median PFS, 9.8 vs. 12.4 months, P=0.476; Fig. 1d). One of the reasons for which the PFS of these patients was not significantly shorter—but they had an obviously poorer OS—might be that some of the patients with liver abscess were dying of infection rather than cancer. Those who recovered sufficiently from the abscess might have a survival similar to those without liver abscess, but the OS of patients who developed liver abscess was statistically inferior. Moreover, adjuvant chemotherapy after hepatic resection in those who developed liver abscess improved the OS (median OS, 38.5 vs. 16.9 months, P=0.032; Fig. 1e). The reason for which there was no significant difference in OS for patients who received liver metastasectomy with adjuvant chemotherapy—but, however, the benefit to OS for those with liver abscess was obvious—may be because the presentation of patients complicated by liver abscess appeared to be more advanced as they had a higher incidence of extrahepatic metastases or treated by bilobar liver resection, as seen in Table 3 (P=0.042 and 0.035, respectively). Therefore, they benefit more from adjuvant chemotherapy, resulting in a survival advantage.

With advances in chemotherapy and the multidisciplinary approach, the proportion of patients receiving extensive hepatic resection and the incidence of its complications have increased greatly in recent years. Indeed, the incidence of liver abscess was 8.3% in our cohort, which was higher than previously reported (1.1–6.9%).[4,5,14,16,17] In our study, resection of the bilobar liver and the occurrence of extrahepatic and/or limited pulmonary metastases were associated with the occurrence of liver abscess after hepatic resection, implying that the incidence of liver abscess formation is related to the difficulty and duration of hepatic surgery. In support, a previous study found that prolongation of the Pringle maneuver, blood transfusion more than 600 ml, biliary leakage, pleural effusion, large-volume liver resection, as well as hemoperitoneum were associated with liver abscess after hepatic resection.[14,19]

The causes of liver abscesses include ascending biliary infection, portal bacteremia, septicemia, direct extension from intraperitoneal infection, direct trauma to the liver, or infection of the liver secondary to tumor metastasis.[20,21] Surgery-related liver abscess has been associated with the translocation of

Table 4 Characteristics of 21 patients with colorectal cancer, liver metastases, and liver abscesses after hepatic resection

		N	Percentage
Patient's age (years old)	≥60	11	52.4
	<60	10	47.6
Patient's gender	Male	16	76.2
	Female	5	23.8
Underlying diabetes mellitus	Yes	4	19.0
	No	17	81.0
Method of diagnosis	Computer tomography	15	71.5
	Ultrasound	6	28.5
No. of abscesses at diagnosis	1	15	71.5
	2	4	19.0
	Multiple	2	9.5
Abscess size, maximum diameter (cm)	<5	3	14.3
	5–10	16	76.2
	>10	2	9.5
Microbiology	*Escherichia coli*	5	23.8
	Polymicrobial	2	9.5
	Pseudomonas aeruginosa	2	9.5
	Proteus vulgaris	1	4.8
	Aeromonas hydrophila	1	4.8
	Klebsiella pneumoniae	1	4.8
	Proteus mirabilis	1	4.8
	Prevotella sp.	1	4.8
	Enterococcus sp.	1	4.8
	Enterobacter cloacae	1	4.8
	MRSA	1	4.8
	Candida glabrata	1	4.8
	Negative culture	7	33.3
Drainage	With	17	82.7
	Without	4	17.3
Duration of the abscess	>3 months	5	23.8
	≤3 months	16	76.2
Period of antibiotic treatment	>1 month	7	43.8
	≤1 month	14	56.2
Abscess treatment results[a]	Complete remission	15	71.4
	Not complete remission	6	28.6
Time of adjuvant chemotherapy administration relative to antibiotic therapy	Concurrent with antibiotics	3	14.3
	After completion of the antibiotic course	12	57.1
	No adjuvant chemotherapy	6	28.6

MRSA Methicillin-resistant *Staphylococcus aureus*

[a] On the last image evaluated or before death

gut-derived bacteria during the prolonged portal clamping required for liver resection and with the impairment of reticuloendothelial system activity after liver ischemia.[19,22] Translocation of gut-derived bacteria during liver resection can explain the appearance of liver abscesses within 3 months after hepatic resection. For liver abscesses appearing more than 3 months after hepatic resection, these have been attributed to infection secondary to tumor metastasis.[23] The latter may also explain why patients with extrahepatic lesions are more prone to developing liver abscesses.

Klebsiella pneumoniae is reported to be the predominant pathogen causing liver abscess in Southeast Asia.[24] In contrast, *E. coli* was the predominant pathogen in the liver abscesses that developed after liver resection in our study. The difference can be attributed to the bacterial source (gut-derived bacteria transferred during hepatic resection).

The standard treatment for liver abscess is percutaneous drainage, which is regarded as safe and effective.[25] In our series, most abscesses were successfully treated by cutaneous drainage and antibiotics.

In our study as well as previous studies, no significant difference in OS was apparent between patients who received adjuvant chemotherapy and those who did not (Table 2).[13,26] However, adjuvant chemotherapy after hepatic resection improved OS in patients with liver abscesses (Fig. 1e). Moreover, in patients with liver abscess after hepatic resection, there was a non-significant trend toward less use of adjuvant chemotherapy (71.4% vs. 86.1%, $P=0.075$; Table 3).

The timing of adjuvant chemotherapy in relation to antibiotic therapy is shown in Table 4. Of the 15 patients (71.4%) who received adjuvant chemotherapy, 12 patients received adjuvant chemotherapy following remission of liver abscess; the other three received adjuvant chemotherapy concurrently with antibiotic therapy. The decision made by physicians to treat these three patients with concurrent chemotherapy and antibiotics was taken because all had a persistent image finding of abscess but were in a relatively stable general condition without symptoms and signs of sepsis, such as fever or abdominal pain. These patients were also at higher risk of relapse; for example, they had more diffuse metastasis prior to liver metastasectomy. Both regimens seemed to provide survival benefit.

In addition, there was no apparent difference in recurrence rate and pattern between patients with and without liver abscess after hepatic resection (Table 3).

The liver abscess in six patients did not completely resolve, and all of these patients died owing to infection or disease progression within 2 months. In our series, some of these abscesses were managed by repeat percutaneous drainage, and none of the patients received surgical intervention.

There were some limitations to our study. The study was retrospective in nature and the number of patients who developed liver abscess was small. There were some false-negative culture results due to the administration of antibiotics immediately after fever onset, which might have hampered culture of the pathogens even though pus was still flowing and could be aspirated from the drainage tube.

Conclusion

We concluded that liver abscess is an independent poor prognostic factor after hepatic resection in patients with liver metastases of colorectal cancer. Adjuvant chemotherapy can improve the OS of patients with liver abscess after hepatic resection and therefore should not be withheld.

Conflict of Interest Statement The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Silencing of the HCCR2 Gene Induces Apoptosis and Suppresses the Aggressive Phenotype of Hepatocellular Carcinoma Cells in Culture

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Abstract
Background The human cervical cancer oncogene HCCR-2 is overexpressed in various malignant tumors and cell lines, and might function as a negative regulator of the p53 tumor suppressor. Here, we used RNA interference strategies to evaluate the role of HCCR-2 in liver cancer, and to explore its potential therapeutic effect.
Methods Changes of HepG2 cells stably transfected by an HCCR-2 RNA interference vector were detected by real-time PCR, MTT staining, plate colony formation, flow cytometry, and cell migration experiments. Apoptosis-related protein Bcl-2 and Bax levels were measured by Western blot.
Results Our results showed that of the three siRNA-expressing vectors, siRNA-H3 had a suppressive effect on the expression of HCCR-2 mRNA, interfering with proliferation and migration of HCCR-2. Moreover, the apoptotic rate also increased, and cells transfected by siRNA-H3 were blocked in the G0/G1 stage. Plate colony formation experiments demonstrated that the single cell clone formation capacity of HepG2-H3 cells was clearly lower than that of HepG2 and HepG2-N cells. Western blot results indicated that the expression of Bcl-2 was inhibited, and the expression of Bax was increased.
Conclusions In summary, RNAi targeting HCCR-2 could be an effective means for suppressing malignant features of hepatocellular carcinoma cells.

Keywords HCCR2 · RNAi · Apoptosis · Invasion · Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide, with over half a million new cases per year,[1] and the third most common cancer killer.[2,3] Asia has a disproportionately large share of the world's HCC, mainly because of the endemicity of hepatitis B and C viruses, infections which can lead to liver cirrhosis and an increased risk of HCC.[4] Although surgery (partial hepatectomy or total hepatectomy with orthotopic liver transplantation) can be curative for localized small liver tumors, therapeutic options for patients with advanced or metastatic HCC are limited, and survival in surgically incurable HCC patients has not increased significantly over the past 30 years.[5] Many chemotherapeutic agents have been tested in HCC, with reported response rates ranging between 10% and 15%, but no survival advantage has been demonstrated. Most of the patients with advanced cancer have poor prognoses due to high rates of recurrence and metastasis. Invasion and metastasis are fundamental properties of HCC cells. Therefore, to improve the overall long-term survival of patients with HCC, more active treatment of recurrence and metastases is necessary.

Adhesion to an appropriate extracellular matrix is important for normal cells to survive, and detachment from such supportive matrices usually triggers a specific type of

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apoptosis termed anoikis.[6] Loss of sensitivity to anoikis has been shown to directly contribute to the ability of tumor cells to metastasize.[7,8] In animal models, tumors that are resistant to anoikis show a higher incidence of metastases and increased cell survival in the blood circulation.[9] Suppression of anoikis, therefore, is likely to be a prerequisite for tumor cells to successfully metastasize to distant sites.[10] A recent study indicated that anoikis-resistant hepatoma cells acquired increased invasiveness, evading therapeutic agents and escaping from immune surveillance after anchorage removal. Acquisition of anoikis resistance may act as a selective pressure to develop more metastatic potential in the development of hepatomas.[11] Therefore, restoring anoikis sensitivity could help limiting the uncontrolled spread of metastatic tumors.

The human cervical cancer oncogene (HCCR) is overexpressed in many human tumors, including liver cancers.[12,13] The HCCR gene is classified into two species, HCCR-1 and HCCR-2, according to their molecular characteristics. HCCR-2 lacks exon 1 of HCCR-1, and is identical in sequence from nucleotides 129 to 2,118.[14] Previous work suggests that cells expressing HCCR-1 or HCCR-2 were tumorigenic in nude mice. Their functional roles in tumorigenesis may be as negative regulators of the p53 tumor suppressor gene.[15,16] The HCCR is elevated according to disease progression from liver cirrhosis to carcinoma, which is more frequently positive in patients with early, small hepatocellular carcinoma.[17] HCCR2-transgenic mice have been shown to develop breast cancers and metastasis.[14] The crucial role of HCCR-2 in the anoikis resistance of HCC cells is still unclear. We hypothesize that HCCR-2 could also be involved in anoikis-resistant HCC cell metastasis. To investigate that possibility, we studied the effects of HCCR-siRNA on anoikis-resistant HCC cells.

Methods

Construction and Transfection of a siRNA Expression Vector

We selected interference sequences targeting HCCR-2 using an online design tool according to the principle of RNAi design to generate three different HCCR-2 siRNAs: siRNA-H1, an interference sequence targeting the HCCR-2 mRNA coding sequence from 475 to 493 bp; siRNA-H2, an interference sequence targeting the HCCR-2 mRNA coding sequence from 611 to 629 bp; and siRNA-H3, an interference sequence targeting the HCCR-2 mRNA coding sequence from 854 to 872 bp. The oligonucleotides 5′-GATCCGACAGATCTGTGCACCAAGATCAAGACG TCTTGGTGCACAGATCTGTTTTTTTA-3′ and 3′-GCTGTCTAGACACGTGGTTCTAGTTCTGCAGAA CCACGTGTCTAGACAAAAAAATTCGA -5′ were used to generate siRNA-H1 oligonucleotides. 5′-GATCCGT AAGATGTGAGAAGCATGGTCAAGACGCCAT GCTTCTCACATCTTATTTTTTA-3′ and 3′-GCATTCTA CACTCTTCGTACCAG TTCTGCGGTACGA AGAGTGT AGAATAAAAAAT TCGA-5′ used to generate siRNA-H2 oligonucleotides. 5′-GATCCGTTGTGCAGCAAGAGAGA CATCAAGA CGTGTCTCTCTTGCTGCACAATTT TTTA-3′ and 3′-GCAACACGTCGTTC TC TCTGTAG TTCTGCACAGAGAGAACGACGTGTTAAAAAATT CGA-5′ used to generate siRNA-H3 oligonucleotides. A scrambled sequence was used as the control siRNA ACTACCGTTGTATAGGTGT. Each oligonucleotide pair (100 pmol) was annealed by incubation at 95°C for 5 min and cooled slowly, and was ligated separately into the pGenesil-1 vector (Genesil Biotechnology Co., Ltd. Wuhan, China) which had been digested with BamHI and HindIII. As a result, four vectors, siRNA-H1, siRNA-H2, siRNA-H3, and a negative control vector, were successfully generated and verified by sequencing. These vectors were transfected into the cell line HepG2 (ATCC, Rockville, MD, USA) using Lipofectamine 2000 (Invitrogen) according to the manufacturer's protocol.

Real-time PCR

Total RNA was extracted from cell lines with Tripure (Invitrogen) according to the manufacturer's instructions. Following DNase I treatment using a DNA-free kit (Ambion), cDNA was generated from total RNA using the Perfect Real Time RT-PCR Kit (Takara, Tokyo, Japan). Real-time quantitative PCR experiments were done using the SYBR Green PCR Core kit (Applied Biosystems) according to the vendor's instructions, using an ABI 7900HT (Applied Biosystems) real-time PCR instrument. The following primer pairs were used to amplify HCCR-2 and actin: HCCR-2 forward, 5′-GGGAGATGGAG CATTTGAG-3′ and reverse, 5′-GCTTCCGGAAAG CATGATAG-3′; actin forward, 5′-GTTGCGTTACACCC TTTCTTGACA3′ and reverse, 5′-GCACGAAG GCTCAT CATTCAAAA3′. Transcript expression levels were normalized using actin levels as an endogenous control. Cycle conditions were 95°C for 5 min followed by 40 cycles of 95°C for 30 s, 58°C for 30 s, and extension for 45 s at 72°C.

Proliferation Assay

MTT experiments were performed according to the manufacturer's protocol. Parental HepG2 cells, negative control cells, and HCCR-2 siRNA cells were seeded at densities of 1×10^4 cells per well in 96-well plates. Three wells of each group of cells were picked out and added to 20 μL MTT (5 mg/mL) every 24 h. DMSO 200 μl was then added to

each well to dissolve the crystals after incubation for 4 h. Incubation went on at 37°C for 10 min. Absorbance was measured at 490 nm using a plate reader.

Soft Agar Colony Formation Assay

Tumor cells (2.0×10^2) were grown in triplicate on 10-cm^2 dishes in a suspension of 0.6% low melting point agarose (Life Technologies) and DMEM supplemented with 10% FCS. After 2 weeks, the plates were photographed under a phase-contrast microscope and assayed for colony number and size. Clones containing at least 50 cells were counted.

Migration and Invasion Assays

Confluent cells grown in 10-cm^2 dishes were wounded using a sterile pipette tip and grown in DMEM with 5% FCS. Eight hours after the wound was made, images of the cells capable of migrating across the scratch were taken with a Nikon Eclipse TE2000-U using Metaview™ software (Universal Imaging Corporation). Cell invasion assays were performed in Boyden chambers with 8-μm pore filter inserts for 24-well plates (BD Bioscience). After 12 h of incubation at 37°C, cells on the underside of the filter were fixed and stained with Giemsa and examined by light microscopy (×200 magnification). Three microscopic fields were counted for each well.

Suspension Culture and Anoikis Assay

Cells were prevented from adhering to the plastic dishes by culturing the cells in dishes coated with PolyHEMA (Sigma, St Louis, MO, USA) as described previously.[18] Briefly, culture of transient- or stable-transfected cells was trypsinized and plated onto 6-well polyHEMA plates (made by applying 1.5 ml of 10 mg/ml solution of polyhydroxyethylmethacrylate in ethanol onto the plate, and drying in a tissue culture hood). After 24 h of growth in suspension, cells were harvested for apoptosis measurements using an annexin V–FITC detection kit (Sigma) as described.[19]

Western Blot Analysis

Proteins were prepared by homogenization of cells in lysis buffer (10 mmol/L Tris–HCl, pH 8.0; 140 mmol/L NaCl; 5 mmol/L EDTA; 0.25 g/L NaN_3; 10 g/L Triton X-100; 10 g/L deoxycholate; 1 g/L SDS; 0.5 mmol/L PMSF; 1 g/L leupeptin; and 1 g/L protinin). Protein concentration was determined by the Coomassie brilliant blue method. Proteins were separated by SDS–PAGE, transferred to PVDF membranes (Millipore, Temecula, CA, USA), blocked with milk/BSA, then probed with the specific mouse antibodies against caspase-8 (Cell Signaling, USA), Bcl-2, Bax, p53, caspase-9, cleaved caspase-3, and β-actin (Santa Cruz, USA) at 1:500 dilution. After washing, the blots were incubated with secondary horseradish peroxidase-conjugated goat anti-mouse, goat anti-rat, and goat anti-rabbit antibodies; visualized using an enhanced chemiluminescence reagent (Pierce Biotechnology, Rockford, IL, USA); and subsequently exposed to autoradiographic film.

Statistical Analysis

Data are presented as the mean±SD for the indicated number of experiments and evaluated by a *t* test. *P* values below 0.05 were regarded as statistically significant. All data were analyzed with SPSS 10.0 software.

Results

siRNA Inhibits the mRNA Expression of HCCR-2 in HepG2 Cells

The three siRNAs targeting the open reading frame of HCCR-2 mRNA were tested to inhibit the expression of HCCR-2 mRNA in HepG2 cells. Real-time quantitative PCR and the relative standard curve method were used to analyze the amounts of HCCR-2 mRNA isolated from parental cells, the negative control cells, and siRNA-H1, siRNA-H2, and siRNA-H3 cells. The generated linear regression equations describing the relative standard curves were $y=-0.31x+9.26$ ($R^2=0.989$) for HCCR-2 mRNA and $y=-0.29x+7.53$ ($R^2=0.999$) for β-actin mRNA. After normalization with these equations, the calculated values of HCCR-2 mRNA relative copies are shown in Fig. 1. These results suggested that siRNA-H1 and siRNA-H3

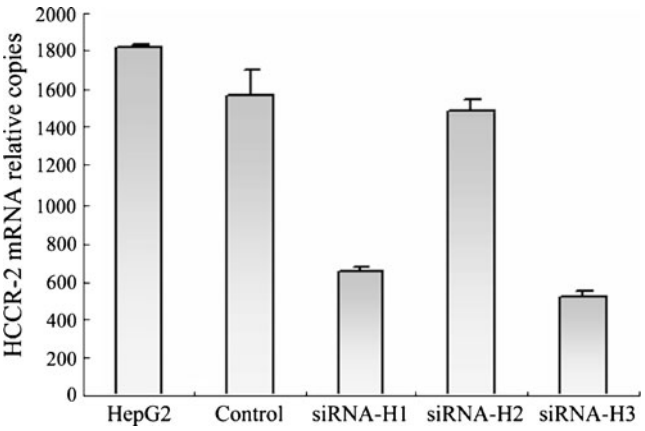

Fig. 1 siRNA effects on the expression of HCCR-2 in HepG2 cells. Relative copies HCCR-2 RNA in HepG2, negative control, siRNA-H1, siRNA-H2, and siRNA-H3 cells as determined by real-time PCR (*$P<0.01$, siRNA-H1 and siRNA-H3 versus HepG2 or HepG2/N)

can attenuate HCCR-2 activity at the mRNA level in HepG2 cells. siRNA-H3 was found to be the most effective. Therefore, we selected siRNA-H3 for subsequent experiments.

RNAi of HCCR-2 Inhibits the Proliferation and Colony Formation Capacity of HepG2 Cells

Cell colony formation capacity of HepG2-si cells was clearly lower (29.6±3.21) than that of parental HepG2 (129.3±13.57) and negative control cells (120.3±9.86) (Fig. 2a). To investigate the impact of siRNA on the proliferation of HepG2 cells, we performed MTT assays. As illustrated in Fig. 2b, negative control cells had similar growth rates compared with parental HepG2 cells, and both were clearly higher than HepG2 siRNA (HepG2-si) cells. These results demonstrated that HCCR-2 RNAi suppressed HepG2 cell proliferation in cell culture.

HCCR-2 RNAi Inhibits Cell Migration and Invasion of HepG2 Cells

Cell migration and matrigel invasion assays showed that HepG2-si cells migrated much more slowly than negative control cells and parental cells (Fig. 3a), suggesting that HCCR-2–siRNA can inhibit cell migration of HepG2 cells culture. The invasive potential of the HepG2-si cells, assessed by measuring the ability of cells to transverse a reconstituted basement membrane of matrigel, was significantly decreased (55.33±3.05), compared with that of the parental (86±4.58) and control cells (81.33±7.37, $P<0.05$) (Fig. 3b).

HCCR-2 RNAi Promote the Anoikis in HepG2 Cells

To confirm the effect of HCCR-2 RNAi on anoikis sensitivity and apoptosis frequency of HepG2-si cells, control and parental cells cultured in poly-HEMA-treated wells for 24, 48, and 72 h were quantified (Fig. 4a). Apoptosis frequency of HepG2-si cells was significantly lower (21.72%±2.23%) than in those for the control (1.56±1.22) and parental cells (2.10%±1.58%, $P<0.05$).

HCCR-2 RNAi Upregulates the Expression of Procaspase-8, Procaspase-9, and Bcl-2, and Downregulates the Expression of Bax in Resistant HCC Cells

To investigate the mechanism by which HCCR-2 RNAi promote anoikis, we checked the mitochondrial pathway. As shown in Fig. 4b, HCCR-2 siRNA clearly increased the expression of procaspase-8, procaspase-9, and Bcl-2 ($P<0.05$) and decreased the expression of Bax in HepG2 cells ($P<0.05$). However, expression of procaspase-3 and p53 in HCCR-2 siRNA cells was not notably different compared with parental and negative control cells ($P>0.05$) (Fig. 4b).

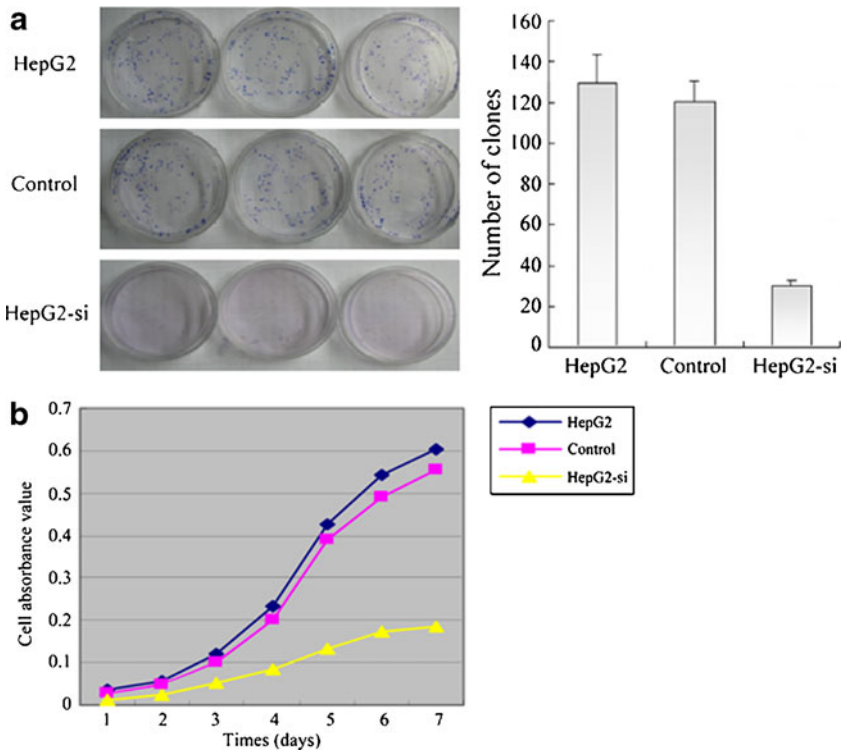

Fig. 2 RNAi of HCCR-2 effects on the proliferation and colony formation capacity of HepG2 cells. **a** The ability of cells to form colonies. RNAi-mediated inhibition of HCCR-2 effects on colony formation in soft agar. **b** Growth curves of HepG2, negative control, and HepG2-si

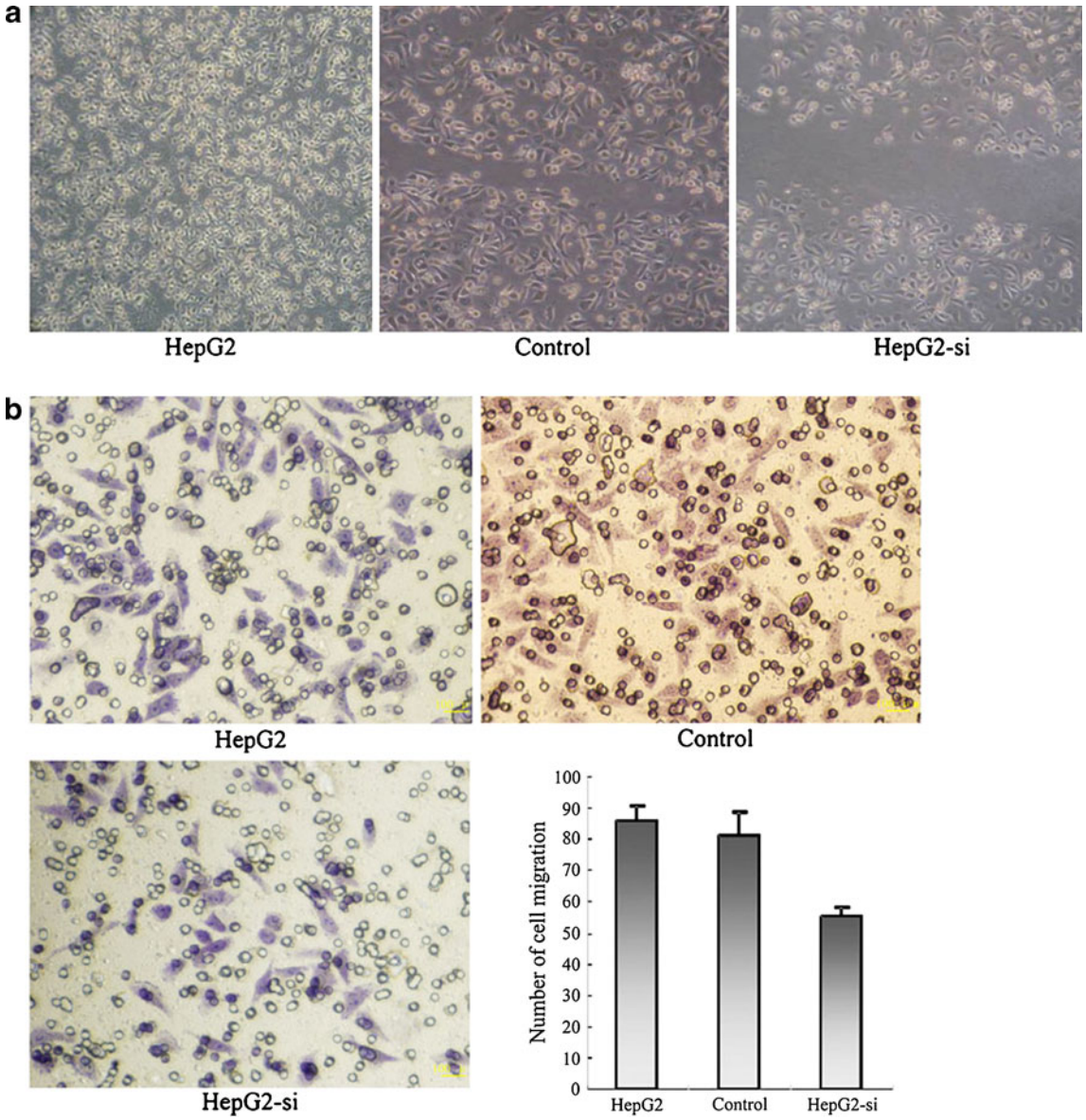

Fig. 3 HCCR-2 RNAi effects on cell migration and invasion of HepG2 cells. **a** Representative photos of haptotactic migration assay with HCCR-2-siRNA, control, and parental HepG2 cells. **b** Matrigel chemoinvasion assay. The number of HCCR-2–siRNA cells that transversed the transwell membranes in matrigel chemoinvasion assays ($P<0.05$). (×200)

Discussion

The effect of downregulation of HCCR-2 on the invasion of HCC is still unclear. Our results indicate that silencing of the HCCR2 gene induces anoikis-like apoptosis and suppresses the proliferation and invasion of HCC cells in culture. Western blot results indicated that the expression of Bcl-2 was inhibited, and the expression of Bax was increased. Our results, along with others, suggest that RNAi targeting HCCR-2 could be an effective means for suppressing proliferation and invasion of HepG2 cells.

To successfully metastasize, cancer cells must acquire the ability to resist anoikis and survive after detachment from their matrix contacts.[20] Anoikis, apoptotic cell death due to loss of cell adhesion, is critical for regulation of tissue homeostasis in tissue remodeling, development, fibrosis, and tumor metastasis.[21] Resistance to anoikis is likely involved in the process of metastasis, specifically during the tumor cell migration through lymph or vascular channels. Here, we showed that decreased HCCR-2 was associated with an increase of anoikis in HCC cells. We postulate that HCCR-2 overexpression may help malignant cells survive in an anchorage-independent manner, leading to a poor prognosis of HCC patients, while silencing of HCCR2 gene induces anoikis-like apoptosis, leading to a good prognosis of HCC patients.

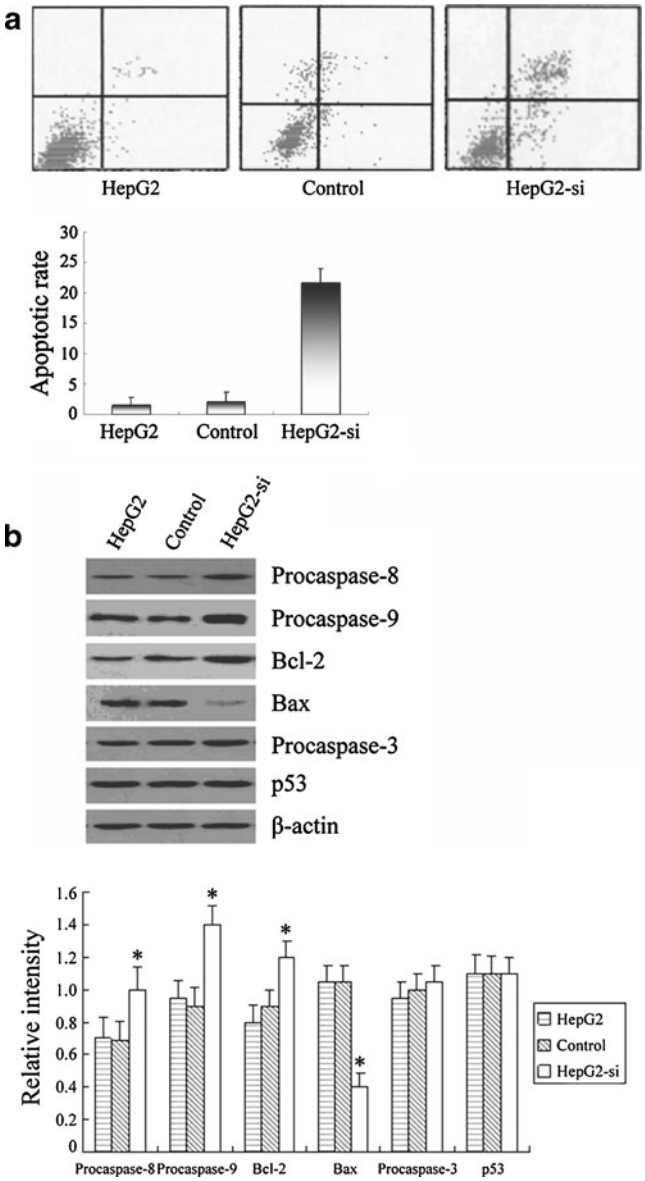

Fig. 4 HCCR-2 RNAi effects on anoikis and regulation of the expression of associated proteins in resistant HCC cells. **a** HCCR-2 RNAi effects on the anoikis of HCC cells. The percentages of dead cells were calculated and compared. *Error bars* indicate means±SD of three independent experiments with duplicate plates. **b** HCCR-2 RNAi regulation of the expression of procaspase-8, procaspase-9, and Bcl-2, and Bax in resistant HCC cells. A densitometric analysis of levels of associated proteins (relative to β-actin levels expressed as mean±SD of three experiments) was used to show the difference among groups (*$P<0.05$, versus HepG2 or HepG2/N)

The molecular mechanisms involved in anoikis induced by HCCR-2 siRNA are not well understood. Most cells undergo apoptosis through the intrinsic, or mitochondrial pathway.[22,23] This is dependent on mitochondrial outer membrane permeabilization, which is mediated by the pro-apoptotic Bcl-2 family proteins, Bax and Bak. During apoptosis, Bax translocates from the cytosol to the outer mitochondrial membrane, wherein it contributes to the formation of pores to release cytochrome-C and a second mitochondrial activator of caspases, which activate the caspases to drive cell death.[24–26] It was found that HCCR encodes a mitochondrial outer membrane protein and suppresses the UVC-induced apoptosis.[27] To identify the molecular mechanism that underlies the enhanced anoikis in HCCR-2 siRNA-treated HCC cells, we tested the effects of HCCR-2 siRNA on Bax and Bcl-2 expression. Results from the Western blot analysis showed that the levels of Bax was increased, while Bcl-2 was decreased in HCCR-2 siRNA HCC cells, compared with parental and negative control cells, indicating that Bax and Bcl-2 is involved in the regulation of anoikis induced by HCCR-2 siRNA in HCC cells. Caspase, as the executioner of apoptosis, plays an important role in the process of apoptosis. There are two pathways in the caspase cascade:[28,29] the cell-surface-death-receptor pathway and the mitochondrion-initiated pathway. In the death-receptor pathway, activation of caspase-8 following its recruitment to the death-inducing signaling complex is the critical event. In the mitochondrion-initiated pathway, caspase-9 is activated. They cleave and activate downstream caspases and executioner caspases such as caspase-3. Therefore, caspase-3, caspase-8, and caspase-9 are the three key caspases in the process of apoptosis. Accordingly, our results showed that the cleavage of proenzymes into the active fragments of caspase-8 and caspase-9 and caspase-3 was only found in HCCR-2 siRNA cells, but not in parental and negative control cells, thus enhancing procaspase-8, procaspase-9, and procaspase-3 expression. These results indicate the importance of an intrinsic mitochondria pathway in HCCR-2 RNAi mediated anoikis.

As a major apoptosis regulator, p53 also plays a critical role in anoikis and metastasis. p53-dependent anoikis has been demonstrated in many cell types.[30,31] Inactivation of p53 promotes metastasis in a number of mouse tumor models. HCCR-2 is overexpressed in HCC, and its functional role in tumorigenesis may reside as a negative regulator of the p53 tumor suppressor gene.[12] However, in this study, we did not find that HCCR-2 siRNA altered p53 protein level in HCC cells. These contradictory roles of p53 in modulating apoptosis could be explained by the fact that cells derived from various tissues might have different genetic backgrounds. In addition, various cell lines derived from the same type of tumors could have different signaling networks, which may result in a different response.

Taken together, it is strongly suggested that HCCR-2 is a crucial regulatory molecule of anoikis resistance in HCC cells. HCCR-2 siRNA induces anoikis-like apoptosis and suppresses the aggressive phenotype of HCC cells in cell culture through the intrinsic or mitochondrial pathway. A better understanding of the mechanism that regulates anoikis sensitivity may help identify targets for HCC therapy.

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ORIGINAL ARTICLE

Caroli's Disease: Report of Surgical Options and Long-Term Outcome of Patients Treated in Argentina. Multicenter Study

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Abstract
Background Caroli's disease (CD) management is still controversial.
Aim The purpose of this study is to report the most frequent clinical features, treatment options, and outcome obtained after surgical management of CD.
Methods A voluntary survey was conducted. Demographic, clinical, surgical, and pathological variables were analyzed.
Results Six centers included 24 patients having received surgical treatment from 1991 to 2009. Seventeen (70.8%) patients were female, with average age of 48.7 years old (20–71), and 95.5% were symptomatic. There was left hemiliver involvement in 75% of the patients. Surgical procedures included nine left lateral sectionectomies, eight left hepatectomies, and four right hepatectomies for those with hemiliver disease, while for patients with bilateral disease, one right hepatectomy and two Roux-en-Y hepaticojejunostomies were performed. The average length of hospitalization was 7 days. For perioperative complications (25%), three patients presented minor complications (types 1–2), while major complications occurred in three patients (type 3a). No mortality was reported. After a median follow-up of 166 months, all patients are alive and free of symptoms. CD diagnosis was confirmed by histology. Congenital hepatic fibrosis was present in two patients (8.3%) and cholangiocarcinoma in one (4.2%).
Conclusions CD in Argentina is more common in females with left hemiliver involvement. Surgical resection is the best curative option in unilateral disease, providing long-term survival free of symptoms and complications. In selected cases of bilateral disease without parenchymal involvement, hepaticojejunostomy should be proposed. However, a close follow-up is mandatory because patients might progress and a transplant should be indicated.

This study was presented during the 2010 IHPBA/AHPBA World Congress in Buenos Aires, Argentina.

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Keywords Liver cyst · Biliary cyst · Caroli's disease · Liver resection · Hepaticojejunostomy

Introduction

Back in 1818, Jacques Caroli described a rare benign congenital disorder characterized by multiple segmental and communicating saccular or cystic dilatations of the intrahepatic bile ducts,[1–3] named Caroli's disease (CD) in his honor. Later on, an autosomal recesive inherited transmission of the disease was recognized, and two major types were described: a simple disease characterized only by the presence of bile duct dilatations and a complex one associated with the presence of congenital hepatic fibrosis (CHF); the latter was entitled Caroli's syndrome.[4,5] The pathogenesis of the disease was associated to a lack of normal involution of the ductal plate at the level of the large intrahepatic ducts in CD. More peripheral interlobular ducts are involved in sclerosing cholangitis and congenital hepatic fibrosis.[6] In 1977, Todani et al. included Caroli's disease as the worst degree (type V) of congenital bile duct cysts.[7] Clinical presentation is related to bile stasis and stone formation, with recurrent cholangitis as the most common presenting symptom. Some authors have reported a high incidence of acute pancreatitis. CHF and biliary cirrhosis are responsible for the development of portal hypertension.[8,9] Diagnosis is usually established by ultrasound, computed tomography (CT) scan, and magnetic resonance cholangiopancreatography[10–12] (MRCP). Even today, literature reports the use of diagnostic endoscopic cholangiopancreatography (ERCP) as a diagnostic method but also as a therapeutic tool in patients with cholangitis.[9,13,14] A wide variety of therapeutic options from endoscopic, percutaneous, or surgical drainage, liver resection or transplantation can be offered to patients suffering from CD. The best treatment to be offered will depend upon the clinical degree of the disease and biliary abnormality localization.[15–17] As far as we are concerned, only six series, with more than 20 cases each, reporting treatment options and long-term outcomes have been published, and the optimal management algorithm is still open for discussion.[13,15,18–22] Therefore, we aim to report the most frequent clinical features, treatment options, and outcome obtained after surgical management as a result of a retrospective multicenter Argentine survey.

Material and Methods

A retrospective voluntary survey aiming to report long-term outcome of patients who received surgical treatment for CD was approved and placed online in the Argentine chapter of International Hepato-Pancreatic-Biliary Association in 2009. The variables included in the survey were: patient demographics, clinical symptoms, and biochemical parameters at presentation, radiologic studies, previous therapeutic nonsurgical interventions, surgical procedures, complications, length of hospital stay, and long-term outcome. Pediatric patients (<15 years old) were excluded from this study. Caroli´s disease diagnosis was performed by clinical parameters, imaging studies, and histopathological findings. Data for evaluation of the hepatobiliary anatomy included ERCP, percutaneous cholangiography, ultrasonography, CT scan, or magnetic resonance imaging (MRI). Extension of intrahepatic disease was defined as unilateral or bilateral, according to imaging studies. Diagnosis of cholangitis was based on the presence of intermittent right upper quadrant pain, intermittent fever, transient jaundice, and increased biochemical markers. The type of hepatic resection was classified according to the International Hepato-Pancreato-Biliary Association classification reported by Strasberg et al.[23] Histopathological analysis was required to include patients in the survey as well as postoperative follow-up. It was considered a positive case of Caroli's disease if one shows the presence of focal dilatations of the intrahepatic bile ducts, predominantly the segmental ducts. Characteristically, enlarged ducts wrap around neighboring hepatic arteries in a crescent-like fashion and are in continuity with the remainder of the biliary system. In Caroli's syndrome, the major ducts of the entire intrahepatic biliary tree, including those of the hepatic hilum, are dilated, and histologic features of congenital hepatic fibrosis are present in the liver corpus.[24] In both cases without resection, the biopsies were evaluated in concordance with the ultrasonography, CT scan, and/or MRI findings and the indirect signs of biliary obstruction and dilatation of bile ducts were compatible with Caroli's disease. The differential diagnosis with other cholestatic disease was established by the correlation between the imagenologic and histopathologic findings.

Among long-term outcome variables requested to be included, the following should be mentioned: laboratory tests, CA 19–9 levels, and ultrasound, performed every 3 months during the first year and then every 6 months until last appointment or death. Statistical analysis was performed using SPSS© v15 for Windows (SPSS Inc., Chicago, IL). Results were expressed in percentages, mean, standard deviation, and range. Categorical variables were compared using Chi-square or *t* test. Kaplan–Meier actuarial survival was obtained.

Results

Six centers included a total of 24 patients having received surgical treatment from 1991 to 2009. Most of the centers

reporting to the survey were located in Buenos Aires (4/2). Seventeen patients (70.8%) were female, with a median age of 48.7 years (range, 20–71 years; Table 1). Symptomatic disease was present in 95.5% of the reported cases, with recurrent cholangitis as the most frequent among the reported symptoms (23/24 patients, 96%), followed by associated symptoms such as right upper quadrant pain in six (25%) and jaundice in seven (29.2%). Seven patients (29.2%) had previously undergone a cholecystectomy for symptomatic gallstones.

Diagnosis was established by means of an abdominal ultrasound (100%), and CT scan, MRCP, and ERCP were performed in 91.6%; 91.6%, and 16.6%, respectively. The three imaging patterns described by Guntz et al., based on aspect and localization of disease, were present in our series (grape bunch type 1, fusiform type 2, and saccular type 3)

The anatomical distribution of CD was unilateral in the majority of the patients included, 21/24 (87.5%), being the left hemiliver the most commonly affected (70.3%), followed by three bilateral (12.5%), and four right hemiliver (16.6%). There was no associated kidney disease reported. The time range between the onset of symptoms and the suggested surgical treatment was 2–60 months (average, 31.7 months). Prior to the definitive surgical treatment, various therapeutic interventions were performed in seven patients (29.2%). Five patients with recurrent cholangitis were treated by endoscopic (1/24, 4.2%) or percutaneous biliary drainage (4/24, 16.7%).

Surgical Treatment

Liver resection was performed in 22 (91.6%) patients. Two patients received Roux-en-Y hepaticojejunostomy. Intraoperative ultrasound was routinely performed in all cases among all centers. According to the disease extent, the surgical procedures performed were:

1. *Unilateral disease*: left lateral sectionectomy in nine patients, left hepatectomy in eight patients, and right hepatectomy in four patients.
2. *Bilateral disease*: right hepatectomy with left intrahepatic bile duct exploration with multiple stone removal and end to side Roux-en-Y hepaticojejunostomy in one patient; cholecystectomy, intrahepatic bile duct exploration with multiple stone removal, liver biopsy, and end to side Roux-en-Y hepaticojejunostomy was offered to two patients.

Table 1 Demographic variables

Age	Max., 71 years Min., 20 years	Mean, 48.7 years
Gender	Female, 17 (70.8%) Male, 7 (29.2%)	

As part of standard liver resection technique, Pringle maneuver was required in seven cases (29.2%). Only four (16.7%) patients required blood transfusion in the perioperative period (three intraoperatively and one at the first postoperative day). There was no patient treated by liver transplant in the present series.

Complications

Postoperative complications occurred in six patients (25%). According to Dindo's classification,[25] three patients (12.5%) presented minor postoperative complications (type I and II) and were treated by conservative measures. Major complications (type IIIa) occurred in 3 patients (12.5%) treated by liver resection, all from the liver cut surface: one choleperitoneum and one intra-abdominal abscess that required surgical drainage due to failure of minimal invasive procedures. Another patient with a biloma was treated by percutaneous drainage. The average length of stay was 7 days (4–21 days). Perioperative mortality was 0%.

Pathological Analysis

Macroscopical examination of the explanted livers showed saccular or fusiform dilatations of segmental or main bile ducts with visible stones. Microscopy was positive for biliary hamartomas, periductal granulomatous reaction, and ductal plate malformation.

The essential diagnosis was established with the presence of focal dilatations of the biliary tree with associated chronic inflammation and peribiliary fibrosis, according to the previous definition. There were two patients with congenital hepatic fibrosis (CHF) and one patient with an associated cholangiocellular carcinoma (CCC). In those cases with bilateral disease, apart from the typical features of CD, moderate fibrosis was found.

Follow-up

At a mean follow-up of 13.8 years (range, 0.68–18.8 years), the 24 surgically treated patients are currently alive. The two patients treated primarily with hepaticojejunostomy are free of symptoms with normal laboratory tests, CA 19–9, and radiologic examinations at 9 and 12 years of follow-up. The patient with incidental CCC is currently alive with no recurrence at 9 months after the operation.

Discussion

Caroli's disease is a rare congenital disorder that belongs to the group of fibrocystic liver diseases characterized by a variable degree of fibrosis and ectasia.[6] The estimated

incidence is less than 1/1,000,000 population.[26] Since the original description, many case reports have been published or included as part of bile duct cysts reports.[27–30] Few series with long-term result reports of more than over 20 cases treated by liver resection or transplant have been published (Table 1). Diagnosis is often delayed, and long periods from the onset of symptoms to the definitive treatment can be frequently seen[20] (2 to 60 months in our study). Unilateral predominance has also been shown by other studies.[9,13,17] In spite of having described a lack of distribution by sex, in our series a female predominance (70.8%) was observed.[14,15,17,18,20,31] Bacterial cholangitis was the most frequent clinical presentation of CD in our patients. We noticed less incidence of acute pancreatitis in comparison with others.[8,9] Diagnosis, as it was reported, was established by ultrasound, CT, and MRCP in most patients. MRCP was used in this study in a higher proportion (89%) than in other recent series.[14,20] Some authors, like Kassahun et al., even today advocate the use of ERCP and the importance of combining it with other image studies.[9,13,14] We preferred not to use invasive diagnostic methods except in the setting of recurrent cholangitis in spite of medical treatment. Therefore, percutaneous biliary drainage was prescribed in 16.7% of our cases. As it was reported by Gillet 10 years ago and more recently by others, 73% to 83% of the patients with CD received numerous interventions before the definitive surgical treatment.[14,20,32] In our study, only 30% had been treated by cholecystectomy and 29.2% by other interventional procedures like ERCP or percutaneous biliary drainage. Some authors advocate a combination of interventional ERCP, extracorporeal shock-wave lithotripsy, and ursodeoxycholic acid treatment.[33]

The optimal timing for surgical management in patients with CD is still a matter of discussion because time and severity in each patient vary substantially.[14] The factors that should be considered to decide the appropriate surgical treatment are localization, extension of the disease, and association of underlying chronic liver disease, such as congenital hepatic fibrosis or biliary cirrhosis, kidney disease, or associated malignancy. As with earlier series, our cases had a higher percentage of localized left lobe disease.[9,13,20,34] Kassahun et al. found 80% of unilateral disease with a nearly equal left–right distribution.[13] Resection seems to be the first surgical option in unilateral CD, and since the disease had predominance on the left side, left side resections are the most commonly described.[8,9,34,35] In cases with bilobar involvement and in the absence of liver fibrosis or cirrhosis, extended liver resections are indicated.[14,17] As shown in Table 1, the association with congenital hepatic fibrosis ranges from 1.8% to 57%, but it is seldom reported. Waechter et al. indicated that the presence of CHF could lead to worsening portal hypertension after resection in patients with CD.[16] Therefore, in the case of hilar involvement, we preferred to propose a surgical drainage; other studies showed 15% to 25% of bile duct excision done in this entity.[13,20]

In cases with bilateral CD without parenchymal involvement or portal hypertension, biliodigestive anastomosis with duct clearance could be an option after ineffective conservative treatment,[3,8,9,15,35,36] but there is some concern associated with the possibility of cholangiocarcinoma development in the long term.[13] In our study, the patient with longer follow-up after biliodigestive anastomosis showed normal liver function and nonprogressive fibrosis at 9-year follow-up. The 4.3% incidence of cholangiocellular carcinoma reported by us is similar to the range published by other series (Table 2).[13,14] Some authors propose liver transplantation under similar conditions. However, liver transplantation becomes the best option in patients with recurrent cholangitis, refractory to conservative measures, secondary biliary cirrhosis, or congenital hepatic fibrosis with portal hypertension, even more in cases with bilateral involvement.[21] Since 2002, several series reported liver transplants for CD.[13,17,20,28,31] The most relevant single-center experience was written by the Pittsburgh group, which included 30 transplants; a report from the ELTR and a report from the UNOS data base[18,21,22] include more than 100 cases. In those reports, secondary biliary cirrhosis and CHF

Table 2 Surgical treatment of CD: published series with >20 patients

Authors	*n*	M/F	U/B	CHF (%)	CHCA (%)	Resection	LTx
Dagli et al. [15]	21	13/8	9/12	57	0	7	0
Pimentel [9]	26	10/16	20/6	NA	0	20	0
Kassahun et al. [13]	33	15/18	25/6	NA	9	29	2
Habib et al. [18]	30	16/14	NA	30	3	0	30
De Kerckhove et al. [22]	110	57/53	NA	1.8	2.7	0	110
Mabrut et al. [20]	33	21/12	26/7	6	6	28	5
Millwala et al. [21]	104	47/57	NA	NA	NA	0	104
Ulrich et al.[8]	40	18/22	32/8	8.1	9	33	4
Current series 2011	24	7/17	21/3	8.3	4.2	22	0

M/F male/female, *U/B* unilobar/bilobar, *CHF* congenital hepatic fibrosis, *CHCA* cholangiohepatocellular carcinoma, *LTx* liver trasplantation, *NA* not analyzed

were the main indications for transplantation, and patient and graft survivals (77% and 72% at 10 years, respectively[21]) were comparable with other etiologies.[18] In spite of the results, there is an agreement that liver transplantation should be the last treatment option.[14] Our series showed that all patients were free from symptoms with normal imaging and serological markers at 13-year follow-up.

Conclusion

CD in Argentina is more common in females with left hemiliver involvement. Delay between onset of symptoms, diagnoses, and surgical therapy is still present. Patients with congenital IHBD dilatations should be referred early for surgical management.

Surgical resection was proposed as the best curative option in unilateral disease, by all centers, providing long-term survival free of symptoms and complications. In selected cases of bilateral disease without parenchymal involvement, hepaticojejunostomy should be proposed. However, a close follow-up is mandatory because patients might progress and a transplant should be indicated.

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ORIGINAL ARTICLE

Liver Resection Without Pedicle Clamping: Feasibility and Need for "Salvage Clamping". Looking for the Right Clamping Policy. Analysis of 512 Consecutive Resections

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Abstract
Background Pedicle clamping during liver resection (LR) is debated. The purpose of this study is to validate non-clamping policy across a large series of LR and to evaluate the need for salvage clamping (SC) and its outcomes.
Methods Five hundred twelve consecutive LR without initial pedicle clamping performed between 2004 and 2009 were analyzed.
Results Among 512 LR (171 major hepatectomies), 90.2% were completed without clampage. Fifty (9.8%) required SC. Blood loss were higher in SC group (555 vs. 175 mL, $p<0.0001$), while transfusion rate was not. No differences were observed in terms of mortality (0%/1.3%), morbidity (38%/38.3%), liver dysfunction (4%/3.7%), and renal dysfunction (0%/1.3%). Bile leak rate was increased in the SC group (20%/10.2%, $p=0.036$). At multivariate analysis, three predictive factors of SC were identified: arterial hypertension ($p=0.007$, SC rate=13%), cirrhosis ($p=0.003$, SC rate=26%), and LR conducted along the right portal scissure ($p=0.010$, SC rate=32%). One protective factor was identified: LR confined to antero-lateral segments (Sg2–6, $p=0.001$, SC rate=2%). Extension of LR had no impact on need for SC.
Conclusions The majority of LR can be safely performed without clamping with excellent outcomes. SC is a safe procedure and does not worsen postoperative outcomes, except for bile leak rate. Clamping policy should be tailored to the type of LR and presence of cirrhosis.

Keywords Liver surgery · Pedicle clamping · Cirrhosis · Liver resection · Blood transfusion · Liver dysfunction

Introduction

Hepatic pedicle clamping during liver parenchyma transection significantly contributed to a safer and faster evolution of liver surgery, by facilitating bleeding control and reducing blood loss.[1] However, thanks to improvement in liver anatomy knowledge, accurate patient selection, standardization of liver surgery technique, adoption of ultrasonography guidance, technological evolution, and refinements in anesthesiological procedures, bleeding risk dramatically decreased in recent years.[2–6] In 2006, a randomized control trial compared liver resections with and without Pringle maneuver.[7] No benefits were observed in the clamping group, suggesting that at present liver resection can be safely performed without any clampage. Even if some centers still systematically adopt pedicle clamping,[4,8,9] an increasing number of surgeons agree with a "non-clamping" policy.[7,10–14]

Despite theoretical feasibility of liver resection without clamping, whenever major bleeding or persisting oozing occur a "salvage clamping" (SC), mainly a Pringle maneuver, is recommended to limit blood loss. At present, the outcomes and safety of this maneuver have never been evaluated.

The aim of the present study was to evaluate in a large series of liver resections initially performed without pedicle clamping the need for SC and the outcomes of this

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maneuver. Further, predictive factors of SC were analyzed in order to improve our clamping policy and liver resection safety.

Material and Methods

Between June 2004 and June 2009, 543 consecutive liver resections have been performed in our department. All resections were considered for the present study. Exclusion criteria were hepatectomies with associated vascular resection and hepatectomies performed under pedicle clamping since the beginning of parenchymal transection.

The need for any type of vascular clamping during parenchymal transection was defined as "SC", independently from its duration. The proportion of cases requiring SC was analyzed. Outcomes of patients undergoing SC were analyzed and compared to those of patients who completed liver resection without any clampage, with special concern about blood loss, need for transfusion, and liver and renal dysfunction. Finally, predictive factors of SC were analyzed at uni- and multivariate analysis by including all preoperative data, i.e., patient characteristics, diagnosis, biochemistry, and planned surgical procedures.

Patient Selection

Preoperative patient selection was based on patient performance status, comorbidities, liver function tests, and indocyanine green retention rate at 15 min (ICGR-15). Only patients having ICGR-15 ≤10% were scheduled for major hepatic resection.

In cirrhotic patients Child-Pugh classification was routinely applied. Only Child-Pugh A patients were considered for resection. Portal hypertension was routinely evaluated by its indirect signs: platelet count + spleen diameter and presence of esophageal varices at endoscopy. Patients with severe portal hypertension (platelet count $<50\ 10^3/mm^3$ and/or grade 2 varices) were excluded from surgery.

If major hepatectomy was planned, CT volumetry of the future liver remnant (FLR) was routinely performed. FLR was considered adequate if >25% in patients with normal liver (non-cirrhotic, non-jaundiced, chemotherapy-free), >30% in jaundiced patients or in those having received preoperative chemotherapy, and >40% in cirrhotics. If FLR was inadequate preoperative portal vein embolization was planned and liver resection was performed 4 weeks later only if sufficient hypertrophy was achieved.

Surgical Technique

The surgical technique has been previously reported.[15,16]

Briefly, intraoperative ultrasonography was regularly performed to identify the number and the site of lesions, their relationship with vascular structures, and to plan adequate resection. In anatomic resections, except for monosegmentectomies, extra-hepatic inflow and outflow vascular control was regularly obtained by ligation and division of appropriate portal veins, hepatic arteries, and hepatic veins. Bile duct was divided at the end of parenchymal transection. Parenchymal transection was performed by crush and clamp technique, bipolar forceps with continuous irrigation, and absorbable clips or ligature for larger vessels or bile ducts. Transection was systematically begun without any clamping, but the hepatic pedicle was always encircled in order to promptly perform SC whenever needed. A low central venous pressure (lower than 4 cm H_2O) was maintained during parenchymal transection to minimize bleeding. SC was performed whenever persisting oozing or major bleeding occurred. After completing the resection, hemostasis and biliostasis were accurately checked. Cholangiography was performed in selected patients. Fibrin glue (Tissucol/Tisseel, Baxter Healthcare, Deerfield, IL) or collagen path coated with a dry layer of the coagulation factors, human fibrinogen and thrombin (Tachosil, Nycomed, Linz, Austria) were routinely applied on the raw cut surface. Even if some randomized trials demonstrated no benefits from routine drainage after liver resection,[17,18] we systematically used abdominal drain to early detect any bile leak.

Definitions

Arterial hypertension was defined as blood pressure >140/90 mmHg or treatment of previously diagnosed hypertension.[19] Liver cirrhosis was defined as F4 fibrosis according to the METAVIR score.[20] Major hepatectomy was defined as the resection of three or more Couinaud segments. Extended hepatectomy was defined as the resection of five or more Couinaud segments. Liver resections were classified according to the Brisbane nomenclature.[21] Operative mortality was defined as death within 90 days after surgery or before discharge from the hospital. Morbidity included all postoperative complications. Liver dysfunction was defined as serum bilirubin >3 mg/dl and/or PT <50% on postoperative day 5 or thereafter.[22] Bile leakage was defined as the drainage of 50 ml or more of bile from the surgical drain or from a drainage of an abdominal collection, lasting 3 days or more.[16]

Statistical Analysis

Data were prospectively collected and retrospectively analyzed. The following data about clamping during resection were prospectively recorded: no clamping vs. initial no clamping followed by SC vs. clamping since the beginning; indications to SC (major bleeding vs. persisting

oozing); site of clamping (whole pedicle, selective right or left pedicle, selective hemiliver total vascular exclusion (TVE), TVE with or without caval flow preservation); type of clamping (continuous vs. intermittent); and duration. Continuous variables were compared between groups by the unpaired *t* test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared by the Chi-square test or Fisher exact test, as appropriate. A $p<0.05$ value was considered significant for all tests. Independent risk factors were calculated by logistic regression of univariate significant variables.

Results

Five hundred forty-three liver resections have been considered for the present study. Sixteen (2.9%) have been excluded because of associated vascular resections: portal vein in 12 cases, inferior vena cava in two, and right hepatic vein in two. In addition, 15 (2.8%) liver resections have been excluded because parenchymal transection was performed under pedicle clamping since the beginning. The reasons for a priori clamping were as follows: contact between tumor and major intrahepatic vessels in seven cases, severe macroscopic liver injuries in six (including five reresections), and large intrahepatic venous shunts due to bulky tumors in two.

The remaining 512 (94.3%) liver resections were began without pedicle clamping and represented the study population. They included 313 (61.1%) male and 199 (38.9%) female patients with a median age of 63 (23–87) years. In 39 (7.6%) cases, liver cirrhosis was diagnosed. All cirrhotics were Child-Pugh A class patients. The most common indications to resection were colorectal liver metastases (288 patients, 56.3%) and hepatocellular carcinoma (HCC; 68, 13.3%). A major hepatectomy was performed in 171 (33.4%) cases. Patient characteristics are summarized in Table 1.

Table 1 Patient characteristics

	n=512
Demographic characteristics	
Age (median, years)	63 (23–87)
Age >70 years	127 (24.8%)
Sex (M/F)	313 (61.1%)/199 (38.9%)
BMI >30 kg/m^2	48 (9.4%)
ASA score >2	274 (53.5%)
Liver cirrhosis	39 (7.6%)
Liver steatosis >30%	84 (16.4%)
Diagnosis	
HCC	68 (13.3%)
Peripheral cholangiocarcinoma	31 (6.1%)
Colorectal metastases	288 (56.3%)
Non-colorectal metastases	41 (8.0%)
Hilar cholangiocarcinoma	16 (3.1%)
Gallbladder cancer	34 (6.6%)
Benign lesions	34 (6.6%)
Technical details	
Major hepatectomy	171 (33.4%)
Extended hepatectomy	53 (10.4%)
Anatomic resection	283 (55.3%)
Reresection	78 (15.2%)
Salvage clamping	50 (9.8%)

The Need for Salvage Clamping

Among the 512 analyzed liver resections, 50 (9.8%) required SC: intermittent pedicle clamping in 40, continuous pedicle clamping (21 min) in one, selective right total vascular exclusion in five, and TVE in four (with caval flow preservation in three). SC was needed because of persisting oozing in all but three patients: two had major bleeding from the right hepatic vein at the end of parenchymal transection during segment 7 resection and during right hepatectomy extended to segment 1, respectively; the remaining patient had inferior vena cava bleeding during segment 1 resection. The SC was never needed because of hemodynamic instability of the patient. Median transection time was 94 min (31–228); median SC duration was 35 min (14–109), it corresponded to 36.8% (10.4–86.3) of the overall transection time.

Outcomes of Patients Requiring a Salvage Clamping

Blood Loss and Transfusion Rate

Eighty-seven (17.0%) patients had blood loss over 500 mL, including 15 (2.9%) having blood loss over 1,000 mL. SC was applied in nine out of 15 (60%) patients with blood loss over 1,000 mL and in 15 out of 72 (20.8%) with blood loss between 500 and 1,000 mL. Median blood loss was significantly higher in the SC group: 555 mL (110–2,040) vs. 175 mL (0–1,900), $p<0.0001$. The need for SC was associated with blood loss over 500 mL at both univariate and multivariate analysis [$p<0.0001$, OR 6.145 (CI 95% 3.095–12.201)]. At multivariate analysis, one additional predictive factor of blood loss over 500 mL was identified: the need for major hepatectomy [$p=0.0001$, OR 3.035 (CI 95% 1.721–5.354)]. One independent factor was associated with the absence of blood loss over 500 mL: resection confined to antero-lateral liver segments (Sg2–6) [$p=0.009$, OR 0.289 (CI95% 0.113–0.730)].

Seventy-three (14.3%) patients required blood transfusions. Transfusion rate was higher in the SC group (22% vs 13.4%), but the difference was not significant (p=0.099). The need for transfusion was strictly related to blood loss (165 mL in no transfused patients vs. 400 mL in transfused ones, p<0.0001).

Postoperative Outcomes

Mortality was nil in the SC group and 1.3% among patients without any clampage (six patients). Overall morbidity rate and hospital stay were similar between the two groups: 38% (19 patients) and 9.5 (5–53) days in the SC group vs. 38.3% (177) and 9 (3–114) days in the non-SC group, respectively. Details about postoperative complications are summarized in Table 2. No differences were encountered in terms of liver dysfunction (4% vs. 3.7%) and renal dysfunction (0% vs. 1.3%) rates. No major postoperative bleeding occurred in the SC group, while eight (1.7%) cases occurred in the group without clamping (p=n.s.). The only difference concerned bile leak rate: it was significantly higher in the SC group: 20% (10 patients) vs. 10.2% (47), p=0.036. These data were confirmed also considering only patients without biliary anastomosis: bile leak occurrence was significantly higher in the SC group [9/49 (18.4%) vs. 28/413 (6.8%), p=0.010]. Bile leak site never corresponded to the clamping site.

Predictive Factors of Need for Salvage Clamping

Univariate Analysis (Tables 3–4)

Among patient characteristics, two variables were significantly associated with the need for SC: arterial hypertension (15.3% vs. 6.7%, p=0.003) and liver cirrhosis (25.6% vs. 8.5%, p=0.002). Presence of moderate to severe liver steatosis (> 30%) was not associated with higher SC rates. Neoadjuvant chemotherapy administration did not increase the need for SC, even considering patients with prolonged treatment. Different chemotherapy regimens, i.e., oxaliplatin, irinotecan, and biologics, did not impact on clamping policy (data not reported). Patients affected by HCC often required SC (20.6% vs. 8.1%, p=0.005), as well as those with low platelet count (<140 10^3/mm^3, 22% vs. 8.4%, p=0.005). PT values were lower and INR values were higher in patients who required SC (94% vs. 99%, p=0.022 and 1.04 vs. 1.01, p=0.031, respectively), but proportion of patients with abnormal PT and INR values was low and similar into the two groups. Among liver function tests, ICGR-15 values were higher in patients needing for SC (6.5% vs. 4%, p=0.014).

Extension of resection did not impact on feasibility of transection without clamping, while the transection plane did: SC rate was significantly higher during resections conducted along the right portal scissure (including left trisectionectomy, mesohepatectomy, bisegmentectomy Sg6–7, and bisegmentectomy Sg5–8, 32% vs 8.6%, p=0.001). In anatomic resections, inflow ligature before transection did not decrease clamping rate. The need for SC was also influenced by liver segments included in the resection: it was increased during resections including segment 7 (13% vs. 7.3%, p=0.03) or segment 8 (13.5% vs. 6.4%, p=0.007), while was reduced during resections confined to antero-lateral segments (Sg2–6; 1.8% vs. 13.5%, p<0.0001).

Multivariate Analysis (Table 5)

At multivariate analysis, three factors were identified as independent predictive factors of need for SC: arterial

Table 2 Postoperative outcomes

	No clamping (n=462)	Salvage clamping (n=50)	p value
Mortality	6 (1.3%)	–	n.s.
Morbidity	177 (38.3%)	19 (38%)	n.s.
Liver dysfunction	17 (3.7%)	2 (4%)	n.s.
Hemoperitoneum	8 (1.7%)	–	n.s.
Bile leak	47 (10.2%)	10 (20%)	0.036
Abdominal abscess	19 (4.1%)	3 (6%)	n.s.
Ascites	20 (4.3%)	1 (2%)	n.s.
Renal dysfunction	6 (1.3%)	–	n.s.
Pulmonary morbidity	62 (13.4%)	5 (10%)	n.s.
Sepsis	24 (5.2%)	1 (2%)	n.s.
Reoperation	16 (3.5%)	–	n.s.
Hospital stay	9 (3–114)	9.5 (5–53)	n.s.

Table 3 Univariate analysis of predictive factors of the need for salvage clamping: preoperative characteristics

	No clamping (n=462)	Salvage clamping (n=50)	p value
Demographic characteristics			
Age >70 years	111 (24.0%)	16 (32%)	n.s.
Sex (M)	279 (60.4%)	34 (68%)	n.s.
BMI >30 kg/m^2	42 (9.1%)	6 (12%)	n.s.
ASA score >2	244 (52.8%)	30 (60%)	n.s.
Antiaggregant therapy	54 (11.7%)	9 (18%)	n.s.
Oral anticoagulant therapy	14 (3.0%)	1 (2%)	n.s.
Arterial hypertension	155 (33.5%)	28 (56%)	0.003
Diabetes	65 (14.1%)	9 (18%)	n.s.
Chronic renal dysfuntion	9 (1.9%)	2 (4%)	n.s.
Liver cirrhosis	29 (6.3%)	10 (20%)	0.002
Liver steatosis >30%	75 (16.2%)	9 (18%)	n.s.
Neoadjuvant Chemotherapy			
No	261 (56.5%)	33 (66%)	n.s.
1–6 cycles	104 (22.5%)	8 (16%)	n.s.
7–12 cycles	77 (16.7%)	7 (14%)	n.s.
>12 cycles	20 (4.3%)	2 (4%)	n.s.
Diagnosis and tumor characteristics			
HCC	54 (11.7%)	14 (28%)	0.005
Peripheral cholangiocarcinoma	28 (6.1%)	3 (6%)	n.s.
Colorectal metastases	265 (57.4%)	23 (46%)	n.s.
Non-colorectal metastases	37 (8.0%)	4 (8%)	n.s.
Hilar cholangiocarcinoma	15 (3.2%)	1 (2%)	n.s.
Gallbladder cancer	34 (7.4%)	–	0.064
Benign lesions	29 (6.3%)	5 (10%)	n.s.
Number >1[a]	185/383 (48.3%)	25/46 (54.3%)	n.s.
Diameter >50 mm[a]	107/383 (27.9%)	14/46 (30.4%)	n.s.
Diameter >100 mm[a]	27/383 (7.0%)	2/46 (4.3%)	n.s.
Coagulation parameters			
PT (%)	99 (64–133)	94 (66–126)	0.022
PT <70%	6 (1.3%)	1 (2%)	n.s.
PTT (s)	33.4 (23.4–58.0)	35.0 (29.3–44.7)	n.s.
PTT >40 s	28 (6.1%)	4 (8%)	n.s.
INR	1.01 (0.82–1.38)	1.04 (0.90–1.22)	0.031
INR >1.2	12 (2.6%)	3 (6%)	n.s.
Platelet count (10^3/mm^3)	235 (47–779)	186.5 (93–458)	0.0003
Platelet count <140 10^3/mm^3	39 (8.4%)	11 (22%)	0.005
Bilirubin (mg/dL)	0.62 (0.1–23.1)	0.65 (0.2–2.88)	n.s.
AST (UI/L)	25 (11–761)	26 (12–124)	n.s.
ALT (UI/L)	24 (7–569)	26 (9–252)	n.s.
Albumin (g/L)	39 (13–50)	38.1 (31–50)	n.s.
ICGR-15[b] (%)	4 (0.1–43.5)	6.54 (0.4–33)	0.014

Continuous variables are reported as median (range)

ICGR-15 indocyanine green retention rate at 15 min

[a] Available in 429 patients (non in klatskin, gallbladder cancer, lithiasis)

[b] Available in 346 patients

hypertension (p=0.007), liver cirrhosis (p=0.003), and resections conducted along the right portal scissure (p= 0.010). One independent factor was correlated with the absence of need for SC: resection confined to antero-lateral liver segments (Sg2–6; p=0.001).

In patients undergoing resection confined to the antero-lateral segments (Sg2–6) median blood loss were 60 mL (0–750) and SC was rarely required (1.8%). On the contrary, in patients receiving resections conducted along the right portal scissure median blood loss were

Table 4 Univariate analysis of predictive factors of the need for salvage clamping: intraoperative and technical data

	No clamping (n=462)	Salvage clamping (n=50)	p value
Major hepatectomy	158 (34.2%)	13 (26%)	n.s.
Extended hepatectomy	47 (10.2%)	6 (12%)	n.s.
Anatomic resection	257 (55.6%)	26 (52%)	n.s.
Emergency resection	3 (0.6%)	–	n.s.
Reresection	73 (15.8%)	5 (10%)	n.s.
Inflow control before transection	167 (36.1%)	17 (34%)	n.s.
Type of hepatectomy			
Right hepatectomy ± Sg1	86 (18.6%)	6 (12%)	n.s.
Right trisectionectomy ± Sg1	26 (5.6%)	1 (2%)	n.s.
Left hepatectomy ± Sg1	32 (6.9%)	2 (4%)	n.s.
Left trisectionectomy ± Sg1	7 (1.5%)	3 (6%)	0.064
Mesohepatectomy	2 (0.4%)	1 (2%)	n.s.
Bisegmentectomy Sg2–3	32 (6.9%)	2 (4%)	n.s.
Bisegmentectomy Sg4b–5	25 (5.4%)	–	n.s.
Bisegmentectomy Sg6–7	5 (1.1%)	4 (8%)	0.003
Bisegmentectomy Sg5–8	3 (0.6%)	–	n.s.
Main portal scissure	123 (26.6%)	9 (18%)	n.s.
Right portal scissure	17 (3.7%)	8 (16%)	0.001
Resected segment			
Segment 1	65 (14.1%)	9 (18%)	n.s.
Segment 2	134 (29.0%)	11 (22%)	n.s.
Segment 3	147 (31.8%)	11 (22%)	n.s.
Segment 4a	103 (22.3%)	13 (26%)	n.s.
Segment 4b	156 (33.8%)	12 (24%)	n.s.
Segment 5	230 (49.8%)	26 (52%)	n.s.
Segment 6	196 (42.4%)	28 (56%)	0.066
Segment 7	194 (42.0%)	29 (58%)	0.030
Segment 8	212 (45.9%)	33 (66%)	0.007
Antero-lateral segments (Sg2–6)	160 (34.6%)	3 (6%)	<0.0001

450 mL (20–2,040) and SC was required in 32% of cases.

Table 5 Multivariate analysis of predictive factors of the need for salvage clamping

	p value	OR (CI 95%)
Arterial hypertension	0.007	2.356 (1.269–4.375)
Liver cirrhosis	0.003	3.718 (1.573–8.788)
HCC	n.s.	
Platelet count <140 $10^3/mm^3$	n.s.	
ICGR-15	n.s.	
Right portal scissure	0.010	3.500 (1.351–9.065)
Segment 7	n.s.	
Segment 8	n.s.	
Antero-lateral segments (Sg2–6)	0.001	0.133 (0.040–0.443)

ICGR-15 indocyanine green retention rate at 15 min

Discussion

In liver surgery, the need for pedicle clamping is debated. Some authors suggest that liver resection should be routinely performed under pedicle clamping in order to prevent bleeding.[4,8,9,23] However, in the last years liver surgery has became safer and bleeding risk dramatically decreased thanks to deep anatomic knowledge, accurate patient selection, careful technique and transection with low central venous pressure.[2–6,24,25] Two papers collecting more than 1,000 hepatectomies reported a simultaneous reduction of blood loss, transfusion rate, and need for clamping across the last decades.[2,5] Recent studies, including a metanalysis and a randomized trial, demonstrated that liver resections without pedicle clamping can be safely performed and are not associated with increased blood loss.[5,7,11–14] However, these studies analyzed a limited number of patients which could be inadequate to disclose real risks of non-clamping policy. Present series collected

more than 500 consecutive liver resections performed without initial pedicle clamping, including 171 major hepatectomies. Safety of non-clamping policy was confirmed at least twofold. First, liver resection was completed without any clampage in more than 90% of cases and mean blood loss were lower than 200 mL. Second, excellent postoperative outcomes were observed: mortality rate was 1.2% and liver dysfunction rate was 3.7%.

Safety of non-clamping policy could be questioned in patients in whom bleeding occurred. In the present series, among 512 liver resections 87 (17%) had blood loss over 500 mL. Pedicle clamping does not completely prevent this risk: similar results, with some cases having high blood loss, have been reported by authors who systematically apply clamping.[4,8,9] Further, clamping can be secondarily performed during parenchymal transection if bleeding occurs, as a "salvage clamping". In 2004, Scatton et al.[12] reported a series of 50 major liver resections performed without initial clampage: pedicle clamping was required in 4% of cases. In the randomized trial by Capussotti et al.,[7] SC was needed in two out of 63 patients (3.2%). In the present series, SC was needed in about 10% of cases. However, is SC as effective as clamping since the beginning? In the literature, no specific analysis is available and the small number of reported cases is inadequate to draw any conclusions. Present series may offer some interesting insights.

Patients requiring SC had higher blood loss and increased blood transfusion rate. These data just reflect the application of SC in more difficult cases when bleeding occurred. SC was rarely needed because of major bleeding; in the large majority of cases it was due to persisting oozing which hampered progression during transection. Further, bleeding reduction was usually observed after SC application.

Safety of SC was further confirmed by postoperative outcomes: mortality was nil and liver and renal dysfunction rates were low and similar to non-clamped patients. Present results favorably compare with those reported by authors regularly performing liver resection under pedicle clamping.[4,8,9] Only postoperative bile leak was significantly more common among patients requiring SC. Some hypotheses can be advanced. First, persisting oozing during transection could lead to less accurate identification and ligation of bile ducts. Second, SC was required in more difficult resections which have per se higher bile leak risk.[15,26–28]

The right clamping policy is probably far from dogmatic positions (always vs. never clamp) and should be tailored to every single case. Clamping is always better than bleeding because of negative impact of blood loss and transfusions on postoperative outcomes,[29–32] but clamping is associated with ischemia–reperfusion injuries and its impact on prognosis is debated.[33–36] In order to define the optimal clamping policy, patient characteristics have to be considered. In cirrhotic patients, parenchymal transection is more difficult and bleeding risk is increased. In present series one fourth of patients with cirrhosis required SC, independently from extension and type of liver resection. However, livers with chronic disease are more sensitive to ischemia–reperfusion injury and have higher risk of liver failure.[37–40] A balanced strategy can be hypothesized: resection can be cautiously attempted without any clamping, but early clampage has to be applied whenever bleeding is not adequately controlled. Clamping policy should obviously consider technical features. Resections of antero-lateral segments had extremely low blood loss (60 mL) and exceptionally required SC (less than 2%). In these cases routine clamping is not justified. It has been confirmed by laparoscopic liver resections, which usually involve antero-lateral segments (the so-called laparoscopic segments) and for which safety of non-clamping policy is established.[41,42] Even major hepatectomies can be safely performed without any clamping: among 171 cases only 7.6% required SC. On the contrary, resections along the right portal scissure (left trisectionectomy, mesohepatectomy, bisegmentectomy Sg6–7, and bisegmentectomy Sg5–8) were associated with high blood loss and required SC in about one third of cases. This is probably related to the wide and deep transection plane and to the congestion occurring during transection because of liver mobilization. In patients scheduled for these resections, clamping since the beginning should be considered to limit blood loss.

Some bias may affect present study. First, SC was performed according to surgeon evaluation and not to standardized criteria. It could have underestimated the need for SC. At the same time, late application of SC could have limited its effectiveness. Second, effectiveness of SC was not completely assessed. Variation of blood loss before and after SC should be computed. Finally, outcomes of SC should be compared with those of clamping since the beginning. In our center non-clamping policy has been regularly adopted and control group was missing. However, owing to the large patient cohort studied, present study offers a way forward to clarify the controversial issues related to the need for clamping during liver resection.

Conclusions

The majority of liver resections can be safely performed without any clampage with excellent outcomes. Salvage clamping is needed in about 10% of cases, rarely because of major bleeding. It is a safe procedure and does not worsen postoperative outcomes, except for bile leak rate. Clamping policy should be based on a case-by-case

evaluation. Resections of antero-lateral segments can be safely performed without any clampage. In cirrhotic patients, liver resections can be attempted without any clamping, but early salvage clamping has to be considered. In resections along the right portal scissure systematic pedicle clamping can be proposed. Early salvage clamping is always recommended whenever bleeding is not adequately controlled.

Conflicts of interest None to declare

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ORIGINAL ARTICLE

Hepatic Hydatid: PAIR, Drain or Resect?

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Abstract
Study Background Hydatid disease of the liver is endemic in India and is a common health problem. Although various treatment options have been described ranging from pharmacotherapy to radiological interventions and surgical procedures (both conservative and radical), the best treatment option in an individual case continues to be debated.
Methods We did a retrospective analysis of patients with hydatid disease of the liver who were managed at our centre between January 2000 and December 2009. All cysts were classified as per the Gharbi's classification. The various treatment options used to treat hydatid cysts of the liver included percutaneous aspiration, injection and reaspiration (PAIR) or PAIR with drainage (PAIR-D) and surgery (both conservative and radical). The immediate and long-term outcomes following such management were analysed.
Results During the study period, 128 patients with hydatid cyst of the liver were managed with PAIR/PAIR-D (n=52), radical/excisional surgery (n=61) and conservative surgery (n=33). In ten patients, the PAIR procedure was abandoned due to either bile or pultaceous material aspirated after the initial puncture and these patients subsequently underwent surgical management. The PAIR was unsuccessful in eight of the 42 patients in whom it was attempted and these subsequently underwent surgery. The mean intraoperative blood loss and the duration of surgery were comparable in patients who underwent either conservative or radical surgery (p=0.35 and 0.19, respectively). Postoperative bile leaks and cavity abscesses were significantly higher in patients who underwent conservative surgery (p= 0.032 and p=0.001, respectively). Five patients (one following a radical operation and four following a conservative surgery, p=0.05) developed recurrence in a mean follow-up period of 28 months and these were managed medically.
Conclusion Several treatment options are available for the management of hydatid disease of the liver and the treatment modality chosen should be tailored to the individual patient. While percutaneous drainage (with PAIR/PAIR-D) is reserved for more favourable cases of type I and II cysts, the others are best managed surgically. Complete excision (cystopericstectomy or resection) of the hydatid cyst is the preferred approach and 61 of the 94 patients who were managed surgically were suitable for it. Although excisional surgery minimizes the risk of long-term recurrence and cavity-related complications, it may be hazardous in cysts located close to major biliovascular channels. In these cases (considering that it is benign disease), a drainage operation is preferable. Both conservative and radical surgery can be safely performed laparoscopically.

Keywords Hydatid · Cystopericystectomy · PAIR · *Echinococcus*

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Introduction

Echinococcosis is a zoonotic disease caused by the larval stage of *Echinococcus granulosus*. The disease is a significant health problem especially in Eastern Europe, Mediterranean countries, South America and Far East including India.[1] The infection results in development of hydatid cysts most commonly in the liver (60–70%) and the

lungs (20–30%).[2] Although benign, the disease may have a variable clinical course and maybe complicated by infection or rupture. Surgical management has traditionally been the treatment of choice for most patients with hydatid cysts of the liver, however, advent of laparoscopic surgery and percutaneous techniques like percutaneous aspiration, injection and reaspiration (PAIR) or PAIR with catheter drainage (PAIR-D) has resulted in a change in the current treatment strategy. Which option should be preferred in a given situation is often a debatable issue, i.e. when to use PAIR, drainage or complete excision for the management of hydatid disease of the liver.

Ours is a high volume centre for management hepatobiliary diseases. We manage about 10 to 15 cases of hydatid cyst of the liver every year. The aim of this study was to report our approach and experience in managing this difficult problem.

Methods

We did a retrospective review of all patients of hydatid disease of the liver who were managed at our centre between January 2000 and December 2009. The data were collected from a prospectively maintained liver disease database and analysed. All patients with suspected hydatid disease of the liver were evaluated with an ELISA for *Echinococcus* antibody, ultrasound and contrast-enhanced CT scan of the abdomen. The cyst morphology on ultrasound was classified according to the Gharbi classification.[3] An MRCP was added in patients with jaundice (cyst–biliary communication or rarely due to suspected compression of the bile ducts by the cyst). An ERCP was done in selected cases of cholangitis or where there was a preoperative suspicion of cyst–biliary communication. In addition, all patients underwent hydatid serology by ELISA and routine haematological and biochemical investigations. All patients received a course of albendazole perioperatively as per WHO protocol.[4]

Patients with deep-seated Gharbi type I and II cysts (Fig. 1) were managed with PAIR or PAIR-D therapy (Fig. 2). Superficially located cysts, those with major extrahepatic component (including type I and II), most type III/IV cysts, and those in whom PAIR was either not possible (due to technical reasons) or failed were considered for surgical intervention. Patients managed in the emergency for ruptured cyst, patients with asymptomatic type V cysts (which were managed conservatively) and those with extrahepatic cysts were excluded from this analysis. Patients with infected hydatid cyst were managed like liver abscess with percutaneous drainage and were also excluded from the study. PAIR/PAIR-D was performed under ultrasound or CT scan guidance using light sedation and local anaesthesia. An initial transhepatic needle puncture was done and 10–20 mL of fluid was aspirated to exclude cyst–biliary communication. The cavity was instilled with a scolicidal agent (95% alcohol) which was re-aspirated after 20–30 min. If the cyst size was more than 5 cm, a catheter was placed which was subsequently used for instillation of scolicidal agent and drainage. This catheter was withdrawn in the follow-up once the drain output was minimal. The patients were followed up with serial ultrasound abdomen or CT scan.

The various surgical procedures performed included radical resections like cystopericystectomy (Fig. 3) and formal liver resection (Fig. 4) and conservative procedures like drainage of the cyst and dealing with the cavity. In the latter part of the study, patients with type I and II cysts that were located peripherally were managed laparoscopically (Fig. 5). Cystopericystectomy was the preferred surgical treatment approach. Drainage was considered in patients with deep-seated cysts close to major vessels/pedicle. In all the patients, the cysts were isolated using betadine (10%) soaked sponges. During a surgical drainage, the cysts were initially aspirated using a wide bore needle to decrease the intracystic pressure prior to opening the cyst cavity. In the absence of bile staining of the cyst fluid, equal volume of 10% betadine solution was injected inside the cyst to sterilize its contents. After radical resection or drainage, the cut surface of the liver or the residual cavity was inspected for evidence of bile leaks. If present, these were suture repaired. T tube drainage of the common bile duct was done in selected cases of major biliary communication based on the surgeon's discretion. The residual cavity after drainage was managed by either external drainage or omentopexy. Patients were regularly followed up after discharge from the hospital with serial ultrasound and CT scan of the abdomen to look for disease recurrence. The clinical presentation, type and location of cysts, various surgeries performed, postoperative complications and outcomes were analysed.

Results

During the period between January 2000 and December 2009, 128 patients (with 164 hydatid cysts of the liver) were managed at our department. Of the 128 patients, 82 were females (64.06%) and the mean age of the patients was 39 years (range, 11–62 years). Abdominal pain was the most common presenting symptom (n=115) followed by lump abdomen (n=14) and jaundice (n=7). The most common location of the hydatid cyst was in the right lobe of the liver (n=76) followed by the left lobe (n=30). In 22 patients, the cysts were present in both the lobes of the liver. On ultrasound imaging, the cysts were classified according

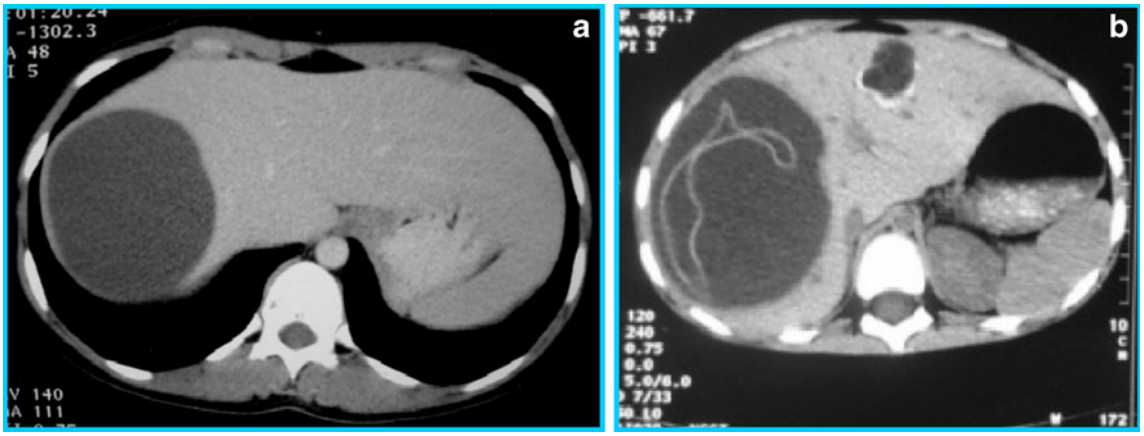

Fig. 1 Contrast-enhanced CT scan showing hydatid cyst of liver. **a** Type I **b** Type II

to the Gharbi's classification.[3] Type III cysts were the most common and were seen in 71 patients (55.4%). Fifty patients had type I or type II cysts and seven patients had type IV cysts. The average size of the cyst was 8.4×8.6 cm.

Eight patients with cholangitis and suspected cyst–biliary communication underwent a preoperative ERCP. In four patients, the cyst–biliary communication could be confirmed. In addition, in one patient hydatid membranes were seen in the bile duct, which were removed and a stent was placed. Two patients had transient hyperamylasemia following ERCP, and one patient developed severe acute pancreatitis. This patient was managed with antibiotics and percutaneous drainage and subsequently underwent surgical management for the hydatid cyst.

Fifty-two patients with type I and II cysts were planned for PAIR or PAIR-D. In seven, the procedure was abandoned due to aspiration of bile on the initial cyst puncture and in three because of aspiration of thick pultaceous contents. These were managed surgically by drainage (open = 4, laparoscopic = 1) or radical resection (n=5). PAIR or PAIR-D was attempted in 42 patients. The average size of the cysts in these patients ranged from 5 to 16 cm. In 30 patients, the PAIR required only a single session, whereas in four, more than one session was required. In eight patients, PAIR was not successful the cyst cavity did not resolve and the patients remained symptomatic. In all these eight patients, size of the cyst was more than 9 cm (average 10.6 cm) with a large extrahepatic component; however, no correlation of the failure of PAIR was found as regards the segmental location of the cyst. These patients were subsequently managed surgically (surgical drainage = 5, cystopericystectomy =2 and left lateral hepatectomy = 1). The cyst was considered to have disappeared if it was no longer visualized on ultrasonography or was replaced by an ill-defined echogenic area or normal echo pattern. In few patients, only small echogenic area was left behind.

Ninety-four surgical procedures were performed and included radical resections in 61 patients (cystopericystectomy in 52, left lateral hepatectomy in six, left hepatectomy in one, left hepatectomy with caudate lobectomy in one and right hepatectomy in one patient) and conservative surgery

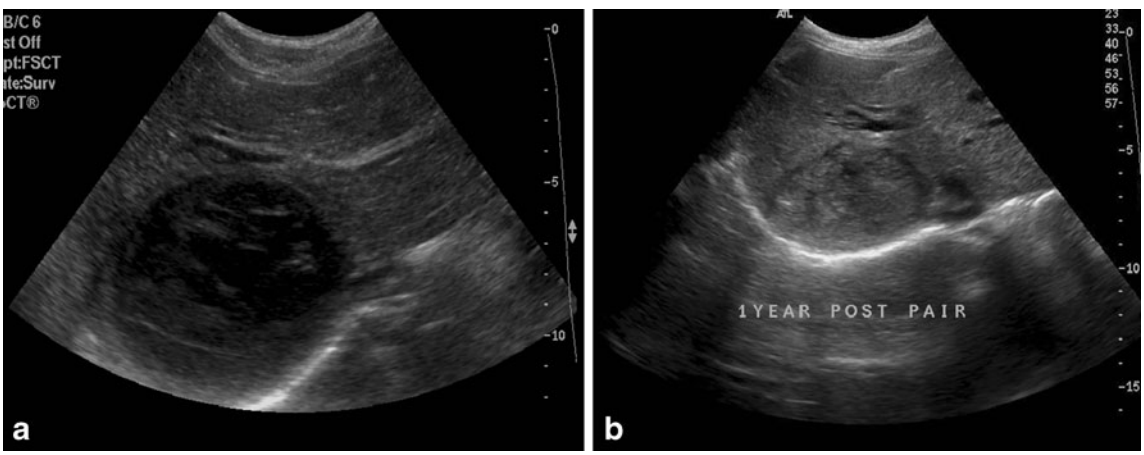

Fig. 2 PAIR procedure **a** before PAIR and **b** 1 year post-PAIR

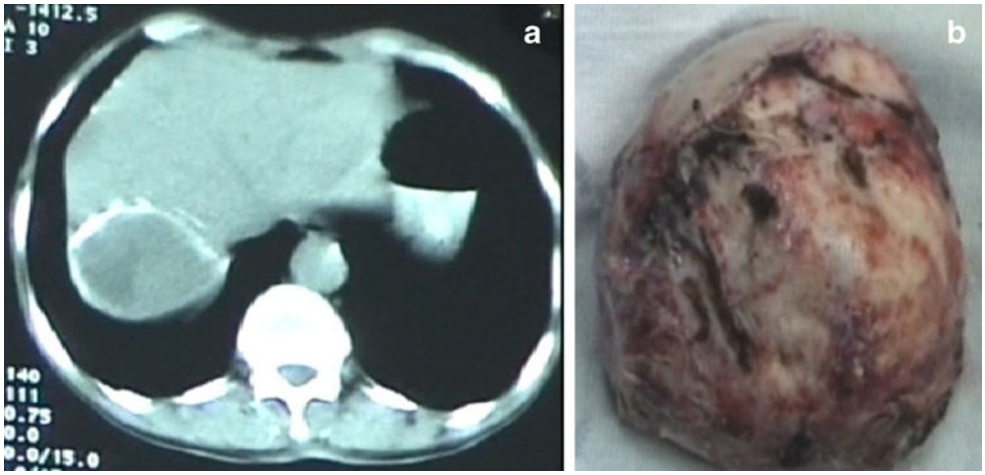

Fig. 3 **a** CECT showing a peripherally located hydatid cyst in segment VI of liver. **b** Cystopericystectomy specimen of the same patient

in 33 patients. Most of these surgical procedures were done by conventional open surgery. However, in the latter half of the study, hydatid cysts in favourable locations (peripheral and anterior segments) were managed laparoscopically by cystopericystectomy (in four), left lateral hepatectomy (in two) and drainage (in nine patients).

The estimated mean intraoperative blood loss (173.7± 121.4 and 150.7±95.7 mL) and the mean duration of surgery (234.7±55 and 219.4±50.4 min) were similar in patients undergoing either radical or conservative operations (p=0.35 and 0.19, respectively). Major complications following surgery included bile leaks and residual cavity-related abscess. Bile leak occurred in 13 patients (13.8%). The incidence was significantly higher in patients who underwent conservative surgery (n=8, p<0.032; Table 1). All patients with bile leaks were managed with continued external drainage and were started on hyoscine butylbromide. The leaks healed spontaneously in all cases except in two who required an ERCP and stent insertion. The mean duration of bile leak was 19.3±14.2 days (range 3–55 days). Cavity abscess occurred in six patients following drainage. These were managed by percutaneous drainage and antibiotics. The mean duration of postoperative hospital stay was 10±5 days in patients who underwent radical surgery and 9.6±5 days in those who underwent drainage (p=0.75).

The mean duration of surgery for patients who underwent laparoscopic management of hydatid cyst was 226.6± 47.3 min, and the mean estimated intraoperative blood loss was 161.6±182 mL. This was not significantly different from patients who underwent open surgeries (p=0.8 and 0.9, respectively).

The mean duration of follow-up following surgery was 28.05±14.5 months (6–62 months). Overall, five patients had recurrence (one in radical surgery group and four in patients undergoing conservative surgery; p=0.05). Two patients developed disseminated hydatid disease and both were managed medically with albendazole therapy. Another two patients who had an isolated intrahepatic recurrence refused further intervention and were subsequently lost to follow-up. One patient with an isolated recurrence is currently being managed with PAIR. None of the patient who underwent laparoscopic treatment had a recurrence.

Discussion

Hydatid cyst of the liver is caused by *E. granulosus* and is a common health problem in India.[5] The disease although benign may be complicated by secondary infection, biliary or peritoneal rupture, the consequences of which may be life threatening. Thus treatment is required in most cases.

Various options have been used for the management of this disease ranging from medical treatment alone to radical surgical operations and recently minimally invasive PAIR and laparoscopy (Table 2). The goal of any form of treatment for hydatid disease is inactivation and complete removal of all viable scolices and germinal membranes and management of the residual cavity with minimal morbidity and mortality. Various drugs used to treat hydatid cyst include benzimidazole compounds (albendazole, mebendazole) and praziquantel. This treatment (especially with albendazole) has been shown to be effective; however, the success rate with medical management alone ranges from 20 to 50%[6,7] with a risk of relapse of 3–30%.[7] Considering such a high failure rate, its use as a definitive therapy is limited. It is mainly used in conjunction with other treatment modalities like PAIR or surgery to decrease the chances of recurrence. It has also been used in high surgical risk patients and those with disseminated hydatidosis. All the patients in the current series received a course of albendazole starting at least 2 weeks prior to the planned intervention (PAIR or surgery).

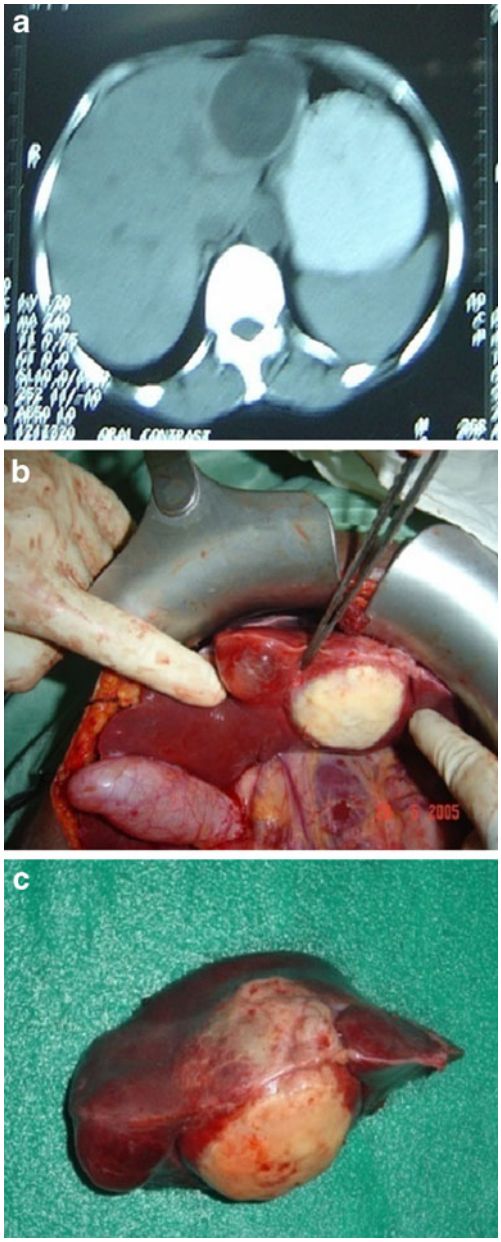

Fig. 4 **a** CECT scan of a patient showing hydatid cyst occupying the whole left lateral segment. **b** Intraoperative picture of the same patient. **c** Resected left lateral segment

Surgery remains the cornerstone of therapy for hepatic hydatid cysts. Traditionally, two types of surgical procedures have been described. The conservative surgical operations popularly the drainage procedures involve opening the cyst cavity in a controlled fashion (avoiding peritoneal spillage) and inactivating the protoscolices by instillation of a scolicidal agent. The cyst contents are then drained and the residual cavity is managed by various options like external drainage, omentopexy, capsulorrhaphy, capitonnage and marsupilization. Radical operations aim at complete removal of the cyst (including the pericyst). This may be done by cystopericystectomy or a formal liver resection. The optimal surgical management (conservative or radical) continues to be debated. Several large series have supported the radical surgery in the form of cystopericystectomy and formal liver resections for hydatid disease. They have highlighted that it may be done with minimal morbidity in high volume centres and the cavity-related complications, risk of bile leaks and postoperative recurrences are significantly reduced.[6,8] However, radical surgery is not without complications, is technically

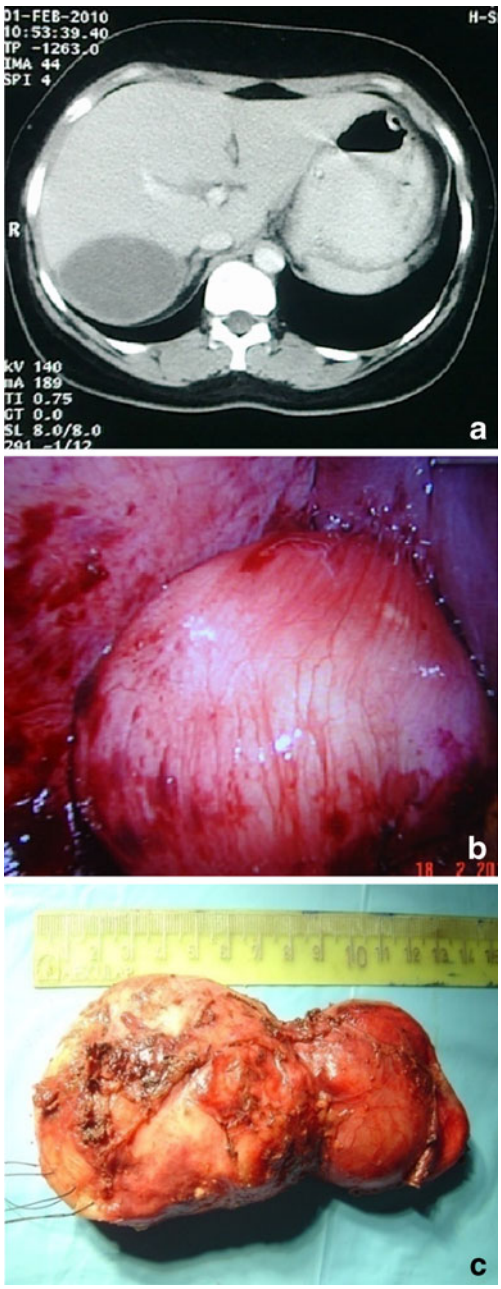

Fig. 5 **a** CECT of type I hydatid in segment VI. **b** Intraoperative photograph of laparoscopic resection for hydatid in segment VI. **c** Resected specimen

Table 1 Results of radical and conservative surgeries

Variable	Conservative surgery (n=33)	Radical surgery (n=61)	p value
Intraoperative blood loss (mL)	151 (50–500)	174 (50–750)	0.35
Duration of surgery (min)	219 (120–300)	235 (150–360)	0.19
Postoperative complications			
Bile leak, n (%)	8 (24.24%)	5 (8.2%)	0.032
Abscess, n (%)	6 (18%)	0	0.001
Postoperative hospital stay, (no. of days)	9.6 days	10 days	0.75
Duration of follow-up (months)	29 (6–62)	28 (6–55)	0.834
Recurrence, n (%)	4 (12.12%)	1 (1.6%)	0.05

n number of patients

demanding and may be associated with higher intraoperative blood loss.[7] In the present series, we did 61 radical surgeries and 33 conservative operations for hydatid cyst of the liver. The choice of surgical technique was based on the size, site and type of the cyst, presence of complications and the performance status of the patient. Cystopericystectomy was the preferred surgical approach and was aimed at decreasing the postoperative cavity-related complications, bile leaks and recurrence. The procedure was done for peripherally and superficially located cysts. Formal liver resections were done in patients where the hydatid cyst occupied the whole lobe of the liver. The radical surgeries could be accomplished with minimal morbidity and the intraoperative blood loss and duration of surgery was similar to conservative operation (p=0.35 and 0.19, respectively). In the initial part of the study, patients with large deep-seated cysts or cysts located close to the hilum or major vessels underwent a surgical drainage procedure. In the latter half, these patients (especially type I/II cysts) were managed with PAIR. A cystopericystectomy or liver resection was the preferred surgical procedure for patients with Type III/IV cysts and favourably located type I/II cysts. In patients with type III/IV cysts close to a major biliovascular channel and those in whom a complete cystopericystectomy could not be done, a near-total cystopericystectomy was performed. This procedure involved removal of as much cyst wall as possible leaving behind only a small rim of remnant cyst wall adhered to an important biliovascular structure. This was done with an aim to reduce the cavity-related complications akin to radical surgery.

Postoperative bile leaks occurred in 13 patients. Although all attempts were made to look for bile leaks after completion of the procedure in both conservative and radical surgery groups, the incidence of postoperative bile leak was significantly higher in the conservative group (24.24% versus 8.2%, p= 0.032). This may have been due to opening up of the biliary communications after the decompression of the cyst (following drainage). In addition, during cystopericystectomy and formal liver resections, individual ligation of the biliary radicals during transection and optimal visualization of the cut liver surface may have resulted in decrease bile leak rates. Most of these leaks responded to conservative management except in two patients who required an endoscopic biliary stenting. Radical surgeries also avoided the cavity-related complications that occurred in six patients. The residual cavity that remains following conservative surgeries is difficult to

Table 2 Various treatment options for hydatid cyst

	PAIR	Conservative surgery	Radical surgery
Indications	• Type I/II cysts	• All cyst types	• Superficial and peripherally located • Those involving whole lobe of the liver
Contraindications	• Type V cysts • Cysts with biliary communication • Infected cysts	• Type V cysts	• Centrally located cysts close to major biliovascular structures
Complications			
• Anaphylaxis	Yes	If uncontrolled spillage	If uncontrolled spillage
• Bile leaks	4–35%[16,17]	25–30%[6,18,19]	7%[6]
• Cavity-related complications like abscess	0.4–2%[7,16]	12–30%[6,19]	0–3%[6]
Recurrence	2–5%[1,20]	11–25%[9,18]	0–4%[9,18]

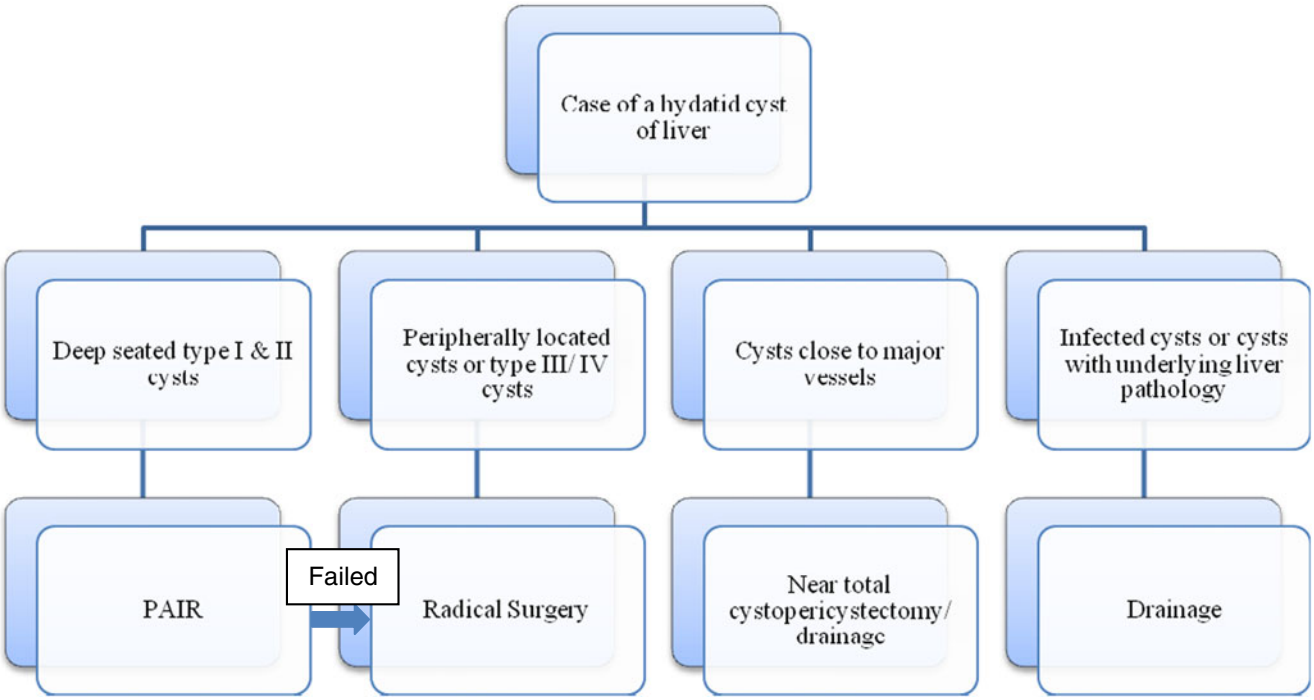

Fig. 6 Algorithm showing management of patient of a hepatic hydatid cyst. *PAIR* percutaneous aspiration, injection and reaspiration

obliterate and may get infected increasing the morbidity and readmission rates. Similar results of increased morbidity following conservative surgery have been reported in the literature. In a comparative study (radical surgery—92, conservative surgery—129), Aydin et al.[8] reported significantly higher bile leaks and cavity abscesses in patients who underwent conservative surgery. In another series (radical surgery—162, conservative surgery—210) the incidence of bile leak and cavity-related complications was significantly lower in the radical surgery group (4.3% versus 25.6%, respectively; $p<0.0001$).[6] In a study from India,[9] 14 of the 86 patients developed postoperative bile leaks and all had undergone conservative surgery.

Although in the present series, the incidence of complication was higher in patients who underwent conservative surgeries, the mean hospital stay was similar as most of the complications could be managed conservatively.

The mean follow-up after discharge was 28.05± 14.5 months. During this period, five patients developed a recurrence (one following a cystopericystectomy and four following deroofing and drainage, $p=0.05$). In all these cases, the recurrences were either multifocal in the liver or extrahepatic and these patients were managed medically. Similar results have been reported in the literature. In a study of 232 patients by Puliga et al.,[10] recurrences were seen in only those who underwent conservative surgery. In another large retrospective series, there were significantly higher recurrences following a conservative surgery as compared to radical surgery (11.9% vs 1.85%).[6]

Overall 65% patients in our series underwent radical surgeries. In the earlier part of this series, a significant proportion of patients underwent open drainage operations. But with growing expertise in performing complex hepatobiliary surgeries, the number of radical surgeries for hydatid cysts has increased. In patients where a drainage operation is indicated (cysts close to major biliovascular pedicles), the laparoscopic approach is preferred.

Laparoscopic surgery for hydatid cyst of the liver has been reported to be safe and effective.[11] Peripherally and anteriorly located small cysts are ideal for laparoscopic management. Both cystopericystectomy and drainage can be done; however, drainage procedures may have a higher risk of spillage thereby increasing the chances of recurrence. We did laparoscopic management of hydatid cysts in 15 patients. The indications of conservative versus radical procedure were the same as for an open surgery. Nine patients underwent drainage of the cysts, four a cystopericystectomy and two a left lateral hepatectomy. The mean duration of surgery and the intraoperative blood loss was similar to the patients undergoing open surgery ($p=0.8$ and 0.9 respectively). Till date, there has been no recurrence in the patients treated laparoscopically. However, the limited follow-up (mean, 16.7 months) of these patients may be a confounding factor. Laparoscopic surgery for hydatid cyst has been reported from a few centres. Chowbey et al.[12] successfully performed partial cystopericystectomy in 11 patients with minimal morbidity. In another series Palanivelu et al.[13] reported the feasibility of performing both

drainage and radical operations laparoscopically. Although these studies demonstrate the technical feasibility of the procedure, the results of outcomes over long period of follow-up are still awaited.

PAIR or PAIR-D for hydatid cyst of the liver is a non-surgical technique especially suited for small type I/II cysts with no cystobiliary communication. It was planned in 52 patients in the present series but was abandoned in ten patients due to either cystobiliary communication (n=7) or thick pultaceous material aspiration (n=3) on the initial puncture. In the initial part of our experience PAIR was done even in large cysts with extrahepatic component. Although these might not have been the ideal cysts to be treated with PAIR, all these cysts in addition had a significant intrahepatic component as well and the puncture was done transhepatically to avoid any peritoneal spillage. The higher proportion of patients being managed with PAIR in the present series may be due to a referral bias as this procedure is done in only a few specialized centres in our country. Most patients require surgical treatment, and only a few are suitable for PAIR therapy. In the current series, 34 patients were effectively treated with PAIR. In a series by Kapoor et al., only three of the 89 patients of hydatid cysts were managed with PAIR.[9] The procedure has been reported to have a higher failure rate for cysts other than types I/II,[14,15] and hence, in our series, this was not attempted in patients with such cysts. However, reconsideration may be given to PAIR in selected patients with type III cysts which are not amenable to radical surgery.

In conclusion, hydatid disease is a significant cause of morbidity in endemic areas requiring an individualized approach based on the cyst morphology, location and patients performance status (Fig. 6). In the present series, 61 patients underwent radical resections, 33 a conservative surgery and 34 (out of 128) were successfully treated by PAIR. These data highlight the need for a individualized approach for management of these patients. In most cases of deep-seated type I and II cysts, PAIR is the initial preferred treatment option. Surgery should be the preferred modality in patients with peripherally located type I/II cysts (ideally suited for cystopericystectomy), type III/IV cysts, cysts with biliary communication or following failure of PAIR. Complete removal of the cysts is preferable to drainage in centres where it can be accomplished with acceptable morbidity. Laparoscopy management should be adopted whenever feasible for both cystopericystectomy and drainage procedures.

Although, this study may have drawbacks of any retrospective analysis, this is one of the few studies which amalgamates all treatment modalities for hydatid disease of the liver and tries to give an algorithmic approach for its management. Future prospective/randomized studies may help to further substantiate the proposed management protocol.

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ORIGINAL ARTICLE

Usefulness of Histopathological Examination in Nontraumatic Perforation of Small Intestine

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Abstract
Introduction Nontraumatic perforation of small intestine (NTPSI) is a fairly common cause of peritonitis in developing world requiring early surgical intervention. Various etiological factors have been proposed for the cause of small bowel perforation. This retrospective study was conceded with an aim to determine the prevalence patterns of the different etiologies of NTPSI.
Materials and Methods A total of 164 patients were included in the study who had segments of small intestine removed for perforation during emergency procedures. Preoperative definitive diagnoses were not known in these cases. On gross examination, most of the small intestine perforations, $n=110$ (67%), were found in the terminal ileum. On microscopy, the most frequent category was that of ulcers of nonspecific etiology, $n=61$ (37.2%), which showed general features like inflammatory granulation tissue, serositis, and foreign body giant cell reaction.
Results In cases where a definite opinion could be established, infection was the commonest cause, $n=71$ (43.3%), wherein tuberculosis (49, 29.9%) and typhoid (22, 13.4%) constituted the greatest number of cases. There were two cases of lymphoma and one case of metastatic adenocarcinoma involving the small intestine. Thus, histopathological examination of operated specimen is a useful guide for the surgeon to decide further management of the patient especially in the case of infections.

Keywords Histopathology · Perforation · Small intestine

Introduction

Intestinal perforation is a common cause of peritonitis necessitating immediate surgical intervention. Nontraumatic perforation of small intestine (NTPSI) refers to those perforations in which external trauma as an etiology has been excluded.[1,2] Various etiologies have been suggested for NTPSI; however, the distribution of these etiologies across the globe is variable. This condition is seldom seen in the western world[3] where it is mostly attributable to foreign bodies, Crohn's disease, primary ischemic events, and as a part of systemic disorders.[3–5] However, in developing countries infectious conditions like typhoid and tuberculosis predominate the etiology of NTPSI.[6,7] The operating surgeons should thus be aware of the diverse etiologies of NTPSI, which would affect the management and hence the prognosis of the patient. In view of the significant number of intestinal segments that we receive in our department for histopathology, this study was carried out to study the prevalence patterns of the different etiologies of NTPSI.

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Materials and Methods

This retrospective study was conducted in the Department of Histopathology of our Institute during 2007–2008. Segments of small intestine excised for perforation during

emergency procedures were included in the study. Preoperative definite diagnoses were not known in these cases. Cases in which only ulcer edge biopsies were taken were excluded. The intestinal segments were fixed in buffered formalin. Appropriate sections were taken from the ulcer edge, stricture, tubercles, and lymph nodes, if any, and embedded in paraffin. Routine hematoxylin and eosin-stained sections were available in all cases, and special stains were performed whenever required.

Results

A total of 164 patients were included in the study, of which 94 were males and 70 were females, with a male/female ratio of 1.34:1. There was a wide age range, with the youngest patient being a two-and-a-half-year-old female child and the eldest being a 72 years old male (Fig. 1). The mean age of the patients was 27 years.

The most common presenting complaints of patients were abdominal pain, vomiting, constipation, and abdominal distension. A plain abdominal X-ray was available preoperatively in all cases and showed gas under diaphragm and multiple air fluid levels.

On performing gross naked eye examination of formalin fixed specimen, it was found that majority of the small intestine perforations, 110 (67%), were present in the terminal ileum (Fig. 2). Multiple perforations involving the ileocecal region and both ileum and jejunum were found in 25 (15%) and 14 (8.5%) cases, respectively. Isolated jejunal perforation was seen in 13 (7.9%) cases.

While 92 cases showed presence of perforation only, 36 patients had perforations along with stricture and/or ulcer. Twenty-eight patients had an ulcer accompanying the perforation, while eight cases had a stricture along with the perforation. Tubercles were found studded on serosal aspect in 13 cases, and in 35 cases, enlarged lymph nodes could be dissected out.

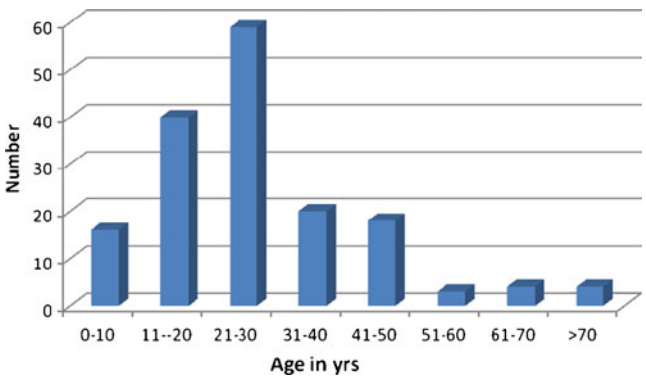

Fig. 1 Age-wise distribution of intestine perforations

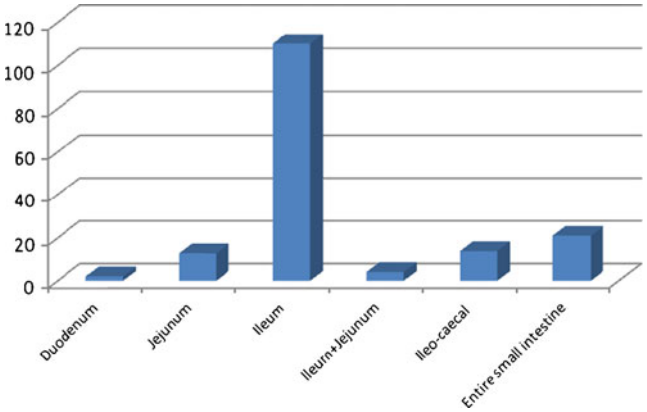

Fig. 2 Distribution of perforations on the basis of site

Histological examination revealed that maximum number of cases (n=61) had nonspecific features like inflammatory granulation tissue, serositis, and foreign body giant cell reaction (Fig. 3). Amongst the cases where a definitive opinion could be given, most were diagnosed as intestinal tuberculosis, followed by typhoid (Table 1).

Cases with tuberculosis showed epithelioid cell granulomas. Caseous necrosis was seen in most of these cases. All the 13 tubercles which were examined showed granulomatous inflammation, some showing caseous necrosis too (Fig. 4). Segments with typhoid perforation showed erythrophagocytosis in the region of ulcer associated with histiocytic granulomas (Fig. 5). Ischemic necrosis of variable extent was seen in the intestinal segments involved by gangrene. Strangulated hernias and volvulus were diagnosed grossly and showed similar findings. Perforation due to worms (*Ascaris lumbricoides*) and Meckel's diverticula were also gross diagnoses. Incidentally, one of the two patients with worms showed epithelioid cell granulomas with necrosis and the other showed erythropha-

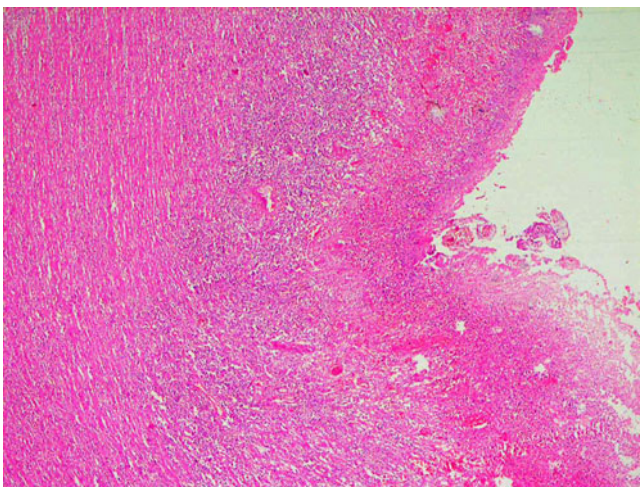

Fig. 3 Section from nonspecific ulceration showing denuded mucosa lined by inflammatory granulation tissue. H&E ×40

Table 1 Etiology of small intestine perforations

Diagnosis	No. of cases (%)
Nonspecific features	61 (37.2)
Tuberculosis	49 (29.9)
Typhoid	22 (13.4)
Gangrene	17 (10.4)
Strangulated hernia	3 (1.8)
Meckel's diverticular perforation	4 (2.4)
Volvulus	3 (1.8)
Worms	2 (1.2)
NHL	2 (1.2)
Adenocarcinoma	1 (0.6)

gocytosis, indicative of tuberculosis and typhoid respectively, suggesting worms as coincidental findings

There were two cases of non-Hodgkin lymphoma involving small intestine. Both showed a monomorphic lymphoid cell population of small to medium sized cells involving the layers of intestine (Fig. 6). Lymphoepithelial lesion was seen in one of them. There was only one case of metastatic adenocarcinoma, showing irregularly shaped glands of variable sizes and highly pleomorphic cells infiltrating the wall of intestine from serosal aspect.

In all the cases with lymph nodes examined, the findings in the lymph nodes supplemented those of the intestinal segment. Only in two of the 35 cases, histopathology of lymph nodes clinched the diagnosis even though the intestinal segment showed nonspecific features. In these cases, there was erythrophagocytosis in the lymph nodes which favored a diagnosis of typhoid even though no such features were seen in the intestinal segment.

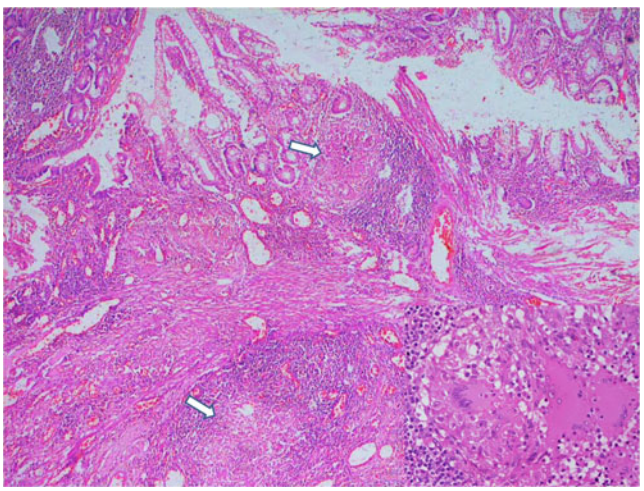

Fig. 4 Section from tuberculosis intestine with numerous epithelioid cell granulomas with giant cells and necrosis (*arrows*). *Inset* shows a higher power view of epithelioid cell granuloma and Langhans' giant cells. H&E ×40

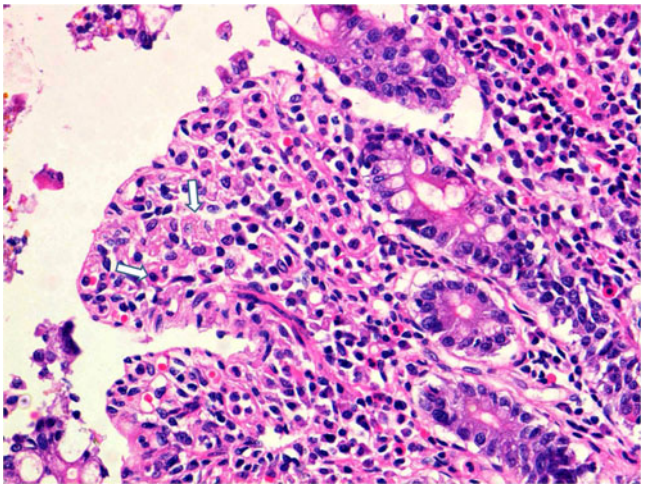

Fig. 5 Section from typhoid ulcer shows lymphoid hyperplasia with clusters of erythrophagocytic histiocytes (*inset*, *arrow*). H&E ×400

Discussion

A wide range of etiological factors have been proposed for the causation of small bowel perforation. Knowledge of the possible etiologic factors is of great importance to the surgeon as a guide to adapting the operative procedure for the intestinal lesion.

Nontraumatic perforation of the small intestine is a rare entity in the western literature.[3] However, with the large number of cases diagnosed every year, NTPSI appears to be fairly common in the tropics.[8,9] In the present study, most of the patients were in the age group of 21–30 years which is in contrast to studies in the western countries where it primarily occurs in the elderly.[3] This may be explained by the difference in the settings in which these perforations occur. The western literature suggests that foreign body,

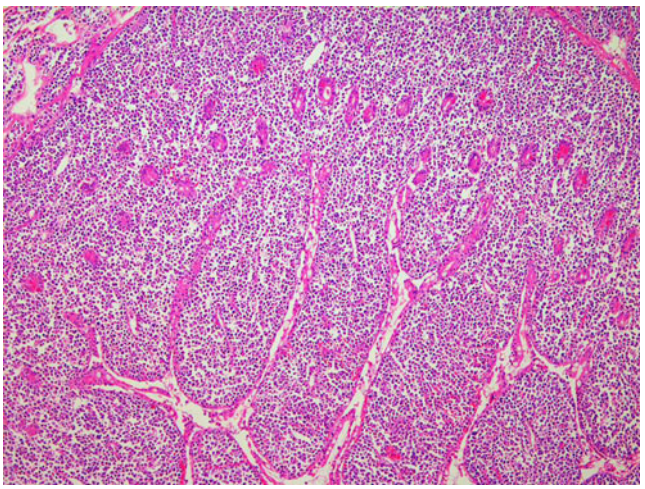

Fig. 6 Section showing mucosa, submucosa, and muscularis propria infiltrated by monomorphic lymphoid population in non-Hodgkin lymphoma. H&E ×100

ischemia, radiotherapy, diverticula, Crohn's disease, etc. are the main causes of perforation, which are more commonly seen in elderly patients.[5] In contrast to this, infection is the commonest cause of such perforations in developing countries. This includes typhoid fever and tuberculosis which are quite common in young.[5,6,10] The findings in the present study are consistent with this trend; as in 71 (43.3%) cases, an infectious etiology, either due to tuberculosis or typhoid, could be established.

Despite considerable progress made in therapy and prophylaxis, abdominal tuberculosis is still common in developing countries[11] and its incidence is increasing in the western world too.[12] Although perforation due to abdominal tuberculosis is supposed to be uncommon because of reactive thickening of the peritoneum and formation of adhesions with surrounding tissues,[13] it is still a serious complication that occurs in 1–10% of all patients with abdominal tuberculosis.[13,14] The perforation is most commonly found in the distal ileum. Of the 49 patients, 36 patients had perforation, stricture, as well as ulcer; eight cases had a stricture along with the perforation, while five patients had only perforation. The ulcers lie transverse to the intestine axis which can be explained by the lymphatic network distribution in that area. Histopathology of the intestinal segments revealed epithelioid cell granulomas with or without caseous necrosis. The histopathology of the tubercles and the associated lymph nodes was consistent with tuberculosis in all cases. Subsequent to histopathologic diagnosis, patients were started on a standard four-drug anti-tubercular treatment (Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol) for 4 months, followed by a two-drug treatment (Isoniazid and Rifampicin) for 2 months.

Perforation, a lethal complication of typhoid fever, occurs due to necrosis of Peyer's patches in the terminal ileum, this being the most common site where the bacteria *Salmonella typhi* colonizes. Hence, the ulcers lie longitudinally along the axis of the intestine in the direction of Peyer's patches. On histopathology, erythrophagocytosis by histiocytes along with the formation of histiocytic granulomas was found in the region of the ulcer. In two cases, the intestinal segment showed nonspecific features of perforation, while the lymph node showed erythrophagocytosis. Hence, an active lookout for these can help in reaching the diagnosis in a significant number of cases.[17] In all cases, the diagnosis needs to be confirmed by serology and/or culture. The patients were treated with Ceftriaxone initially. Other antibiotics were given according to culture and antibiotic sensitivity.

Studies have shown that worldwide, typhoid fever is the most common cause of small intestine perforation.[7,15,16] In a previous study done by authors on the role of ulcer edge biopsy in diagnosing NTPSI, it was found that amongst the cases diagnosed as a definitive pathology, typhoid is the commonest diagnosis.[17] However, in the present study, tubercular enteritis (n=49) was more common than typhoid perforation (n=22). Waisberg et al. also found similar results, wherein tuberculosis was the most frequent specific factor comprising 20.7% of the cases.[18] A possible explanation could be that, in case of typhoid perforation, the operative management consists of liberal peritoneal lavage with closure of perforation.[10] Thus, getting the entire ileal segment for histopathology is uncommon in such cases until and unless the terminal ileum is grossly inflamed with multiple perforations. On the contrary, simple closure is contraindicated in case of tuberculosis as there is always a chance of stricture, reperforation, and fistula formation. Thus resection is almost always done, which is sent for histopathological confirmation.

Next to infectious diseases, the most frequent category was that of ulcers of nonspecified etiology (37.2%). This is in concordance with studies done by Waisberg et al. wherein a specific etiology could not be found in 29.5% of the patients.[18] The histopathological examination of these nonspecific ulcers showed an ulcer base which was formed by granulation tissue and fibrinopurulent exudate. This was usually accompanied by foreign body giant cell reaction and serositis. In the previous study done by authors on perforation edge biopsy, it was found that typhoid and tuberculosis were the main causes in which etiology could be established on histopathology.[17] However, in majority of cases, no etiologic factor was apparent on biopsy specimen and those were reported as ulcers of nonspecific etiology. The patients were given a course of antibiotics in the postoperative period according to culture and sensitivity reports, and were advised follow up in outpatient department.

Strangulation in external hernia and mesenteric ischemia are known to cause small intestine perforation.[5] There were 17 cases of gangrene due to mesenteric ischemia and three cases due to strangulation of inguinal hernias. In both the conditions, there was widespread ischemic necrosis of the intestine. Perforation as a complication is a rare event in jejunoileal diverticula.[19] Leijonmarck et al. found only three cases of perforated Meckel's diverticulum.[3] The etiology is probably on a hypermotility basis with symptomatic patients showing active but uncoordinated peristalsis.[20] In three patients, the perforation was due to small bowel volvulus.

In two patients, the intestines were packed with worms, along with presence of perforation preoperatively. Interestingly, there was one patient with coincidental tuberculosis with worms and one with typhoid perforation with worms. Thus the presence of worms was a coincidental finding and not a main cause of perforation.

Lymphomas, sarcomas, and adenocarcinomas are susceptible to intestine perforation[21] probably due to chemo-

therapy or inadequate blood supply.[22] Chaikof et al., in their study, found 17 perforation cases caused by malignancy, of which 12 were metastatic.[23] In our study, we found only one patient with metastatic adenocarcinoma and two patients with non-Hodgkin's lymphoma. All the patients were referred to the Oncology department for further management.

While reviewing the literature, we did not encounter any study based on histologic review of small bowel perforation. In this study, we found that nontraumatic perforation in developing countries can be due to typhoid, tuberculosis, and few cases of malignancy. Even though a significant number of specimens may be nondiagnostic, histopathological examination of operated specimen definitely helps the surgeon in further management of the patient. This is particularly important in case where the etiology is infectious like tuberculosis or typhoid.

In conclusion, diagnosis of nontraumatic perforation is a challenge preoperatively. Clinical findings are usually nonspecific and definite diagnosis can be reached after histopathology. Although specimen examination is an important factor for proper management, histopathological examinations are not always informative.

Conflicts of interest No conflict of interest. No financial support of any form has been taken from any agency for this study.

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ORIGINAL ARTICLE

Intravital Three-Dimensional Dynamic Pathology of Experimental Colitis in Living Mice Using Two-Photon Laser Scanning Microscopy

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Abstract
Background Intravital three-dimensional (3D) visualization of treatment efficacy in experimental colitis in living mice using two-photon laser scanning microscopy (TPLSM) has not been described.
Methods Colitis was induced with dextran sulfate sodium (DSS) in green fluorescent protein (GFP) transgenic mice. The 3D tomographic image of DSS-induced colitis with or without prednisolone was obtained intravitally using TPLSM. A serosal-approaching method was developed, by which we could observe all layers of the cecum from serosa to luminal mucosa without opening and everting the cecum. The dynamic pathology and treatment efficacy were assessed in the same mouse on several occasions.
Results The time-lapse 3D tomographic movie of DSS-induced colitis was obtained in living mice at a magnification of greater than ×600, which demonstrated irregularity of crypts, disappearance of crypts, inflammatory cell infiltrates in the lamina propria, and abscess formation at the bottom of crypts. Intravital TPLSM in the same mice demonstrated fewer infiltrating leukocytes and crypt abscesses on day 14 in the steroid group compared with the nonsteroid group.
Conclusions Intravital 3D tomographic visualization of experimental colitis using TPLSM in combination with the serosal-approaching method can provide dynamic pathology at a high magnification, which may be useful in evaluating treatment efficacy in the same living mice.

Keywords Two-photon laser scanning microscopy · Green fluorescent protein · Dextran sulfate sodium · Colitis · Corticosteroid

Abbreviations

TPLSM	Two-photon laser scanning microscopy
GFP	Green fluorescent protein
DSS	Dextran sulfate sodium

Introduction

Two-photon laser scanning microscopy (TPLSM), relying on the simultaneous absorption of two photons by a molecule, is one of the most exciting recent developments in biochemical imaging. It utilizes near-infrared (NIR) excitation generating twice to multifold enhanced tissue penetration (up to near 1,000 μm from the sample surface), reduced light scattering, and minimized phototoxicity and photobleaching at out-of-focus regions resulting in long-term imaging in living animals, compared with conven-

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tional single-photon excited confocal laser scanning microscopy (CLSM).[1,2]

Because of the deeper tissue penetration and much less phototoxicity (or photobleaching), TPLSM can provide in vivo, real-time, and long-term imaging in living animals.

Although in vivo real-time TPLSM has been used in a number of research fields,[3–5] it has been a technical challenging to visualize intra-abdominal organs, especially in the gastrointestinal tract, because of the adverse effect of respiratory movement and heartbeat. To the best of our knowledge, only a few studies have visualized and evaluated morphology of the intra-abdominal gastrointestinal tract by using in vivo real-time TPLSM.[6]

We have established a novel technique for in vivo real-time TPLSM imaging of intra-abdominal gastrointestinal disease.[7] Our method includes (1) fixation and stabilization of mouse cecum for intravital TPLSM imaging at a magnification of greater than ×600, with much less effect of respiratory movement and heartbeat (organ stabilization system), and (2) observation of all layers of the cecum from serosa to luminal mucosa, without opening the cecal wall (serosal-approaching method). The latter technique enabled us to observe all layers of the cecum under TPLSM in the same mice at different times because of much less surgical stress.

Ulcerative colitis (UC) is characterized by chronic uncontrolled inflammation of colonic mucosa, with relapsing and remitting phases. In several animal models of UC, dextran sulfate sodium (DSS) has been widely used to study the mechanisms of colonic inflammation and to evaluate the effect of any candidate drug. Since corticosteroids remain the principal treatment for acute severe UC, its morphological features in DSS-induced colitis have been poorly described.[8,9]

In this study, we showed in vivo real-time, three-dimensional (3D) TPLSM imaging of all layers of the cecum of DSS-induced colitis in β-actin green fluorescent protein (GFP) C57BL/6 transgenic mice. We also showed the time course of TPLSM imaging in the same mice to evaluate the efficacy of steroid treatment of DSS-induced colitis at different time points.

Material and Methods

Transgenic Mice

GFP transgenic mice [GFP-Tg mice; C57BL/6 TgN(β-act-EGFP)Osb] were kindly provided by Dr. Masaru Okabe (Genome Research Center, Osaka University, Osaka, Japan).[10]

Ten- to 12-week-old male GFP mice (20–22 g) were bred, housed in groups of six mice per cage, and fed with a pelleted basal diet (CE-7; CLEA Japan Inc., Tokyo, Japan) and free access to drinking water. Mice were kept in the animal house facilities at Mie University School of Medicine under standard conditions of humidity (50±10%), temperature (23±2°C), and light (12/12 h light/dark cycle), according to the Institutional Animal Care Guidelines. The experimental protocols were reviewed and approved by the Animal Care and Use Committee at the Mie University Graduate School of Medicine.

Chemicals

DSS with a molecular weight of 40,000 was purchased from MP Biomedicals, Inc. (Solon, OH, USA). Prednisolone was purchased from Sigma-Aldrich, Inc. (St. Louis, MO, USA).

DSS-Induced Colitis

GFP-Tg mice were used between 10 and 12 weeks of age with a mean weight of 21 g (range, 20–22 g). DSS for induction of colitis was dissolved in water at a concentration of 2% (*w*/*v*). All mice were exposed to 2% DSS in the drinking water for 7 days.

Treatment Schedule of Prednisolone for DSS-Induced Colitis

As shown in Fig. 1, GFP mice were assigned to two groups: steroid group (n=10) and nonsteroid group (n=10). In the steroid group, prednisolone was administered intraperitoneally at an estimated daily dose of 1–1.5 mg/kg for five consecutive days after 2% DSS administration. In the nonsteroid group, phosphate-buffered saline was injected according to the same protocol.

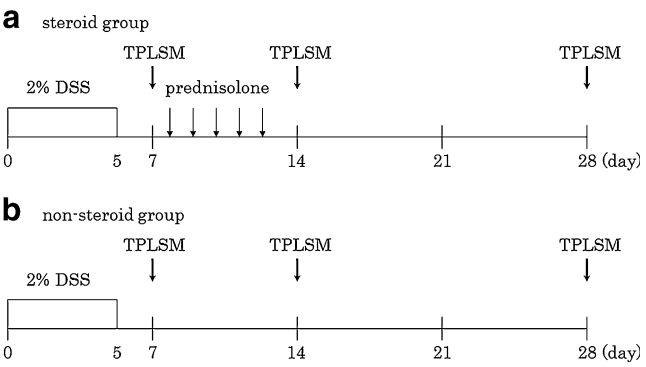

Fig. 1 Treatment schedule and timing of intravital TPLSM. In the same mice, time-course TPLSM images were obtained in both groups. Prednisolone was administered after DSS administration in the steroid group. **a** Steroid group (n=10); **b** nonsteroid group (n=10)

Surgical Procedures

Mice were anesthetized with intraperitoneal injection of chloral hydrate (Sigma-Aldrich, St Louis, MO, USA). Body temperature was kept at 37°C using a heating pad throughout the experiments. Hydration was maintained by intraperitoneal injection of saline (200 μl) at 1- to 2-h intervals.

A lower midline laparotomy was made as short as possible (<15 mm). The cecum and terminal ileum were identified through laparotomy. After exteriorization of the cecum, air was introduced through the tip of the collapsed cecum using a syringe with a small needle. Optimal inflation of the cecum enabled us to visualize vertically all layers of the cecum by observing it through the serosa into the mucosa (serosal-approaching technique). The small needle hole was closed to reduce the risk of peritonitis before abdominal closure. The cecum was placed on wet gauze and kept moist during the experiments. The inflated cecum was positioned appropriately and fixed using an organ-stabilizing system (patent number: 2007-129723). The organ stabilizer was used to minimize the microvibration of the observational area caused by heartbeat and respiratory movement so that we could obtain a clear, high-resolution image of the intra-abdominal organs.[7] Such stabilization and fixation of the cecum were the most important to optimize laser penetration and technically the most difficult part of this experiment. A thin cover glass was gently placed on top of the cecum to reduce microperistalsis. Appropriate physiological saline was dropped in the surgical area to prevent bowel dehydration. Sodium hyaluronate and carboxymethylcellulose membrane (Sepra-film Adhesion Barrier, Genzyme Corporation, Cambridge, MA, USA) was placed between the cecum and abdominal wall to prevent postoperative dense adhesion.

During the entire surgical procedure, the utmost precaution was taken when manipulating the bowel.

TPLSM

We studied the colonic crypts and their microenvironment in DSS-induced colitis in GFP-Tg mice in in vivo real-time TPLSM.

An organ-stabilizing system was used for high-quality TPLSM imaging. A serosal-approaching method was also used, by which we could observe all layers of the cecum at the cellular level by TPLSM, from the serosa to the luminal mucosa, without opening and everting the cecum.

Experiments were performed using an upright microscope (BX61WI; Olympus, Tokyo, Japan) and FV1000-2P laser scanning microscope system. The use of special stage risers enabled this unit to have an exceptionally wide working distance, which permitted the stereotactically immobilized, anesthetized mouse to be placed on the microscope stage. The microscope was fitted with several lenses with high numeric aperture, long working distances as required for in vivo work, and water immersion optics. In TPLSM mode, the excitation source was Mai Tai Ti:sapphire lasers (Spectra Physics, Mountain View, CA, USA), turned, and mode-locked at 910 nm. The Mai Tai produces light pulses of about 100 fs width (repetition rate, 80 MHz). Laser light reached the sample through the microscope objective (×60 LUMPlanFI/IR, water dipping, numerical aperture of 0.9, working distance of 2 mm) connected to an upright Olympus BX61WI microscope. Data were analyzed by FV10-ASW (Olympus).

Microscopic Evaluation of Treatment Efficacy Under TPLSM

TPLSM scanning was done at 512×512 pixels (210×210 μm, original magnification of ×600). Tomographic 3D images (z-stacks) were recorded from the serosal surface, lamina propria, bottom of the crypt, midportion of the crypt, and luminal cryptic orifice.

Infiltrating leukocytes were recognized as bright spots whose size was identical to that of rolling leukocytes in the vessels. TPLSM images (512×512 pixels) were taken at the level of the lamina propria located at the midportion of the crypt. TPLSM images at this level were collected from five randomly selected areas per mouse. The number of infiltrating leukocytes in the pericryptal stroma was counted on each TPLSM image and averaged at the indicated time points in the same mice.

Histology

At each time point, mice were euthanized and the entire colon was excised. The colon length was determined from the rectum to the cecum. The cecum of the excised colon was fixed in a 2% formaldehyde solution for 24 h and then transferred into a 30% sucrose solution for 24 h. They were embedded in Tissue-Tek OCT compound (Sakura Fine Chemical Co., Tokyo, Japan) and frozen in liquid nitrogen. Cryostat sections (7 μm thick) were air-dried at room temperature for 30 min and stained with Mayer's hematoxylin and eosin.

Protein Extraction and Measurement of Cytokine Levels

For the measurement of cytokine levels, the cecum (approximately 5 mm in length) was excised and collected from mice euthanized at each time point for each group (n= 5 each). They were placed in cold lysis buffer (Tris-buffered saline, pH 7.5, containing 1% Triton X-100) and homog-

enized using a Mixer Mill MM 300 homogenizer (Qiagen Inc., Chatsworth, CA, USA). Supernatants were collected and frozen at −80°C until use. The protein concentration was measured by the BCA protein assay (Pierce, Rockford, IL, USA).

Mouse tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) protein concentrations were measured by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's guidelines (R&D Systems, Minneapolis, MN, USA). Protein concentrations of each cytokine were corrected for total protein. The experiment was performed in triplicate.

Statistical Analysis

All statistical analyses were done using JMP version 5 (SAS Institute Inc., Cary, NC, USA). Values were expressed as mean±standard error.

The difference in infiltrative leukocyte count between normal cecum and DSS colitis was evaluated using the Mann–Whitney *U* test. The number of infiltrative leukocytes between steroid group and nonsteroid group were compared and estimated by the Mann–Whitney *U* test.

The differences in tissue concentrations of TNF-α and IL-10 between steroid group and nonsteroid group were assessed using the Mann–Whitney *U* test. *P* values less than 0.05 were considered statistically significant.

Results

3D TPLSM Images of Normal Cecum

TPLSM images of all layers of the cecum were obtained as tomographic images from the serosal surface to the luminal cryptic orifice using the serosal-approaching method. In other words, we could observe the serosal surface, lamina propria, bottom of the crypt, midportion of the crypt, and luminal cryptic orifice in order (Fig. 2; Supplementary Movie 1).

3D TPLSM Images of DSS-Induced Colitis

Administration of 2% DSS for 5 days was associated with significant clinical symptoms, including body weight loss, diarrhea, and appearance of bloody stools. Figure 3 shows 3D, tomographic TPLSM images of DSS-induced colitis

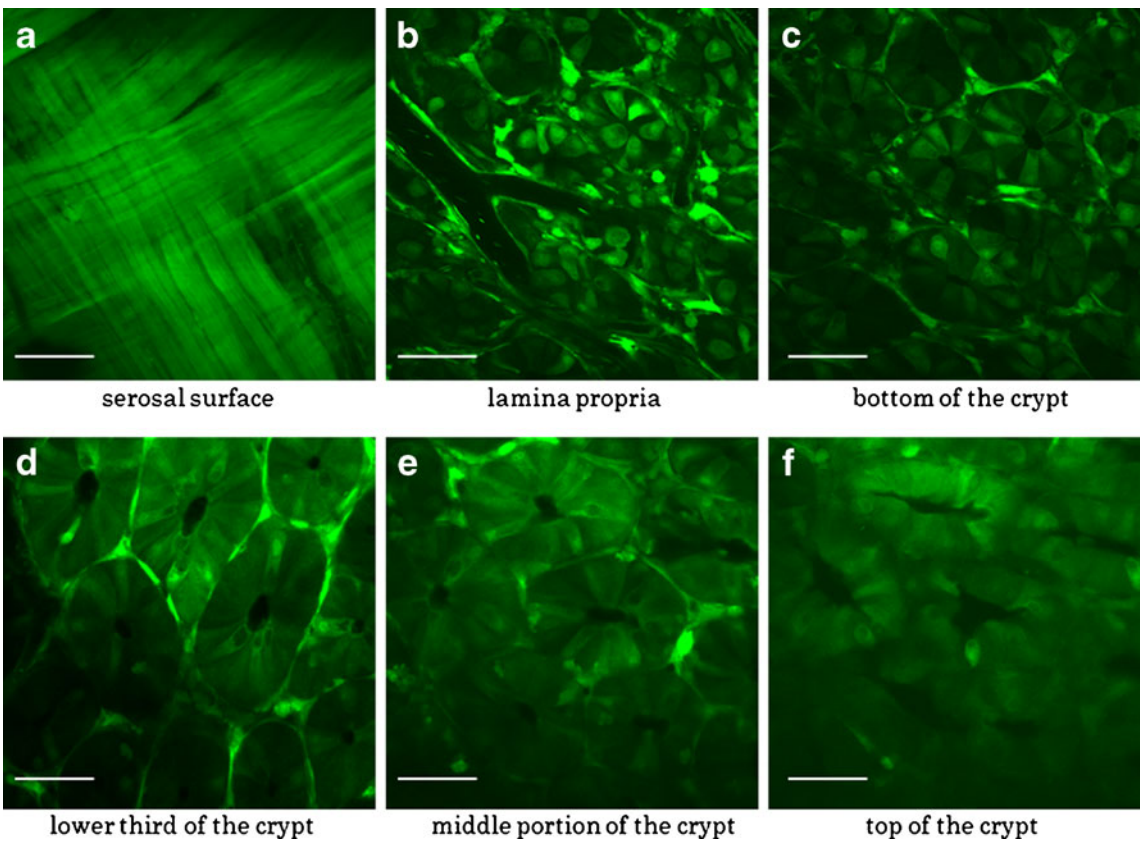

Fig. 2 3D TPLSM images of normal cecum. The serosal-approaching method was used, by which we could observe all layers of the cecum at the cellular level by intravital TPLSM from the serosa to the luminal mucosa, without opening and everting the cecum. **a** Serosal surface; **b** lamina propria; **c** bottom of the crypt; **d** lower third of the crypt; **e** middle portion of the crypt; **f** top of the crypt (bar=50 μm, ×600)

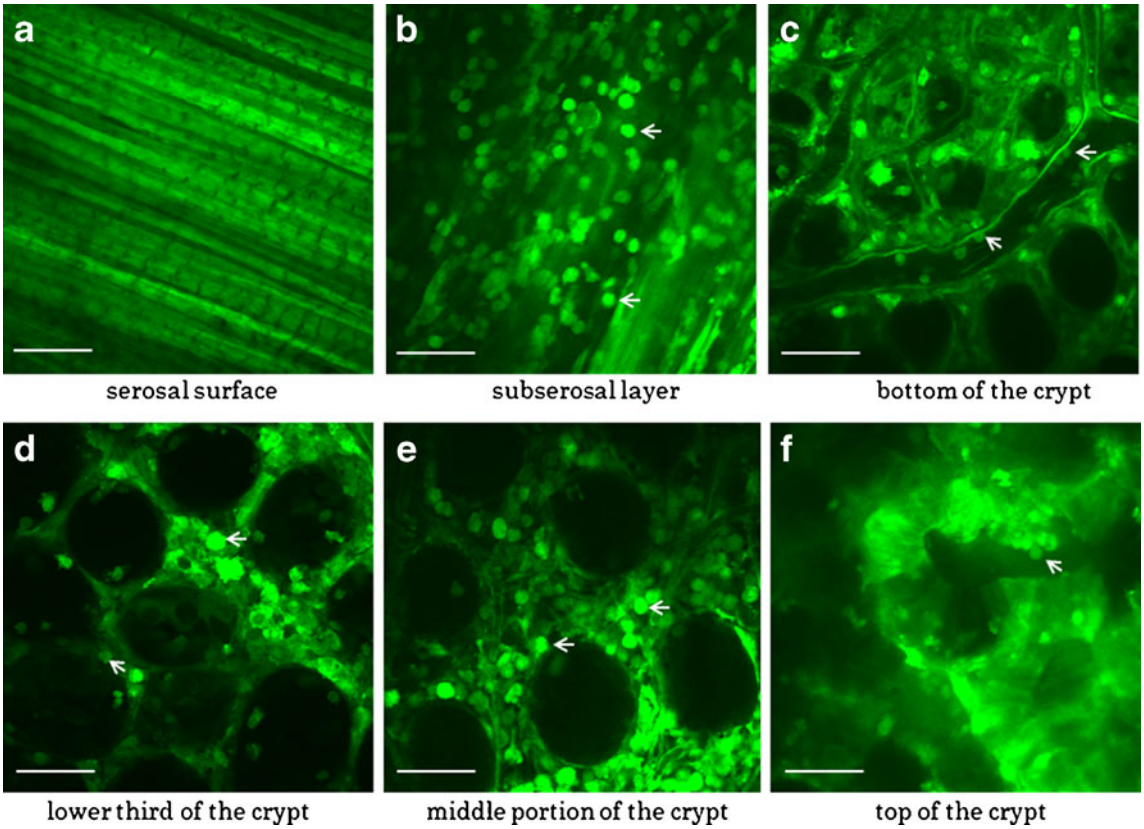

Fig. 3 3D TPLSM images of DSS-induced colitis. Experimental colitis was induced by 2% DSS in drinking water (ad libitum) for 5 days. On day 7, all layers of the cecum were viewed by time-lapse, 3D tomographic images under intravital TPLSM, using the serosal-approaching method. **a** Serosal surface; **b** subserosal layer; **c** bottom of the crypt; **d** lower third of the crypt; **e** middle portion of the crypt; **f** top of the crypt. *Arrows* indicate leukocytes whose size was identical to that of rolling leukocytes in the vessels (bar=50 μm, ×600)

(Supplementary Movie 2). Red blood cells were not identified in GFP mice,[10] leukocytes were recognized as larger round cells, and platelets were recognized as smaller ones within the vessels. Thus, inflammatory cells were recognized as bright spots whose size was identical to that of rolling leukocytes in the vessels.

Inflammatory cell infiltration was mainly observed from the subserosal layer to the lamina propria located at the midportion of the crypt. At lower magnification (×100–200), larger bright spots were scattered on several areas of the serosal surface, which indicated aggregation of inflammatory cells.

The lamina propria located at the midportion of the crypt showed extensive inflammatory cell infiltration and pericryptal stromal edema (Fig. 3d, e). On 3D imaging, crypts were distorted in shape and appeared irregular in size. At the surface of the mucosa (Fig. 3f; crypt at the top), crypt architecture was destroyed and intercryptic space was increased due to stromal edema. In several areas, crypt orifices had disappeared or were not aligned because of severe inflammation.

Inflammatory cells infiltrated the pericryptal stroma and the interepithelial space of the crypt. Inflammatory infiltrates were also observed in several crypt lumens, which suggested early formation of crypt abscesses.

Figure 4 shows leukocyte rolling within microvessels located at the lamina propria and crypt abscesses, along with destruction of adjacent crypts.

When irregular, larger bright spots on the serosal surface were observed at a low magnification, these spots were represented three-dimensionally with a teardrop shape. At a higher magnification (greater than ×600), they were formed by aggregation of inflammatory cells and were diffusely scattered at the bottom of the crypts. Therefore, these spots were considered as crypt abscesses.

Figure 5 shows representative and confirmatory hematoxylin and eosin staining of normal cecum and DSS-induced colitis in longitudinal sections.

Time-Course TPLSM Images of DSS-Induced Colitis

The tomographic 3D images of DSS-induced colitis, with or without prednisolone treatment, were obtained from the same mice using intravital TPLSM. Treatment efficacy or natural repair processes of DSS-induced colitis were observed in the same mice at the indicated time points.

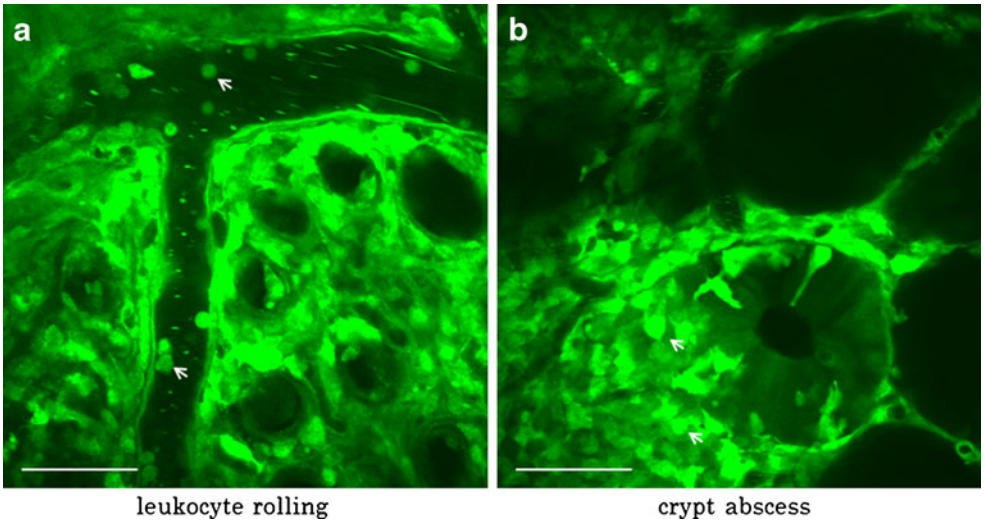

Fig. 4 Intravital TPLSM images of leukocyte rolling and crypt abscess. **a** Leukocyte rolling; **b** crypt abscess. *Arrows* indicate leukocytes whose size was identical to that of rolling leukocytes in the vessels (bar=50 μm, ×600)

In the steroid group, 70% of mice survived at the end of this protocol (on day 28). In contrast, 50% of mice survived in the nonsteroid group. There was no mortality related to repeated laparotomy in both groups. Figure 6 shows the representative time-course TPLSM images obtained in both groups.

On day 7, colitis was the most severe with extensive inflammatory infiltrates, stromal edema, and abscess formation. In the steroid group, cryptic architecture was well maintained after the disappearance of inflammation, compared with that in the nonsteroid group (Fig. 5). In the nonsteroid group, scar formation was observed, with deformity of the surrounding crypts on day 28, which resulted in greater shortening of the colon. The mean length of excised colon on day 14 was longer in the steroid group (8.7 cm) than in the nonsteroid group (6.8 cm). These results suggest that prednisolone contributes to the clearance of local inflammatory cell infiltration and subsequent prevention of colon shortening.

Intravital Evaluation of Treatment Efficacy Under TPLSM

In the normal cecum, leukocyte infiltrates (or residential leukocytes) were found at the base of the crypt, while few leukocytes were observed at the midportion of the crypt. Therefore, infiltrating leukocytes in the pericryptal stroma of the midportion of the crypt were counted for evaluation of treatment efficacy in DSS-induced colitis, with or without prednisolone treatment, under intravital and interval TPLSM.

Figure 7 shows the number of infiltrating leukocytes in the pericryptal stroma at the midportion of the crypt in each group. In both groups, the number of infiltrating leukocytes decreased in a time-dependent manner. On day 28, there were significantly fewer in the steroid group than in the nonsteroid group. The amount of leukocyte rolling in microvessels and crypt abscesses was also lower in the steroid group than the nonsteroid group (data not shown).

Changes in Proinflammatory and Anti-inflammatory Cytokines in DSS-Induced Colitis

To evaluate treatment efficacy in DSS-induced colitis, TNF-α as a proinflammatory cytokine and IL-10 as an anti-inflammatory cytokine were measured by ELISA in the excited cecum at each time point in each group.

The tissue concentration of TNF-α was lower in the steroid group than in the nonsteroid group on days 14 and

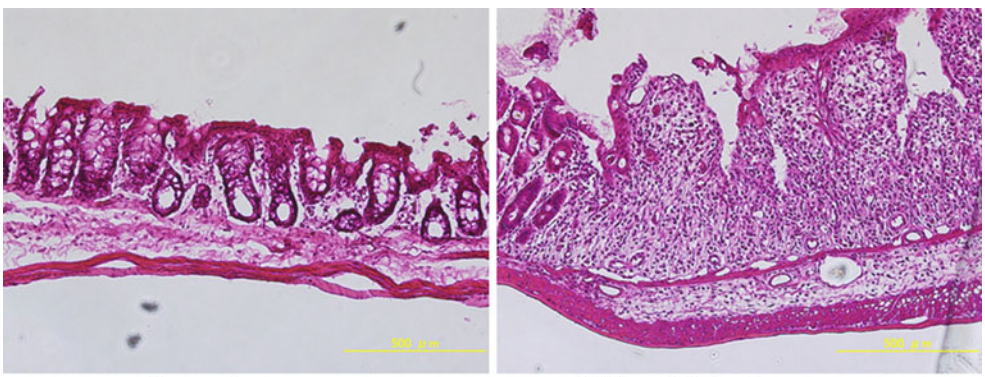

Fig. 5 Histology of normal cecum and DSS-induced colitis (bar=500 μm, ×100)

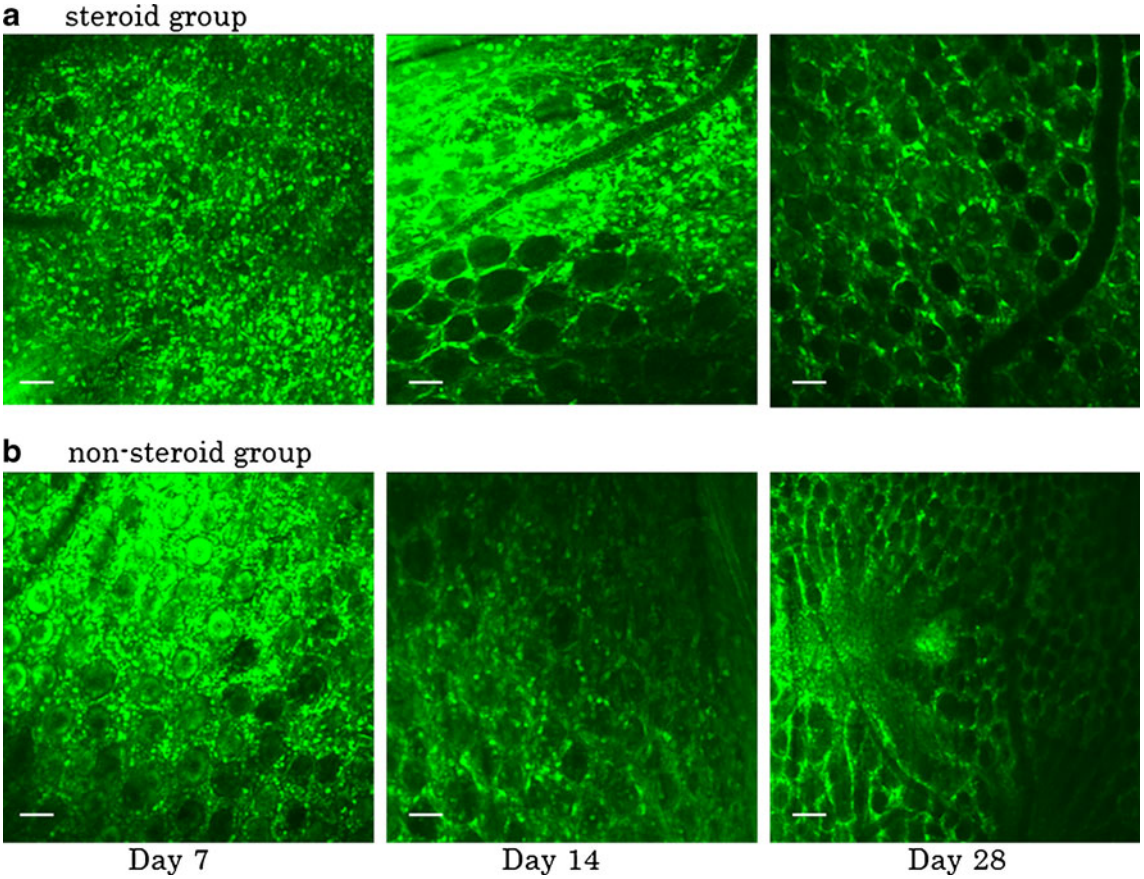

Fig. 6 Time-course TPLSM images of the colon in each group. Representative TPLSM images were taken in the same mice on days 7, 14, and 28. **a** Steroid group (at least five mice); **b** nonsteroid group (at least five mice) (bar=50 μm, ×600)

28. In contrast, the tissue concentration of IL-10 was higher in the steroid group than the nonsteroid group on days 14 and 28 (Fig. 8). These results support microscopic evaluation of treatment efficacy under intravital and interval TPLSM.

Discussion

Histopathological findings of DSS-induced colitis and drug efficacy in a mouse model were extensively studied and

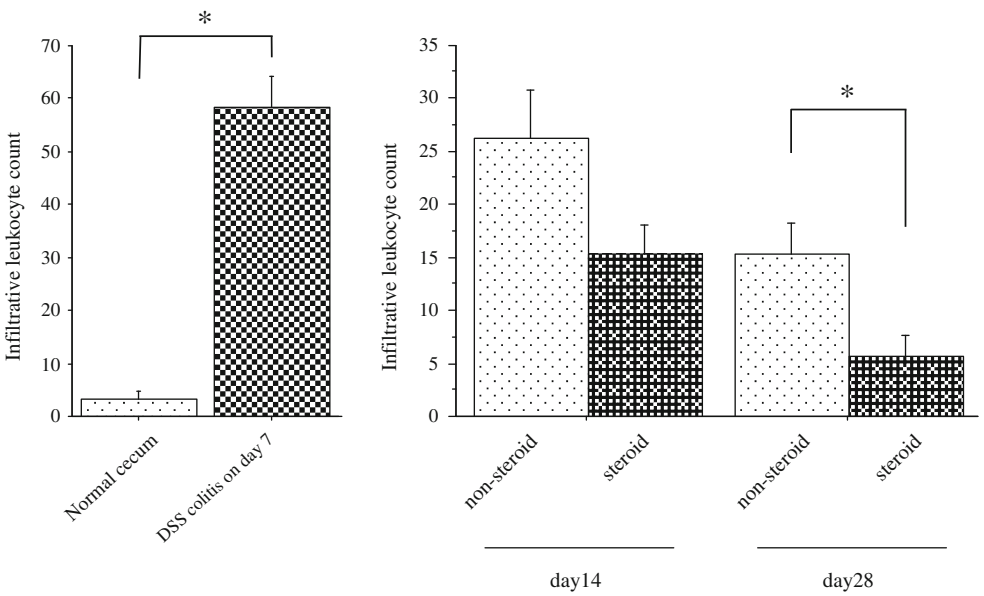

Fig. 7 Intravital TPLSM evaluation of DSS-induced colitis in the cecum. TPLSM images were taken in the same mice in each group on days 7, 14, and 28. Infiltrative leukocytes were counted on TPLSM images (210×210 μm). Values are expressed as mean±standard error. *$P<0.05$

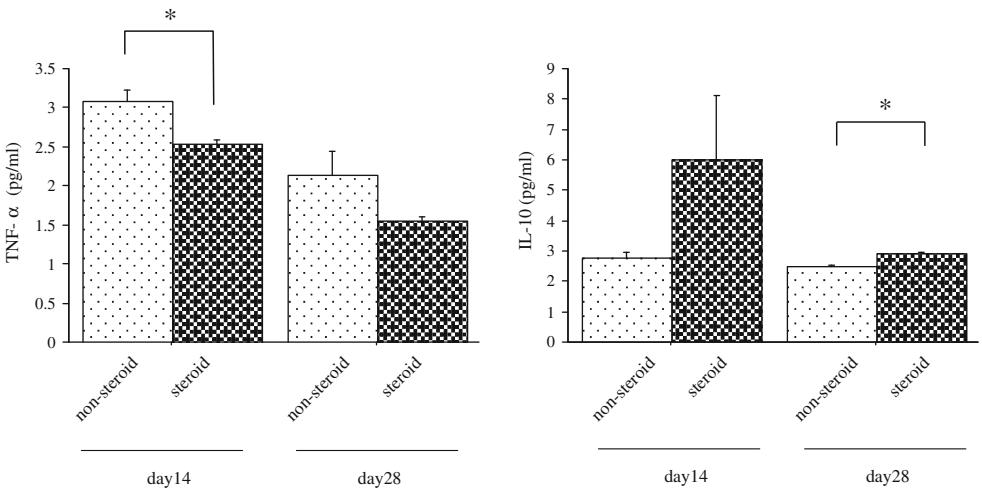

Fig. 8 Changes in tissue concentrations of TNF-α and IL-10. The cecum of DSS-induced colitis was excised in each group at the indicated time points (n=5 each; on days 7, 14, and 28). The tissue concentrations of TNF-α and IL-10 were measured by ELISA. Values are expressed as mean±standard error (in picograms per milliliter of cytokine per milligram of total protein). *P<0.05

reported. We showed the histopathological features of prednisolone efficacy in DSS-induced colitis under intravital TPLSM. However, the novelty of this study was 3D visualization of all layers of the cecum at a cellular level from the serosal layer to the luminal mucosal layer, without the cecal wall opening (serosal-approaching method), and evaluation of treatment efficacy in the same mice, at least three times, using intravital TPLSM.[7]

In the field of fluorescence microscopy, TPLSM has become an indispensable tool because it allows high-quality and high-resolution images of cellular structures, connective tissue stroma, and microvascular capillaries at a depth of almost 1,000 μm from the sample surface in vivo real-time for long-term imaging in living animals.[1,2]

This ability is due to the utilization of NIR excitation generating twice to multifold enhanced tissue penetration, reduced light scattering, and minimized phototoxicity (or photobleaching) at out-of-focus regions in comparison with single-photon excited CLSM.

Intravital TPLSM, in combination with organ stabilization, enabled us to assess the dynamic pathology in mouse intestinal disease under functionally and physiologically intact cellular conditions. This allowed us to reduce the number of sacrificed mice necessary for histopathological confirmation.

Histopathological examination is still a standard method and is currently performed with static images of excised tissues. However, this standard method has some limitations such as processing artifacts, sampling error, availability of excised, nonviable tissues, and interpretive variability. In contrast, dynamic 3D pathology using intravital TPLSM has several advantages, as mentioned above, and might be superior to standard histopathological examination.

UC is one of the major inflammatory bowel diseases, which is characterized by chronic uncontrolled inflammation of intestinal mucosa, with unknown pathogenesis. Conventional medical treatment relies on the use of aminosalicylates, corticosteroids, immunosuppressive drugs (azathioprine, 6-mercaptopurine, methotrexate, and cyclosporin), and antibiotics. None of these yields a satisfactory outcome for UC patients. In vivo experiments using a mouse model will continue to be important for the evaluation and validation of new drug candidates for UC.[5,6]

We also demonstrated the time-course morphological features of steroid efficacy in DSS-induced colitis in the same GFP mice, using intravital TPLSM. The time-course, in vivo histopathological evaluation of treatment efficacy using intravital and interval TPLSM could be useful in the preclinical study for screening and evaluating the new therapeutics for UC.

Recently, confocal laser endomicroscopy has been clinically applied as a new technology which provides in vivo real-time histological examination of a variety of mucosal abnormalities of the gastrointestinal tract including inflammatory bowel disease.[11,12] However, confocal laser endomicroscopy has the limitation of imaging at a depth of approximately 250 μm from the mucosal surface and the increased phototoxicity for gastrointestinal mucosa. Thus, the development of a multiphoton (or two-photon) endomicroscopy could, therefore, provide deeper penetration imaging and less phototoxicity, allowing a high-resolution in vivo real-time histopathology of gastrointestinal diseases in clinical practice.[13,14]

However, there were several limitations to our method. First, artifacts such as intestinal peristalsis could be minimized by additional anesthesia, but not completely suppressed. This is crucial for intravital TPLSM imaging at a magnification of greater than ×600. Second, postoperative adhesion between the cecum and abdominal wall could be prevented by the Seprafilm Adhesion Barrier, but not completely. Further improvement will be needed to take clearer images of experimental colitis in the same mice at several time points, under intravital TPLSM.

In conclusion, intravital 3D tomographic visualization of experimental colitis using TPLSM can provide dynamic pathology at high magnification. Intravital TPLSM combined with the serosal-approaching method will enable more accurate in vivo evaluation of the status of gastrointestinal disease and its treatment efficacy in living mice on multiple occasions.

Conflict of Interest Statement None declared.

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ORIGINAL ARTICLE

Primary Colorectal Lymphoma—Clinical Outcomes in a Population-Based Series

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Abstract
Purpose The purpose of this study was to investigate the characteristics and the outcomes of primary colorectal lymphomas using a population-based registry.
Methods All cases of colorectal lymphoma diagnosed between 1980 and 2007 were identified using a provincial cancer registry. Patients meeting Dawson's criteria and having a negative bone marrow biopsy were included.
Results One hundred ten cases of colorectal lymphoma were identified, 43 met the inclusion criteria. The majority of patients was male (86%), and the median age at diagnosis was 62 (range 26–82)years. Tumors were mostly located in the cecum (51.1%) and rectum (20.9%). The 5-year overall survival rate calculated by the Kaplan–Meier method was 57%. Age under 60 was associated with a better median survival time (265 vs 54 months; $p<0.0001$). The surgical treatment was associated with a better overall survival compared to medical treatment alone (110 vs 56 months; $p=0.083$). Tumors located in the rectum were associated with a decreased overall survival (41 months vs 110 months; $p=0.065$).
Conclusions Primary colorectal lymphoma is a rare disease. The age at diagnosis is an important predictor of outcome. Surgical resection may be associated with improved survival. Rectal lymphoma appears to be associated with a worse outcome and may warrant more aggressive therapy.

Keywords Lymphoma · Colorectal neoplasms · Colectomy · Radiotherapy

Introduction

Colon or rectal involvement by lymphoma is an unusual condition representing only 0.2–0.6% of large bowel malignancies.[1] In some cases, this represents secondary invasion of colon or rectum by a widespread systemic lymphoma. However, up to one third of non-Hodgkin's lymphoma will present with extranodal manifestations only. The stomach remains the most common site involved in primary gastrointestinal lymphoma, but colorectal involvement is also frequent, representing up to 10–20% of cases.[2–4] Dawson's criteria were developed to make the distinction between primary intestinal lymphoma and systemic lymphoma with secondary intestinal involvement.[5]

Immunosuppression and inflammatory bowel disease (IBD) are considered the most important risk factors in developing colorectal lymphoma.[6] Biologics and other therapeutic agents used in the treatment of IBD have also been associated with an increased risk of lymphoma.[7] The treatment of primary colorectal lymphoma is still a matter

Poster Presentation This study was included as a poster presentation during the ASCRS Annual Meeting on May 15–19, 2010 at Minneapolis, MN, USA.

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of debate, but usually involves a multimodality approach combining surgery, chemotherapy, and in selected cases, radiotherapy.[6] Clinical data remain scattered with most of published series coming from Asian centers. Several differences have been described in the distribution of lymphoma between eastern and western countries.[8] The purpose of this study was to evaluate clinical presentation, treatment, and outcomes of primary colorectal lymphoma using a North American population-based registry.

Patients and Methods

A search was done through the Alberta Cancer Board database to identify all patients with a diagnosis of colorectal lymphoma during the period of time from January 1980 to January 2007. All cases of cancer in the province of Alberta are included in this prospective database. Provincial legislation requires mandatory registration of all malignancies by the primary physicians, as well as the pathology and health record departments. The database was created in 1980 and maintained prospectively thereafter. This database collects data concerning diagnosis, treatment, and survival. The database is linked to provincial government registry such as the capture of death event or living status is updated periodically. During this 27-year period, 110 patients with lymphoma involving colon or rectum were identified. During the same period, 31,014 patients were diagnosed with colorectal malignancy in the province of Alberta.

Patients were included in the study based on standard diagnostic criteria of primary colorectal lymphoma, as established by Dawson et al. in 1961 (Table 1).[5] In addition, only patients with a normal bone marrow biopsy examination and histologically confirmed primary colorectal lymphoma were included. In-depth retrospective review of the medical records was carried out in all five regional cancer centers within the province by the lead author (SD). Demographic variables, comorbidities, type of lymphoma, presenting symptoms, methods of diagnosis, type of treatment, and outcomes were collected.

Table 1 Dawson's diagnostic criteria for primary intestinal lymphoma

The diagnosis of primary intestinal lymphoma is entertained when
1. The patient is first seen there is no palpable superficial lymphadenopathy.
2. Chest radiographs show no obvious enlargement of the mediastinal lymph nodes.
3. The white blood cell counts, total and differential, are within normal limits.
4. At laparotomy, only regional lymph nodes are affected by disease.
5. The liver and spleen appear free of tumor.

The type of lymphoma was classified according to the 2008 version of the WHO classification system.[9] All classifications used in older reports were converted to this classification. For staging, the modification of Ann Arbor system for gastrointestinal lymphoma, proposed by Musshoff was used.[10] When different staging systems were used, an estimation of Musshoff's stage was calculated retrospectively using all available data. The follow-up data from each regional cancer center were collected including the most recent examination, date of discharge from the department, or time of death. Additional data were also collected from electronic medical records to complete missing data on follow-up. Death status was determined using the Alberta Cancer Registry.

Overall survival was considered the primary end point and was determined using the Kaplan–Meier's method. Time at risk began when the diagnosis was confirmed and ended at the date of death or at the last available follow-up. At the time of analyses, the median follow-up was 54 months (range 1–278). Univariate analyses using log-rank (Mantle–Cox) and chi-square tests were performed to assess the influence on overall survival of age, gender, histologic type, tumor site, tumor staging, and type of treatment (surgical resection, chemotherapy, radiation, or a combination). Multiple analyses were performed with different stratification of prognostic variables using log-rank test (Mantle–Cox) and chi-square test. All statistical analyses were performed using PASW® (V.17; formerly SPSS; 2010, Chicago, Illinois), and differences were considered statistically significant at a p value less than or equal to 0.05.

Results

Patient Demographics and Risk Factors

Of the 110 patients registered with colorectal lymphoma, 43 cases corresponding to the diagnosis criteria of primary colorectal lymphoma were found. A total of 67 cases were excluded for: the presence of disseminated disease (25), the absence of bone marrow biopsy (19), the presence of other lymphoproliferative intestinal disorders (posttransplant lymphoproliferative disorder, multiple lymphomatous polyposis; 5), unavailable/incomplete (12) charts, and patients that received primary treatment outside the province (6).

These 43 cases comprised 0.14% of all cases of colorectal malignancies diagnosed during this period. The incidence in the general population increased twofold, from 0.38 to 0.74 cases per 100,000 persons per decade, from the first to the last decade of the study. Thirty-seven were males (86%), and the median age at diagnosis was 62 (range 26–82)years. Males tended to be younger than females although this difference was not statistically significant (median age 62 vs 73; $p=$

0.53). Four patients (9.3%) had IBD, three with ulcerative colitis, and one with Crohn's disease. One patient (2.3%) was diagnosed with AIDS during his initial work up of rectal lymphoma.

Initial Presentation and Diagnosis

The chief presenting symptoms included abdominal pain in 14 patients (32.5%), change in bowel habit in eight patients (18.6%), bloody stool in eight patients (18.6%), and abdominal mass in four patients (9.3%). Two patients presented with symptoms of appendicitis (4.7%), and one had peritonitis from colon perforation (2.3%). Twenty-four patients (55.8%) were diagnosed preoperatively with colonoscopy. Three additional patients had a non-diagnostic colonoscopy. Findings at colonoscopy included a mass in 21 patients (77.8%), ulcerations in three patients (11.1%), and concomitant bleeding in two patients (7.4%). Diagnosis was made on final pathology after resection in the remaining 19 patients. The distribution of lymphomas was as follows: cecum in 22 cases (51.1%), rectum in nine cases (20.9%), transverse colon in five cases (11.6%), ascending colon in three cases (7.0%), sigmoid colon in three cases (7.0%), and appendix in one case (2.3%).

Tumor Characteristics

Histologically, the lymphomas were classified using the 2008 version of WHO classification system.[9] All cases were non-Hodgkin lymphomas. The histology was diffuse large B-cell lymphoma in 32 cases (74.4%), Burkitt's lymphoma in six cases (14.0%), extranodal marginal zone B-cell lymphoma in three cases (7.0%), and Mantle cell lymphoma in two cases (4.7%; Table 2). In 29 patients (67.4%), the tumor was confined to the large bowel (stage EI), involvement of the regional lymph node was noted in ten patients (23.2%; stage EII1), infiltration of lymph node beyond the regional area was noted in one patient (2.3%; stage EII2), and regional spread to the omentum or adjacent organ was found in three patients (7.0%; stage EIV).

Table 2 Prognostic factors for survival log-rank test (Mantle–Cox)

Prognostic factor	No. of cases	Median survival time (months)	95% CI	*p* value
Age				
<61 years	20	265.0	114.3–415.7	<0.0001
≥61 years	23	54.0	13.4–94.5	
Gender				
Male	37	101.0	45.7–156.3	0.946
Female	6	42.0	0–115.2	
Tumor site				
Colon	34	110.0	52.7–167.3	0.065
Rectum	9	42.0	4.3–79.7	
Clinical stage				
EI	29	62.0	51.2–72.7	0.559
EII1	10	110.0	15.6–204.4	
EII2	1	137.0	NA	
EIV	3	3.0	0-6.2	
Histology				
DLBC	32	101.0	36.2–165.7	0.601
Burkitt lymphoma	6	137.0	0–334.6	
MALT lymphoma	3	62.0	0–143.6	
Mantle cell lymphoma	2	42.0	NA	
Treatment				
Surgery and chemotherapy	29	110	67.5–152.4	0.297
Surgery alone	5	62	52.4–71.6	
Chemotherapy/radiotherapy	9	42	0–90.7	
Surgical resection	34	110.0	51.8–168.2	0.083
No resection	9	56.0	1.1–110.9	
Chemotherapy regimen				
CHOP	13	89.9	34.8–167.2	0.934
R-CHOP	17	53.8	37.0–70.7	
Total	43	101.0	49.9–152.1	–

NA not applicable

Treatment

Overall, 34 patients (79.0%) underwent surgical resection. Of this group, 25 had elective resection (73.5%) and nine patients (26.5%) had emergent surgery. Of the patients who required emergent surgery, six (66.7%) presented with acute obstructive symptoms, two (22.2%) with suspicion of appendicitis, and one (11.1%) with colonic perforation.

Chemotherapy was used in 37 patients (86.0%). The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone) was used in the majority of cases (81.0%). Seventeen patients also received the anti-CD20 monocolonal antibody rituximab in addition to CHOP. The majority of patients treated with surgical resection received adjuvant chemotherapy (78.3%). Nine patients (20.9%) were treated with chemotherapy and/or radiotherapy without resection.

Rectal lymphoma contrasted from other anatomic locations by a wide variation in the modality of treatment used. Patients received radiation or chemotherapy alone (two; 22.2%), combined chemoradiation (three; 33.3%), diverting colostomy followed by chemotherapy (two; 22.2%), or surgical resection associated with adjuvant treatment (two; 22.2%). The majority of colon lymphomas was treated by a combination of resection (32; 94.1%) and chemotherapy (30; 88.2%).

Outcome

The median survival time was 101 months (range 1–278), and overall five-year survival was 57%. The 29 patients treated by surgical resection and adjuvant chemotherapy achieved a 5-year survival rate of 62%, which was not statistically significant. Twenty-five patients died during the follow-up, 18 (72.0%) from progressive disease or treatment-related complications, and seven patients (28.0%) died of unrelated causes. The majority of deaths related to lymphoma occurred in the first year following the diagnosis (11; 61%). However, death related to disease recurrence was recorded as far as 23 years after the initial diagnosis. Eighteen patients (41.9%) were alive at the time of data analysis, one having undergone recent treatment for a recurrence, whereas the other 17 were in remission. Nineteen patients achieved long-term (> 5 years) survival. All but two of these patients had undergone surgical resection. Fifteen patients (78.9%) received chemotherapy, while four (21.0%) patients had surgical resection alone.

Six variables were tested in univariate analyses for their prognostic influence on survival: age, gender, tumor site, clinical stage, histologic type, and type of treatment (Table 2). The effect of rituximab as part of the chemotherapy regimen was also evaluated. Age at diagnosis was a predictor of overall survival with patients less than 60 years old having an increased median survival time (265 vs. 54 months; $p<0.0001$). Rectal lymphoma was associated with a median survival of 42 months compared to 110 months for the colon cases ($p=0.065$). Surgical resection was associated with a median survival of 110 months compared to 56 months for patients treated with a non-surgical approach ($p=0.083$). Histology and clinical stage did not correlate with survival in this series. Emergent surgical resection was not associated with a worse outcome when compared to elective resection ($p=0.801$). Multiple analyses were performed with different stratification of variables to compare the type of treatment with tumor characteristics (site, histology, and stage), but no specific correlations were found with survival analysis (Fig. 1). Patients having rectal lymphoma appear to be older (64.9 vs. 58.7 years old; $p=0.31$) but not statistically different from patients having colon lymphoma. Patients who underwent surgical resection also tended to be younger (57.9 vs. 68 years old; $p=0.09$).

Discussion

Primary colorectal lymphoma is a rare diagnosis; in our series, it represented 0.14% of all colorectal malignancies diagnosed during that time period. The incidence varied from 0.1% to 0.9% in other series.[11–15] We identified a twofold increase in the rate of new cases by decade in the general population during the study period. The incidence of colorectal cancer in Alberta increased by 5%, whereas the incidence of all lymphomas increased by 10%, during the same period (1980–2007).

Some factors have been linked to the development of colorectal lymphomas. Inflammatory bowel diseases, in particular ulcerative colitis, have been associated with the development of colorectal lymphoma.[16, 17] Histopathological studies have revealed the existence of monoclonal lymphoid proliferations in tissues affected by long-standing IBD, raising the possibility of chronic antigenic stimulation as a possible trigger for malignant lymphoid transformation.[18] Canada has been reported to have one of the highest incidences of IBD worldwide.[19] In our cohort, only four patients had IBD (three UC and one Crohn disease) for a prevalence at diagnosis of 9%. Immunosuppression has also been linked to colorectal lymphomas. In particular, human immunodeficiency virus (HIV) positivity has been reported to be associated with a higher incidence of gastrointestinal lymphomas.[20] Only one patient in our cohort was HIV positive. However, the serologic testing was not carried out in all patients as suggested by some authors.[15] Transplant recipients are also reported to be at increased risk of developing lymphomas at any location.[13] However, there were no transplant patients in our cohort.

There is an important male predominance in our series (male/female=37:6). Others have reported similar findings

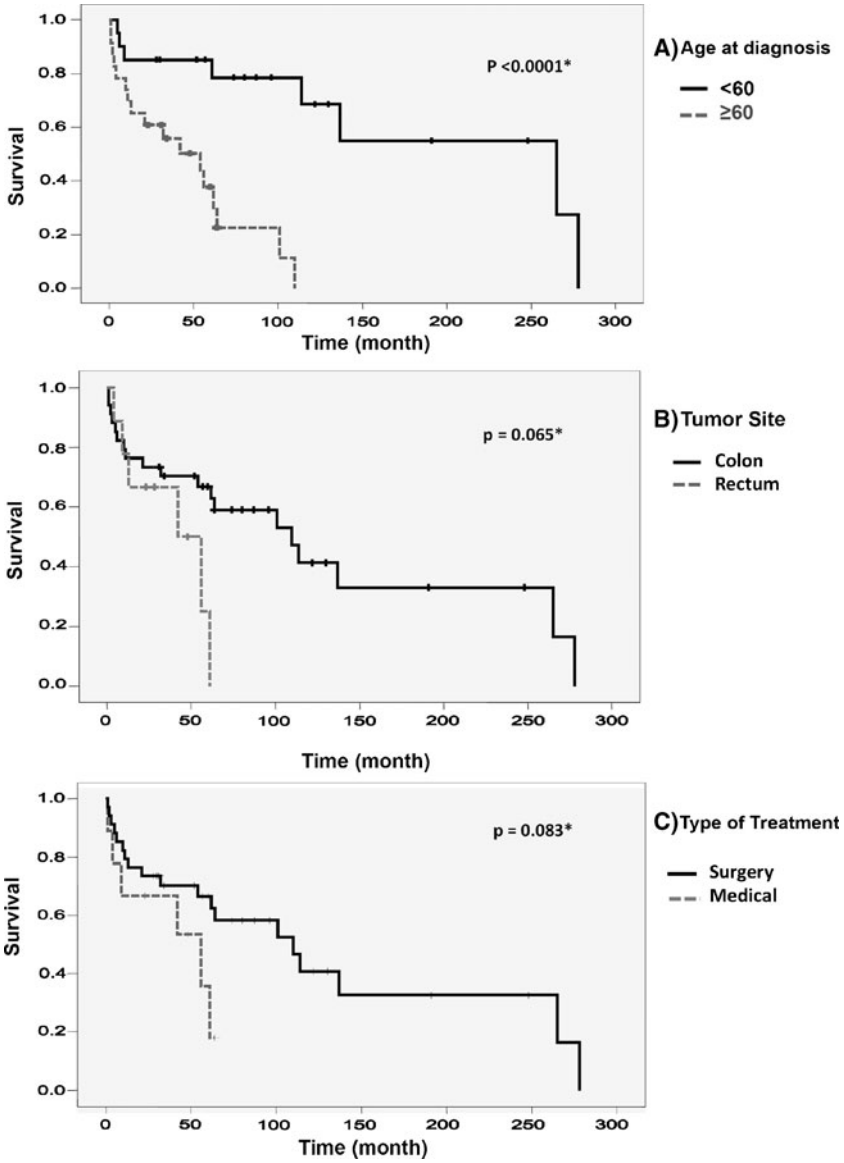

Fig. 1 Survival analysis according to age at diagnosis (**a**), tumor site (**b**), and type of treatment (**c**)

for colorectal lymphoma.[11, 12, 21] Maximal incidence of PCL has been reported between 5th and 7th decade with a mean age between 44 and 65 years.[12] In our cohort, the median age was 62 years. In our series, the age lower than 60 years old at diagnosis was the only variable associated with a better outcome. This differs from a previous study that found no difference in survival for patients under 60 years old in a series of 37 cases of primary colorectal lymphoma in Taiwan.[22]

Abdominal pain (32.5%), change in bowel habit (18.6%), and bloody stool (18.6%) were the most common presenting symptoms. Others have also reported similar symptoms in previous series.[11–15, 23] Endoscopic evaluation was carried out in 27 patients and allowed for histological diagnosis in the majority of them (88.9%). In most of the cases, colonoscopy has shown mucosal irregularity or polypoid mass; few patients had ulceration or active bleeding. In a series of 13 patients, Wang et al. found polypoid lesions (54%) or ulcerations (31%) to be the most common findings on endoscopy.[24] Myung et al. also review colonoscopic findings of 32 cases of ileocolonic lymphomas; most of the cases presented as a fungating mass with (31%) or without (39%) ulcerations.[25]

Within the large bowel, the cecum is constantly reported to be the most common site of lymphoma.[3, 11, 12, 14, 15, 22, 23] The relation with the presence of abundant lymphoid tissue in this region has been proposed as an explanation.[12] In our series, 51% of the cases was located in the cecum and 21% in the rectum. Rectal cases were associated with a trend toward shorter median survival time compared to other locations in our series (42 vs 110 months; p=0.065). Few other data are available on primary rectal lymphoma. In 1986, Devine et al. described 12 cases of lymphomas confined to the rectal region and compared them to 49 cases

of secondary rectal involvement by diffuse lymphoma; the overall five-year survival was 50% and 15%, respectively. In this series, six patients having lymphoma confined to the rectum underwent surgical resection and four experienced long-term survival.[26] Perry et al. described 22 cases of primary malignant lymphoma of the rectum from St-Mark's Hospital in 1972 and concluded that surgical resection with or without radiation was associated with better results.[27]

In our study, the treatment of rectal lymphomas was inconsistent. It seems that the medical management of rectal lymphoma was preferred in a majority of patients most likely to achieve sphincter preservation. The relative fixity of the rectum also allows for the use of radiation therapy, which is usually not an option for colon cancer. The difficulty and morbidity associated with pelvic surgery could also have influenced the decision-making in the management of these patients. Nevertheless, the median survival of these patients was lower than expected. At this point, it is difficult to conclude whether rectal lymphomas have a different behavior or if medical management without resection is associated with a decreased survival time.

The place of surgical resection in the treatment of gastrointestinal lymphoma is in evolution. Most gastric lymphomas are now treated medically, with surgery being reserved for failed medical management or complications.[28] Intestinal lymphoma is difficult to diagnose, and surgery is often used as a diagnostic tool, to treat complications and to prevent perforation during chemotherapy. Some have reported better survival with resection and adjuvant treatment compared to chemotherapy alone in this setting.[29, 30] In the other series of PCL, the majority of patients underwent surgical resection.[11, 12, 14, 22] Several authors believe that surgical resection: (1) provides important prognosis information, including histology, tumor extent, and stage; (2) may offer a chance for cure with or without adjuvant therapy; and (3) prevents complications such as hemorrhage, obstruction, or perforation.[11, 14, 22] In our series, surgery was performed in the majority of cases and seems to be associated with a better median survival time compare to medical treatment (110 vs. 56 months; $p=0.083$). Cai et al. reported a series of 43 patients in which more than half of those required an emergent surgery.[21] In our series, a third of patients who underwent resection had an emergent procedure.

Adjuvant treatment is often used after resection. Fan et al. found a significant improvement in survival for patients with positive nodes (stage II) who received adjuvant chemotherapy.[22] In our series, 86% of patients received chemotherapy as part of their treatment. Our analysis has not revealed a survival advantage for these patients. However, only five patients had surgical resection without adjuvant chemotherapy. Chemotherapy has been recommended in the treatment of locally advanced primary colorectal lymphomas or for metastatic disease in an attempt to control residual microscopic disease and prolong survival.[23] The CHOP regimen is traditionally used in most patients. The addition of rituximab has been reported to increase survival in the treatment of lymphomas.[31] In our cohort, 17 patients had rituximab in addition to CHOP regimen. When compared to patients who received CHOP alone, the analysis did not reveal a survival advantage ($p=0.934$). Radiation therapy has been used sparingly to treat colorectal lymphoma. Some have suggested that it may have a role in the control of local disease, such as following an incomplete resection.[15] In our cohort, only five patients received radiotherapy as part of their treatment for rectal lymphomas. Radiotherapy could be considered in rectal lymphoma to achieve tumor regression before resection or as adjuvant therapy to decrease local recurrence. However, there is little evidence to recommend its use or to choose its timing in relation with multimodality treatment in rectal lymphoma.

Our study has several limitations. First, we chose to use Dawson's criteria to define our population. This has the advantage of being very specific to identify primary colorectal lymphoma. On the other hand, it led to the exclusion of a large portion of our initial cohort because of incomplete work up or missing data. We wanted to address the specific question of the optimal treatment for lymphomas limited to the large bowel, and these criteria remain the only accepted ones to define this group of patients. This series is also limited by its retrospective nature, which is often associated with incomplete data and missing information. The small number of patients analyzed also limits the power of our study. Other than age at diagnosis, no other variables were associated with better survival. However, this may not reveal to be true in a larger cohort of patients. Unfortunately, the incidence of this condition, being very rare, limits the possibility to identify a large number of patients.

Conclusions

This is the first population-based series of primary colorectal lymphoma. The disease is rare, but the incidence has increased significantly in the last decade. Age at diagnosis is an important predictor of outcome. Surgical resection is part of the treatment in the majority of patients and seems to be associated with improved survival. There is a wide variation in the treatment of rectal lymphoma. More studies are needed to define the optimal treatment, as this location appears to be associated with a worse outcome.

Disclaimers/Conflicts No conflicts of interest exist.

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ORIGINAL ARTICLE

Preoperative Radiotherapy Combined with Capecitabine Chemotherapy in Chinese Patients with Locally Advanced Rectal Cancer

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Abstract

Background This phase II study is performed to evaluate the efficacy and safety of capecitabine combined with preoperative radiotherapy (RT) in Chinese patients with locally advanced rectal cancer (LARC).

Methods Between February 2007 and December 2008, 62 patients with LARC were treated with capecitabine (825 mg/m^2, twice daily) and concurrent RT (50.4 Gy/28 fractions). Patients underwent surgery after 6–8 weeks of combined therapy, followed by 4 cycles of adjuvant capecitabine (1,250 mg/m^2, twice daily on days 1–14, every 3 weeks). The primary endpoint was the rate of pathologic complete response (pCR).

Results Fifty-eight patients (93.5%) completed the preoperative chemoradiation course as initially planned. The most severe hematologic adverse event was leucopenia, which occurred with grade 2 intensity in 12 (19.7%) patients and grade 3 in 2 (3.3%) patients. Grade 3 diarrhea and hand–foot syndrome (HFS) were observed in one (1.6%) and two (3.3%) patients, respectively. However, no grade 4 toxicity was observed. There were no treatment-related deaths during this study. Of the 59 patients treated with surgery, all had radial margins (R0 resections). Among the 29 patients with the primary tumor ≤5 cm from the anal verge, 18 (62.1%) underwent sphincter-preserving surgical resections. pCR was found in eight patients (13.6%). The pathologic stage was lower than the initial clinical stage in 57.6% (34/59), 63.4% (26/41), and 81.4% (48/59) of the resected tumors for the primary tumor (T), lymph node (N), and combined TN categories, respectively. The estimate of disease-free survival and overall survival at 24 months were 80.6% (95% CI, 70.8–90.4%) and 92.5% (95% CI, 85.9–99.1%), respectively.

Conclusion Preoperative chemoradiotherapy with capecitabine and RT appears to be a safe, well-tolerated, and effective neoadjuvant treatment modality for LARC.

Jianhua Jin, Hua Meng, and Guanghua Zhou made equal contribution to this study.

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Keywords Locally advanced rectal cancer · Capecitabine · Chemoradiotherapy

Introduction

Approximately 40,740 patients annually are diagnosed with rectal cancer in the USA.[1] Preoperative chemoradiotherapy (CRT) is considered the preferred treatment option for locally advanced rectal cancer (LARC) to reduce the incidence of local recurrence. Four recent randomized European trials addressed whether the addition of 5-fluorouracil (5-FU) chemotherapy to a preoperative long-course radiation strategy is more efficacious than preoperative radiotherapy alone: the European Organization for the Research and Treatment of Cancer 22921 trial,[2] the Fondation Française de Cancérologie Digestive 9203 trial,[3] and the Groupe de Recherche Chirurgical dans le Cancer du Rectum 1 trial from France,[4] and a Polish Colorectal Study Group multicenter effort.[5]

A continuous infusion (ci) of 5-FU during radiotherapy (RT) has been shown to be superior to bolus 5-FU in terms of disease-free years and overall survival.[6] The concurrent administration of ci-5-FU with radiotherapy (RT) offers the biological advantage of achieving a prolonged exposure of tumor cells to effective levels of 5-FU, thereby improving 5-FU radiosensitization activity.[7] However, the need for long-term venous access for portable pumps may limit the use of ci-5-FU therapeutic regimens. Capecitabine is an oral fluoropyrimidine that imitates the pharmacokinetics of a continuous 5-FU infusion and is preferentially converted to its active metabolite within tumor cells by exploiting the higher activity of the enzyme thymidine phosphorylase in tumor tissue compared to normal tissue.[8] This tumor-selective activation of capecitabine is improved further when combined with RT, which upregulates thymidine phosphorylase in tumor cells but not in healthy tissue.[9] Therefore, capecitabine offers an interesting alternative to ci-5-FU, especially in combination with RT. Based on these considerations, we conducted a phase II study to evaluate the efficacy and safety of capecitabine combined with preoperative RT in Chinese patients with LARC.

Patients and Methods

Eligibility Criteria

Patients with pathologically confirmed (by endoscopic ultrasound [EUS]) clinical stages II or III resectable adenocarcinoma of the rectum, defined as a primary tumor <15 cm from the anal verge excluding the anal canal, who were deemed medically operable were eligible for this trial. The anal verge is the level of the intersphincteric groove, an indistinct groove in the anal canal, forming the lower border of the pecten analis, marking the change between the subcutaneous part of the external anal sphincter and the border of the internal anal sphincter. Tumors were also classified by location in the upper (11–15 cm), middle (6–10 cm), or lower rectum (1–5 cm) according to tumor distance from the anal verge. EUS-guided fine-needle aspiration cytology was done to confirm the status of lymph nodes during the same EUS examination. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status <2, were between 18 and 80 years of age, and had adequate hematologic, liver, and renal function. The disease was staged according to the 2002 classification of the American Joint Committee on Cancer (6th edition).

Exclusion criteria included the following: previous RT to the pelvic region or previous chemotherapy; patients with serious illness or medical conditions, including significant cardiac disease, a history of significant neurological or psychiatric disorders, a serious uncontrolled active infection; pregnant or lactating women and women with child-bearing potential unless using a reliable contraceptive method; sexually active males unwilling to use contraception during the study; patients with a history of previous malignancy, except cured non-melanoma skin cancer and in situ cervical carcinoma; patients with an absolute neutrophil count $<2\times10^9$/L or a platelet count $<100\times10^9$/L, a total bilirubin >1.5 times the upper normal limits (UNL) of the institutional normal values, a transaminase, or alkaline phosphatase >1.5 times UNL, and a creatinine >1.6 mg/dl. The institutional review board of the author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Pretreatment Evaluation

All patients underwent a complete colonoscopy, an EUS, and a CT of the abdomen and pelvis with intravenous and oral contrast. Positron emission tomography (PET) scans were not required but were performed when feasible. Staging of the chest consisted of either a chest X-ray, a CT of the chest, or a PET scan. All patients had a complete blood cell count, carcinoembryonic antigen, creatinine, blood urea nitrogen, electrolytes, and liver function tests. Pre-study cardiac assessments were made by physical examinations with further specific studies ordered by the examining physician. All required evaluations were done within 14 days of signing consent. All patients were also assessed prior to beginning treatment by a surgical oncologist to determine whether a sphincter-sparing procedure was expected to be possible.

Radiation Therapy

A radiation dose of 45 Gy was given to the posterior portion of the pelvis to include the tumor, the mesorectum, the posterior walls of the bladder and prostate/vagina, and the internal iliac nodes (clinical target volume 1 [CTV1]), followed by a boost of 5.4 Gy limited to the tumor and the corresponding mesorectum with a 2-cm margin (clinical target volume 2 [CTV2]) for a total dose of 50.4 Gy. For T4 tumors, the external iliac nodes were also included in the CTV1. A conventional fractionation of 1.8 Gy/day, 5 days a week, was used for an overall planned treatment time of 5.5 weeks. Patients were treated in the prone position using a dedicated device to minimize exposure to the small bowel. A three- or four-shaped field box technique with high-energy photons (≥6 MV) was used. A computed tomography-based treatment planning system was mandatory to define the planning target volume (CTV+1-cm margin).

Chemotherapy

Capecitabine (Xeloda, Roche Laboratories, Inc.) was administered orally at a dose of 825 mg/m^2 twice daily, approximately 12 h apart, within 30 min of the ingestion of food, only on days that the patient received radiation. Patients were instructed to take the morning dose of capecitabine within 1 to 3 h of their radiation treatments. To comply with this requirement, radiation was delivered between 8:00 A.M. and 10:30 A.M. After surgery, 4 cycles of capecitabine were given to patients whom the treating physician determined would potentially benefit from post-operative therapy. Capecitabine was administered at a dose of 1,250 mg/m^2 twice daily on days 1–14, every 3 weeks.

Surgery

Surgery was planned between 5 and 8 weeks after the completion of CRT. Patients underwent transabdominal resection, and sphincter preservation was preferable if technically feasible. For those patients with tumors in the upper rectum, a low anterior resection (LAR) was performed, extended several centimeters past the tumor distally with subsequent creation of a colorectal anastomosis; for those tumors in the low rectum, the patients underwent total mesorectal excisions with colorectal or coloanal anastomosis or alternatively, an abdominoperineal resection (APR) with the creation of a colostomy.

Pathologic Assessment

The resection specimen was oriented, and a gross description of the tumor was made, including the distance from the proximal, distal, and radial margins. Fine serial cuts at 2 to 4-mm increments were made through the tumoral regions of the specimen. A negative margin (R0) was recorded if the distance from tumor to the circumferential margin was more than 1 mm. The pathologic response determination was completed by a single gastrointestinal pathologist (Z.X.). A pathologic complete response (pCR) was defined as no identifiable viable cancer and without acellular mucin lakes. If mucin lakes are seen in the rectal resection margins at the time of the intraoperative microscopic examination of frozen sections, extension of the surgery should be done in the current study.

Toxicity Assessment and Dose Modifications

Toxicity was evaluated weekly in each patient with a physical examination, complete blood count with differential and blood chemistry. The intensity of clinical adverse events was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0).[10] HFS was graded as described in previous reports.[11] The following recommendations for a dose reduction of capecitabine were used: for grades 2 or 3 toxicity considered mainly related to capecitabine, drug administration was interrupted until toxicity resolved to grades 0–1, and then restarted at 75% of the original dose. If a grade 2 or greater toxicity recurred, capecitabine was discontinued again until toxicity resolved to grade 0 or 1, and then restarted at 50% of the original dose. The RT program was not altered unless the severity of toxicity worsened; in that case, RT was also discontinued until toxicity recovery. If the toxicity was considered mainly related to RT and occurred at grade 2 or greater, RT was discontinued until toxicity resolved to grades 0 or 1, and then restarted. Capecitabine administration was not altered unless the toxicity worsened, in which case capecitabine was also discontinued. If any grade 4 toxicity developed, combined treatment was discontinued.

Endpoints

The primary endpoint for this trial was the pCR rate. The secondary objectives included a toxicity assessment, the downstaging rate, the sphincter preservation rate, overall survival (OS), and disease-free survival (DFS). Downstaging was determined by comparing the pathologic TNM stage to the pretreatment clinical TNM stage (as determined by EUS). A sphincter preservation procedure was defined as any procedure whereby the rectal tumor was removed while leaving behind the anal sphincter. A temporary colostomy was considered a sphincter-sparing procedure as long as the anal sphincter was spared.

Statistical Analysis

According to the results of the National Surgical Adjuvant Breast and Bowel Project R-03[12] and the study by Sauer et al.,[13] a pCR rate of 8% can be expected when using infusional 5-FU and concomitant radiotherapy. However, in a number of published reports using capecitabine with radiotherapy, pCR rates of 4–10% were reported.[14–19] We aimed to evaluate whether we could produce a 12% pCR rate with our approach. Setting 4% as the lowest pCR rate of interest, with an alpha error of 5% and a power of 80%, at least 55 evaluable patients were needed. The targeted accrual was 62 patients, with an expected withdrawal rate of 10%.

Results

Patient Characteristics

Between February 2007 and December 2008, 62 patients with locally advanced rectal cancer were enrolled in this study. The characteristics of these patients are summarized in Table 1. Their ages ranged from 35 to 78 years (median 57 years). All patients had newly diagnosed rectal cancer with excellent performance status (ECOG 0–1). Of the tumors, 72.6% were staged clinically as T3N0 or T3N1-2 by abdominal/pelvic CT and EUS.

Table 1 Patient characteristics (n=62)

Characteristics	No. of patients (%)
Age (years)	
Median	57
Range	35–78
Gender	
Male	48 (77.4)
Female	14 (22.6)
ECOG performance status	
0	58 (93.5)
1	4 (6.5)
TNM clinical stage by EUS	
T3N0	10 (16.1)
T3N1-2	35 (56.5)
T4N0	11 (17.7)
T4N1-2	6 (9.7)
Histologic differentiation	
Well differentiated	10 (16.1)
Moderately differentiated	44 (71.0)
Poorly differentiated	8 (12.9)
Tumor distance	
Upper	18 (29.0)
Middle	15 (24.2)
Lower	29 (46.8)

ECOG Eastern Cooperative Oncology Group, *TNM* Tumor–Node–Metastasis, *EUS* endoscopic ultrasound

Neoadjuvant Chemoradiation Outcomes

Fifty-eight patients (93.5%) completed the preoperative chemoradiation course as initially planned. The chemotherapy dose was reduced due to leukocytopenia in two (3.3%) patients. A radiation dose of 50.4 Gy was not delivered in two patients (44 and 46 Gy) due to the development of symptoms consistent with a mechanical ileus, which were relieved with supportive care. Radiation therapy was interrupted for a maximum of 2 days related to treatment. Overall, preoperative capecitabine and RT were well tolerated, and the most commonly reported events are shown in Table 2. The most severe hematologic adverse event was leucopenia, which occurred with grade 2 intensity in 12 (19.7%) patients and grade 3 intensity in 2 (3.3%) patients. Anemia occurred with grade 2 intensity in seven (11.5%) patients. However, no grade 3 neutropenia was observed. Diarrhea, proctitis, and HFS were the most common non-hematological toxicities. Grades 1 or 2 diarrhea, proctitis, and HFS were observed in 22 (36.1%), 16 (26.2%), and 12 (19.7%) patients, respectively. Grade 3 diarrhea and HFS were observed in 1 (1.6%) and 2 (3.3%) patients, respectively. However, no grade 4 toxicity was observed. There were no treatment-related deaths during this study.

Surgical Outcomes

After completing neoadjuvant CRT, three patients did not undergo surgery for their primary tumor, resulting in an

Table 2 Toxicity during preoperative chemoradiotherapy (by patients)

Toxicity	Grade (n,% of patients, n=61)[a]			
	1	2	3	4
Hematological				
Anemia	13 (21.3)	7 (11.5)	–	–
Leucopenia	25 (41.0)	12 (19.7)	2 (3.3)	–
Thrombocytopenia	11 (18.0)	4 (6.6)	–	–
Non-hematological				
Diarrhea	14 (23.0)	8 (13.1)	2 (3.3)	–
Proctitis	10 (16.4)	6 (9.8)	–	–
Cystitis	6 (9.8)	9 (14.8)	–	–
Hand–foot syndrome	7 (11.5)	5 (8.2)	1 (1.6)	–
Radiation dermatitis	3 (4.9)	10 (16.4)	–	–
Weight loss	3 (4.9)	2 (3.3)	–	–

[a] National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0

overall resectability rate of 95.2% for the study group. Surgery was not performed because of the development of metastatic disease (one patient) or refusal after a complete clinical response (two patients). All patients underwent radical resections, and all primary tumor resections had negative proximal, distal, and radial margins (R0 resections). The distance from tumor to the circumferential margin was more than 2 mm in 94.9% (56/59) of patients, other three patients with margin range from 1 to 2 mm. Twenty-three out of 59 patients (39.0%) underwent LAR, while 36 patients underwent APR (Table 3). Among the 29 patients with the primary tumor ≤5 cm from the anal verge, 18 (62.1%) underwent sphincter-preserving surgical resections. Five out of 18 patients (27.8%) were treated differently after the down-staging than planned based on clinical staging. The median interval between the completion of chemoradiation and surgery was 6 weeks (range 5–8 weeks). Four patients experienced postoperative complications (two patients with wound dehiscence and two patients with a wound infection/abscess). There were no intraoperative or post-operative deaths.

Pathologic Responses

Complete disappearance of the primary tumor on the pathology specimen (pCR-T) was observed in 10 patients (16.9%), and 26 (44.1%) patients had no tumor cells in their lymph node specimens (pCR-N). However, two of the pCR-T patients had residual tumor cells in a lymph node. Thus, complete tumor disappearance in both the rectum and the lymph nodes was found in eight patients (13.6%). The pathologic stage was lower than the initial clinical stage in 57.6% (34/59), 63.4% (26/41), and 81.4% (48/59) of the resected tumors for the primary tumor (T), lymph node (N), and combined TN categories, respectively (Table 4).

Table 3 Surgical procedure

Clinical stages	No.[a]	Surgical procedure, no. (%)	
		LAR	APR
cT3N0	9	4 (44.4)	5 (55.6)
cT3N1-2	34	11 (32.3)	23 (67.6)
cT4N0	10	5 (50.0)	5 (50.0)
cT4N1-2	6	3 (50.0)	3 (50.0)

LAR low anterior resection, *APR* abdominoperineal resection

[a] Three patients did not undergo surgery because of (1) multiple metastases and (2) because of refusal

Disease-Free Survival and Overall Survival

The median follow-up period was 25.2 months (range 16.5–36.5 months). The estimate of DFS and OS at 24 months were 80.6% (95% CI, 70.8–90.4%) and 92.5% (95% CI, 85.9–99.1%), respectively (Fig. 1).

Discussion

The potential for a curative surgical resection is the most important component of the multimodal management of rectal cancer. Techniques that improve or allow surgical resection are increasingly important.[20] Preoperative CRT represents the current standard adjuvant care for patients with clinical stages II or III rectal cancer. The important goals of preoperative CRT in LARC are to achieve local tumor control and to improve the chances of sphincter preservation in patients initially judged to require abdominoperineal resection.[14]

The primary endpoint of this study was to determine the pCR rate. Compared with the clinical stage at baseline, tumor and nodal downstaging were observed in 57.6% and 63.4% of evaluable patients, including eight patients (13.6%) with pCR. The pCR rate ranged from 7% to 31% in most of the previously reported studies with capecitabine and RT,[14,21–30] and FOLFOX and radiation therapy and 5-FU and radiation therapy up to a level of 18–25%.[31–34] The pCR rate in the current study (13.6%) is comparable to those found by Kim et al. (12%),[21] Craven et al. (9.2%),[24] Velenik et al. (9.1%),[25] Elwanis et al. (9.3%),[26] and De Brunie et al. (13%).[27] On the other hand, it is lower than that reported by De Paoli et al. (24%),[22] Krishnaw et al. (18%),[23] Dupuis et al. (20%),[29] Korkolis et al. (23%),[30] and Kim et al. (31%).[14] The higher figures in these studies in comparison to the present study may be due to a more favorable distribution of the T stage,[22] the use of a radiation boost to the tumor, or the use of leucovorine in addition to capecitabine.[14] These discordant results may be due to differences in staging of the primary tumor; as we know, EUS seems to provide more accurate staging for mobile T1 and T2 lesions, whereas MRI seems to be superior for fixed, more locally advanced disease. However, both modalities provide comparable overall T- and N-staging, with EUS currently being the less expensive of the two.

The toxicity of the combined regimen was, as expected, low, and grade 4 toxicity was not reported, while grade 3 toxicity was observed in only five patients (8.2%). This includes hematological (3.3%) and non-hematological (4.9%) toxicity, which confirms the results of other studies of rectal cancers.[14,21–30] These data compare favorably with those reported of preoperative RT combined with ci or bolus 5-FU. The results of published series with preoperative RT

Table 4 Comparison of pretreatment clinical and pathologic stages

Clinical stages (n=62)	Pathologic stages (n=59)[a]									
	pT0N0	pT1N0	pT2N0	pT3N0	pT4N0	pT0N1	pT1N1	pT2N1	pT3N1	pT4N1
cT3N0 (n=10)	1	2	2	2	–	–	–	1	2	–
cT3N1-2 (n=35)	4	2	3	14	–	1	2	4	4	–
cT4N0 (n=11)	2	1	1	2	1	–	–	–	1	1
cT4N1-2 (n=6)	1	–	1	1	–	1	–	–	1	1

[a] Three patients did not undergo surgery because of (1) multiple metastases and (2) because of refusal

and 5-FU-based CT show a high incidence of grade 3+ toxicity (15–25%).[35–37] It is well-known that capecitabine is extensively metabolized by the liver. The pharmacokinetics of capecitabine is not affected in patients with mild to moderate hepatic dysfunction. Capecitabine was better tolerated with a lower incidence of diarrhea, stomatitis, and neutropenia.[8] In addition to those, oral chemotherapy is more convenient and appealing to patients than continuous intravenous infusions. According to Liu et al., most cancer patients (89%) preferred oral chemotherapy to intravenous chemotherapy.[38] The major reasons for choosing oral chemotherapy are convenience, avoiding problems associated with intravenous access or needles, and a better environment for receiving chemotherapy.[14]

In our study, definitive surgery was performed approximately 6 weeks after the completion of CRT to increase the tumor downstaging and the chance of successful sphincter preservation surgery. This time interval was based on the results of a randomized trial that evaluated the role of the interval between preoperative radiotherapy and surgery.[39] In this study, sphincter preservation was possible in 18 of 29 (62%) patients treated with surgery for distal rectal cancer, i.e., tumors located 5 cm or less from the anal verge, which is comparable to published data of sphincter preservation rates ranging from 47% to 72%.[21,22,25–29] There were several similar published studies of preoperative radiotherapy combined with capecitabine chemotherapy in patients with locally advanced rectal cancer from UK,[24] Italy,[22] France,[29] Germany,[28] the Netherlands,[27] Egypt,[26] South Korea,[21] Slovenia,[25] and Greece.[30] However, no prospective studies from China were published in English, only one paper published in Chinese.

In summary, although a longer follow-up period is necessary to determine the long-term survival and local control effects, these preliminary results suggest that preoperative CRT with capecitabine and RT appears to be a safe, well-tolerated, and effective neoadjuvant treatment modality for LARC. The favorable safety profile of this combination might warrant the use of capecitabine and RT with other effective new drugs.

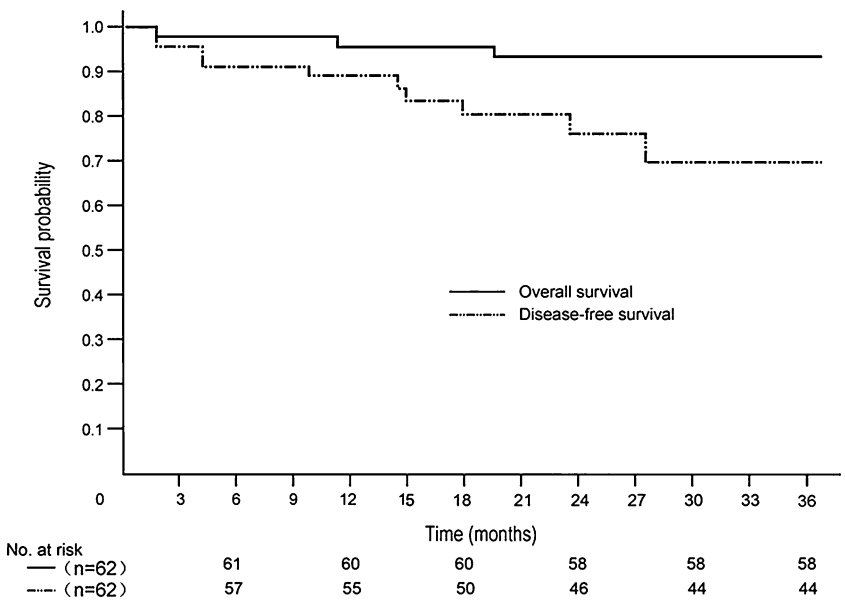

Fig. 1 Diseas-free survival and overall survival for all patients

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Conflict of Interest None declared.

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HOW I DO IT

Laparoscopic Treatment of Epiphrenic Diverticula: Preoperative Evaluation and Surgical Technique. How I Do It

Piero Marco Fisichella · Matthew Pittman · Paul C. Kuo

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Abstract
Introduction Traditionally, epiphrenic diverticula have been managed through a left thoracotomy. With the advancement of minimally invasive techniques, a laparoscopic approach has gained widespread popularity. Unfortunately, the preoperative evaluation of patients with epiphrenic diverticula, and their surgical management, is still not well characterized.
Discussion The goal of this article is to illustrate our approach to patients with epiphrenic diverticula in terms of preoperative evaluation and surgical technique. The final discussion will focus on the evidence-based rationale for our preoperative assessment and surgical approach.

Keywords Gastroesophageal reflux disease (GERD) · Laparoscopic antireflux surgery (LARS) · Epiphrenic diverticula · Esophageal function testing

Introduction

Epiphrenic diverticula are acquired, false, or pseudo-diverticula that result from herniation of the mucosa and submucosa through the muscular wall of the distal esophagus. They are also called "pulsion" diverticula, as their pathophysiology usually involves the presence of an underlying esophageal motility disorder, which is thought to cause an increased intraluminal pressure against a closed or nonrelaxing lower esophageal sphincter. Epiphrenic diverticula are rare and although their treatment is usually performed in experienced tertiary care centers, inconsistencies in preoperative evaluation or surgical techniques has led to a wide range of reported complications, with leak rates as high as 23%.[1] Evidence has shown that in order to achieve good results, the evaluation of patients with epiphrenic diverticula must begin with a careful preoperative evaluation to correctly localize the diverticulum and identify the underlying esophageal motility disorder usually associated with it (e.g., achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter). Following these essential steps, a carefully planned operation involving stapling of the diverticulum's neck, contralateral cardiomyotomy extending onto the stomach, and a partial fundoplication should then be performed. The following is a description of our preoperative evaluation, followed by a step-by-step description of our technique with a final discussion of the evidence-based rationale for our preoperative assessment and surgical approach.

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Preoperative Evaluation

All patients with epiphrenic diverticula undergo a preoperative assessment that consists of a symptomatic evaluation that includes a comprehensive 21-point questionnaire, a barium swallow, an upper endoscopy, and ambulatory esophageal manometry. While each test has its individual indication, the

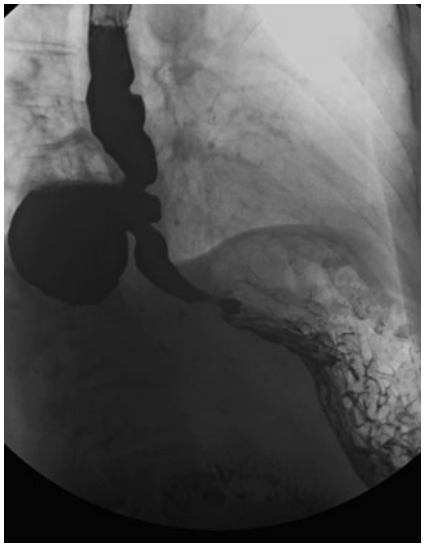

Fig. 1 Barium swallow showing a 6×7 cm epiphrenic diverticulum and a corkscrew esophagus. In this 88-year-old male, the diverticulum was located high in the mediastinum and the barium swallow allowed planning a thoracoscopic resection

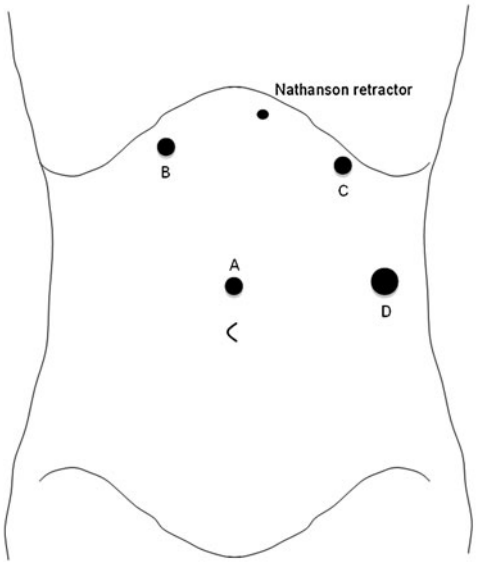

Fig. 3 Position of operative ports and Nathanson retractor

collective data gathered from them best allows for the optimal surgical treatment of these patients.

A barium swallow is usually the first test performed to determine the location and size of the diverticulum as it provides a "roadmap" of the esophageal anatomy. The anatomic information gleaned from this test helps in the operative planning because, if the diverticulum is located more than about 10 cm higher than the diaphragm, its resection might be easier accomplished thoracoscopically (Fig. 1). Occasionally, the barium swallow may detect esophageal dysmotility when ambulatory esophageal manometry is normal (Fig. 1).

Ambulatory esophageal manometry is the "golden standard" in the diagnosis of esophageal motility disorders and it always performed to document the underlying esophageal abnormalities that are frequently associated with the diverticulum (Fig. 2). An upper endoscopy is routinely performed to rule out esophagitis, Barrett's esophagus, or peptic ulcers.

Preoperative Considerations

The patient is positioned on the operative table on a beanbag. Pneumatic compression stockings are used as prophylaxis against deep vein thrombosis and preoperative antibiotics are administered prior to skin incision. A rapid sequence induction is always performed to prevent aspiration of particulate matter present inside the diverticulum or inside the esophagus of patients with achalasia. After intubation, a Foley catheter is inserted, the lower extremities are placed in stirrups, and the beanbag is inflated. The abdomen is then prepped and draped and the patient is positioned in steep reverse Trendelenburg.

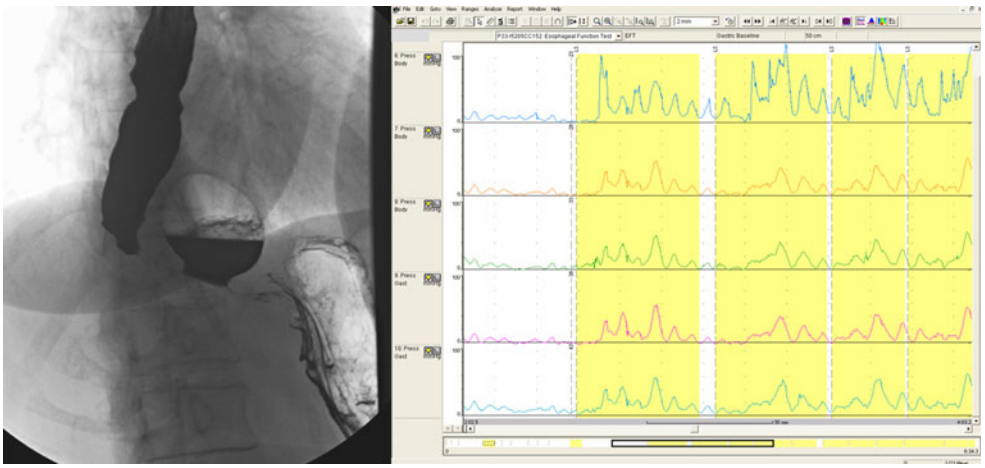

Fig. 2 Ambulatory esophageal manometry (*right panel*) showing high-amplitude, simultaneous, and repetitive contractions, characteristic of diffuse esophageal spasm in a 73-year-old female, in whom an epiphrenic diverticulum was discovered during an upper endoscopy. The barium swallow on the same patient (*left panel*) incorrectly suggested achalasia and shows mild tertiary esophageal contractions and a 5×6 cm epiphrenic diverticulum

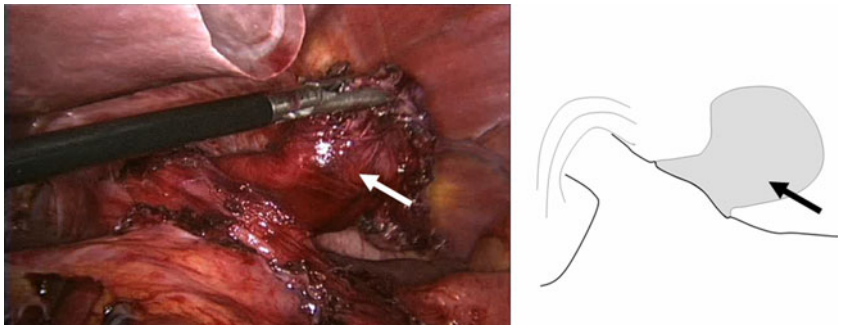

Fig. 4 An epiphrenic diverticulum (*white arrow*, *left panel*) is shown extending below the diaphragm, with the esophageal mucosa and submucosa herniating from the esophageal musculature. The artist's representation (*right panel*) shows the diverticulum (*black arrow*) located at the 2 o'clock position with respect to the body of the esophagus

Operative Technique

Laparoscopic Access and Placement of Trocars

After complete neuromuscular paralysis is achieved, a 1-cm transverse midline incision is made in the skin 1 in. above the umbilicus, the fascia is grasped with a Kocher clamp, a Veress needle is inserted, a water drop test is performed, the abdomen is insufflated to 14 mmHg, and an 11-mm Kii Optical Fixation Trocar ™ (Applied Medical, Rancho Santa Margarita, CA, USA) is inserted into the abdominal cavity under direct visualization. Then three Kii Advanced Fixation Trocars ™ (Applied Medical, Rancho Santa Margarita, CA, USA) are placed, as illustrated in Fig. 3. Port B and C are 11 mm working ports through which the graspers, the laparoscopic Ligasure™ Vessel Sealing System (Valleylab, Boulder, CO), and the suturing instruments are introduced. Port D is a 12-mm port used for manipulation of a laparoscopic atraumatic Allis clamp, the Ligasure™ to take down the short gastric vessels, and the insertion of a laparoscopic stapler. Finally, a 5-mm incision to the left of the xyphoid process is made to insert a Nathanson retractor, which retracts the left lobe of the liver and exposes the diaphragmatic hiatus and the gastroesophageal junction.

Identification and Resection of the Diverticulum

Once all ports are properly positioned, the laparoscopic Allis clamp is applied onto the anterior wall of the stomach to allow lateral traction of the gastroesophageal junction; the gastrohepatic ligament is divided with the Ligasure™ until the right diaphragmatic crus becomes visible; the phrenoesophageal ligament is divided anteriorly, from the apex of the right crus to the apex of the left crus, and the anterior vagus nerve is identified; the esophagus is then bluntly dissected away from the right crus and the posterior vagus nerve is localized. The dissection is continued into the posterior mediastinum, where the diverticulum lies; after the diverticulum is discovered, this is bluntly dissected off the pleura and the esophagus until its neck is clearly isolated (Fig. 4). A bougie (54–58 F) is then placed into the esophagus to stent its lumen and prevent a dangerous stenosis by stapling in excess of the mucosa and submucosa of the diverticulum. The diverticulum's neck is then stapled with a roticulating laparoscopic stapler equipped with a 2.5-mm vascular cartridge and oriented longitudinally to the esophagus (Fig. 5). The bougie is removed and the defect of the esophageal musculature is closed with 2-0 silk interrupted sutures to imbricate the staple line (Fig. 6). Finally, the diverticulum is placed into a bag and retrieved.

Cardiomyotomy and Partial Anterior Fundoplication

A cardiomyotomy is always performed contralateral to the location of the stapled diverticulum; it extends approximately 7 cm cranially onto the esophagus and 3 cm caudally onto the anterior wall of the stomach (Fig. 7). It is performed with a combination of blunt dissection with a laparoscopic Maryland dissector and cautery of the circular fibers with Ligasure™. After the cardiomyotomy is

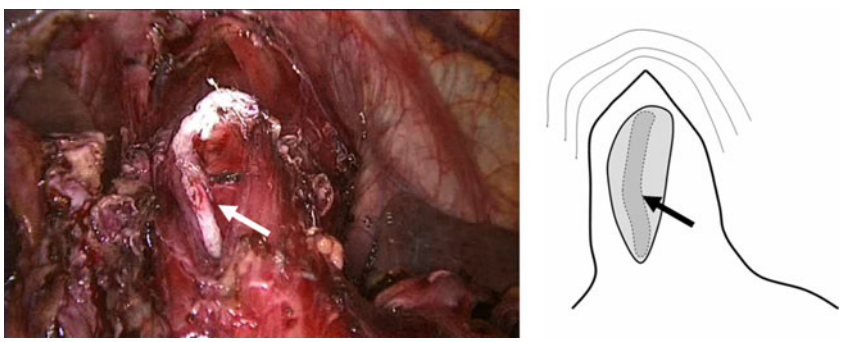

Fig. 5 The stump of the neck of the diverticulum (*white arrow*, *left panel*) is shown after its stapled transaction alongside the esophagus. The artist's representation (*right panel*) shows the longitudinal staple line (*black arrow*) across the esophageal submucosa

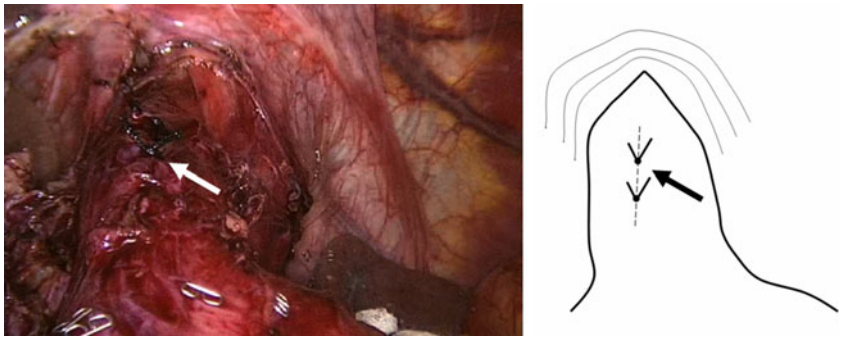

Fig. 6 The defect of the esophageal musculature is closed with interrupted sutures to imbricate the staple line (*white arrow*, *left panel*). The artist's representation (*right panel*) shows these sutures and the imbricated staple line (*black arrow*)

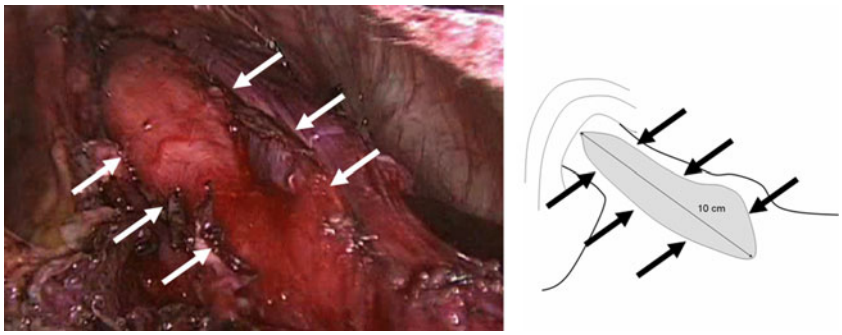

Fig. 7 A contralateral cardiomyotomy (*white arrows*, *left panel*) is shown extending onto the body of the esophagus and onto the anterior wall of the stomach. The artist's representation (*right panel*) shows the cardiomyotomy with the underlying esophageal submucosa (*black arrows*). The cardiomyotomy is 10 cm long and it is located at the 10 o'clock position with respect to the body of the esophagus

completed, the hiatus is always closed with few intracorporeally tied, interrupted #0 silk sutures. Then, the short gastric vessels are divided with the Ligasure™ and a partial anterior fundoplication is performed. This is fashioned by suturing the gastric fundus to the apex of the left crus and the left edge of the myotomy, folding the stomach over the myotomy, and suturing the gastric fundus along the right crus (Fig. 8). Although an upper endoscopy is seldom performed to assess the adequacy of the cardiomyotomy or the integrity of the staple line, we routinely perform it in difficult cases when a perforation is suspected. In these situations, the mucosa is submerged under saline during gentle insufflation to check for a perforation.

Conclusion of the Operation

At the end of the operation, the Nathanson retractor and all trocars are removed under direct visualization and the fascia of the optical port and the 12-mm incision are closed with a figure-of-eight 2-0 absorbable suture. The Foley catheter is removed in the operating room.

Postoperative Care

Postoperatively, all patients are admitted overnight in the surgical floor. They are started on a soft mechanical diet the morning of postoperative day 1, after a Gastrografin™ followed by a barium swallow have ruled out a leak. They are asked to keep this dietary regimen for the first 2 weeks postoperatively after which they are instructed to advance their diet to more solid foods.

Discussion

Inconsistencies in the preoperative evaluation and the variation in surgical techniques have led to a wide range

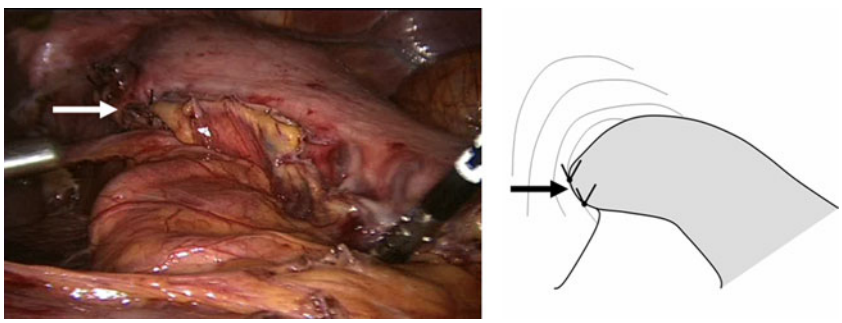

Fig. 8 Completed partial anterior fundoplication is shown (*white arrow*, *left panel*). The artist's representation (*right panel*) shows the fundoplication (*black arrow*) fashioned by folding the gastric fundus over the myotomy and suturing it along the right crus

of outcomes for patients with epiphrenic diverticula. Leak rates have been reported up to 21% in open series[2–6] and up to 23% in laparoscopic reports.[1,7–10] Similarly, mortality rates in open and laparoscopic series have been reported up to 9% and 7%, respectively.[1,4]

Our standard preoperative assessment aims to confirm the location and size of the diverticulum and document the esophageal motility disorder usually associated with the diverticulum. The rationale of our evaluation is supported by studies showing a large percentage of underlying motility disorders in patients with epiphrenic diverticula. This high incidence of esophageal dysmotility has been reported uniformly by several authors ranging from 75% to 100%,[2,5,6,9–13] and has led to believe that a cause–effect relationship exists between esophageal motility disorders and the development of epiphrenic diverticula. This has important implications as it supports our policy to perform in all symptomatic patients a routine cardiomyotomy even in those few cases in which the intermittent nature of the motility disorder precludes the identification of the dysmotility preoperatively.

The laparoscopic approach is our approach of choice in most cases, except in those with a large diverticulum that is located very high in the posterior medistinum; for these patients, a transthoracic resection may be easier to perform. Our choice is based on the observation that, when compared to the thoracoscopic approach, the laparoscopic techniques allow: (a) an easy resection of the diverticulum; (b) a straightforward closure of the diaphragmatic hiatus; (c) a superior exposure of the anterior wall of the stomach and the fundus of the stomach, which facilitates the distal extension of the cardiomyotomy and the performance of a partial anterior fundoplication; (d) the avoidance of a double-lumen endotracheal tube, let alone single lung ventilation during the operation; and (e) the avoidance of an uncomfortable chest tube postoperatively. Several studies have provided a solid argument for this approach. Kilic et al., Soares et al., and Thomas et al. in their reviews of literature showed that a laparoscopic approach to epiphrenic diverticula offered reduced operative mortality, decreased length of stay, and similar symptom relief compared with open surgery in the hands of experienced laparoscopic surgeons.[14–16] The results of those studies also demonstrated that the laparoscopic approach showed "potential benefits without compromising effectiveness and safety"[16] and that it "should be the approach of choice in most cases".[15]

Our surgical technique is based on the routine resection of the diverticulum and addresses at the same time any associated esophageal motor disorder diagnosed preoperatively. Our strategy is based on the almost unanimous consensus that these diverticula are caused by an underlying motility disorder, which, if left untreated, may cause persistent or recurrent symptoms or a potential disruption of a staple line. In fact, symptoms may not be exclusively attributable to the diverticulum alone and a leak may occur when high intraesophageal pressures from the unrelieved distal obstruction caused by the motor disorder persistently stress the staple line. Further supporting this approach, a comparison of published results has shown higher leak rates and higher incidence of recurrent and persistent symptoms following diverticulectomy without a cardiomyotomy.[16] Similarly, leaks have been associated with a mortality of 35% following simple diverticulectomy compared to 15% in those who also had a cardiomyotomy.[16]

Finally, it is our preference to add a partial anterior fundoplication, which has the dual goal to reduce postoperative gastroesophageal reflux and to cover both the myotomy and the imbricated staple line of the stump of the diverticulum's neck. Evidence has shown that the incidence of acid reflux symptoms appears significantly less when a partial fundoplication is added.[16]

Conclusions

Our surgical strategy takes into consideration the current evidence, which supports the laparoscopic approach as a safe and effective treatment for patients with epiphrenic diverticula in most cases, and which does not favor a diverticulectomy without a cardiomyotomy, while it emphasizes the need of accurate preoperative imaging and esophageal motility assessment. When performed in institutions with extensive experience in laparoscopic esophageal procedures, this approach and surgical strategy can achieve excellent outcomes with minimal morbidity and short hospital stay. Numerous studies have strengthened these arguments and have provided the evidence-based justification for our preoperative evaluation and standard surgical management.

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REVIEW ARTICLE

The Effects and Efficacy of Antireflux Surgery in Children with Gastroesophageal Reflux Disease: A Systematic Review

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Abstract

Background Antireflux surgery (ARS) for gastroesophageal reflux disease (GERD) is one of the most frequently performed major operations in children. Many studies have described the results of ARS in children, however, with a wide difference in outcome. This study aims to systematically review the efficacy of pediatric ARS and its effects on gastroesophageal function, as measured by gastroesophageal function tests. This is the first systematic review comprising only prospective, longitudinal studies, minimizing the risk of bias.

Methods Three electronic databases (Medline, Embase, and the Cochrane Library) were searched for prospective studies reporting on ARS in children with GERD.

Results In total, 17 eligible studies were identified, reporting on a total of 1,280 children. The median success rate after ARS was 86% (57–100%). The success rate in neurologically impaired children was worse in one study, but similar in another study compared to normally developed children. Different surgical techniques (total versus partial fundoplication, or laparoscopic versus open approach) showed similar reflux recurrence rates. However, less postoperative dysphagia was observed after partial fundoplication and laparoscopic ARS was associated with less pain medication and a shorter hospital stay. Complications of ARS varied from minimal postoperative complications to severe dysphagia and gas bloating. The reflux index (RI), obtained by 24-h pH monitoring (n=8) decreased after ARS. Manometry, as done in three studies, showed no increase in lower esophageal sphincter pressure after ARS. Gastric emptying (n=3) was reported either unchanged or accelerated after ARS. No studies reported on barium swallow x-ray, endoscopy, or multichannel intraluminal impedance monitoring before and after ARS.

Conclusion ARS in children shows a good overall success rate (median 86%) in terms of complete relief of symptoms. Efficacy of ARS in neurologically impaired children may be similar to normally developed children. The outcome of ARS does not seem to be influenced by different surgical techniques, although postoperative dysphagia may occur less after partial fundoplication. However, these conclusions are bound by the lack of high-quality prospective studies on pediatric ARS. Similar studies on the effects of pediatric ARS on gastroesophageal function are also very limited. We recommend consistent use of standardized assessment tests to clarify the effects of ARS on gastroesophageal function and to identify possible risk factors for failure of ARS in children.

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Keywords Gastroesophageal reflux · Antireflux surgery · Fundoplication · Children

Introduction

Gastroeophageal reflux disease (GERD) is a frequently encountered condition, affecting 7–20% of the pediatric population.[1–3] Most symptomatic children respond well to medical treatment.[3] However, when medical treatment fails and reflux symptoms persist, antireflux surgery (ARS) may be considered.[4] ARS is one of the most frequently performed major operations in children, and over the last decades, numerous studies have been published on this subject. The efficacy of ARS and the relationship between ARS and gastroesophageal (GE) function in children is difficult to deduce from these publications, since most studies are underpowered, retrospective, and have heterogeneous study designs, as well as a heterogeneous pediatric patient population.

Therefore, in order to provide the best evidence on the efficacy of pediatric ARS, this article aims to systematically review all prospective, longitudinal studies, and randomized controlled trials (RCTs). In addition, this review aims to study the effects of ARS on GE function in children, as measured by pre- and postoperative assessment tests.

Material and Methods

Study Selection

Using predefined search terms, PubMed (from 1960), Embase (from 1980), and the Cochrane library (issue 11, 2010) were systematically searched for all articles published until November 10, 2010. For PubMed, the following search terms were used: (fundoplication[Title/Abstract] OR nissen[Title/Abstract] OR thal[Title/Abstract] OR toupet[Title/Abstract] OR boerema[Title/Abstract] OR antireflux surgery[Title/Abstract]) AND (child[Title/Abstract] OR children[Title/Abstract] OR infant[Title/Abstract] OR infants[Title/Abstract] OR pediatric[Title/Abstract] OR pediatrics[Title/Abstract] OR pediatric[Title/Abstract] OR pediatrics[Title/Abstract]). The same search strategy was used in EMBASE (replacing "[TIAB]" by ":ti,ab"). In addition, the Cochrane library was manually searched.

Assessment of Study Eligibility

Inclusion Criteria

Each article was independently assessed for eligibility using the following criteria: study population—infants and children (0–18 years), who underwent ARS; type of intervention—open or laparoscopic Nissen, Thal, or Toupet fundoplication; study design—only prospective study format; study results—operative results reported using symptom questionnaires, or clearly defined reflux symptoms, or GE function tests, both before and after ARS.

Exclusion Criteria

Studies were excluded if they did not meet the inclusion criteria or if the outcomes of interest were not reported. Articles in non-English languages were excluded. In case of multiple studies reporting on an overlapping population, only the study with the largest patient population was included.

Outcomes of Interest

Reflux specific symptom questionnaires; clearly defined reflux symptoms; reoperation rate; postoperative dilatations and GE functions tests: 24-h pH monitoring; combined 24-h pH-multichannel intraluminal impedance (pH-MII); manometry; endoscopy; scintigraphy of the stomach (gastric emptying studies) and barium swallow radiography.

In this systematic review, success of pediatric ARS will be defined as complete relief of reflux symptoms.

Data Extraction

The titles and abstracts of all identified studies were reviewed by two independent authors (WS, MH) according to the MOOSE criteria.[5] Full publications were obtained for articles that appeared potentially relevant. References in these selected articles were also screened for cross-reference.

The following data were extracted from each selected article: Study design, study population, surgical method, outcome assessment techniques, duration of follow-up, and study outcomes of interest.

Results

In total, 1,260 articles were identified and screened. Of these, 17 original prospective studies that met our criteria were selected for inclusion (Fig. 1).[6–23]

Included trials were published between 1995 and 2010 and reported on a total of 1,280 children. Most studies only presented very short-term follow-up; however, a wide range in follow-up duration was present (1–96 months). Age at time of surgical intervention varied widely between the included studies from 0.25 to 20 years (Table 1).

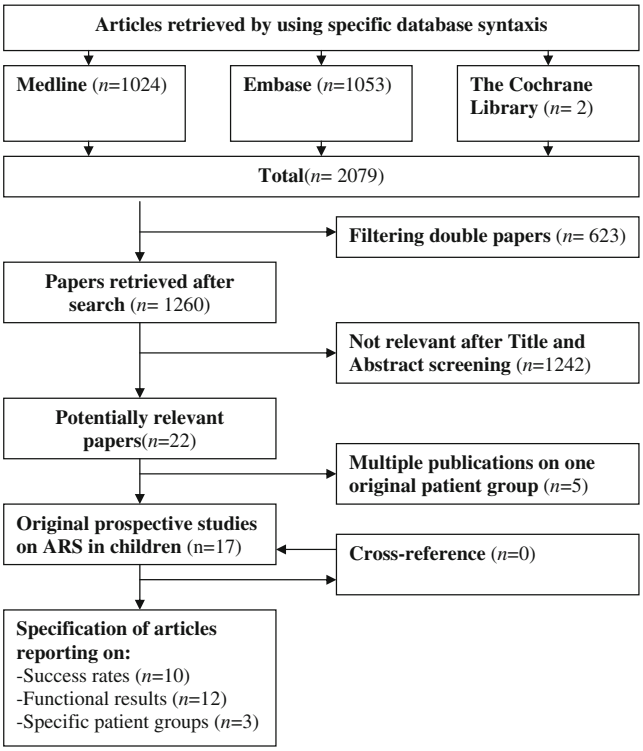

Fig. 1 Flow chart illustrating details of selection of studies on results of anti-reflux surgery in children

Only two RCTs were identified, and only five articles used control groups to verify their results.[6,8–10,14,23] Most studies used standardized surgical methods and investigation techniques and reported adequate on lost to follow-up. However, the overall methodological quality was generally poor. All potential threats to validity are summarized in Table 2.

Success Rate

Overall Success Rate

In 10 out of 17 (59%) studies (Table 3), the success rate of antireflux surgery in eliminating reflux symptoms was reported. Short-term success rates (within 6 months after surgery) were reported in seven of the ten studies and varied from 57–100% (median 86%). Long-term success rates (follow-up period longer than 6 months) were reported in three of the ten studies and varied from 70–96% (median 72%). In one study, the outcome after redo ARS (in 5% of patients) was included, which resulted in a secondary success rate of 99% after long-term follow-up.[6] Symptom severity scores were available in only one study,[10] showing a significant reduction in symptom severity after laparoscopic anterior partial (Thal) fundoplication.

Failure was not defined in most studies. Some studies reported the failure rate only as the need for reoperation. In nine studies,[6,7,9,10,15,19–23] a redo percentage was reported, varying from 0–3.8% (median 1%). The indication for redo operation was recurrent reflux in all cases.

Success Rate in Selected Patient Groups

Four studies reported solely on neurologically impaired (NI) children undergoing ARS.[7,8,20,22] Success rates varied from 57–79% (median 70%). Two studies compared outcome of ARS in NI patients to neurologically normal (NN) children. The first study demonstrated that recurrence of reflux was significantly higher in NI patients than in NN patients (18% vs. 2%, $p=0.01$).[6] The second study demonstrated a small, but significant difference in favor of NI patients concerning relative postoperative improvement of symptom severity, but no significant differences in 24-h pH monitoring, gastric emptying, or quality of life scores between patient with or without neurological impairment.[9,10]

In three studies, patients were included who had previously been operated for esophageal atresia, but none reported results for this group separately.[14,19,21] No prospective studies have been published showing only results in children with esophageal atresia undergoing antireflux surgery.

Success Rate Depending on Surgical Technique

Recently, an RCT was published comparing complete versus partial fundoplication in children.[14] In this study, no significant difference in short-term outcome between laparoscopic Nissen fundoplication and laparoscopic Thal fundoplication was seen. However, a higher rate of severe dysphagia and complications were found after Nissen fundoplication.

A prospective, non-randomized study comparing open Nissen fundoplication to open Toupet fundoplication showed similar recurrence rates.[23] In this study, Toupet fundoplication also resulted in less postoperative dysphagia. Furthermore, Toupet fundoplication resulted in lower reoperation rates, shorter time to first feeding, and shorter hospital stay. Patients were, however, assigned to either technique based on preoperative symptoms, gastroesophageal motility, age, and learning curve of the surgeon (Table 2).

Durante et al. randomly allocated patients to either Nissen fundoplication or vertical banded gastroplasty and showed no significant differences between these procedures. However, the number of patients included in this trial was very small (seven patients per group).[8]

No RCTs comparing laparoscopic to open fundoplication were published. Two prospective studies comparing open with laparoscopic fundoplication were identified, showing

Table 1 Details on included prospective clinical trials on ARS in children

Study (year)	Period	Method	*n*	Follow-up (months)	Patient characteristics	
					Comorbidity	Age: mean or range (years)
Capito (2008)[6]	1992–2003	LNF	127	66	All	0.25–20
Cheung (2006)[7]	1999–2004	ONF+G	9	36–60	Only NI	8.5 (SD 3.5)
		LNF+G	11			
Durante (2007)[8]	2003–2004	ONF±G	7	3	Only NI	0.33–12.25
		VGP±G	7			
Engelmann (2010)[9,10]	2001–2006	LThF	76	6	All	7 (SD 6.1)
Estevão-Costa (2010)[11]	NR	ONF	20	6–12	All	NR
		LNF	5			
		Boix–Ochoa	4			
Kawahara (1998)[12]	1996–1997	NF+Stamm	7	1–3	All	
Kawahara (2000)[13]	1998–1999	LNF	12	1–2	All	0.5–13
Kubiak (2010)[14]	1998–2007	LNF	89	1.5	All	5.2 (SD 4.7)
		LTouF	86			
Mattioli (2002)[15]	1998–2002	LNF	254	6–54	All	4.8 (0.025–14)
		LTouF	5			
		LThF/LJ	29/10			
Mattioli (2002)[16]	1993–2000	ONF	17	6	No NI	5 (SD 6.3)
		LNF	49			
Menon (2002)[17]	1993–1999	LNF	11	12	No NI	9–15
		LTouF	1			
Mousa (2006)[18]	NR	ONF	6	3–7	All	0.5–18
		LNF	7			
Soyer (2007)[19]	2003–2004	NF	13	1–3	All	6.7 (SD 3.3)
Srivastava (2007)[20]	2005–2006	O+LNF+G	63	1	Only NI	1.8 (SD NR)
Van der Zee (1999)[21]	1993–1996	LThF	53	10	All	NR
Weber (1995)[22]	1991–1993	ONF	56	12–36	Only NI	0.5–12
Weber (1999)[23]	1990–1997	ONF	102	12–96	No NI	0.25–16
		LTouF	154			

NF Nissen fundoplication (open or laparoscopic unknown), *ONF* open Nissen fundoplication, *LNF* laparoscopic Nissen fundoplication, *LThF* laparoscopic Thal fundoplication, *LTouF* laparoscopic Toupet fundoplication, *LJ* Lortat Jacob, *VGP* vertical gastric placation, *G* gastrostomy, *Stamm* Stamm gastrostomy, *EA* esophageal atresia, *NI* neurologically impaired, *All* all patients, *SD* standard deviation, *NR* not recorded

similar recurrence rates.[7,16] However, patients after laparoscopic ARS required less pain medication (one vs. six doses, $p<0.05$), and had a shorter hospital stay (2 vs. 7 days, $p<0.05$).

Complications

Complications were not consistently reported. Perioperative complication rates varied widely between 0% and 54%, including esophageal perforation, pneumonia, and wound infections. The highest complication rates were found in studies that only included neurologically impaired patients.[22]

Nine studies reported on dysphagia, demonstrating postoperative dysphagia in zero to 33% of patients.[6,9,12–14,16,17,21,23] However, this rarely lasted after the first few months following surgery. In two studies, balloon dilatation was used to treat postoperative dysphagia.[14,17] Only one study reported prolonged dysphagia postoperatively.[6] Postoperative dysphagia was more commonly reported after complete fundoplication than after partial fundoplication.[23] Postoperative gas bloating was not reported in any of the prospective studies.

Overall mortality during follow-up ranged from 0% to 29%. Surgery-related mortality rate was 0% in eight studies[7,8,15,17,19,21–23] and 0.7% in one study.[6] In this particular study, the patient died of peritonitis following postoperative detachment of a simultaneously placed gastrostomy.

Pre- and Postoperative Assessment Tests

In most (15/17) studies, 24-h pH monitoring was performed prior to ARS.[6–10,12–17,19–23] Postoperative pH monitoring

Table 2 Risk of bias summary

Study (year)	Capito et al.[6]	Cheung et al.[7]	Durante et al.[8]	Engelmann et al.[9,10]	Estevão-Costa et al.[11]	Kawahara et al.[12]	Kawahara et al.[13]	Kubiak et al.[14]	Mattioli et al.[15]	Mattioli et al.[16]	Menon et al.[17]	Mousa et al.[18]	Soyer et al.[19]	Srivastava et al.[20]	Van der Zee et al.[21]	Weber et al.[22]	Weber et al.[23]
Randomization	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−
Controlled	+	−	+	+	−	−	−	+	−	−	−	−	−	−	−	−	+
Standardization	+	−	+	+	+	+	+	+	−	+	−	+	+	+	+	−	−
Adequate report on loss to follow-up	+	NA	NA	+	+	+	+	NA	NA	NA	NA	+	NA	−	+	−	−
Potential other source bias			+[a]	+[b,c]				+[d]	−	+[e]		+[c]		+[b]			+[f]

NA not applicable (no lost to follow-up)

[a] No power calculation, underpowered

[b] High drop-out percentage

[c] Male/female imbalance

[d] Significant baseline imbalance in weight between the two arms

[e] Time horizon determines method of surgical approach (open vs. laparoscopic)

[f] Patient assignment based on patient characteristics: *Toupet Fundoplication* in patients with symptoms or radiological signs of gastroesophageal dysmotility and adolescent patients and *Nissen Fundoplication* in patients with life-threatening symptoms or esophageal strictures

Table 3 Success rate (complete resolution of gastroesophageal reflux symptoms) of ARS in children

Study	Short-term SR (%) (FU<6 months)	Long-term SR (%) (FU>6 months)	Long-term SR (%) after second ARS
Capito et al.[6]	NR	72	99
Cheung et al.[7]	NR	70	NR
Durante et al.[8]	57	NR	NR
Kawahara et al.[12]	100	NR	NR
Mattioli et al.[15]	NR	96.2	NR
Menon et al.[17]	100	NR	NR
Soyer et al.[19]	86	NR	NR
Van der Zee et al.[21]	75	NR	NR
Weber et al.[22]	79	NR	NR
Weber et al.[23]	93	NR	NR

SR Success rate, *FU* follow-up, *NR* not recorded

was routinely performed in eight studies.[6–10,12,17,19,21] All these studies reported a decrease in incidence and/or severity of reflux after ARS, including a reduction in RI (percentage of time with a pH <4) and the number and duration of reflux episodes. Four of these eight studies actually published the numbers of the RI before and after surgery[7,8,12,19] (Table 4). Data on symptom association probability scores were not reported.

Three studies reported manometry data before and after Nissen fundoplication.[12,13,19] Although the lower esophageal sphincter (LES) pressure seemed to increase after ARS, this was not statistically significant in any of the studies. In one study, the number of transient LES relaxations had significantly decreased postoperatively from 13 to 7 ($p<0.05$).[12] ARS did not seem to affect esophageal motor function.[13,19]

Table 4 Studies reporting reflux indices pre- and postoperatively in children

Study	*n*	Reflux index preoperatively (%)	Reflux index postoperatively (%)	*p*
Cheung et al.[7]	20 (NI)	5.7	0.15	0.009
Durante et al.[8]	7 (Nissen)	14.8	4.3	0.002
	7 (VGP)	25.7	12.1	0.042
Kawahara et al.[12]	10	15	0	NR
Soyer et al.[19]	13	24.7	0.9	<0.05

NI Neurologically impaired, *VGP* vertical gastric placation, *NR* not recorded

Three studies reported on gastric emptying before and after ARS using scintigraphy. In two studies, ARS had no significant effect on gastric emptying rate.[10,18] The third study demonstrated a significant acceleration of the gastric emptying rate after ARS.[11]

In two studies, a reflux specific symptom severity score was employed, showing significantly improved scores after ARS.[9,10,17] In one other study, a quality of life (QoL) questionnaire was performed to evaluate the results of ARS, showing a significant improvement in quality of life after ARS.[20]

In none of the studies, MII monitoring, endoscopy, or barium swallow radiography was performed before and after ARS.

Discussion

Our systematic review identified more than 1,000 publications after searching the available databases for pediatric ARS. Most of these articles were found to be retrospective studies or case reports. Only 17 prospective, longitudinal studies, using reflux symptom scores and/or GE tests could be identified that described the outcome of ARS in pediatric GERD patients. This indicates that the vast majority of studies on pediatric ARS are of poor quality.

In this systematic review, success was defined as complete relief of reflux symptoms. The median reported success rate after pediatric ARS was 86%, but varied widely (57–100%), due to several reasons. First, in most studies, heterogeneous patient groups and different surgical techniques were included and compiled in one general data pool. Second, although guidelines of the NASPHGAN[4] have been published, an actual unanimous definition of therapy-resistant GERD is lacking. This results in a large variety of presumed GERD and non-GERD patients that are included in studies on pediatric ARS.

Our systematic review further shows that the quality of life has been highly underexposed in the evaluation of pediatric ARS, even though validated QoL questionnaires are available for different age groups and development levels.[24] In only one study, QoL questionnaires were performed, showing a significant improvement after ARS.[20]

Several studies have postulated that NI patients are predisposed to a worse outcome after ARS. But in fact, only two studies[6,10] actually compared NI patients with NN patients. These two studies reported conflicting results. Capito et al.[6] found a significantly higher recurrence rate in NI patients. Engelmann et al.[10], however, demonstrated that NI patients showed relatively more improvement than NN patients. Nevertheless, we have to realize that drawing conclusions on the efficacy of ARS in specific groups, such as NI patients or patients after esophageal atresia is challenging, because of a lack of well-designed prospective comparative studies.

Clinical trials comparing laparoscopic to open ARS in pediatric GERD patients have not been published. However, prospective studies in this systematic review have shown that the results of laparoscopic ARS were not different from those of open ARS with regard to reflux symptoms during short-term follow-up. The main benefits of laparoscopic ARS include a shorter hospital stay and a reduced need for pain medication.[5,12] Recently, the New Technology Committee of the American Pediatric Surgery Association published a position paper favoring laparoscopic fundoplication. This advice was, however, based on results from case series and retrospective reviews.[25]

In only three studies, different types of ARS were compared.[8,14,23] Two of these studies compared complete versus partial fundoplication demonstrating less postoperative dysphagia in the partial fundoplication group. Reflux control, on the other hand, was comparable in both groups.[14,23] Similar results were demonstrated by a recently published systematic review and meta-analysis on RCTs comparing complete posterior (Nissen) with partial posterior (Toupet) fundoplication in adults.[26]

Finally, we noticed that following ARS, values of 24-h pH monitoring significantly decreased, LES-pressure seemed to increase, and gastric emptying was either unchanged or accelerated. However, no definite conclusions of the effects of ARS on GE function can be drawn, since too few studies have performed standardized GE function tests and the number of patients included in these studies was too small. Only if GE function tests are consistently performed before and after ARS in a sufficient amount of patients, the effects of ARS on GE function may be clarified. Moreover, these tests may then also provide us with the opportunity to identify prognostic factors for failure of ARS.

In conclusion, ARS in children shows a good overall success rate (median 86%) in terms of complete relief of symptoms. The success rate in NI patients may not be worse compared to NN patients. The outcome of ARS does not seem to be influenced by different surgical techniques, although postoperative dysphagia may occur less after partial fundoplication. The strength of these conclusions is, however, bound by the lack of high-quality prospective studies on pediatric ARS. Similar studies on the effects of pediatric ARS on gastroesophageal function are also very limited. Therefore, future studies should be performed in a well-designed prospective format, either as an RCT comparing different types of ARS, or as a prospective, age- and sex-matched study comparing different patient groups. But, even more crucial is the use of standardized GE function tests to clarify the effects of ARS on GE function and to identify possible risk factors of failure of ARS in children.

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REVIEW ARTICLE

Advances in the Etiology and Management of Hyperinsulinemic Hypoglycemia After Roux-en-Y Gastric Bypass

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Abstract
Introduction Hyperinsulinemic hypoglycemia with severe neuroglycopenia has been identified as a late complication of Roux-en-Y gastric bypass (RYGB) in a small number of patients.
Discussion The rapid resolution of type 2 diabetes mellitus after RYGB is probably related to increased secretion of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), and patients with post-RYGB hypoglycemia demonstrate prolonged elevations of GIP and GLP-1 compared to non-hypoglycemic post-RYGB patients. Nesidioblastosis has been identified in some patients with post-RYGB hypoglycemia and is likely due to the trophic effects of GIP and GLP-1 on pancreatic islets.
Conclusions Treatment of hypoglycemia after RYGB should begin with strict dietary (low carbohydrate) alteration and may require a trial of diazoxide, octreotide, or calcium-channel antagonists, among other drugs. Surgical therapy should include consideration of a restrictive form of bariatric procedure, with or without reconstitution of gastrointestinal continuity. Partial or total pancreatic resection should be avoided.

Keywords Roux-en-Y gastric bypass · Hypoglycemia · Glucose-dependent insulinotropic polypeptide (GIP) · Glucagon-like peptide-1 (GLP-1) · Nesidioblastosis

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Introduction

Obesity is one of the ten leading US health indicators and is associated with an increased risk for cardiovascular disease, diabetes, and certain forms of cancer. The escalating epidemic of obesity has resulted in a concomitant rise in type 2 diabetes mellitus (T2DM), and a linear relation between body mass index and mortality has been demonstrated.[1–4] Obesity and diabetic insulin resistance together form the foundation elements of metabolic syndrome resulting from impaired glucose metabolism. The patients who suffer from both conditions are therefore considered to suffer from obesity associated diabetes mellitus, more recently termed diabesity.[5] Within the adult US population surveyed in 2005, 60.5% of individuals were overweight, 32.2% were obese, and up to 5.3% were extremely obese.[6,7]

A number of treatment strategies have been introduced to decrease obesity including prevention, lifestyle and dietary changes, behavioral therapy, and pharmacotherapy.

At present, bariatric surgery is the most effective method to achieve major, long-term weight loss.[8,9] Postsurgical weight loss improves all obesity-related co-morbidities, and the net effect is an increase in quality of life and a decrease in overall mortality.[10–12] In addition, these procedures also achieve diabetes resolution in most of the patients with diabesity. As a result, these procedures are now considered metabolic operations,[13] which can sometimes provide such significant physiological augmentation that they have been considered as "bionic" procedures.[14]

Roux-en-Y gastric bypass (RYGB) is the most commonly performed metabolic bypass operation accounting for 40% of over 344,000 metabolic operations performed worldwide in 2008.[15] Recently, severe recurrent hyperinsulinemic hypoglycemia has been described as a consequence of RYGB surgery in small series of patients.[16–19] Pancreatic nesidioblastosis has been postulated to be the cause of the disorder based on histopathologic examination of pancreatic resection specimens in some of these early cases. In this review, we describe recent advances in the understanding of the etiology and management of hyperinsulinemic hypoglycemia after the RYGB procedure.

Hyperinsulinemic Hypoglycemia After Gastric Bypass

Incidence of Hyperinsulinemic Hypoglycemia

Severe hypoglycemia is considered a rare consequence of RYGB surgery and occurs in both diabetic and non-diabetic individuals. In a minority of patients who have undergone gastric bypass, hyperinsulinemic hypoglycemia occurs 1 to 3 h after eating and can be associated with severe neuroglycopenia. The prevalence of this syndrome is unknown, and it appears to be observed only after procedures which divert nutrients into the mid-small bowel and not after purely restrictive procedures such as adjustable gastric banding. The phenomenon of post-gastric bypass hypoglycemia has been increasingly recognized, and Kellog et al. estimate a post-operative prevalence of at least 0.36%.[20] In a review of the Swedish Bariatric Surgery registry, Marsk et al. reported the incidence of post-RYGB patients who required hospitalization for hypoglycemia as less than 1%,[21] although this frequency likely underestimates the true prevalence of the complication,

The problem of hypoglycemia after gastric surgery is not new. In 1942, Evensen described hypoglycemia as a complication in 12% of patients treated with gastroenterostomy and gastric resection.[22] Subsequently, other reports appeared which confirmed the occurrence of hypoglycemia which developed from a few months to as many as 5–8 years after partial gastrectomy.[23–25] From the 1940s through the early 1970s, when the complications of virulent peptic ulcer disease and subsequent ulcer operations were common, post-gastrectomy syndromes of metabolic complications were the nemesis of gastric surgery. Hypoglycemia was a recognized component of "early dumping," which typically occurred within an hour of eating due to concentrated nutrients and carbohydrates rapidly entering the small bowel.[26] This complication occurred in as many as one third of gastrectomy patients.[22,24] The syndrome known as "late dumping," which typically occurred 2–3 h after eating, was also associated with hypoglycemia and generally developed later in the post-operative course, but with an etiology that was less clear. Goligher et al. analyzed over 400 patients treated with gastroenterostomy and gastrectomy, and reported that in addition to an incidence of early dumping in 9–21% of various operations performed for peptic ulcer disease, late dumping associated with hypoglycemia developed in 1–6% of patients.[27]

Etiology of Hyperinsulinemic Hypoglycemia

Following the development of the insulin radioimmunoassay method by Yalow and Berson in 1960,[28] the presence of one or more "gut factors" which enhanced the insulin response to ingested glucose was demonstrated by McIntyre et al.,[29] and these as yet unidentified factors were named "incretins," as originally proposed by LaBarre,[30] for their ability to augment the insulin response to nutrients. The presence of excessive or inappropriate insulin secretion was confirmed as the etiology of post-gastrectomy hypoglycemia by Roth and Meade [31] and by Holdsworth et al.,[32] although it remained unclear whether or to what degree incretins had a role. In 1971, Schultz et al. reported that post-gastrectomy hypoglycemia was caused by "an inducible gastrointestinal factor which potentiates glucose-stimulated insulin release."[33] Also in 1971, Brown and Dryburgh identified gastric inhibitory polypeptide, or GIP,[34] and this was subsequently shown to function as a glucose-dependent incretin by Dupre et al. [35] and by Andres' group,[36,37] so that the name was changed to glucose-dependent insulinotropic polypeptide. In 1983, Bell et al. identified glucagon-like peptide-1 (GLP-1) as a cleavage product of the pre-pro-glucagon gene product,[38] and this was shown to function as an even more potent glucose-dependent incretin than GIP.[39,40] GIP levels were found to be altered after gastrectomy in some patients,[41] but interest in further studies on post-gastrectomy hypoglycemia decreased as the performance of gastric ulcer surgery rapidly plummeted following the introduction of histamine receptor antagonist and proton-pump inhibitor therapy of peptic ulcer disease.

The Roux-en-Y gastric bypass was developed in the late 1960s as an improved method to achieve weight loss, compared to jejuno-ileal bypass or vertical gastric banding.[42] The RYGB procedure rearranges the gastrointestinal

tract so that ingested nutrients directly enter the small bowel and bypass a large part of the stomach and duodenum. This operation improves quality of life in the majority of patients [43] and carries a 30-day mortality of 0.3%.[44,45] It is recognized as a leading metabolic procedure in view of its low morbidity compared with other bypass procedures such as biliopancreatic diversion [46,47] and its metabolic superiority compared with non-bypass procedures such as gastric banding.[48] RYGB achieves a number of physiological effects as a consequence of bile flow alteration, reduction of gastric size, altered flow of nutrients, vagal manipulation, and gut hormone modulation. The operation results in a number of beneficial effects on systemic metabolism through its effects on glucose metabolism [49] and the proposed entero-cardiac and entero-renal axes.[50]

Although T2DM was recognized as a component of morbid obesity that was intended to benefit from the weight loss induced by RYGB, interest in the physiologic changes induced by RYGB increased when it was recognized that RYBG patients with T2DM demonstrated prompt resolution of their diabetes before any significant weight loss had occurred post-operatively.[51–53] A reversal in insulin resistance and improved glucose metabolism do occur as a consequence of progressive weight loss,[54–56] but the rapid normalization of hyperglycemia in T2DM patients after RYGB suggested a dramatic effect on the so-called "entero-insular axis" induced by the diversion of nutrients into the small intestine. The prompt amelioration of insulin-dependent diabetes had been reported in patients undergoing partial gastrectomy and gastroenterostomy for peptic ulcer disease [57] and cancer,[58] although these early reports preceded the identification of the components of the entero-insular axis.

As recently reviewed by Bose et al.,[59] numerous factors contribute to the resolution of T2DM after bariatric procedures, including reduced caloric intake, decreased gastric emptying, and alterations in circulating levels of ghrelin, leptin, adiponectin, peptide YY (PYY), GIP, GLP-1, and insulin (Fig. 1). The principal cause of early normalization of diabetes after RYGB is enhanced post-prandial insulin secretion, thought due primarily to increased secretion of GIP and, especially, GLP-1. Although post-prandial GIP levels have been seen to be modestly increased after RYGB in some studies,[60,61] GLP-1 levels are now well documented to be increased two- to fivefold after RYGB [60–69] (Fig. 2). The timecourse of post-operative elevations of incretins suggests that these changes are largely present early, even as soon as 2 days after RYGB,[63,67,68] and that levels of GIP and GLP-1 may decline after one or more years, as substantial weight loss and normalization of insulin sensitivity occurs.[70,71] In patients with post-RYGB hypoglycemia, elevated levels of GIP and GLP-1 have been shown to persist for years after surgery and are associated with hypersecretion of insulin in the setting of normal blood glucose levels.[60,71,72] Furthermore, as many as one third of

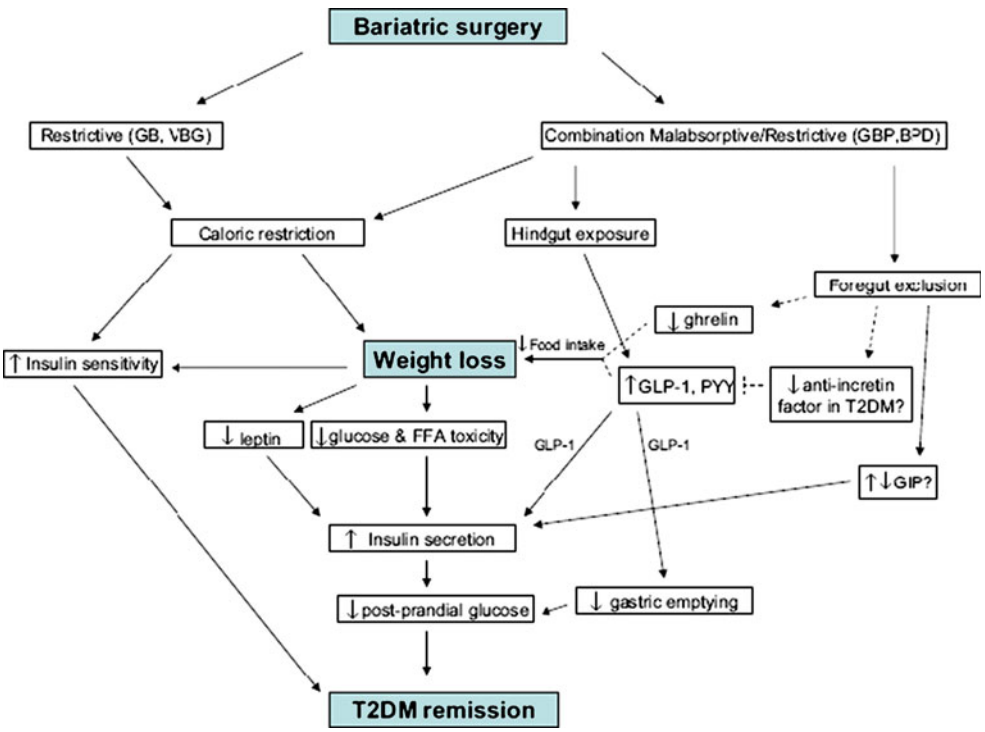

Fig. 1 Proposed model for resolution of T2DM after gastric bypass surgery. From Bose et al. (ref. 59) with permission

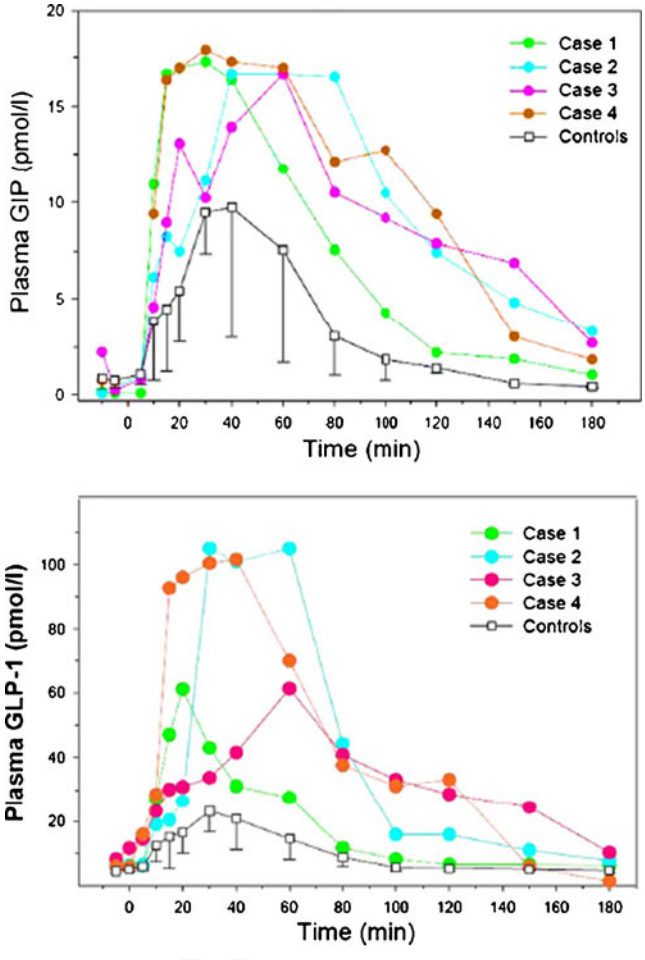

Fig. 2 Plasma GIP levels (*upper panel*) and GLP-1 levels (*lower panel*) in four patients with neuroglycopenia occurring 2–3 years after Roux-en-Y gastric bypass (*colored symbols*, cases 1–4) and in five asymptomatic patients 1 year after Roux-en-Y gastric bypass (controls—*open circles*) following a standardized test meal. From Rabiee et al. (ref. [71]) with permission

post-RYGB patients who are asymptomatic also demonstrate reactive hypoglycemia after an oral glucose load, some of which also have elevated GLP-1 levels.[60,72] Insulin sensitivity as well as beta-cell GLP-1 receptor availability, sensitivity to GLP-1, and sensitivity to glucose have all been shown to be normal in patients with post-RYGB hypoglycemia,[60,71–73] so an inappropriately exuberant insulin response with subsequent hypoglycemia appears to be due to the persistently excessive secretion of GLP-1 after oral nutrients. It remains unclear whether persistent incretin hypersecretion is a consequence of pre-existing conditions which affect intestinal or beta-cell function, a consequence of the technical details of the RYGB procedure (e.g., the location of the origin of the efferent jejunal limb) or a consequence of post-operative factors such as dietary composition.

Nesidioblastosis

Definition and Incidence of Nesidioblastosis After RYGB

The neuroglycopenia which occurs after gastric bypass is considered as part of the non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS), originally described by Service et al.[74] This condition is characterized by pancreatic beta-cell hypertrophy, islet hyperplasia, and increased beta-cell mass. When these anatomic findings are accompanied by ectopic islet tissue or cells, multilobulated islets, enlarged and hyperchromatic beta-cell nuclei, and ductulo-insular complexes (close association of islet-cell clusters with small pancreatic ducts), the histopathologic criteria for the diagnosis of nesidioblastosis are met [75–80] (Fig. 3). Nesidioblastosis associated with hypoglycemia was traditionally considered to be a condition largely limited to newborn infants and was rarely reported in adults.[77,81] However, 40 cases of nesidioblastosis have now been reported associated with hyperinsulinemia after gastric bypass.[82] The finding that nesidioblastosis also occurs in adults after gastric bypass has been considered as a weight loss-independent effect of diabetes resolution in association with increased insulin release, but it is unknown whether this condition occurs in a large percentage of post-RYGB patients or only in those with hypoglycemia. Some authors controversially propose that nesidioblastosis does not exist after gastric bypass and that the hyperinsulinism observed results purely from hyperfunctioning beta-cells persisting from the prolonged preoperative obesity.[83,84] Consistent with this view are the findings that some patients with post-RYGB hypoglycemia who underwent pancreatic resection did not have histologic criteria for nesideoblastosis.[85,86] Furthermore, it remains unknown whether some patients harbor nesidioblastosis or a pre-nesidioblastosis lesion prior to their surgery, due to genetic or obesity-related effects [87] (Fig. 4). Therefore the incidence and specific causes for NIPHS after RYGB remain subjects of ongoing investigation.

Possible Mechanisms of Nesidioblastosis

The mechanisms that cause acquired nesidioblastosis after gastric bypass are likely to include those that are also responsible for the resolution of diabetes mellitus. These include adaptive responses to severe dumping syndrome, a condition of obesity-induced adaptive beta-cell hypertrophy, inappropriate growth factor release, and altered gut hormonal signaling.[16,18,80,86,88] The fact that gastric bypass increases plasma levels of gut incretin hormones is believed to be an important contributory factor, as both GIP and GLP-1 have been implicated in increasing pancreatic beta-cell mass in rodent models.[89–91] GLP-1 induces the

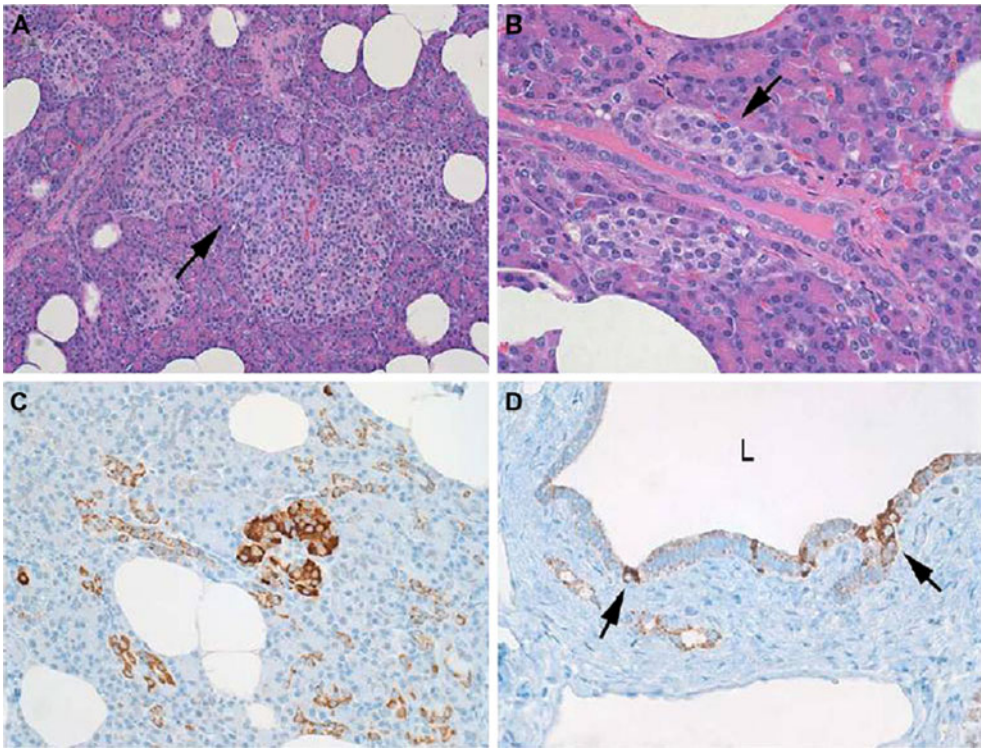

Fig. 3 Characteristic histologic and immunocytochemical features of nesideoblastosis in a patient with neuroglycopenia after Roux-en-Y gastric bypass. **a** Extreme variation in islet size and the presence of large lobulated islets (*center of panel*). **b** Ductulo-insular complexes. Endocrine cell clusters are intimately connected with a small pancreatic duct. **c** Insulin positive endocrine cell clusters are scattered throughout the acinar parenchyma. **d** Insulin positive cells are seen scattered amongst the pancreatic duct epithelium. From Rabiee et al. (ref. 71) with permission

expression of the transcription factor pancreatic-duodenum homeobox-1 (PDX-1),[91] which has been shown to regulate islet growth.[92] Rabiee et al. investigated the role of GIP and GLP-1 in four subjects who developed recurrent neuroglycopenia 2 to 3 years after RYGB and found a persistent exaggerated hypersecretion of both hormones.[71] In one subject who underwent sub-total pancreatectomy for persistent symptoms, nesidioblastosis was observed in the resected specimen, and PDX-1 expression was noted to be increased compared to control tissue (Fig. 5). They concluded that increased PDX-1 expression, induced by prolonged hypersecretion of GLP-1, likely played a role in the development of nesidioblastosis.

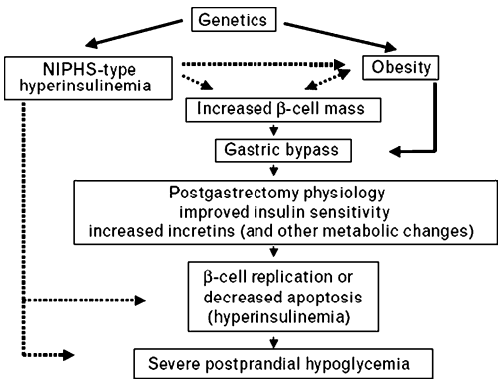

Fig. 4 Potential mechanisms for the development of hyperinsulinemic hypoglycemia after gastric bypass. Familial or genetic syndromes may contribute to hyperinsulinemia and islet hyperplasia, which is unmasked by weight loss and the altered hormonal milieu after gastric bypass. Persistence of expanded islet mass despite weight loss coincides with increased rates of islet-cell replication. Stimulation of expanded islet mass by continued high levels of incretin hormones results in inappropriate insulin secretion. Modified from Goldfine et al. (ref. [87]) with permission

Ghrelin has also been considered as a candidate mediator of nesidioblastosis, as it has been implicated in a number of pancreatic hyperplastic and neoplastic states.[93–95] Its release can also be affected by other upper gastrointestinal operations such as gastric banding [96] and esophagectomy [97] where cases of nesidioblastosis and hyperinsulinemic hyperglycemia have been reported. Ghrelin levels have been shown to be decreased after RYGB,[98,99] however, making its possible role as an inhibitor of incretin release more likely than its role as an inducer of nesidioblastosis.

Overexpression of insulin-like growth factor 2, insulin-like growth factor-1 receptor alpha, and transforming growth factor-beta receptor-3 has been reported in explanted pancreatic tissue from cases of nesidioblastosis [80] which raises the possibility that overexpression of insulin-like growth factor receptor isoforms may contribute to the development of nesidioblastosis. There are a small number of cases of hypoglycemia after gastric bypass that have subsequently revealed the presence of an underlying insulinoma, which can be concurrent with the nesidioblastosis.[85] The variety of islet pathology reported after gastric bypass suggests the presence of a spectrum of changes from initial hyperplasia to subsequent nesidioblastosis to neoplasia which can be induced in some patients. Understanding the factors which

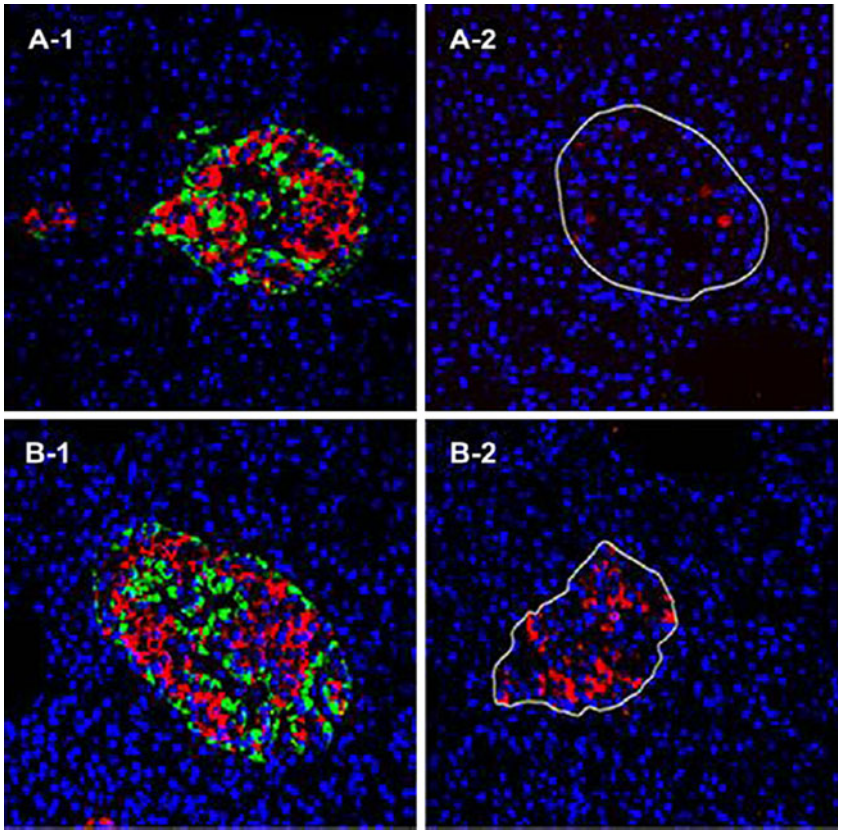

Fig. 5 Fluorescent immunohistochemical staining of representative pancreatic islets from an age- and gender matched control subject (*panels A-1 and A-2*) and a patient with hyperinsulinemic hypoglycemia 3 years after Roux-en-Y gastric bypass (*panels B-1 and B-2*). In *panels A-1* and *B-1*, beta-cells are stained in *red* and glucagon cells are stained in *green*. In *panels A-2* and *B-2*, PDX-1 is stained in *red*. Islet PDX-1 expression was uniformly increased in the hypoglycemic patient. From Rabiee et al. (ref. [71]) with permission

mediate this susceptibility may have far reaching implications and benefits.

Treatment of Hyperinsulinemic Hypoglycemia After RYGB

The most common treatment options for this condition begin with a modified low-carbohydrate diet.[100] Kellogg et al. reported good results with careful dietary control in more than half of their series of symptomatic hypoglycemic post-RYGB patients,[101] and this recapitulates the older observations of Schultz et al. that a carefully monitored and persistent low-carbohydrate diet was successful in reversing post-gastrectomy hypoglycemia.[33] When dietary alterations fail, consideration should be given to a trial of the beta-cell inhibitor diazoxide, the secretory inhibitor octreotide, alpha-glucosidase inhibitors (such as acarbose), or calcium-channel blockers (such as verapamil and nifedipine),[87,102–104] or post-operative feeding to the bypassed proximal gut by gastrostomy tube.[105] When medical treatment options fail, surgery has been advocated.

Pancreatic resection has been advocated for patients with refractory hypoglycemia due to the life-threatening risk of severe neuroglycopenia.[16–19] The diagnosis of unregulated insulin release requires verification of inappropriate insulin and C-peptide levels. Recently, selective arterial calcium-stimulation tests have been used to identify the anatomical areas of pancreas responsible for hyperinsulinism.[19,106] Partial and sub-total pancreatic resections have been employed, although some patients have required completion (total) pancreatectomy for resolution of hypoglycemia. This creates the condition of severe apancreatic or type 3c diabetes, which carries significant risks of iatrogenic hypoglycemia and has the same risks of retinal and renal disease as type 1 diabetes.[107,108]

The most direct surgical solution is reversal of the RYGB, as this avoids the morbidity of sub-total or total pancreatectomy,[100] although persistent hyperinsulinemic hypoglycemia has been reported after RYGB reversal in at least one patient.[16] Patients are frequently reluctant to undergo reversal due to the risk of weight gain, however, and surgeons may be unfamiliar with methods of reversal. Laparoscopic reversal of the RYGB has been described,[109] as well as laparoscopic conversion of RYGB to a sleeve gastrectomy.[110] Placement of an adjustable gastric band has been reported to reverse symptoms of hypoglycemia in most patients and maintain weight loss,[111] probably due to the added restriction to gastric emptying. Conversion of RYGB to a gastric sleeve theoretically provides protection against weight gain and restores normal gastrointestinal continuity, and anecdotal reports suggest that this may result in a resolution of hypoglycemia (Magnuson, personal

communication; Roslin, personal communication). However, Valderas et al. recently reported that elevated GLP-1 levels are seen after sleeve gastrectomy as well.[112] Following reversal or conversion to a different bariatric procedure, a prolonged and well-supervised period of low-carbohydrate diet is probably critical to the eventual resolution of excessive incretin secretion and the risk of hypoglycemia.

Summary and Conclusions

The gut plays a major role in glucose homeostasis, regulating both insulin secretion and sensitivity. Diversion of nutrients from the proximal stomach into the small intestine has been a known cause of hypoglycemia in a small percentage of patients for over 60 years. RYGB achieves improved glucose homeostasis through a variety of weight-dependent and weight-independent mechanisms including phenomena related to exclusion of the gastric fundus and upper intestine from contact with ingested nutrients, and enhanced nutrient stimulation of hormones from the mid- and lower-intestine. The secretion of the principal incretin hormones GIP and GLP-1 is rapidly and perhaps transiently increased, which is a major cause of the prompt resolution of T2DM after RYGB. In a small minority of patients, severe non-insulinoma hyperinsulinemic hypoglycemia develops due to persistent hypersecretion of GIP and GLP-1, which may induce nesidioblastosis with hyperinsulinemia due, in part, to increased expression of PDX-1. The factors which cause this phenomenon remain unknown. Dietary and drug therapy of hyperinsulinemia may provide relief in some patients, and those with refractory symptoms are candidates for surgical conversion to a restrictive form of bariatric procedure, with or without restoration of gastrointestinal continuity. Partial or total pancreatectomy should be avoided. A prolonged period of strict carbohydrate restriction after surgical correction appears necessary to reverse the abnormal pattern of entero-insular function.

Conflict of Interest Statement No conflicts of interest are declared.

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CASE REPORT

Primary Midgut Volvulus in Adults: Report of Two Cases and Review of the Literature

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Abstract
Introduction This is a report of two male patients (35 and 54 years old, respectively) admitted to our surgical department with signs of small-bowel obstruction.
Case Presentations Diagnostic workup with plain abdominal radiographs and, more specifically, computed tomography suggested the possibility of bowel rotation. In order to exclude any possibility of associated intestinal ischemia, both patients underwent exploratory laparotomy, which revealed a midgut volvulus without any associated obvious cause or pathology.
Discussion Both patients had an eventful outcome. Epidemiologic characteristics, clinical presentation, diagnostic workup, surgical treatment, and morbidity–mortality rates of small-bowel volvulus have been reviewed and thoroughly discussed.

Keywords Midgut volvulus · Small-bowel obstruction · Malrotation · Intestinal ischemia

Introduction

Twisting of the small bowel around its mesenteric artery axis is termed midgut volvulus, frequently causing luminal obstruction and most importantly compromising blood flow to and from the bowel wall threatening intestinal viability.[1–3] Midgut volvulus can be primary, without finding any associated underlying cause, or secondary to other congenital or acquired conditions. It is frequent in geographical areas, such as Middle East, Asia, and Central Africa, related to factors such as lower socioeconomic status, fiber consumption after prolonged fasting (Muslims during the Ramadan), parasitic infections and diabetic autonomous neuropathy, while it has a low incidence in Western countries.[1,4] Small bowel volvulus is considered an emergency necessitating prompt operative intervention, in order to prevent or treat the development of intestinal ischemia which is associated with high morbidity and mortality. Primary midgut volvulus is more frequent in children and young adults and is rarely present in adults in whom secondary volvulus is more prevalent. In this report, we present two cases of primary small bowel volvulus in adults.

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Case Presentations

Case 1

A 54-year-old male patient, with a past medical history of irritable bowel syndrome and laparoscopic cholecystectomy, was admitted to our surgical department complaining of colicky epigastric and periumbilical pain radiating diffusely to the abdomen, diarrhea, and bilious vomiting. Similar milder symptoms presented 1 week before admission and were conceived as gastroenteritis, unsuccessfully relieved by spasmolytic medication. Clinical examination revealed abdominal distension and diffuse tenderness without signs of peritonitis. Abdominal radiograph showed air-fluid levels of the small intestine (Fig. 1a). An abdominal computed tomography (CT)

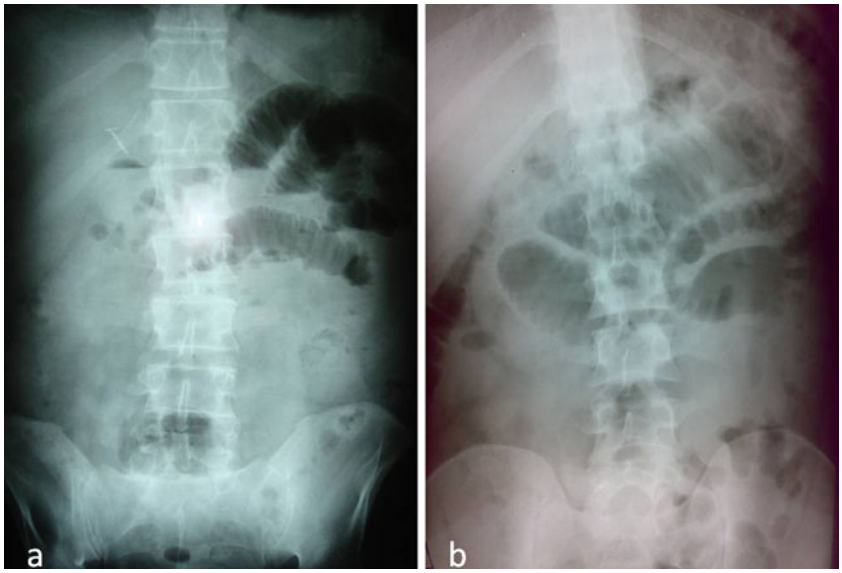

Fig. 1 Abdominal films in an upright position showing **a** distended and **b** air-filled small-bowel loops, with findings indicating a small-bowel obstruction

scan was performed which demonstrated dilatation of the small intestine, mesenteric and bowel wall thickening, and a "clockwise" rotation of the mesentery around the mesenteric vessels, possibly due to intestinal volvulus (Fig. 2). The exploratory laparotomy showed a volvulus of the small intestine without any obvious underlying cause or pathology, and an untwisting of the bowel was performed. Prolonged ileus for 5 days which resolved spontaneously was followed by an uneventful recovery, and the patient was discharged on the 11th postoperative day.

Case 2

A 35-year-old male patient, with a negative past medical history, was admitted to our surgical department with colicky abdominal pain and diarrhea in the preceding 4 days, conceived to be gastroenteritis, complaining of diffuse and severe abdominal pain and vomiting. The abdominal films showed distended air-filled bowel loops (Fig. 1b). Abdominal computed tomography scan demonstrated distension of the midgut with air-fluid levels, thickening of the bowel wall, and the associated mesentery and mesenteric fat. Exploratory laparotomy revealed a midgut volvulus without evidence of bowel ischemia or any underlying pathology, and the small intestine was untwisted. The patient postoperatively suffered of a prolonged ileus for about 1 week, which gradually resolved and was finally discharged on the 14th postoperative day.

Discussion

The term volvulus is derived from the Latin word *volvere*, which means to turn or roll.[1] Pathophysiologically, a greater than 180° twisting of the small bowel about its mesentery occurs, resulting in intestinal obstruction and in vascular inflow and outflow compromise, leading subse-

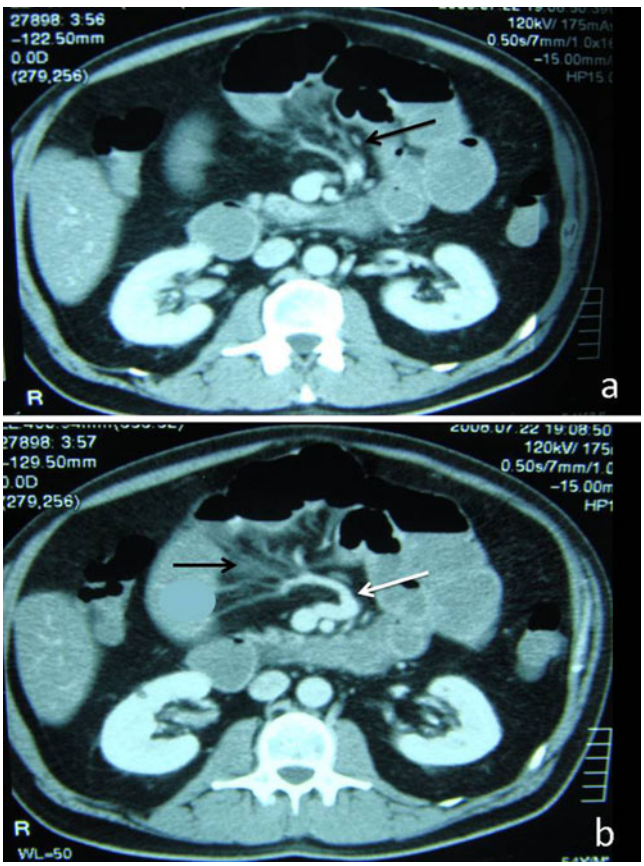

Fig. 2 Abdominal computed tomography demonstrating dilated small-bowel loops, with **a** thickening of the involved mesentery (*black arrow*) and **b** "clockwise" rotation of branches of the superior mesenteric vein (*white arrow*) around the superior mesenteric artery ("whirl sign")

quently to bowel ischemia and necrosis. The annual incidence of midgut volvulus is smaller in Western countries (1.7–5.7 per 100,000 population) and larger in Africa and Asia (24–60 per 100,000 population).[2] Similarly, midgut volvulus is presented as small bowel obstruction in 3–6% of patients in the first group and in 20–50% of patients in the second group.[5,6]

Small bowel volvulus is categorized as primary and secondary. Primary small bowel volvulus occurs usually in children and young males, in which there is no predisposing abnormality found during laparotomy. Anatomically, the small bowel in high-risk populations and the corresponding mesentery are longer with a narrower insertion and a lack of mesenteric fat.[7] On the other hand, secondary midgut volvulus occurs usually in older patients (sixth to eighth decade of life), affecting equally both sexes, in which the intestine is twisted around an underlying point of fixation.[8] The most frequently encountered cause is postoperative adhesions. However, many other causes have been reported in case reports or series, including internal hernias, tumors, mesenteric lymph nodes, Meckel's diverticulum, mesenteric lipoma, mesenteric lymphangioma, pregnancy, endometriosis, abscess, mycobacterial disease, aneurysms, and hematomas.[9–16]

Clinical presentation of primary midgut volvulus is usually nonspecific. An abrupt onset of signs and symptoms of small-bowel obstruction in a patient without previous abdominal surgery or other obvious causes (hernias), preceded by colicky epigastric or periumbilical pain several days before, should raise suspicion for this entity.[1] More importantly, "pain out of proportion" of the degree of obstruction as seen in acute mesenteric ischemia and signs of systemic inflammatory response (tachycardia, fever, tachypnea, and leukocytosis) or peritonitis should prompt the surgeon to urgently operate the patient, due to ensuing intestinal vascular compromise.

Preoperative diagnostic workup includes plain abdominal films, ultrasonography (US), abdominopelvic CT scan, and, more recently, multidetector CT (MDCT) angiography. Abdominal radiographs can demonstrate nonspecifically signs of intestinal obstruction, such as air-fluid levels and dilated bowel loops and signs of intestinal ischemia or necrosis, such as thumbprinting and pneumatosis intestinalis or in extreme cases portal vein gas. However, plain films have low accuracy in diagnosing midgut volvulus.[8] Doppler US has been reported to be helpful in the diagnosis of midgut volvulus, identifying the encircling of the intestinal loops and the superior mesenteric vein (SMV) around the superior mesenteric artery (SMA), which is termed the "whirlpool sign," with 92% sensitivity and 100% specificity.[17–19] Disadvantages of US are the fact that it is operator dependent and that gas interposition can limit its sensitivity.

Abdominopelvic CT is currently considered as the imaging modality of choice because it can demonstrate signs of small bowel obstruction (dilatation of closed or air-filled bowel loops), pathognomonic signs of the volvulus (the rotated mesentery and SMV encircling clockwise the SMA termed "whirl sign" and mesenteric thickening) and signs of intestinal ischemia (thickening or presence of air in the bowel wall, portal vein gas, and free peritoneal fluid).[2,17,20–23] Angiographic appearance of the twisted mesenteric vessels, termed as the "barber pole sign," is pathognomonic for midgut volvulus as well.[24] Additional signs of catheter angiography include tapering or abrupt termination of the mesenteric vessels, prolonged contrast transit time, absent venous opacification, or a dilated SMV.[17] However, it is time-consuming and invasive. Instead, MDCT angiography has been introduced and widely accepted, producing multiplanar three-dimensional images, providing information about the presence of the volvulus, the degree and location of intestinal obstruction, the presence of intestinal ischemia, and any associated anomalies of adjacent organs.[17,25]

Clinically assumed and radiologically demonstrated volvulus necessitates immediate operative intervention due to the associated risk of intestinal ischemia. Devolvulation (untwisting) of the involved bowel is frequently the only maneuver need to be done, although some authors recommend intestinal fixation or even resection in order to avoid a recurrence of the volvulus.[2,8,26] Almost half of the patients will undergo an intestinal resection for a gangrenous small intestine.[12] Currently, there are several reports describing the laparoscopic management of midgut volvulus, considering the benefits of shorter postoperative hospital stay, reduced postoperative complications, and possibly reduced subsequent adhesion formation compared to the open approach.[27–29]

The outcome of patients with small-bowel volvulus is worse when there is a delay in diagnosis (due to its rarity, especially in Western countries), involvement of older patients with associated comorbidities and development of intestinal ischemia and necrosis. Thus, although mortality in patients explored surgically for midgut volvulus is 10–35%, it increases dramatically to 20–60% in patients with gangrenous bowel.[2]

In conclusion, primary midgut volvulus should be suspected in every patient presenting with abrupt onset of abdominal pain and signs of intestinal obstruction, without previous abdominal surgery or other obvious causes. Plain X-rays are nonspecific, and US is operator dependent. The imaging modality of choice is the CT scan and the newest MDCT angiography, which can demonstrate the rotated small bowel and mesentery, providing simultaneously information for any associated intestinal ischemia. Early diagnosis and immediate operative intervention are key factors associated with a better prognosis for this group of patients.

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CASE REPORT

Combined Esophagectomy and Pancreaticoduodenectomy: Expanded Indication for Supercharged Jejunal Interposition

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Abstract
Introduction Combined pancreaticoduodenectomy and esophagectomy poses a challenge for reconstruction.
Case Report We report a case of a combined pancreaticoduodenectomy and esophagectomy for synchronous pancreatic and esophageal cancer, with reconstruction using a supercharged jejunal interposition.
Discussion The supercharged jejunal anastomosis is a versatile option for foregut reconstruction.

Keywords Esophageal cancer · Pancreatic cancer · Esophagectomy · Pancreaticoduodenectomy · Whipple · Jejunal interposition

Introduction

A gastric conduit is most commonly used for reconstruction after esophagectomy. However, the stomach cannot be used for many patients. For these patients, colonic interposition has been the traditional alternative method of esophageal reconstruction. We have previously reported on the use of "supercharged" jejunal interposition for these patients in lieu of colon.[1] As our experience with this procedure has increased, we have expanded the indications for its use at our institution. Here, we report a case of combined esophagectomy and pancreaticoduodenectomy with a supercharged jejunal interposition, reconstructed in a Roux-en-Y fashion.

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Case Report

A 65-year-old man with chronic gastroesophageal reflux disease presented with a 2-month history of epigastric pain radiating to the back and a 10-lb weight loss. He had no dysphagia or chest pain. He reported loose stools, but no jaundice or acholic stools. His abdomen was non-tender on physical exam without any lymphadenopathy. A computed tomography (CT) scan of his abdomen showed a 6-cm, multi-cystic mass in the head of the pancreas invading the second portion of the duodenum and abutting 50% of the superior mesenteric vein. There was also a suggestion of a

mass in the distal esophagus. An upper endoscopic ultrasound was performed to biopsy the pancreatic mass. On endoscopy, a mass was seen in the distal esophagus (38–44 cm) involving half the circumference of the esophagus extending into the stomach. The endoscopic ultrasound showed invasion of the adventitia (uT3) without any suspicious lymph nodes. A multi-cystic pancreatic mass was also seen on ultrasound and biopsied. Pathology of the esophageal tumor revealed poorly differentiated signet ring carcinoma. The pancreatic mass was adenocarcinoma in a background of mucin. Combined positron emission tomography (PET)/CT showed metabolic activity in both tumors, but no evidence of metastatic disease (Fig. 1).

The patient received chemotherapy with eight cycles of folinic acid, 5-fluorouracil, and oxaliplatin. This was followed by chemoradiation with capecitabine and 50.4 Gy of intensity-modulated radiation therapy given to include both tumors in the field. Restaging positron emission tomography, CT, and endoscopy showed good response in both tumors; thus, the patient was admitted for a combined resection.

The patient underwent a pancreaticoduodenectomy and transhiatal esophagectomy. The stomach was not a suitable conduit due to sacrifice of the gastroduodenal artery as part of the pancreaticoduodenectomy. The bile duct and pancreatic ducts were reconnected to a 40-cm limb of jejunum, and a supercharged jejunal interposition was used for esophageal reconstruction (Fig. 2). Operative time was 16 h with 1 l of estimated blood loss. The patient's postoperative course was uncomplicated except for atrial fibrillation, which was controlled with amiodarone. His barium swallow demonstrated no leak. He was discharged to home in good condition enjoying a regular diet supplemented with jejunal tube feeds. Final pathology revealed a 4-cm mucinous adenocarcinoma of the pancreas with less than 1% viable tumor and a 2.1-cm poorly differentiated adenocarcinoma in the esophagus infiltrating into the muscularis propria with 50% viable tumor. All lymph nodes were free of tumor.

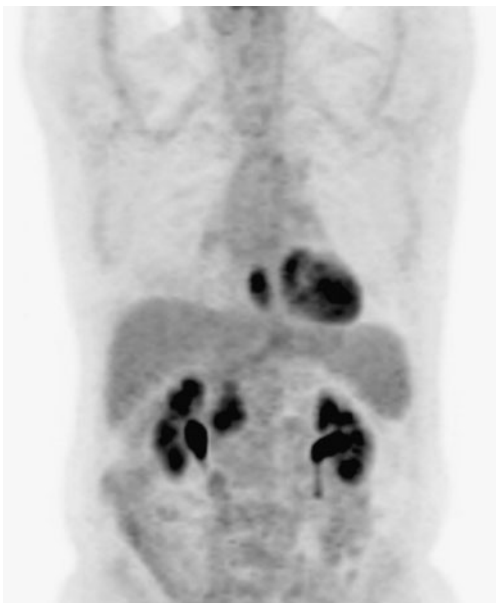

Fig. 1 Maximum intensity projection of PET. Both the pancreatic and esophageal cancers exhibit increased FDG uptake

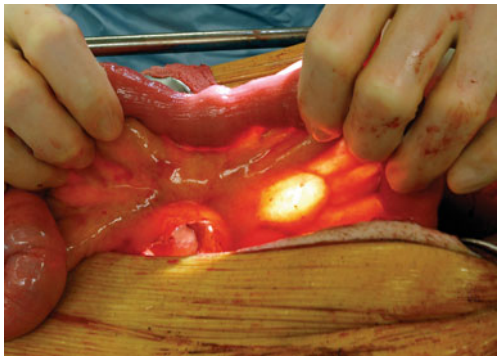

Fig. 2 Mobilization of the jejunal conduit and preparation of the second jejunal branch of the superior mesenteric artery for division and anastomosis in the neck

Discussion

The incidence of adenocarcinoma of the esophagus has increased dramatically in recent years. Likewise, the incidence of intraductal papillary mucinous tumors of the pancreas has also risen. Despite advances in adjuvant therapy, surgery is usually necessary for cure in both diseases. Reflecting the complexity of these operations, data have demonstrated improved operative mortality at high volume centers.[2] Combining the two operations in a sub-total foregut resection poses a challenge for reconstruction. In our review of the literature, we found two previous reports of combined pancreaticoduodenectomy and esophagectomy.[3,4] In one case, the right gastroepiploic artery was preserved, and the stomach was used as a conduit. In the other case, colonic interposition was used. At our institution, we prefer supercharged jejunal interposition for cases in which the stomach is an inadequate conduit. We have previously reported on the functional advantages of the jejunal interposition, which more closely resembles the native esophagus.[1] The versatility of the flap allows it to be used for a wide range of complex scenarios, including the case we have reported here. This case underscores the utility of the supercharged jejunal interposition as an

additional option for esophageal reconstruction when the stomach is not a viable option.

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GI IMAGE

Mesenteric Castleman's Disease in a 12-Year-Old Girl

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Abstract
Introduction Castleman's disease is a rare disorder characterized by proliferation of the lymphoid tissue usually presenting as an asymptomatic mediastinal mass in children. The location of the disease in the mesentery is rare.
Discussion We report a case of a 12-year-old girl with an isolated mass of mesenteric root presenting with vague abdominal pain. The surgical resection of the mass revealed the hyaline-vascular type of Castleman's disease. The patient had an uneventful postoperative course.

Keywords Castleman's disease · Mesenteric · Children

Case Report

A 12-year-old girl was admitted to our hospital complaining of intermittent vague abdominal pain for 3 months. The physical examination revealed the presence of a palpable, mobile, and nontender mass in the umbilical region. The initial laboratory testing showed anemia with a hemoglobin level of 8.3 g/dl. Computed tomography confirmed a 3.8× 3.7-cm well-defined homogeneous soft tissue mass was located in the root of mesentery with a moderate enhancement after the injection of contrast material (Fig. 1). The patient underwent a laparotomy with resection of a well-encapsulated mesenteric mass (Fig. 2). On sectioning, the cut surface showed a solid, homogeneous, and gray mass (Fig. 3). Histologic examination showed that the nodulus lymphaticus shrank with a striking number of capillary vessels (Fig. 4). This pattern was consistent with the diagnosis of the hyaline-vascular type of Castleman's disease. The postoperative course was uneventful, and the patient was discharged from the hospital in good condition on the seventh postoperative day. Observation of the patient by physical examination and CT scan of the abdomen for 12 months postoperatively showed no evidence of recurrence; meanwhile, the anemia has totally been resolved.

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Discussion

Castleman's disease is a rare benign lymphoproliferative disorder of unknown etiology. It can present at any site where there is lymphoid tissue; but more than 70% of cases involve the mediastinum, with less than 10% being intraabdominal.[1]

The disease falls under two categories according to pathological changes: hyaline-vascular type and plasma-cell type. The former, the most frequent, is characterized by small hyaline vascular follicles and capillary proliferation; the plasma cell type, in which large lymphoid follicles are separated by sheets of plasma cells. Clinically, Castleman's

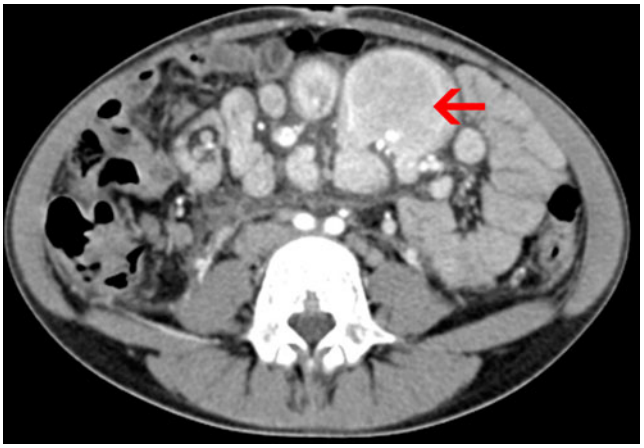

Fig. 1 CT showing a mass with moderate contrast enhancement in abdomen (*arrow*)

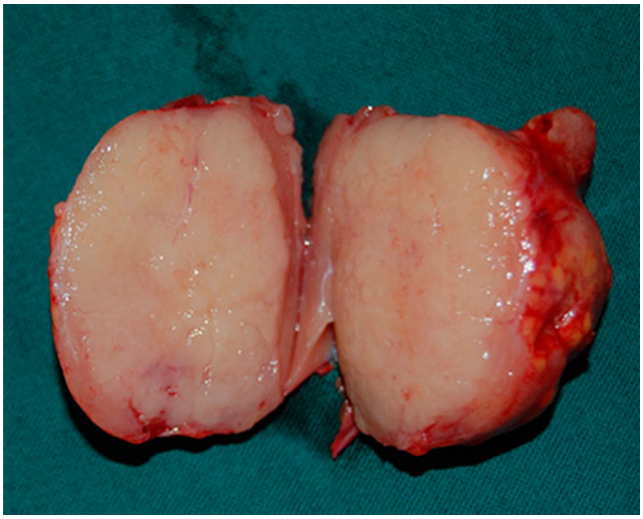

Fig. 3 The *cut surface* showing a solid, homogeneous, and gray mass

disease is classified into two subgroups: localized or disseminated.[2] Of the localized type, 96% are hyaline-vascular type. The vast majority of patients are asymptomatic with favorable prognosis; but the disseminated form, on the contrary, is associated with various symptoms, such as fever, splenomegaly, and leukocytosis.[2]

Most Castleman's disease typically appear as well-defined masses on radiographs and show good enhancement on CT and MRI; however, the images of Castleman's disease are similar to other masses including lymphoma, tuberculosis, sarcoidosis, and retroperitoneal sarcomas.[3] Diagnosis is exclusively achieved with histopathologic and immunohistochemical findings after resection.

Prognosis and treatment of Castleman's disease depend on clinical categories. Complete surgical excision is curative in cases of localized type, with a five-year rate of survival of 100%.[4] Unfortunately, there is no established treatment option in disseminated form. Radiotherapy, chemotherapy, steroid therapy, and/or immunosuppressive agents have been applied in refractory cases, resulting in the improvement of clinical symptoms.[5,6] However, it has been reported recently that the splenectomy could be reconsidered awaiting remission of the symptoms of disseminated patient.[7] This therapy may be useful in the future. In our patient, a complete surgical excision was accomplished; and thus far, there is no evidence of recurrence.

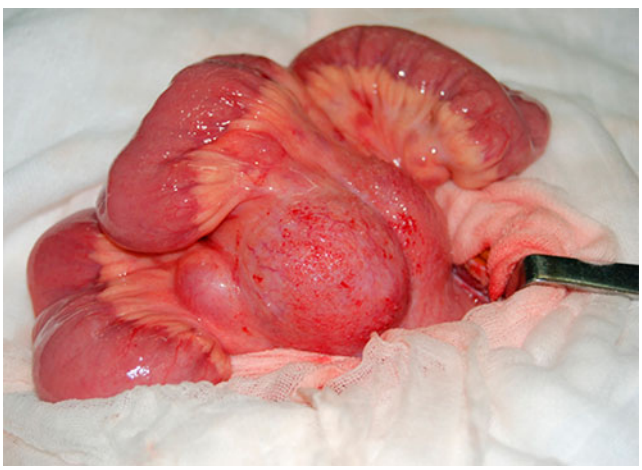

Fig. 2 Laparotomy revealing the mesenteric mass

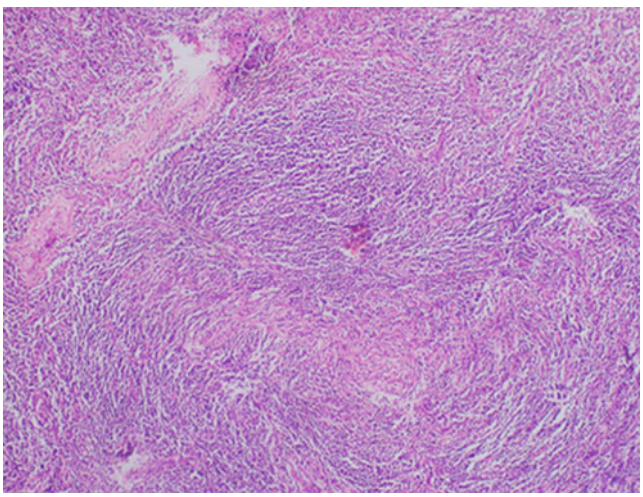

Fig. 4 Histologic examination revealing nodulus lymphaticus shrank with a striking number of capillary vessels (hematoxylin and eosin, 100×)

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GI IMAGE

Pseudoaneurysm of the Hepatic Artery

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Abstract
Introduction Hepatic artery pseudoaneurysms are a rare complication of biliary tract surgery and have an associated mortality that approaches 50%.
Case Report A case of massive haemobilia caused by a hepatic artery pseudoaneurysm several months following laparoscopic cholecystectomy is described.
Discussion It was successfully managed by angiographic embolisation, with the patient making a complete recovery.

Keywords Cholecystectomy · Pseudoaneurysm · Heaptic artery · Angiography · Embolisation

Case Report

A 32-year-old female had undergone a difficult cholecystectomy 5 months earlier for acute cholecystitis. At the time of the procedure, some bleeding was encountered adjacent to the cystic duct that was controlled by clip application. The patient made an uneventful recovery. She re-presented with sudden onset of epigastric pain followed by haematemesis and melena. An urgent gastroscopy showed fresh blood in the stomach and duodenum without an obvious source. Over the following 24 h, 2 U of packed red blood cells (PRBC) were administered. She also became clinically jaundiced. Repeat gastroscopy for re-bleeding identified fresh blood in the duodenum without an obvious source. A further 2 U of PRBC were given. An urgent computed tomography (CT) was performed revealing a 4-cm right hepatic artery pseudoaneurysm (Fig. 1). The patient underwent urgent angiographic embolisation of the pseudoaneurysm (Fig. 2a, b). Significant bleeding was encountered during the coiling of the pseudoaneurysm, requiring occlusion of the right hepatic artery. Endoscopic retrograde cholangiography (ERCP) was then performed and some clot removed from the bile duct. Minor narrowing of the bile duct was noted adjacent to the previously placed clips, not requiring any intervention (Fig. 2c). A repeat angiogram several days later showed complete occlusion of the pseudoaneurysm (Fig. 2d). The patient was well at 6 months post-embolisation.

Discussion

Hepatic artery pseudoaneurysm (HPsA) is an uncommon complication of laparoscopic cholecystectomy. HPsA remains an important consideration and a diagnosis to exclude in any patient at any time interval presenting post-biliary surgery with an acute abdomen or haemobilia.

The mechanism of HPsA formation is multifactorial. Direct vascular injury, vessel erosion due to clip encroachment,

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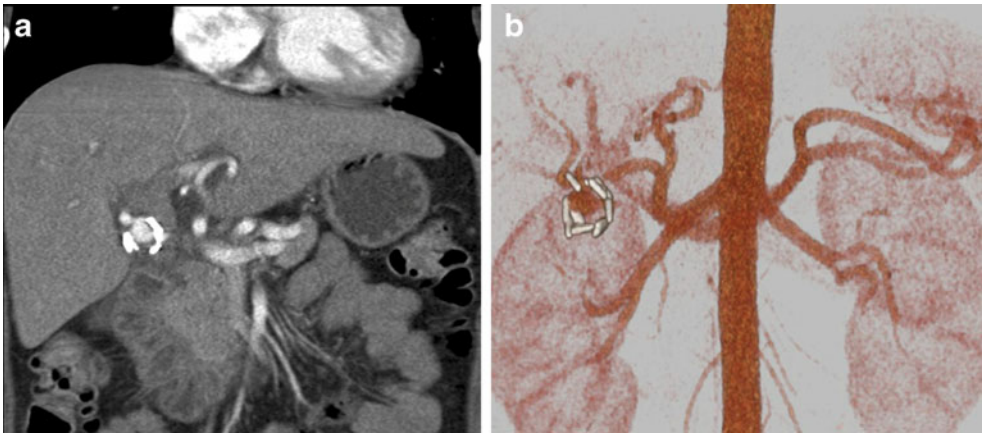

Fig. 1 **a** Coronal image of right hepatic artery pseudoaneurysm surrounded by metallic clips on CT angiogram. **b** CT angiogram reconstruction of visceral blood vessels clearly demonstrating the location of the right hepatic artery pseudoaneurysm

diathermy injury as well as post-operative intra-abdominal sepsis and bile leak have all been implicated as possible contributing factors.[1] HPsA has been reported following cholecystectomy, bile duct and pancreatic surgery, liver transplantation and percutaneous liver biopsy. Hematemesis and abdominal pain are the two most frequent symptoms.[1] In some cases, these pseudoaneurysms occur in an intra-hepatic location.[2]

It has been suggested that in the setting of bile duct injury following laparoscopic cholecystectomy between 4% and 6% of patients may develop HPsA.[3] The exact timing of presentation from the time of cholecystectomy has not

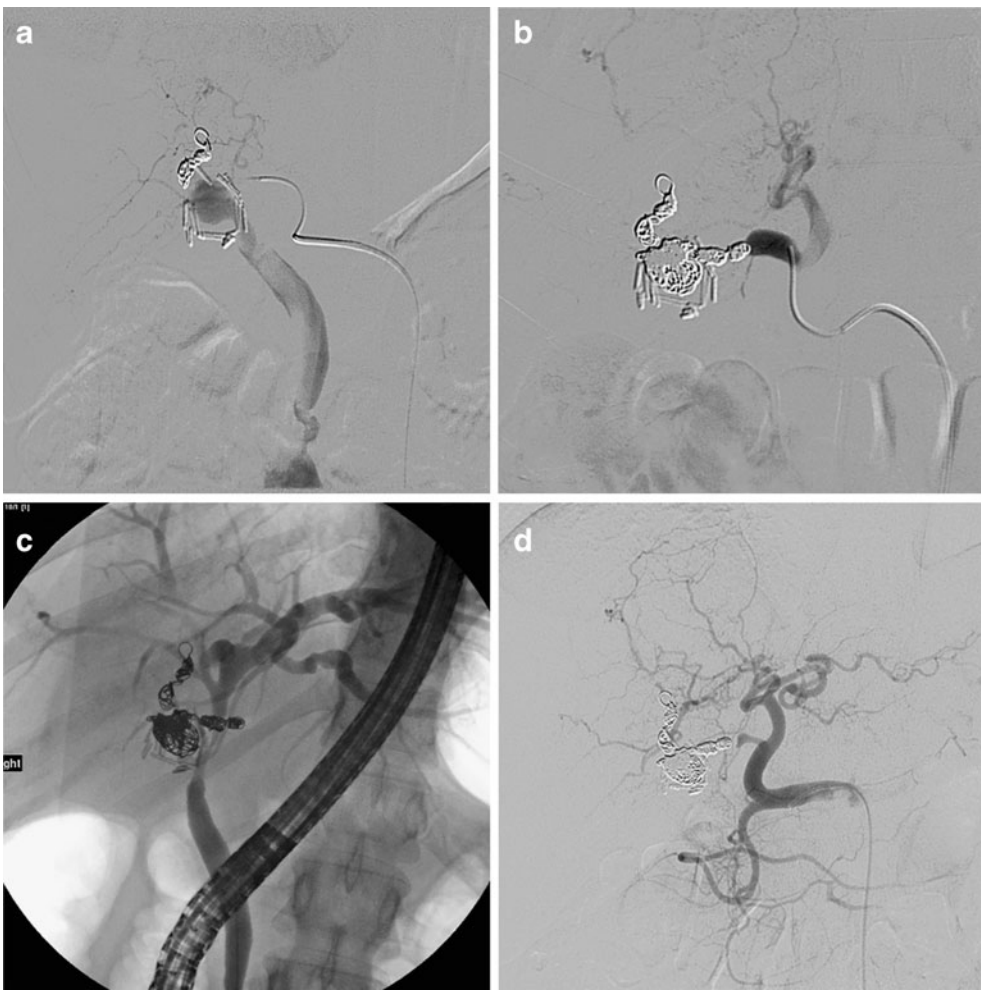

Fig. 2 **a** Angiogram showing communication between right hepatic artery pseudoaneurysm and the bile duct. **b** Complete occlusion of the right hepatic artery using coils, with no further communication with the bile duct noted. **c** Endoscopic retrograde cholangiogram showing minor bile duct narrowing with no evidence of any bile leak. **d** Follow-up angiogram without evidence of pseudoaneurysm filling

been defined. In the case described, a minor bile duct stricture was noted at ERCP, though no recognition of bile duct injury was noted at the time of surgery or in the immediate post-operative period.

The natural history of HPsA is for ongoing enlargement complicated by rupture in 21–80% of cases.[4–7] Aneurysm size greater than 5 cm in particular confers a ten-fold risk of rupture.[8] Diagnosis is usually made by CT imaging or ultrasonography.

The overall mortality rate of HPsA associated with biliary surgery is between 25% and 50% in some series.[2,3] The standard management of this condition is hepatic angiography and embolisation of the vessel using coils, with success rates of 83%.[2,8] Surgery is rarely necessary, and complications following angiographic treatment of HPsA are rare.[9] Hepatic artery thrombosis, liver infarction, coil dislocation and erosion into the common bile duct, however, have been reported.

In conclusion, it is important to be aware of HPsA as a cause for emergent re-admission of critically unwell patients with haemobilia or an acute abdomen in the setting of hepatobiliary surgery. The current evidence suggests optimal management of this condition is carried out via angiography with coil embolisation. All such cases appear best managed in a specialist tertiary centre.

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GI IMAGE

An Abdominal Mass

Giuseppe R. Nigri · Paolo Aurello · Giovanni Ramacciato

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Abstract
Background A 93-year-old woman, with life-threatening comorbidities, was admitted to our hospital for fever, nausea, vomiting, and a large and tender abdominal mass. The CT scan showed a gallbladder empyema with a large stone inside.
Results Having considered the age of the patient and the presence of life-threatening comorbidities, we decided to drain percutaneously the gallbladder under US guidance. After drainage, the patient showed immediate relief from pain and she made a fast and full recovery.
Conclusion Percutaneous drainage of gallbladder empyema is an effective procedure and a good alternative for patients unfit to undergo surgery due to severe comorbidities.

Keywords Percutaneous drainage · Interventional radiology · Abdominal mass

Clinical Image (200 words)

A 93-year-old woman, with mild cognitive impairment, was admitted to the Emergency Department of our hospital for nausea, vomiting and a large abdominal mass associated with diffuse abdominal pain. Past medical history was positive for coronary ischemic disease, chronic obstructive

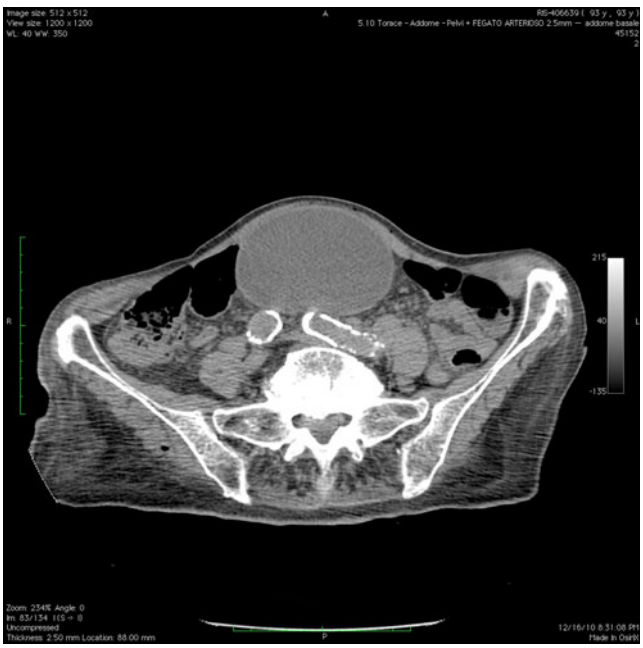

Fig. 1

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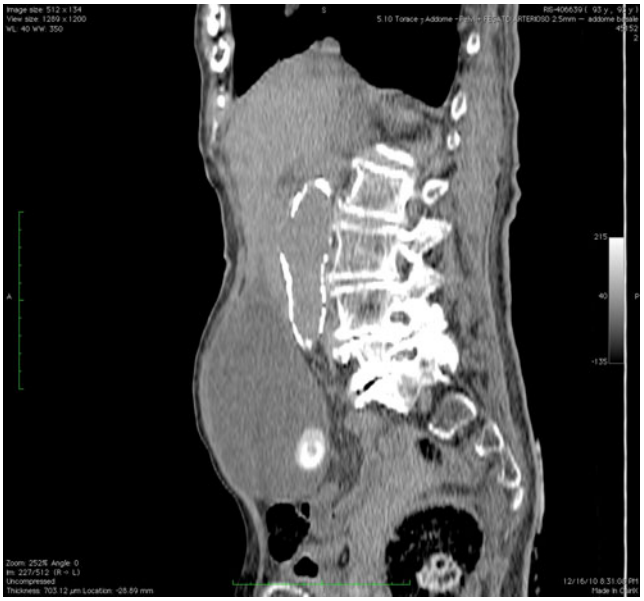

Fig. 2

pulmonary disease, peripheral vascular disease and chronic liver failure.

Temperature was 38/104°F. Physical examination revealed a tender abdominal mass located along the median line, from the epigastric area to the sub-umbilical area. Routine blood tests showed elevated WBC (14.39×10^3 μL), neutrophils (87.9%) and C-reactive protein (11.7 mg/dL). The CT scan showed a gallbladder empyema with a large stone inside (Figs. 1 and 2). Having considered the age of the patient and the presence of life-threatening comorbidities, we decided to drain percutaneously the gallbladder under US guidance. About 950 cc of purulent material was drained, and the microbiologic exam showed the presence of *Escherichia coli.* Antibiotic (piracillin/tazobactam) was administered for 5 days. After drainage, the patient showed immediate relief from the pain and she made a fast and full recovery; she was discharged on postoperative day 5. Percutaneous drainage of gallbladder empyema is an effective procedure and a good alternative for patients unfit to undergo surgery due to severe commorbidities.[1]

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LETTER TO THE EDITOR

Underlying Mechanisms of Anastomotic Leakage and Systemic Recurrences in Colorectal Cancer

Steven Oosterling · Hein Stockmann · Gerben van der Bij · Eric Belt · Marjolein van Egmond

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Dear Sir,

With interest we read the recent article of Katoh et al. in which the contribution of anastomotic leakage to the risk for systemic recurrence in a series of 207 stage II colorectal cancer patients was investigated.[1] In their multivariable analysis, anastomotic leakage proved the most robust independent prognostic factor for a 5-year disease-free survival. The authors address in their discussion a main factor that might contribute to increased risk of recurrences. The use of perioperative blood transfusions was reported as a risk factor for anastomotic leakage and has earlier been established as a prognostic factor for cancer recurrence. As stated by the authors, blood transfusions are associated with impaired cell-mediated immune responses which might facilitate development of (micro) metastases.

Here, we would like to discuss several other biological mechanisms that might be responsible for increased recurrences seen following anastomotic leakages. In the case of anastomotic leakage or otherwise failure of the barrier function, the gut provides a major source of endotoxins that ubiquitously circulate while leading to sepsis. Endotoxins or lipopolysaccharides (LPS), which are cell-wall constituents of Gram-negative bacteria, have been shown to enhance tumor cell adhesion and metastasis outgrowth in experimental models.[2,3] Mice that received endotoxin injections showed increased metastatic burden compared to those receiving a saline injection. This increase was reflected in higher tumor cell proliferation and decreased apoptosis within lung metastases.[2] We earlier showed in several experimental models that the perioperative milieu itself facilitates both local and systemic tumor metastasis formation.[4,5] Electron microscopic investigation demonstrated that abdominal surgery resulted in endothelial stress, leading to impaired liver vessel integrity and subsequent exposure of underlying extracellular matrix, which served as preferred adhesion sites for tumor cells leading to enhanced metastasis outgrowth.[5] In accordance, in a recent in vitro study, LPS enhanced tumor cell adhesion and invasion, both fundamental processes in tumor progression.[3] Moreover, continued and repetitive exposure to endotoxins, such as during abdominal sepsis, results in reduced immune responsiveness or even immune paralysis. This is exemplified by diminished capability of innate immune cells, such as macrophages, to produce the cytotoxic tumor necrosis factor α. Since liver macrophages, the so-called Kupffer cells, have been shown to be pivotal in arresting and eliminating circulating tumor cells in liver sinusoids,[6] this immunosuppression may impede an effective antitumor response. Thus, endotoxins such as LPS seem to play an important role in the observations of Katoh et al. and might be connected as one of the main responsible mechanisms for increased recurrence following anastomotic leakage. As such, the link between endotoxins and tumor recurrence is a further subject of our current investigation.

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LETTER TO THE EDITOR

Reply to Letter to the Editor: Anastomotic Leakage Contributes to the Risk for Systemic Recurrence in Stage II Colorectal Cancer

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Dear Dr. Oosterling,

We would like to thank Dr. Oosterling et al. for their interest and comments on our recent article on prognostic impact of anastomotic leakage in stage II colorectal cancer (CRC).[1] The reason why anastomotic leakage facilitates systemic metastasis in stage II CRC is the intriguing point of this current study because it would actually suggest a therapeutic target in the specific clinical situation. Accordingly, we are greatly interested in the explanation of the mechanism that circulating endotoxins or LPS in the situation of anastomotic leakage promotes metastasis.

Our multivariable analysis suggested that transfusion and systemic inflammation (and subsequent immune modification represented by SIRS status) may synergistically affect the prognosis of patients with postoperative leakage in stage II CRC,[1] and as Dr. Oosterling et al. advocated, endotoxin-induced inflammation must be a part of the mechanism to affect CRC progression. Our earlier gastric cancer study[2] as well as other's[3] in terms of proximal gastrectomy with or without splenectomy also suggested that transfusion and immune modification by splenectomy may play a crucial role in cancer patient prognosis, which can at least partly account for the contribution of transfusion to cancer patient prognosis as a synergistic effector.[1]

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The inflammation mediator TNF-α[4] activates the Wnt/β-catenin pathway through inhibition of GSK3β.[5] Wnt/β-catenin pathway increases cancer cell proliferation and keeps cancer progenitor cells undifferentiated,[6] therefore, endotoxin may cause cancer progression and metastasis. Dr. Oosterling et al. actually showed in several experimental models that the perioperative milieu that modifies inflammation induced by systemic injuries facilitates tumor metastasis formation.[7,8] Most importantly, such perioperative intervention may thus have a great potential to improve patient outcome with leakage in stage II.

On the other hand, we unexpectedly found that detrimental effect of anastomotic leakage on patient prognosis was not seen in cases of stage III CRC.[9] This finding indicated a more complex mechanism of metastatic development in stage III CRC with anastomotic leakage. For example, Iinuma H. et al. recently reported that circulating tumor cells including cancer stem-like cells in peripheral blood predict worse prognosis in stage II and III CRC,[10] while not in stage I CRC. Moreover, tumor necrosis alpha-related apoptosis inducing ligand receptor, DR4, was recently identified as a biomarker in stage III CRC treated with adjuvant chemotherapy.[11] Such tumor factors including treatment sensitivity must definitely affect patient prognosis independently of anastomotic leakage.

We believe further rigorous investigation is needed, including animal experimental models, on this issue which must lead to not only resolution of the mechanism between anastomotic leakage and metastasis but also a novel diagnostic or therapeutic treatment strategy in a specific situation of the individual cancers.

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