Endoscopic Sphincterotomy Permits Interval Laparoscopic Cholecystectomy in Patients With Moderately Severe Gallstone Pancreatitis

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Patients with moderately severe gallstone pancreatitis with substantial pancreatic and peripancreatic inflammation, but without organ failure, frequently have an open cholecystectomy to prevent recurrent pancreatitis. In these patients, prophylactic endoscopic retrograde cholangiography (ERC) with endoscopic sphincterotomy (ES) may prevent recurrent pancreatitis, permit laparoscopic cholecystectomy, and decrease risks. The medical records of all patients with pancreatitis undergoing cholecystectomy from 1999–2004 at the University of North Carolina Memorial Hospital were reviewed. Data regarding demographics, clinical course, etiology of pancreatitis, operative and endoscopic interventions, and outcome were extracted. Moderately severe gallstone-induced pancreatitis was defined as pancreatitis without organ failure but with extensive local inflammation. Thirty patients with moderately severe gallstone pancreatitis underwent ERC and ES and were discharged before cholecystectomy. Mean interval between ES and cholecystectomy was 102 ± 17 days. Cholecystectomy was performed laparoscopically in 27 (90%) patients, open in three (10%) patients, and converted to open in two (7%) patients, with a morbidity rate of 7% (two patients). No patient required drainage of a pseudocyst or developed recurrent pancreatitis. Interval complications resulted in hospital readmission in seven (23%) patients. In conclusion, recurrent biliary pancreatitis in patients with moderately severe gallstone pancreatitis is nil after ERC and ES. Hospital discharge of these patients permits interval laparoscopic cholecystectomy, but close follow-up is necessary in these potentially ill patients. (J GASTROINTEST SURG 2006;10:1–5)

KEY WORDS: Gallstone pancreatitis, endoscopic sphinterotomy, pseudocyst, cholecystectomy

The association between gallstones and pancreatitis was initially made by Opie[1,2] in 1901, when he described two potential etiologies of gallstone-induced pancreatitis. His initial hypothesis suggested that a gallstone impacted at the papilla would prevent pancreatic juice outflow and induce pancreatitis.[1] Subsequently, he surmised that a gallstone may divert the flow of bile into the pancreatic duct with biliopancreatic reflux and resultant pancreatitis—the frequently referred to "common-channel hypothesis."[2] Because of Opie's postulate, elective cholecystectomy has evolved as the treatment to prevent recurrent attacks of gallstone-induced edematous pancreatitis.[3] Recurrent gallstone pancreatitis may occur in 30%–50% of patients by six weeks if the gallbladder remains in situ.[4–6] This risk is highest in the first month after the index case of gallstone pancreatitis.[7] These findings led to the current practice of performing cholecystectomy, once symptoms have resolved, during the initial hospitalization for gallstone pancreatitis.

Although most patients with gallstone pancreatitis develop mild, edematous pancreatitis, approximately 10%–20% of patients manifest pancreatic necrosis with systemic organ failure.[8,9] In these patients with

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severe gallstone-induced, necrotizing pancreatitis, endoscopic retrograde cholangiography (ERC) with endoscopic sphincterotomy (ES) has been shown to provide benefit in select patients.[10–13] Patients with extensive necrosis frequently develop infection and undergo necrosectomy with concomitant cholecystectomy, whereas others undergo cholecystectomy months after the initial attack, or not at all.

A distinct subset of patients with pancreatitis present with mild necrosis associated with fluid collections or extensive peripancreatic regional inflammation, but without organ failure. Typically, these patients resolve their symptoms over 7–10 days, but computed tomography reveals persistent inflammation that likely precludes successful laparoscopic cholecystectomy during the index hospitalization. This presents a management dilemma of either performing open cholecystectomy with potential infection of a peripancreatic fluid collection, or observing the patient and subjecting them to the risk of recurrent pancreatitis. Early operation is associated with more complications and increased treatment of fluid collections or pseudocysts.[14,15] Recently, ERC with ES alone has been proposed as definitive treatment for gallstone pancreatitis in select patients, but long-term follow-up suggests that biliary symptoms requiring cholecystectomy are not infrequent in these patients.[16–18] Therefore, ERC with ES alone does not adequately treat patients with gallstone-induced pancreatitis.

The aim of this study was to determine if in-hospital ERC with ES safely permitted interval outpatient laparoscopic cholecystectomy in patients with moderately severe gallstone pancreatitis. We found that ERC with ES was not associated with recurrent pancreatitis and that nearly all patients had subsequent laparoscopic cholecystectomy.

METHODS

This study was reviewed and approved by the University of North Carolina Committee on the Protection of Human Rights. The medical records of all patients with pancreatitis undergoing cholecystectomy from 1999–2004 at the University of North Carolina Memorial Hospital were reviewed from a computerized index search. From these records, data regarding demographics, clinical course, etiology of pancreatitis, operative and endoscopic interventions, and outcome were extracted from patients. Pancreatitis was defined as an episode of acute-onset, epigastric pain associated with an elevated serum lipase or amylase. The determination of gallstones as the etiology was made by the presence of gallstones or biliary sludge on ultrasound and the absence of alcohol consumption, hyperlipidemia, hypercalcemia, pancreas divisum, or trauma. Moderately severe gallstone pancreatitis was arbitrarily defined by computed tomography findings, including pancreatitis with mild (less than 30%) necrosis but extensive pancreatic and peripancreatic inflammation associated with fluid collections. Patients included in the study did not exhibit any symptoms, signs, or laboratory evidence of systemic organ failure. All patients underwent ERC with ES, were discharged from the hospital, and returned for elective cholecystectomy at least 1 month after ES.

Data are presented as mean plus or minus the standard error of the mean, unless otherwise stated.

RESULTS

Thirty patients, who underwent ERC with ES were discharged home and underwent interval cholecystectomy at least 1 month after the index episode of moderately severe gallstone pancreatitis, were identified (Fig. 1.). Of these patients, 14 were male with a mean age of 52.4 ± 3.5 years (Table 1). Edematous pancreatitis was identified in 77% of patients, whereas minor pancreatic necrosis was found in 23% of patients. Peripancreatitic fluid collections were evident in 12 (40%) patients. Mean bilirubin and serum lipase were 3.5 ± 0.5 mg/dL and 12,009 ± 4,174 IU/dL, respectively.

All patients underwent ERC with ES for gallstone pancreatitis (Table 2). In addition, a concomitant pancreatic duct sphincterotomy was performed in one patient. Biliary stents were placed in six (20%) patients, and both pancreatic and biliary stents were placed in two patients. Common bile duct stones were identified in 18 (60%) patients, and the bile duct was cleared of stones at ERC in all but one patient.

Cholecystectomy was performed in all patients at a mean of 102 ± 17 days after ERC and ES (range, 28–462; Table 3). An open procedure was deemed necessary in three (10%) patients initially thought to be candidates for laparoscopic cholecystectomy, and two (7%) patients underwent conversion from a laparoscopic to an open procedure. Planned open cholecystectomy was deemed necessary in two patients, because a necrosectomy was required concomitantly, and in one patient due to extensive prior right upper quadrant surgery. No patient required operative management of a pancreatic pseudocyst, and the morbidity from interval laparoscopic cholecystectomy was 7% (two patients). Mean and median postoperative length stays for all patients undergoing cholecystectomy were 3 ± 1 days and 1 day, respectively (range, 1–26 days).

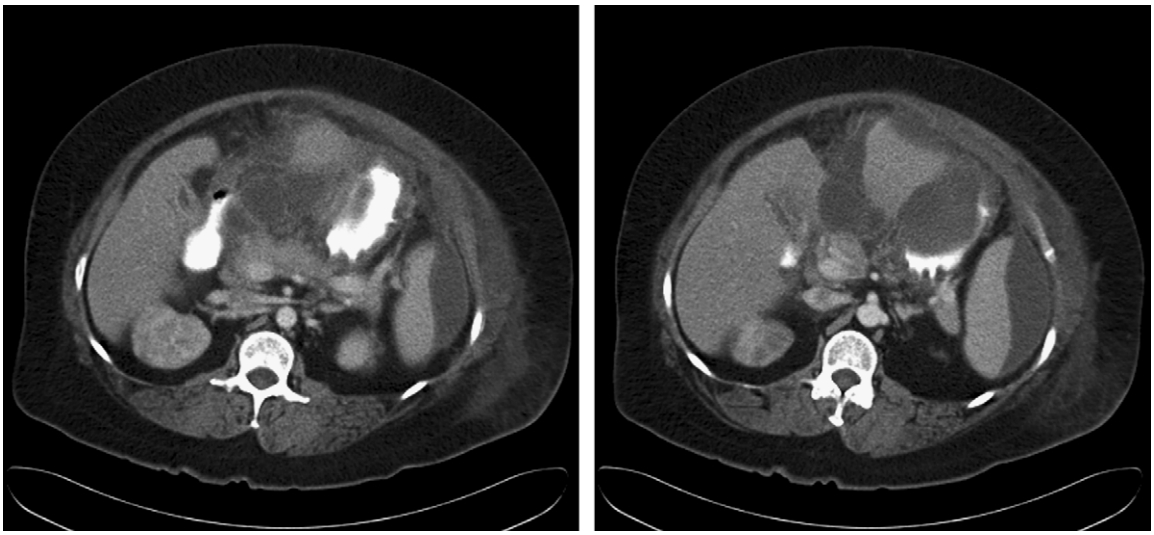

Fig. 1. Representative images from computed tomography of a patient with large peripancreatic fluid collection secondary to gallstone pancreatitis. Fluid is seen occupying the lesser sac and surrounding the spleen. Laparoscopic cholecystectomy was performed safely 56 days after endoscopic sphincterotomy.

Interval complications requiring hospital readmission developed in seven (23%) patients (Table 4). Cholangitis was present in two (7%) patients, with one patient requiring biliary stent removal before laparoscopic cholecystectomy. Abdominal pain, pneumonia, nausea and vomiting, and an infected peripancreatic fluid collection comprised the remaining patients. Importantly, no patient developed signs of recurrent acute pancreatitis. Two patients required endoscopic biliary stent removal, and one patient required biliary stent placement and endoscopic drainage of an infected peripancreatic fluid collection.

DISCUSSION

We hypothesized that ES would protect against recurrent pancreatitis and permit safe interval laparoscopic cholecystectomy in patients with moderately severe gallstone pancreatitis. All patients in this study experienced an episode of moderately severe gallstone pancreatitis, were treated with ERC and ES before discharge, and underwent interval cholecystectomy without evidence of recurrent pancreatitis. Furthermore, no patient required operative management of a pancreatic pseudocyst. Finally, over 90% of patients had successful laparoscopic removal of their gallbladder, but 23% of patients required hospital readmission in the interim between ES and cholecystectomy.

Although the benefit of ERC with ES in patients with severe necrotizing gallstone pancreatitis[10–13] has been established and the limited value of this intervention in edematous pancreatitis is known,[13] no study has assessed the utility of ERC and prophylactic ES in patients with moderately severe gallstone pancreatitis. Patients with moderately severe gallstone pancreatitis have persistent symptoms including abdominal pain, nausea and vomiting, inability to tolerate a diet, and sustained elevation of amylase or lipase and cholestatic liver-associated enzymes. Patients who meet these criteria should undergo a CT scan to look for peripancreatic inflammation

Table 1. Demographics

Number	30
Age (yr)	52.4 ± 3.5
Male/female	14/16
Laboratory Data	
Bilirubin (mg/dL)	3.5 ± 0.5
Lipase (IU/dL)	12,009 ± 4741
Pancreatitis	
Edematous	23 (77%)
Necrotizing	7 (23%)
Peripancreatic fluid collection	12 (40%)

Table 2. Endoscopic interventions

ERC with ES	30 (100%)
Biliary stent	6 (20%)
Pancreatic stent	2 (7%)
Choledocholithiasis	18 (60%)
Clearance of CBD w/ERC + ES	17/18 (94%)

ERC = endoscopic retrograde cholangiography; ES = endoscopic sphincterotomy; CBD = common bile duct.

Table 3. Operative management

Planned open cholecystectomy	3 (10%)
Laparoscopic cholecystectomy	27 (90%)
Conversion to open procedure	2 (7%)
Mean interval from ES to LC (days)	102 ± 17
Range (days)	29–462
Mean postoperative length of stay (days)	3 ± 1
Median	1
Range	1–26
Concomitant procedures	
Necrosectomy	2 (7%)
Pseudocyst drainage	0 (0%)
Complications	2 (7%)

ES = endoscopic sphincterotomy; LC = laparoscopic cholecystectomy.

Table 4. Interval complications

No. of patients with complications (%)	7 (23%)
Complications	
Cholangitis	2 (7%)
Abdominal pain	2 (7%)
Pheumonia	1 (3%)
Infected pancreatic fluid collection	1 (3%)
Nausea and vomiting	1 (3%)
Recurrent pancreatitis	0
Interventions	
Biliary stent removal	2 (7%)
Biliairy stent placement	1 (3%)
Endoscopic drainage of fluid collection	1 (3%)

and/or a fluid collection. In these patients, laparoscopic cholecystectomy at the time of the index admission is technically difficult and is frequently converted to an open procedure.[14,15] Moreover, cholecystectomy at the initial hospitalization may increase the risk of infection in pancreatic and peripancreatic necrosis. Furthermore, existing fluid collections or pseudocysts, which likely would resolve over a longer period of observation, are frequently addressed surgically or percutaneously.[14] For these reasons, we empirically treated patients who had moderately severe gallstone pancreatitis, complicated by regional inflammation, with prophylactic ES to prevent recurrent pancreatitis and permit safe interval laparoscopic cholecystectomy. This approach appeared to be justified, based on literature that documents an exceedingly low (0%–4%) risk of recurrent pancreatitis after ES.[19–21] Additionally, because early cholecystectomy in an inflamed setting is associated with increased morbidity,[14,15] delayed removal of the gallbladder would likely increase the success rate of laparoscopic cholecystectomy and be safer for the patients. However, our protocol deemed eventual cholecystectomy necessary in all fit patients, because numerous studies have shown that patients treated by ES alone have a substantial risk of biliary symptoms that require intervention.[19,22,23] The data in this study confirm our hypothesis that ES can protect against recurrent pancreatitis, and that interval laparoscopic cholecystectomy is feasible and safe in the majority of patients.

Prophylactic ES followed by interval cholecystectomy offers the additional advantage of time for fluid collection or pseudocyst resolution after the onset of moderately severe pancreatitis. Pancreatic fluid collections or pseudocysts complicate acute pancreatitis in 10%–20% of patients, but many of these collections will resolve over time without intervention.[24–26] We chose to follow patients by serial computed tomography to determine resolution of the pseudocyst and found that at a mean of approximately 15 weeks, no patients required concomitant treatment of a pseudocyst at the time of cholecystectomy. Our protocol requires complete CT-proven resolution of peripancreatic fluid collections before laparoscopic cholecystectomy. This approach contrasts with that of Nealon et al.,[14] who found that 60% of patients required pseudocyst drainage at the time of delayed (7 weeks) cholecystectomy. In this study, however, a pseudocyst was arbitrarily deemed persistent at 6 weeks. Our findings suggest that pseudocysts resulting from moderately severe gallstone pancreatitis will resolve over time, and that with careful observation, only laparoscopic cholecystectomy is required after prophylactic ES.

Even though prophylactic ES followed by interval laparoscopic cholecystectomy prevented recurrent pancreatitis, these patients with moderately severe pancreatitis require close monitoring because nearly one quarter were readmitted to the hospital. Most readmissions were related to biliary or pancreatic complications, including infection. Early in our experience, two patients had cholangitis likely related to biliary stent placement at the time of ERC with ES. Currently, we limit biliary stent placement to those patients who have a high likelihood of retained bile duct stones or debris. In addition, these patients may have mild necrosis of the pancreas or peripancreatic fat, and ERC with inadvertent pancreatography may introduce bacteria into the necrosis. In this series, one patient required pancreatic debridement for infected necrosis. Whereas there is reason for concern that ERCP may result in bacterial contamination of pancreatic necrosis and/or pancreatic fluid collections, it was rarely seen in this patient population. In addition, these patients with peripancreatic fluid collections receive prophylactic antibiotics before endoscopic procedures. Furthermore, the infrequent patient with moderately severe pancreatitis will

have persistent abdominal pain, nausea, vomiting, and inability to eat well, thus mandating pancreatic necrosectomy for "failure to thrive."[27] Therefore, although these patients have less advanced disease than patients with severe necrotizing pancreatitis with organ failure, they require careful clinical follow-up to diagnose and treat potential complications.

CONCLUSION

Moderately severe gallstone pancreatitis characterized by local/regional inflammation without organ failure is adequately treated by prophylactic ERC with ES to eliminate the risk of recurrent pancreatitis. Interval cholecystectomy can be accomplished safely by a laparoscopic approach, and with careful long-term follow-up, treatment of associated pseudocysts is infrequent. This approach may transform the approach to moderately severe pancreatitis such that these patients with a life-threatening illness receive only an ERC with ES, and a minimally invasive cholecystectomy without major operations for fluid collections or pancreatitis.

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Does Repeated Surgery Improve the Prognosis of Colorectal Liver Metastases?

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Hepatic resection for colorectal metastases was performed for 188 patients. Overall survival rates after the first hepatectomy are 41.4% and 32.7% for 5 and 10 years, respectively. The survival rate of 116 cases with unilobar hepatic metastases (H1) is significantly higher than those of 48 cases with two to four bilobar metastases (H2) and 24 cases with more than four (H3), respectively. However, the differences between the survival rates from H1 with multiple metastases, H2, and H3 are not significant, even though the H3 group has no 10-year survivors. The 5-year survival rates after the second hepatectomy (30 patients) and the resection of the lung (26 patients) are 30.3% and 35.2%, respectively, in this series. In those patients, the 5-year survival rates from the first metastasectomy are 43.4% and 50.3%, respectively. There are 14 5-year survivors with multiple metastases and 8 of those patients underwent multiple surgeries. There are 13 patients with three or more repeat resections of the liver and/or lung. The 5-year survival rates of the patients from the first and third metastasectomy are 53.9% and 22.5%, respectively. Repeat operations for the liver and the lung contribute to the improving prognosis. (J GASTROINTEST SURG 2006;10:6–11)

KEY WORDS: Colorectal cancer, liver metastasis, hepatectomy, lung metastasis, surgery

Hepatic resection for colorectal metastases has become an established procedure. The application of the procedure should be considered in the first step of the therapeutic strategy, because it is now the only means that can provide the patients a possibility of cure, with a 25–50% 5-year survival rate.[1–4] Furthermore, recent improvements of the surgical techniques reduced the mortality and morbidity, and at present, the application of the procedure tends to be expanding.[5–7] However, there remain several controversies, including the following questions. How does the resection of multiple lesions contribute to the prognosis? How do repeat resections of the recurrent liver metastases contribute to the prognosis? How do the surgical procedures for the extrahepatic lesions, especially the lesions in the lung, improve the prognosis?

We evaluate the impacts of (1) hepatectomy for the multiple lesions, (2) repeat hepatic resections for recurrent liver metastases, (3) metastasectomy for lung metastases, and (4) the results from patients who underwent multiple repeat (more than three) operations, in our series of patients who underwent hepatic resection for colorectal liver metastases.

PATIENTS AND METHODS

Hepatic resection for colorectal metastases, as a complete resection of the lesions, was performed for 188 patients, 221 times, from 1974 through 2004 in our hospital. There was no operative death after hepatectomy during this period. Among them are 96 patients with multiple metastases. There are 116 cases with unilobar hepatic metastases (H1, including 24 cases with multiple metastases: H1-multi), 48 cases with two to four bilobar hepatic metastases (H2), and 24 cases with more than four bilobar metastases (H3). The survival curves of overall

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patients, patients with solitary metastasis, patients with multiple metastases, and in the groups of H1, H1-multi, H2, and H3, after the first hepatectomy, were calculated.

In our series, 30, 26, and 13 patients underwent repeat hepatectomy, pulmonary resection for the metastases (after and/or before the hepatectomy), and multiple repeat (three or more times) resections of the liver and/or lung, respectively. The backgrounds (age, gender, number and size of metastases, time of diagnosis, differentiation, Dukes stage, and lymph-node metastases of original site) of these three groups of patients were compared with those of the other patients, and there were no significant differences, except that the ages of the patients in these three groups are significantly younger than that of the other patients without repeat operations. There is a tendency for repeat surgery groups to have more synchronous patients, but it is not significant (Table 1). The survival curves of the patients with repeat hepatectomies, pulmonary resection, and multiple repeat resections, after the first and the last resection of the metastases, were calculated.

Statistical Analysis

For deceased patients, the cause of death was determined based on data from their medical records. Survival curves were constructed using the Kaplan-Meier method. Mortalities from other causes were treated as censored cases. Differences in survival were evaluated using the log-rank test. All statistical evaluations were performed using SPSS 8.0J (SPSS Japan Inc., Tokyo, Japan) software package. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Overall survival rates of cases after the first hepatectomy are 41.4% and 32.7% for 5 and 10 years, respectively (Fig. 1).

Multiple Metastases

The 5- and 10-year survival rates of patients with multiple liver metastases are 28.5% and 18.8%, respectively, and significantly lower than those of patients with a solitary metastasis (Fig. 2). The survival rates of H1 cases are 50.9% and 44.4% for 5 and 10 years and significantly higher than those for the H2 and H3 cases. However, the differences between the survival rates from H1-multi, H2, and H3 are not significant, even though the H3 group has no 10-year survivors (Fig. 3). Although four H3 patients actually survived more than 5 years with repeat metastasectomies and chemotherapy, two of them died of recurrence after 5 years.

Repeat Metastasectomies

Repeat metastasectomies include repeat hepatectomy, pulmonary resection after and/or before hepatectomy, and multiple (three or more times) repeat surgeries for the liver and/or the lung. The 5-year survival rates after the second hepatectomy and pulmonary resection are 30.3% and 35.2%, respectively (Figs. 4 and 5). The 5-year survival rates from the first metastasectomy in those two groups are 43.4% and 50.3%, respectively, which are higher than overall survival after the first hepatectomy (Figs. 4 and 5). The 5-year survival rates for patients with multiple repeat surgeries from the first and third

Table 1. Summary of the backgrounds of patients without repeat surgery (Group A: 139 patients), with repeat hepatectomy (Group B: 30 patients), with pulmonary resection (Group C: 26 patients), and with multiple repeat (>3 times) resections (Group D: 13 patients)

	Group A*	Group B	Group C	Group D
Age (yr)	60.9 ± 10.6	56.2 ± 10.3	55.5 ± 8.34	54.0 ± 8.51
Gender (M/F)	97:42	23:7	19:7	11:2 NS†
Primary lesions (n)				
Site (colon-rectum)	75:64	16:14	10:16	6:7 NS†
Histology (well-others)	87:52	20:10	14:12	8:5 NS†
Lymph node (no or para-lesional metastases-beyond para-lesional metastases)	96:43	23:7	16:10	9:4 NS†
Dukes stage (A or B-C)	49:90	8:22	8:18	9:4 NS†
Metastatic lesions (n)				
Synchronous-metachronous	58:81	19:11	14:12	8:5 NS†
Solitary-multiple	69:70	15:15	12:14	7:6 NS†
Tumor size (<3 cm ⩾ 3cm, <5 cm ⩾ 5 cm)	57:46:36	18:9:3	11:7:8	7:3:3 NS†

*Group A had a significant higher age than the other three groups: $P < 0.05$ calculated with Student's t test.
†With χ^2 test.

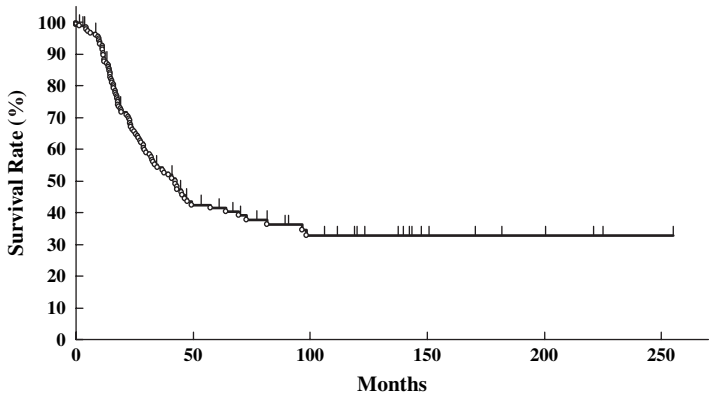

Fig. 1. Overall survival rates of cases after the first hepatectomy are 41.4% and 32.7% for 5 and 10 years, respectively.

metastasectomy are 53.9% and 22.5%, respectively (Fig. 6). Among 134 patients more than 5 years after the hepatectomies, 40 patients survived longer than 5 years. They include 14 cases with multiple metastases from a total of 69 cases, and 8 of those 14 patients underwent repeat surgeries.

DISCUSSION

It is reported that almost half of patients with colorectal carcinoma will eventually develop liver metastases[8] and resection is the only treatment that offers chances of long-term survival or a cure at the present. Since recent improvements of surgical techniques reduced the mortality and morbidity, the application of the procedure tends to be expanding.[5,6] Although prognostic factors had been indicated and used as criteria of eligibility for surgery in the past, nowadays, a more liberal attitude that the main criterion should only be complete resectability of the tumors, prevails.[7] We should now evaluate the benefits of aggressive surgery, such as resection of multiple metastases and repeat metastasectomy for intra- and extra- (especially lung) hepatic recurrent metastases.

Our data show, as in previous reports, that the survival rate of patients with multiple liver metastases is significantly lower than that of patients with a solitary metastasis. However, 5- and 10-year survival rates are not negligible, and the fact that quite a few patients with multiple metastases actually survived more than 5 years after the hepatectomy encourages application of that procedure for those patients, since long-term survival is hardly obtained by other modalities. According to the classification of Japanese Society for Cancer of the Colon and Rectum, unilobar, two to four bilobar, and more than four bilobar liver metastases are classified as H1, H2, and H3, respectively.[9] This classification is supposed to reflect the number and location of the metastases. Because the survival rates are not significantly different between H1-multi, H2, and H3 groups in patients with multiple metastases, the number and the location of the metastases are not

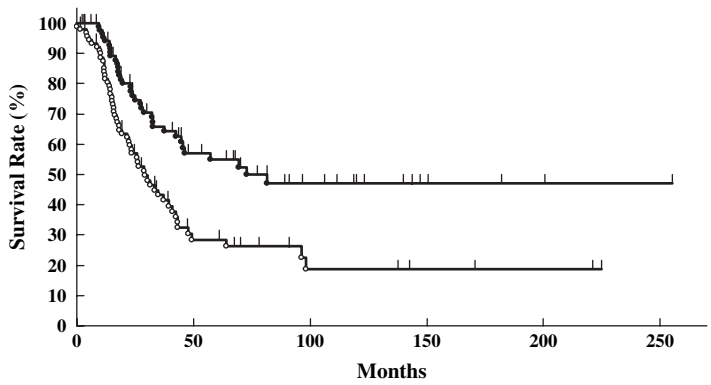

Fig. 2. The 5- and 10-year survival rates of the patients with multiple liver metastases (*open circle*) are 28.5% and 18.8%, respectively, and are significantly lower than those of the patients with solitary metastasis (*closed circle*) ($P < 0.001$).

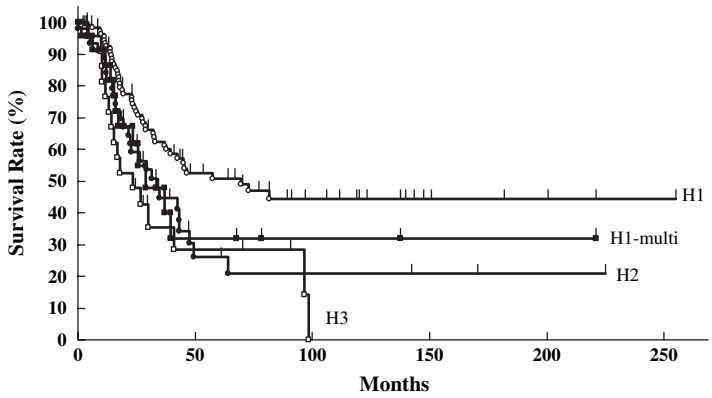

Fig. 3. The survival rates of H1 cases (*open circle*) are 50.9% and 44.4% for 5 and 10 years, respectively, and significantly higher than H2 (*closed circle*) and H3 (*open square*) cases ($P < 0.05$). However, the differences between the survival rates from H1-multi (*closed square*), H2, and H3 are not significant, even though H3 group has no 10-year survivors. H1 = 116 cases with unilobular hepatic metastases (including 24 cases with multiple metastases: H1-multi); H2 = 48 cases with four or fewer bilobular hepatic metastases; H3 = 24 cases with more than four bilobular metastases.

significant prognostic factors in patients with multiple metastases in our series. However, H3, the group with patients who died of recurrence after 5-year survival and without any 10-year survivors, might be a poor factor for long-term survival of more than 5 years. For these (H3) patients and patients with advanced diseases in the aspect of the primary lesion, multidisciplinary treatments, including adjuvant and/or neoadjuvant chemotherapy combined with surgery, should be taken into consideration.[4,10,11]

We previously reported that using computed tomography during angiography as a preoperative evaluation improves the rate of detection of minute metastases and the rate of nonrecurrence in the liver.[12] However, detecting minute metastases did not lead to improving the actual survival rate in this series (data not shown). Although the patients with recurrences only in the liver are supposed to benefit from the examinations, they compose only one third of all recurrent patients[3] and tend to undergo repeat hepatectomy. For the patients with multiple metastases, a strategy would be needed that can deal with extrahepatic, usually overlooked small metastases and intrahepatic micrometastases, below the recognition level of imaging diagnosis. Positron emission tomography–computed tomography might be a useful means for the detection of extrahepatic small metastases.[13,14] Neoadjuvant chemotherapy might also be useful for selection of a candidate for interval surgery and the control of micrometastases below the recognition level, which can lead to postoperative recurrences.[15–17]

In this series, a specific regimen of adjuvant chemotherapy was not used for the patients. However,

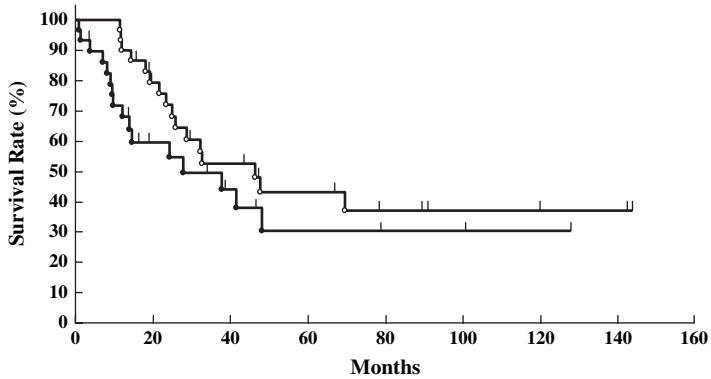

Fig. 4. The 5-year survival rate after the second hepatectomy (*closed circle*) is 30.3%. The 5-year survival rate from the first metastasectomy in this group of patients (*open circle*) is 43.4% and higher than overall survival after the first hepatectomy.

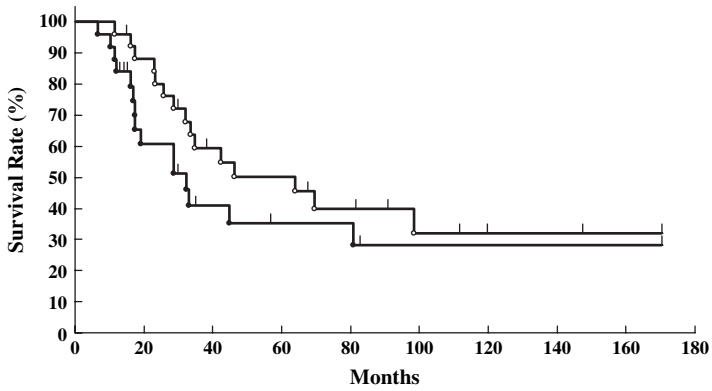

Fig. 5. The 5-year survival rate after the pulmonary resection (*closed circle*) is 35.2%. The 5-year survival rate from the first metastasectomy in this group of patients (*open circle*) is 50.3% and higher than overall survival after the first hepatectomy.

adjuvant chemotherapy (mostly oral and, in some cases, intravenous or transarterial) using 5-FU and related agents were undertaken for most cases. CPT-11 and oxaliplatin were not used in adjuvant chemotherapies in this series. A report says hepatic arterial infusion after liver resection affected the long-term survival of the patients.[18] In our series, patients with multiple metastases tend to receive "heavier" adjuvant therapy (intravenous, transarterial), and it is possible that their survival was affected by the therapies. However, in our series, the number of the patients with hepatic arterial infusion was small and the impact of the adjuvant therapy is thought to be limited. The effect of various adjuvant chemotherapies should be a subject for further investigation.

Repeat resections of liver and lung metastases contribute to improved prognosis.[19–21] The survival after repeat operations was comparable to that after the first hepatectomy or the first pulmonary resection. Interestingly, the 5-year survival rate from the first operation in those groups of patients with repeat surgeries was higher than the overall 5-year survival rate after the first surgery. Also, the 5-year survival rate from the first operation in the patients with multiple (three or more) repeat operations was much higher, even though the number of the patients was small. Limited to the liver and the lung, repeat surgery had a "pile-up effect" on the survival rate. The survival curve after the first operation for the patients who underwent repeat operations shifts to the "right" compared with the overall survival curve. Eight of 14 patients with multiple metastases, who actually survived more than 5 years, had undergone repeat operations. However, the longer (10 or more years) survival for those patients tends to be equal to overall survival. That fact may mean that, in many cases, the procedures only extend survival and do not provide cure. Also, this beneficial effect of repeat surgery is partially due to the selection of patients who can undergo repeat surgery without other noncurative factors and who are of a younger age. However, a number of people did undergo repeat surgery,

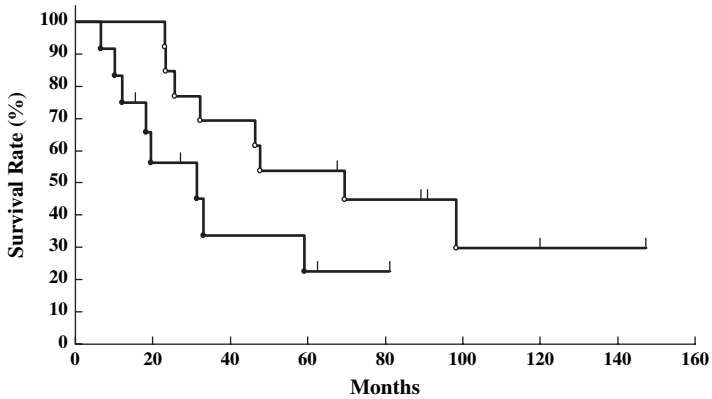

Fig. 6. The 5-year survival rates of the patients from the first and third metastasectomy are 53.9% (*open circle*) and 22.5% (*closed circle*), respectively.

and the procedure benefits them either with or without complete cure of the disease.

CONCLUSION

From our data, complete surgical resection of colorectal liver metastases offers a cure for around 30% of overall patients and around 20% of patients with multiple metastases. Repeat operations improve the prognosis. Furthermore, repeat operations on liver and lung add an extending effect on survival of the other patients without providing a cure. At present, a strategy that aims for long-term survival using repeat operations combined with adjuvant therapies (i.e., adjuvant and/or neoadjuvant chemotherapies) is recommended for those patients.

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Assessment of Diaphragmatic Stressors as Risk Factors for Symptomatic Failure of Laparoscopic Nissen Fundoplication

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An important limitation of antireflux surgery is a 5%–10% failure rate. We investigated the correlation between various diaphragm stressors and failure of antireflux surgery. Forty-one study cases who underwent a reoperative antireflux operation from 1997 to 2001 and 50 control patients who had undergone a successful laparoscopic Nissen fundoplication during the same period without clinical or symptomatic evidence of failure were randomly selected for comparison. A retrospective analysis was conducted utilizing a standardized diaphragm stressor questionnaire, addressing the period between the primary and secondary operation. Stressors considered in the study included height, body mass index (BMI), postoperative gagging, vomiting, weight lifting (greater than 100 pounds), coughing, hiccuping, motion sickness, retching, belching, antidepressant use, smoking, preoperative grade of esophagitis, size of hiatal hernia, lower esophageal sphincter pressure, esophageal body pressures, and preoperative response to proton pump inhibitors. Of the potential stressors investigated, the following were significantly associated with surgical failure after adjusting for other variables through multivariate analysis: gagging ($P = 0.005$), belching ($P = 0.02$), and hernia size greater than 3 cm ($P = 0.04$; Table 1). Other potential risk factors show trends as obvious in Fig. 2. Vomiting was significant ($P = 0.01$) in the earlier models but lost significance when logistic regression was applied. Patients with postoperative gagging and an intraoperative hiatal hernia (greater than 3 cm) have a poorer outcome, whereas patients with postoperative belching have a better long-term outcome. (J GASTROINTEST SURG 2006;10:12–21)

KEY WORDS: Diaphragmatic stressors, failed antireflux repair, failed Nissen fundoplication

The surgical management of gastroesophageal reflux disease (GERD) has improved with a better understanding of the underlying pathophysiology of the disease and technical refinements of the antireflux repair.[1] However, the failure rate of all antireflux procedures, both open and laparoscopic, is reported to be 10%, ranging from 3%–30%.[1–6] The most common pattern of fundoplication failure is anatomical; this includes fundoplication disruption, crus closure failure, paraesophageal hernia formation, a slipped Nissen, and a too tight fundoplication.[7,8]

Recent studies have shown that a sudden increase in the intra-abdominal pressure, such as lifting a heavy object, motor vehicle accidents or bouts of coughing and/or vomiting, can precipitate anatomical failure of the fundoplication and symptom recurrence.[9–11] In addition, large hiatal hernias, early postoperative vomiting, and obesity may result in the anatomic failure of laparoscopic antireflux surgery.[2,8,12] The purpose of this study is to objectively identify factors that predispose to antireflux surgical failure.

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MATERIAL AND METHODS

A retrospective case-control study was completed to determine the influence of diaphragm stressors on antireflux surgery failure by retrospectively analyzing the data accumulated by a standardized telephone questionnaire. Forty-one study cases that underwent reoperative antireflux and recurrent hiatal hernia surgery and 50 control group patients without clinical or symptomatic evidence of failure after primary antireflux surgery were evaluated. Control patients were all operated upon by the senior author C. J. F., and their selection was based on patient availability, operative date (at least 18 month follow-up), and ability of the patient to reliably complete the phone interview. The phone questionnaire was administered after the primary surgery to assess the stressors involved (Table 1).

Study Characteristics

Postoperative stressors considered in the study included gagging, vomiting, induced vomiting, lifting weights (greater than 100 pounds), coughing, hiccuping, body weight, height, body mass index (BMI), motion sickness, retching, belching, antidepressant use, and smoking. Objective assessment of the preoperative degree and severity of the disease process was determined by preoperative grade of esophagitis (on endoscopy), size of hernia (if any), lower esophageal sphincter pressure, esophageal body pressures, and preoperative response to proton pump inhibitors (PPIs). The Savary-Miller classification was used to assess the grade of esophagitis (grade I, one or more nonconfluent mucosal lesions with or without exudate or superficial erosions; grade II, confluent erosions; grade III, circumferential erosions; and grade IV, ulceration, peptic stricture, Barrett's esophagus, mural fibrosis, or short esophagus.)

Inclusion Criteria

All patients within the control group underwent a primary laparoscopic Nissen fundoplication (LNF) for GERD at Creighton University Medical Center and demonstrated no symptomatic evidence of failure at 1.7 or more years of follow-up (mean 2.8 years). The control group patients were chosen from a pool that had undergone a previous LNF by the senior author (C. J. F.) and were not matched or temporally related to the study group. All patients within the study group had a hiatal hernia after

Table 1. Study questionnaire

Questions	Before 1st operation	Before 2nd operation
1. Do you gag when you brush your teeth?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
2. Do you induce vomiting?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
3. Do you vomit frequently?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
4. Do you frequently lift heavy objects?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
5. Do you cough frequently?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
6. Do you hiccup frequently?	Yes No __times per day/week/month	Yes No __times per day/week/month
7. What is your current weight?		__lbs.
8. Are you on an antidepressant medication?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
9. Do you suffer with motion sickness?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
10. Do you retch when you swallow solid food?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
11. Do you retch when you swallow liquids?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
12. Do you retch shortly after you eat?	Yes__ No__ __times per day/week/month	Yes__ No__ __times per day/week/month
13. Do you smoke?	Yes__ No__	Yes__ No__
14. Do you belch often?	Yes__ No__	Yes__ No__

a previous LNF and were reoperated upon by either of two coauthors (C. J. F. or S. K. M.).

Exclusion Criteria

All adult patients that had undergone a primary open laparotomy, a thoracic repair, an associated myotomy for achalasia, placement of an Angelchik prosthesis, a laparoscopic Hill or Toupet fundoplication were excluded.

Preoperative Assessment

All patients underwent upper endoscopy and manometry. Upright esophagograms and 24-hour pH monitoring were performed selectively. Proof of a postoperative hiatal hernia in the study group was obtained retrospectively by review of the operative notes. The patient's response to PPIs was assessed by the degree of preoperative symptom improvement.

All patients on antidepressants (n = 24) were assessed separately so as to determine indications for surgery. Indications in this subgroup were pain secondary to incarcerated hernia (n = 4), recurrent symptoms refractory to medication (n = 12), unwillingness to take life-long medications (n = 5), and a combination of the above (n = 3). Associated respiratory symptoms were present in 6 out of 24 patients.

Radiographic technique for hiatal hernia measurement. Hiatal hernia size was determined preoperatively by an upright esophagogram. A full chest anterior-posterior esophagogram view was obtained with a superimposed centimeter ruler. The distance from the extrapolated hemidiaphragm confluence at the midline to the gastroesophageal junction was measured.

Surgical Indications

Patients with uncontrollable symptoms underwent reoperative surgery. Objective findings on testing were correlated with symptomatology. Esophageal dilation was performed preoperatively in patients with dysphagia. Chest pain secondary to hiatal hernia formation was differentiated from GERD by 24-hour pH monitoring.

Surgical Technique: Laparoscopic Nissen Fundoplication

Control group. Five-millimeter trocars were placed through the abdominal wall and both limbs of the right diaphragmatic crus were dissected. The short gastric vessels, including posterior short gastric vessels, were divided using a harmonic scalpel (Ethicon Endosurgery, Cincinnati, OH). A Penrose drain was passed around the distal esophagus and the crural defect was closed using interrupted nonabsorbable sutures, after which a 60 French bougie was passed into the stomach to assure proper tightness of the crural closure. A portion of the fundus was pulled by a Babcock clamp behind the esophagus and then released to determine if sufficient laxity had been gained. The Penrose drain was removed and a 60 French bougie was again introduced into the stomach. A 2-0 Prolene U stitch was used for the fundoplication. An additional 3-0 silk suture was passed through the right and left plication limbs to complete the 1.5 cm fundoplication. The pneumoperitoneum was allowed to escape, and all wounds were closed with subcuticular absorbable sutures.

Postoperative management. All patients in the control and the study group were routinely given intravenous antiemetics in the operating room and during hospitalization. No postoperative nasogastric decompression was used for control group patients. A clear liquid diet was routinely initiated within the first 24 hours, and the diet was gradually advanced thereafter. A Zofran (ondansetron hydrochloride) and Reglan (metoclopramide) prescription was given to all patients at hospital discharge. Patients were instructed to call their physician if any uncontrollable nausea, dry heaving, or vomiting occurred.

Study Group

The primary LNF technique for the reoperative study group varied significantly, and the operative note was not always available for review. The experience of the operating surgeon for the study group was not obtained. The postoperative care regimen was not retrieved; however, the questionnaire addressed the diaphragm stress factors active during the postoperative period. All patients in the control group and nine patients in the study group were primarily operated upon by the senior author C. J. F. All patients in the study group had a hiatal hernia as determined by operative notes. Not all hernias led to the primary indication for surgery, but were, at the least, associated with the failure.

Administration of questionnaire. All patients were followed up by office visits and phone calls. The questionnaire (Table 1) was administered to all reoperative patients and addressed the period between the primary and secondary operation. The control group questionnaire was administered 1.7 or more years after the LNF and assessed the postoperative period. A standard questionnaire (Table 2) to determine symptom management within both groups,

plus a random group of 76 preoperative GERD patients, was used.

Statistical analysis. Data was maintained on an Excel spreadsheet, and statistical analysis was performed using Intercooled Stata Version 7.0 (Stata Corporation, Houston, TX). All predictors were recorded as "Yes" or "No", except for age, sex, weight, height, BMI, and the objective assessors of the disease severity, which included grade of esophagitis, size of hernia, lower esophageal sphincter pressure, esophageal body pressures, and preoperative response to PPI. The alpha level for the entire analysis was set at 0.05, and all tests were two-sided. The univariate analysis was performed using the unpaired *t* test, chi-square test, the Fisher exact modification, and the Wilcoxon rank sum (Mann-Whitney two sample) test, when appropriate. Multivariate analysis was done using logistic regression modeling. Model checking was performed using the standard tests for the form of the linear predictor, the Hosmer-Lemeshow test for goodness of fit (systematic errors) and rechecking the model after excluding highly influential points. Correlation between variables was checked without using the Bonferroni correction.

RESULTS

Baseline Characteristics

Our sample consisted of 41 patients who underwent laparoscopic reoperative antireflux surgery for a failed Nissen fundoplication and 50 patients who had no clinical or symptomatic evidence of failure, until at least 18 months after primary antireflux surgery. The baseline characteristics in the two groups were similar, with the mean age being 50 years in the case group (range, 29–75) and 52 years (range, 16–78) in the control group ($P = 0.6$). There were 39% males in the case group, and 38% males in the control group ($P = 0.92$), and the average BMI was slightly higher in the case group, 31 kg/m^2 (range, 25–41), as compared to 30 kg/m^2 in the control group (range, 19–41). A comparison of all baseline characteristics has been shown in Table 3. The mean duration between primary and redo surgery in the study group was 3.12 years (range, 0.4–6.2 years), whereas the mean duration of follow-up in the control group was 2.87 years (range, 1.7–4 years).

Stressors

Of the potential stressors investigated, preoperative hernia size greater than 3 cm, postoperative gagging, and decreased belching were found to be associated with failure of reflux surgery after adjusting for other variables through multivariate analysis (Table 4). Comparison of stressors between the case group and the control group has been illustrated in Figs. 1 and 2.

Gagging. Postoperative gagging was measured as number of episodes per week, and we found that 29% (range, 15%–43%) of patients in the study group and 8% (range, 0.4%–15%) of the control group had gagging postoperatively ($P = 0.03$; Fig. 1). Only one patient who had gagging also induced vomiting.

Vomiting. Early postoperative vomiting, which has previously been shown to have significant association with failure, was significant only in the univariate analysis (4% vs. 12%, $P = 0.01$). Induced vomiting was present in only 3.3% of our sample, and this behavior was not associated with failure of surgery or with other comorbidities like retching ($P = 0.57$, chi-square) or antidepressant medication use ($P = 0.56$, chi-square).

Retching. Postoperative retching was strongly correlated with vomiting ($r = 0.4$, $P = 0.0001$), and there was a higher percentage of patients who retched in the case group compared to the control group (32% vs. 18%), though this difference was not statistically significant ($P = 0.15$).

Other mechanical stressors. Including postoperative hiccups, coughing episodes per week and weight lifting per month were not significant in the analysis. Upon analyzing the relationship between body pressure and these variables in each group, we found no statistical association ($P > 0.20$ by chi-square) or correlation ($r = -0.11$ for hiccups, $r = 0.11$ for cough, $r = 0.02$ for weight lifting, $P > 0.2$). The percentage of patients with depression amongst the control group and the case group was not statistically different (23% vs. 29%, $P = 0.6$).

BMI. Preoperative BMI has been quoted as an independent predictor of failure in previous studies, whereas we did not find a significant difference between the two groups ($P > 0.2$). We found that in those shorter than 165 cm, there was some evidence to suggest that shorter people were associated with less failure to surgery (OR = 0.87 [range, 0.74–1.0], $P = 0.07$).

Belching. Early postoperative belching demonstrated an inverse association with risk for failure, with belching being more common in the control group than in the case group (40% vs. 20% control group). Belching was not associated with increased body pressures ($P = 0.8$) within the group.

Grade of esophagitis. Although the preoperative grade of esophagitis, as related to surgical failure, did not reach statistical significance ($P = 0.8$), there was a gradual transition from a negative odds ratio (0.96, decreased risk) for an esophagitis grade of

Table 2. Questions used for symptom assessment

	Heart burn	Chest pain	Regurgitation	Nausea/vomiting	Dyshagia	Odynophagia	Others
Grading	0	None	0 None	0 None	0 None	0 None	
	1	Minimal Occasional episodes, no Rx required	1 Mild After straining or large meals	1 Occasional episodes of nausea	1 Minimal Occasionally with coarse foods	1 Yes	
	2	Moderate Controlled with medication	2 Moderate Predictable, with position change/lying down/straining	2 Frequent nausea or episodic vomiting	2 Moderate Requires clearing with liquids		
	3	Severe Constant, marked disability, not controlled with medication	3 Severe Constant regurgitation ± aspiration	3 Continuous nausea or frequent vomiting	3 Severe Semiliquid diet, meat impaction		
Medications							
Name							
How often?							
Duration between procedure and symptoms							
Subjective surgery outcome							
Excellent							
Good							
Fair							
Poor							
Dilations performed							
Number							
Size of dilator							

Table 3. Baseline characteristics and predictor variables classified by subgroups used in univariate analysis

Factors	Controls (N = 50)	Study group (N = 41)	*P* value
Age[‡]	52	51	0.6
Sex[¶]			
Male	19	16	0.92
Female	31	25	
BMI[‡]	29.8 (4.9)	31.1 (5)	0.24
Weight (lbs)[‡]	182 (29)	193 (28)	0.08
Height (inches)[‡]	65.5 (3.5)	66.2 (4.8)	0.4
LESP (mean)[†,‡,‖]	5.1 (0.6)	5.5 (0.8)	0.6
Body pressure[†,‡,††]	2 (1–3)	2 (1–3)	0.54
Grade of esophagitis (0–4)[§,‡]	0 (0–4)	0 (0–4)	
Patients with esophagitis[¶]			
0	25 (50%)	22 (54%)	
1	6 (12%)	5 (12%)	
2	12 (24%)	4 (10%)	
3	4 (8%)	2 (5%)	
4	1 (2%)	5 (12%)	0.8
Smoking[*,¶]			
Smoker	9 (18%)	4 (10%)	
Ex-smoker	16 (32%)	11 (27%)	
Nonsmoker	25 (50%)	26 (63%)	0.4
Coughing[*,¶]	14 (28%)	16 (39%)	0.4
Gagging[*,¶]			
At least once/wk	4 (8%)	12 (29%)	
Never	46 (92%)	29 (71%)	0.01**
Weight Lifting[*,¶] (>100 lbs)	10 (20%)	12 (30%)	0.32
Vomiting[*,¶]			
At least once/wk	4 (8%)	12 (29%)	
Never	46 (92%)	29 (71%)	0.01**
Induced vomiting[*,¶]	1 (2%)	2 (5%)	0.58
Hiccups/wk[*,¶]	10 (20%)	5 (13%)	0.40
Retching/wk[*,¶]	9 (18%)	13 (32%)	0.15
Belching/wk[*,¶,#]	20 (40%)	8 (20%)	0.06
Motion sickness[†,¶]	8 (16%)	4 (10%)	0.5
Antidepressant usage/day[†,¶]	11 (23%)	12 (29%)	0.6
Response to PPIs preoperatively[¶]			
Good	19 (42%)	9 (24%)	
Poor	13 (28%)	16 (42%)	0.3
Never taken	5 (12%)	3 (10%)	
% with hiatal hernia[†]	82%	78%	NS
Hiatal hernia size[†,¶]			
⩽ 3 cm	33 (75%)	17 (50%)	
> 3 cm	11 (25%)	17 (50%)	0.032**

NS = not significant; LESP = lower esophageal sphincter pressure; PPI = proton pump inhibitors.
*All factors considered in the immediate postoperative period.
[†]Factors considered before primary surgery in both groups.
[‡]Values reported as mean (standard error) except grade of esophagitis and body pressure reported as median (range).
[§]Two sample *t* test used; Wilcoxon rank sum test was used for grade and body pressure.
[‖]N = 33.
[¶]Values represented by n (%). Chi-square test and Fisher exact test used to test significance.
[#]Belching although was near-significant in the univariate analysis, was significant at $P = 0.02$ in the multivariate analysis.
**Significant at alpha 0.05.
[††]Body pressures categorized as 1 = low, 2 = normal, and 3 = high.

Table 4. Logistic regression model

Variable	Odds ratio (95% CI)	*P* value
Grade of esophagitis (0–4)	0.93 (0.62–1.42)	0.76
Height[†]		
<165 cm	0.87 (0.74–1.0)	0.07
>165 cm	1.06 (0.97–1.16)	0.20
Hernia size >3 cm	3.17 (1.04–9.69)	0.04*
Belching/wk	0.22 (0.06–0.82)	0.02*
Gagging/wk	10.4 (2.0–54.0)	0.005*
Smoking status (smoker, ex-smoker, nonsmoker)	0.58 (0.25–1.38)	0.22
Weight (kg)	1.02 (0.98–1.07)	0.33

*Significant at alpha 0.05. Smoking assumed to have a dose response effect, odds of smoker/ex-smoker = odds of ex-smoker/nonsmoker. Hence, odds of smoker to nonsmoker = 0.58 = 0.34. Separate models for individual testing of the three categories were also performed.
[†]Height was divided into spline terms at 165 cm (or 5ft 5in). This is a continuous variable.

0 to a positive ratio (1.44, increased ratio) for a grade of 4, which was logical.

Hernia size. Hernia size has previously been described as a risk factor, and we found that patients with preoperative hiatal hernias greater than 3 cm were associated with failure after antireflux surgery (OR = 3.17, $P = 0.04$). Although the percentage of patients with a hiatal hernia preoperatively was higher amongst the control group than the study group (82% vs. 78%), the number of patients with hernia of more than 3 cm in size was significantly higher in the study group.

Response to proton pump inhibitors. Only 41 patients in the study group and 33 patients in the control group had data available. The analysis with this limited data set revealed more patients with a good response to PPIs in the control group (46% in the control group vs. 27% in the study group). The odds ratio for risk of failure with improving response to PPIs is 0.69 (95% CI = 0.48–1.0, $P = 0.05$).

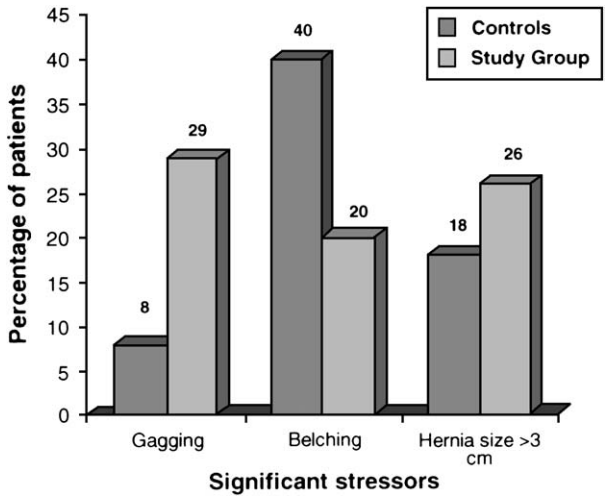

Fig. 1. Comparison of significant predictors of antireflux surgical failure between the control group and the study group.

Frequency of stressors. The study group had a higher percentage of patients with more frequent vomiting and retching (12% and 15%, respectively, greater than five times/month), whereas those in the control group had almost 22% of the population with a higher frequency of belching (greater than five times a month; Table 5).

There was no interaction between gagging and retching (interaction term $P = 0.89$, likelihood ratio test). We do believe that patients may sometimes confuse gagging and retching, and we performed an analysis by combining both gagging and retching into a single variable. On combining them, we found that the odds ratio for surgical failure, when either gagging or retching was present, was 3.06 (range, 0.97–9.6, $P = 0.05$). This odds ratio is lower than that for gagging alone in our model (10.4; range, 2.0–54.0, $P = 0.005$).

To further validate our study, a random group of 76 preoperative GERD patients appearing at our clinic were presented with the questionnaire to compare the prevalence of significant stressors in the general GERD population with those included in this study and to better understand the incidence of frequent gagging in GERD patients. This showed that 22% of these patients (vs. 8% in the control group and 32% in the study group) had gagging, 50% (vs. 40% in the control group and 19% in the study group) had belching, and 9% had vomiting (vs. 8% in the control group and 29% in the study group), which is comparable to our data.

Most believe that the short esophagus and Barrett's esophagus are risk factors for antireflux surgery failure. Twenty percent of patients in our study group had Barrett's esophagus before reoperation, and five patients (12%) had a Collis gastroplasty during reoperation, suggesting that a short esophagus was present at the time of the initial operation. The proportion of both of these conditions is much higher than usually reported; however, our study was not powered sufficiently to detect statistical differences between the case and control groups for these risk factors.

DISCUSSION

This study demonstrates that gagging and moderate to large hiatal hernias (greater than 3 cm) are significant risk factors for failure of antireflux surgery,

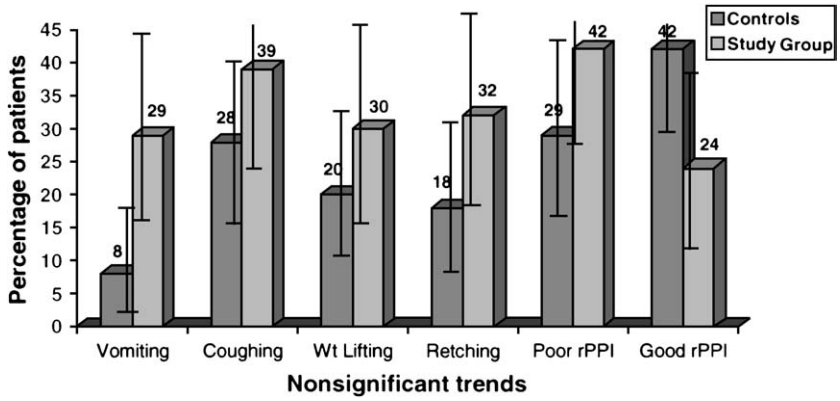

Fig. 2. Nonsignificant trends in predictors of antireflux surgical failure between the control group and the study group.

and belching is a predictor associated with a favorable outcome. Vomiting has some significance, but loses it when gagging and other stressors are added to the multivariate model. Coughing, retching, weight lifting (greater than 100 pounds), and grade 3 and 4 esophagitis are potential risk factors for failure, but none achieved statistical significance in our study.

Fundoplication is commonly complicated by abdominal bloating.[13] Although postfundoplication difficulty in belching has been shown to be a complication of surgery, previous studies have not used postoperative belching as a prognostic indicator for surgical outcome. The inverse association of belching with failure can probably be attributed to lower chronic intragastric and intra-abdominal pressures in this patient population. This raises a concern for the postoperative prognosis of patients with aerophagia.

Some studies have reported gagging as a postoperative complication, but its importance as a predictor of surgical outcome has never been recognized. In our study, it is the strongest of all diaphragm stressors investigated (OR = 10.4). Whether gagging in the immediate postoperative period is a complication of surgery, or a behavior developed over a period of time contributing to the underlying disease itself, is yet to be determined.

Vomiting, retching, and coughing failed to achieve statistical significance by multivariate analysis (Fig. 2). Because both vomiting and coughing are significantly associated with gagging by chi-square tests, we could hypothesize that their direct effect, if any, is being decreased after adjusting for other variables. In this study, 13.3% of patients who did not gag and 37.5% of those who did gag also vomited ($P = 0.03$). Similarly, 56.2% of patients with cough, whereas 28% of those without cough, also had gagging ($P = 0.041$). Moreover, both vomiting and coughing had a weak correlation with gagging in our study (vomiting and gagging $r = 0.24$, $P = 0.02$; coughing and gagging $r = 0.23$, $P = 0.02$). The role of vomiting and coughing as independent stressors might achieve significance with a larger study population.

Similarly, weight lifting more than 100 pounds was nonsignificant; a trend toward more patients lifting weight (greater than 100 pounds) is shown in Fig. 2. A significant trend toward higher weights being lifted was seen in the study group, but this observation was skewed by a few influential observations.

Our previous retrospective data has shown that early postoperative vomiting, events that increase intra-abdominal pressure, and surgeon inexperience are risk factors for hiatal hernia recurrence.[10,11] Caniano et al.[14] reported that 29% of failed laparoscopic Nissen fundoplications in children were due to forceful emesis, and most of them had crural disruption as the underlying cause. Postoperative retching is documented as a major problem in neurologically impaired children and has been reported as a cause of antireflux surgical failure in three patients.[15] It has been suggested that fundoplication may sensitize the emetic reflex because animals have been shown to respond to a previously subemetic dose of a centrally acting opiate receptor agonist such as Imodium (loperamide).[16] Orringer et al.[17] showed a significantly higher recurrence rate if the procedure was performed by residents as compared to staff surgeons. This highlights the importance of vomiting, retching, and the experience of the surgeon in avoiding surgical failures, and also the need for paying meticulous attention to suture placement, knot tying, complete dissection, and a tension-free closure of the diaphragm.

It is conventional wisdom that vomiting needs to be avoided in the early postoperative period as the fundoplication can herniate into the mediastinum,

Table 5. Causes of LNF failure

Known	1. Postoperative vomiting[†]
	2. Postoperative gagging[*]
	3. Postoperative failure to belch[*]
	4. Preoperative large hiatal hernia (>3 cm)[*]
	5. Obesity
	6. Inexperience
	7. Depression
Possible	1. Increased postoperative retching/coughing/straining
	2. Postoperative weight lifting
	3. Inexperience
	4. Improper calibration of crus closure
	5. Technical causes
	Suture pullout
	Suture breakage
	Knot failure
	6. Crus closure under tension
	Elderly patient
	Attenuated crus
	7. Collagen metabolic disorders

[*]Causes proven by our study ($P < 0.05$).
[†]Causes that reached near significance in our study.

necessitating immediate reoperation. Measures to prevent vomiting include an alteration in the anesthetic agent, intravenous antiemetics given intraoperatively, scheduled medications during hospitalization, medication before traveling (if motion sickness is a problem), written and verbal patient instructions/education on the importance of antiemetic measures, and refillable prescriptions for the long-term avoidance of vomiting. A single intravenous dose of preoperative steroids has been shown to significantly reduce the incidence and severity of postoperative nausea and vomiting.[18] However, these studies involve limited surgical trauma such as tonsillectomy, dental procedures, and laparoscopic cholecystectomy. Intuitively, this approach may be used in laparoscopic Nissen fundoplication procedures and especially in patients who have been determined to have a preoperative propensity to gag.

Stressors that achieved significance in other studies, but failed to do so in our analysis, include obesity and depression. GERD is highly prevalent in the obese population.[12,19,20] This could be due to chronically elevated intra-abdominal pressure leading to an increased gastroesophageal gradient.[12,20] Another study has shown that laparoscopic failure had no correlation with age, sex, American Society of Anesthesiology classification, and duration of symptoms.[21] GERD patients with concomitant major depressive disorder who underwent laparoscopic antireflux surgery gained less symptomatic relief and suffered from postoperative dysphagia.[22] Patients with psycho-emotional disorders and chronic pain syndromes were dissatisfied with outcomes of antireflux surgery due to persistent or new somatic complaints.[23] It should be noted that objective criteria were met to demonstrate failure of surgery in our study, but previous reports emphasize that objective data does not correlate with failure in this particular set of patients.

We have demonstrated that there is an observable difference in the prevalence of stressors such as vomiting, gagging, and belching in the general GERD population that has not undergone surgery, when compared to patients who develop failure after antireflux surgery. Studies with more subjects are required to further elucidate this relationship.

Thus, in patients with large hiatal hernias (greater than 3 cm), the surgeon should be circumspect when advocating antireflux surgery. In addition, further analysis of technical factors allowing post-Nissen fundoplication patients to belch is appropriate. Once the predictors of antireflux surgical failure are outlined as in Table 6, studies should determine cutoffs that predict definitive failure if the underlying stressors continue to act. Steps should be enforced to

Table 6. Frequency of stressors in each study group

	Symptom occurrence 0–1 times/mo		Symptom occurrence 1–5 times/mo		Symptom occurrence >5 times/mo	
Symptom	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Involuntary vomiting	38 (92.7%)	49 (98.0%)	2 (4.9%)	—	0	1 (2.0%)
Vomiting	31 (75.6%)	47 (94.0%)	5 (12.2%)	1 (2.0%)	5 (12.2%)	2 (4.0%)
Hiccuping[*]	34 (82.9%)	43 (86.0%)	1 (2.4%)	5 (10.0%)	4 (9.8%)	2 (4.0%)
Retching	29 (70.7%)	44 (88.0%)	1 (2.4%)	2 (4.0%)	9 (22.0%)	4 (8.0%)
Gagging	27 (65.9%)	46 (92.0%)	0	0	12 (29.3%)	4 (8.0%)
Belching	32 (78.0%)	31 (62.0%)	0	4 (8.0%)	6 (14.6%)	15 (30.0%)

[*]Data missing for two patients in the study group.

prevent the stressors preoperatively and to manage them vigorously should they develop in the immediate postoperative period.

CONCLUSION

Diaphragmatic stress factors should be assessed before and after laparoscopic antireflux surgery. In particular, patients with postoperative gagging, vomiting, or a hiatal hernia (greater than 3 cm) have a poorer outcome, whereas patients with postoperative belching have a better long-term result. Preemptive antiemetic regimens and possible use of postoperative steroids are supported by this study.

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Mapping the Rectum: Spatial Analysis of Transanal Endoscopic Microsurgical Outcomes Using GIS Technology

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Transanal endoscopic microsurgery (TEM) is a technically challenging procedure hindered by rectal anatomic constraints. To study the relationship of lesion position with performance of TEM, a novel approach of spatial analysis using Geographic Information Systems (GIS) was developed. A retrospective review was conducted on 144 consecutive TEMs, analyzing clinical, pathologic, and positional characteristics. Two- and three-dimensional maps of rectal topology were developed. GIS was used for spatial analysis, accounting for regional position and clustering of lesions. Lesions were located at a mean distance of 9.3 ± 4.9 (SD) cm from the dentate line, with an average size of 3.1 ± 1.4 cm. Proximal regions were associated with prolonged operative time. Regions between the rectosigmoid junction and the peritoneal reflection were associated with peritoneal breach. In spatial regression analysis, regional characteristics that were significantly associated with operative time included distance, presence of cancers, and positive margins; peritoneal breach was significantly associated with lesion size and location; conversions were associated with distance ($P < 0.05$). Specific knowledge of lesion size and location in the context of anatomic relationships is important for optimizing operative intervention. GIS provides a valuable tool in organizing spatial information and can be extended into clinical research topics involving the distinction of anatomic relationships. (J GASTROINTEST SURG 2006;10:22–31)

KEY WORDS: Transanal endoscopic microsurgery, rectal anatomy, rectal neoplasm, health geographics, geographic information systems

Transanal endoscopic microsurgery (TEM) using the technique of Buess is a minimally invasive procedure utilized as an alternative to traditional transanal approaches in the excision of rectal neoplasms. Despite sophisticated features including binocular stereoscopic magnification, precise instrumentation, and improved access to proximal lesions,[1,2] the procedure is technically challenging and has shown limited incorporation into surgical management compared with other minimally invasive procedures. Intrinsic limitations in TEM must be considered, related to the dimensions of the scope and the natural spatial conflicts that occur when manipulating multiple parallel-positioned instruments. The angled optic also requires optimal patient positioning, with the lesion situated in a dependent position. It is uncertain whether the location of the lesion within the rectum influences difficulty in performing the procedure.

Geographic Information Systems (GIS) has been used in various studies related to epidemiology, analyzing disease patterns, spatiotemporal relationships with health outcomes, and relationships of disease incidence with various environmental factors.[3] In order to test the hypothesis that the location of rectal lesions influences performance of TEM, a novel approach to spatial analysis of the rectum was developed using GIS technology.

METHODS

Clinical Data Acquisition

After institutional review board approval, a retrospective review was conducted on all patients

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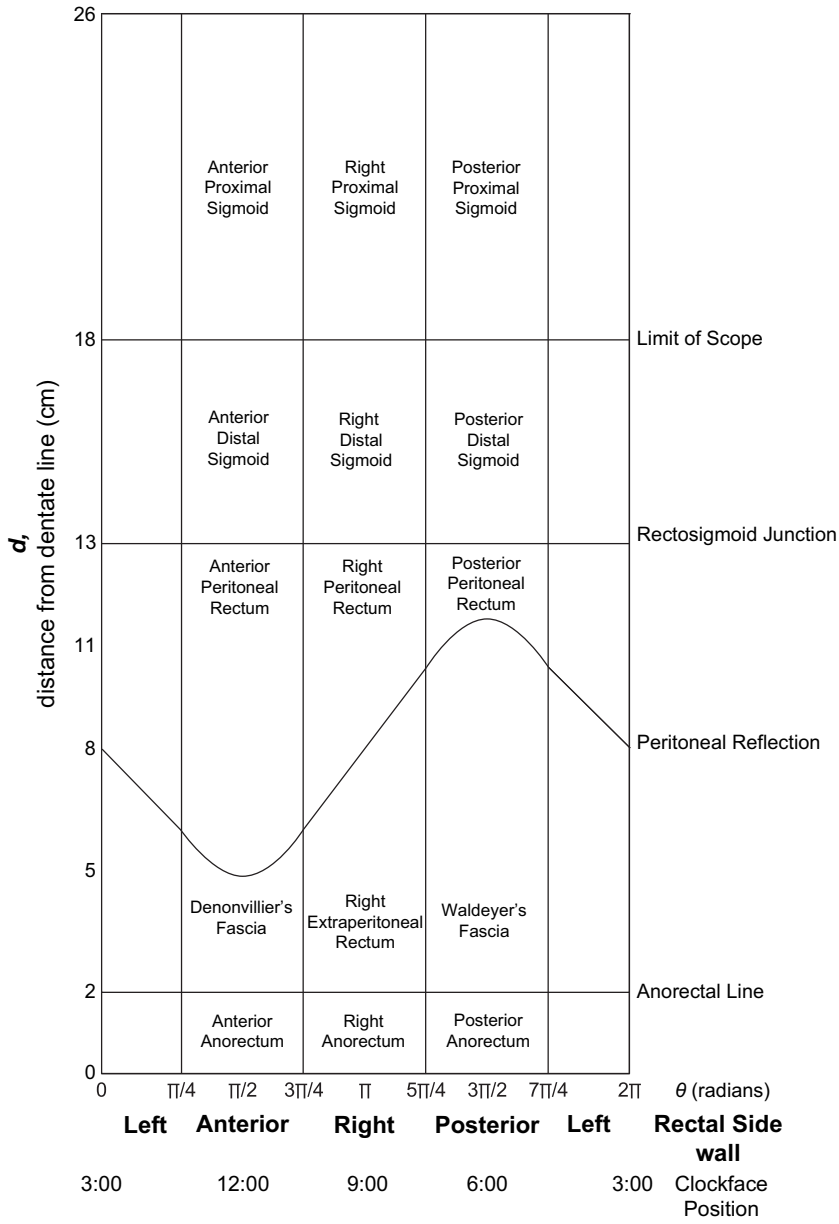

Fig. 1. A two-dimensional map of rectosigmoid topology was constructed using cylindrical coordinates *{θ, d}*. Twenty regions were created by dividing the angular dimension *(θ)* into four quadrants (anterior, posterior, right, and left), with further division based on distance from the dentate line *(d)*, delineated by the anorectal line *(d = 2)*, the peritoneal reflection *(d = 8 − 3sinθ)*, the rectosigmoid junction *(d = 13)*, and the limit of the scope (*d = 18)*.

undergoing TEM at Baystate Medical Center in Springfield, MA, between November 1993 and October 2004. Clinical data abstracted from medical records included age, gender, location of lesion, type of procedure completed, patient position, peritoneal entry (breach), conversions, operative time (minutes), hospital length of stay (hours), lesion pathology, lesion size, presence of positive margins, and complications. Outcomes detailing actuarial recurrence and survival probabilities have been previously reported on this database.[4]

Location of lesion was assessed by operative sigmoidoscopic evaluation detailing clockface position and distance of lesion. Clockface position of lesion was determined, noting 24 possible angles, with 12-o'clock as anterior, 3-o'clock as left lateral, 6-o'clock as posterior, and 9-o'clock as right lateral. Distances were recorded caudocranially, in centimeters from

the dentate line. Size of lesion was based on its maximum diameter in centimeters, as determined from the pathologic specimen ex vivo.[5] Patient position was characterized as dorsal lithotomy, prone, or right or left lateral decubitus.

All procedures were performed by a single surgeon (A.I.A.), who used TEM as the exclusive technique of local excision of sessile lesions of the rectosigmoid colon. Bowel preparation and topical estrogen cream for females were administered prior to surgery. TEM operative technique was conducted as previously described[6,7] under general anesthesia using a 4-cm-diameter, 20-cm-long operating rectoscope (Richard Wolf, Knittlingen, Germany) fixed by a Martin arm. Carbon dioxide insufflation was used. Patients were positioned such that the lesion was in a dependent position. Lesions were excised with at least 10-mm margins using cautery via either partial-thickness excision (mucosectomy) or full-thickness excision to perirectal fat. All defects were closed transversely using absorbable suture secured by a silver clip.

Construction of Rectal Map

A map of rectosigmoid topology was developed, presuming the rectum to be of a cylindrical form when conforming to the operating rectoscope (Fig. 1). Cylindrical coordinates $\{\theta, d\}$ were used to create a two-dimensional map, with the angular dimension, θ (radians), as the abscissa, and distance from the dentate line, d (cm), as the ordinate. Angular quadrants characterized anterior $\{\pi/4 < \theta \leq 3\pi/4\}$, right lateral $\{3\pi/4 < \theta \leq 5\pi/4\}$, posterior $\{5\pi/4 < \theta \leq 7\pi/4\}$, and left lateral $\{7\pi/4 < \theta \leq \pi/4\}$ divisions.

Further subdivisions were determined based on distances from the dentate line, representing the anorectum $\{0 < d \leq 2\}$, the extraperitoneal rectum $\{2 < d \leq 8 - 3sin\theta\}$, the peritoneal rectum $\{8 - 3sin\theta < d \leq 13\}$, the distal sigmoid $\{13 < d \leq 18\}$, and the proximal sigmoid $\{d \geq 18\}$. These regions were based on representations of the anorectal line[8] ($d = 2$), the peritoneal reflection ($d = 8 - 3sin\theta$), the rectosigmoid junction[9] ($d = 13$; 15 cm from anal verge), and the limit of the scope ($d = 18$; 20 cm from the anal verge). The peritoneal reflection ($d = 8 - 3sin\theta$) was characterized such that its equation accommodated anteroposterior anatomic variability; it was defined in location as 7 cm from the anal verge anteriorly and 13 cm from the anal verge posteriorly based on averaging of ranges reported for both genders.[10–12]

In order to allow representation in three dimensions, data recorded in cylindrical coordinates were translated into Cartesian coordinates, where $\{x, y, z\} = \{rcos\theta, rsin\theta, -d\}$ (Fig. 2). The radius, r, was assigned a value of 2, accounting for the 4-cm diameter of the operating rectoscope.

Data Analysis

Data compilation, descriptive statistics, and nonparametric statistical analyses were conducted using *EpiInfo* (Centers for Disease Control and Prevention,

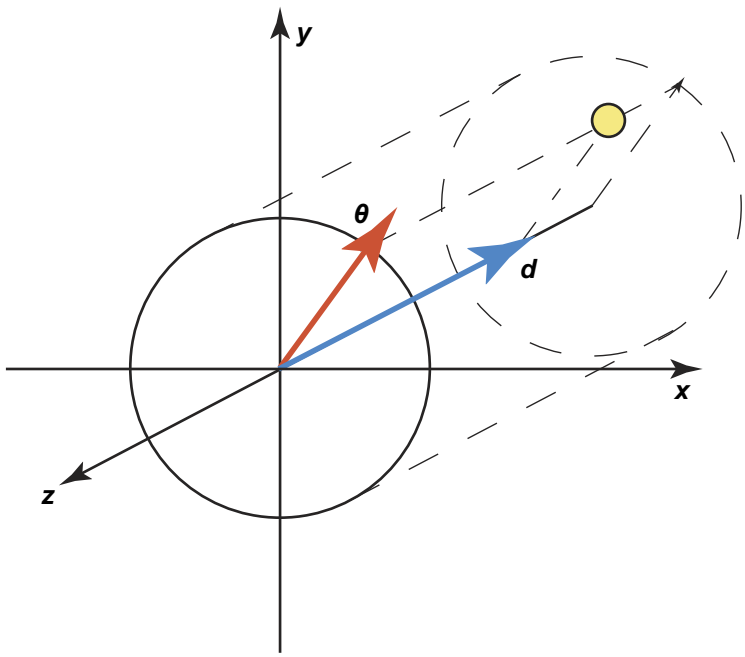

Fig. 2. Diagram representing conversion from cylindrical coordinates $\{\theta, d\}$ to Cartesian coordinates $\{x, y, z\} = \{rcos\theta, rsin\theta, -d\}$.

Atlanta, GA; 2004). Means are reported with their standard deviation. Medians are reported with their interquartile range (IQR). Statistical significance was determined according to an α of .05. *ArcGIS* (ESRI, Redlands, CA; 2004) was used for spatial representation and visualization of anatomic regions and lesions in both two and three dimensions. Choropleth maps were created demonstrating the proportion of lesions with a clinical variable within an anatomic region. Spatial autocorrelation (clustering) of outcomes across local anatomic regions was tested using Moran's I-statistic. Analysis of point clustering across the global study area was performed using Nearest Neighbor analysis.[13] The *S-plus* (Immersion Corporation, Seattle, WA; 2000) extension for *ArcView GIS* (ESRI, 2004) was used to perform spatial regression analysis,[14] identifying relationships between anatomic regional characteristics with clinical outcomes.

RESULTS

Operative and Pathologic Characteristics

A total of 144 TEMs were attempted during the study interval. Patients had a mean age of 64 ± 14 years, with a male-to-female ratio of 1.09. Lesions were located at a mean distance of 9.3 ± 4.9 cm from the dentate line, with an average maximal dimension of 3.1 ± 1.4 cm. Figure 3 demonstrates localization of these lesions in three dimensions. Final pathologic diagnosis was adenoma in 63%, adenocarcinoma in 31%, carcinoid tumor in 3%, and other in 4%. Positive margins were noted in 9% of specimens.

Patient operative position was dorsal lithotomy in 41%, prone in 33%, left lateral decubitus in 16%, and right lateral decubitus in 10%. Full-thickness excision was completed in 64% of cases; mucosectomy was performed in 24% of cases. Conversion to low anterior resection occurred in 6% of cases secondary to difficult access of lesion or lack of progress; conversion to local excision by the technique of Parks and Stuart[15] occurred in 1% of cases secondary to proximity to the anal verge. Median operative time for full-thickness and partial-thickness excisions by TEM was 82 minutes (IQR, 58−120) compared with 203 minutes (IQR 173−235) for conversions (Mann-Whitney rank sum test, $P = 0.0003$). Median hospital length of stay was 29 hours (IQR 25−31) for completed TEM compared with 112 hours (IQR 38−288) after conversions (Mann-Whitney rank sum test, $P < 0.0001$). Lesions with size greater than 4 cm were associated with longer operative time (median 120 versus 76 minutes; Mann-Whitney rank sum test, $P < 0.0001$).

Intraoperative complications occurred in 14% of patients, including conversions in 7%, peritoneal breach in 6%, and repositioning of the patient in 1%. Postoperative complications occurred in 10% of patients who completed TEM. This included urinary retention in 5%, bleeding in 1%, abdominal or rectal pain in 1%, suture line dehiscence in 1%, and other in 2%. There were no deaths related to the technique.

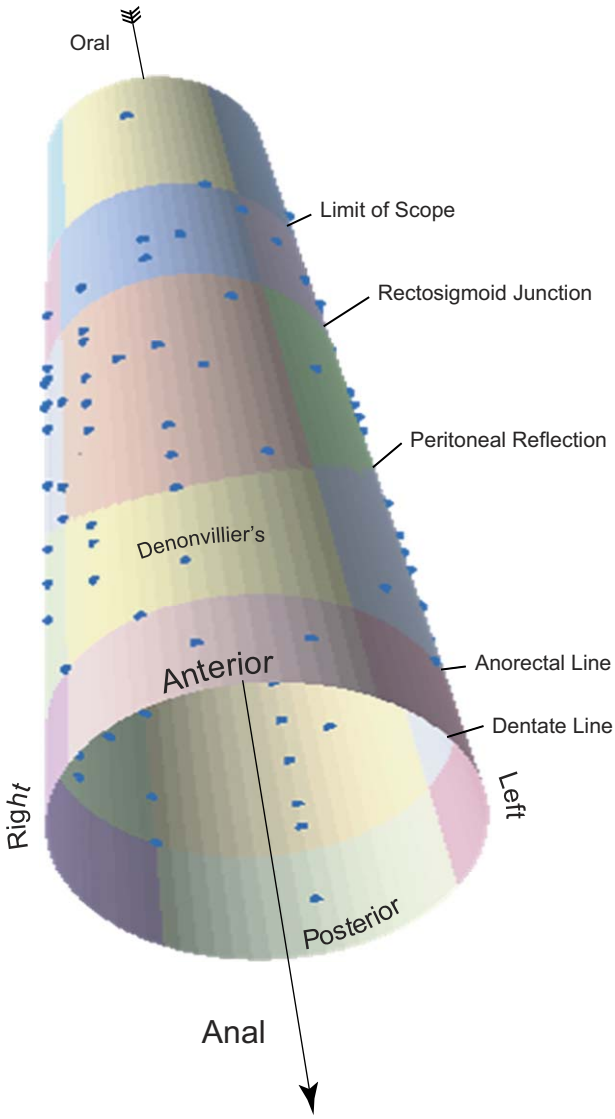

Fig. 3. Three-dimensional representation of rectosigmoid region rendered using *ArcGIS* software. Points represent location of lesions subjected to transanal endoscopic microsurgical excision (n = 144).

Spatial Analysis

Figure 4 demonstrates the number of lesions per anatomic region. The Moran's I-statistic showed no significant local clustering of lesions across anatomic regions according to any variable; however, significant global clustering of lesions was observed

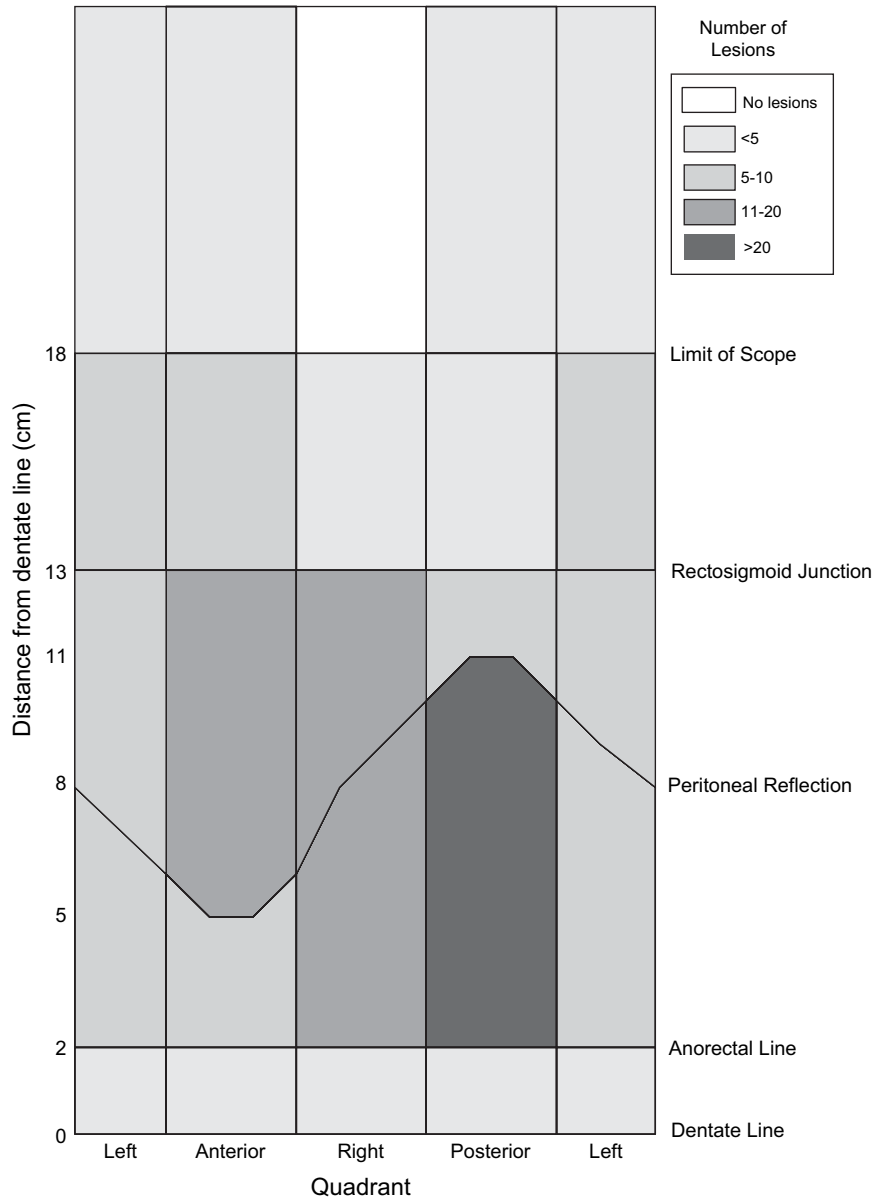

Fig. 4. Choropleth map of number of lesions per rectosigmoid anatomic region.

over the study area ($z = -3.9$; $P < 0.01$). Figure 5 demonstrates the relationship between operative time and anatomic region. No region distal to the rectosigmoid junction was associated with an average operative time greater than 2 hours. In spatial regression analysis, anatomic regional characteristics that were significantly associated with operative time included proportion of cancerous lesions in the region ($P = 0.02$), proportion of lesions with positive margins ($P = 0.0003$), and distance of lesions from the dentate line ($P = 0.0001$).

The relationship between peritoneal breach and rectosigmoid anatomic region is depicted in Figure 6. A greater proportion of procedures resulted in peritoneal breach within the region between the peritoneal reflection and the rectosigmoid junction. Significant regional predictors of peritoneal breach in spatial regression analysis were average lesion size ($P = 0.006$), proportion of lesions greater than 4 cm ($P = 0.004$), and location ($P = 0.04$). Type of procedure performed (full-thickness or mucosectomy) was not an independent predictor of peritoneal breach.

Figure 7 demonstrates the relationship between anatomic region and conversions to anterior resection or transanal excision. A large proportion of conversions occurred in the sigmoid regions, as well the

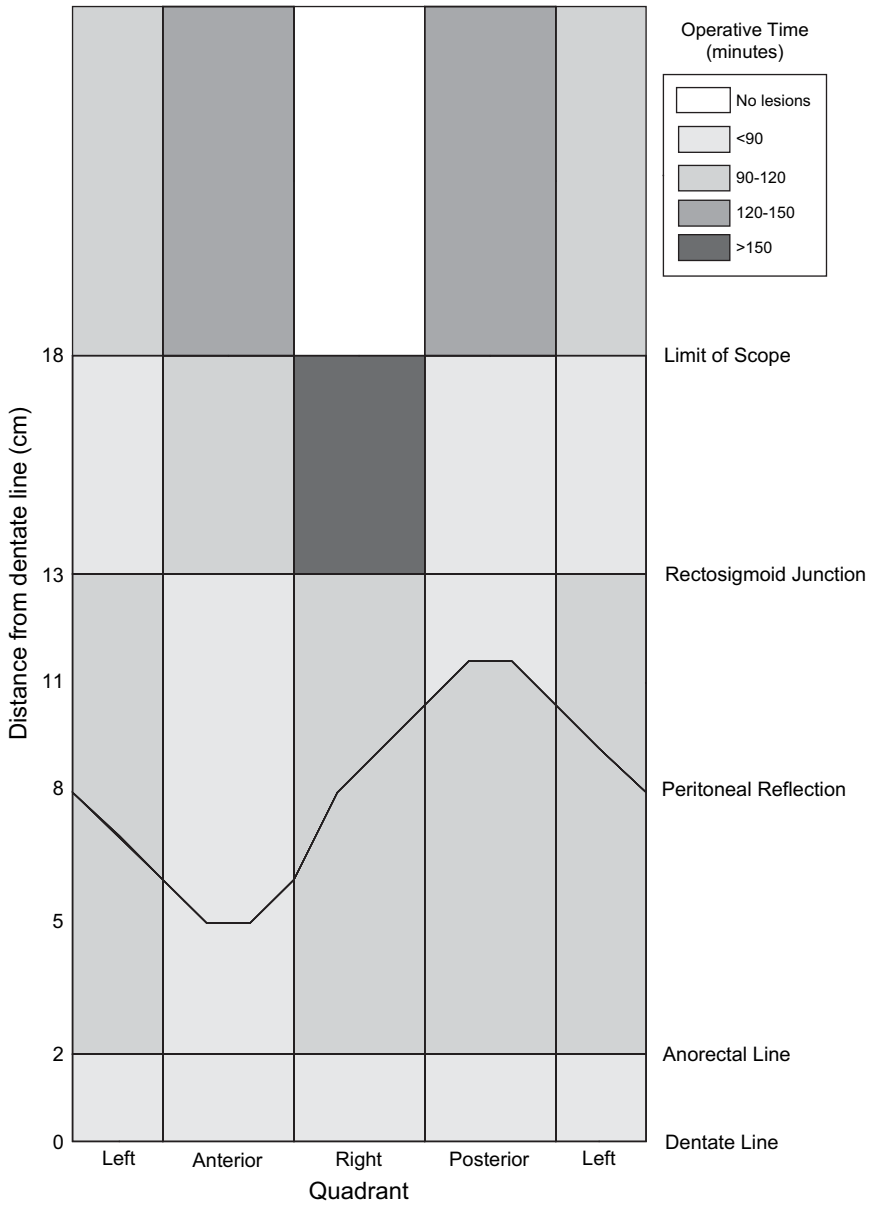

Fig. 5. Choropleth map of average operative time (minutes) by rectosigmoid anatomic region.

lateral aspects of the rectum. In spatial regression analysis, only distance from the dentate line was an independent predictor of conversion ($P = 0.0004$). Figure 8 demonstrates the relationship between postoperative complications and anatomic region. In spatial regression analysis, there were no anatomic regional characteristics that were predictors of postoperative complications.

DISCUSSION

Anatomic mapping is hardly an innovative concept. The segmental anatomy of the liver as described by Couinaud, for example, is a representation based on vascular supply with extreme functional consequence but without definite geographic surface demarcation.[16] As a surgeon, with knowledge of the utility of such a map, one is able to take what may be a complex and variable structure and simplify it into that which is approachable; our map thus informs us. We can distinguish differences between right- and left-sided colon cancer, conceptualize information conveyed pictorially through imaging modalities, predict the location of a gastrinoma, and imagine the lymphatic drainage of a melanoma, all through the use of mental anatomic maps. The use of

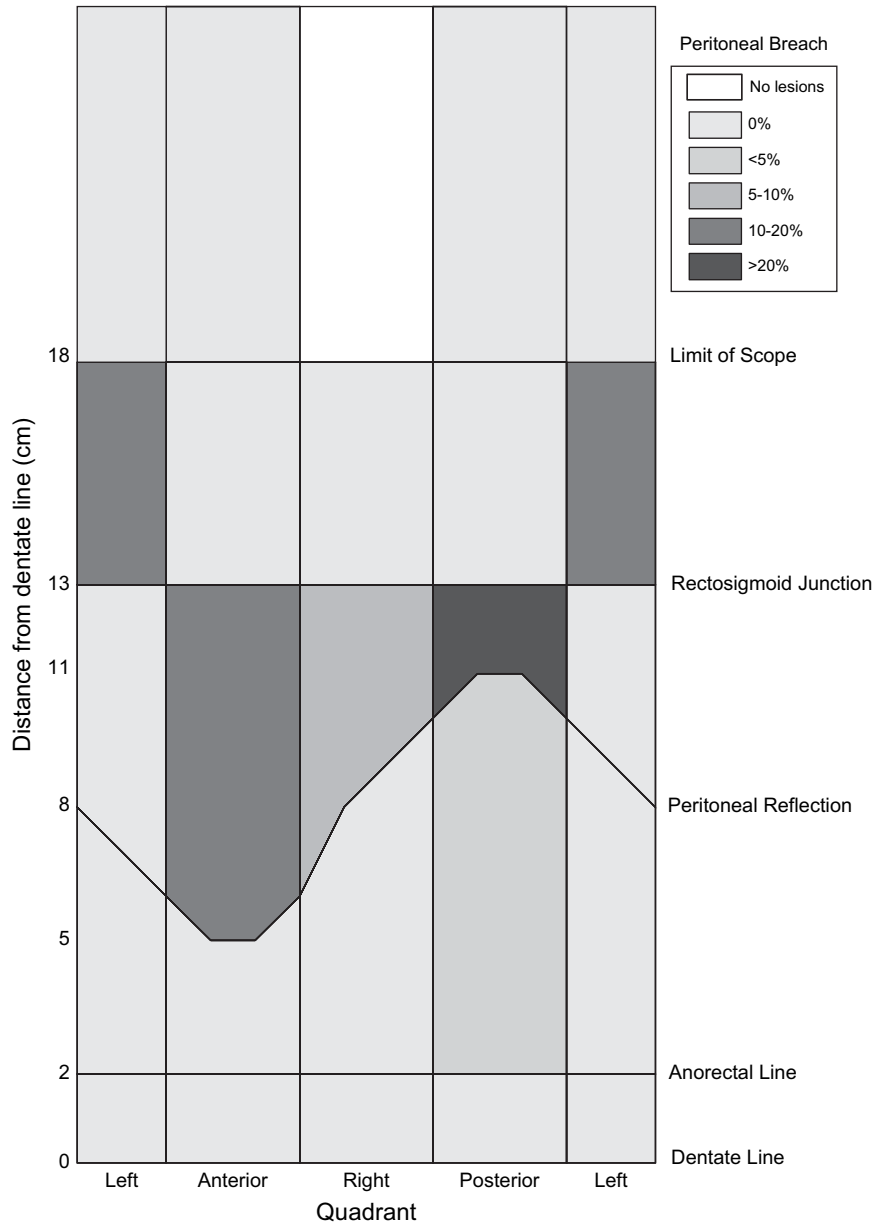

Fig. 6. Choropleth map of peritoneal breach rate by rectosigmoid anatomic region.

structured anatomic maps allows us to communicate, classify, process, and understand clinical information with greater precision.

The decision to create our map of the rectum was based on anatomic features relevant to performance of TEM. Proximal sigmoid lesions are difficult to access; this created the delineation of the regions beyond the rectosigmoid junction and the limit of the 20-cm-long scope. While full-thickness excisions are a preferred method of excision by TEM,[17] proximal to the peritoneal reflection they risk entry, thus compelling the surgeon to perform a mucosectomy. The depiction of the peritoneal reflection was thus formed to gain a better understanding of the relationship between anatomic location and peritoneal breach. Distal lesions were assumed to be difficult to perform with TEM secondary to inability to properly fixate the apparatus and maintain pneumorectum[1]; this resulted in the inclusion of the anorectal line.

Anatomically, the rectum is more complex than the map depicts, angulating sharply at the anorectal ring, curving laterally with the valves of Houston, and conforming to the sacral concavity.[10] The rectum is an anatomic structure that poses a challenge to the surgeon in several ways. Although pathologic

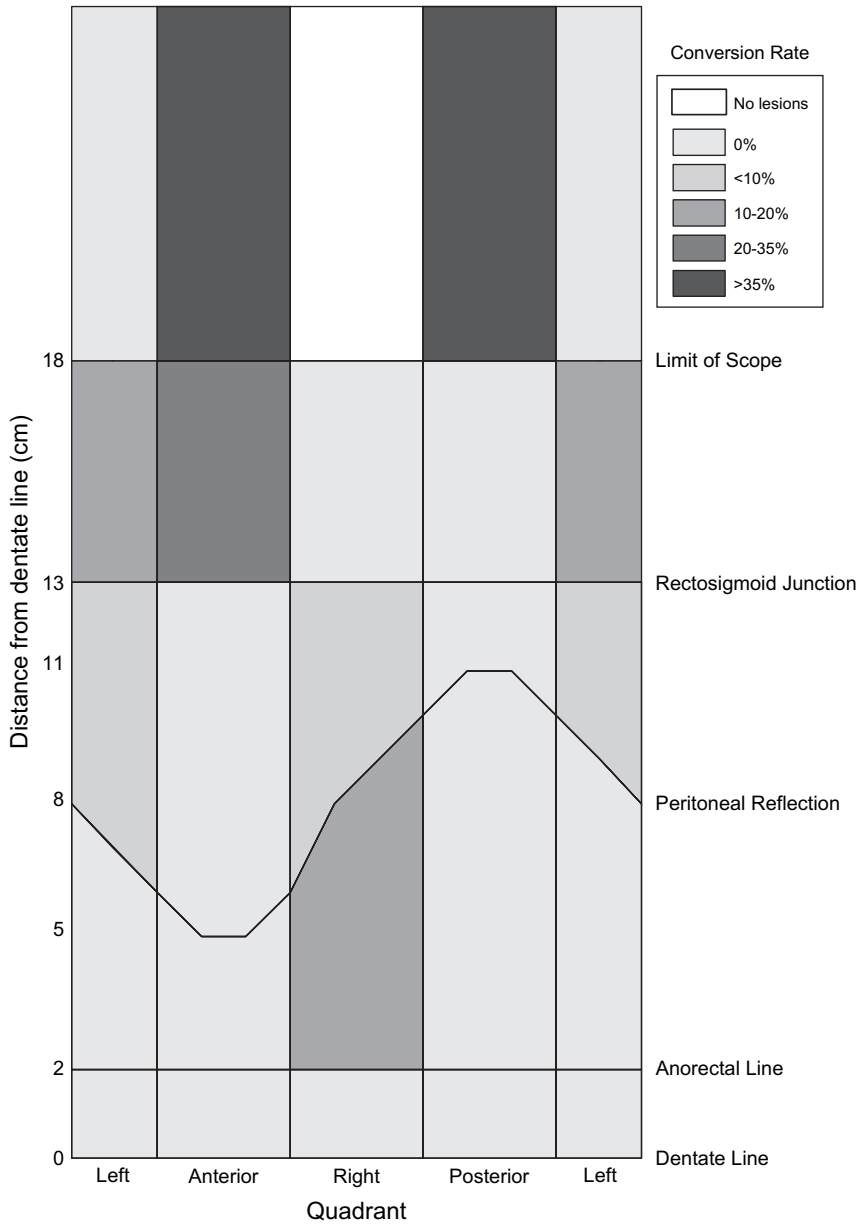

Fig. 7. Choropleth map of conversion rate (to anterior resection or transanal excision) by rectosigmoid anatomic region.

features such as invasion, lymphatic involvement, and histologic grade are critical features in the decision-making process, the ability to conduct local excision of a rectal neoplasm is heavily influenced by exposure and access. In addition, proximity to the vagina or prostate must be appreciated when dealing with anterior extraperitoneal lesions. Anorectal, sexual, and bladder function may also be compromised by the procedure chosen, especially with abdominal approaches.

In prior studies on TEM, distance of lesions from the anal verge is a feature that has been graphically depicted in histograms.[18,19] Diagrammatic representations of rectal lesion distribution related to clock-face position and distance have also been conducted.[20] In addition, in the scope of rectal cancer, analysis of an outcome measure, such as the accuracy of endorectal ultrasound staging relative to tumor location, has been studied, accounting for tumor position relative to general quadrant and distance subdivisions.[21] Despite the value in traditional methods of descriptive and comparative statistics, a grasp of the intricacies of the anatomic region may be limited. GIS allows for the ability

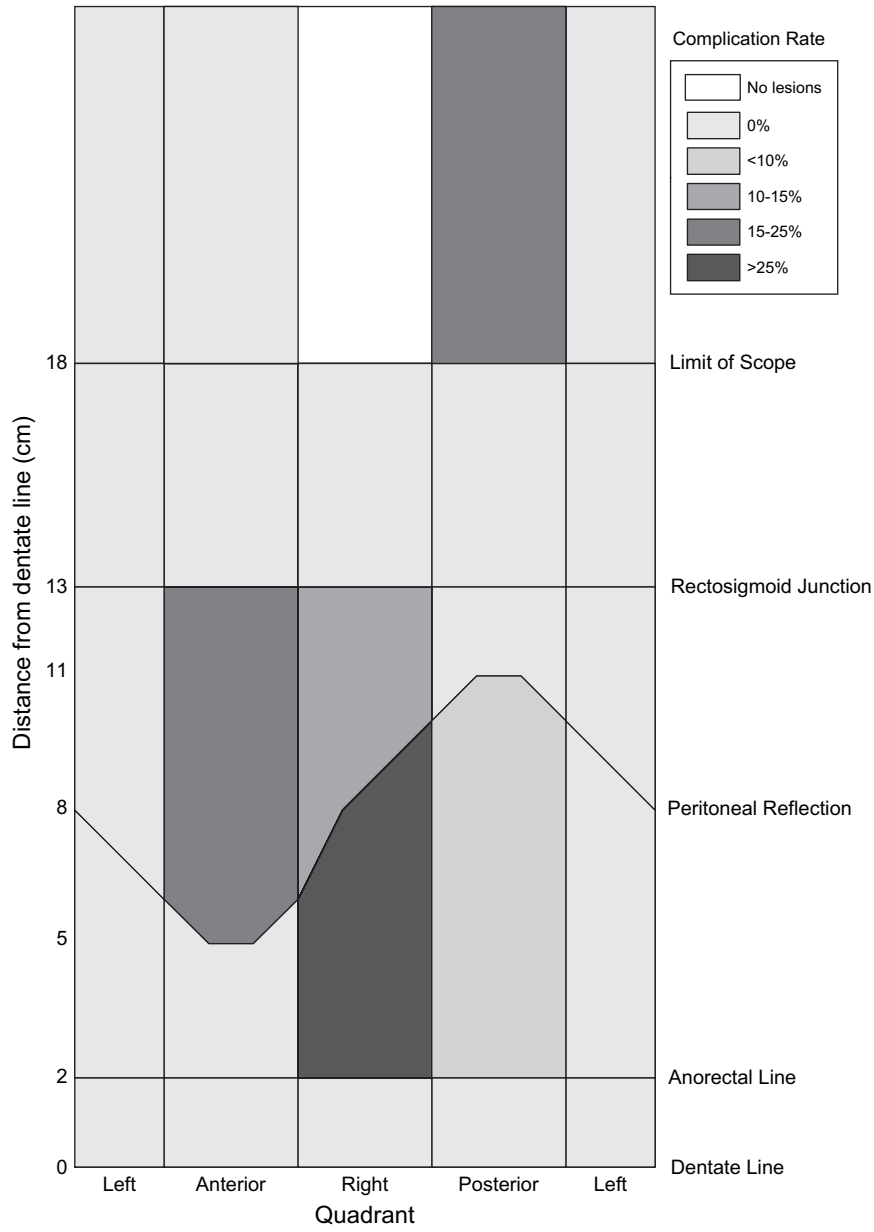

Fig. 8. Choropleth map of postoperative complication rate by rectosigmoid anatomic region.

not only to graphically depict geographic incidence but also to analyze patterns, clustering, and regional density. Spatial regression analysis can also be performed, accounting for multiple variables including interrelationships with neighboring regions. However, the application of GIS to anatomic mapping has to date been limited to dentistry and conceptualizing microvascular networks.[22,23]

Despite the inability to properly assess indicators of the difficulty of a procedure retrospectively, it appears that prolonged operative time was associated with the more proximal regions and may be an adequate indicator of difficulty. In spatial regression analysis, predictors of regions with prolonged operative time included greater distance and proportion of lesions with cancers. In addition, there were a greater proportion of lesions with positive margins in regions with longer operative times. Conversions appeared to be associated with the sigmoid colon and the lateral walls of the rectum and were predicted by distance from the dentate line.

Peritoneal entry was associated primarily with regions between the depicted peritoneal reflection and the rectosigmoid junction. Predictors of breach

included size of lesion and location and were not influenced by depth of excision. In a prior study on TEM, no association had been demonstrated between peritoneal breach and the incidence of short-term complications.[24] Indeed, in our series, all episodes of peritoneal entry were managed endoscopically by primary closure and did not necessitate conversion to laparotomy. However, one of the nine cases of peritoneal breach was associated with the development of a perirectal abscess. This patient had submucosal invasion on pathology and later developed a cancerous recurrence necessitating abdominoperineal resection.

Using nonparametric analysis, a statistically significant difference was shown in operative time and hospital length of stay between patients who completed TEM and those requiring conversion; these reflect the expected times for patients undergoing anterior resection. Knowledge of regions associated with a longer operative time and a higher rate of conversion allows for better planning of operative intervention.

Despite the challenge of TEM, it is a technique that merits further adoption. The precision of visualization, magnification, and instrumentation that TEM allows in the excision of rectal lesions cannot be achieved by traditional methods. Understanding rectal topology has allowed us to better comprehend the limitations of TEM. GIS has proved to be an effective tool in organizing spatial information and should be extended into clinical research topics involving the distinction of anatomic relationships.

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CO_2 Abdominal Insufflation Pretreatment Increases Survival After a Lipopolysaccharide-Contaminated Laparotomy

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Carbon dioxide (CO_2)-pneumoperitoneum is known to favorably modify the systemic immune response during laparoscopic surgery. The presented studies were designed to determine whether treating animals with CO_2 abdominal insufflation before undergoing a lipopolysaccharide (LPS)-contaminated laparotomy would serve as "shock prophylaxis" and thus improve survival and attenuate cytokine production. Rats were randomized into five groups: CO_2-pneumoperitoneum, helium-pneumoperitoneum, anesthesia control, laparotomy/LPS control, and LPS only control. Animals in the first four groups all received a laparotomy and a lethal dose of LPS. Immediately preceding their laparotomy, animals in the pneumoperitoneum groups received a 30-minute pretreatment of abdominal insufflation with either CO_2 or helium. The anesthesia control group received a 30-minute pretreatment of isoflurane. Animal mortality was then recorded during the ensuing 72 hours. Subsequently, a similar protocol was repeated for measurements of cytokines. CO_2-pneumoperitoneum increased survival at 48 hours compared with LPS control ($P < .05$), and decreased interleukin-6 plasma levels at 2 hours ($P < .05$). Abdominal insufflation with CO_2 before the performance of a laparotomy contaminated with endotoxin increases survival and attenuates interleukin-6. The beneficial immune-modulating effects of CO_2-pneumoperitoneum endure after abdominal insufflation. CO_2-pneumoperitoneum pretreatment may improve outcomes among patients undergoing gastrointestinal surgery who are at high risk for abdominal fecal contamination. (J GASTROINTEST SURG 2006;10:32–38)

KEY WORDS: Carbon dioxide, pneumoperitoneum, laparotomy, sepsis, survival

Although laparoscopic surgery was initially viewed with skepticism, it was eventually received with enthusiasm as a minimally invasive means for removal of the gall bladder. Today laparoscopic surgery is used to perform a variety of complex procedures and is an integral part of surgical resident training.[1] Its popularity is attributable to decreased postoperative pain, faster recovery, decreased tissue trauma, and a more rapid return to oral intake.[2–5] Since its introduction, many studies have been performed to delineate which gas should be used to create the visual intraoperative field. Carbon dioxide (CO_2) has generally been accepted as the best gas because of its biologic properties: colorless, stable, buffered in the blood, low risk of venous embolism, and nonflammable/nonexplosive.[6,7]

Creating a pneumoperitoneum with CO_2 is only recently being recognized as an added benefit of laparoscopic surgery. CO_2-pneumoperitoneum has the added independent benefit of modifying the inflammatory response to injury. Our laboratory has shown that CO_2-pneumoperitoneum has the ability to attenuate the acute phase response in sepsis induced by LPS and cecal-ligation-puncture.[8,9] Furthermore, we have demonstrated that CO_2-pneumoperitoneum decreases tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 production while up-regulating the anti-inflammatory cytokine IL-10.[10–12] Consistent with our findings, others have shown that CO_2-pneumoperitoneum reduces levels of TNF-α mRNA, IL-6, IL-1 receptor antagonist, and soluble TNF receptor-1.[13–15] More important, our

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laboratory has shown that CO_2-pneumoperitoneum increases survival in rodents challenged with endotoxin.[16] However, the mechanism underlying this phenomenon is only partially understood. Although smaller incisions in laparoscopic surgery have been advocated as the main factor in decreasing the inflammatory response,[14] our research highlights the active biologic state induced by CO_2 as integral to the mechanism behind the potentially beneficial immunomodulatory properties observed during laparoscopic surgery. We have shown that CO_2 insufflation given immediately after an LPS-contaminated laparotomy (6 cm) protects rodents from endotoxic shock.[16]

Intra-abdominal infection and sepsis continue to be a problem in surgical and critically ill patients.[17,18] Sepsis continues to have a high mortality (30%–70%) despite advanced technology and intensive therapy.[19] This study explores the possibility of an alternative means of preventing intra-abdominal sepsis. We hypothesized that CO_2-pneumoperitoneum pretreatment would also offer protection against sepsis after a lipopolysaccharide (LPS)-contaminated laparotomy. Specifically, here CO_2 insufflation was used as a prophylactic agent to prevent the development of endotoxic shock.

MATERIALS AND METHODS

General Procedures

Adult male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) weighing approximately 250 to 350 g were housed in plastic cages where standard chow and water were available ad libitum. Animals were acclimatized to their environment for 3 to 5 days after arrival and were then fasted for 16 hours before procedures. The animal housing environment maintained a 12-hour light/dark cycle, a temperature of 72°F, and a humidity ranging between 30% and 70%. All surgical procedures were performed under aseptic conditions. Before surgery, rats were preanesthetized rapidly in a 15 × 15-inch glass jar using vaporized isoflurane ("IsoFlo," Abbot Laboratories, North Chicago, IL). Spontaneously breathing anesthetized animals were placed supine and restrained with adhesive tape. Anesthesia was maintained by delivering 2.5% vaporized isoflurane through a nose cone. Pneumoperitoneum was achieved by delivering each respective gas through an 18-gauge angiocatheter placed percutaneously through the abdominal wall. Insufflation pressure was maintained at 4 mm Hg. LPS was from *Escherichia coli* serotype 026:B6 (Sigma-Aldrich, St. Louis, MO). After the completion of the experiments, all rats were euthanized by anesthetic overdose. All animal procedures were performed on a protocol approved by Johns Hopkins Medical Institution Animal Care and Use Committee.

Survival Study and Lipopolysaccharide Model

Sixty-five rats were randomized into five groups \ (n = 13): CO_2-pneumoperitoneum, helium-pneumoperitoneum, anesthesia control, laparotomy/LPS control, and LPS only control. Animals in the first four groups all received a 6-cm midline laparotomy that was followed by instilling a lethal dose of LPS (10 mg/kg) in the right colic gutter. All laparotomies were immediately repaired using a double-layer 4-0 Vicryl closure. The LPS only control group received an intraperitoneal injection of LPS at the same dose. Immediately preceding their laparotomy, animals in the pneumoperitoneum groups received a 30-minute pretreatment of abdominal insufflation (4 mm Hg) with either CO_2 or helium. The anesthesia control group received a 30-minute pretreatment of isoflurane. Animal mortality was then recorded during the ensuing 72 hours.

Cytokine Response Study

Sixty-two rats (n = 8) were randomized into four groups: CO_2 pneumoperitoneum, helium pneumoperitoneum, anesthesia control, and laparotomy/LPS only control. The first three groups received 30 minutes of preconditioning with their respective treatments followed by a 6-cm midline laparatomy for 10 to 30 minutes. Simultaneous to laparotomy, rats received intraperitoneal LPS (1 mg/kg) in the right colic gutter. The laparotomy/LPS only control group received no preconditioning. Blood samples for serum cytokine assays were collected through cardiac puncture 2 hours after LPS injection. Plasma was isolated by centrifugation and stored at −80°C. Plasma levels of TNF-α, IL-6, and IL-10 protein were determined by enzyme-linked immunosorbent assay using commercially available kits (Biosource, Camarillo, CA).

Statistical Analysis

Statistical significance for survival studies was determined by Kaplan-Meier analysis using the log-rank test. Cytokine data are expressed as mean ± standard error of the mean. One-way analysis of variance test was used to detect general differences in serum cytokine levels among all groups. To elucidate specific significances in these parameters between groups, multiple pairwise comparisons were performed using the Student-Newman-Kelus method.

Differences between groups were considered significant when the *P* value was less than .05. Analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and SigmaStat (SPSS Incorporated, Chicago, IL) software.

RESULTS

Survival Study

To determine whether CO_2 pneumoperitoneum pretreatment for 30 minutes had the potential to prevent the detrimental effects of an LPS-contaminated laparotomy, a survival study was performed. Figure 1 demonstrates that at 24 hours after an LPS-contaminated laparotomy was performed, there was no significant difference in mortality among groups ($P = 0.317$ for CO_2 vs. LPS control). However, CO_2-pneumoperitoneum significantly increased survival compared with LPS control at 48 hours (85% vs. 46%, $P = .037$). Helium pneumoperitoneum, laparotomy/LPS control, and anesthesia control had intermediary survival (77% vs. 46%, $P = .124$; 62% vs. 46%, $P = .387$; 69% vs. 46%, $P = .278$, respectively). At 72 hours, a trend

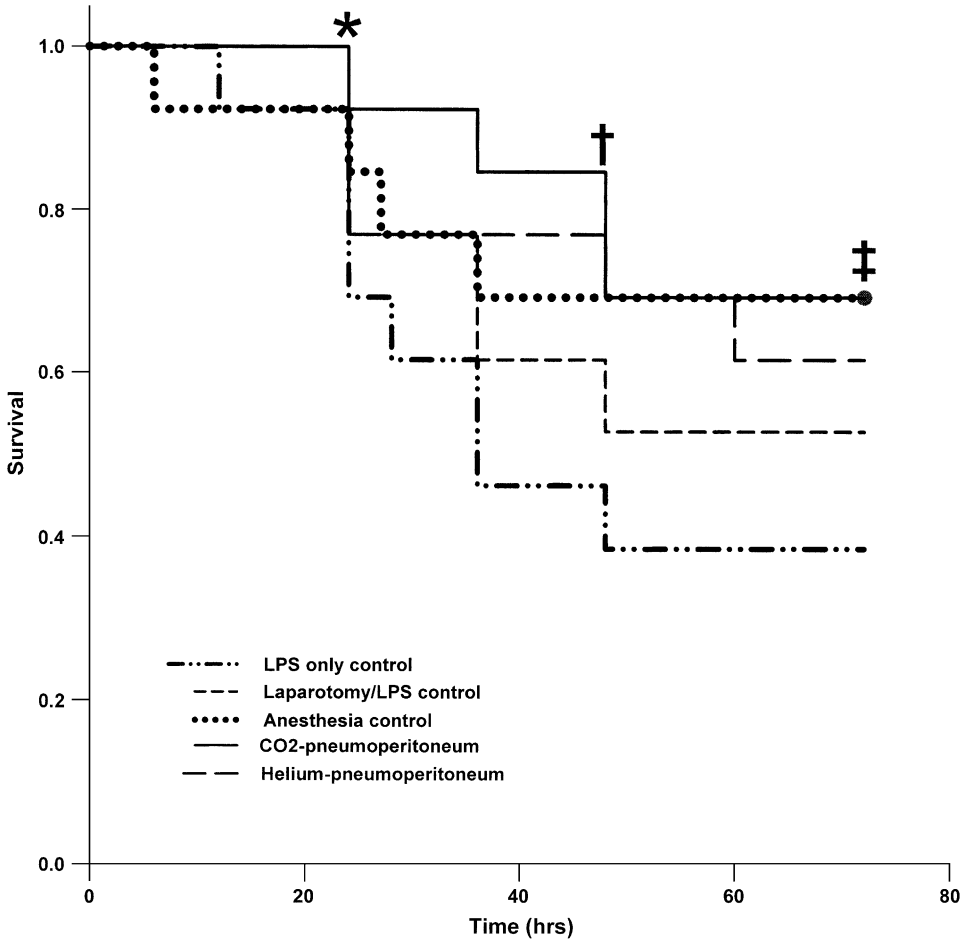

Fig. 1. Kaplan-Meier survival analysis among rats (n = 65) pretreated for 30 minutes with CO_2 pneumoperitoneum, helium pneumoperitoneum, or anesthesia control. Laparotomy/LPS control received no pretreatment, whereas LPS control animals did not receive a laparotomy. At 24 hours, there was no significant difference between groups, $^*P = .317$ for CO_2 versus LPS control. At 48 hours, CO_2-pneumoperitoneum significantly increased survival compared with LPS control (85% vs. 46%, $^\dagger P = .037$), whereas helium pneumoperitoneum, laparotomy/LPS control, and anesthesia had intermediary survival (77% vs. 46%, $P = .124$; 62% vs. 46%, $P = .387$; 69% vs. 46%, $P = .278$, respectively). Furthermore, at 72 hours CO_2-pneumoperitoneum increased survival compared with LPS control (69% vs. 38%, $^\ddagger P = .07$), whereas helium pneumoperitoneum, laparotomy/LPS control, and anesthesia had intermediary survival (62% vs. 38%, $P = .124$; 54% vs. 38%, $P = .400$; 69% vs. 38%, $P = .162$, respectively). CO_2 = Carbon dioxide; LPS = lipopolysaccharide.

existed toward CO_2 pneumoperitoneum increasing survival compared with LPS control, but this difference did not reach statistical significance (69% vs. 38%, $P = .07$), whereas helium pneumoperitoneum, laparotomy/LPS control, and anesthesia again had intermediary survival (62%vs. 38%, $P = .124$; 54% vs. 38%, $P = .400$; 69% vs. 38%, $P = 0.162$, respectively). Animals treated with CO_2-pneumoperitoneum exhibited fewer clinical signs of abdominal sepsis during the 72-hour observational period (e.g., piloerection, diarrhea, hypoactivity).

Cytokine Response Study

To determine whether our previous observations would correlate with a reduction in proinflammatory cytokine levels and an increase in the anti-inflammatory cytokine IL-10, a similar protocol was conducted. Plasma levels of the proinflammatory cytokine IL-6 were significantly suppressed in animals pretreated with CO_2-pneumoperitoneum compared with laparotomy control, anesthesia control, and helium pneumoperitoneum (71%, 66%, and 65%, respectively, $P < .05$, Fig. 2). Moreover, plasma levels of the proinflammatory cytokine TNF-α were suppressed in the group pretreated with CO_2 when compared with laparotomy control, anesthesia, and helium pneumoperitoneum (30%, 34%, and 28%, respectively), although this difference did not reach statistical significance (Fig. 3). IL-10 levels were not significantly different between groups, although there was a high IL-10 response among all groups.

DISCUSSION

The experiments presented herein were designed to determine whether pretreatment with CO_2-pneumoperitoneum for 30 minutes would serve as "shock prophylaxis" in animals whose peritoneal cavity was instilled with LPS during a laparotomy. We found that CO_2-pneumoperitoneum pretreatment prevented early mortality at 48 hours post-LPS injection in the setting of a laparotomy. Moreover, at 72 hours, CO_2 insufflation pretreated had borderline significance (statistical significance may been reached if our sample size was greater). This survival study corroborates the results of our prior work in which 30 minutes of CO_2-pnuemoperitoneum treatment increased survival even when the lethal dose of LPS was injected 2 hours after treatment, and in which CO_2 insufflation immediately after laparotomy and LPS administration increased 72-hour survival.[16] The current study confirms that CO_2 insufflation does indeed modify the inflammatory response induced by LPS, and most important, that

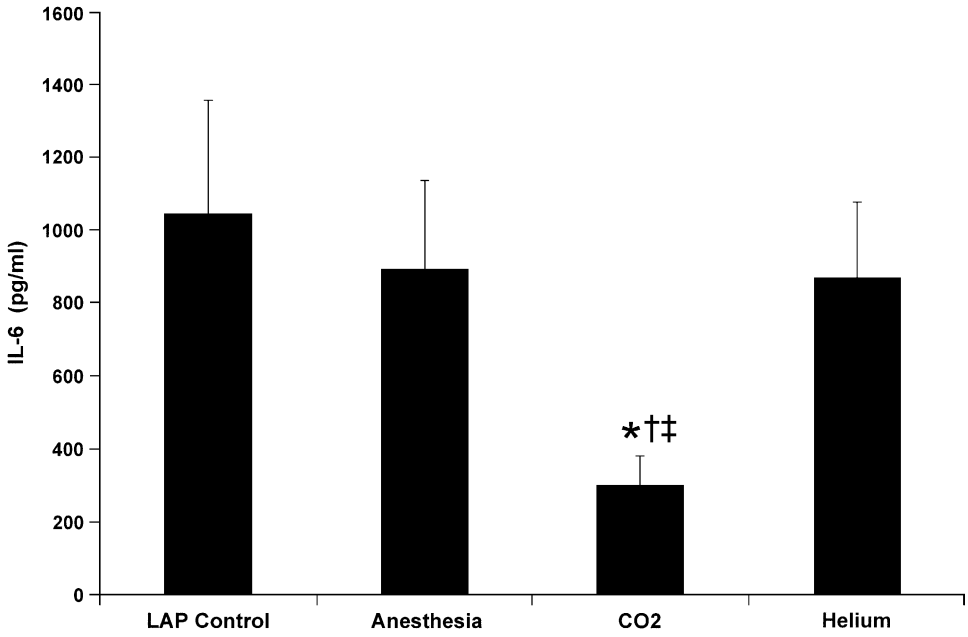

Fig. 2. Down-regulation of IL-6 plasma levels by 30 minutes pretreatment with CO_2 insufflation after a contaminated laparotomy. Plasma levels of IL-6 in animals pretreated with CO_2 pneumoperitoneum for 30 minutes were significantly suppressed when compared with laparotomy control, anesthesia control, and helium pneumoperitoneum (71%, 66%, and 65%, respectively). Data presented as mean ± SEM. *$P < .05$ versus LAP (laparotomy) control, †$P < .05$ versus anesthesia, ‡$P < .05$ versus helium pneumoperitoneum. IL = interleukin; SEM = Standard error of mean.

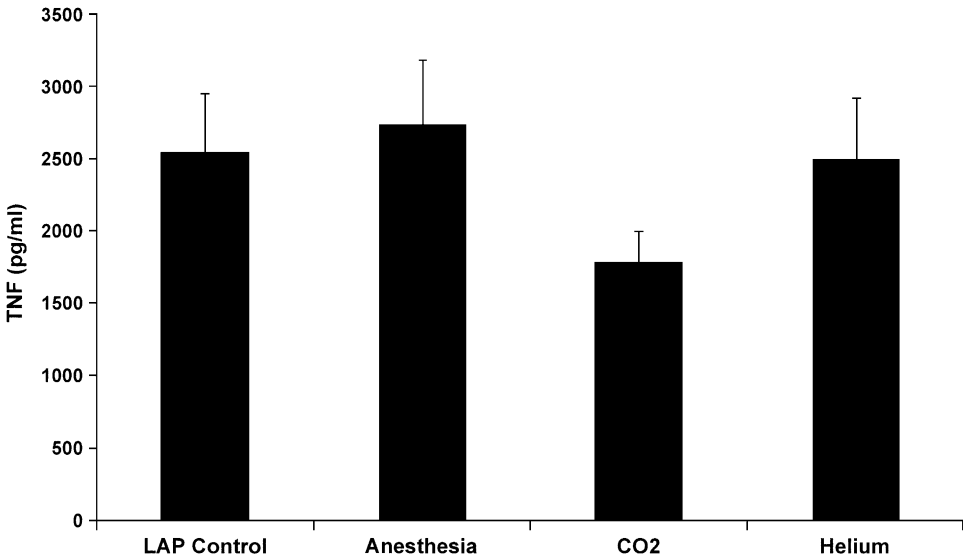

Fig. 3. TNF-α plasma levels after 30 minutes of their respective pretreatment after an LPS-contaminated laparotomy. Plasma levels of TNF-α in animals pretreated with CO_2 pneumoperitoneum were suppressed when compared with laparotomy control, anesthesia, and helium pneumoperitoneum (30%, 34%, and 28%, respectively), although these differences did not reach statistical significance by one-way analysis of variance. TNF = tumor necrosis factor; LAP = laparotomy; LPS, lipopolysaccharide.

the effects are durable, producing a prophylactic effect against subsequent laparotomy and intra-abdominal LPS administration. Furthermore, our cytokine data support the concept of a mechanism whereby CO_2 insufflation increases survival by attenuating the cytokine storm induced by LPS. We observed that IL-6 was significantly decreased in the CO_2 pneumoperitoneum group, whereas there was a trend toward TNF-α being suppressed. Consistent with these findings, we previously showed that CO_2-pneumoperitoneum decreases TNF-α and IL-6 responses sepsis.[11,12,16] Previous studies showed that cholecystectomy by laparoscopic surgery attenuates IL-6 whereas cholecystectomy by laparotomy has a significant elevation of IL-6.[14] Although the authors of the former study concluded that their results show that less surgical stress with laparoscopic surgery is the main cause of the difference between open laparotomy and laparoscopic surgery, in our study, animals pretreated with CO_2 insufflation and that then had a laparotomy still displayed decrease levels of IL-6. This suggests that the unique biology of the CO_2-pneumoperitoneum is more important than the size of incision.

The clinical implications of our study are that CO_2-pneumoperitoneum might have potential as a therapeutic agent to prevent or treat surgical sepsis. This study suggests that CO_2-pneumoperitoneum pretreatment may play a role as an adjuvant or a perioperative agent used in operations with a high risk of abdominal fecal contamination. CO_2 anti-inflammatory effects are not unique to minimally invasive surgery, but may be relevant in different clinical areas. CO_2 insufflation used in flexible endoscopy has gained increased popularity over air because of less pain and discomfort after the procedures.[20] It has been proposed that rapid CO_2 absorption is the main factor for less patient discomfort.[20] CO_2 insufflation is also applied to prevent airembolism, during drainage of subdural hematomas and during cardiac surgery.[21–23] Furthermore during cardiac surgery, CO_2 insufflation has also been reported to significantly reduce the risk of airborne contamination and postoperative wound infection.[24] All these benefits are attributed to the active biologic state of CO_2. This study provides evidence that other procedures in which CO_2 could be applied instead of air or saline to create a visual field should consider switching to CO_2.

One limitation of our study is that, in an attempt to measure cytokines levels at a time that would allow consideration of both TNF-α and IL-6, we harvested blood samples at 2 hours, when TNF-α and IL-10 generally peak somewhat earlier. In this study, plasma levels of TNF-α were modestly suppressed in the CO_2 group, and IL-10 levels were similar among the study groups. Only IL-6 was significantly suppressed in the CO_2 group when compared with the

other groups. At 2 hours, TNF-α and IL-10 levels already began to fall, making differences harder to appreciate between groups. This limitation in experimental design might explain why, in this study, IL-10 levels were not significantly up-regulated in the CO_2-pneumoperitoneum group as seen in our previous studies.[16] In this study, the laparotomy is known to cause an acute phase response with the release of proinflammatory cytokines such as TNF-α and IL-6 with the subsequent release of anti-inflammatory mediators such as IL-10 and transforming growth factor-beta.[25,26] Moreover, studies suggest that during a laparotomy the T-helper (Th1)/Th2 ratio shifts toward a Th2-dominated cytokine profile (anti-inflammatory), whereas during laparoscopic surgery the Th1/Th2 balance is maintained.[25,26] This may in part also explain the difference in cytokine profile in this study.

We showed previously that abdominal insufflation with CO_2 causes local peritoneal acidosis without affecting systemic acid-base status if properly ventilated.[27] West et al.[28] also showed that the cystosolic pH of macrophages significantly decreased with CO_2, whereas macrophages incubated with air and helium had no effect. Furthermore, West et al.[29] also showed that cultured peritoneal macrophages stimulated with LPS had a significant reversible decrease in TNF-α and IL-1 production when exposed to CO_2 in vitro with no inhibition with helium or air. This group suggests that local tissue acidification caused by peritoneal CO_2 insufflation might explain the decrease in the inflammatory response. Likewise, in previous studies we demonstrated that helium pneumoperitoneum does not cause local peritoneal acidosis or increase survival, whereas CO_2-pneumoperitoneum does cause local peritoneal acidosis and does increase survival in an LPS model of sepsis.[16,27] Taken together, CO_2-pneumoperitoneum–mediated acidification of the peritoneal cavity may explain the increase in survival. In this study, pretreatment with CO_2 insufflation "primed" the peritoneal cavity and prevented subsequent sequelae of endotoxic shock from laparotomy and a lethal dose of LPS.

Future work should be conducted to evaluate CO_2-pneumoperitoneum pretreatment in the face of a more clinically relevant model of sepsis such as cecal ligation and puncture. Furthermore, studies should be conducted to evaluate whether CO_2 protection observed in the abdominal cavity holds true in other macrophage-rich anatomic locations such as the pleural cavity. This study suggests that CO_2-pneumoperitoneum pretreatment may play an important role as an adjuvant or perioperative agent used in operations with a high risk of abdominal fecal contamination. Studies should also attempt to elucidate the specific mechanism whereby CO_2-pneumoperitoneum—whether by acidification or other means—"primes" the peritoneal cavity to subsequent infection or injury.

CONCLUSION

Our data demonstrate that 30 minutes of CO_2-pneumoperitoneum pretreatment increases survival among animals subjected to subsequent LPS-contaminated laparotomy. Furthermore, CO_2-pneumoperitoneum pretreatment significantly decreases IL-6 plasma levels 2 hours after LPS-contaminated laparotomy. Finally, this study further supports our and others' findings that CO_2-pneumoperitoneum is a potent anti-inflammatory agent with possible therapeutic properties.

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Comparative Evaluation of Gastrointestinal Transit and Immune Response Between Laparoscopic and Open Gastrectomy in a Porcine Model

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Several reports have shown advantages of laparoscopic gastrointestinal (GI) procedures when compared with their open counterparts. The aim of this study was to assess the differences of GI transit and immune response between laparoscopic and open gastrectomy in a porcine model. Fourteen pigs were assigned to undergo partial gastrectomy, either by laparoscopy (lap group) or by laparotomy (open group). GI transit was assessed using 24 markers and measured until half of markers were evacuated. To assess immune response, we used delayed-type hypersensitivity skin antigen testing (DTH) with vaccine antigen. DTH was evaluated at 48 hours after the primary injection for induration. After 2 weeks, all animals underwent necropsy and were evaluated for adhesion formation using a scoring scale. Operation time was significantly longer in the lap group. The GI transit in the postoperative phase was significantly prolonged compared with the preoperative measured times. Postoperatively, the GI transit in the open group was significantly prolonged compared with the lap group. Immune response measured by DTH was better preserved in the lap group than in the open group. Adhesion formation was significantly less in the lap group. We concluded that laparoscopic gastrectomy resulted in faster bowel recovery and less immune suppression. (J GASTROINTEST SURG 2006;10:39–45)

KEY WORDS: Laparoscopy, gastrectomy, gastrointestinal transit, immune response

Advances and experiences in laparoscopic surgery have made it possible to perform complex surgical procedures, including complex gastric surgery.[1,2] Evident benefits of laparoscopic procedures include better cosmesis, lesser postoperative pain, and faster recovery than conventional surgery. Efforts were made to compare the surgical stress response in different surgical procedures.[3–5] Laparoscopic gastric surgery is still not widely adapted. This is attributed partially to the complexity of the procedure and to the controversy over the applicability of laparoscopy in malignancy.

After surgical trauma, the inflammatory cascade causes changes in the activity of a wide variety of chemical substances, including catecholamines, nitric oxide, glucocorticoids, the complement-coagulation cascade, the kinin-bradykinin system, cytokines (including tumor necrosis factor, and interleukins), eicosanoids (arachidonic acid and its derivatives; leucotrienes, prostaglandins, and thromboxanes), endothelins, heat-shock proteins, platelet-activating factor, and macro radicals.[6–8] These cascades may interact by stimulating and aggravating various other mechanisms of the inflammatory response, which may lead to circulatory dysfunction and multiple organ failure. This physiological response, influenced mainly by the magnitude of the surgical trauma, is influenced by several factors such as anxiety, operative time, pain, hemorrhage, and infection. To minimize the surgical-related stress, improvements in anesthetic and operative techniques were suggested. Considering the significantly lesser trauma to the upper abdominal wall, laparoscopic surgery seems to present more appealing possibilities with respect to

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stress than traditional laparotomy.[6,7] Several reports have shown more preserved immune function after laparoscopic intervention in comparison to open techniques.[3–5,7] In a canine model, laparoscopic pancreatectomy demonstrated faster gastrointestinal (GI) transit and less stress response than open surgery.[4] In another experimental model, Burpee et al.[3] described a diminished stress response using delayed-type hypersensitivity (DTH) testing in laparoscopic liver resection when compared with open resection.

Laparoscopic surgery for early gastric cancer is gaining increased acceptance. Several case series have shown the objective advantages of laparoscopic gastrointestinal surgery.[9–13] Nevertheless, stress responses and GI transit after surgery are still inadequately addressed. We hypothesized that laparoscopic gastrectomy is associated with earlier recovery of GI transit and a lesser degree of stress response when compared with its open counterpart.

MATERIALS AND METHODS

Experimental protocols were reviewed and approved by the Institutional Animal Care and Use Committee of the Mount Sinai Medical Center, New York, NY. Experiments were performed in 14 Yorkshire female pigs weighing 30 to 40 kg. The animals were randomly allocated into two groups. In the laparoscopic group (lap group), seven pigs underwent laparoscopic partial (distal) gastrectomy, and in laparotomy group (open group), seven other pigs underwent a similar procedure. The animals were housed in an animal facility 7 days before intervention. They were maintained nil per os 12 hours before intervention with ad lib access to water. On the morning of surgery, they were premedicated with intramuscular injections of tiletamine (Telazol, 4.4 mg/kg)/xylazine hydrochloride (2.2 mg/kg) and 0.004–0.04 mg/kg of atropin. In the operating room, an intravenous line with ringer lactate was started at 100 ml/hour. General anesthesia was induced with intravenous 20 mg/kg thiopental intravenously. After endotracheal intubation, anesthesia was maintained with 1.0%–2.0% isoflurane and air/oxygen (FiO_2 = 0.50). Anesthetic methods and techniques were the similar in both groups. An antibiotic prophylaxis (intravenous amoxicillin, 7 mg/kg) was administered at the beginning of the procedure.

Five days before surgery, the preoperative baseline studies were performed in each animal for DTH skin testing and GI transit time. The anesthetic method was used in the same fashion.

Surgical Procedures

Laparoscopic group. Through a 10 mm skin incision in the supraumbilical area, a Veress needle was inserted and pneumoperitoneum was accomplished by insufflation with carbon dioxide up to 15 mmHg. A 12 mm diameter trocar was inserted through the incision, and a 30-degree laparoscope was introduced into the abdominal cavity. Four additional trocars were inserted under direct vision, including two 15 mm trocars in the right and left upper quadrant at the midclavicular line, one 12 mm trocar in the right of the lateral side, and one 5 mm trocar in the left side of the lateral abdomen (Fig. 1, *A*). An omentectomy was performed using

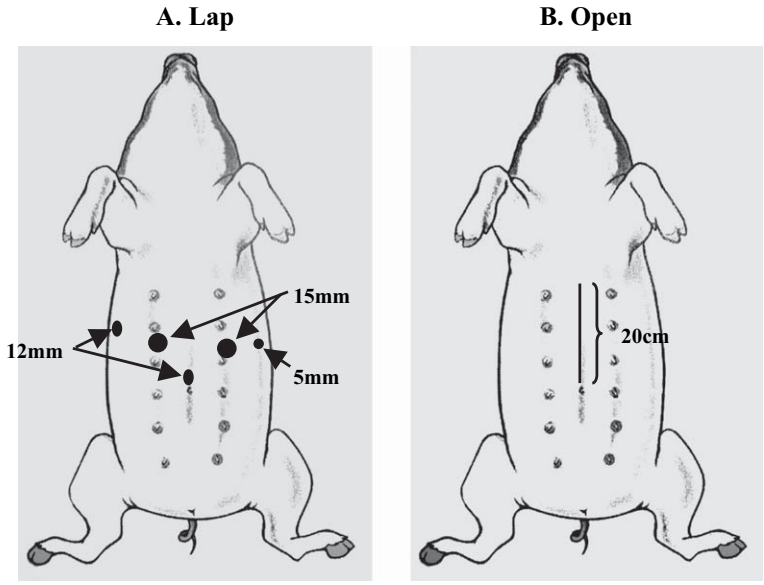

Fig. 1. (**A**) Trocar placement for lap group; (**B**) skin incision for open group.

ultrasonically activated shears (harmonic scalpel, UltraCision Inc., Smithfield, RI). This dissection was carried out to the right until the right gastroepiploic vessels were identified. These vessels were then divided with endoclips (United States Surgical Corp., Norwalk, CT) at their origin. To the left, the omentectomy was continued until the middle part of the spleen and the left gastroepiploic vessels were divided with either endoclips or the harmonic scalpel. The lesser omentum was opened using the harmonic scalpel. The right gastric artery was ligated with endoclips and divided. The short gastric vessels and left gastric artery were preserved. The first part of the duodenum was cleared by dividing the small vessels with the harmonic scalpel and transected with an Endo-GIA 30-3.5 (United States Surgical Corp.) approximately 2 cm distal to the pylorus. The proximal stomach was divided, and thus, subtotal gastrectomy was completed by using Endo-GIA 45-4.8. The specimen was retrieved in a sterilized nylon retrieval bag and removed through the 15 mm trocar site that was extended to approximately 2.5 to 3 cm. Next, the jejunum was divided 50 cm distal to the ligament of Treitz with Endo-GIA 30-3.5, and side-to-side anticolic isoperistaltic gastrojejunostomy with the distal limb was performed with Endo-GIA 45-4.8. The gastroenterostomy was closed with single-layer continuous 3-0 silk. A jejunojejunostomy was fashioned 100 cm below the gastrojejunostomy site as a side-to-side anastomosis with Endo-GIA 45-3.5, and the enterotomies were closed with single-layer continuous 3-0 silk. The mesenteric defects were left open, and all trocar sites were closed with 1-0 Vicryl for the fascia and 3-0 nylon for the skin.

Open group. A 20 cm skin incision was made at the upper midline (Fig. 1, *B*). The same procedure was carried out as with the laparoscopic technique using the same endoscopic stapler. The wound was closed with 1-0 Vicryl for fascia and 3-0 nylon for the skin.

Postoperative Care

After completion of the procedure, the animals were maintained nil per os for the first 12 hours, then gradually advanced from water to small frequent feedings of soft chow over the next 24 hours. Over the next days, they gradually progressed to a normal amount of solid food. Intravenous fluids were given until the animals were able to drink sufficient amounts. A heat lamp and/or pad were used if the measured body temperature was below 100° F. Cefazolin (25 mg/kg) was given for 5 days.

For intraoperative analgesia, one dose of intravenous buprenorphine (0.01 mg/kg) was administered at the beginning of the procedure. Postoperatively, a transdermal patch of fentanyl (100 μg for 72 hours), intramuscular Terazol (0.3–0.7 mg/kg) and/or Banamine (0.5–2.2 mg/kg) were used as judged necessary.

Blood Samples

Blood samples for complete blood count, chemistry (K, Na, Cl, glucose, total bilirubin, alkaline phosphate, aspartate aminotransferase, alanine aminotransferase, cholesterol, total proteins, albumin, gamma globulins, blood urea nitrogen, blood urea nitrogen/creatinine ratio), and C-reactive protein were collected in prechilled tubes as follows: before surgery, 4 hours, and 1, 2, 3, and 7 days after surgery.

Gastrointestinal Transit Study

Fed state GI transit times were measured using a divided nasogastric tube (0.5 cm pieces, number = 24) as X-ray visible markers (Fig. 2, *A*). Five days before surgery, the preoperative baseline study was performed on each pig. The 24 markers were introduced through a thick orogastric tube into the stomach with a small amount of water. An abdominal X-ray film was taken after placement of markers into the stomach for confirmation (Fig. 2, *B*). A GI transit time was defined as an interval from the insertion into the stomach to the point where half of the markers were evacuated (stomach-to-anus transit). For the postoperative GI transit study, the 24 markers were placed intraoperatively into the remnant stomach before closing the gastrojejunostomy. The GI transit time was measured using the same endpoints described above.

Stress Response Study

All animals were immunized with Rhinogen BPE vaccine antigen (Bordetella bronchiseptica–Pasteurella multocida–Erysipelothrix rhusiopathiae bacterin-toxoid, Intervet Inc., Millsboro, DE) at the age of 3 months as a presensitization. Each animal was given an intradermal 0.2 ml injection of Rhinogen BPE in the skin of the right forelimb. The greatest diameter of induration was measured in millimeters 48 hours after injection. The preoperative study was performed 5 days before surgery. When finishing the operation, 0.2 ml of Rhinogen BPE was injected in the skin of the left forelimb for experimental study.

Necropsy

Two weeks after surgery, the animals were sedated with Telazol (0.3–0.7 mg/kg intramuscular) and euthanized with an anesthetic overdose of

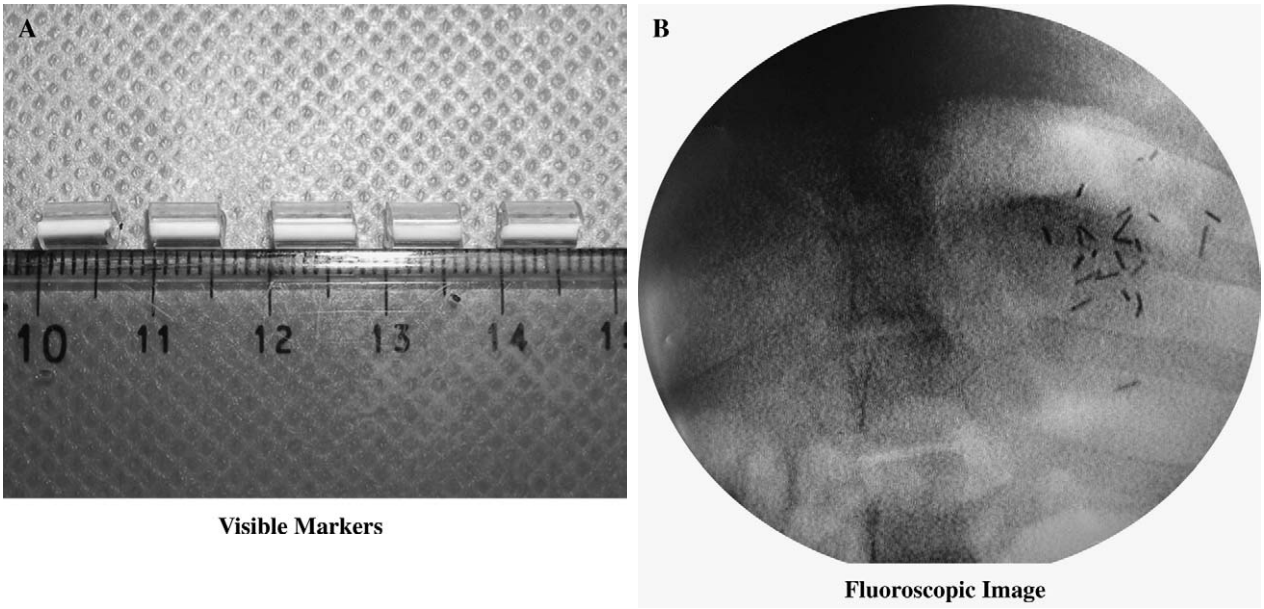

Fig. 2. GI transit time was measured using (**A**) X-ray visible markers made from a nasogastric tube that was divided in 5–7 mm sections. (**B**) Twenty-four markers were confirmed by abdominal fluoroscopic imaging after placement into the stomach.

pentobarbital (120–150 mg/kg IV) and then autopsy was performed. Adhesions were evaluated using the score described by LeBlanc et al.[14] (Table 1).

Statistical Analysis

StatView software version 5.0 (SAS Institute Inc., Cary, NC) was used for data analysis. Operative results and adhesion scores were compared using Student's *t* test (two-tailed). The blood test results were analyzed using repeated measures analysis of variance (ANOVA). GI transit time and DTH skin test results were analyzed using the Tukey-Kramer method. A *P* value of less than 0.05 was considered to be statistically significant. Results are expressed as mean ± SD (standard deviation).

RESULTS

Surgical Results

Surgical procedures were accomplished without any remarkable adverse events. Operation time was significantly longer in the lap group (157 ± 32 min) compared with the open group (109 ± 31 min). There were no significant differences in estimated blood loss between the two groups. Skin incisions were significantly longer in the open group (18.3 ± 2.2 cm vs. 10.5 ± 2.8 cm in the lap group). All operative results are shown in Table 2. In the postoperative phase, six (two in the lap group, four in the open group) of 14 animals experienced vomiting episodes and loss of appetite but recovered postoperatively within 2 or 3 days. Two animals had severe postoperative complications and were treated by conservative therapy such as infusions and antibiotics. We then decided to sacrifice the animals, because they had deteriorated. During the necropsy, we found the cause of deterioration; one in the open group had idiopathic ileoileal intussusception and another one in the in lap group had failure of the gastrojejunal anastomosis. The remaining 12 animals were observed for 2 weeks after surgery.

Gastrointestinal Transit Time

The baseline GI transit time was 56.6 ± 3.3 hours in the lap group and 58.1 ± 7.8 hours in the open

Table 1. Adhesion scoring scale

Score	0	1	2	3
Extent	0 adhesions	0%–25%	26%–50%	>50%
Severity	0 adhesions	Filmy/avascular	Vascular and/or dense	Cohesive
Dissection	0 adhesions	Falls away with gentle traction	Requires blunt dissection	Requires sharp dissection

LeBlanc et al.[14]

Table 2. Operative results

	Lap group	Open group	*P*
Body weight (kg)	32.6 ± 5.7	31.5 ± 4.1	NS
Operating time (min)	157 ± 32	109 ± 31	0.01
Established blood loss (ml)	68 ± 39	51 ± 47	NS
Skin incision (cm)	10.5 ± 2.8	18.3 ± 2.2	<0.0001
Adhesion score	4.8 ± 1.1	6.7 ± 1.4	0.03

Adhesion score was assessed in 12 animals (lap group, n = 6; open group, n = 6). NS = not significant. Values are means ± SD.

group. The mean transit time in the baseline study was 57.4 ± 6.0 hours. There were no significant differences between the two groups with regards to the baseline study. Postoperative GI transit time was 111.5 ± 10.7 hours in lap group and 137.9 ± 12.6 hours in the open group. The GI transit times in the postoperative phase were significantly prolonged compared with the preoperative measured times (Fig. 3). The postoperative GI transit time in the open group was significantly prolonged compared with that in the lap group ($P = 0.008$).

Delayed-Type Hypersensitivity Skin Testing

DTH skin testing for baseline study was performed at the same time as the GI transit time baseline study. The mean maximal diameter at 48 hours of the baseline study for both groups is shown in Fig. 4. No differences were observed between both groups.

The lap group had a significantly greater response to the DTH skin test than the open group ($P = 0.002$). There were no significant differences compared with the baseline study in this group. On the other hand, the open group had significantly lesser responses compared with the baseline study.

Blood Test Results

There were no significant differences between the two groups in terms of complete blood count and biochemical parameters analyzed.

Adhesion Formation

Adhesion formation was assessed during necropsy. The results of this analysis are shown in Table 2. At 2 weeks postoperatively, there were fewer adhesions in the lap group compared with the open group ($P = 0.03$). The most frequent locations for adhesions were the small intestine and the abdominal wall, or the gastrectomy staple line and the liver and spleen.

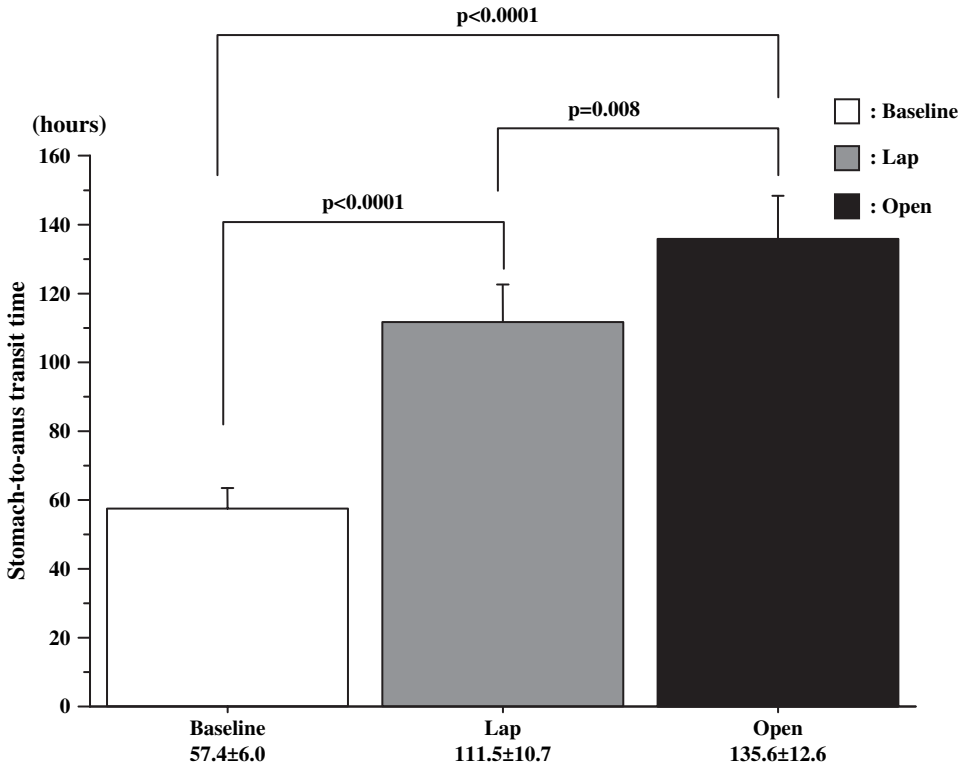

Fig. 3. Gastrointestinal transit time results.

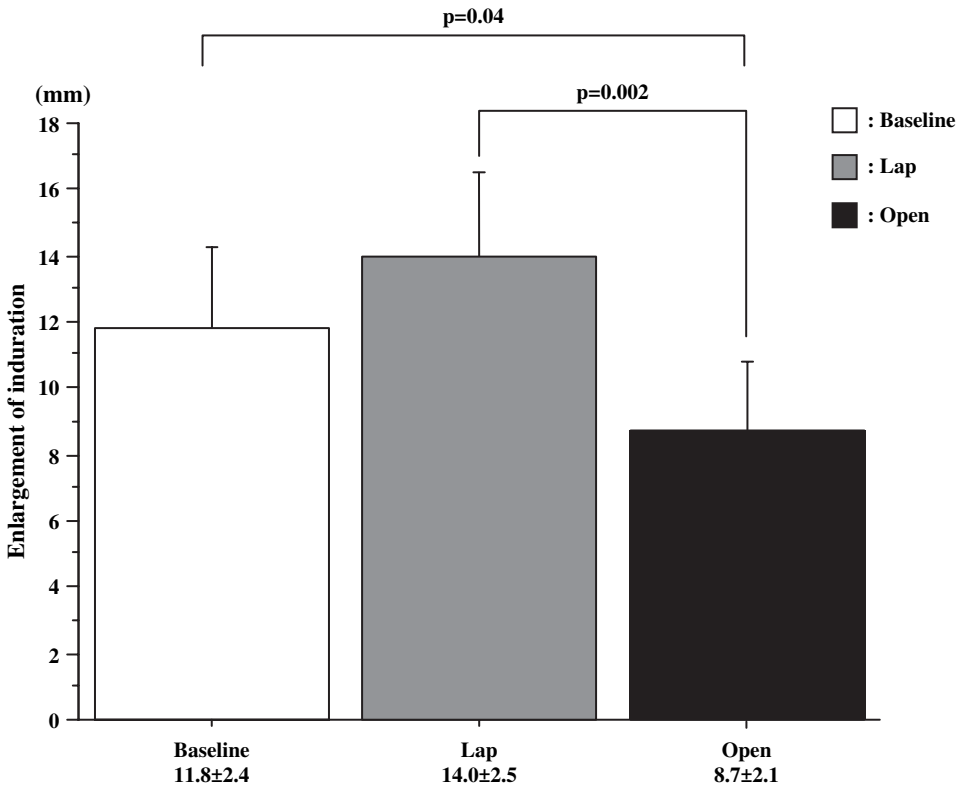

Fig. 4. Delayed-type hypersensitivity skin test.

DISCUSSION

Most experimental studies addressing immunologic postoperative changes reported less pronounced inflammation and changes in various immunologic parameters, as well as better preservation of the immune function, after laparoscopic procedures compared with conventional open surgery.[15–18] Minimally invasive surgery decreases the degree of abdominal wall tissue injury and theoretically allows better preservation of the body's immune integrity compared with open surgery.[19] These theoretical benefits might affect stress response and gastrointestinal recovery after surgery.

The DTH response is an in vivo assay of cell-mediated immune function.[20] DTH recall antigen testing involves the intradermal injection of a specific antigen to which the patient has been previously exposed. Bessler et al.[21] demonstrated that there is significantly less inhibition of DTH in animals after laparoscopic colectomy compared with those undergoing open colectomy. In a pig model using DTH as a reflection of T-cell function, Burpee et al.[3] reported a greater DTH response after laparoscopic liver resection compared with open surgery. Our study provides further evidence to support this concept. We found that laparoscopic partial gastrectomy was associated with better preservation of the immune response as measured in DTH skin testing, even though the operating time in the laparoscopic technique was longer. These results suggest that DTH response is affected by the degree of surgical trauma. However, the exact mechanism by which surgery causes immunosuppression is not fully understood.

Gastrointestinal motility is known to be affected by surgical trauma. Comparisons between laparoscopy and laparotomy of the gastrointestinal transit times have been well demonstrated by several authors.[4,22,23] In this study, we measured this as stomach-to-anus transit time using visible markers created from a divided nasogastric tube. This method is simple and associated with low cost. The laparoscopic technique resulted in faster recovery of the gastrointestinal tract than the open procedure.

During the necropsy, we assessed the adhesion formation utilizing the adhesion scoring scale described by LeBlanc et al.[14] There were significantly fewer adhesions in the lap group than the open group. Adhesion formation is a complex multistep process that occurs at the site of peritoneal injury. The surgical trauma represents the balance of fibrin deposition and degradation, which is regulated by

plasminogen activator 1 and 2 (PAI-1 and PAI -2), and tissue plasminogen activator (tPA) as an antagonist.[24] The fibrinolytic response is regulated by a number of cytokines, including interleukins-1 and -6, and tumor necrosis factor α, which increase PAI-1 secretion by mesothelial cells, thus enhancing fibrin deposition.[25] Laparoscopic surgery may also have an effect on mesothelial cell secretions of the proinflammatory cytokines as seen with macrophages, in particular interleukin-6, which is an autocrine cytokine for mesothelial cells.[26] As indicated in our results, laparoscopic surgery is associated with better preserved immune response than open surgery, which is reflected in less adhesion formation.

CONCLUSIONS

Laparoscopic gastrectomy was associated with stronger DTH response and faster bowel recovery when compared with open surgery in a porcine model. Diminished stress response may have resulted in fewer adhesions as well. Although further evaluation is needed, these experimental findings may be translated into practical clinical advantages after laparoscopic gastric resections.

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Immune-Enhancing Diet and Cytokine Expression During Chronic Sepsis: An Immune-Enhancing Diet Containing L-Arginine, Fish Oil, and RNA Fragments Promotes Intestinal Cytokine Expression During Chronic Sepsis in Rats

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Chronic feeding with enteral immune-enhancing diets (IEDs) provides benefits based on composition of the diet, route of feeding, and timing of feeding in relation to timing of trauma or surgery. Our prior studies of acute feeding in naïve rats demonstrated that IED promotes blood flow and proinflammatory cytokines in the ileum. We hypothesized that chronic feeding with IED would shift gut immune status to an anti-inflammatory state during chronic sepsis, resulting in an altered state of cytokine expression in the gut. Five days prior to feeding, gauze was implanted subcutaneously in the backs of male Sprague-Dawley rats, which were fed for 3 days with either control diet (CD, Boost; Mead-Johnson, Evansville, IL) or IED (Impact; Novartis) and randomly assigned to one of four groups: saline control (NS) + control diet (CD), sepsis (EC) + CD, NS + IED, or EC + IED. EC rats were inoculated with 10^9 CFU *Escherichia coli* and 10^9 CFU *Bacteroides fragilis* in 2 ml normal saline into the back sponge while NS rats received 2 mL normal saline alone. After 3 days, animals were anesthetized and gut tissue samples were harvested and frozen at –80°C. Tissue protein was extracted and ELISA was performed for interleukin (IL-1β, IL-5, IL-6, IL-10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ. In saline controls, IED feeding decreased IL-1β, IL-5, IL-6, TNF-α, and IFN-γ and increased IL-10 compared with CD-fed animals. In septic animals, IED feeding increased IL-5 and IL-6, while decreasing IFN-γ and IL-10 in the distal third of the small intestine compared with CD-fed septic rats, whereas IL-1β and TNF-α levels were unchanged. Chronic IED feeding produced a anti-inflammatory state via decreased IFN-γ and increased IL-5 and IL-6, which both promote gut IgA class switching, suggesting that the gut is shifted toward humoral immunity during chronic IED feeding in septic rats. (J GASTROINTEST SURG 2006;10:46–53)

KEY WORDS: IL-1β, IL-5, IL-6, IL-10, interferon-γ, TNF-α, immunonutrition, GALT, MALT, gut blood flow

Despite advances in treatment and therapies, severe sepsis presents a major health problem in the United States with 215,000 deaths per year, or 9.3% of all deaths, and approximately $17 billion in estimated medical expenses.[1] Affected patients develop a postinjury hypermetabolic state that leads to negative nitrogen balance and the loss of lean body mass, which primes the development of multiple organ failure.[1] In the past 20 years, the role that nutrition plays in reducing septic complications in ICU patients has been examined, including route of nutrient delivery (parenteral versus enteral),[2,3] timing of initiation of therapy,[4] and composition of individual diets.[5–13] Early enteral feeding with immune-enhancing diets (IED) decreased the rate of septic complications in some patients. Immune-enhancing nutrients include glutamine, L-arginine, ω-3 fatty acids, and RNA fragments, and many IEDs

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are available, such as Immun-Aid (McGaw, Irvine, CA), Nutren (Clintec, Chicago, IL), and Impact (Novartis, Minneapolis, MN).

The mechanisms whereby IEDs enhance immunity are diverse. Meta-analysis[14–16] of IEDs in the prevention of septic complications, length of hospital stay (LOS), and mortality concluded that IED reduced septic complications compared with standard diets in surgery patients.[14] In one study, critically ill and elective surgery patients who received IED had shorter LOS and decreased ventilator use compared with patients who received standard diets with comparable caloric and nitrogenous content. Interestingly, meta-analyses published to date have not demonstrated a benefit in mortality in IED-fed patients. How immunonutrients provide the benefits of decreased septic complications, decreased hospital stay, and decreased ventilator use remains a source of debate and the focus of intense basic science and clinical research.

Potential mechanisms of IED benefits include enhanced gut mucosal immunity, altered inflammatory processes, maintenance of intestinal tissue oxygenation and/or barrier function, and improved systemic nitrogen balance. We proposed that some of IED benefits might involve improved blood flow during nutrient absorption in the small intestine.[17–19] Postprandial hyperemia is dependent on nutrient composition and site of nutrient absorption.[20] The gut is the largest immune organ and contains approximately 80% of the immunoglobulin cells located in the gut-associated lymph tissue (GALT) of the ileum.[21] Adequate blood flow and nutrient delivery to the GALT tissue might help promote a well-directed immunological response to infection. In the present study, we hypothesized that chronic IED feeding in rats with chronic sepsis would stimulate an anti-inflammatory state by decreasing the Th1 proinflammatory cytokines interleukin (IL)-1β, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α and increasing the Th2 anti-inflammatory IL-10. We further proposed that chronic IED would increase IL-5 and IL-6 promoting antibody class switching to IgA and thus enhancing mucosal immunity. To produce chronic sepsis, we injected bacteria or saline into subcutaneous back sponges in Sprague-Dawley rats and randomly assigned these animals to be fed either IED or CD for 3 days prior to gut tissue harvest to measure cytokine expression in the small intestine (IL-1β, IL-5, IL-6, IL-10, TNF-α, and IFN-γ).

MATERIAL AND METHODS

Animal Care

Animals were maintained in a facility approved by the American Association for the Accreditation of Laboratory Animal Care. The research protocol was approved by the institutional Animal Care and Use Committee and Biohazard Safety Committee at the Louisville VA hospital. Thirty-two male Sprague-Dawley rats (200–220 g) were acclimated for 2 weeks prior to experimental use, during which time the animals received standard rat chow (20 g/day) and water ad libitum. Animal weights were recorded daily to ensure positive weight gain. Animals were housed in individual metabolic cages to prevent coprophagia, and a constant room temperature of 25 °C was maintained.

Chronic Sepsis Model

The current study used a model of chronic sepsis first described by Mela-Riker et al.[22] Over the years, our laboratory has adapted the model for use in microcirculation studies,[23,24] and it is briefly described here. Rats were anesthetized using intramuscular xylazine (60 mg/kg) and ketamine (150 mg/kg). Food, but not water, was withheld the evening prior to surgery. Using standard aseptic techniques, animals were prepped and draped in a designated survival surgical suite. An approximately 3-cm skin incision was made between the scapulas. Through a subcutaneous tunnel a sterile 5 × 5-cm^2 gauze sponge was placed near the base of the tail on the lower back. Incision was closed with interrupted 4-0 silk sutures. Animals were allowed free access to food and water during a 5-day recovery period. After the recovery period, a pooled bacterial inoculum consisting of 10^9 colony forming units (CFU) in 1 ml of *Escherichia coli* and 10^9 CFU in 1 ml of *Bacteroides fragilis* was injected percutaneously in the implanted sponge. Forty-eight hours following the first injection, animals received a second injection of pooled bacterial inoculum. Control animals were treated the same as septic animals but received 2 ml of saline percutaneous injections versus the bacterial inoculum. Experiments involving tissue harvest for cytokine assay were carried out 24 hours after the second sponge injection of either bacteria inoculum or saline (total of 72 hours sepsis or 72 hours saline control).

Feeding Regimen

Animals were fed 20 g/day of standard rat chow and water ad libitum for 5 days following sponge implantation. On the day of the first saline/bacteria injection, rats were fed 10 g of rat chow at 08:00. After bacteria or saline injections at 12:00, rats were fed either 30 ml of control diet (CD) or 30 ml of IED at 15:00. For the next 2 days, animals received a total of 60 ml of IED (1.00 kcal/ml) or 60 ml of CD

(1.01 kcal/ml) with half the dose (30 ml) at 08:00 and the other at 15:00. The dose of IED or CD given (60 ml/day) matched the caloric content of 20 g of standard rat chow (3.00 kcal/g) that our rats are normally fed on a daily basis. On the day of tissue harvest (72 hours after first bacteria/saline injection), rats were fed the 08:00 dose of IED or CD and then prepared for surgery/tissue harvest at 12:00. Table 1 shows the nutritional composition of the two diets. Boost CD was chosen because it is the best available match in nitrogen and caloric content of the IED used (Impact). Figure 1 outlines the experimental protocol timeline for sepsis, feeding regimen, surgery, tissue harvest, and cytokine assays.

Surgery and Tissue Harvest

At 12:00, 72 hours following the first injection of bacteria/saline, animals were anesthetized by intraperitoneal urethane (800 mg/kg) and α-chloralose (60 mg/kg) with supplemental urethane (25% of original dose) given as needed to maintain a surgical plane of anesthesia throughout the experimental protocol. Prior to surgery, animals received 1 ml of subcutaneous normal saline to maintain body fluid homeostasis. Body temperature was monitored and maintained at 37.0° ± 0.5°C using a heating pad and rectal thermistor. Using PE240 tubing, a tracheostomy was performed and animals spontaneously breathed room air. The right carotid artery was cannulated with PE50 tubing for measurements of mean arterial pressure (MAP) and heart rate (HR). Animals were allowed to equilibrate for 45–60 minutes following completion of the surgery. Following equilibration, animals' MAP and HR were recorded and averaged over a 20-minute period. Under deep surgical anesthesia, the small intestine was harvested and divided into thirds, and the gut contents removed and weighed. Tissue was placed in a 10% Triton X-100 reagent (1 ml/10 mg tissue), homogenized, and stored at −80°C until cytokine assay was performed. When assays were ready, samples were thawed and cytokine ELISAs for IL-1β, IL-5, IL-6, IL-10, IFN-γ, and TNF-α were performed. Protocols for the ELISAs followed the directions included in the individual kits (R&D Systems, Minneapolis, MN). Samples from the distal third segment of the small intestine (ileum) were assayed in triplicate with appropriate blanks and controls.

Table 1. Nutritional comparison of enteral diets used

Component (units)	CD (Boost)	IED (Impact)
Calories (kcal/ml)	1.01	1.00
Protein (mg/ml)	61	56
Carbohydrates (mg/ml)	139	132
Fat (mg/ml)	25	28
Sodium (mg/ml)	0.928	1.068
Potassium (mg/ml)	2.068	1.400
Osmolarity (mOsm/mg H_2O)	650	375
Immune-enhancing components	—	L-Arginine, ω-chain fatty acids, RNA fragments

Comparison of IED versus CD. Summary of composition differences between the control diet (CD, Boost; Novartis) and the immune-enhancing diet (IED, Impact; Novartis). Major differences include the presence of immune-enhancing components in the IED and the hyperosmolarity and increased potassium in the CD.

Statistical Analysis

Data are expressed as mean ± SEM, and differences between groups were determined by two-way analysis of variance (ANOVA). The null hypothesis was rejected a priori at $P < 0.05$. When differences were found using ANOVA, the post hoc Tukey-Kramer honestly significant different multiple range test was performed.

RESULTS

There were no significant differences in animal body weights found among the four groups of animals (Fig. 2). Some of the IED animals developed diarrhea during days 2 and 3 of feeding compared with no diarrhea in CD animals. We previously found that chronic diarrhea developed in all animals fed an IED diet during day 3 of feeding.[19] All animals had free access to water ad libitum and exhibited positive weight gain during the protocol. No differences in mean arterial blood pressure were observed between the four groups. As has been well described in the past, our chronic sepsis model resulted in a sustained tachycardia in both the IED and CD groups compared with saline controls. Similarly, septic animals had significantly increased spleen weights compared with saline controls (Fig. 2). Both tachycardia and increased spleen weights suggest a state of chronic inflammation produced by the sepsis model used.

Chronic feeding of CD and IED in animals given inoculums of bacteria or control injections of saline produced different patterns of cytokine expression in the small intestine. Figure 3 shows the levels of IL-1β, IL-5, IL-6, and TNF-α measured in the distal third of the small intestine, while Figure 4 shows the levels of IL-10 and IFN-γ in the distal, middle,

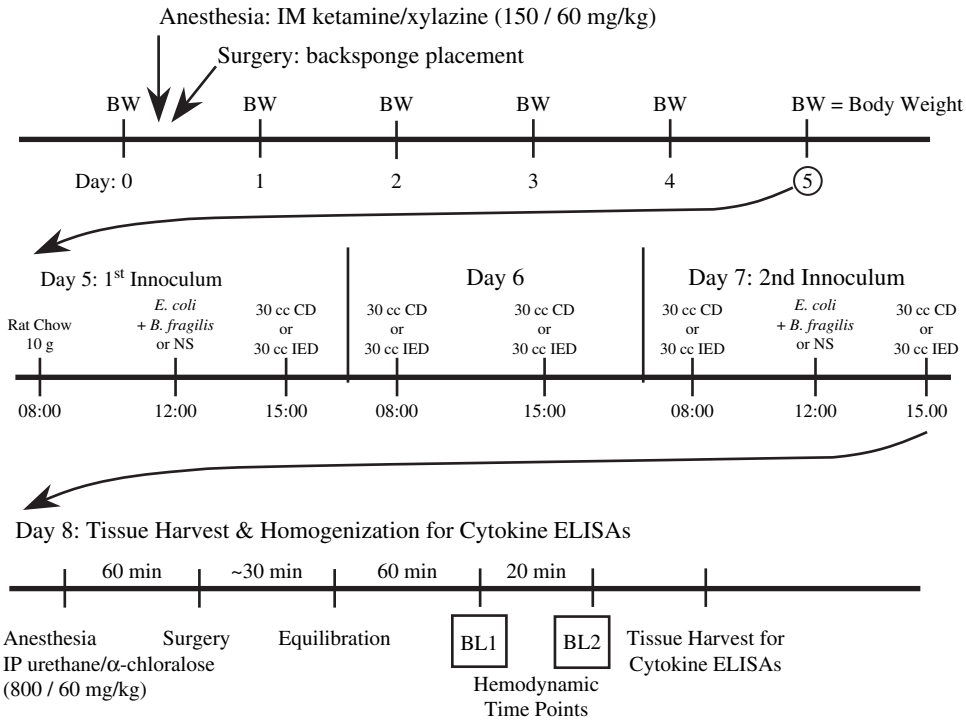

Fig. 1. Schematic of the protocol followed. *E. coli* = *Escherichia coli*, 10^9 CFU in 1 ml normal saline (NS); *B. fragilis* = *Bacteroides fragilis*, 10^9 CFU in 1 ml NS; BW = body weight measurement; CD = control diet, Boost, Novartis; IED = immune-enhancing diet, Impact, Novartis; IM = intramuscular; IP = intraperitoneal; BL = baseline.

and proximal thirds of the small intestine. IED saline decreased levels of IL-1β, IL-5, IL-6, and TNF-α in ileal segments when compared with CD-fed saline animals. IED saline significantly increased tissue levels of IL-10 in all three small intestine segments (Fig. 4, *A*) compared with CD saline. Conversely, IED saline IFN-γ tissue levels are decreased in all three segments versus CD saline (Fig. 4, *B*). IED sepsis increased IL-5 and IL-6 but remained unchanged in IL-1β and TNF-α compared with CD sepsis. IFN-γ levels remained unchanged in proximal and middle thirds; however, IED sepsis decreased IFN-γ in the distal third compared with CD sepsis. IL-10 levels were unchanged in proximal, but decreased in middle and distal, IED sepsis.

Sepsis and saline produced another set of distinct cytokine patterns in each individual diet. IED and CD saline IL-1β tissue levels remained unchanged compared with IED and CD sepsis (Fig. 3). Sepsis increased IL-5 and IL-6 in IED but significantly decreased tissue levels in CD-fed animals (Fig. 3, *C* and *D*). TNF-α levels remained unchanged by sepsis in CD animals and increased in IED-ed animals (Fig. 3, *B*). IL-10 levels in all three intestinal segments in CD animals remained unchanged by sepsis, with all three tissue levels being significantly lower in IED animals (Fig. 4, *A*). Conversely (Fig. 4, *B*) IFN-γ levels were significantly increased in IED saline versus IED sepsis in all tissue. IFN-γ levels remained unchanged by sepsis in CD-fed animals.

DISCUSSION

In a recent editorial opinion, Singer and Cohen[25] stated that despite advances in inflammation research, the application of these findings is complex, including with regard to the appropriate use of immunonutrition. The metabolic response to stress requires a physiologic insult to initiate cytokine release (IL-1β, IL-2, IFN-γ, and TNF-α), to activate cellular immunity, and promote the proinflammatory systemic inflammatory response syndrome (SIRS).[26] Simultaneous with upregulation is feedback inhibition by the inflammatory process to release anti-inflammatory cytokines (IL-4, IL-10, and IL-13). The pattern of cytokine secretion that predominates will determine immune competence to respond to trauma, illness, or surgery. This process is been called the mixed antagonist response syndrome (MARS).[27]

Recent studies focused on the ability of specific immune-enhancing nutrients to stimulate immunity

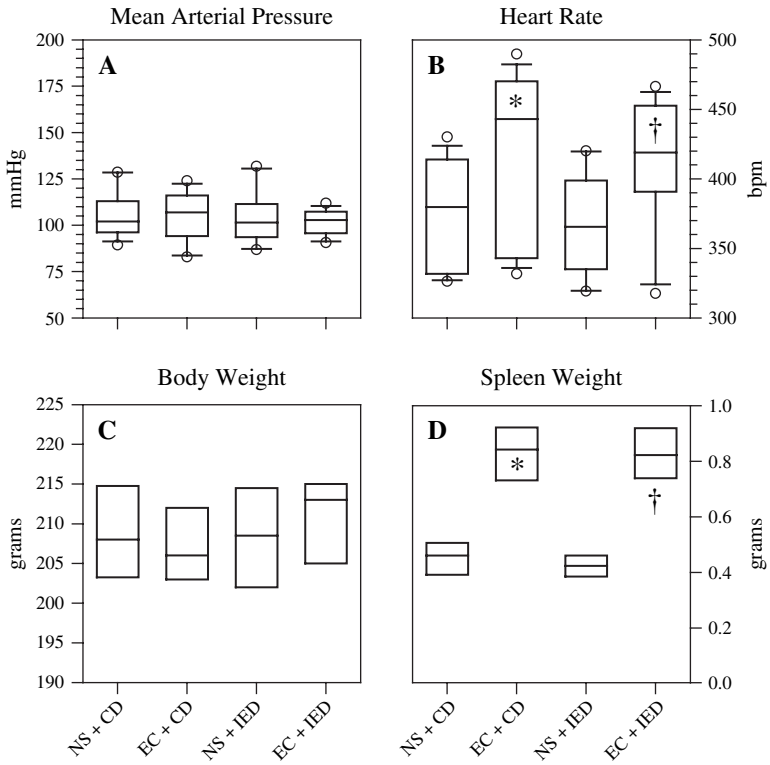

Fig. 2. (**A**) Mean arterial blood pressure, (**B**) Heart rate, (**C**) Body weight, and (**D**) Spleen weight in septic (EC) or control (NS) rats after 72 hours of feeding with either control diet (CD) or immune-enhancing diet (IED). *$P < 0.05$ versus corresponding saline control group.

to promote healing.[28,29] Nutrients that possess immune-enhancing properties include L-arginine, glutamine, taurine, ω-3 fatty acids from fish oil, messenger RNA fragments, antioxidant vitamins (vitamin A, vitamin E, and vitamin C), and trace minerals (zinc, selenium, and copper).[30] The use of immune-enhancing nutrients alone or in combination in immune-enhancing enteral diets (IEDs) has stimulated debate and research to elucidate the proper role of these IEDs in the treatment of critically ill patients. Suggested roles of IEDs range from use in acute illness or trauma to use in chronic debilitating illnesses such as inflammatory bowel disease and rheumatoid arthritis. Meta-analyses[14–16,29] assess the current literature with conclusions ranging from endorsements of IEDs to suggestions that IEDs might promote morbidity and mortality in some disease conditions and/or patient populations. These findings are not surprising. We[19] and others[25] have pointed out that the constant flux of immune cells and mediators results in a dynamic state that responds differently to stimuli depending on the stage of the disease process, the combination of specific immune-enhancing nutrients administered to various patient populations, and the dosage, timing, and route of the IED administration.

The response of the gut to physiologic insult is complex.[31] Mucosal immunity, inflammation, and tolerance to bacterial pathogens require $CD4^+$ T-lymphocytes (including both Th1 and Th2 subsets), $CD8^+$ cytotoxic T cells, and other T-cell subsets (T regulatory cells).[32,33] B-lymphocytes are also required and undergo commitment through $\mu \rightarrow \alpha$ class switching.[34] Interactions between B cells and $CD4^+$ T cells induce plasma cells to stimulate polymeric IgA production.[35] Mucosal immunity also depends on antigen-presenting cells ($CD4^+$ T cells, $CD8^+$ T cells, and epithelial cells) to produce cytokines to regulate the overall immune process as outlined above. The mix of cytokines produced in large measure determines the response of the system to shift toward humoral or cellular immunity. Naïve $CD4^+$ T regulatory cells, which have never encountered antigen, can differentiate into activated (effector) cells or memory cells.[32,33] The mucosal migration patterns of these three T regulatory cell subsets (naïve, effector, and memory) along with B cells form the basis of gut mucosal immunity. In the presence of foreign peptide antigens, naïve $CD4^+$ T regulatory cells and antigen-presenting cells become differentiated to effector $CD4^+$ T regulatory cells and, depending on the overriding cytokine milieu,

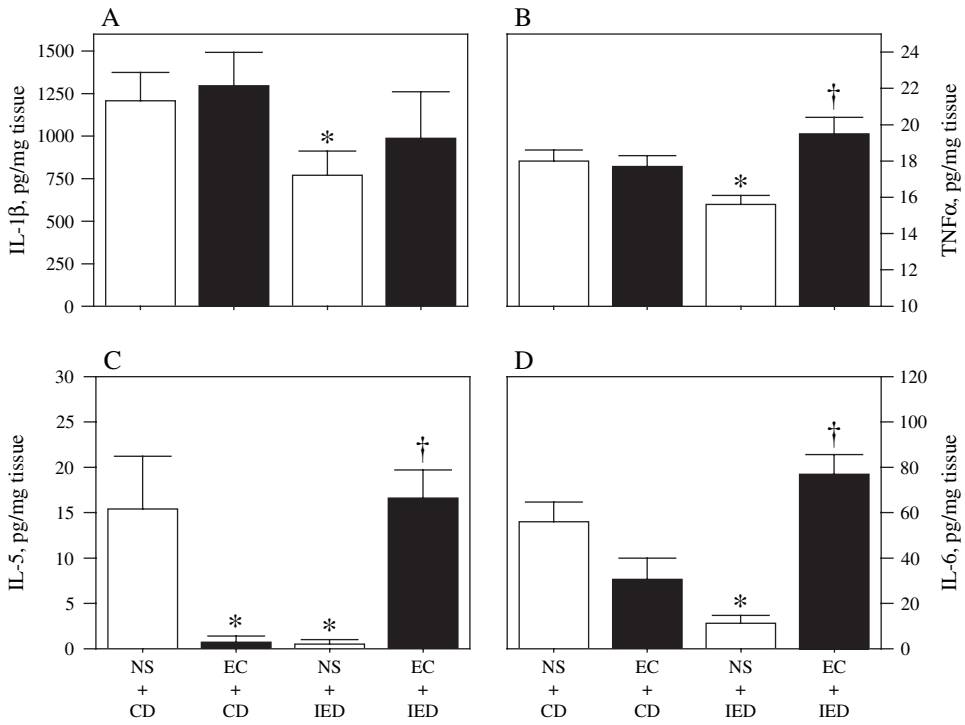

Fig. 3. (**A**) Interleukin-1β (IL-1β) protein levels expressed as picograms per milligram of tissue in the last third of the small intestine in the septic (EC) versus control (NS) groups fed either CD or IED. (**B**) IL-5 protein levels in the last third of the small intestine demonstrating decreased IL-5 in septic rats compared with saline control and decreased IL-5 in IED-fed rats compared with CD-fed saline rats. IED feeding in septic rats restored IL-5 to control levels. (**C**) IL-6 protein levels in the last third of the small intestine demonstrating a similar pattern to that observed for IL-5. Again, IED reversed the effects of sepsis on IL-6 level. (**D**) TNF-α protein levels in the distal third of the small intestine. IED decreased TNF expression in the saline groups while increasing TNF expression in the septic animals. *$P < 0.05$ versus NS + CD group. †$P < 0.05$ versus NS + IED.

promote either the cell-mediated Th1 immunity or the humoral-mediated mucosal antibody Th2 response.[32,33] Thus, the cytokine environment of the mucosa-associated lymphoid tissue (MALT) reservoirs of Th cells determines the induction of the cell subsets to stimulate humoral or cellular processes. Iwasaka and Noguchi[36] have shown that in human patients with severe sepsis, Th2 cell–mediated processes predominate (humoral immunity), which they suggest might lead to immunosuppression in these patients.

Furthermore, mucosal IgA is regulated by Th1 versus Th2 cell subsets.[37] As already noted, $CD4^+$ T helper cells are required for the mucosal IgA response to protein-based antigens. Th2 cells are more efficient at regulating this process, and significant cross-regulation exists between the two pathways. Th1 cells produce IFN-γ, which facilitates isotype switching from IgM to IgG_{2a} and inhibits IL-4-induced isotype switching, to inhibit Th2 cell proliferation.[34] Conversely, Th2 cells produce IL-4 despite enhanced, ongoing Th1 responses to inhibit Th1 cytokine secretion.[38] The presence of IL-12 promotes the continuation of the Th2 response.[39] In the present study, we focused on the pattern of cytokine protein levels in the tissue to assess the functional response to septic shock of the terminal ileum, the site of most GALT in the gastrointestinal system. In order to characterize the GALT response to sepsis and IED, studies are needed to analyze the subclass response of IgG, IgE, and IgA in this model.

In the present study, we describe the gut cytokine response after chronic feeding with IED or CD in septic versus saline control rats. These data demonstrate a decrease in proinflammatory cytokines (IL-1β, IL-6, IFN-γ, and TNF-α) in animals fed IED compared with CD and an increase in the anti-inflammatory cytokine IL-10. The cytokines measured in this study have multiple effects.[40] In the gut, IL-1β from macrophages activates the vascular endothelium and lymphocytes and increases the proliferation of effector cells, with the end result of producing fever and increasing IL-6. IL-6 from macrophages stimulates lymphocyte activation and increases

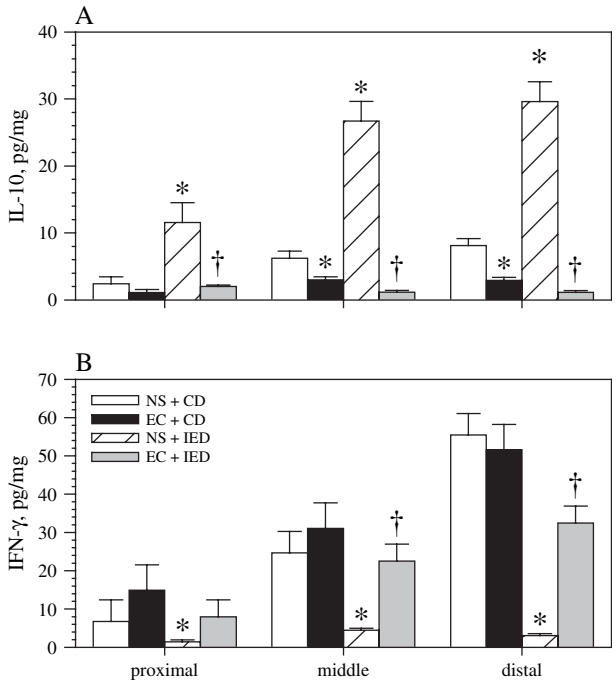

Fig. 4. (**A**) IL-10 protein levels in the small intestine of rats. IED stimulates IL-10 production in all three segments of the small intestine compared with CD-fed rats, but sepsis reverses this finding. (**B**) IFN-γ protein levels suggesting that IED protects IFN-γ production in septic rats in the terminal ileum (distal third). *$P < 0.05$ versus NS + CD group. †$P < 0.05$ versus NS + IED.

antibody production, which also promotes fever and induces acute-phase protein reactants. TNF-α from macrophages and Th1, some Th2, and cytotoxic T cells activate and induce nitric oxide production (inducible nitric oxide synthase) and activate the vascular endothelium. Overall, these three cytokines activate complement opsonization, promote phagocytosis, decrease viral and bacterial replication (through increased body temperature), increase antigen processing, and facilitate the adaptive immune response to antigen. IL-5 from Th2 cells promotes differentiation of B cells and production of IgA as well as eosinophil growth and differentiation from hematopoietic bone marrow stem cells. Th2 cells also produce IL-10, which promotes switching to MHC class II in B cells, inhibits Th1 cells, inhibits cytokine release from macrophages, and stimulates mast cell growth from hematopoietic cells. Th1 and cytotoxic T cells produce IFN-γ to activate macrophages and promote MHC class I and class II in macrophages and somatic cells as well as promoting B-cell differentiation and IgG_{2a} synthesis, inhibiting T cell growth, activating natural killer cells, and promoting other antiviral processes. In our study, sepsis decreased IL-10 and IFN-γ in the IED-fed rats compared with the saline control IED-fed rats and also reversed IL-5 and IL-6 expression in the terminal ileum, suggesting that IED promotes IgA class switching in the terminal ileum, presumably at the site of MALT.

CONCLUSIONS

IEDs have received significant interest in recent years, including the 1995 study of Bower et al,[41] which reported that in septic patients who received adequate doses of Impact, an IED, the IED imparted equal safety, decreased rate of infectious complications, and reduced length of hospital stay compared with standard liquid diets. In our study, we examined the small intestinal production of proinflammatory (IL-1β, IL-6, IFN-γ, and TNF-α) versus anti-inflammatory (IL-10) cytokines in septic rats chronically fed either IED containing L-arginine, mRNA fragments, and ω-3 fatty acids or an isonitrogenous, isocaloric control diet lacking immune-enhancing nutrients. We found that septic rats fed IED for 72 hours after the onset of sepsis had decreased GI production of proinflammatory cytokines, increased anti-inflammatory cytokines, and enhanced IgA class switching in B cells via increased IL-5. Thus, the cytokine milieu of the IED-fed septic rats promoted gut mucosal humoral immunity and immunoglobulin production via a predominantly Th2 pathway.

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Gastroesophageal and Pharyngeal Reflux Detection Using Impedance and 24-Hour pH Monitoring in Asymptomatic Subjects: Defining the Normal Environment

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Airway symptoms are often caused by aspiration of refluxed materials into the larynx. In this study we sought to define the frequency, character, and proximal extent of refluxed contents — including nonacid reflux—in normal subjects using intraluminal impedance to improve our understanding of the relationship between reflux and aspiration. Ten subjects, who had no symptoms of gastroesophageal reflux disease or airway disease, underwent impedance/pH monitoring with a catheter that allowed simultaneous esophageal and pharyngeal monitoring. Impedance detected 496 gastroesophageal reflux episodes in the 10 subjects during 240 hours of study. The majority, 399 (81% of the total) were acid reflux episodes (pH $<$ 4). Ninety-seven were nonacid (pH $>$ 4). Most reflux episodes (348 of 496) reached the mid esophagus (9 cm above lower esophageal sphincter). There were 51 reflux episodes that reached the pharynx (PR). Only 13 (25%) of PR were acidic (pH $<$ 4), while 38 were nonacid. Twenty-six PR episodes were liquid and 25 were mixed (liquid and gas). The median number of PR episodes measured with impedance was 5 (0–10). In asymptomatic subjects, most episodes of gastroesophageal reflux are acidic and reach the midesophagus. Reflux into the PR appears to be more common than previously believed, and most of these episodes are not acidic. Thus, traditional 24-hour pH monitoring may underestimate the presence of pharyngeal reflux. The combination of impedance with pH monitoring markedly enhances our ability to accurately detect potential microaspiration. (J GASTROINTEST SURG 2006;10:54–62)

KEY WORDS: Gastroesophageal reflux, respiratory symptoms, extraesophageal symptoms, airway symptoms, pharyngeal reflux detection, esophageal impedance

Gastroesophageal reflux is a normal phenomenon that results from transistory loss of gastroesophageal competence due to a decrease of lower esophageal sphincter (LES) pressure, an increase in abdominal pressure, gastric distention, and a variety of other physiologic conditions. When the number, the duration, or the upper extension of these episodes exceeds a certain threshold and/or when the patient develops symptoms or mucosal damage, physiologic reflux becomes gastroesophageal reflux disease (GERD).

Most previous studies have analyzed the physiology and pathophysiology of reflux episodes using 24-hour pH monitoring. Indeed this technique remains the goal standard to differentiate physiologic from pathologic reflux. However, 24-hour pH monitoring has limitations, particularly in that it is not able to detect episodes of reflux unless the pH is

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below 4 and usually measurements are limited to relatively short segments of the esophagus.

A better understanding of the character, composition, and proximal extension of gastroesophageal reflux and of pharyngeal reflux in normal people may yield valuable information and set the basis for a more thorough explanation of ways in which reflux causes esophageal and extraesophageal pathology. We undertook this study to examine these and other aspects of normal reflux episodes. We wished to determine how often a *normal* reflux episode was acidic or nonacidic, how high it reached in the esophagus, whether its composition changed while in the esophagus, and whether some of these episodes reached the pharynx. To do this end, we used impedance and 24 hour pH measurements. Impedance provides information about (a) the physical characteristics of the refluxate (liquid, gas, or mixed); (b) the direction of the flow (oral or aboral); and (c) the acidity of the reflux event by placing pH sensors on the catheter. Since microaspiration is a major component of GERD-related airway disease, we hypothesized that combined pH/impedance pharyngeal monitoring would provide valuable information regarding the mechanism by which aspiration occurs.

METHODS

Patient Selection

Ten subjects (seven males and three females) were provided a self-administered, standardized symptom questionnaire. The questionnaire queried the frequency (0 = never, 1 = once/month, 2 = once/week, 3 = once/day, 4 several times/day) of the following 18 symptoms: heartburn, regurgitation, chest pain, solid dysphagia, liquid dysphagia, bloating, odynophagia, hoarseness, abdominal pain, nausea, postprandial pain, bloating, globus, aspiration, wheezing, cough, shortness of breath, and sore throat. Each subject answered "never" for all symptoms, and this was confirmed by a study investigator.

This study was approved by the University of Washington's Human Subjects review board (HSD-02-4684-D02).

Manometry/Impedance

A solid-state combined manometry and impedance measurement catheter was used to exclude motor disorders and to accurately identify the location of the upper esophageal sphincter (UES) and LES. The design combines five manometry channels with four pairs of impedance sensors, each separated by 5 cm. A station pull-through measurement of the LES pressure determines the characteristics of the sphincter. The LES pressure was averaged over a series of three respiratory cycles. The peristaltic pump of the esophageal body was assessed over a minimum of 10 episodes of deglutition with 5-ml aliquots of normal saline. Ten additional swallows with 5 ml of viscous material (Sandhill Scientific Inc., Highlands Ranch, CO) were performed. Each swallow evaluated the speed, duration, amplitude, and propagation of the peristaltic wave, as well as the clearance of the swallowed bolus across each pair of impedance sensors and through the esophagus. The UES location, pressure, and relaxation were measured before completion of the procedure.

Twenty-Four – Hour Esophageal and Pharyngeal pH and Impedance Monitoring

A specially designed bifurcated solid-state pH/impedance catheter was used (Sandhill Scientific Inc.) (Fig. 1.) The bifurcation allows one branch to be positioned with a pH sensor 5 cm above the LES while the other was placed with the proximal sensor 2.0 cm above the UES as determined by stationary esophageal manometry. In this position, one catheter has four pairs or impedance sensors that were placed in the esophagus 3,5,7, and 9 cm above LES and a pH sensor 5 cm above the LES. The other catheter branch has a pH sensor 2 cm above the UES and a pair of impedance sensors below (5 cm) and above (2 cm) the UES. The catheter was placed transnasally and connected to a recording device worn by the patient for 24 hours. The information was entered into a software program, which reported events (number and duration of reflux episodes) and calculated acid exposure times over the course of the study. Data were acquired with Sleuth Software (Sandhill Scientific Inc.) and analyzed with the Bioview GERD Analysis Software (Sandhill Scientific Inc.) All tracings were individually reviewed, rather than relying on the computer interpretation, to determine reflux episodes and the proximal extent as measured by pH and impedance. Meal periods were excluded from the analysis. All subjects tolerated the procedure well without incident or complications.

Impedance Definitions

Liquid episodes. We defined as "liquid" an episode of reflux that manifested as a drop in the impedance (measured in Ohms) of more than 50% from its baseline. To be considered as reflux, the episode should start in the distalmost sensor and propagate aborally in at least the two distalmost sensors. The height reached within the esophagus by the reflux episode was defined as the most proximal impedance

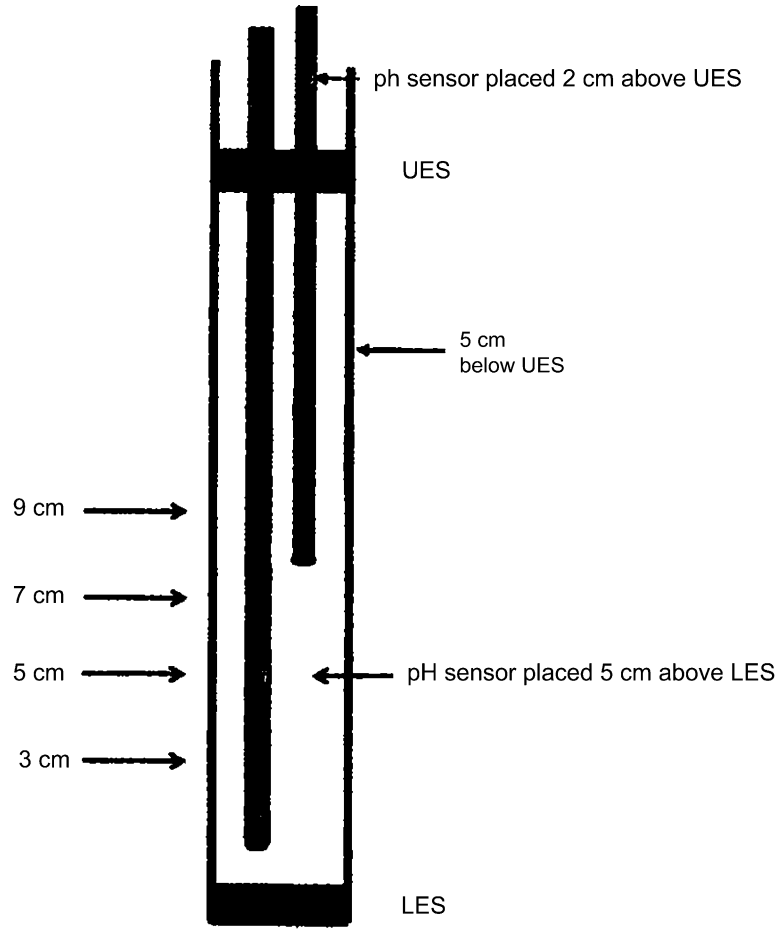

Fig. 1. Bifurcated (proximal and distal branch) impedance/pH catheter.

drop that met all criteria at that level and each of the subsequent distal sensors (Fig. 2).

Gas episodes. We defined a gas reflux episode as one that was associated with an increase in the impedance level (in Ohms) of at least 50% from the baseline level, when there was a simultaneous or aboral propagation from the most distal channel.

Mixed episodes. A mixed episode was one in which there was a combination of liquid and gas criteria in the same episode.

Pharyngeal reflux. For an episode to be categorized as pharyngeal reflux, a 50% drop in the impedance in an aboral direction was required to be present in all sensors, including the most proximal sensor in the pharynx (Fig. 3).

Acid reflux. An esophageal reflux episode by impedance was defined as acid if there was a corresponding drop in the pH sensor below 4 in the sensor located 5 cm above the LES. A pharyngeal reflux episode was defined as acid reflux if the pH in the pharynx concomitantly dropped below 4.

Nonacid reflux. A reflux episode detected by impedance in which the pH in the corresponding pH sensor did not record a pH below 4 (Fig. 4).

RESULTS

Esophageal Motility

Monometry data. The Median LESP was 20.2 mm Hg (12–33.9 mm Hg). Peristalsis was present and normal in 100% of swallows. The average distal esophageal amplitude was 70.7 mm Hg (42–106 mm Hg).

Impedance data. Impedance showed complete bolus transit in 100% of liquid swallows and in 94% of viscous swallows. The median bolus transit time was 7.0 seconds (5–9.2 seconds).

Gastroesophageal Reflux

A total of 496 gastroesophageal reflux episodes were detected by impedance in these 10 subjects. The median number of reflux episodes per patient per 24 hours was 46 (29–82). Of these, 399

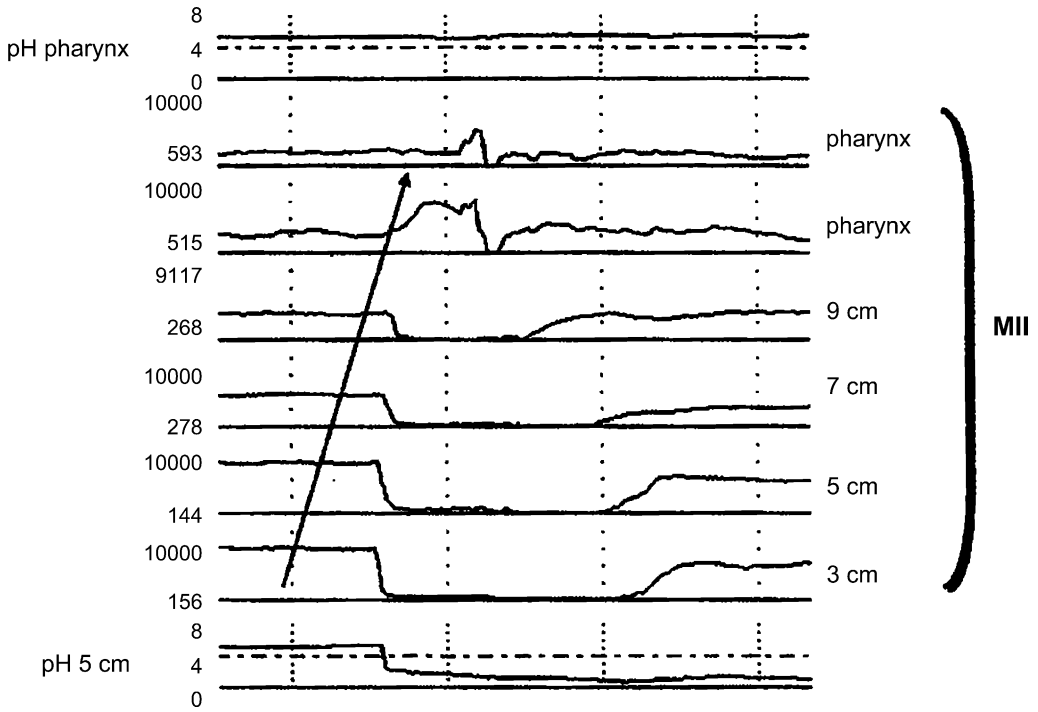

Fig. 2. Nonacid pharyngeal reflux event (liquid).

(80.4%), were acidic (pH < 4) and 97 were nonacid (pH > 4) (Table 1). Three hundred forty eight (70%) of the episodes extended to at least the mid esophagus 9 cm above the LES (Table 2). Only 122 (25%) episodes reached the most proximal esophageal sensor (5 cm below the UES). The mean amount of time that the reflux episode remained in the esophagus before being cleared was 20 seconds (1.5–126 seconds). The average acid exposure time over 24-hour a period at 5 cm above the LES was 2.26% (1.5–3.4%). All reflux episodes detected by pH were detected by impedance as well. None of the subjects recorded any GERD-related symptoms during the study.

Pharyngeal Reflux

Fifty-one episodes of reflux were detected at the level of the pharynx by impedance measurements (Table 1). The median number of episodes measured per patient with impedance was 5 (range, 0–10). The mean was 5.5 (SD=3.8). Of these 51 episodes, 40 had a pH < 4 when in the distal esophagus (5 cm above the LES). When they reached the pharynx, only 13 episodes (25.5%) were still acidic. Twenty-six pharyngeal reflux episodes were purely liquid and 25 were mixed (liquid and gas). The mean amount of time that the reflux episode remained in the pharynx before being cleared was 6 seconds (0.2–18.6 seconds).

There were 15 pharyngeal reflux episodes detected by pH monitoring over the 240 hours of monitoring in these 10 subjects. The median number of pharyngeal reflux episodes detected by pH monitoring in a 24-hour period was 1 (0–6) per subject. Thirteen of these acid reflux episodes were detected by impedance (87%).

DISCUSSION

In this study, we sought to determine the character, composition, and upward extent of reflux episodes that occur in normal individuals. In particular we wished to determine the relationship of distal to proximal reflux and to define the role (if any) of nonacid reflux into the pharynx of normal subjects. We found that impedance, when combined with pH monitoring, produces a wealth of important information regarding esophageal and pharyngeal reflux. Indeed, we found that four of five reflux episodes in the distal esophagus are acid and that about three-fourths of acid and nonacid episodes up to at least 9 cm above the LES. Moreover, our study showed that reflux into the pharynx is more common than was previously believed and that most of these

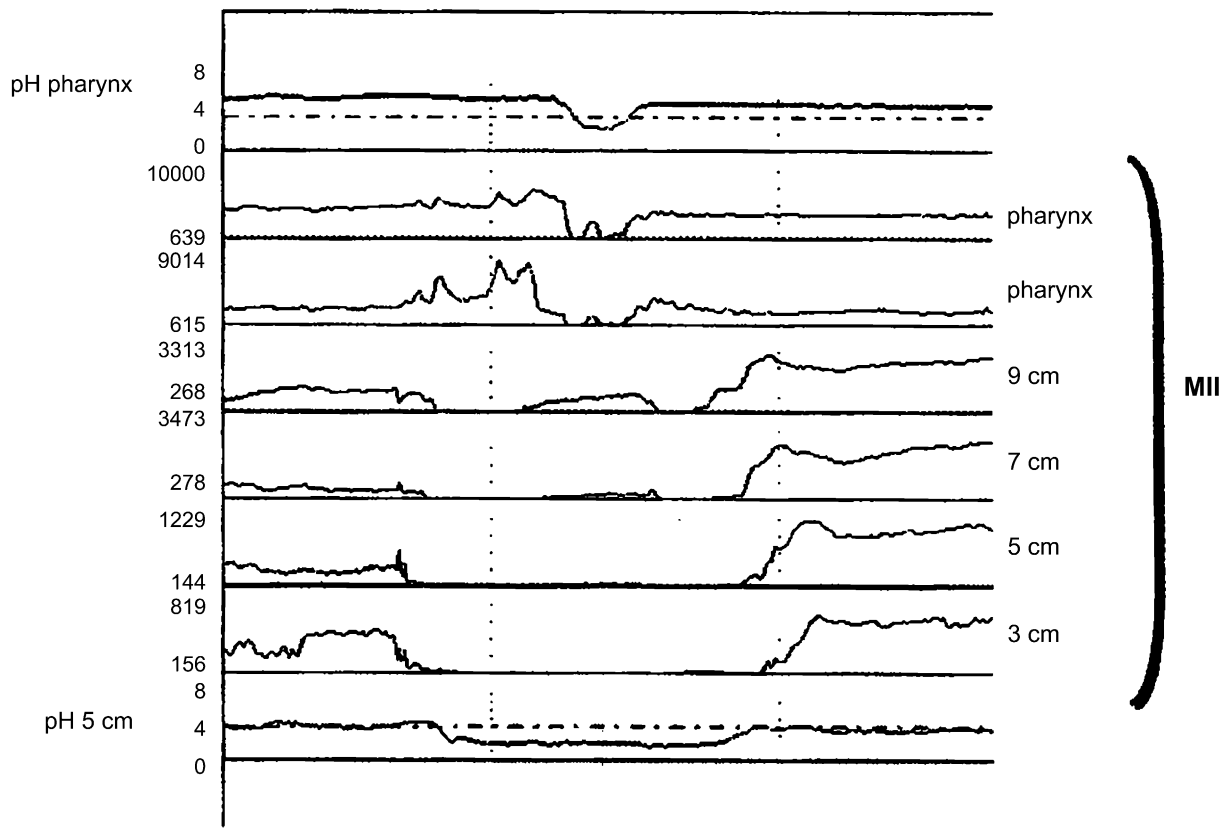

Fig. 3. Acid pharyngeal reflux event (mixed).

episodes (75%) are nonacid, suggesting that as refluxed materials extend further upward into the esophagus, they are at least partially neutralized. Because up to 20% of reflux episodes in the distal esophagus and around 80% of such episodes in the pharynx are nonacid, impedance, combined with 24-hour pH monitoring, provides a unique way to study the importance of nonacid reflux in the pathophysiology of GERD and is likely to greatly improve our understanding of the role that microaspiration has in the pathogenesis of GERD-related respiratory disease.

The Use of Impedance in the Study of Esophageal Physiology

Twenty-four – hour pH monitoring has provided, up until recently, the only reliable way to study gastroesophageal and pharyngeal reflux. Of course, its major shortcoming is that it only detects episodes when the pH is less than 4. With the advent of esophageal impedance we are now able to accurately determine gastroesophageal reflux episodes, regardless of their pH. Impedance is the measurement of electrical resistance. By attaching pairs of electrical sensors to a catheter that is placed within the esophageal and/or pharyngeal lumen, impedance can detect the presence of a refluxed substance. Refluxed material causes a change in the lumen's ionic content, which changes the impedance between the electrical sensors. In the case of liquid refluxate, there is a drop in the impedance; with air, the impedance rises. A catheter that has multiple impedance sensors located at different levels can evaluate the proximal extension of the refluxate. Additionally, impedance provides information about the physical characteristics of the refluxate (liquid, gas, or mixed), the direction of the flow (oral or aboral), and, by placing pH sensors on the catheter, even the acidity of the reflux event. An example is the recognition that the majority of reflux episodes are a mixture of gas and liquid.

Other techniques to measure nonacid reflux have been developed but are currently impractical or have substantial limitations. Some have aspirated esophageal contents to analyze for gastric secretions, but this allows analysis of only short periods and the accuracy of detecting gastric enzymes with this technique is questionable.[1] Scintigraphic methods are expensive, involve radiation exposure, and are of limited duration (<1 hour).[2] The most commonly used method involves combined pH and bilirubin

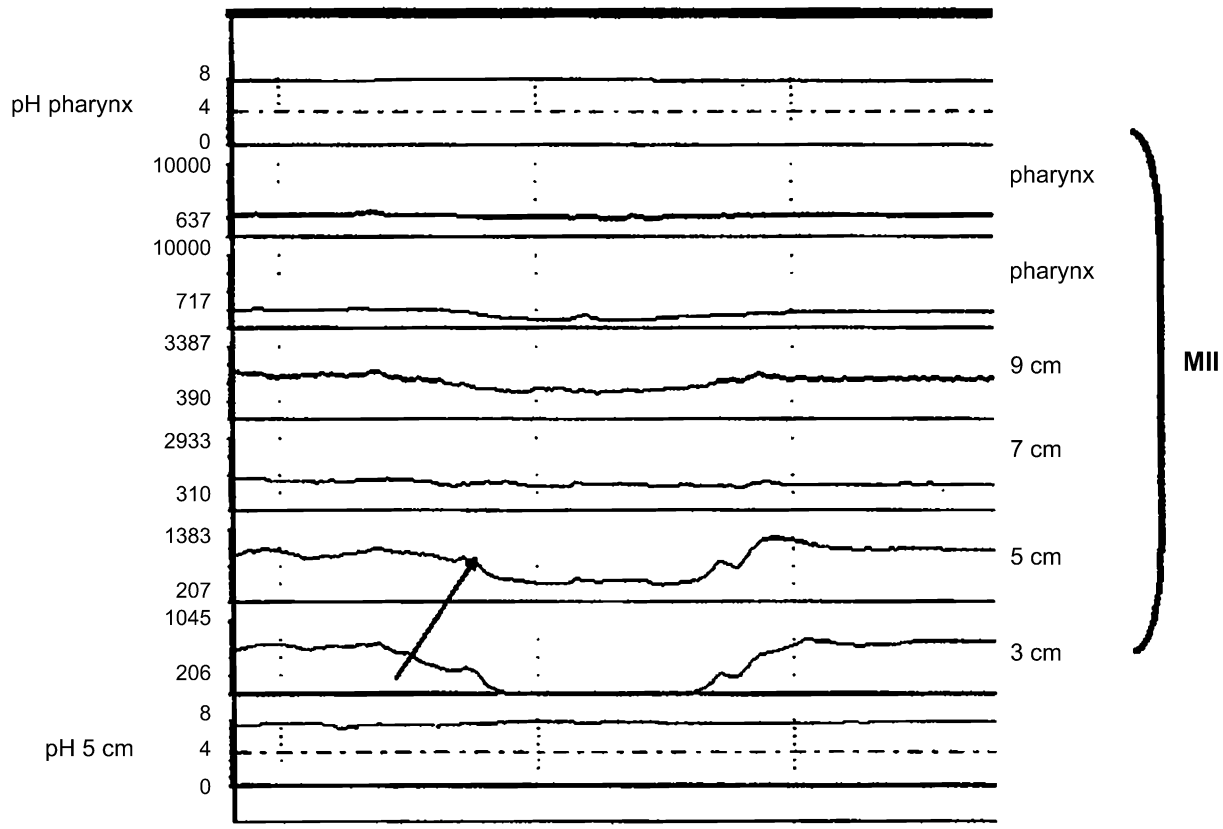

Fig. 4. Nonacid reflux event detected by impedance, reaching 5 cm above the lower esophageal sphincter (LES).

monitoring. However, this only indirectly measures bile by spectrometry, which has limitations, may miss more than 90% of nonacid reflux events because they do not contain bile, and requires a special liquid diet to avoid false-positive readings.[3,4]

Nonacid Gastroesophageal Reflux

We found that nonacid reflux episodes are relatively rare, representing less than 20% of all reflux events into the esophagus. Accurate determination of this type of refluxate to the distal esophagus is important, however, since it may explain the persistence of symptoms despite appropriate medical therapy in some patients. Likewise, duodenal gastroesophageal reflux is believed to be important in the development of Barrett's metaplasia,[5] and some believe that nonacid reflux is central to the pathogenesis of many respiratory diseases (via microaspiration).[6]

Using impedance technology, others have reported that nonacid reflux episodes represent 20–50% of total events in the distal esophagus.[7–11] The reasons why we found fewer reflux episodes in our study is not clear. This may represent normal variations or, more likely, result from modest differences in the interpretation of the studies. Indeed, interpretation of impedance studies relies much more on the reader's interpretation than on pH monitoring, which introduces the potential problem of interobserver reliability. We followed very strict criteria for our study. All studies were read by at least two of the study investigators, and only episodes agreed upon by both investigators were included. Thus, if

Table 1. Characteristics of the Reflux Events Detected by Impedance

Category	Total No.	Liquid	Mixed	Acid	Nonacid
Pharyngeal reflux episodes	51	26 (51%)	25 (49%)	13 (26%)	38 (75%)
Esophageal reflux episodes	445	170 (35%)	247 (56%)	386 (87%)	59 (13%)

Table 2. Number of Reflux Episodes Detected at a Given Length of the Esophagus/Pharynx

Category	3 cm above LES	5 cm above LES	9 cm above LES	5 cm below UES	2 cm above UES
Reflux episodes	496	391	348	122	51

LES=lower esophageal sphincter; UES=upper esophageal sphincter.

anything, our study may have underestimated the number of episodes.

Physiology of the Reflux Event

Another distinct advantage of impedance is that it allows for accurate determination of the proximal extent of a reflux event. In our study, most reflux episodes had its highest level at least to the midesophagus. Similar to our findings, Balaji et al.[12] reported that 45% of reflux episodes reached at least as high as 9 cm above the LES. Upward extent of reflux is important in the pathophysiology of aspiration, and defining the upper extent in normal subjects may help us define another parameter to differentiate patients who may be at risk of airway disease.

We noticed two additional characteristics of a typical reflux episode. First, since impedance measures the "presence time" of the reflux at each level of the esophagus, one may indirectly calculate the volume. As the refluxate moves retrograde, it seems to "shrink," with each aboral sensor registering a shorter presence time (Fig. 5). In fact, each reflux episode that reaches the pharynx is cleared very quickly, with no episode lasting longer than 19 seconds. The other finding is that acidity of a reflux event is neutralized or "buffered" as it progresses aborally. Almost all of the pharyngeal reflux events started out with a pH < 4 in the esophagus (78%), but very few were still acidic when they reached the pharynx (25.5%). This buffering effect has heretofore not been identified but could have an important role in pathologic situations. These two findings may explain why our study[13] and others[14,15] that have used pharyngeal pH monitoring have noted that the exposure of acid decreases as the reflux

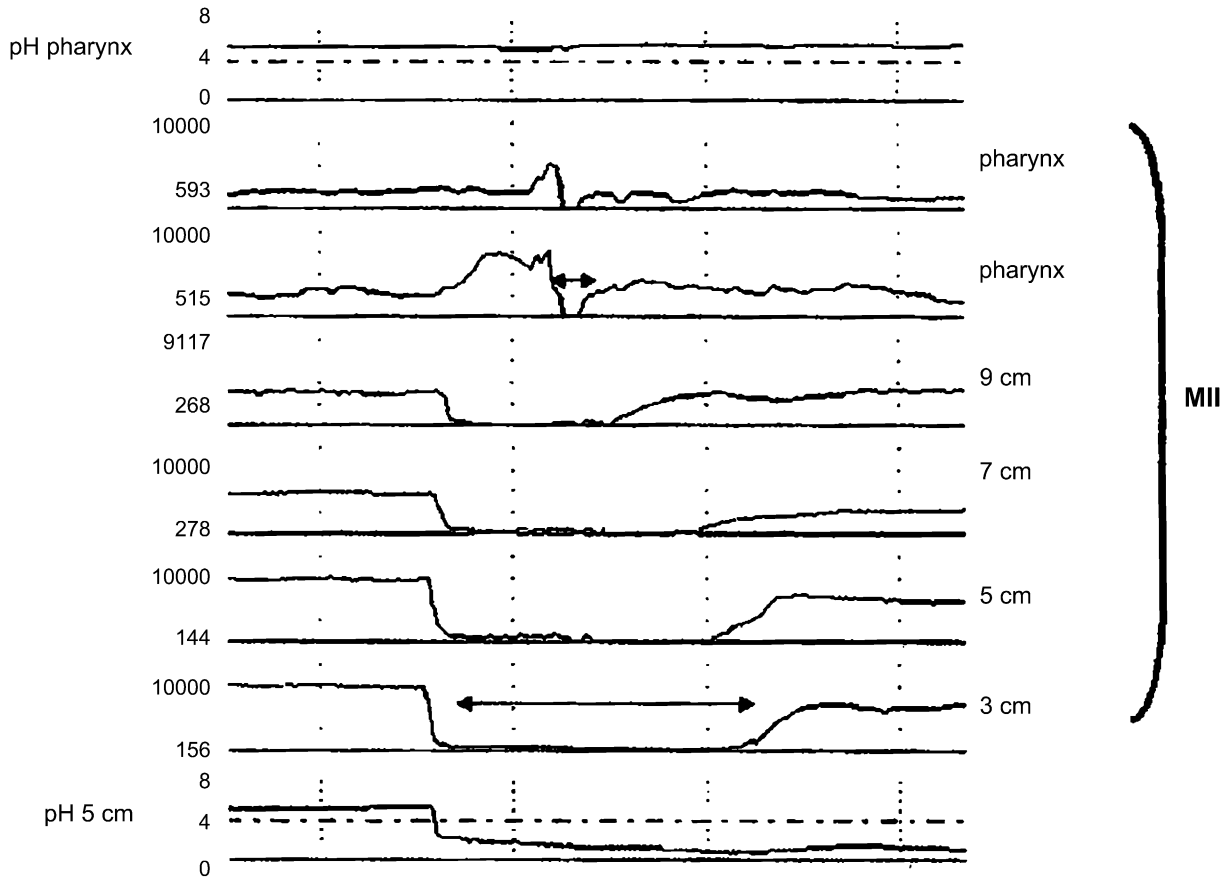

Fig. 5. "Shrinking phenomenon"— the bolus presence time decreases as the refluxate moves aborally.

moves retrograde (because of lesser volume, neutralization, or both) and why pharyngeal reflux episodes are almost always short (<1 minute), occur in an upright position, and are infrequent.[13] While this could represent an artifact in a few cases, the majority of the pharyngeal reflux events can be clearly detected by impedance. The fact that the pharyngeal pH monitor does not record a drop in pH either is a limitation of the pH probes or represents a buffering effect. We suspect it is the latter.

Pharyngeal Reflux

A relationship between the proximal extent of acid reflux and the risk of aspiration has been reported.[13, 15–17] In an attempt to more closely link GERD, aspiration, and airway injury, we, as well other authors, have measured pharyngeal pH.[18,19] Using this technique, we showed that the presence of abnormal amounts of pharyngeal acid reflux is a good predictor of response to both medical[2] and surgical[20] therapy. While the positive predictive value of pharyngeal pH monitoring is good, we have found the negative predictive value is poor, as pharyngeal pH monitoring is normal in many patients with GERD-related respiratory disease. Reasons that have been proposed to explain this phenomenon include (a) some reflux episodes may have a higher pH to start with and (b) many acidic gastroesophageal reflux episodes likely experience a "dilution or buffering" effect so that by the time they reach the pharynx they no longer have a pH < 4.[21] The evidence from this study suggests that both scenarios are likely common. This is important because although refluxate with a pH > 4 rarely causes severe injury in the esophagus, it may damage the airway if aspirated.

The "shrinking" and "buffering" phenomenon that we have described is likely interrelated and may be clinically relevant in two ways. It may explain why solitary aspiration events of refluxed material are in and of themselves imperceptible to the person in whom they occur. It may also make it more likely for them to be undetectable by traditional pH monitoring.

Potential Limitations

A potential limitation of the study is that although these subjects were asymptomatic, they may not represent true controls. This is highly unlikely since they were screened rigorously. Indeed, they all denied having any symptom potentially related to

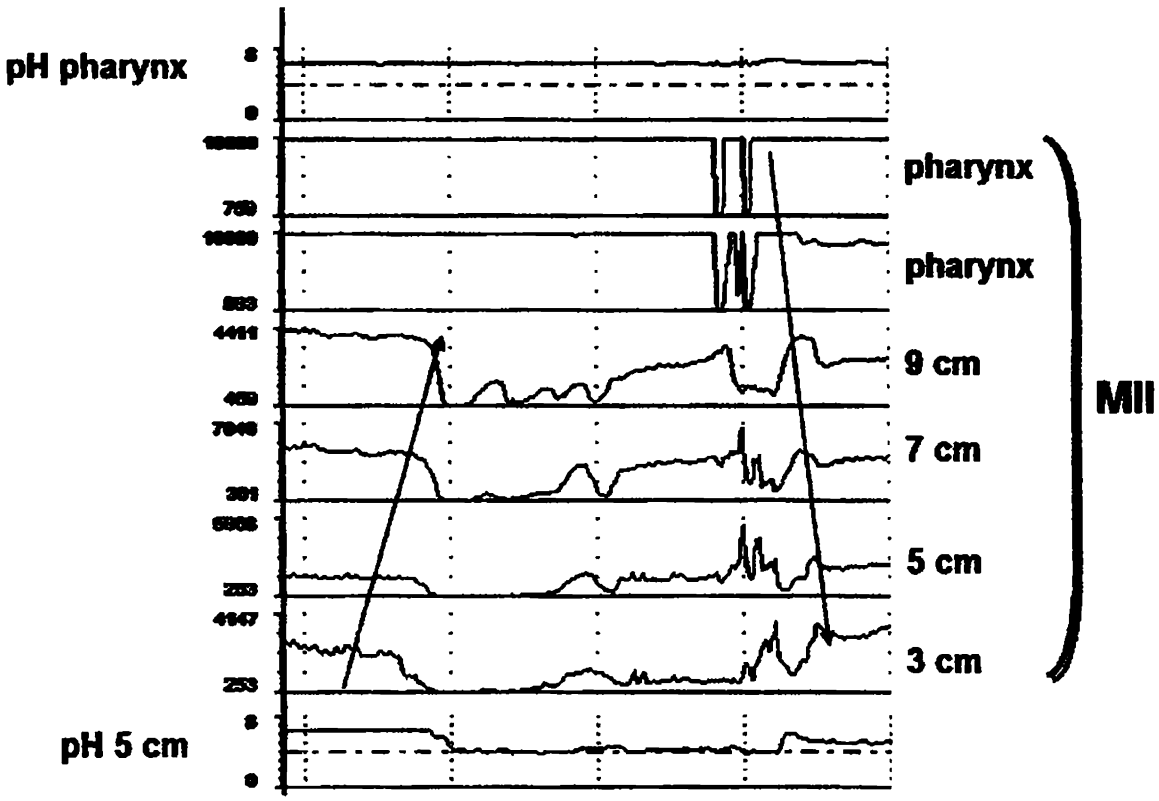

Fig. 6. Swallow triggered in response to a reflux episode.

GERD; they were all found to have normal LES pressure and normal peristaltis by manometry and impedance; and they all had normal esophageal acid exposure (mean of 2.26%).

A second potential limitation is the difficulty in differentiating pharyngeal reflux from the initiation of a swallow by impedance. It is well known that gastroesophageal reflux often triggers a reflexive swallow. If a swallow occurs in a close temporal relationship with a very proximal reflux event, it can be difficult to differentiate whether the drop in impedance in the pharyngeal sensor represents a retrograde movement of reflux or is the beginning of a swallow (Fig. 6). This was the case in 18 of 51 (35%) pharyngeal reflux events. To address this issue, we are developing a new catheter with an additional oropharyngeal sensor proximal to the pharyngeal sensor. This should allow us, in most cases, to determine whether a drop in impedance in the pharyngeal probe corresponds to a reflux episode or a reflexive swallow. Finally, more data and experience are needed to substantiate these findings.

CONCLUSIONS

In asymptomatic subjects, most episodes of gastroesophageal reflux are acidic and reach the midesophagus. The typical reflux event experiences both a "shrinking" and "dilutional" effect as it moves aborally. In fact, reflux to the level of the pharynx, while rare, appears to be more common than previously believed, and most of these episodes are very short and are not acidic. Thus, traditional 24–hour pH monitoring of the esophagus and pharynx may underestimate the presence of pharyngeal reflux. The combination of impedance with pH monitoring has the potential to markedly enhances our ability to accurately detect potential microaspiration. These findings may have significant impact in the diagnosis of GERD-related airway disease.

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Outcome of 1000 Liver Cancer Patients Evaluated at the UPMC Liver Cancer Center

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We evaluated 1000 consecutive patients with liver tumors at the University of Pittsburgh Medical Center (UPMC) Liver Cancer Center over the 4-year period from August 2000 to August 2004. Of the 1000 patients seen, 573 had primary liver cancer and 427 had metastatic cancer to the liver. The mean age of the patients evaluated was 62.2 years, and 61% were male. Treatment consisted of a liver surgical procedure (resection or radiofrequency ablation) in 369 cases (36.9%), hepatic intra-arterial regional therapy (transarterial chemoembolization or ^{90}yttrium microspheres) in 524 cases (52.4%), systemic chemotherapy in 35 cases (3.5%), and palliative care in 72 patients (7.2%). For treated patients, median survival was 884 days for those undergoing resection/radiofrequency ablation, compared to 295 days with regional therapy. These data indicate that over 90% of patients with liver cancer evaluated at a tertiary referral center can be offered some form of therapy. Survival rates are superior with a liver resection or ablation procedure, which is likely consistent with selection bias. Hepatocellular carcinoma was the most common tumor seen due to referral pattern and screening of hepatitis patients at a major liver transplant center. The most common reason for offering palliative care was hepatic insufficiency usually associated with cirrhosis. (J GASTROINTEST SURG 2006;10:63–68)

KEY WORDS: Liver, liver cancer, hepatocellular carcinoma, radiofrequency ablation, trans-arterial chemoembolization, ^{90}yttrium Theraspheres

The liver is an organ that is commonly involved either primarily or secondarily with malignant processes. Hepatocellular carcinoma (HCC) is the most common cancer to originate in the liver. Nearly 500,000 cases of HCC are diagnosed each year, making this one of the most common malignant disorders in the world.[1] There has been an increase in the incidence of HCC in the United States as a consequence of chronic hepatitis C (HCV) infection and the improved survival of patients with cirrhosis.[2] In addition to being a common site for the development of primary malignancy, the liver is also a common site of metastasis from other cancers. Patients with colorectal metastatic disease make up the bulk of patients considered for liver resection of secondary hepatic tumors. Approximately 150,000 patients are diagnosed with colorectal cancer each year in the United States, and over 50% of these patients will eventually develop hepatic metastases.[3] Unlike other malignant processes, liver resection is a curative option in some of these cases since metastatic disease remains confined to the liver in a third of patients who die of colorectal carcinoma.[4]

Long-term survival is rare among patients with most primary or secondary malignancies to the liver who receive systemic chemotherapy or supportive care. The improvement in imaging studies and understanding of the vascular and segmental anatomy

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of the liver has allowed for increasing the number of patients undergoing successful hepatic resections as treatment for primary or metastatic liver tumors. In addition, minimally invasive surgical procedures and liver-directed regional therapies are now available for patients who are not surgical candidates due to insufficient hepatic reserve or technical limitations. These include radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and yttrium-90 glass microspheres.[5–14] Recent randomized studies have shown a survival benefit for TACE in HCC patients.[15,16] Further, liver transplantation is an accepted treatment modality for patients with HCC.[17–19] Over the last decade, we have observed a significant increase in the number of primary and metastatic liver tumor patient referrals to a tertiary University Medical Center. Therefore, the purpose of this study was to provide a descriptive report of the diagnosis, treatment, and outcome of 1000 liver cancer patients evaluated during the 4-year-period 2000–2004.

MATERIAL AND METHODS

A total of 1000 consecutive patients with liver tumors were evaluated at the UPMC Liver Cancer Center (LCC) in Pittsburgh, Pennsylvania over a 4-year period from August 2000 to August 2004. Data was analyzed from an Institutional Review Board-approved hepatic cancer registry. All patients were seen in our Liver Tumor Clinic and were also presented at a weekly multidisciplinary liver tumor conference (Tumor Board); participants included liver transplant and hepatobiliary surgeons, liver transplant pathologists, hepatologists, abdominal imaging radiologists, a hepato-oncologist, and the LCC nursing/support staff. Initial evaluation usually consisted of a triphasic helical CT scan of chest/abdomen/pelvis, routine blood work, hepatitis screen, liver tumor markers (CEA, AFP, CA19-9), and a biopsy of the liver tumor. For patients with metastatic colorectal cancer to the liver, a positron emission tomographic (PET) scan was usually performed as well. All patients were presented at the Liver Tumor Board to consider treatment options after the initial evaluation was complete.

RESULTS

We evaluated 1000 patients with liver tumors at the UPMC Liver Cancer Center over the 4-year-period August 2000 to August 2004. During this time, there was an increase of approximately 10% in the total volume of outpatient clinic patients evaluated during each consecutive year (Fig. 1). In 2004, there were 1432 total outpatient clinic visits. This consisted of 508 new patient visits and 924 follow-up visits (Fig. 2). From the new patient visits in 2004, there were 350 new liver cancer patients, indicating that hepatic cancer accounted for ~70% of new patient referrals. The remaining 30% consisted of benign liver masses, hepatic cysts, or gallbladder disease. For the 350 new liver cancer patients seen in 2004, the breakdown of cancer types is shown in Figure 3. There were 149 HCC, 101 metastatic colorectal cancers, 35 cholangiocarcinomas, 29 neuroendocrine cancers, and 36 other metastatic cancers.

Of the 1000 liver cancer cases diagnosed, 61% were male, and the mean age was 62.2 years. Five hundred seventy-three had primary liver cancer, and 427 had metastatic cancer to the liver. The primary tumors consisted of HCC, cholangiocarcinoma, and gallbladder cancer. HCC was the most common tumor diagnosed at our institute, making up 47% of all hepatic tumors seen (Fig. 4). For those patients with HCC, 77% also had cirrhosis. Metastatic colorectal cancer accounted for 17% of liver tumor patients. Cholangiocarcinoma was the third most frequent tumor seen at 11%, and neuroendocrine cancer accounted for 7%. The remainder consisted of other metastatic cancers, including renal cell, breast, esophageal, gastric, and prostate carcinomas, as well as metastatic melanoma, sarcoma, and adenocarcinoma of unknown primary.

Multiple modalities were used to treat our patients with liver cancer. The majority of treatments consisted of liver surgical procedures or regional therapy depending on the functional status of the patient, the degree of liver insufficiency, and the resectability of the liver cancer (Fig. 5). Surgical procedures included liver resection or RFA. Patients were prioritized to receive hepatic resection (with curative intent) whenever possible, followed by RFA or regional liver perfusion. There were 300 hepatic resections performed during this time period. An additional 69 patients underwent RFA as the primary treatment option. Of the 300 patients undergoing liver resection, ~15% also had simultaneous RFA performed for a distinct tumor nodule that could not be included in the resection field.

Regional therapy consisted of hepatic TACE or ^{90}yttrium glass microspheres. TACE involves the injection of chemotherapeutic agents into the hepatic artery delivered by the interventional radiologist from a transfemoral percutaneous approach. ^{90}Yttrium glass microspheres are 20–30 μm beads containing ^{90}yttrium. The microspheres can also be targeted to specific lesions through selective catheterization of hepatic artery branches to spare healthy tissue. A total of

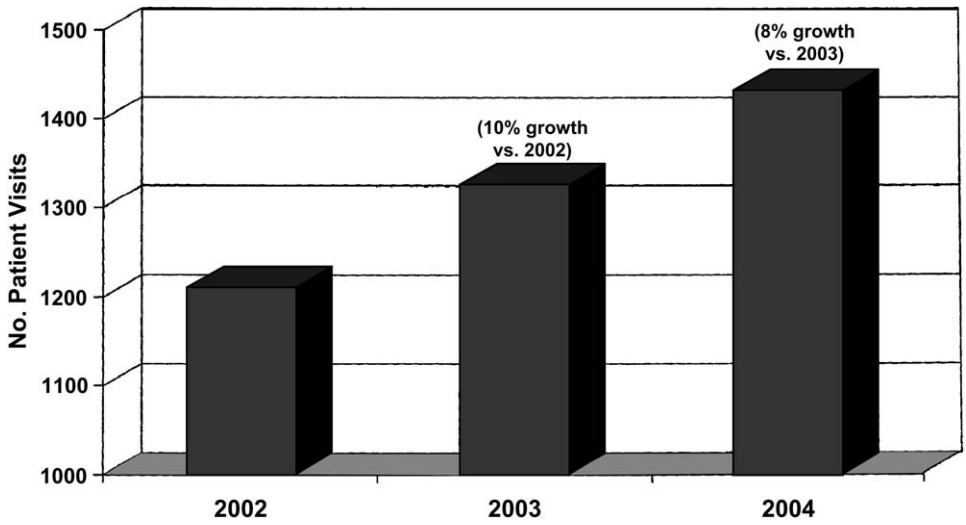

Fig. 1. UPMC Liver Cancer Center (LCC) outpatient clinic visits 2002–2004. Data from the outpatient LCC clinic log demonstrated an increase in the total volume of outpatient clinic patients evaluated during each consecutive year.

401 patients were treated with TACE, and 123 patients received intra-arterial ^{90}yttrium. A small portion of our patients underwent systemic chemotherapy (3.5%), usually for widely metastatic HCC or cholangiocarcinoma. Of note, only 72 patients (7.2%) were offered palliative care at the time of tumor diagnosis. These results indicate that over 90% of patients diagnosed with liver cancer can at least be offered some treatment option. The most common reason for supportive care was HCC with Childs C cirrhosis and serum total bilirubin $>$ 3.0 mg/dL.

When examining patient survival by different treatment modalities, survival rates were superior with a liver resection or ablation procedure (Table 1). This is likely consistent with selection bias in determining therapy option. For patients undergoing a surgical procedure (resection or ablative procedure), the 3 year survival was 37.9% compared to 8.5% for those given regional therapy. The median survival was greater for patients receiving resection or RFA (884 days) than for those receiving regional therapy (295 days). When examined by diagnosis,

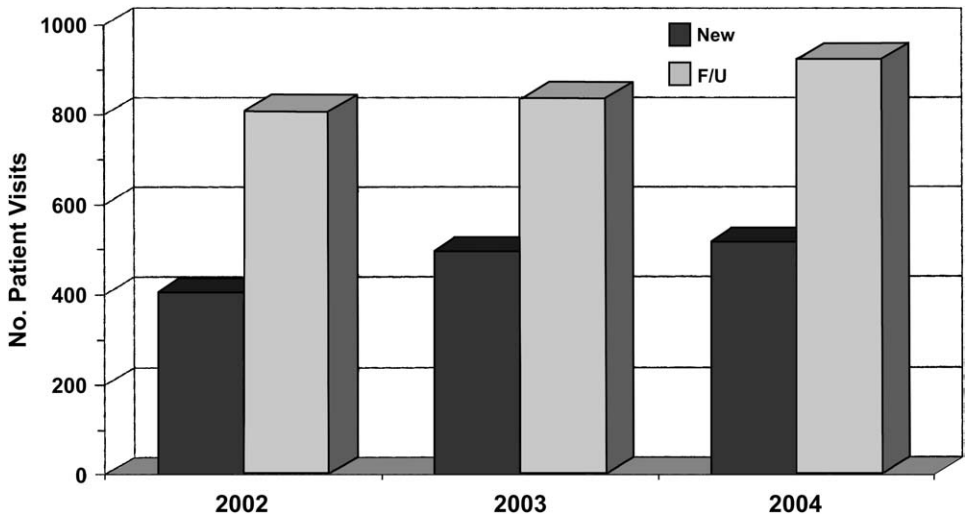

Fig. 2. New vs. follow-up outpatient clinic visits 2002–2004. There was an increase in both new and follow-up outpatient clinic patients evaluated during each consecutive year. From the new patient visits in 2004, there were 350 new liver cancer patients, indicating that hepatic cancer accounted for approximately 70% of new patient referrals. The remaining 30% consisted of benign liver masses, hepatic cysts, and gallbladder disease.

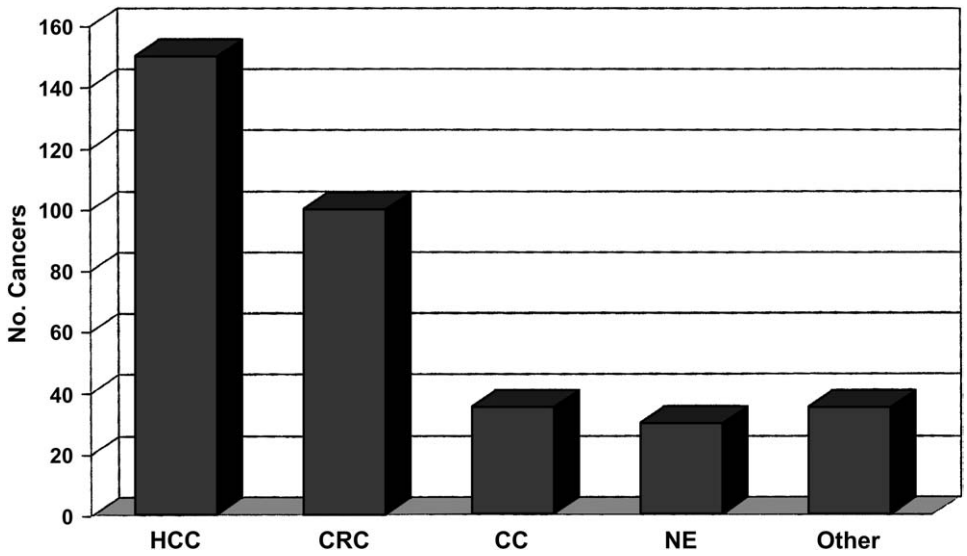

Fig. 3. liver cancer patients 2004. Of the 350 new liver cancer patients seen in 2004, HCC was the most common tumor diagnosed. HCC = hepatocellular carcinoma; CC = cholangiocarcinoma; NE = neuroendocrine tumor; CRC = metastatic colorectal cancer.

median survival was 1396 days for metastatic colorectal cancer, 1135 days for neuroendocrine cancer, 452 days for cholangiocarcinoma, and 395 days for HCC. The median survival of 41.7 months for metastatic colorectal cancer to the liver compares favorably with historical data and likely reflects the combined approach of aggressive surgical techniques and more effective chemotherapy with the newer agents.

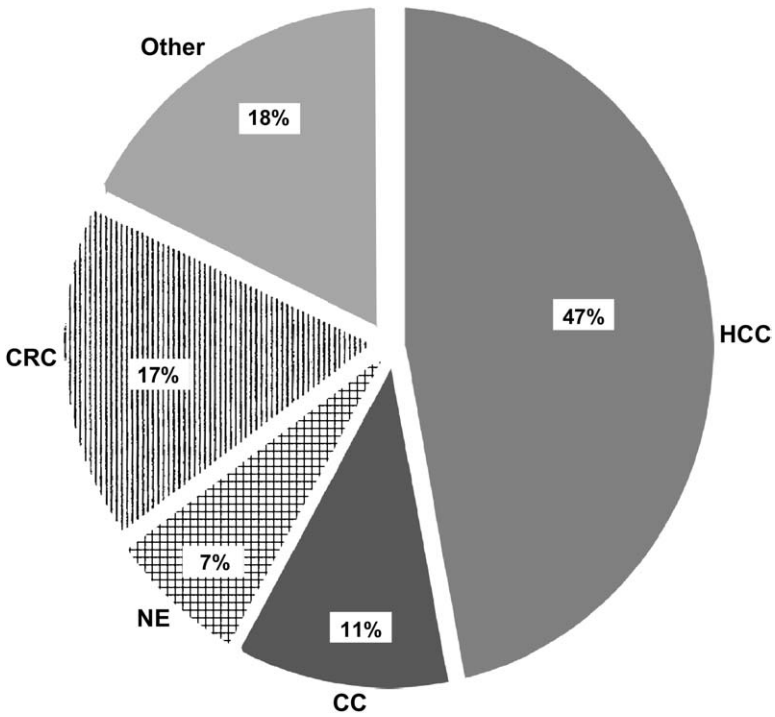

Fig. 4. Liver Cancer Patients 2000–2004. Spanning the four-year-period 2000–2004, 1000 patients were diagnosed with liver cancer at the UPMC Liver Cancer Center. HCC was the most common tumor diagnosed at our institute, making up 47% of all hepatic tumors seen. HCC = hepatocellular carcinoma; CC = cholangiocarcinoma; NE = neuroendocrine tumor; CRC = metastatic colorectal cancer.

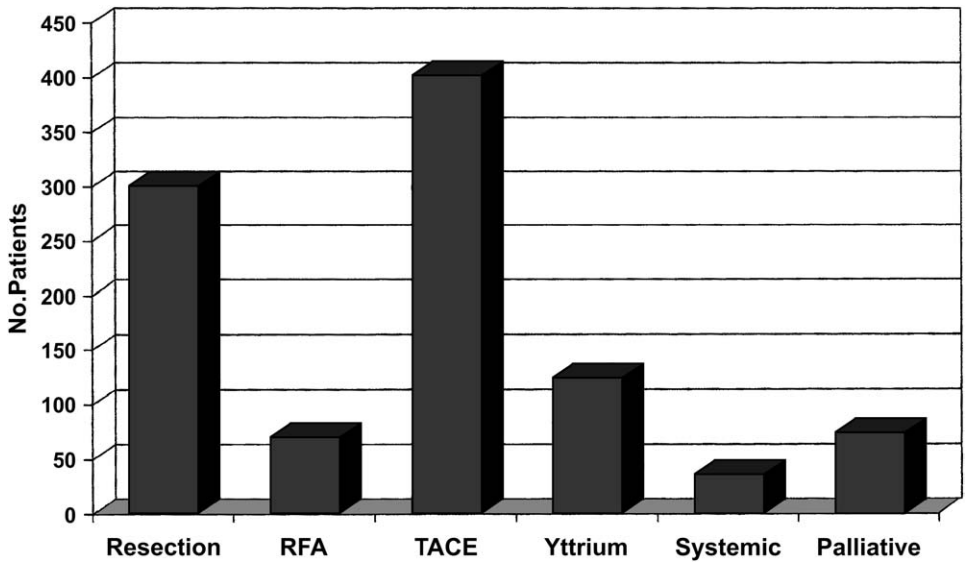

Fig. 5. Treatment of 1000 Liver Cancer Patients. Multiple modalities were used to treat our patients with liver cancer. The majority of treatments consisted of liver surgical procedures (resection, RFA) or regional therapy (TACE, ^{90}yttrium microspheres). A small portion of our patients underwent systemic chemotherapy or palliative care.

DISCUSSION/CONCLUSION

The liver is an organ that is commonly involved either primarily or secondarily with malignant processes. Approximately 150,000 patients are diagnosed with colorectal cancer each year in the United States, and over 50% of these patients will eventually develop hepatic metastases.[3] In contrast, although the incidence of HCC is on the rise, only ~15,000 new cases of HCC are diagnosed each year in the United States,[20] indicating that the incidence of colorectal cancer with hepatic metastases is approximately 5-fold greater than HCC. In spite of this finding, we have observed a significant increase in the referral and diagnosis of HCC in our Liver Tumor Clinic, prompting us to examine the trends in liver cancer diagnoses over the last 4 years.

The major findings of this study are: (1) referrals of patients with liver cancer have increased steadily over the past 4 years; (2) HCC is the most common liver cancer seen in our University Medical Center, even though there are fewer cases of HCC in the United States compared to metastatic colorectal cancer; (3) treatment can be offered to over 90% of patients diagnosed with liver cancer (meaning it is better to refer patients whose cancers are ultimately found to be too advanced for treatment than not to refer patients who could have gained at least some survival benefit from treatment); and (4) survival is better if the tumors are amenable to resection/RFA vs. regional liver therapy.

An important approach in the management of liver cancer is the evaluation by a comprehensive multidisciplinary liver cancer team. Not only does this contribute to the accurate and timely diagnosis and staging of liver cancer, but it also allows the patient to receive the overall best initial treatment approach regardless of which specialist has referred the patient. For example, at the Liver Tumor Board Conference, after confirming the diagnosis and staging, an individual treatment strategy is formulated, such as laparoscopic RFA as a bridge to liver transplantation, or downstaging of the tumor with 3–4 cycles of TACE to facilitate subsequent resection.

Referrals of new liver cancer patients have increased by approximately 10% per year for each of the past 4 years. Although the exact reasons for this increase are unknown, likely factors contributing include: (1) better educational efforts and community outreach for current treatment options; (2) increased screening of Hepatitis B virus negative- and HC virus-positive patients for early HCC; and (3) additional treatment options and improved safety of

Table 1. Actuarial survival of 1000 liver cancer patients evaluated 2000–2004

Procedure	1 yr	2 yr	3 yr	Median (days)
Resection/RFA	71%	59%	38%	884
Regional therapy	45%	23%	9%	295
Overall survival	53%	33%	25%	426

surgical and regional liver therapies. While HCC, cholangiocarcinoma, and metastatic colorectal or neuroendocrine cancer accounted for the vast majority of the liver cancer patients, approximately 20% of patients evaluated were for other metastatic tumors to the liver. In these cases, a liver-directed approach is performed for those patients with liver-only or liver-dominant disease, and the patient is counseled that treatment is usually palliative.

Our approach to the management of HCC is beyond the scope of this article, and has been recently summarized in algorithm [21] and textbook format.[22] As has been reported in most HCC series, over 75% of patients with HCC had a background cirrhotic liver. With regards to liver transplantation for HCC, it is difficult to summarize any concrete treatment patterns during the 4-year period because it includes HCC patients in the pre-model for end-stage liver disease (MELD) era, those in the first year of MELD where stage I and stage II patients received priority points, and those in the current era where only stage II HCC patients receive priority. One observation noted is the trend to avoid open hepatic resection for HCC except in the cases of noncirrhotic livers. For those patients that are early Childs A with a small HCC, preferred treatment approaches are minimally invasive and consist of laparoscopic RFA for small solitary tumors or regional therapy with TACE or ^{90}yttrium glass microspheres, recognizing that many of these patients will eventually progress to liver transplantation. The optimal neoadjuvant therapy of HCC as a "bridge" to liver transplantation remains to be defined, and randomized clinical trials to address this have been proposed.

For treatment, over one-third (36%) of patients were treated by resection or RFA, while 52% received regional therapy. As might be expected, those patients with tumors amenable to resection or ablation had significantly better 1-, 2-, and 3-year actuarial survival. We are careful not to draw any conclusions regarding treatment superiority because the data do not reflect a randomized study. However, it is humbling to note that overall three-year survival of the 1000 liver cancer patients was only 25%, indicating that further research into the biology and treatment of liver cancer is required to improve these outcomes.

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Novel Two-Step Resection for Lesions Between the Middle Hepatic Vein and Vena Cava Which Allows the Middle Hepatic Vein to Be Preserved

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Patients with bilobar colorectal cancer metastases to the liver present a unique problem in terms of resection. They sometimes require a staged approach to resection that takes advantage of the liver's ability to regenerate, as well as the newer chemotherapeutic agents (e.g., oxaloplatin, irinotecan (CPT-11), and bevacizumab) that have become available. In cases of multiple bilobar metastases, if segment IV is clear of tumor, a left lateral segmentectomy (LLS) can be performed, followed several months later by a formal right hepatectomy. The remnant liver composed of the hypertrophied segment IV is drained by the middle hepatic vein (MHV). In this context, patients with lesions between the origin of the MHV and the inferior vena cava (IVC) present a particularly difficult problem. Conventional excision would require an extended hepatectomy and division of the MHV along with either the right or left hepatic veins (RHV, LHV). This would make it impossible to continue with a formal resection of the remaining lesions in the contralateral liver without sacrificing the sole remaining hepatic vein. We present a novel two-step hepatectomy for lesions between the MHV and the IVC that allows the MHV to be preserved and all lesions to be resected. (J GASTROINTEST SURG 2006;10:69–76)

KEY WORDS: Neoplasm metastasis, colorectal neoplasms, hepatic veins, hepatectomy, liver regeneration

Approximately 150,000 patients are diagnosed with colorectal cancer yearly in the USA.[1] Of these patients, up to 25% will already have a metastasis to the liver at the time they present,[2,3] and almost 50% will develop a recurrence within their lifetime. The liver is the primary site of such recurrence.[4,5] Surgical resection is now the standard of care for colorectal cancer liver metastases, with 5-year survival, after complete resection, being reported between 25%–45%.[5–18] Unfortunately, only 10%–20% of patients are amenable to surgical resection when they present with their metastasis.[19] As the available chemotherapeutic options have improved, and morbidity from liver resection has decreased, long-term survival after multiple or staged hepatectomies is being reported.[20,21] Radical excision of colorectal cancer metastases in the liver provides effective palliation, and in a small number of patients, offers the chance of a cure;[5,17] therefore, surgeons are becoming increasingly aggressive in their management of colorectal cancer metastases.

Patients with bilobar colorectal cancer metastases to the liver present a unique problem in terms of resection. They sometimes require a staged approach to resection that takes advantage of the liver's ability to regenerate, as well as the newer chemotherapeutic agents (e.g. oxaloplatin, irinotecan (CPT-11), and bevacizumab) that have become available. In cases of multiple bilobar metastases, if segment IV is clear of tumor, a left lateral segmentectomy (LLS) can be performed, followed several months later by a formal right hepatectomy. The remnant liver composed of the hypertrophied segment IV is drained by the middle hepatic vein (MHV).

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hepatectomy and division of the MHV along with either the right or left hepatic veins (RHV, LHV). This would make it impossible to continue with a formal resection of the remaining lesions in the contralateral liver without sacrificing the sole remaining hepatic vein. We present a novel two-step hepatectomy for lesions between the MHV and the IVC that allows the MHV to be preserved and all lesions to be resected.

METHODS

Case Report 1

A 25-year-old man presented with bilobar hepatic colorectal metastases. Segments II/III contained large-volume disease, and all segments contained metastatic deposits, including one sited between the MHV and IVC in segments I/IV and abutting segment VIII. The patient received neoadjuvant systemic chemotherapy with 5FU/leucovorin and CPT-11. The CT scan following this systemic chemotherapy is shown in Fig. 1. The main problem was that he had metastases close to the origin of all three hepatic veins. In order to be able to perform an R0 resection, at least one of these veins would have to be preserved. In March 2004, the patient underwent the first stage of a planned multistaged liver resection, aiming initially to clear the left side of his liver of disease and install a hepatic arterial infusion pump for postoperative hepatic arterial infusion chemotherapy. The pump was installed because his tumor was progressing on chemotherapy. Intraoperative ultrasound was used to confirm the CT scan findings. A LLS was performed in standard fashion, using endovascular staplers to transect and ligate the LHV and portal structures. The LLS allowed the metastasis lying between the MHV and IVC to be approached from the lateral aspect through the cut liver surface (Fig. 2).

The liver dissection was continued medially through the cut surface of the liver. The dissection was continued between the MHV and the metastasis lying in front of the IVC and was extended around all sides of the metastasis to encircle it. Extension of the dissection into segment VIII allowed the tumor to be excised with a clear margin of surrounding liver tissue (Fig. 3). Nonanatomic resection of two further lesions in segment IVa and segment V was then performed. A Codman model 3000 (30 ml

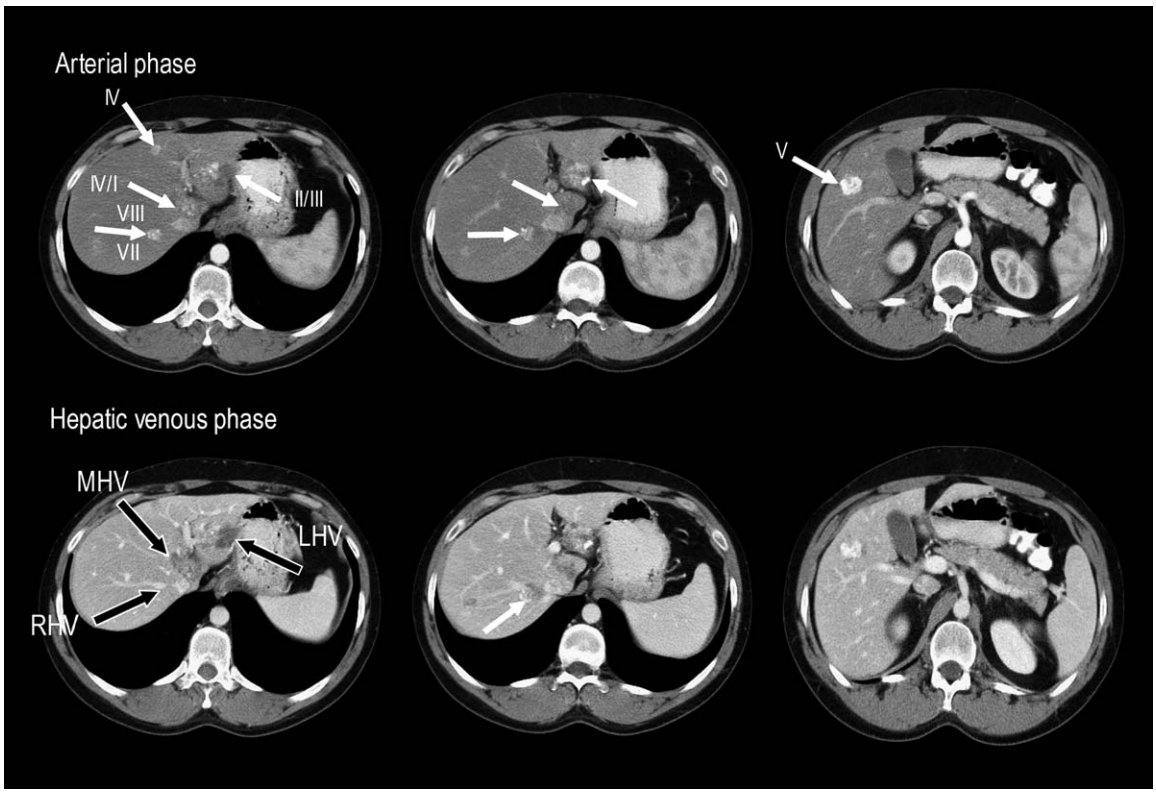

Fig. 1. Postchemotherapy triphasic CT scan of the first patient, from January 2004. Colorectal cancer hepatic metastases are indicated by *white arrows*, and the number indicates the hepatic segment that is involved. Each metastasis is only numbered once. The relationship of the metastases to the RHV, MHV, and LHV is indicated by the *black arrows*.

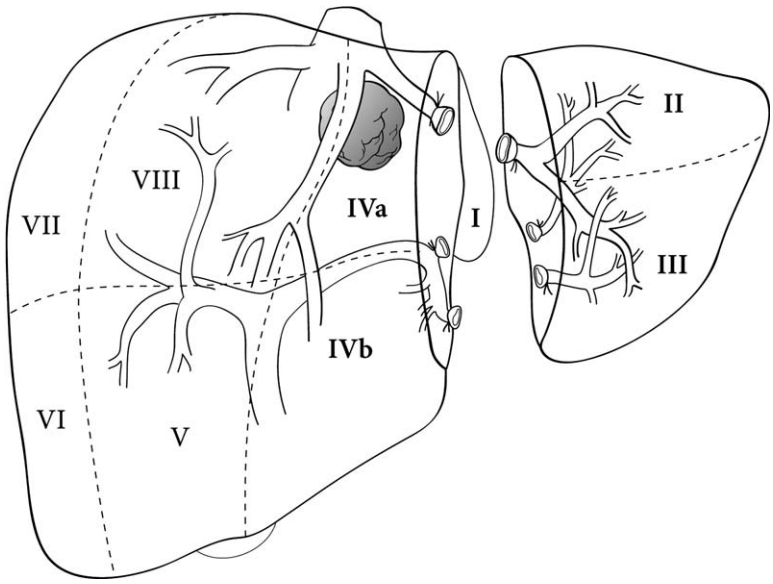

Fig. 2. Step one is a left lateral segmentectomy (LLS). This allows access to the area lying between the MHV and IVC. The LLS is carried out regardless of whether there are colorectal cancer metastases in segments II and III.

capacity) constant flow implantable pump was installed using the gastroduodenal artery.

Postoperatively, he received both systemic and hepatic arterial infusion chemotherapy. A postoperative CT scan performed in August before his further surgery (Fig. 4) showed the residual metastases in the right liver in segments V, VII, and VII/VIII. Liver regeneration between March and August was followed by serial CT scans (Fig. 5). In September 2004, the VII/VIII lesion surrounding the RHV was resected along with all remaining metastases. The RHV had to be divided during the resection. This left only the MHV to drain the liver remnant. Carcinoembryonic antigen level was 39.87 μg/L (range, 0–4.9) in August 2004 and fell to less than 0.5 μg/L following resection of the remaining metastases.

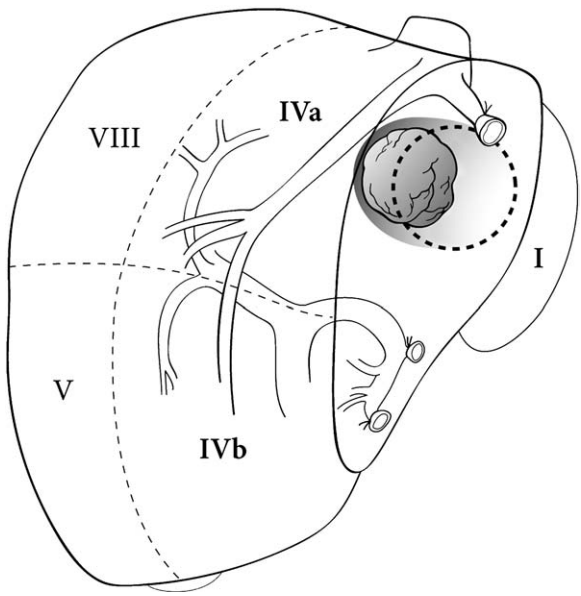

Fig. 3. Step two is a nonanatomical resection of the lesion between the MHV and IVC through the cut surface of the liver via the lateral aspect.

Histology (March 2004). Six lesions were identified on final histology. Two metastases were identified in the resection specimens from segments II/III and segment V, and one metastasis in segments I/IV and IV. All were consistent with metastatic colonic adenocarcinoma that had been completely excised. The non-neoplastic liver was mildly steatotic. Several of the lesions consisted only of necrotic material, calcification, and mucin pools without viable tumor.

Histology (September 2004). Four lesions were identified in resection specimens from segments V, IV/V, VII, and VII/VIII. On histology, all were consistent with moderately differentiated metastatic colonic adenocarcinoma that had been completely excised. In some samples non-neoplastic liver demonstrated mild to moderate multifocal steatosis, but no fibrosis. Most lesions again showed evidence of significant necrosis, calcification, and mucin pools with only microscopic residual tumor.

The first step, which enabled us to preserve the MHV, was the left lateral segmentectomy. In this first patient, it was indicated because segments II and III contained extensive colorectal cancer metastases, but it also permitted step two to follow. The second

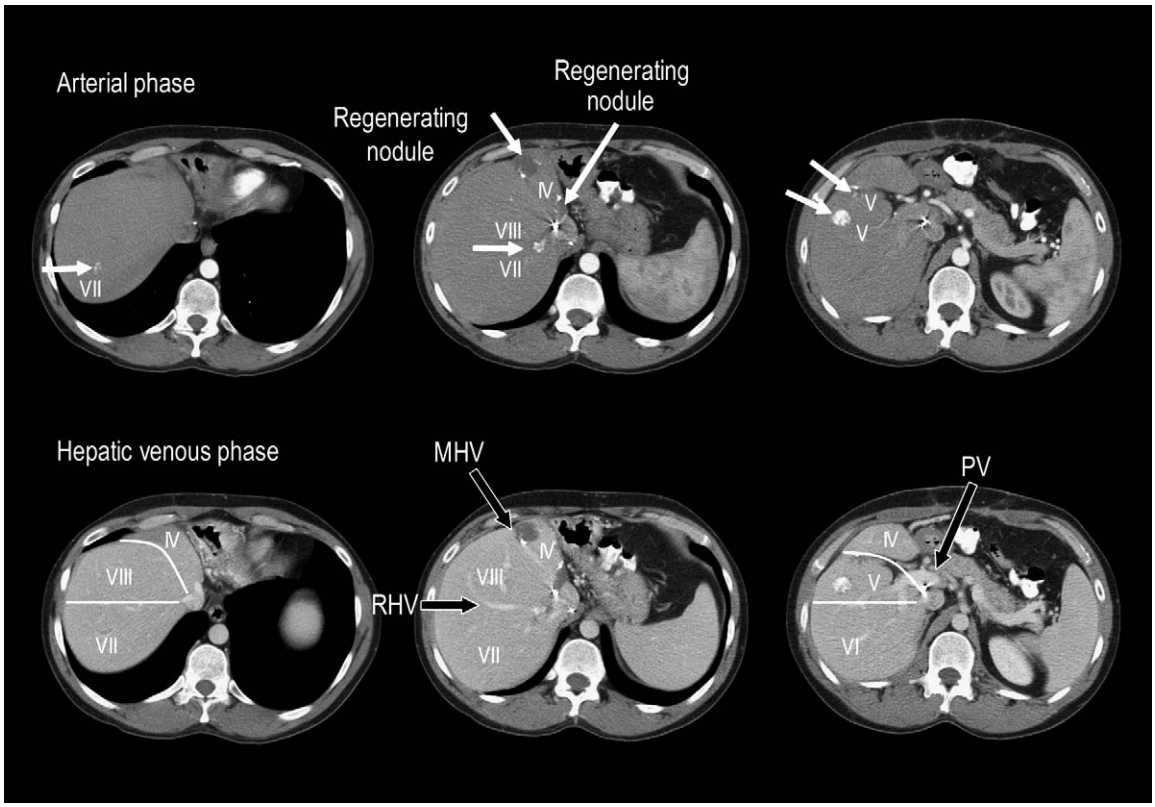

Fig. 4. A triphasic CT scan of the first patient taken 5 months after resection of the metastases in the left hemi-liver. Segments II and III have been resected along with the metastasis situated between the MHV and IVC. Metastases in the right hemi-liver are indicated by *white arrows*, and the number indicates the hepatic segment that is involved. Each metastasis is only numbered once. The RHV, MHV, and portal vein (PV) are indicated by *black arrows*. The segment IV remnant is undergoing regeneration.

step was resection of the segment I/IV lesion lying between the MHV and IVC, approaching the lesion from the lateral aspect, through the cut surface of the liver, which enabled us to preserve the MHV.

In summary of the first patient, the left hemi-liver was cleared of tumor and both the MHV and RHV were preserved. A subcutaneous continuous infusion pump was implanted for postoperative hepatic arterial infusion chemotherapy. Two months later, nonanatomical resections of the remaining metastases in segments V–VIII were carried out at the expense of the RHV. All resection margins were clear of tumor,

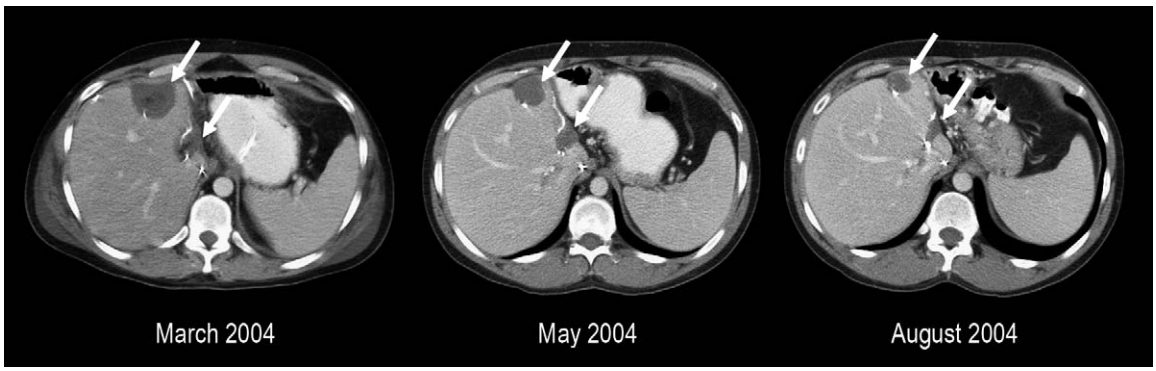

Fig. 5. Portal venous phase CT scans of the first patient, taken from consecutive series of triphasic CT scans performed between March and August 2004. *White arrows* point to resected areas in segment IV that are filling in due to liver regeneration. Persistent metastatic disease is seen around the RHV in segments VII/VIII.

and ultimately it proved possible to complete an R0 resection in this patient. The liver remnant depended on the preserved MHV for venous drainage. The patient is disease free twelve months later with a carcinoembryonic antigen in the normal range.

Case Report 2

A 67-year-old man presented with colorectal cancer hepatic metastases that were felt to be unresectable. His CT scan is shown from July 2002. He commenced systemic chemotherapy in January 2003. He had received eight monthly cycles of 5-FU/leucovorin and CPT-11 when a repeat follow-up CT scan in July 2003 (Fig. 6) showed that his tumor had responded to the chemotherapy and was potentially resectable. The main problem was a large metastasis in the caudate lobe involving segment IV. The metastasis extended between the MHV and IVC and was abutting segment VIII. The liver was moderately fatty and the left lateral segments were relatively small, and therefore an extended right hepatectomy was not considered feasible. Other metastases were more peripheral and sited in segments V and VIII.

The abdomen was entered through a bilateral subcostal incision and the liver fully mobilized. Intraoperative ultrasound was used to examine the liver and confirm the CT scan findings. There was no evidence of extrahepatic disease. A left lateral segmentectomy was carried out in standard fashion using the same technique as described in the first patient.

The liver dissection was continued through the cut surface of the liver where the segment I tumor extended between the RHV and MHV near their junction with the IVC. The right liver had to be taken completely off the IVC. The caudate lobe encircled the cava and was taken off the cava by careful ligation and transection of all venous branches to the caudate. The dissection was continued into the right liver and was extended around the tumor, freeing it completely from the right liver. It then became apparent that the tumor was adherent to the IVC and that this was the last point of attachment. A side-biting Satinsky clamp was placed on the IVC, and the tumor was resected along with a portion of the caval wall. This defect in the cava was then repaired. The right hemi-liver was found to be extremely edematous after the resection of this lesion, and resection of the remaining lesions was therefore postponed.

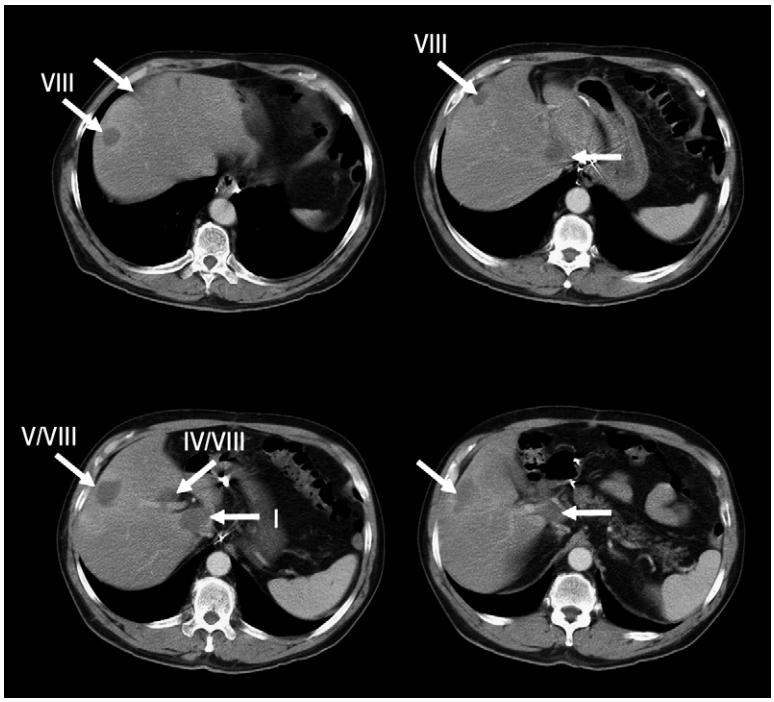

Fig. 6. Postchemotherapy portal venous phase CT scans of the second patient taken from a triphasic CT scan performed in July 2002. The scans show the extent of the metastatic disease prior to resection. Hepatic metastases are marked by *white arrows*, and the number indicates the hepatic segment that is involved. Each metastasis is only numbered once.

The patient returned to the operating room on the fourth postoperative day, at which time the metastases in segments V and VIII were resected non-anatomically after first performing intraoperative ultrasound to confirm the anatomy. Again he tolerated the procedure well.

Histology (December 2002). All lesions from segments I, II, III, V, and VIII were consistent with metastastic adenocarcinoma from a colonic primary that had been completely excised. The non-neoplastic liver showed moderate steatohepatitis. Again, only microscopic residual disease was found on histological examination, and two lesions were composed of areas of necrosis with less than 5% viable adenocarcinoma.

In summary of the second patient, the left hemiliver was cleared of tumor, and both the MHV and RHV were preserved. A left lateral segmentectomy was carried out even though segments II and III were free of tumor. The caudate lobe along with the segment I/IV lesion were resected. The lesion was adherent to the wall of the IVC, which was resected along with the lesion. Resection margins were free of tumor. Two days later at a second operation, the lesions in segments IV, VI/VII, and VIII were resected. The patient recovered well and is free from recurrence 18 months postresection, having undergone an R0 resection.

DISCUSSION

Two-stage hepatectomy procedures combined with portal vein embolization for the treatment of patients with otherwise unresectable multiple and bilobar colorectal liver metastases were developed as a way to avoid leaving small-for-size liver remnants. Portal vein embolization was designed to induce atrophy of the hemi-liver which had been embolized while promoting hypertrophy of the opposite hemi-liver.

Many centers are now resecting even more extensive metastatic disease with the aim of clearing the liver of macroscopic disease. Despite the increase in the number and size of resections being performed, the associated mortality in most units remains low at less than 5%. The mortality was 2.8% in the series of 1001 consecutive liver resections reported by Fong.[17] Although patient survival can be predicted by factors such as the number and size of metastatic lesions present in the liver, bilobar disease, primary tumor biology, and extrahepatic disease, survival to 5 years and beyond is still possible when multiple adverse factors are present.[17]

Unresectable colorectal hepatic metastases can be made resectable in 12.5% of cases using a multimodality approach to treatment.[22] This therapeutic approach, which combines preresection and postresection chemotherapy, radio frequency ablation, portal vein embolization, and multiple-staged hepatic resections can achieve 33% survival at 5 years in patients with tumors that respond to treatment and become resectable.[22]

Bismuth's group has led the way with multimodality treatment of hepatic metastases. Multiple-staged hepatectomies, second, and even third hepatectomies[20,21] have been shown to have a similar survival benefit to one-stage hepatectomy when the aim is an R0 resection, and they are integrated into an intended multimodal strategy for tumor eradication. Treatment has shown that long-term survival can be achieved if metastatic colorectal disease can be made resectable.[19,21–28]

Several patients with extensive metastatic disease at our institution have undergone multiple-staged hepatic resections and have ultimately been left with part of a single hepatic segment, usually segment IV. In general, these patients have undergone multiple-staged liver resections combined with portal vein embolization, preresection and postresection systemic chemotherapy, and hepatic arterial infusion. The aim of surgery was to achieve an R0 resection while leaving part or all of a single hypertrophied hepatic segment with a patent bile duct, portal vein, and hepatic vein branch. The patients have usually started with extensive bilobar metastatic disease confined to the liver and sparing only a segment drained by the MHV.

A single lesion situated between the MHV and the IVC would normally demand an extended right hepatectomy (trisegmentectomy) to resect it. This would require sacrificing the RHV and MHV, leaving the patient with only the LHV. If the patient also had extensive disease in the left-sided segments, it would not be possible to design an operation that could achieve clearance of the disease in the liver by this approach, even if the central liver segments were otherwise free of metastatic disease. An extended left hepatectomy would be an alternative to an extended right hepatectomy but would require the LHV and MHV to be sacrificed. If the patient had extensive disease in the right liver as well, it would again not be possible to design a staged resection that could achieve clearance of the hepatic disease, even if the central liver segments were otherwise free of metastatic disease.

Our novel two-step approach to resection of centrally placed liver lesions situated between the MHV and the IVC should be of interest to liver surgeons who undertake multiple-staged hepatic resections for extensive liver disease. It is also useful in situations where preservation of liver parenchymal

volume is paramount, such as in patients who would otherwise require an extended right hepatectomy but who would be unlikely to survive a resection of this magnitude. The approach has proved safe in our hands, even when combined with portal vein embolization and systemic and hepatic arterial infusion chemotherapy, and has even allowed the wall of the IVC to be partially excised where it was felt to be involved.

CONCLUSION

Conservation of liver mass and preservation of more than one hepatic vein during liver resection serves to increase the options available for the future surgical management of the patient. This approach is especially relevant now that newer, more effective chemotherapy agents such as oxaloplatin and irinotecan (CPT-11), and antiangiogenic agents such as bevacizumab, are available, and there is willingness, at least in some units, to take an aggressive surgical approach in patients with colorectal cancer hepatic metastases. It would not have been possible to clear the liver of the first patient we described of disease if the MHV had been divided at the first operation. The exposure created by resection of segments II/III, whether they are involved by tumor or not, as the first step to gain access to the area between the MHV and the IVC was even sufficient to allow safe resection of the wall of the IVC. Our approach increases the chances of preserving the MHV while conserving liver mass, and thereby reduces the size of the liver resection that patients have to undergo.

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Long-term Evaluation of Biliary Reconstruction After Partial Resection of Segments IV and V in Iatrogenic Injuries

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Roux-en-Y hepatojejunostomy is the procedure of choice for biliary reconstruction after complex iatrogenic injury that is usually associated with vascular injuries and concomitant ischemia of the ducts. To avoid the ischemic component, our group routinely performs a high repair to assure an anastomosis in noninflamed, nonscarred, and nonischemic ducts. If the duct bifurcation is preserved, the Hepp-Couinaud approach for reconstruction is an excellent choice. Partial liver resection of segments IV and V allows adequate exposure of the bile duct at its bifurcation with an anterior approach of the ducts (therefore not jeopardizing the circulation), allowing a high quality anastomosis. Long-term results of bile duct reconstruction using this approach are described. Two hundred eighty-five bile duct reconstructions were done between 1989 and 2004 in a tertiary care university hospital. The first partial-segment IV resection was done in 1994; 94 cases have been reconstructed since then using this approach. All of them had a complex injury (Strasberg E1–E5), and although in many cases the bifurcation was preserved (E1–E3), a high bilioenteric anastomosis was done to facilitate the reconstruction. In 70 cases, the bifurcation was identified, and in the 24 in which the confluence was not preserved, the right and left ducts were found except in one case. In three patients, the right duct was found unsuitable for anastomosis, and a liver resection was done. In the remaining 21, an anastomosis was done using a stent (transhepatic, transanastomotic) through the right duct. According to Lillemoe's criteria, 86 cases had good results (91%). In four of the eight remaining patients, there was the need to operate again due to the presence of an obstruction and/or cholangitis. In the rest, radiological instrumentation was done. Four of these cases have developed secondary biliary cirrhosis, two of which have died while waiting for a liver transplant, four and six years after reconstruction. Partial segments IV and V resection allows adequate exposure of the confluence and the isolated left or right hepatic ducts. Anterior exposure of the ducts allows an anastomosis in well-preserved, nonischemic, nonscarred, or noninflamed ducts. Parenchyma removal also allows the free placement of the jejunal limb, without external compression and tension, obtaining a high quality anastomosis with excellent long-term results. (J GASTROINTEST SURG 2006;10:77–82)

KEY WORDS: Bile duct injury, hepatojejunostomy

The surgeon that repairs complex bile duct injuries can face several scenarios. In a minority of cases (30% or lower), the injury is identified during surgery, giving the opportunity for its repair. Most cases are identified several days after the cholecystectomy, and the manifestations are variable. In some of these cases, there has been an attempt to repair the injury. A minority of patients arrives weeks or months after the injury with obstructive manifestations.[1]

Complex injuries are defined as those suffered by the common bile duct or its tributaries that require a circumferential anastomosis.[2] Most surgeons agree that the best approach to the reparation is a Roux-en-Y hepatojejunostomy. Other types of bilioenteric anastomosis have also been attempted.[3]

The success of a bilioenteric anastomosis depends on several factors; those in which the anastomosis is tension-free, wide, and mucosa mucosa have a better prognosis. Finding nonscarred, noninflamed,

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nonischemic ducts is also one of the keys to obtaining a high-quality anastomosis.[4] In many cases, to obtain such characteristics of the duct, exposure of the confluence is necessary (if preserved), as well as isolation of the right and left ducts. To obtain these we remove the hilar plate and liver parenchyma. Partial removal of segments IV and V (Strasberg) allows the exposure of the ducts at this level, giving the appropriate conditions for a high-quality bilioenteric anastomosis.[5,6] Herein, we report the long-term results of Roux-en-Y bilioenteric anastomosis done for repair of bile duct injuries with the technical aid of partial segment IV resection during surgery.

METHODS

Patients referred to our hospital with a confirmed or suspected bile duct injury are evaluated according to their general condition and time of evolution of the injury. Unstable patients with sepsis, secondary to cholangitis and /or intra-abdominal collections, as well as those with intestinal fistulas and hydroelectrolitic disorders are managed conservatively to improve their general condition. When necessary, percutaneous drainage of the duct is done, as well as drainage of intra-abdominal collections. Limited laparotomies are also done in some cases to drain collections when the percutaneous approach is not possible.

Once the patient has been stabilized, routine laboratory tests are completed and efforts are directed to outline the anatomy of the biliary tree and the type of injury. Stable elective patients that arrive several weeks or months after the injury are also initiated on their protocol. The ultrasound, as well as the CAT scan, are useful tools because they help us to detect intra-abdominal collections. Intrahepatic and often extrahepatic bile ducts are depicted, particularly if they are dilated. Stable, elective patients in whom the intrahepatic and extrahepatic ducts are dilated can have surgery without further studies.

Endoscopic retrograde cholangiography (ERC) is done in almost all patients that arrive several days after the injury. The ERC gives us the possibility of outlining the biliary tree anatomy, and in some cases, even classifying the injury. In those cases in which small duct injuries have happened, 60–70% are in continuity with the biliary system, with or without cystic duct leak; placing an endoprosthesis can be an excellent treatment. Complete interruptions of the bile duct or giant leaks are treated surgically. Efforts are directed to outline the intrahepatic bile duct anatomy in these cases; this is achieved by means of magnetic cholangio resonance. In selected patients, percutaneous transhepatic cholangiography is done to identify the anatomy and establish drainage of the biliary tree. Our group does not routinely place percutaneous drains in every case.

Surgery is planned when the patient is stable, without sepsis, and when the biliary anatomy has been outlined and the injury classified. Injuries are divided using the Strasberg classification. According to the individual state of each patient, surgery is planned for an early or late repair. Late repair is also done in cases in which intestinal fistulas are demonstrated, as well as in those where abdominal wall defects are present. Angiography is not routinely done to investigate arterial injury. When the patient arrives with subhepatic drains, fistulography is done to rule out intestinal fistulas and to evaluate if the biliary tree fills. Nuclear magnetic resonance allows identification of all major components of the biliary tree so that the operation can be planned. Careful evolution of the study with intraoperative comparison is essential to achieve complete bile duct drainage.

Operative Technique

Once all the adhesions of the right upper quadrant have been sectioned, dissection of the jejunal limb is performed (if it was done before in an attempt to repair) because misplacement and erroneous construction of the Roux-en-Y has been found in some patients.[7] For a correct hilar dissection, it is necessary to avoid the interruption of arterial branches as much as possible. No effort is done to dissect completely the arterial supply to the liver.

Hilar plate is sectioned and the hilus is retracted caudally. If bile leak is observed, thin bile dilators are carefully inserted and their dissection assessed to identify the main ducts. If we find both the ducts and the confluence preserved, the dilator is placed to find the anterior and posterior right duct. The left duct is also explored. The anterior aspect of the common duct is cut, and the section is directed to the left duct. Small arterial bleeding is controlled with isolated stitches of 5-0 absorbable monofilament. When opening the anterior aspect of the duct, confluence is visible, and once again, exploration of the ducts is done. The longitudinal anterior section is directed to the left duct, opening it as wide as possible. If the confluence is low, no further maneuver is necessary to perform a high-quality anastomosis.

If the bifurcation is lost, with isolated right and left component, and/or the confluence is high and deep in the liver, dissection of the ducts is not easily obtained. There are circumstances in which

adequate ducts are found, giving us the opportunity to retract only segment IV. Liver resection of the segment IV base is done when the liver is overhanging the upper ducts, allowing adequate exposure of the left duct. It is very important to stay in the coronal plane where the left duct is found, as stated by Strasberg.[6] If the confluence is not preserved in the same coronal plane, the dissection is directed to the gallbladder bed to expose the right duct. Resecting liver parenchyma of segments IV and V to allow identification of the right duct (Figs. 1 and 2) has been extensively and masterly described by Strasberg.

Liver resection at this level may result in venous bleeding that can be easily controlled with temporary compression, electrocoagulation, argon beam cautery, and/or dehydrated cellulose. To obtain a complete view of the confluence and/or the isolated right and left hepatic ducts, liver parenchyma can be removed. When adequate exposure has been achieved, parenchyma removal is also done to allow the free placement of the jejunal limb, so that when the retractors are released, no external compression is obtained over the jejunum. Finding the right duct can be difficult sometimes. Strasberg's anterior approach is very useful to identify the duct. If we fail to find it, partial segments IV and V resection can be considered.

The anastomosis is complete when a healthy duct is found, allowing a wide and tension-free anastomosis. This is achieved by placing 5-0 everted absorbable monofilament stitches. If isolated ducts are found and the distance between them is appropriate (less than 1 cm), a new confluence can be created by placing everted stitches anastomosing the medial and lateral borders of the right and left ducts. The bilioenteric anastomosis is performed all around the circumference of the new confluence. If the distance between both ducts is greater than 1 cm, we will be compelled to perform two separated anastomoses. Sometimes, in this situation, a transanastomotic stent on the right side is placed temporarily.

Stents are not used routinely, only when small diameter (less than 4 mm) or unhealthy ducts are found. Under these circumstances, a transanastomotic stent is used. Therefore, a mucosa-mucosa anastomosis is very difficult to achieve, and the tendency is to perform a portoenterostomy over the prosthesis to allow drainage of the bile into the intestinal lumen.

Two hundred eighty-five bile duct reconstructions were done in a 15-Year period (1989–2004) in a tertiary care university hospital. The files of these patients were reviewed, and the cases in which partial segment IV removal was done were evaluated. Postoperative outcome after reconstruction was

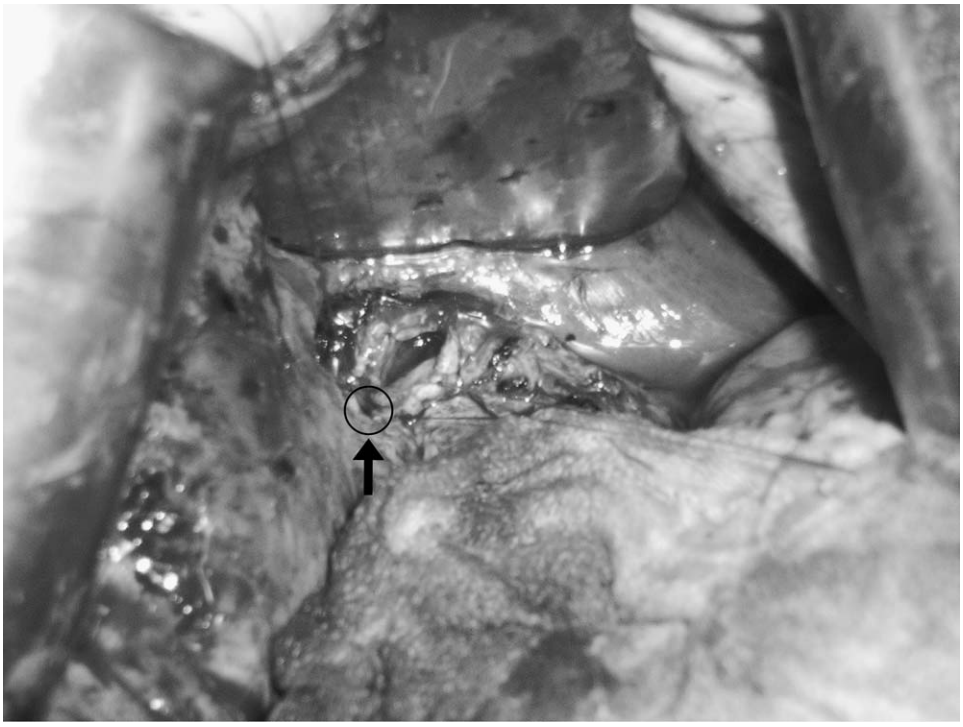

Fig. 1. View of the hepatic hilus once the plate has been removed and the base of the segment IV has been resected. The left duct is open longitudinally, exposing the confluence and the right duct (*arrow*).

Fig. 2. Left and right duct lumen exposed. Anterior openings of the left duct have been done.

evaluated. Lillemoe's criteria were used to grade the outcome (good = resolution of obstructive episode and/or cholangitis, without symptoms and normal bilirubin; poor = the opposite).[8]

RESULTS

Ninety-four patients of the 285 treated had a partial segments IV and V resection. All of them had complex injuries (Strasberg E1–E5). Mean age was 42 years (range 17–75); 68 were female patients. Four cases were repaired at the initial operation, in which the surgeon called our team to realize the reparation (two injuries at our own institution, two from outside hospitals). Twenty-four patients arrived with less than 1 month since the injury occurred, and 66 cases arrived with a previous attempt of reparation: 35 had a failed hepato-choledochoduodenostomy, 20 with failed hepatojejunostomy, three with internal biliary fistula secondary to prolonged subhepatic drains, and finally, eight with an external biliary fistula. Table 1 shows the type of injuries according to the Strasberg classification.

Resection of partial segments IV and V was indicated when one of the following situations was found: (a) confluence preserved with inadequate common hepatic duct: 60 cases (low diameter, suspected or demonstrated ischemia); (b) unpreserved confluence: 24 cases; and (c) nonsufficient space for jejunal limb: 10 cases. In both (a) and (c) groups, a high-quality bilioenteric anastomosis was performed. In group (b), both ducts where found using the segments IV and V approach, except in one case in which no right duct was found. This patient had a reduced-size right lobe, and a resection was needed. In two cases, very small, scarred ducts were found (less than 2 mm in diameter) so resection was also done.

In the remaining 21 cases, we were able to do an anastomosis. In eight patients, there was the need to perform two anastomoses; in the remaining 13, we

Table 1. Scenario and classification

No. patients (n = 94)	Time of injury	Strasberg's classification	No. of cases
4	Acute	E1-E2	4
24	<1 month	E1-E2	8
		E3	12
		E4	2
		E5	2
66	Previous attempt	E1-E2	6
		E3	46
		E4	8
		E5	6

did an anastomosis to the left duct and a type of Porto enterostomy to the right duct, with a transanastomotic stent. No operative deaths were reported.

According to Lillemoe's criteria, good results were found in 86 cases. No obstructive jaundice and/or cholangitis were reported in 86 patients (91%). The patients returned to normal life and activity, including four pregnancies. Here were included the 70 cases with preserved junction, seven of the eight cases with two separated anastomoses, and 7 cases with the transhepatic transanastomotic stents, which were removed 6 to 9 months after the operation.

In the remaining eight cases, four needed a new surgery and a radiological instrumentation was attempted in the rest. In the four reoperated subjects, transhepatic transanastomotic stents were placed. Two of these developed secondary biliary cirrhosis with bleeding portal hypertension; they died waiting for a liver transplant. Two remained with percutaneous stents for another 6 months and are waiting for a donor. The four patients with radiological instrumentation are being managed with periodical change of the prostheses. Only four cases were lost for follow-up.

DISCUSSION

When a complex injury that cannot be treated by an endoscopic procedure is found, Roux-en-Y hepatojejunostomy is the preferred approach for reparation of the bile duct.[9] Although other variants of bilioenteric anastomosis have been described with success, such as hepatoduodenostomy or choledochus duodenostomy, most surgeons prefer a Roux-en-Y hepatojejunostomy. Duct-to-duct anastomosis has a high failure rate, and most surgeons with experience in bile duct repair do not recommend it. After a biliary injury, finding two well-preserved ducts is not as common as one would expect, contrary to what happens on the reconstruction after a liver transplantation. The former results in a high-tension anastomosis, due in many cases to the loss of substance and devascularized stumps found on this pathology.[4]

In our complete series, we have identified failure of the duct-to-duct anastomosis (46/285). These cases showed obstructive jaundice with a stricture at the middle of the duct; it is intended that they be managed by an endoscopist. Failures were treated surgically, and a hepatojejunostomy was performed. Because there were good lengths of the common hepatic duct, segment IV resections were not required.

The Hepp-Couinaud technique has shown good results for patients in which a bilioenteric anastomosis is needed.[10] Because the left hepatic duct is "extrahepatic" at the base of segment IV, section of the anterior surface of the duct at this level allows the visualization of the confluence. A wide tension-free mucosa-mucosa anastomosis allows the entire drainage of the biliary tree. As stated by Strasberg, is the ideal approach for reparation of E1–E3 injures.[6] If an injury or its consequences, such as biloma, collections[11] or ischemia, involve the ducts above the bifurcation or confluence, the right and left ducts are found separately. Moreover, ducts can be found scarred and/or ischemic.

The goal is to obtain a high-quality bilioenteric anastomosis, meaning a wide tension-free, nonischemic mucosa-mucosa anastomosis, with adequate drainage. To achieve this we have to section the anterior surface of the common duct, directing it to the anterior surface of the left duct. A minimum opening of 1 cm is desirable. Tension-free anastomosis is obtained by having enough space for the placement of the jejunal limb, or obtaining an adequate free limb by means of preparing the mesenterium, with preservation of the vascular arcades. If there is any doubt about the tension of the anastomosis and if it is not possible to obtain more free limb, mobilization of the liver from the falciform ligament and/or coronary ligament might be necessary. Nevertheless, this is an uncommon condition. Healthy, noninflamed, nonischemic, nonscarred ducts are necessary.

Types of sutures are also very important, as has been emphasized by Lee et al.[11] Heavy nonabsorbable sutures are more likely to produce granulomas with consequent obstruction. Also, the inflammatory reaction to this type of suture produces scarring that may obstruct the anastomosis. Five (5-0) absorbable monofilament everted sutures produce an excellent apposition of mucosa to mucosa. We recommend that the jejunal limb be fixed to the liver capsule to prevent twisting of the limb and tension at the level of the anastomosis.

Finally, it is very important to rule out dysfunction of the Roux-en-Y limb. Although it has been suggested that the Roux-en-Y limb may have some motor disturbances, in our experience we have found erroneously built Roux-en-Y limbs with the consequent malfunction.[7] If a high-quality anastomosis can be done in a patient in whom the bifurcation is preserved, the rate of success is very high.

Resection of segments IV and V has the following after advantages:

1. Morbidity and mortality of the resection is null. Bleeding can be easily controlled, and in the majority of cases, it is not significant.

2. When an isolated right duct is found, prolonging the dissection to the gallbladder bed (Strasberg) allows the localization of the main right duct as well as the right anterior or posterior duct.
3. The posterior walls of the main, left, and right ducts are left undisturbed. In addition, the lateral aspects are respected, preventing ischemic damage. An undisturbed posterior wall limits the potential damage to the portal vein and artery.
4. Resection allows identification of healthy ducts.
5. Resection gives enough space for placement of the jejunal limb. In Strasberg's experience as well as ours, it is needed only in about one third of the cases.
6. Partial segment IV resection, as stated by Strasberg, is a useful adjunct to the approach of segment V resection to find the isolated right duct.

The final goal is to obtain optimal conditions to do a high-quality bilioenteric anastomosis. Partial liver resections of segments IV and V, when needed, are excellent assets to reach this condition.

Several other instances have to be considered to obtain a high-quality bilioenteric anastomosis. Classifying the injury allows adequate planning of the operation. Elective repair with all collections drained, as well as identification of the biliary anatomy, allows correct planning of the operation. Nevertheless, there are some patients in which an early repair gives us the opportunity to perform a high-quality procedure.[6]

Our results show that partial liver resection improves the conditions for a high-quality bilioenteric anastomosis. In our experience after a 5-year follow-up, neither morbidity nor mortality has been associated to this maneuver, therefore showing excellent results in patients in which the bifurcation is preserved.

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Alcoholic Hepatitis With Leukemoid Reaction After Surgery

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Alcoholic hepatitis (AH) is a clinicopathologic syndrome resulting from an excessive intake of alcohol. Leukemoid reactions (LRs) are characterized by a strikingly elevated granulocyte count over 40,000–50,000 cells/mm^3. Although a leukocytosis of 15,000–18,000 cells/mm^3 is frequently seen in AH, LRs are rare in this context. AH-associated LRs are a sign of poor prognosis and have a high mortality. A 64-year-old male with a history of heavy alcohol intake underwent a right hemicolectomy for cecal carcinoma. Preoperative laboratory data were normal with the exception of an albumin of 2.1 g/dL. Liver biopsies that were taken because of a nodular appearance revealed micronodular cirrhosis, steatohepatitis, and Mallory bodies. Postoperatively, the patient developed a leukocytosis that progressively increased to 72.6 cells/mm^3. He also developed signs of impaired hepatic and renal function. Extensive workup failed to reveal a source of infection. A trial of intravenous antibiotics had no impact on the leukocytosis. Methylprednisolone at a dose of 40 mg IV daily was started on postoperative day 9. The patient experienced a progressive decline in white blood count (WBC), which reached 25.2/mm^3 on postoperative day 14. However, he died on postoperative day 16. We conclude that the patient had AH-associated LR in the postoperative period, but died despite successful treatment of the LR with steroids. (J GASTROINTEST SURG 2006;10:83–85)

KEY WORDS: Alcoholic hepatitis, leukemoid reaction, Mallory bodies, steroid therapy

Alcoholic hepatitis (AH) is a clinicopathological syndrome resulting from an excessive intake of alcohol.[1] The presence of AH is not related to the degree of alcohol consumption, and the severity can be estimated by a "discriminant function" (DF): DF = 4.6 × prothrombin time (seconds) + serum bilirubin (mg per dL).[2] Mortality can be as high as 75% for patients with a DF over 93.[2] Leukemoid reactions (LR) are characterized by a strikingly elevated granulocyte count as a result of infection, stress, chronic inflammation, or neoplasm.[3] The threshold between leukocytosis and LR is usually established at 40,000–50,000/mm^3.

Although a leukocytosis of 15,000–18,000/mm^3 is frequently seen in AH, LRs are rare in this context; only 14 patients have been reported in the literature. AH-associated LR is a sign of poor prognosis with a high short-term mortality, even with a low DF.[4] There have been two cases of AH-associated LR that were treated with steroids and survived.[1,5] We report a patient with AH and cecal adenocarcinoma who developed LR after surgery and was treated with steroids. Although his LR improved, he did not survive.

CASE REPORT

A 64-year-old Hispanic male underwent a right hemicolectomy for a cecal adenocarcinoma. He had a history of drinking six cans of beer and three glasses of gin every day for 35 years. On admission, his physical exam was unremarkable. His preoperative laboratory results were as follows: white blood count 11,500 cells/mm^3; platelets 365,000/mm^3; prothrombin time 14.9 seconds; albumin 2.1g/dL; electrolytes, liver function tests, and chest roentgenogram were normal.

During the operation, his liver appeared congested and nodular; biopsies revealed micronodular cirrhosis, steatohepatitis, and Mallory bodies (Fig. 1). Histologic sections of the right colon that was removed confirmed the presence of an adenocarcinoma. Postoperatively, the patient developed a leukocytosis that progressively increased to 72,600/mm^3 on

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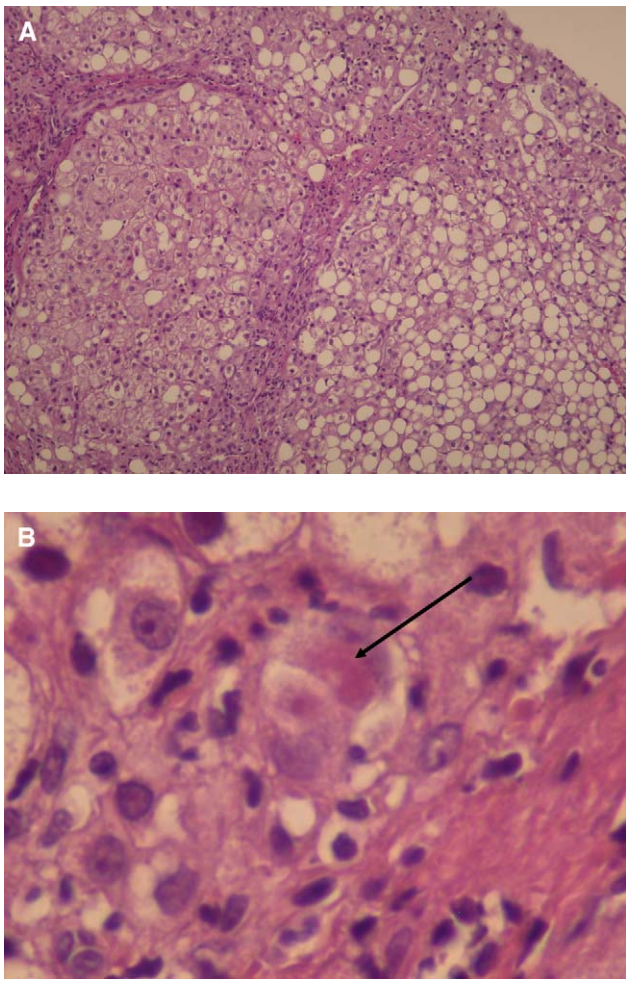

Fig. 1. Liver biopsy microphotograph (Hematoxylin and Eosin) showing (**A**) steatohepatitis and (**B**) a Mallory body (cytoplasmic inclusion) (*arrow*) within a degenerated hepatocyte.

postoperative day 9. Extensive workup did not reveal the presence of infection or leukemia. Methylprednisolone 40 mg IV qd was begun on postoperative day 9. The patient experienced an immediate improvement 24 hours later. His leukocytosis decreased to 46.7/mm^3. By the 14th postoperative day, his white blood count had further decreased to 25.2/mm^3. However, despite this hematologic improvement, the patient's kidney and liver function continued to deteriorate, and he expired on postoperative day 16.

DISCUSSION

Fifteen cases of AH-associated LR, including ours, have been reported in the literature (Table 1). The patient reported here is a case of AH-associated LR after an abdominal operation. In 1977, Maddrey et al. described a *discriminant function* to analyze the results of treatment of AH with corticosteroids. An association was found between death, prolongation of prothrombin time, and the level of serum bilirubin. The discriminant function (DF) formula that best predicted survival was DF = 4.6 × prothrombin time (seconds) + serum bilirubin (mg per dL). All deaths occurred in patients whose initial DF was greater than 93, and corticosteroids significantly improved mortality over placebo (12% vs. 75%).[2]

Mitchell et al. reported eleven patients with AH-associated LR.[4] Six patients in this group died even though they had a DF lower than 93. Our patient also died despite a DF of 69. The reason for this increased mortality is not clear, but AH-associated LR might be a bad prognostic factor. If this is the case, the DF formula may not be applicable under these circumstances. To validate this hypothesis, a large number of cases would need to be collected to perform a valid statistical analysis.

The pathophysiology of LR in these patients has not been elucidated. The release of excessive amounts of tumor necrosis factor-alpha (TNF-α) has been postulated to be instrumental in the causation of leukemoid reaction in alcoholic patients.[6] However, Arguelles-Grande et al. reported a patient in which the cytokine profile did not demonstrate increased amounts of TNF-α. In their patient, levels of IL-18 and IL-1β were increased. IL-1β stimulates the proliferation and maturation of neutrophils in the bone marrow both directly by the induction of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF); thus the postulated pathogenic sequence for LR: increased IL-18 produces increased IL-1β, which along with increased IL-8 (described in severe AH) produces neutrophilia. In this setting, corticosteroids may play a role by their reported inhibition of IL-1β transcription.[1]

Steroids have been used to treat AH-associated LR in only three patients, including ours. Two of them survived after their LR improved with steroids. In our patient, the LR dramatically improved after steroids, but he died of hepatorenal syndrome. The remaining twelve patients described in the literature did not receive steroids. Eleven of these had no change in their LR and subsequently died of hepatorenal syndrome. Even though the experience with steroids in the management of AH-associated LR is small, its use should be considered before the development of hepatorenal syndrome.

SUMMARY

We describe a patient with severe alcoholic hepatitis and a leukemoid reaction after surgical intervention for a right hemicolectomy for cecal adenocarcinoma. Alcoholic hepatitis and leukemoid

Table 1. Previously recorded cases of alcoholic hepatitis with leukemoid reaction

Date	Author	Presenting WBC (cells/mm^3)	Highest WBC (cells/mm^3)	Response	PT (s)	TB (mg/dl)	DF	Outcome
1961	Colman et al.[7]	38,900	57,000	None	15.8	10.4	83	Died HD 16
1962	Edmundson et al.[8]	57,400	129,000	None	16.25	11.7	86	Died HD 18
1962	Edmundson et al.[8]	86,000	86,000	69,000	16.8	5.4	83	Died HD 9
1962	Edmundson et al.[8]	50,400	50,400	33,000	19.25	10.9	99	Died HD 115
1968	Reynolds et al.[9]	61,000	61,000	None	20.75	25	120	Died HD 46
1975	Wallach et al.[10]	46,000	78,000	96,000	15.8	4.9	78	Survived
1975	Baur et al.[11]	34,900	82,500	34,900	14.7	11.8	79	Died HD 28
1978	Hawkins et al.[12]	14,000	51,000	None	16	35	108	Died HD 7
1991	Mitchell et al.[4]	33,600	105,000	None	16.5	13.8	90	Died HD 27
1991	Mitchell et al.[4]		57,000	None	14.25	0.5	66	Died HD 44
1991	Mitchell et al.[4]		41,000	None	16.8	23.8	101	Died HD 60
1993	Larvol et al.[5]	45,000	84,100	7,500				Survived
1998	Juturi et al.[6]	80,000	136,000	None	20	23.4	115	Died
2002	Arguelles et al.[1]		37,500	8,400		9.2		Survived
2004	Morales et al.*	11,500	72,600	25,280	14.9	0.6	69	Died HD 16

WBC = white blood count; PT = prothrombin time; TB = total bilirubin; DF = discriminant function; HD = hospital day.
*Our patient.

reaction have been reported in 14 other cases, representing a subgroup of alcoholic hepatitis with a particularly high mortality. In two of these patients, the use of steroids improved their outcome. However, although the leukocyte count of our patient did improve, our patient died.

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Comparison Between Hepatic Wedge Resection and Anatomic Resection for Colorectal Liver Metastases

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Some investigators have suggested that wedge resection (WR) confers a higher incidence of positive margins and an inferior survival compared with anatomic resection (AR) of colorectal liver metastases (CLM). We sought to investigate the margin status, pattern of recurrence, and overall survival of patients with CLM treated with WR or AR. We identified 253 consecutive patients, in a multi-institutional database from 1991 to 2004, who underwent either WR or AR. WR was defined as a nonanatomic resection of the CLM, and AR was defined as single or multiple resections of one or two contiguous Couinaud segments. Clinicopathologic factors were analyzed with regard to pattern of recurrence and survival. One hundred six WRs were performed in 72 patients and 194 ARs in 181 patients. There was no difference in the rate of positive surgical margin (8.3%), overall recurrence rates, or patterns of recurrence between patients treated with WR vs. AR. Patients who had a positive surgical resection margin were more likely to recur at the surgical margin regardless of whether they underwent WR or AR. The median survival was 76.6 months for WR and 80.8 months for AR, with 5-year actuarial survival rates of 61% and 60%, respectively. AR is not superior to WR in terms of tumor clearance, pattern of recurrence, or survival. WR should remain an integral component of the surgical treatment of CLM. (J GASTROINTEST SURG 2006;10:86–94)

KEY WORDS: Margin, liver, wedge resection, segmentectomy, colorectal metastases

Given recent improvements in surgical technique and the development of more effective chemotherapy, the indications for surgical resection of colorectal liver metastases are expanding, with staged and repeat hepatic resections now commonplace.[1–6] The basic tenets for the resection of both primary and secondary hepatic malignancies include a clear pathologic surgical margin and the preservation of sufficient functional hepatic parenchyma.[7,8] Although the performance of a systematic anatomic resection has been reported to improve tumor clearance and outcome in patients with hepatocellular carcinoma,[9–12] similar findings have not been clearly demonstrated in patients with colorectal liver metastases (CLM).[8,13–15] Some investigators have reported a higher incidence of positive surgical margins and an inferior survival in patients who undergo a wedge resection compared to those who undergo an anatomic resection of CLM, concluding that an anatomic resection is a superior oncologic procedure for CLM.[16] Other studies, however, report similar rates of positive margin and similar outcome in patients treated with wedge resection or anatomic resection.[14,15,17] In this study we report our experience with 253 patients, who underwent either a wedge or anatomic resection for CLM, to assess the oncologic efficacy of these two approaches to the surgical treatment of CLM.

METHODS

We identified 253 consecutive patients, who underwent either a wedge or anatomic hepatic resection for CLM between March 1991 and May 2004,

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from an international multicenter database with contributors from three institutions: the University of Texas M. D. Anderson Cancer Center (Houston, TX), the Surgical Oncology Unit, Institute of Research and Cure of Cancer (Candiolo, Italy), and the Division of Digestive Surgery, University Hospital (Geneva, Switzerland). Before surgery, all patients were evaluated with a baseline history and physical examination, serum laboratory tests, and appropriate imaging studies (computed tomography or magnetic resonance imaging scan of the abdomen and pelvis and chest radiography or a chest computed tomography scan) at the discretion of the treating physician. All patients with CLM and no clinical, radiographic, or intraoperative evidence of extrahepatic disease were eligible for resection. Patients were deemed to have resectable disease only if it was anticipated that the metastasis could be resected with a negative margin.

The liver segments are as described by Couinaud,[18] and the operative procedures in the anatomic group were defined according to the Brisbane 2000 terminology of liver anatomy and resections,[19] in which a segmentectomy is a resection of a Couinaud segment[9] and a sectionectomy is a resection of one of Healey's segments.[20] Anatomic resection was defined as a segmentectomy, multi-segmentectomy, sectionectomy, or segmentectomy plus sectionectomy. Anatomic resection (AR) was performed for large, deeply situated, or multiple-clustered CLMs located in one part of the liver. Wedge resection was defined as a nonanatomic resection of the CLM to include a rim of microscopically normal tissue. Wedge resection (WR) was performed for small, peripheral, isolated CLMs. Patients who underwent hemihepatectomy, trisectionectomy, or combined WR and AR were excluded from this analysis. The cohort of the present study represents a subpopulation of a previous study concerning 557 hepatic resections for CLM.[21]

The following data were collected for each patient: demographics; laboratory data, including carcinoembryonic antigen (CEA); tumor number and location; operative details; pathologic margin status; disease status; site of recurrence; date of last follow-up; and date of death. Data were recorded as follows: clinical features, present or absent; age, <65 years or $\geqslant 65$ years; CEA level, $\leqslant 200$ ng/mL or >200 ng/mL; tumor number, <3 or $\geqslant 3$; tumor size, <5 cm or $\geqslant 5$ cm; and surgical margin status, positive or negative. A positive margin was defined as the presence of exposed tumor along the line of transection or the presence of tumor cells at the line of transection detected by histologic examination. Synchronous metastases were defined as concurrent metastases.

After hepatic resection, all patients were regularly followed and prospectively monitored for recurrence by serum CEA levels, a chest radiograph, and a computed tomography or magnetic resonance imaging scan of the abdomen every 3 months up to 2 years, and then every 6 months thereafter. Complete follow-up imaging was available for 252 of 253 patients, and recurrences were categorized as at the surgical resection margin, other intrahepatic site, or extrahepatic site. One patient was lost to follow-up.

Statistical analyses were performed with SPSS statistical software (SPSS Inc, Chicago, IL). Actuarial survival was calculated using the Kaplan-Meier method from the time of diagnosis of CLM, and differences in survival were examined using the log-rank test. A P value < 0.05 was considered significant.

RESULTS

Clinicopathologic Characteristics

Two hundred fifty-three patients underwent either a WR or AR for CLMs, including 159 (63%) men and 94 (37%) women. The median age was 61 years (32–88 years). The primary colorectal carcinoma was located in the colon in 155 (61%) patients and in the rectum in 63 (25%) patients; in 35 (14%) patients the location was unknown. At the time of the initial resection of colorectal cancer, positive lymph nodes were identified in 159 (62.8%) patients, and synchronous liver metastases in 98 (38.7%) patients. The remaining 155 (61.3%) patients developed metachronous CLMs at a median disease-free interval of 16 months (2–120 months) from the time of resection of the primary colorectal cancer. The disease-free interval was less than 12 months in 55 (35.5%) patients. The CEA level at the time of hepatic resection exceeded 200 ng/mL in only eight (3.2%) patients. One hundred and forty-four patients (57%) had a single liver metastasis, 70 (28%) patients had two or three metastases, and 39 patients (15%) had more than three metastases. The median diameter of the largest CLM was 2.7 cm (0.3–18 cm). The size of the largest metastasis was less than 5 cm in 212 (84%) patients. On final pathologic analysis, the surgical margin was microscopically positive in 21 (8.3%) patients.

The clinicopathologic features of the wedge resection and anatomic resection groups are presented and compared in Table 1. The sex distribution, age, primary tumor site, primary lymph node status, synchronous diagnosis of CLM, preoperative CEA level, and number of liver tumors were similar between the two groups. Patients who underwent WR, however,

Table 1. Comparison of the clinicopathologic features between the two groups

Variables	Wedge resection (n = 72)	%	Anatomic resection (n = 181)	%	*P*-value
Sex					
Female	26	36	68	37.6	0.8
Male	46	64	113	62.4	
Age					
<65 years	44	61	120	66.3	0.4
⩾65 years	28	39	61	33.7	
Primary tumor site					
Colon	42	58.3	113	62.4	0.9
Rectum	17	23.6	46	25.4	
Unknown	13	18.1	22	12.2	
Primary lymph node status					
Negative	28	38.9	66	36.5	0.7
Positive	44	61.1	115	63.5	
Timing of CLM					
Synchronous	25	34.7	73	40.3	0.4
Metachronous	47	65.3	108	59.7	
Disease-free interval	(n = 47)		(n = 108)		
Median	12 months		18.5 months		0.006
<12 months	23	49	32	29.6	0.02
⩾12 months	24	51	76	70.4	
CEA level					
<200 ng/mL	63	87.5	160	88.4	0.3
⩾200 ng/mL	1	1.4	7	3.9	
Unknown	8	11.1	14	7.7	
Number of tumors					
Single	45	62.5	99	54.7	0.3
Multiple	27	37.5	82	45.3	
⩽3 nodules	65	90.3	149	82.3	0.1
>3 nodules	7	9.7	32	17.7	
Largest tumor size Median (range; cm)	2.1 cm (0.5–6)		3 cm (0.3–18)		0.001
<5 cm	68	94.4	144	79.6	0.004
⩾5 cm	4	5.6	37	20.4	
Surgical margin					
Positive	6	8.3	15	8.3	0.9
Negative	66	91.7	166	91.7	

CEA = carcinoembryonic antigen; CLM = colorectal liver metastasis; n = number of patients.

were more likely to have a disease-free interval of less than 12 months (49% vs. 30%; $P = 0.02$) and a largest tumor size of less than 5 cm (94% vs. 80%; $P = 0.004$) compared with patients who underwent AR.

Surgical Treatment

Three hundred hepatic resections were performed in 253 patients: 106 (35%) wedge resections in 72 patients and 194 (65%) anatomic resections in 181 patients. The hepatic resections are listed in Table 2. A single wedge resection was performed in 54 (75%) of the 72 patients, whereas 18 (25%) of the 72 patients had two or more WRs. The most common anatomic resection was a left lateral (S2–3) bisegmentectomy in 88 (49%) patients, followed by bisegmentectomy 5–6 in 15 (8.3%) patients. Monosegmentectomies were performed in 42 (23%) patients and resection of two discontiguous segments in 13 (7%) patients.

Outcome

The outcome of patients undergoing wedge resection vs. anatomic resection for CLMs is presented in Table 3. The median length of stay was 7 days for both groups. There was only one (1.4%) postoperative death after a wedge resection, and two (1.1%) after anatomic resections ($P = 0.6$). The complication rate was similar between the two groups (28% vs. 23%; $P = 0.4$).

Table 2. Types of hepatic resection

Liver resection	No. of patients (n = 253)	No. of procedures (n = 300)
Wedge		
Single	54	54
Two	10	20
Three	3	9
Four	2	8
Five	3	15
TOTAL	72	106
Anatomic		
Monosegmentectomy	42	42
Segment 5	12	12
Segment 6	8	8
Others	22	22
Bisegmentectomy	126	126
Left lateral (S2–3)	88	88
S5–6	15	15
S6–7	9	9
Others	14	14
Discontiguous segmentectomies	13	26
TOTAL	181	194

On final pathologic analysis, 21 (8.3%) patients had a positive surgical resection margin. There was no difference in the rate of positive surgical margins per patient in the wedge resection group (6/72, 8.3%) compared to the anatomic resection group (15/181, 8.3%). Moreover, the rate of positive surgical margins was similar between the two groups when calculated per resection (WR, 6/106, 5.7% vs. AR, 15/194, 7.7%; $P = 0.5$).

At a median follow-up of 25 months, 100 patients (39.5%) have recurred. The overall recurrence rates were comparable between the two groups (37.5% vs. 40.3%; $P = 0.4$). The median time to recurrence was longer in the wedge resection group (16.2 months vs. 11.4 months), but this did not reach statistical significance ($P = 0.07$). The pattern of recurrence did not differ between the two groups (Table 4).

Nine (3.6%) patients developed a recurrence at the site of the surgical resection margin, two (2.8%) in the WR group and seven (3.9%) in the AR group. Interestingly, only three of these nine surgical margin recurrences occurred in patients with a positive resection margin (Table 5). Patients with a positive resection margin were more likely to recur at the surgical margin (positive 14.3% vs. negative 2.6%; $P = 0.03$), regardless of whether they underwent WR or AR (WR, 17% vs. AR, 13%; $P = 0.8$; data not shown).

Analysis of Prognostic Factors for Survival

The overall 1-, 3-, and 5-year survival rates for the entire cohort of 253 patients were 96.7%, 74.7%, and 59.2%, respectively (Table 3). Synchronous presentation, tumor size, CEA level, and nodal status of the primary tumor had no impact on survival ($P > 0.05$; data not shown). There was no difference in the median or overall 5-year survival in patients treated with WR (77 months, 61% survival) compared to those treated with AR (81 months, 60% survival; Table 3 and Fig. 1).

Prognostic factors for survival were analyzed for the entire group of 253 patients, and the results are summarized in Table 6. By univariate analysis, survival was significantly worse for patients with multiple tumors ($P = 0.016$), especially more than three tumors ($P = 0.007$), a time of recurrence of less than 12 months ($P = 0.0001$), and recurrence at the surgical margin (0.005). Of note, the type of resection performed (WR vs. AR) and the status of the surgical

Table 3. Outcome of patients undergoing wedge resection vs. anatomic resection for CLM

Variable	All patients (n = 253)	Wedge (n = 72)	Anatomic (n = 181)	*P*-value
Median (range) LOS (days)	7 (3–42)	7 (4–27)	7 (3–42)	0.6
Complications	61 (24%)	20 (28%)	41 (23%)	0.4
Postoperative death	3 (1.1%)	1 (1.4%)	2 (1.1%)	0.6
Positive surgical margin	21 (8.3%)	6 (8.3%)	15 (8.3%)	0.9
Total recurrences	100 (39.5%)	27 (37.5%)	73 (40.3%)	0.4
Median time to recurrence (months)	12.3	16.2	11.4	0.07
Median follow-up (months)	25	25.8	24.73	0.5
Median survival (months)	80.8	76.6	80.8	0.15
Survival (%)				
1 year	96.7%	100%	95.4%	
3 years	74.7%	83.3%	71.5%	0.15
5 years	59.2%	60.5%	59.5%	

LOS = length of stay.

Table 4. Comparison of the patterns of recurrence of the WR and AR groups

Site of recurrence	No. (%) patients who recurred by type of resection		
	WR (n = 72)	AR (n = 181)	*P*-value
Surgical margin	2 (2.8)	7 (3.9)	0.5
Other intrahepatic	10 (13.9)	17 (9.4)	0.2
Extrahepatic	8 (11.1)	25 (13.8)	0.4
Intra + extrahepatic	7 (9.7)	24 (13.2)	0.3
Any recurrence	27 (37.5)	73 (40.3)	0.4

AR = anatomic resection; WR = wedge resection; No. = number of patients.

resection margin (positive vs. negative) had no impact on survival.

DISCUSSION

Complete hepatic resection offers the best chance for long-term survival for patients with colorectal carcinoma liver metastases. In a recently published series, we reported a 5-year overall survival rate of 58% in patients who underwent hepatic resection of CLM, a superior survival to that achieved with radiofrequency ablation (RFA) alone or in combination with resection in patients with unresectable disease.[22] The major limitation to the complete resection of CLM in the majority of patients who present with bilobar or bulky disease is the need to preserve a sufficient functional liver remnant. Advances in hepatic surgery and perioperative care have enabled extensive hepatic resections of up to 80% of the functional liver parenchyma with low rates of morbidity and mortality in major centers.[23,24] Yet despite these improvements, the majority of patients with CLM are not candidates for curative resection owing to the extent of their disease.

Table 5. Recurrence at the surgical margin according to the margin status at the time of hepatic resection

Type of recurrence	No (%) patients with margin recurrence, by margin status and resection		
	Positive margin (n = 21)	Negative margin (n = 32)	*P*
Surgical margin	3	6	
Rate/patient	3/21 (14.3%)	6/232 (2.6%)	0.03
Rate/procedure	3/21 (14.3%)	6/279 (2.1%)	0.007
Any recurrence	11	89	
Rate/patient	11/21 (52.4%)	89/232 (38.4%)	0.2

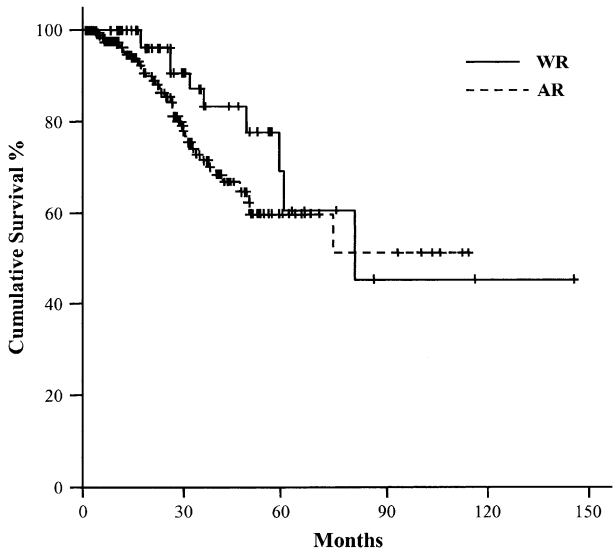

Fig. 1. Overall survival stratified by surgical procedure. WR = wedge resection (n = 72; solid line); AR = anatomic resection (n = 181; broken line). Median survival was 76.6 months in patients with WR and 80.8 months in patients with AR; the 5-year survival rate was 61% and 60%, respectively (P = 0.15).

Strategies to increase the proportion of patients who are candidates for curative resection have emerged over the past several years, including neoadjuvant chemotherapy,[25,26] portal vein embolization,[27,28] two-stage hepatectomies,[1,5] and repeat hepatic resections.[29,30] The goal of all of these strategies is to permit resection of all metastases with negative histologic margins while preserving sufficient functional hepatic parenchyma. The resection strategy must be individualized for each patient based on the size, number, location, and distribution of the metastases. Extensive or multiple-clustered metastases in one lobe of the liver are best treated with a hemihepatectomy or extended hepatectomy; a single, large (>5 cm) metastasis, especially when located deep within the liver, is best treated with an anatomic, segment-oriented resection; and lastly, a small, superficial metastasis is best treated with a nonanatomic wedge resection. In patients with extensive bilobar disease in whom a two-stage approach is planned, the metastases in the left hemiliver (the functional liver remnant) are typically cleared by wedge resections in the first stage. A right portal vein embolization is then performed, followed by a right or extended right hepatectomy to resect the right liver metastases as the second stage.[31] The advantage of performing a limited, nonanatomic wedge resection in the first stage is the preservation

Table 6. Univariate analysis of prognostic factors for survival

Variable	No.	%	5 years survival (%)	Median survival (months)	*P*-value
Type of resection					
Wedge	72	28.5	60.5	80.8	0.15
Anatomic	181	71.5	59.8	76.6	
Number of tumors					
Single	144	56.9	71.2	112.2	0.016
Multiple	109	43.1	39.1	58.2	
⩽3 nodules	214	84.6	64.6	105.7	0.007
>3 nodules	39	15.4	39.2	49.6	
Surgical resection margin					
Positive	21	8.3	17.1	58.2	0.28
Negative	232	91.7	66.7	101.9	
Recurrence posthepatectomy					
Yes	100	39.7	44.1	58.2	0.06
No	152	91.7	86.4	92.8	
Time to recurrence					
<12 months	48	48	21.5	33.3	0.001
⩾12 months	51	51	60.7	80.8	
Site of recurrence					
Surgical margin	9	3.6	48.6	35.8	0.005
Intrahepatic only	27	10.7	68.6	109.2	
Extrahepatic only	33	13	40	58.2	
Intra + extrahepatic	31	12.3	18.6	41.6	

of a maximal amount of liver parenchyma that will hypertrophy after portal vein embolization to become the functional liver remnant. Implicit in this and other resection strategies is an equivalent outcome for each type of resection in terms of the incidence of positive margins, recurrence, and survival. However, is this the case?

Many authors have retrospectively studied the prognostic impact of the choice of surgical resection approach to CLM.[13,14,32–43] Most studies found that the type of hepatic resection performed, whether a major, anatomic resection or a limited, nonanatomic resection, had no impact on survival.[13,14,32–41] Two studies reported a slightly better outcome in patients treated with a nonanatomic, limited resection.[42,43] Other authors, however, have asserted that survival is superior in patients treated with an anatomic resection compared to those treated with a wedge resection.[16,34,35] DeMatteo et al.[16] compared 119 patients who underwent a wedge resection to 148 patients who underwent an anatomic resection of CLM from 1985–1998. Patients who had a segmental resection had a significantly lower rate of positive margins (2% vs. 16%) and a longer median survival (53 months vs. 38 months) compared to those who had a wedge resection. They concluded that a segmental resection is oncologically superior to a wedge resection, and thus is the procedure of choice for the resection of CLM.

In this multi-institutional study, we found no difference in the incidence of positive margins or survival in patients treated with either anatomic resection or wedge resection. We found an identical 8.3% incidence of positive margins after both anatomic resection and wedge resection and 5-year survival rates of approximately 60% in both groups, similar to the findings of others in their recent studies.[15,44] Elias et al.[15] reported a 7.1% in situ recurrence rate in patients undergoing a wedge resection compared to 12.5% in the patients in the anatomic resection group. Kokudo et al.[14,44] found similar rates of a "minimal margin" of less than 2 mm (27% AR vs. 21% WR) and 5-year survival (46% AR vs. 40% WR) for the two types of resection.

In keeping with a more aggressive surgical approach to CLM over the past several years, 43% of the patients in this series had multiple metastases, and 12% of patients underwent more than one wedge or anatomic resection at the time of surgery. Accordingly, liver parenchyma had to be carefully preserved in these patients to permit multiple and perhaps additional hepatic resections. This is in contrast to previous series[16,34,45] in which the vast majority of the patients had one liver metastasis and underwent a single procedure, and so the predicted surgical margin was large. This may explain why our rate of positive margin was 8.3% in the anatomic resection group

compared to only 2% in the study by DeMatteo et al.[16] However, it does not explain the relatively high incidence of positive margins after wedge resection reported by Scheele et al.[45] (30%), Fong et al.[46] (17%), and DeMatteo et al.[16] (16%). In this multicenter study, the surgeons at each center were diligent about preserving an adequate margin throughout the wedge resection, being careful not to fracture the liver parenchyma along the interface between the hard tumor and the softer normal liver substance.

The incidence and patterns of recurrence were similar between the wedge and anatomic resection groups (Table 4), comparable to the findings of Kokudo et al.[14] As expected, there was an increased risk of a surgical margin recurrence in patients with a positive surgical margin at the time of hepatic resection. Though the presence of a positive surgical resection margin has been shown to be a negative prognostic factor in many studies,[16,35,46,47] we did not find it to be a predictor of survival in this study (Table 6). Nonetheless, the median survival of patients with a positive resection margin was only 58 months compared with 102 months for patients with a negative margin. This difference was not statistically significant, perhaps owing to the small number of patients in the positive margin group.

The concept of performing limited, nonanatomic wedge resections with narrow margins is supported by the fact that CLM are histologically well-circumscribed,[8] micrometastases in the liver parenchyma surrounding CLM are rare and are primarily confined to the immediate vicinity of the tumor border,[44] and satellitosis and Glisson sheath extension are uncommon.[35,44] In our previous study,[21] we demonstrated that the width of a negative surgical margin does not affect the risk or site of recurrence or the overall survival. In the present study, we specifically addressed whether surgical technique (wedge vs. anatomic resection) affects outcome of resection for CLM. The data demonstrate no inherent oncologic benefit to an anatomic resection, thereby validating the continued use of nonanatomic wedge resections when clinically appropriate. Further support for the performance of a limited wedge resection comes from studying the patterns of recurrence. The incidence of an isolated intrahepatic recurrence after a wedge resection is only 14% compared to 9% after an anatomic resection ($P = 0.2$). Performing a large, anatomic resection does not prevent or lower the incidence of intrahepatic recurrence by simply removing more hepatic parenchyma at risk. Tumor biology dictates the likelihood and pattern of recurrence. These findings are in agreement with those of Kokudo et al.,[14] who noted an ipsilateral intrahepatic recurrence rate of 19.6% after wedge resection and found that 90% of these recurrences were resectable with favorable patient survival after the second hepatectomy.

CONCLUSION

An anatomic segment-oriented hepatic resection of CLM is not superior to a nonanatomic wedge resection in terms of the incidence of positive margins, the pattern of recurrence, or survival. The type of resection(s) chosen for a particular patient should be based on the anatomy of the lesion(s) and the goal of preserving an adequate volume of functional liver parenchyma. A nonanatomic wedge resection of CLM is a safe, simple, and oncologically equivalent alternative to anatomic resection and should remain an integral component of the surgical treatment of CLM.

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Case-Control Comparison of Laparoscopic Versus Open Distal Pancreatectomy

Vic Velanovich, M.D.

Laparoscopic distal pancreatectomy is becoming an increasingly used modality in the surgical treatment of pancreatic disease. The assumption is that this will lead to shorter hospitalization and faster recovery. However, actual comparative data between open and laparoscopic distal pancreatectomy is lacking. The purpose of this study is to compare these surgical procedures. All patients who underwent either laparoscopic or open distal pancreatectomy/splenectomy were reviewed. Fifteen patients underwent laparoscopic resection, whereas 41 underwent an open resection. The 15 laparoscopic patients were matched to 15 open patients for age, gender, and pancreatic pathology. Data gathered included length of stay, pancreatic leak, postoperative complications, and return to normal activity. Of the 15 laparoscopic patients, three were converted to open operations. Laparoscopic patients had a median length of stay of 5 days (range, 3–9) compared with 8 days (range, 6–23) for the open patients ($P = 0.02$). The pancreatic leak rate was 13% in each group. Overall postoperative complication rate was 20% in the laparoscopic group compared with 27% in the open group. Laparoscopic patients reported a return to normal activity in 3 weeks (range, 2–7) compared with 6 weeks (range, 4–10) for open patients ($P = 0.03$). Laparoscopic distal pancreatectomy/splenectomy does lead to shorter hospital stay and faster return to normal activity. Pancreatic leak rate and overall complication rate appear similar. (J GASTROINTEST SURG 2006;10: 95–98)

KEY WORDS: Laparoscopic pancreatectomy, pancreatic neoplasms, distal pancreatectomy

Distal pancreatectomy with or without splenectomy is a standard operation for many pancreatic diseases.[1] As laparoscopic surgery has extended its horizons beyond cholecystectomy to more complex operations with improved quality of life,[2] it was a natural progression that laparoscopic distal pancreatectomy be developed. There have been several reports documenting the feasibility and safety of laparoscopic distal pancreatectomy with and without splenectomy;[3–12] however, none of these have compared the laparoscopic approach to the open approach. The purpose of this study was to determine if laparoscopic distal pancreatectomy did lead to shorter hospital stays, faster return to normal activity, yet with similar complication rates.

METHODS AND MATERIALS

Patients

Laparoscopic distal pancreatectomy with splenectomy was introduced into Henry Ford Hospital in October 2003. Since that time, 15 laparoscopic distal pancreatectomies have been performed by the author. Forty-one distal pancreatectomy/splenectomy operations have also been performed since October 1996 by the author. The records of these patients have been reviewed for gender, age at time of the operation, pancreatic pathology, occurrence of pancreatic leak, other complications, and length of stay.

Operations

Although the author's technique for laparoscopic distal pancreatectomy/splenectomy has been previously published,[12] a brief description is still appropriate. After general, endotracheal anesthesia is induced, the patient is positioned in a 45 degree right lateral decubitus position with the patient's hip at the break in the table. The operating table is flexed to open the space between the patient's costal margin and iliac crest. After appropriate antisepsis is achieved, the abdomen is entered under direct vision superior to the umbilicus with a Hasson cannula.

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The abdomen is insufflated with CO_2 gas to the appropriate volume and pressure. Under direct vision, 10 mm ports are placed in the epigastrium and left posterior axillary line, and a 12 mm port is placed in the left midclavicular line.

The lesser sac is entered by dividing the gastrocolic ligament from the right gastroepiploic vessels to the gastric fundus, so that the entire gastrocolic and gastrosplenic ligaments are divided. The pancreas is identified and the retroperitoneum divided along the inferior border of the pancreatic body and tail. Using gentle retraction, the retropancreatic space is developed proximal to the tumor. Care is taken to ensure that the splenic artery and vein are included with the pancreatic body. The retroperitoneum superior to the pancreas is divided to allow a grasper to be visualized. A one-half inch Penrose drain is brought around the pancreas as a "lasso." Using the Penrose drain lasso, the pancreas can be retracted away from the retroperitoneum, and the completion of the retropancreatic dissection to the tail of the pancreas completed. The splenic flexure of the colon and the remaining splenic peritoneal attachments are divided to mobilize the pancreas and spleen completely. The pancreas is divided proximal to the tumor with an endo-GIA stapler with vascular staples, allowing from enough normal pancreas for an adequate margin. The distal pancreas and spleen are placed in a laparoscopic retrieval bag and brought out through the 12 mm port, which usually has to be enlarged to accommodate the specimen. The operative site is inspected for bleeding. A 10 mm flat, Jackson-Pratt drain is placed next to the pancreatic remnant and brought out through the left posterior axillary line port. The fascia and skin are closed in the customary fashion.

The open operation was done either through an upper, midline incision or a left, subcostal incision. Otherwise, the conduct of the operation was similar except for the following details. The pancreas was divided using a TA-60 stapler, occasionally incorporating the splenic vessels, and frequently ligating and dividing the splenic artery and vein separately from the pancreatic parenchyma. A 10 mm flat Jackson-Pratt drain was placed next to the cut remnant of the pancreas and brought out through a separate stab incision. The abdomen was closed in layers, and the skin closed with staples.

Case-Control Comparison

The 15 laparoscopic patients were matched to 15 open, control patients based on age (within 10 years), gender, and pancreatic pathology (malignant lesions, cystic lesions, neuroendocrine tumors, or chronic pancreatitis). The priorities of matching were tissue diagnosis, gender, and then age. The matching was successful for these characteristics. Weight was not used in the matching, but will be reported. The medical records of each laparoscopic and matched, open control were reviewed for length of stay, occurrence of pancreatic leak (defined as amylase-rich fluid of any amount from the operatively placed drain after 3 days), and postoperative complications of Clavien class II or higher.[13] Patients were questioned, either at the time of postoperative office visit or by telephone, as to when they felt like they returned to normal activity. As patients were asked to recall this event, it was believed that they could not be very precise; therefore, "weeks" was chosen as the unit of measure.

Statistical Analysis

As this was a retrospective case-control study design, continuous data (i.e., length of stay and return to normal activity) were analyzed using the paired signed rank test. Nominal data (pancreatic leak rate and overall complication rate) were analyzed using Fisher's exact test. A P-value of $P < 0.05$ was considered significant.

RESULTS

Of the patients in the laparoscopic group, nine were female and six were male. The average age ($\pm$ standard deviation) was 65 $\pm$ 14 years. Although weight was not used in the matching process, the average weight for the laparoscopic group was 75.2 $\pm$ 8.5 kg, whereas in the open group, it was 80.3 $\pm$ 13.4 kg. Of the 15 cases begun laparoscopically, three (20%) were converted to an open laparotomy (these cases were kept in the laparoscopic group). One was for bleeding; the other two for retroperitoneal tumor adherence. In all three of the converted cases, the final pathology of the tumor was ductal adenocarcinoma. Table 1 presents the distribution of pathology for both the laparoscopic and open cases.

Table 1. Distribution of pathology by operation type

	Laparoscopic (n = 15)	Open (n = 41)
Ductal or cystic adenocarcinoma	20%	32%
Benign or indeterminate cystic neoplasm	53%	15%
Neuroendocrine tumor	13%	10%
Chronic pancreatitis	13%	29%
Other	—	15%

Case-Control Analysis

The median hospital length of stay for the laparoscopic group was 5 days (range, 3–9 days) compared with 8 days (range, 6–23 days) for the open controls ($P = 0.02$). Two of 15 (13%) laparoscopic patients developed pancreatic leaks compared with 2 of 15 matched controls (P = NS). Significant complications occurred in three (20%) laparoscopic patients and four (27%) open patients (P = NS). In the laparoscopic group, these complications included two wound infections and one urinary tract infection. In the open group, these complications included two wound infections, one pneumonia, and one intra-abdominal abscess. The median length of time to when patients felt that they had returned to normal activities was 3 weeks (range, 2–7) in the laparoscopic group compared with 6 weeks (range, 4–8) in the open group ($P = 0.03$).

DISCUSSION

This study demonstrates that laparoscopic distal pancreatectomy not only can be performed as safely as open distal pancreatectomy for selected patients, but also leads to shorter hospital stays and faster return to normal activity. The complication rates were similar between both groups, and similar to previously published morbidity data.[1,14,15] A literature search of previous publications did not find another study directly comparing the laparoscopic to the open, laparotomy approach. Therefore, this study confirms what is anticipated about a minimally invasive approach to distal pancreatectomy.

Of particular interest is that all three conversions to open laparotomy occurred in patients with pancreatic adenocarcinoma. After conversion, all three patients did have their tumors resected. Some have suggested that pancreatic adenocarcinoma is a contraindication to laparoscopic resection.[11] Certainly, it is well-known that adenocarcinoma of the body and tail of the pancreas has a lower resectability rate than tumors of the head of the pancreas.[16] This has been attributed to patient presentation at a more advanced stage. In laparoscopic distal pancreatectomy, local fibrosis or inflammatory response caused by the tumor is probably the cause of the difficult laparoscopic dissection. Nevertheless, laparoscopy in pancreatic cancer has distinct advantages even if the resection cannot be completed laparoscopically. Firstly, peritoneal or liver metastases that were missed by CT scan may identify unresectable patients before laparotomy.[17] Those patients may be referred sooner to definitive chemoradiation or other nonsurgical therapies.[18] In addition, laparoscopy does not seem to increase the risk of peritoneal or trocar site recurrence.[19]

Although this study is consistent with other studies comparing open to laparoscopic surgery for a variety of operations, this study does have limitations. Firstly, this is not a prospective, randomized trial and therefore suffers from the limitations of retrospective studies. Some of these limitations are mitigated by the case-control design and by the fact that all of the operations were done by the same surgeon. Length of stay is an easily documented end point, as are the in-hospital complications. Nevertheless, as the patients studied were treated over a nine-year period, changes in discharge planning and supportive care may have affected length of stay in more recent years. However, the return to normal activity end point was the most difficult one with respect to precision. Patients were contacted after the fact and were asked to remember how soon they felt they had returned to normal activity. Hence, this end point does suffer from recall bias. There is no way around this criticism. It would seem reasonable to assume that whatever imprecision there was would be distributed equally among both groups, but there is no way to verify this assumption. However, the magnitude of the difference seems reasonable.

Despite the limitations of this study, it does support the assertion that laparoscopic distal pancreatectomy yields equivalent surgical results, with shorter hospitalization and faster return to normal activity. Obviously, a prospectively designed randomized trial would better prove this point. Still unresolved is whether or not pancreatic adenocarcinoma of the body and tail of the pancreas is consistently feasible with the laparoscopic approach.

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Does the Literature Support an Indication for Hepatic Metastasectomy Other Than for Colorectal Primary?

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Hepatic resection for colorectal hepatic metastatic disease has been demonstrated to have a significant outcome benefit for selected patients. Advances in anesthetic and surgical technique have resulted in a significantly reduced morbidity and mortality for this procedure, and this management approach has become widely practiced. This hepatic resection paradigm is also being applied to hepatic metastatic disease of noncolorectal origin. The purpose of this report is to review and summarize the reported literature in order to define if the current data support an indication for hepatic metastasectomy. The specific cancer primaries that this analysis evaluated include breast, melanoma, gynecologic, neuroendocrine, sarcoma, and gastric cancer. Based on the data examined, we propose that although hepatic metastasectomy for noncolorectal cancer may be a promising component of overall oncologic treatment, the role of surgical resection cannot be generalized and at present should be individualized based on the patient's clinical course and by the biologic behaviors of specific malignancies. (J GASTROINTEST SURG 2006;10: 99–104)

KEY WORDS: Hepatic resection, liver, cancer, metastasectomy, survival

The treatment of metastatic lesions in the liver has, over the past decade, changed significantly. Advances in anesthesia, operative instrumentation, and improved imaging technologies have, in combination, resulted in improved patient selection for hepatic resection and reduced surgical blood loss, operative time, and related perioperative morbidities and mortality.[1–3] Hepatic metastasectomy has been proved to be safe and effective for colorectal metastases. The current recommendation is that patients with colorectal cancer metastases confined to the liver should be considered for a resection as long as a resection can leave ~25% or more of functional parenchyma.[1–3] With this in mind, can an outcome benefit be expected for hepatic metastasis from primary malignancies other than colorectal? And does the literature support an "indication" for this procedure? In order to examine this more carefully, we undertook a literature analysis to determine if there are data to support hepatic metastasectomy for malignancies other than colorectal cancer.

Approximately 13,000 liver resection procedures are performed annually in the United States. Although no specific data are available to define the underlying pathology, we propose that the majority of these procedures are performed in the treatment of colorectal cancer (CRC) metastases.

The American Cancer Society (ACS) listed the 11 most prevalent malignancies in 2004.[4] These included, in order of incidence, the following: prostate cancer, breast cancer, lung cancer, colorectal cancer, non-Hodgkin's lymphoma, bladder cancer, malignant melanoma, uterine/cervical cancer, ovarian cancer, pancreatic adenocarcinoma, and kidney cancer. The liver is an uncommon site for metastases for several of these malignancies, including prostate, bladder, uterine/cervical, and kidney cancers. In addition, the treatment for non-Hodgkin's lymphoma is primarily medical, rather than surgical, and is not commonly associated with hepatic lesions.

Of the remaining six malignancies in the ACS list, hepatic metastasis from a primary tumor in the lung

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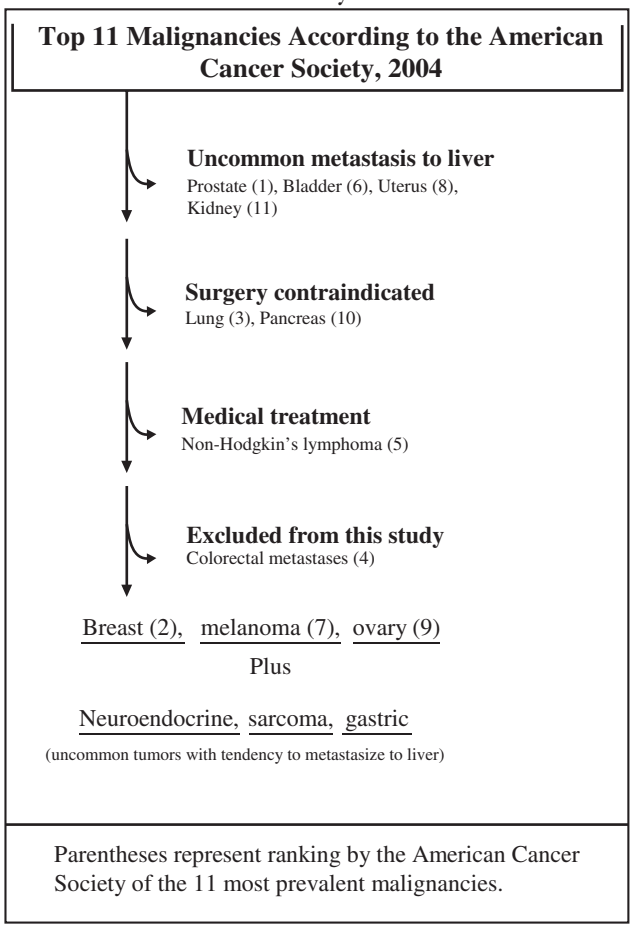
represents advanced and incurable disease and resection is contraindicated, because it is without any shown benefit in survival or quality of life.[5–8] Pancreatic adenocarcinoma frequently metastasizes to the liver; however, hepatic resection for this disease has never been shown to result in a survival benefit.[9] In contradistinction, resection of colorectal metastases to the liver has been shown to improve survival.[1–3] For the purpose of this discussion, however, it is excluded from our study.

After excluding the malignancies in the ACS list that do not commonly metastasize to the liver or are not routinely treated with resection due to the advanced stage of the disease, the remaining common malignancies that may meet criteria for hepatic metastasectomies are breast cancer, melanoma, and ovarian cancer. Other uncommon malignancies with an annual incidence of less than 20,000 cases in the United States include neuroendocrine tumors, sarcoma (specific subtypes), and gastric cancer. These are included due to their propensity to metastasize to the liver. Table 1 provides an overview of the ACS list of malignancies and those ultimately chosen for investigation in our literature search.

Table 1. Selection of Primary Cancers to Search



However, the question at hand—Is metastasectomy "indicated"? The purpose of this study is to examine the literature and assess if any aggregate outcome benefit, either for survival or for quality of life, has been reported following metastasectomies for noncolorectal hepatic metastasis.

METHODS

An integrative online literature search was performed of the English language medical literature using MEDLINE, EBM-ACP, COCHRANE, and DARE databases. The key words "disease" and "malignancy" were used for a primary sort of related articles. Additional representative key words were used to refine the literature search, including "noncolorectal metastasis," "hepatic resection," "liver resection," "survival," "metastasectomy," "quality of life," "clinical trial," and "randomized." Any literature detailing anecdotal case reports, a series of less than 10 patients, or "ablative" (RFA/cryoablation/ethanol injection) therapies were excluded from our search. The search was further limited to literature published in the years 1993–2003.

RESULTS

As anticipated, the number of studies identified was limited and we were unable to identify articles detailing the results of randomized trials for any of the six primaries in our search, that is, trials comparing resection of metastasis with current nonsurgical treatment. The articles described studies that were all retrospective in nature, although a few included data that were prospectively collected, and most had small numbers of patients (Table 2). Furthermore, the reported data in these articles were not uniform, with different end points being reported and lack of specified selection criteria for resection in others. The results of the literature search was sorted according to the six primary cancer types—breast, melanoma, ovary, neuroendocrine, sarcoma, and gastric—and are summarized in Table 2. The studies related to each of these six malignancies are also briefly discussed below.

Breast Cancer

Four single institutional studies were identified. These included sample sizes ranging from 20–54 patients, in which all patients had their sole metastasis to the liver. Recognizing that breast cancer is the most common cancer in females (32% of all cancers) with about 250,000 cases in 2003 alone,[4] breast cancer–related hepatic resection is undertaken in less than

1.0% of patients afflicted. In these studies, survival benefit was attainable for selected patients undergoing resection, albeit for a very limited subset. In addition, a consistently designated selection factor in these studies for a survival advantage was a lengthened interval from primary resection to the development of metastases. On the other hand, the issue of estrogen receptor status remains unclear, with some evidence to suggest that patients with a negative hormonal status do worse; this was not consistent throughout the studies reviewed. Resection of metastases in these studies constituted a component of total oncologic treatment.[10–13]

Malignant Melanoma

One study was identified that included data from the two largest, prospectively collected melanoma databases (John Wayne Cancer Center and Sydney Melanoma Unit). The data were obtained from a total of 1750 patients (combined), with 34 patients demonstrating, preoperatively, disease limited to the liver. These 34 patients (2%) underwent exploratory laparotomy, and 24 (71%) patients underwent resection (1.4% of the total). Of these 24 patients, 18 had a complete hepatic resection with curative intent, and 6 were resected with palliative intent. Median overall survival improved in the resected patients versus the patients who underwent exploration but were not resected (28 months versus 4 months). Resection constitutes a component of total oncologic treatment.[7]

Ovarian/gynecologic Cancer

Data were limited to two studies with 12 and 26 patients, respectively, from two specialty centers with mixed disease populations. Median survival following resection was similar at approximately 27 months. The selection factor for survival advantage was a prolonged interval (>12 months) from primary resection to the development of metastases. Resection constitutes a component of total oncologic treatment in carefully selected patients.[8,14]

Neuroendocrine Cancers

The largest amount of data found in our literature search are related to these diseases. The data in the three studies found by the literature had patient samples ranging from 15 to 170. In one of the studies, by Elias et al,[15] the data are not clearly defined as carcinoid and pancreatic neuroendocrine and nonpancreatic neuroendocrine cancers, rather simply as well-differentiated endocrine neoplasms. What is consistent in these studies is the high (>66%) recurrence rate after hepatic resection. Differing observations have been made concerning the biologic behavior of carcinoid versus islet cell neuroendocrine disease; however, whether this has an effect on survival or quality of life in the fast of resection is not clear. Symptom relief is reported following hepatic resection, although recurrence of symptoms is commonplace across the series. All reports, evaluated by this review, have long-term survivors, although no specific selection criteria can be discerned. Resection is, however, justified in the face of demonstrated improvement in quality of life,[15,16] although not permanent, and on the shown effect on survival.[15–17]

Sarcoma. Our review identified two studies detailing hepatic resection in sarcoma patients. One of the studies is a large single-center experience of 331 sarcoma metastases to the liver, of which 56 patients underwent resection of all gross hepatic disease. Gastrointestinal stromal tumor (GIST) and gastrointestinal leiomyosarcoma comprised the majority of disease subtypes. The 1-, 3-, and 5-year survival rates (median, 39 months) were significantly improved compared with those for incompletely resected patients. A separate study specifically addressing leiomyosarcoma metastases of 26 patients revealed a similar survival advantage. Factors significant for positive outcome benefit included complete resection and the interval from primary resection to the development of subsequent hepatic metastases (>2 years).[18,19]

Gastric Cancer

Opposing patient selection criteria were presented in the Japanese and Western Center studies. The three studies identified included patient cohorts ranging in size from 15 to 22, each treated with hepatic metastasectomy. Metachronous disease and a solitary metastasis were associated with a survival advantage. The tumor size and location of the primary tumor were also seen as prognostic indicators in one study. Interestingly, the Japanese report, which represents the 17-year experience of a specialty center, strongly supports that heptatic metastasectomy for gastric cancer is only potentially possible in a very select patient population; nevertheless, it demonstrated that resection constitutes a component of total oncologic treatment.[20–22]

CONCLUSIONS

The identified and available data on the topic of hepatic metastasectomy for the a priori defined malignancies (breast, melanoma, ovarian, neuroendocrine, sarcoma, and gastric) in this literature analysis were derived from class III evidence, retrospective case series, or database review. In general, data support

Table 2. Non colorectal cancer hepatic metastasectomy

First Degree	Reference	Design	n	Median follow-up (mo)	OS (%)	DFS (%)	Prognostic Indicators (+/−)	Resection Indicated	Comments/Other findings
Breast	Elias et al.[1] (2003)	Retrospective (collected prospectively)	44	32	3 yr	5 yr	3 yr 5 yr Negative hormonal status (−)	OS QOL	Sole to liver. Stable disease
					50	34	42 22	+	No impact: R status, Hilar node, number of LM HAIC ↓ liver recurrence, with no change in OS
	Maksan et al.[2] (2000)	Retrospective	9	29	51		Long DFI (+) Node negative 1° Ca (+)	+	
	Procard et 1l.[3] (2000)	Retrospective	52	23	49		DFI >48 mo → 82% 3 yr OS <48 mo → 45% 3 yr OS	+	Allowed for discontinuation of chemotherapy in 46% of patients
	Scheuerlein et al.[13] (1998	Retrospective	21		60* (2 yr)		R status: R0 (+)	+	R0 • 60% 2 yr OS R1/R2 • 16.7% 2 yr OS
Melanoma	Rose et al.[4] (2001)	Retrospective (collected prospectively)	24		Median OS 28 mo	Median DFS 12 mo	R0 status significantly improved OS and DFS (+)	+	metastases limited to liver
					5 yr OS 29%	5 yr OS 12%			Median OS for LM resection group vs. exploration only group 28 mo vs. 4 mo respectively

Gynecologic	Chi et al.[5] (1997)	Retrospective	12	25	Median OS 27 mo 5 yr OS 50%		Median DFS 12 mo	Metachronous metastases (+)	+		Median DFI 32 mo Solitary lensions 1°: Ovary (7), cervix (2), endometria (2), fallopiar (1)
	Merideth et al.[6] (2003)	Retrospective	26		Median OS 26.3 mo			DFI >12 mo (+) Optimal cytoreduction (+)	+		1°: Ovarian (8) 31% alive at 33 mo
Neuroendocrine	Elias et al.[7] (2003)	Retrospective (collected prospectively)	47	62	5 yr 71	10 yr 35	75% 10 yr LRR	None for OS DFS: R0 status, <10 LM, pancreatic origin	+	+	Well-differentiated endocrine tumors (n = 23) Pancreatic 53% R0 status 77% also had extrahepatic tumor resected
	Chen et al.[19] (1998)	Retrospective (collected prospectively)	15	27	73		66% (10/15) LRR 21 mo (median)	R0 status significantly improved OS and DFS (+)	+		5-yr actuarial survival resected (73%), unresected (29%) Similar tumor burden both groups
	Sarmento et al.[8] (2003)	Retrospective	170		61	35			+	+	1°: (120) carcinoid, (52) pancreatic, (85) ileum 104/108 patients with symptom relief. 59% 5 yr recurrence of symptoms
Sarcoma	Lang et al.[14] (2000)	Retrospective	26	Median OS 32 mo 5 yr OS 33%			R0 status (+)		OS	QOL	Benefit even in the presence of extrahepatic sarcoma Repeat resection for recurrence is worthwhile All leiomyosarcomas
	DeMattoo et al.[9] (2001)	Retrospective	56	Median OS 39 mo; 1, 3, 5 yr OS 88%, 50%, 30%		DFI >2 yr (+)			+		All R0 All GIST tumors Non-resected patients: 4%, 5 yr OS
Gastric	Okano et al.[11] (2002)	Retrospective	19	1 yr 77	3 yr 34	5 yr 34	Metachronous presentation (+) Solitary metastases (+)		+		3 patients lived >3 yr
	Sakamoto et al.[10] (2003)	Retrospective	22	73	38	38	Solitary metastases (+) LM <5 cm (+)		+		5 patients lived >3 yr
	Zacherl et al.[12] (2002)	Retrospective	15	Median OS 8.8 mo			Metachronous presentation (+) Unilobar LM (+)				
							1° Distal/middle third of stomach (+)		+		2 patients lived >3yr

OS = overall survival; DFS = disease-free survival; DFI = disease-free interval (from primary cancer to discovery of metastases); HAIC = hepatic artery infusion chemotherapy; LM = liver metastasis; LRR = liver recurrence rate; GIST = gastrointestinal stromal tumor.

that hepatic hepatectomy can be performed safely; however, there were few commonalities in these series with respect to the optimal factors for patient selection. The reported resection outcome experience for breast, melanoma, ovarian, and gastric cancers suggests that hepatic resection is a component of total oncologic therapy rather than a "stand-alone" procedure. Hepatic resection for GIST and leiomyosarcoma metastases had the most consistent emerging data to support the procedure, as increasing interval to hepatic disease and complete resection conferred an appreciable and significant survival advantage. The neuroendocrine disease–hepatic resection data did not allow any conclusions to be drawn due to the heterogeneity of the reports. The data contained in the reviewed series suggest that symptom relief following hepatic resection is attainable, although complete and long-term cure is less common.

Although a promising component of overall treatment, the role of surgical resection for non–colorectal cancer–related hepatic metastases cannot be generalized and at present should be individualized based on the patient's clinical course and by the biologic behaviors of the specific malignancy.

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Staphylococcal Liver Abscess and Acute Cholecystitis in a Patient With Crohn's Disease Receiving Infliximab

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We present an unusual case of empyema of the gallbladder associated with a pyogenic liver abscess in a patient with Crohn's disease on Infliximab. It manifested by weakness, weight loss, and vague abdominal pain, which eventually localized to the right upper quadrant 4 days prior to admission. Diagnostic evaluation, which included ultrasonography and computed tomography, revealed cholelithiasis, gallbladder wall thickening, and a low-attenuation, complex mass in the left hepatic lobe. Cholecystectomy and open drainage of the liver abscess were successfully performed. There are few reports of intrahepatic abscess associated with Crohn's disease. The relationship between acute cholecystitis and Crohn's disease has also been documented. However, this report documents the unusual complication of pyogenic liver abscess secondary to acute cholecystitis in the unique population of Crohn's disease patients on Infliximab. (J GASTROINTEST SURG 2006;10:105–110) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Crohn's, infliximab, cholecystectomy, liver abscess

The prevalence of cholelithiasis in the general population is a well-known and established fact. The estimated prevalence of gallstones has been determined by ultrasonography to range from 11% to 15% in women and 3% to 11% in men under 50 years of age. Gallstone formation increases with age, with a prevalence as high as 50% in women and 15% in men 60 years of age or older. Individuals with a family history of gallstones; who belong to certain ethnic groups (i.e., Native Americans); who have obesity, diabetes, small bowel malabsorptive syndromes, rapid weight loss, or multiparity; and those on hyperalimentation are at increased risk of developing gallstones.[1] The relationship between inflammatory bowel disease and biliary tract disease has also been well documented.[2] A common complication of symptomatic cholelithiasis is acute calculus cholecystitis, which usually results from impaction of a gallstone in the cystic duct or the neck of the gallbladder that completely obstructs the organ.

Pyogenic abscesses represent the most common type of hepatic abscess encountered in the United States.[3] The incidence may approximate as high as 20 cases per 100,000 patient admissions. Patients with Crohn's disease have a higher incidence of liver abscess (114–297 per 100,000) than the general population.[4]

Infliximab (Remicade) is a chimeric (human-mouse) monoclonal antibody targeted at human tumor necrosis factor-α (TNF-α), a proinflammatory cytokine that may be important in the pathogenesis of Crohn's disease. Although Infliximab's mechanism of action is incompletely understood, its action is thought to target the immune system by its ability to bind precursor cell-surface TNF, perhaps leading to monocyte apoptosis. Infliximab antagonizes the biological activity of TNF-α by binding to it on macrophage and T-cell surfaces. The most frequent adverse effects of Infliximab are headache, nausea, and upper respiratory tract infections, and some anecdotal case reports of an increased propensity in *Staphylococcus auerus* infections. We recently successfully treated a patient with Crohn's disease who presented with a true intrahepatic abscess associated with acute cholecystitis. This patient was also being treated with Infliximab.

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CASE REPORT

A 28-year-old man with a 19-year history of Crohn's disease presented to his primary care physician with complaints of vague abdominal pain, a 10-pound weight loss, and weakness over the past 3 months. The pain localized to the right upper quadrant 4 days prior to admission. The pain was unremitting, sharp, and nonradiating and was associated with nausea, without vomiting, fevers, chills, or diaphoresis. He denied changes in his bowel habits or any urinary symptoms. His past medical history was significant only for Crohn's disease. His medications included Pentasa, Prilosec, and Infliximab, which he had been receiving for 7 months prior to this current illness for episodic inflammatory flare-ups intractable to standard therapies.

Physical examination revealed a thin male in no acute distress. Pertinent physical findings disclosed no evidence of scleral icterus or jaundice. His abdomen was soft and mildly distended with moderate right upper quadrant tenderness. No masses were palpable, and rectal examination was negative for occult blood.

Laboratory results were as follows: white blood cell count, 9.0 K/mm^3 (4.0–10.0); total bilirubin, 0.4 mg/dl (0.1–1.2); alkaline phosphatase, 337 IU/L (37–107); AST, 18 IU/L (12–45); ALT, 21 IU/L (3–40); amylase, 34 U/L (44–128) and lipase, 62 U/L (40–175). Right upper quadrant ultrasonography revealed a thickened gallbladder wall, no pericholecystic fluid, multiple small filling defects consistent with cholelithiasis, no intrahepatic ductal dilatation, and a common bile duct measuring 4 mm in diameter. An abnormal hypoechoic intrahepatic lesion measuring approximately $6 \times 4 \times 6$ cm was noted posterior and medial to the gallbladder. Abdominal computed tomography scan, which was performed to further delineate this intrahepatic finding (Fig. 1), revealed a complex low-attenuation mass in the lateral segment of the left hepatic lobe. This was consistent with an abscess. The gallbladder demonstrated uniform wall thickening with pericholecystic inflammatory changes. Several distal small bowel loops were found to be thickened, presumably secondary to active Crohn's disease.

Based on these findings and the patient's clinical examination, he was taken to the operating room with the diagnosis of acute cholecystitis with an intrahepatic abscess. Upon exploration, he was found to have gallbladder empyema. No gross perforation was noted. In the lateral segment of the left lobe of the liver, an obvious mass was palpable clearly separate from the gallbladder. Needle aspiration was performed, which revealed a purulent fluid collection. An incision was made over the mass, and using the liver finger-fracture technique, the abscess was drained and cultures were obtained. Two drains were left in place, and the wound was copiously irrigated. The small bowel in this area appeared mildly inflamed, but no perforation or intraloop abscess was noted.

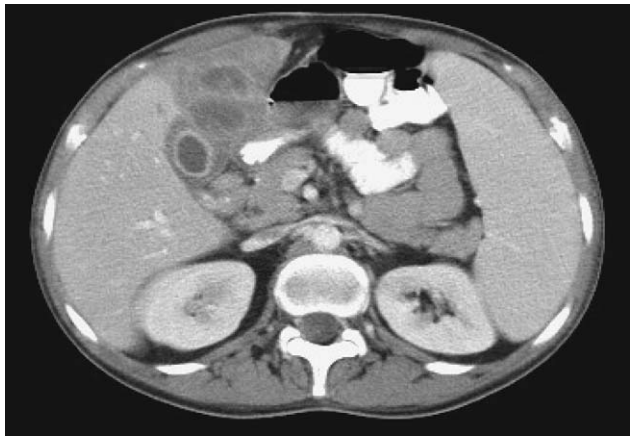

Fig. 1. Computed tomography scan of the abdomen revealing acute cholecystitis and evidence of a hepatic abscess.

The patient's postoperative course was remarkably uneventful. He was initially kept on broad-spectrum antibiotics until the intraoperative culture results were obtained. Pentasa and Prilosec were continued, while the Infliximab was discontinued. Intraoperative cultures grew *S. aureus* (methicillin sensitive) from both gallbladder and the liver. Antibiotics were appropriately manipulated, and he was kept on oral antibiotic therapy for 4 weeks. Echocardiography revealed no evidence of valvular heart disease. The patient was discharged on postoperative day 6, tolerating oral intake, on oral antibiotics, with home wound care. Pathologic examination of the gallbladder revealed acute cholecystitis with areas of focal wall necrosis and cholelithiasis.

DISCUSSION

Hepatic abscess is a relatively rare problem. The most common cause of pyogenic liver abscess is ascending cholangitis secondary to benign or malignant biliary tract obstruction. Other causes include portal vein bacteremia or pylephlebitis resulting from intestinal infections such as appendicitis or diverticulitis; hepatic artery bacteremia from systemic infections such as endocarditis; direct extension from adjacent infections such as gangrenous cholecystitis, pancreatic abscess, or subhepatic abscess; Crohn's disease; secondary infections of traumatic hepatic hematomas; necrosis of hepatic neoplasms; and cryptogenic, in which no obvious cause can be identified (Table 1).

Crohn's disease is associated with various hepatobiliary disorders, including pericholangitis, sclerosing cholangitis, granulomatous hepatitis, and cholelithiasis.[5–7] Liver abscess is rare; only 30 reported cases of Crohn's disease with liver abscess could be identified with variable data[8] (Table 2).

Crohn's disease may predispose a small subset of these patients to aggressive microbial invasion of the portal venous system with seeding of the hepatic parenchyma.[5] Indeed, frequent portal venous bacteremia has been documented in inflammatory bowel disease.[9] The more common and well-known complications of Crohn's disease, such as fistulization, perforation, and intra-abdominal abscess formation, create conditions known to otherwise be favorable to the development of liver abscess.[10,11] The frequent use of adrenal corticosteroid therapy, malnutrition, and the presumed underlying immunologic abnormalities in Crohn's disease may also play a role.[12]

It has been well established that patients with Crohn's disease, regardless of gender and age, have almost a doubled risk of developing cholelithiasis compared with the general population.[13] The prevalence has been reported to be between 13% and 34%.[13–15] The pathogenesis of gallstones and the increased incidence in Crohn's disease is unknown.

Cholesterol gallstones account for more than 80% of the gallstones in the Western world; however, patients with Crohn's disease are more prone to pigment (calcium bilirubinate) than cholesterol gallstone formation. Previous reports have demonstrated normal cholesterol saturation with increased content of bilirubin in the bile of patients having had an ileal resection due to Crohn's disease.[16] Patients with more extensive Crohn's disease, especially those including the duodenum, may have impaired mucosal release of cholecystokinin and, as a consequence, decreased gallbladder motility.[17–20]

In this case, Crohn's disease quite possibly precipitated the formation of gallstones and cholecystitis, leading to empyema of the gallbladder and an intrahepatic abscess. Hepatic abscess secondary to cholecystitis usually occurs as a direct extension of infection. Local factors such as chronic inflammation and gallbladder wall ischemia as well as systemic factors, such as immunosuppression, may all be contributory to abscess formation.

The finding of *S. aureus* as the organism growing from both the gallbladder and abscess culture sites further supports our belief that both processes were related. There have been reports of *S. aureus* being cultured from pyogenic liver abscesses in Crohn's

Table 2. Reported Cases of Liver Abscesses in Patients With Crohn's Disease

Author	Year	Associated Clinical Findings
Snavely JR	1946	Diarrhea and abdominal tenderness
Taylor FW	1949	Pylephlebitis
Lerman B	1962	Suppurative pylephlebitis
Sparberg M	1965	Hepatic abscess alone
Zarnow H	1976	Duodenobiliary fistula
Watts HD	1978	Multiple hepatic abscesses
Nelson A	1979	Hepatic abscess alone
Labatto S	1980	Hepatic abscess alone
Hatoff DE	1983	Perineal Crohn's disease
Brositus TA	1983	*Streptococcus meningitis intermedius*
Macpherson DS	1985	Hepatic abscess alone
Valero V	1985	Thoracic empyema
Teague M	1988	Hepatic abscess alone
Kotengi H	1991	Hepatic abscess alone
Vakil N*	1994	Staphylococcal hepatic abscess with cutaneous infection

Modified from Vakil N, Hayne G, Sharma A, Hardy DJ, Slutsky A. Liver abscess in Crohn's disease. Am J Gastroenterol 89:1090–1095, 1994.
*Retrospective review; all other publications are case reports.

Table 1. Causes and prognostic indicators of liver abscesses

Causes of Liver Abscesses	Types of Organisms	Poor Patient Prognostic Indicators
Cryptogenic (40%)	Gram-negative aerobes (50–70%)	Age >70, WBC >20,000, albumin <2
Biliary tract obstruction (37%)	Gram-positive aerobes (30%)	Increasing bilirubin, SGOT
Portal bacteremia (11%)	Anaerobes (40–50%)	Multiple abscesses, aerobic abscess
Systemic bacteremia (6%)	Fungal (26%)	Diabetes, septicemia, malignancy
Direct extension (4%)	Sterile (7%)	Biliary etiology, complication
Other (2%)		Polymicrobial bacteremia

Data from Seeto RK, Rockey DC. Pyogenic liver abscess: Changes in etiology, management and outcome. Medicine 1996;75:99–113; Garrison RN, Polk HC. Liver abscess and subphrenic abscess. In: Blumgart LH, ed. Surgery of the liver and biliary tract, 2nd ed. Edinburgh: Churchill Livingstone, 1994. p. 1091–1102; Zinner MJ, Schwartz SI, Ellis H. Liver abscess and hydatid cyst disease. In: Zinner MJ, Schwartz SI, Ellis H, eds. Maingot's Abdominal Operations, 10th ed. Stamford, CT: Appleton & Lange, 1997.

patients, but these patients reported cutaneous infections in the weeks preceding the diagnosis of the abscess. The common organisms involved with pyogenic hepatic abscesses are listed in Table 1.

The historical standard treatment of a solitary pyogenic liver abscess is surgical drainage with identification and correction of the underlying process coupled with systemic antibiotics for 2–6 weeks to treat concurrent smaller and undiagnosed purulent collections within the liver.[21–24] Medical treatment with antibiotics alone can be successful early in the course of the disease, in patients with small multiple abscesses (<1.5-cm diameter) and when there is no surgically correctable factor. Computed tomography– or ultrasonography-guided percutaneous drainage can be successful in poor-risk patients or in patients with a solitary abscess, who do not have other indications for surgical exploration. Laparoscopy has been used for both diagnosis and drainage when percutaneous attempts have failed.[25] In this case, our patient had an obvious surgically correctable etiological factor and thus a clear indication for

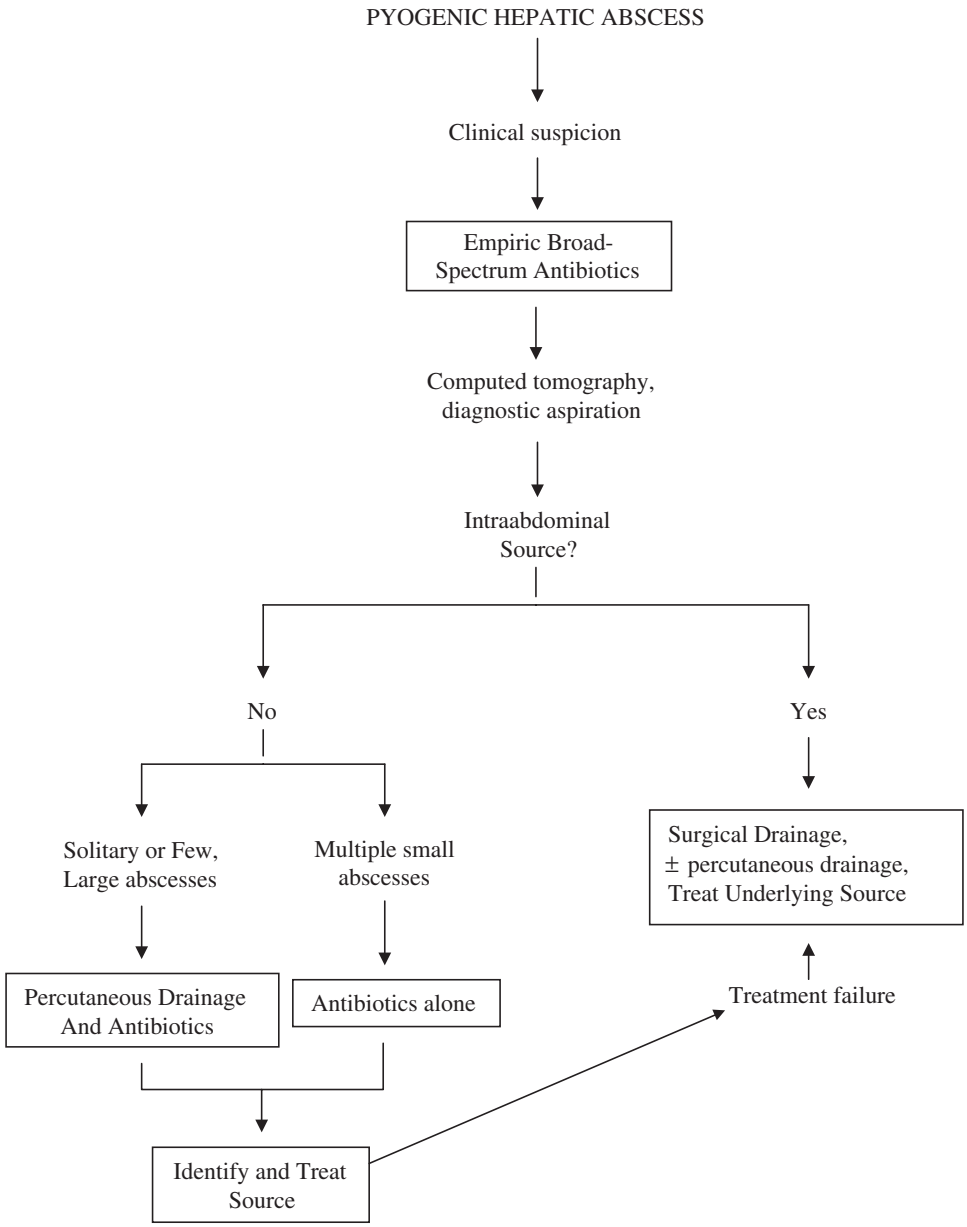

Fig. 2. Treatment algorithm for patients with pyogenic hepatic abscess. Adapted from Glasgow RE, Mulvihil SJ. Hepatic abscess. In: Cameron JL, ed. Current Surgical Therapy, 6th ed. St. Louis, MO: Mosby, 1998. p. 314–321.

exploration. Figure 2 presents and summarizes a treatment algorithm for patients with a pyogenic hepatic abscess.

If untreated, nearly all pyogenic liver abscesses prove fatal. Modern diagnostic imaging, antibiotics, and aggressive early surgical or percutaneous drainage have further improved mortality statistics to 80–90% survival. Several factors, such as delayed diagnosis, undrained or poorly drained collections, multiple small undrainable abscesses, and untreated primary etiologic sites, however, are still associated with a poor prognosis in patients with pyogenic hepatic abscesses (Table 1).

A heightened awareness of the risks of Infliximab use is crucial in patients with chronic infections or iatrogenic induced immunodeficiency. TNF-α, a major proinflammatory cytokine, plays an important role in host defense against infection. Inhibition of its activity could therefore be anticipated to augment the risk of infection in patients with preexisting abnormalities of immune regulation. Infliximab's anti–TNF-α properties target the immune system, raising concerns about the potential for immune sensitization and immunosuppressive sequelae.[26] The relationship between cytokine inhibition and infection may also be associated with comorbidities such as diabetes mellitus, heart disease, disability, and concurrent immunosuppressive medication.[27] Many cases have been reported where the use of Infliximab therapy has been associated with unusual bacterial infections such as *Escherichia coli* colitis, aseptic streptococcal meningitis, and staphylococcal intramyocardial inflammation. In the latter case, a chronic inflammatory process was activated by infliximab, suggesting in this case that an underlying chronic biliary infection was further stimulated by this immunosuppressive drug.[28–30]

CONCLUSION

Pyogenic hepatic abscess can be a challenging clinical problem and, despite modern modalities, is still associated with a rather high morbidity and mortality. Patients with Crohn's disease are more prone to liver abscess formation and are also at higher risk of developing cholelithiasis. An increased use of Infliximab may put these patients at increased risk of developing an unusual bacteriologic flora potentially leading to acute cholecystitis with or without a hepatic abscess. Appropriate diagnostic evaluations and aggressive treatment should improve the prognosis for this potentially life-threatening complication.

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The Value of Reoperative Procedures After Unusual Reconstructions in the Gastrointestinal Tract Associated With Substantial Morbidity

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Reconstructive procedures of the gastrointestinal tract after resection or for bypass surgery are well established and almost completely standardized but still may cause significant morbidity. Deviations from standard reconstructive procedures have pitfalls, especially when complex reconstructions are required, and may lead to substantial morbidity. Scientific evidence for the indication to reoperate as well as the best methods to be applied is lacking and surgical experience indispensable. We report on 10 reoperative cases between 1999 and 2003 after uncommon reconstructive procedures in the gastrointestinal tract associated with substantial morbidity. In five cases (five of seven), operative correction of uncommon reconstructions in the upper gastrointestinal tract after gastrectomy, completion gastrectomy, or distal gastric resection could completely alleviate the complaints including reflux esophagitis, whereas incomplete relief of symptoms was achieved in the remaining two cases (two of seven). Corrective procedures used end-to-side esophagojejunostomy or end-to-side gastrojejunostomy with a retrocolic isoperistaltic jejunal Roux-en-Y loop and end-to-side jejunojejunostomy approximately 40 cm distal to the proximal anastomosis for biliary and exocrine pancreatic drainage. After biliodigestive anastomosis, problematic cholangitis could be completely alleviated in three cases (three of three) using end-to-side hepaticojejunostomy with a retrocolic isoperistaltic jejunal Roux-en-Y loop and end-to-side jejunojejunostomy 40 cm distal to the hepaticojejunostomy for reconstruction of the continuity of the gastrointestinal tract. Compliance with well-established standard reconstructive procedures is of elementary importance in the gastrointestinal tract. Operative correction of uncommon reconstructions associated with morbidity is usually indicated. (J GASTROINTEST SURG 2006;10:111–122)

KEY WORDS: Reflux esophagitis, biliary reflux, cholangitis, reconstruction after gastrectomy, biliodigestive anastomosis

Reoperation of the foregut and midgut remains a frequent challenge for the general surgeon. Complex reconstructive procedures following major gastrointestinal surgery in this area can lead to a series of physiologic and functional complications that, in some cases, require a second operation.[1,2] The most frequent long-term complications are biliary reflux following gastrectomy and recurrent cholangitis following biliodigestive anastomosis. Both symptoms can occur individually or in combination following pancreaticoduodenectomy. Some uncommon reconstructive procedures can have widely varying and dramatic consequences in individual patients.[2–4] Patients who have undergone uncommon reconstructive procedures of the gastrointestinal tract associated with morbidity are often referred to tertiary referral centers like our institution for further therapy. We analyzed the data for such problematic reconstructive procedures that was collected retrospectively over the last 5 years in our institution. Using selected cases, we illustrate the problems associated with uncommon reconstructive procedures and bring the approach to them into discussion. At the outset, it must be pointed out that the examples chosen are individual cases and the symptoms and the possible surgical procedures used should be discussed within that context.

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Because all reconstructive procedures are associated with specific advantages and disadvantages, we aim to stimulate the discussion of the indications for reoperation and the procedures used for corrective surgery after uncommon reconstructions associated with morbidity.

MATERIAL AND METHODS

We report on 10 reoperative cases (six men and four women; average age, 63 years) between 1999 and 2003 after uncommon reconstructive procedures in the upper gastrointestinal tract or biliary tract associated with substantial morbidity (Table 1). All 10 cases were reviewed retrospectively using the patient's hospital records. Follow-up was performed for this study by telephone inquiry to obtain a recent medical history update.

RESULTS

Case 1

A 59-year-old patient presented with esophageal reflux symptoms following gastrectomy for gastric carcinoma 2 years previously. He complained of heartburn and regurgitation, in particular, postprandially and at night. Diagnostic work-up revealed reflux esophagitis. According to the available operative report, an end-to-side esophagojejunostomy using a jejunal omega loop was performed. From 5 to 6 cm distal to the end-to-side esophagojejunostomy, a side-to-side jejunojejunostomy over a length of 20 cm using the omega loop was described, probably with the intention of providing a substitute reservoir after total gastrectomy (Fig. 1). This description of the previous reconstruction could be confirmed during reoperation. Under the assumption that reflux esophagitis in this patient was the consequence of the close positioning of the side-to-side jejunojejunostomy to the esophagojejunostomy, the corrective procedure comprised a reconstruction with end-to-side esophagojejunostomy using a retrocolic isoperistaltic jejunal Roux-en-Y loop after dismantling of the previous end-to-side esophagojejunostomy and resection of the side-to-side jejunojejunostomy. The patient was discharged after 10 days without any perioperative complications and went home with no remaining complaints. Follow-up for the purpose of this study revealed that our patient had gained a lot of weight and was still free of heartburn and regurgitation 2 years after reoperation.

Table 1. Overview of our patients' clinical characteristics including follow-up and results of reoperative surgery

Patient	Symptoms leading to reoperation	Interval between primary operation and symptoms	Anatomic description after primary operation	Follow-up after reoperation	Relief of symptoms
1	Postprandial heartburn, regurgitation	2 years	Correct	2 years	Complete relief and weight gain
2	Postprandial fullness, intermittent vomiting, reflux esophagitis	3 months	Not correct	3 years	Incomplete relief (development of recurrent cholangitis)
3	Early dumping, extreme reflux esophagitis	2 years	Not correct	4 years	Incomplete relief (persistent early dumping)
4	Postprandial reflux with heartburn, postprandial fullness, hiccough	2 years	Correct	3 years	Complete relief
5	Biliary reflux with heartburn	3 months	Not correct	3 years	Complete relief
6	Intestinal nutrition not possible, severe vomiting	3 months	Not correct	4 years	Complete relief and weight gain
7	Biliary reflux with heartburn	30 years	Correct	3 years	Complete relief and weight gain
8	Recurrent cholangitis	3 years	Not correct	3 years	Complete relief
9	Recurrent cholangitis	2 years	Correct	3 years	Complete relief and weight gain
10	Cholangitis with sepsis, elevated transaminases	4 weeks	Not correct	1 year	Complete relief

Interestingly, the anatomic description of the primary reconstruction proved to be incorrect during reoperation in most cases. The use of a isoperistaltic retrocolic Roux-en-Y reconstruction with a jejunal limb of 40 cm during reoperation attained complete relief of symptoms in 8 of 10 cases and incomplete relief in the remaining 2 cases.

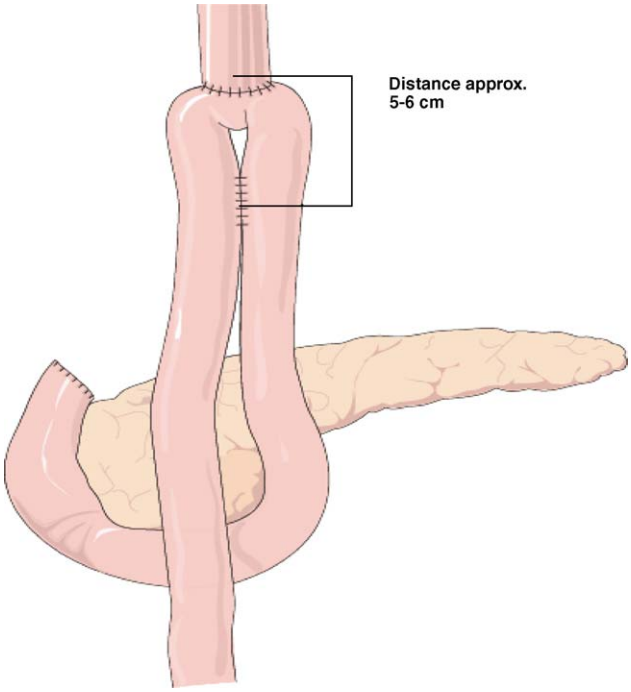

Fig. 1. Reconstruction following gastrectomy with an end-to-side esophagojejunostomy using a jejunal omega loop and an about 5- to 6-cm distally positioned side-to-side jejunojejunostomy over a length of approximately 20 cm. As a consequence, postprandial and night-time heartburn and regurgitation occurred in case 1, leading to reoperation.

Case 2

A 49-year-old female patient complained of postprandial feeling of fullness, digestive problems, intermittent vomiting, and typical symptoms of reflux esophagitis, 3 months after undergoing a distal gastric resection with Roux-en-Y-reconstruction for recurrent gastric ulcerations intractable to conservative treatment. Her medical history revealed that ERCP and endoscopic papillotomy followed by laparoscopic cholecystectomy had been carried out for biliary pancreatitis several years previously. Recent radiographic contrast studies revealed delayed emptying of the residual stomach. During gastroscopy, abnormal stomach-emptying contractions and an antiperistaltic jejunal loop distal to the gastrojejunostomy were observed. This established the indication for reoperation. During reoperation, an end-to-side gastrojejunostomy with an antecolic, antiperistaltic first loop of the jejunum was found with an end-to-side jejunojejunostomy approximately 20 cm distal to the gastrojejunostomy. It became evident that the wrong end of the divided proximal jejunum was used for gastrojejunostomy instead of the created Roux-en-Y limb (Fig. 2). This uncommon reconstruction of the digestive tract explained the complaints of our patient. During reoperation, the gastrojejunostomy was dismantled and the end-to-side jejunojejunostomy removed by resection of the distal part of the first loop of the jejunum, which was used for gastrojejunostomy. A new reconstruction with end-to-side gastrojejunostomy using a retrocolic, isoperistaltic Roux-en-Y-limb and an end-to-side jejunojejunostomy 35–40 cm distal to the gastrojejunostomy was performed. The patient was discharged symptom free after 3 weeks of convalescence without complications. For the purpose of this study, we investigated this case further and learned that the patient is now complaining of recurrent cholangitis, 3 years after corrective surgery. An episode of necrotizing pancreatitis has also developed. However, the symptoms that led to corrective surgery did not reappear.

Case 3

A 62-year-old female patient presented with hyperglycemia-hypoglycemia syndrome accompanied by dumping and extreme reflux symptoms with reflux esophagitis, 2 years after undergoing subtotal gastric resection and later completion gastrectomy. According to the operative report, the reconstruction was done using an omega loop and a gastric substitute with a pouch. Radiographic studies and endoscopy could show the pouch but failed to describe it in detail. Due to the severity of symptoms, reoperation was indicated. Intraoperatively, an antecolic jejunal loop was found that was used for end-to-side esophagojejunostomy. Directly underneath the esophagojejunostomy, a side-to-side jejunojejunostomy was found. However, this anastomosis was positioned horizontally on the same jejunal loop about 30 cm distally, so that the end-to-side esophagojejunostomy and the side-to-side jejunojejunostomy lay directly over one another (Fig. 3). The symptoms were easy to understand, given the intraoperative picture. The patient could be partially helped by resection of the pouch and conversion into an end-to-side esophagojejunostomy with a retrocolic, isoperistaltic Roux-en-Y loop. The patient was discharged following convalescence after a complicated course with intra-abdominal adhesions and a stricture leading to ileus and consequently another operative revision with extensive adhesiolysis. Four years following corrective surgery, the patient still complains of early dumping, although without reflux symptoms and without any reflux esophagitis detectable by endoscopy.

Case 4

A 56-year-old female patient presented with biliary reflux with heartburn, postprandial feeling of being

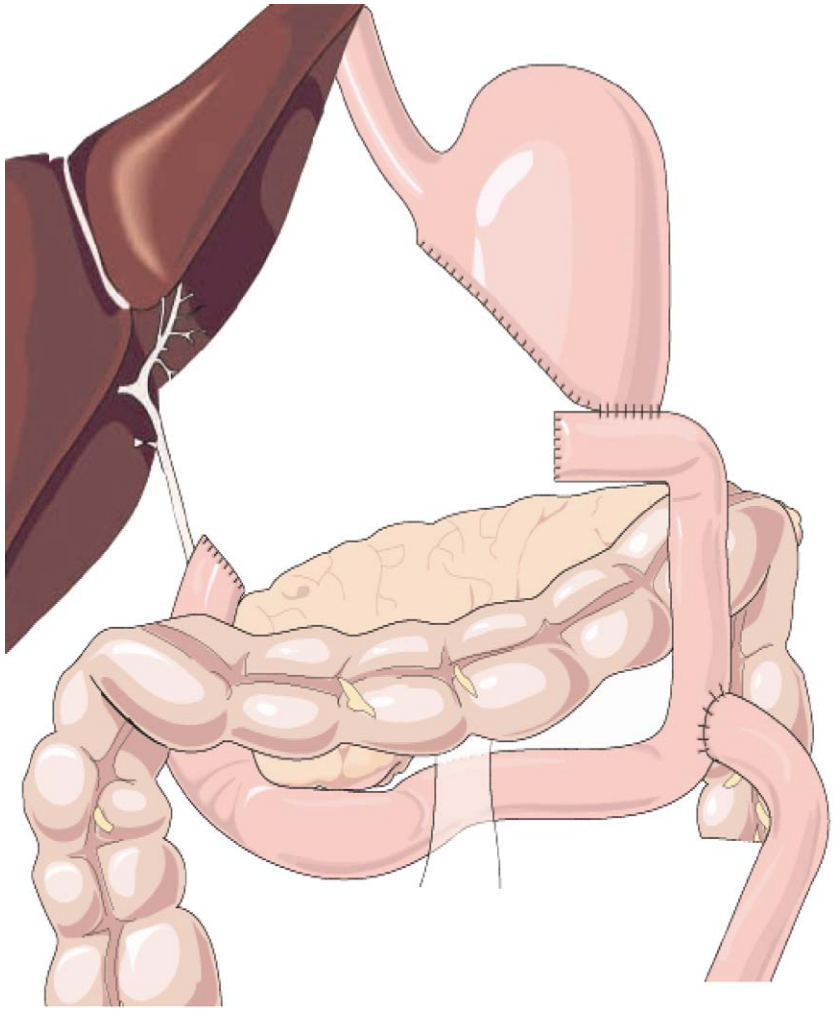

Fig. 2. Reconstruction following distal gastric resection with an end-to-side gastrojejunostomy using an antecolic, antiperistaltic first loop of the jejunum with an end-to-side jejunojejunostomy approximately 20 cm distal to the gastrojejunostomy in case 2. It became evident that the wrong end of the divided proximal jejunum was used for gastrojejunostomy instead of the created Roux-en-Y limb. As a consequence extreme symptoms of postprandial feeling of fullness, intermittent vomiting, digestive problems, and typical symptoms of reflux esophagitis occurred.

full, and hiccough. Gastric banding had been previously carried out to treat morbid obesity, and later a distal gastric resection was performed due to intractable ulcerations. According to the operative report, reconstruction following distal gastric resection was performed using an antecolic, jejunal Roux-en-Y loop for end-to-side gastrojejunostomy. Diagnostic work-up revealed an end-to-side jejunojejunostomy approximately 20 cm distal to the gastrojejunostomy. The assumption that the distance between the gastrojejunostomy and the jejunojejunostomy was too short and therefore enabled reflux, together with the assumption that compression of the Roux-en-Y limb between the colon and the abdominal wall could cause disturbed gastric emptying, established the indication for reoperation. Intraoperatively, the descriptions of the operative report concerning the reconstructive method used could be confirmed (Fig. 4). The short antecolic Roux-en-Y loop was resected. Reconstruction was performed using a retrocolic, isoperistaltic Roux-en-Y jejunal loop for end-to-side gastrojejunostomy. End-to-side jejunojejunostomy was performed approximately 40 cm distal to the gastrojejunostomy. The patient was discharged symptom free 12 days later following a complication-free convalescence. The patient was contacted by telephone, and it was established that 3 years following corrective surgery she had remained symptom free and her weight stable.

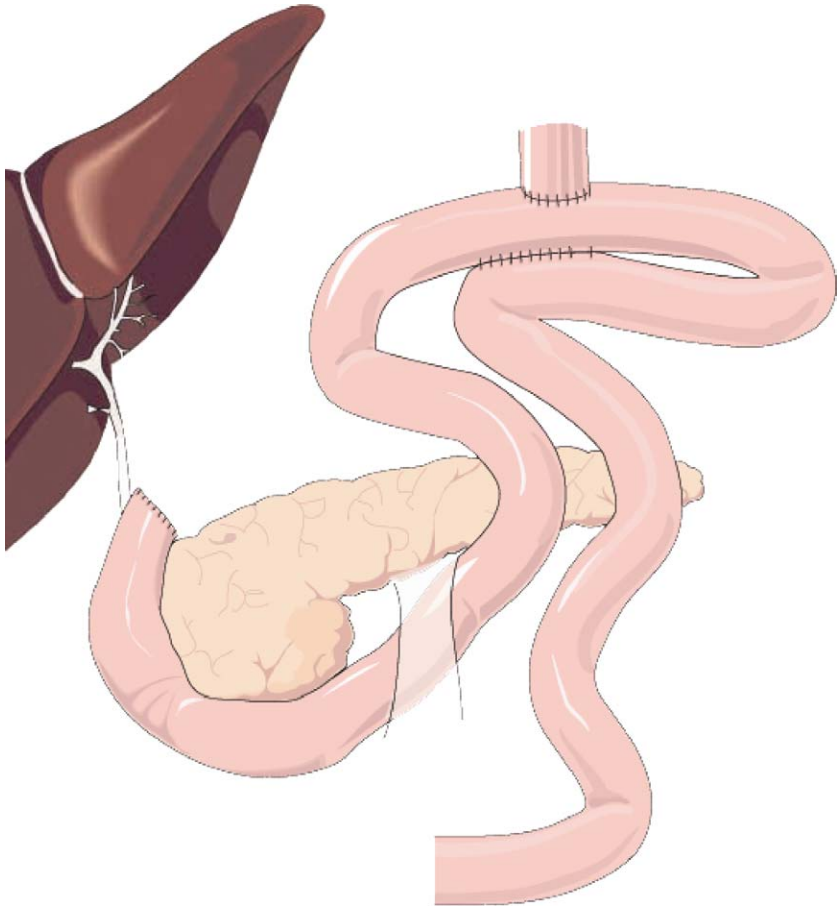

Fig. 3. Reconstruction following completion gastrectomy with an antecolic jejunal omega loop that was used for end-to-side esophagojejunostomy in case 3. During reoperation a side-to-side jejunojejunostomy was found directly underneath the esophagojejunostomy, so that the end-to-side esophagojejunostomy and the side-to-side jejunojejunostomy lay directly over one-another. As a consequence serious reflux symptoms with reflux esophagitis occurred. Further, this patient suffered from with hyperglycemia-hypoglycemia syndrome accompanied by dumping.

Case 5

This case was similar to case 4. A 67-year-old male patient underwent a distal gastric resection and had a reconstruction with a very short retrocolic Roux-en-Y loop with an end-to-side jejunojejunostomy approximately 15 cm distal to the gastrojejunostomy. He suffered from biliary reflux with heartburn (Fig. 5). Biliary reflux and heartburn could be successfully eliminated by dismantling the jejunojejunostomy and repositioning it approximately 40 cm distal to the gastrojejunostomy. This patient was discharged symptom-free following a 2-week stay in hospital. A telephone inquiry established that our patient was symptom free with stable weight 3 years following reoperation.

Case 6

A 67-year-old female patient was referred to us who had 3 months previously undergone a partial duodenopancreatectomy, to treat pancreatic carcinoma that had infiltrated the duodenum. Reconstruction had been performed with only one loop. Since the operation, the patient had been fed intravenously, because intestinal nutrition was not possible. Every time intestinal feeding was started, a feeling of fullness occurred followed by severe vomiting. Radiographic contrast studies showed an occlusion of the proximal small bowel. This finding prompted reoperation. Intraoperative investigation revealed an end-to-side gastrojejunostomy with an omega loop and triple side-to-side jejunojejunostomy. This reconstruction resulted in a closed short-cut system because distal to the third side-to-side jejunojejunostomy, the point of entry for the GIA stapler into the lumen was closed too tightly with a running suture, so that the distal gut lumen was functionally closed (Fig. 6). The pancreas, the bile duct, and the gastric stump were all connected to the first loop of the omega loop. These

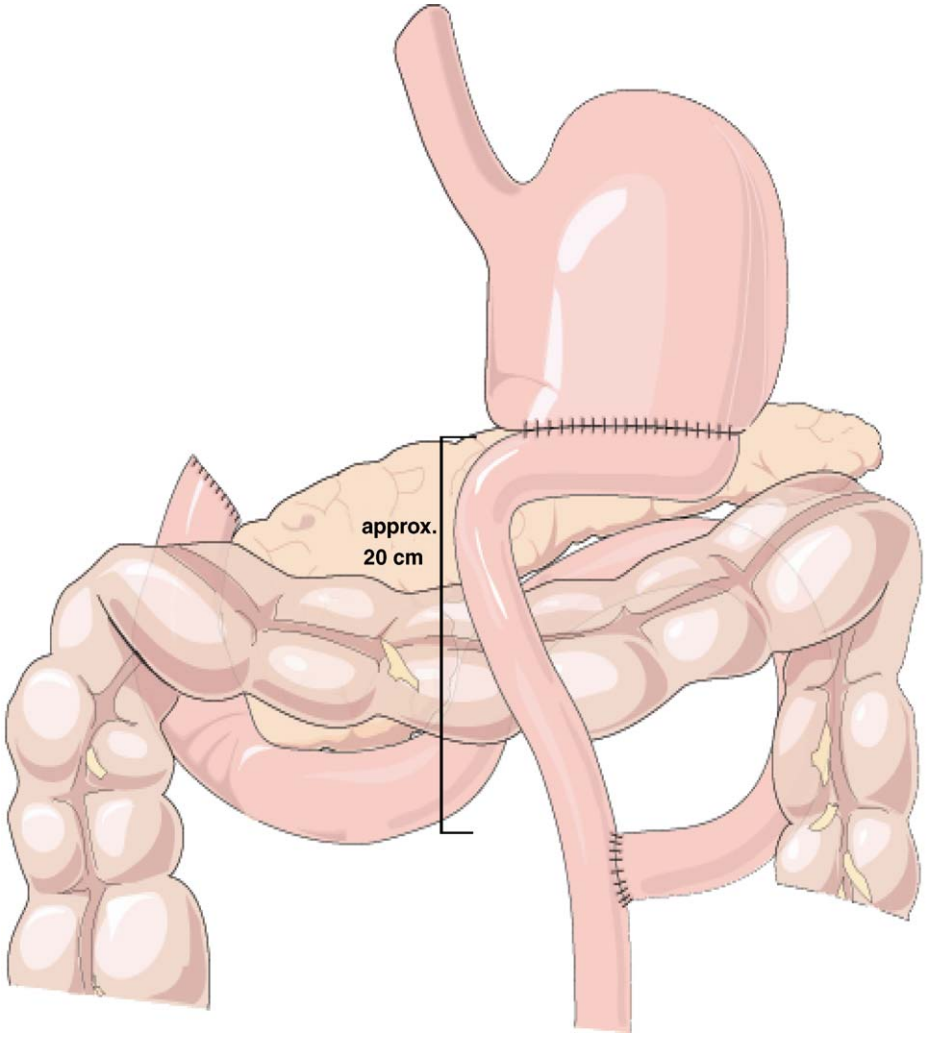

Fig. 4. Following stomach resection, reconstruction with a short antecolic, jejunal Roux-en-Y loop for end-to-side gastrojejunostomy was performed in case 4 leading to reoperation due to biliary reflux with heartburn, postprandial feeling of being full, and hiccough.

intraoperative findings easily explained the symptoms presented. Following removal of the gastrojejunostomy, the omega loop including the three jejunojejunostomies was resected. The new reconstruction involved a retrocolic, isoperistaltic Roux-en-Y limb for end-to-side gastrojejunostomy and an end-to-side jejunojejunostomy approximately 40 cm distal to the gastrojejunostomy to drain the bile and exocrine pancreas. The passage of food was eventually possible and problem free through this conversion into a two-loop reconstruction. As a consequence of the previous difficult clinical course, before reoperation, the patient became anxious of vomiting and was reluctant to eat, and it took 2 months for normal digestion and normal food passage to resume. Follow-up revealed that our patient was symptom free 4 years after reoperation and enjoyed a steady weight gain. Tumor recurrence of pancreatic carcinoma has not been detected to date.

Case 7

A 61-year-old male patient was referred to us with reflux symptoms. His medical history revealed that distal gastric resection had been performed for gastric ulceration 30 years previously. Reconstruction had been carried out with an end-to-side gastrojejunostomy using the first jejunal loop (Fig. 7). The patient was symptom free for many years. Over the past few years, however, he had developed reflux symptoms that were unresponsive to medication. Endoscopy revealed second-grade esophagitis and gastritis with obvious significant biliary reflux. The patient was discharged symptom free 16 days following removal

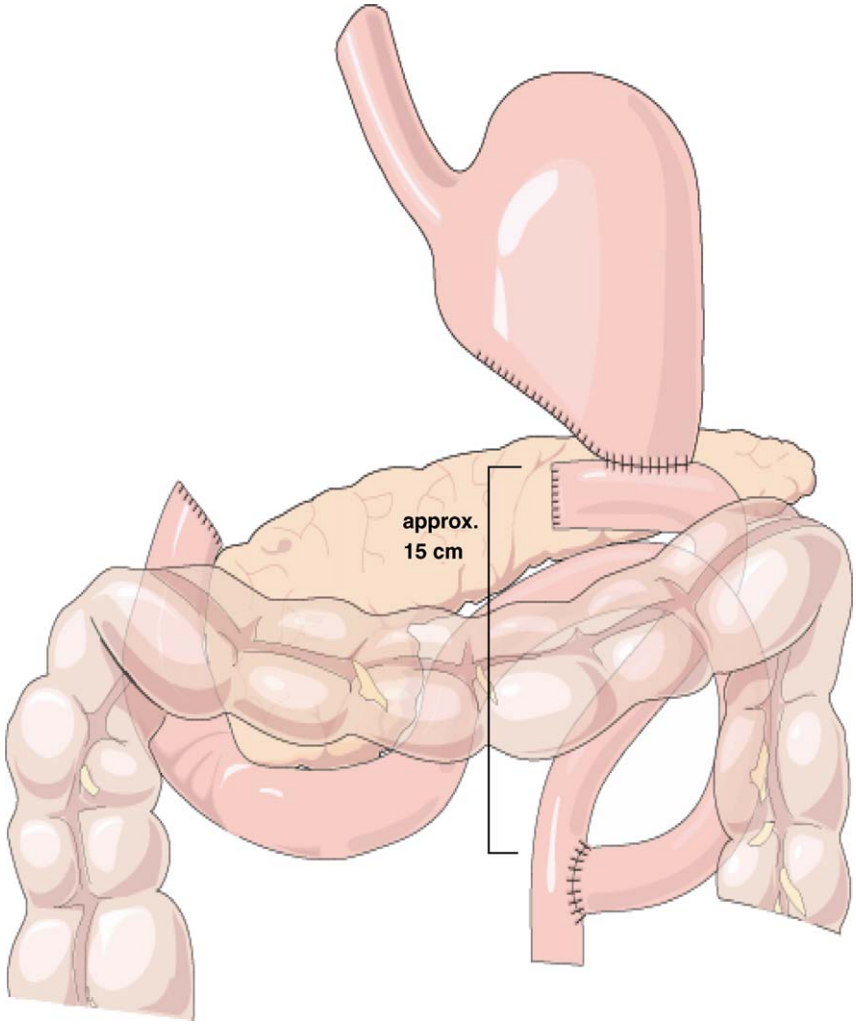

Fig. 5. Reconstruction was performed after distal stomach resection with a very short retrocolic Roux-en-Y loop with an end-to-side jejunojejunostomy approximately 15 cm distal to the gastrojejunostomy, which caused biliary reflux in case 5. The symptoms were eradicated by distal repositioning of the end-to-side jejunojejunostomy.

of the gastrojejunostomy and reconstruction with a retrocolic, isoperistaltic Roux-en-Y limb and an end-to-side jejunojejunostomy approximately 40 cm distal to the gastrojejunostomy for biliary and exocrine pancreatic drainage. From telephone contact, we learned that the patient was still symptom free 3 years after reoperation and was slowly gaining weight.

Case 8

A 63-year-old male patient with cholecysto- and choledocholithiasis was treated by end-to-side hepaticojejunostomy. Since then the patient had complained of recurrent cholangitis. According to the operative report reconstruction was carried out with an approximately 30-cm-long Roux-en-Y limb. Three years after the initial procedure, reoperation was performed. During reoperation, it became evident that the retrocolic Roux-en-Y limb for hepaticojejunostomy was only 15 to 20 cm long (Fig. 8). The patient was discharged symptom-free after 2 weeks following removal of the hepaticojejunostomy and creation of a new end-to-side hepaticojejunostomy using a 40-cm-long retrocolic, isoperistaltic Roux-en-Y limb and an end-to-side jejunojejunostomy 40 cm distal to the hepaticojejunostomy to reestablish the continuity of the gastrointestinal tract. Inquiry by telephone established that 3 years after corrective surgery, the patient was symptom free and without antibiotic treatment. Recurrent cholangitis did not reappear during follow-up.

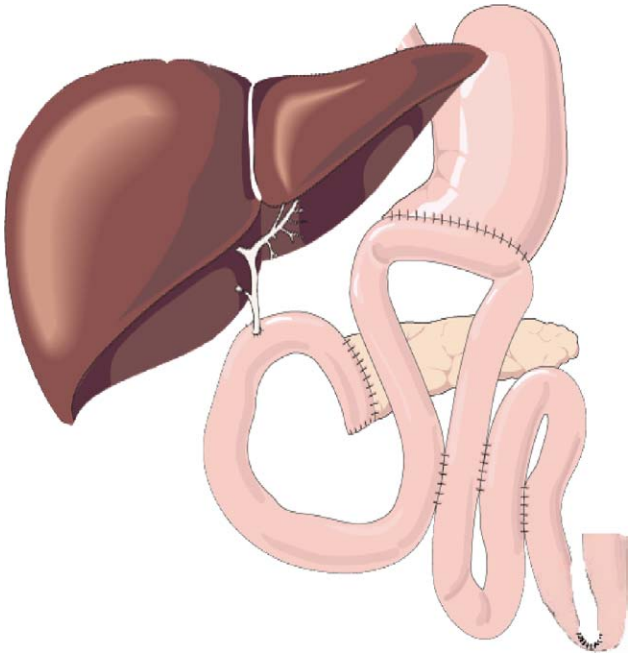

Fig. 6. Reconstruction in case 6 with an end-to-side gastrojejunostomy using an omega loop and triple side-to-side jejunojejunostomy after partial duodenopancreatectomy. This reconstruction resulted in a closed short-cut system because distal to the third side-to-side jejunojejunostomy the point of entry for the GIA stapler into the lumen was closed too tightly with a running suture, so that the distal gut lumen was functionally closed.

Case 9

A 62-year-old male patient presented himself to us with recurrent cholangitis, 2 years after having undergone a biliodigestive anastomosis in another hospital for inflammatory bile duct obstruction. We deduced from the operative report that the anastomosis had been performed with a nonexcluded jejunal loop (Fig. 9). According to our understanding, the underlying reason for recurrent cholangitis was a consequence of this surgical approach. We therefore performed a reoperation with removal of the anastomosis, flushing of the bile duct system, and end-to-side hepaticojejunostomy with a retrocolic, isoperistaltic Roux-en-Y jejunal limb and an end-to-side jejunojejunostomy approximately 40 cm distal to the hepaticojejunostomy in order to reconstruct the continuity of the gastrointestinal passage. The patient was discharged symptom free after 2 weeks following a complication-free convalescence. For the purpose of this work, we questioned the patient 3 years after reoperation and he was still symptom free and had gained a significant amount of weight.

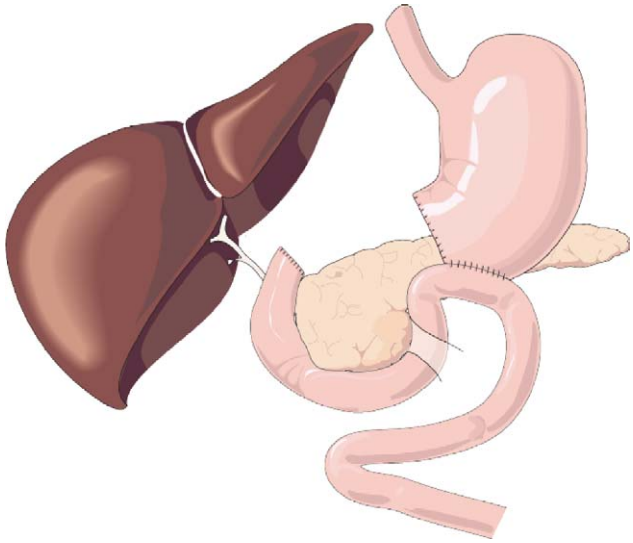

Fig. 7. Reconstruction in case 7 following distal gastric resection with an end-to-side gastrojejunostomy using the first jejunal loop. After about 30 years, serious reflux esophagitis and gastritis with biliary reflux developed leading to reoperation.

Case 10

A 61-year-old male patient was referred to our institution with cholestasis due to gallbladder carcinoma. Following tumor resection, extrahepatic bile duct reconstruction was carried out using end-to-side hepaticojejunostomy. In the postoperative course, cholangitis developed with elevated transaminases. Reoperation was carried out due to the development of sepsis without any obvious reason. During reoperation, an end-to-side hepaticojejunostomy with a retrocolic, antiperistaltic first limb of the jejunum was found with an end-to-side jejunojejunostomy approximately 40 cm distal to the hepaticojejunostomy. It became evident that the wrong end of the divided proximal jejunum was used for hepaticojejunostomy instead of the created Roux-en-Y limb (Fig. 10). This erroneous reconstruction of the extrahepatic bile duct explained the development of cholangitis with sepsis since chymus was transported by peristalsis directly from the duodenum into the biliary tree. Reoperative reconstruction involved conversion of the previous reconstruction into a Roux-en-Y reconstruction with the correct Roux-en-Y limb and end-to-side anastomosis of the jejunal limb that was previously used for hepaticojejunostomy to the Roux-en-Y limb approximately 40 cm distal to the rehepaticojejunostomy. Two weeks after reoperation, the patient could be discharged symptom free. Recurrent cholangitis did not reappear during follow-up.

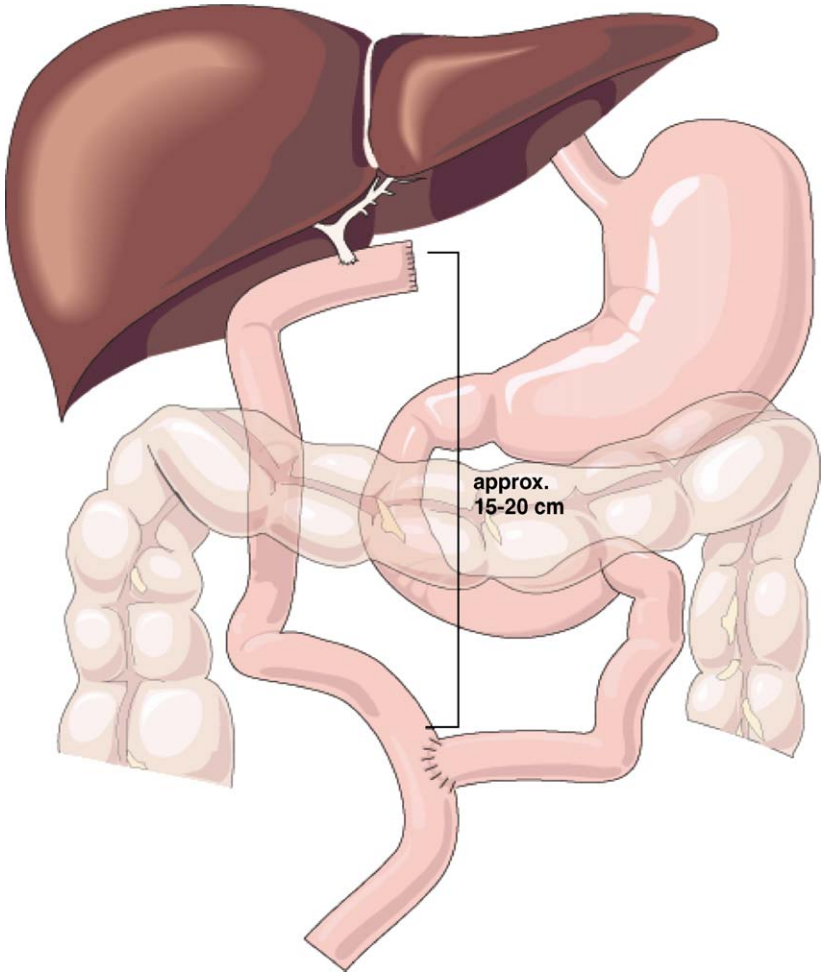

Fig. 8. Reconstruction of the extrahepatic biliary tract in case 8 using a retrocolic Roux-en-Y limb for hepaticojejunostomy that was only 15–20 cm long. As a consequence this patient suffered recurrent cholangitis. This problem was solved by reconstructive surgery of the bile duct with a 40-cm-long Roux-en-Y limb.

DISCUSSION

Following gastrectomy, some of the most frequent problems associated with gastrointestinal reconstruction are heartburn and reflux esophagitis caused by biliary reflux and regurgitation of food.[1–3] The early and late postprandial dumping syndromes are well-known complications after gastrointestinal reconstruction following partial or total gastrectomy. There is no method available to date that is able to avoid these complications completely.[5,6] Case 3 illustrates that early dumping remains a potential problem after reoperative surgery using a jejunal Roux-en-Y limb, the method generally favored by us for reconstruction. In this case, an improvement was attained in terms of reflux symptoms, including reflux esophagitis. No improvement was, however, achieved with respect to early dumping. Unfortunately, the results of remedial surgery for dumping are variable and unpredictable.[3] Our cases demonstrate that different reconstructions including loop (non-Roux) reconstructions (cases 1, 3, 6, 7, and 9) either with or without omega configuration as well as short Roux limbs (cases 4, 5, and 8) or antiperistaltic or inverted Roux limbs (cases 2 and 10) can lead to substantial morbidity. In 8 of 10 of these cases, complete relief of symptoms could be achieved by the uniform application of the 40-cm-long, isoperistaltic retrocolic Roux-en-Y limb during reoperative reconstruction. In the remaining two cases (cases 2 and 3), only incomplete relief of symptoms could be attained (Table 1).

Loop (Non-Roux) Reconstructions With or Without Omega Configuration

After partial gastric resection, serious morbidity can be caused by afferent-loop syndrome, efferent-loop

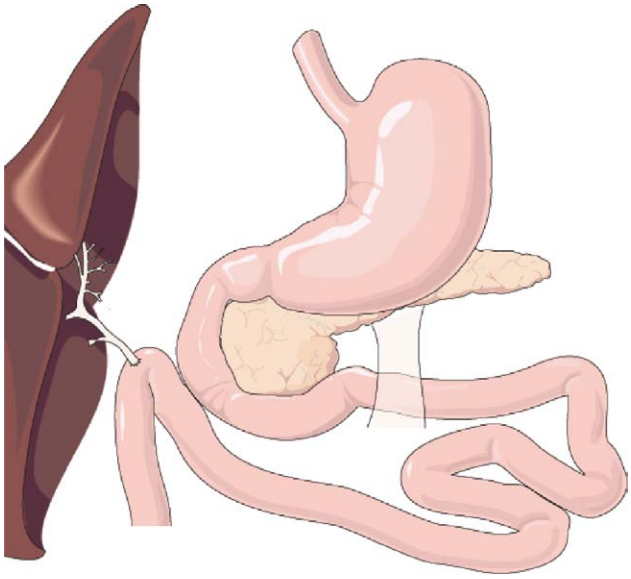

Fig. 9. Biliary tract reconstruction in case 9 was performed with a nonexcluded jejunal loop leading to recurrent cholangitis and reoperation.

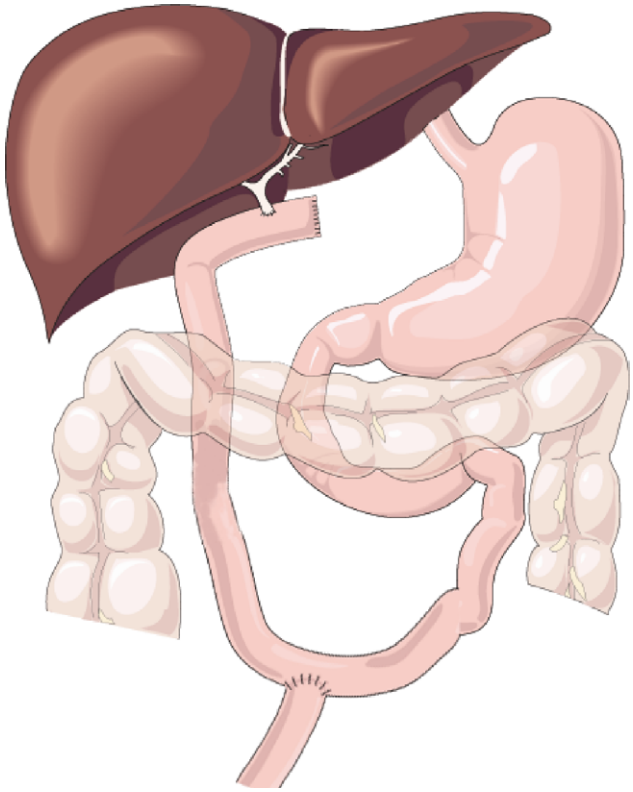

Fig. 10. Biliary tract reconstruction was carried out with the wrong end of the divided proximal jejunum, and it was used for hepaticojejunostomy instead of the created Roux-en-Y limb in case 10. This situation was leading to early postoperative cholangitis with sepsis prompting operative revision.

syndrome, and blind-loop syndrome.[7–10] In many cases, these complications are avoidable if the reconstruction of the gastrointestinal tract is performed according to well-established and almost completely standardized surgical methodology. Afferent-loop syndrome originates either from outflow obstruction of the afferent omega loop caused by a constricting side-to-side jejunojejunostomy or from a too-wide outflow opening so that the gastric or esophageal contents fill the afferent loop, in both cases leading to bacterial overgrowth in the afferent loop as well as obstruction of intestinal transport of bile and exocrine pancreas secretions.[9] In our series, the afferent-loop syndrome was a major problem in cases 1 and 3. Affected patients frequently complained of lack of appetite, vomiting bile, bloated feeling, and diarrhea. Vomiting typically alleviates these symptoms immediately in the short term. Omega loop reconstruction with side-to-side jejunojejunostomy after gastrectomy appears to be potentially problematic in our view because it may cause afferent-loop syndrome, especially when the side-to-side jejunojejunostomy is created proximal to the esophago- or gastrojejunostomy as reported in case 1. If an omega loop reconstruction is used for reconstruction, it should be carried out with side-to-side jejunojejunostomy approximately 15−20 cm distal to the esophago- or gastrojejunostomy to avert afferent-loop syndrome. Case 6 demonstrates that for complex reconstructive surgery of the digestive tract, sufficient operative experience with the specific procedure is essential. In efferent-loop syndrome, stomach emptying is hindered through a mechanical bend, for example, caused by adhesion, invagination, or a constricting anastomosis.[11] Overgrowth of the blind loop with gut bacteria can lead to maldigestion and vitamin B_{12} deficiency. Case 6 in our series represents a drastic case of efferent-loop syndrome with iatrogenic mechanical stenosis of the efferent loop following erroneous reconstruction after partial duodenopancreatectomy. Case 7 demonstrates that jejunal loop reconstruction without an omega configuration can lead to severe reflux gastritis and esophagitis due to inverted transport of bile and exocrine pancreatic juice into the stomach and esophagus. The additional development of afferent loop syndrome could be expected. In our experience, good to very good clinical results of reoperative surgery for afferent- or efferent-loop syndrome can be attained with a retrocolic, isoperistaltic Roux-en-Y jejunal limb. This limb is typically used as an end-to-side esophagojejunostomy or an end-to-side gastrojejunostomy. An important principle here is that the Roux-en-Y limb is long enough proximal to the end-to-side jejunojejunostomy to avoid reflux.

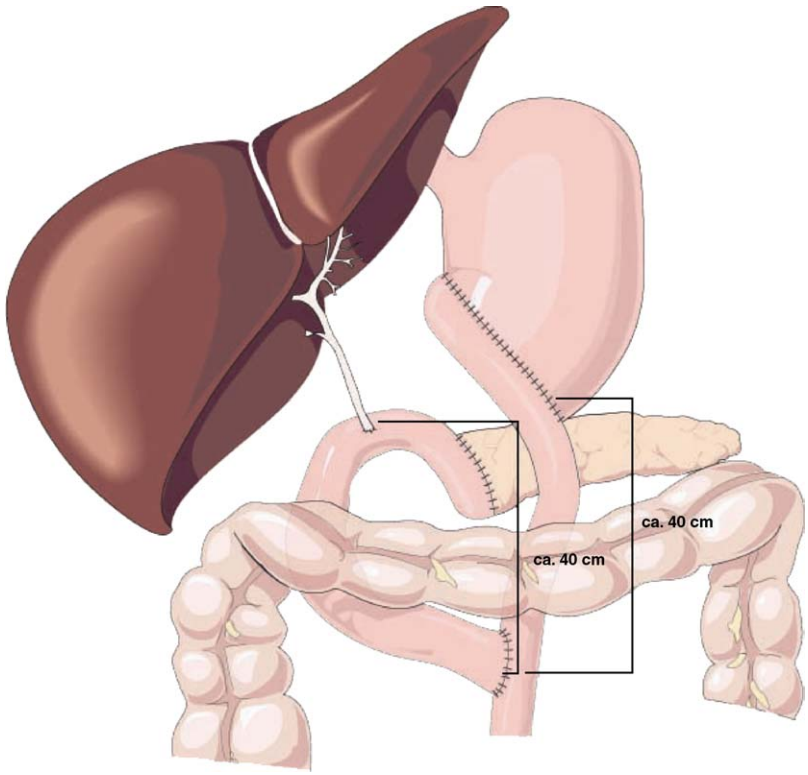

Fig. 11. Our standard reconstruction approach with a retrocolic, isoperistaltic Roux-en-Y jejunal limb with a length of approximately 40 cm for gastrointestinal as well as extrahepatic biliary tract reconstruction.

In our view, the cholangitis illustrated in case 9 is a consequence that is to be expected after biliary tract reconstruction using an end-to-side hepaticojejunostomy with the jejunum in its continuity. It appears obvious that bacteria in the chymus can easily ascend into the biliary tract in this constellation. With regard to the latter, it should be remembered that recurrent cholangitis may also complicate state-of-the-art reconstruction of the extrahepatic biliary tract with a Roux-en-Y limb. Nevertheless, we are convinced that reoperation should usually be carried out in cases with recurrent cholangitis after hepaticojejunostomy, because otherwise recurrent cholangitis may lead to life-threatening sepsis, chronic necessity of antibiotic treatment, and secondary sclerosing cholangitis followed by chronic liver failure. In our experience, a rehepaticojejunostomy with a Roux-en-Y limb and an end-to-side jejunojejunostomy 40 cm distally appears to be the best strategy in such reoperative cases.

Short Roux Limbs

Both reflux esophagitis (cases 4 and 5) after distal gastric resection and recurrent cholangitis (case 8) following hepaticojejunostomy are often the result of a too-short Roux-en-Y limb. Following collective surgical experience as well as the experience of our series, we consider a length of 40 cm for the Roux-en-Y limb to be ideal to best avoid reflux of bile and pancreas secretions and thus reflux esophagitis or reflux of gastric contents into the biliary tract and thus cholangitis.[3,11–13] In our reoperative cases presented here, the initially used limbs for reconstruction were on average between 15 and 20 cm long and therefore clearly too short. In these cases, reoperation using a Roux-en-Y jejunal limb with a length of 40 cm was able to eradicate recurrent cholangitis as well as reflux esophagitis for the long term. In this context, it should be noted that the inaccuracy of intraoperative measurement of bowel length is notorious, partially due to the varying contractile state of the bowel.

Antiperistaltic or Inverted Roux Limbs

Cases 2 and 10 demonstrate that the use of the wrong end of the divided proximal jejunum for gastrojejunostomy or hepaticojejunostomy does lead to biliary reflux after distal gastric resection or cholangitis after hepaticojejunostomy due to antiperistaltic instead of isoperistaltic anastomosis. We believe that both complications could be the consequence of lack of attention to relevant detail during the procedure. In both cases, the symptoms prior to reoperation

could be completely corrected with the use of an isoperistaltic, retrocolic Roux-en-Y limb with a length of 40 cm.

CONCLUSIONS

Our illustrative collection of cases shows that reconstructions of the gastrointestinal tract that are complicated by significant morbidity should usually prompt reoperation as soon as possible. In our view, these cases impressively show the value of a retrocolic, isoperistaltic Roux-en-Y jejunal limb with a length of approximately 40 cm for gastrointestinal as well as extrahepatic biliary tract reconstruction in reoperative cases (Fig. 11). Compliance with well-established standard reconstructive procedures is of elementary importance in the gastrointestinal tract. In conclusion, operative correction of uncommon reconstructions associated with morbidity is usually indicated.

The potential problems associated with bias and the fact that uncontrolled data are used in this report result from the significant methodologic difficulties that are encountered when reoperative procedures and their values are to be evaluated in a systematic manner, aiming at a high grade of scientific evidence. Therefore, reoperative surgery in digestive tract reconstruction is still characterized by the need for further case studies and scientific methodologic innovation combined with extensive personal clinical experience.

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Postoperative Bezoar Ileus After Early Enteral Feeding

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Postoperative enteral nutrition is a widely accepted route of application for nutrition formulas due to a low complication rate, a good acceptance by patients. and a favorable cost-effectiveness. We report three cases of bezoar ileus after early postoperative enteral nutrition, using a fine needle jejunostomy (FNJ) in two cases and a nasoduodenal tube in one case. A male patient who underwent gastric resection for a gastrointestinal stroma tumor and was nourished through an fine needle jejunostomy developed an acute abdomen on the seventh postoperative day. Surgical exploration revealed a mechanical ileus caused by denaturated nutrition formula distal to the catheter tip. The second case, a female patient, underwent gastric resection for a gastric cancer and on the fourth postoperative day developed acute onset of abdominal pain. Intraoperative findings were the same as described in the first case. The third case, a male patient with necrotizing cholecystitis, underwent open cholecystectomy. Postoperative enteral feeding was performed using a nasoduodenal tube. He developed a small bowel obstruction on the 17th postoperative day that was caused by an intraluminal bezoar. In conclusion, bezoar formation represents an underestimated complication of postoperative enteral feeding. Acute onset of abdominal pain and the development of small bowel obstruction are the main clinical symptoms of this severe complication. The pathogenesis of bezoar formation remains unclear. (J GASTROINTEST SURG 2006;10:123–127)

KEY WORDS: Enteral nutrition, complications, feeding catheter jejunostomy, nasoduodenal tube, bezoar ileus

Malnutrition represents a well known risk factor that increases postoperative morbidity and mortality.[1] Therefore, early enteral nutrition is now widely used after major gastrointestinal (GI) surgery in many institutions.[2] Enteral nutrition represents the physiologic route of food application and is increasingly preferred due its low complication rate (e.g., no central line infections) and its favorable lower costs compared to parenteral nutrition.[2–4]

Whereas oral food application is often not possible after major surgery of the upper GI tract during the first postoperative days, postpyloric and jejunal feeding can easily be performed by either using nasojejunal tubes or percutaneous catheter jejunostomy (FNJ).[5] The reported complication rates in the literature are very low, ranging in most series from 1.6 % to 2.7%.[5–7]

Enteral nutrition using a small-bored needle catheter jejunostomy (9 French, Freka FCJ; Fresenius Kabi GmbH, Stans, Switzerland) is routinely performed after esophageal, gastric and pancreatic resections in our institution. Major advantages of the FNJ are the possibility of a prolonged administration of enteral nutrition over several weeks and that oral nutritional intake is not hampered by the presence of a nasoduodenal tube.

We report three cases of bezoar ileus after early postoperative enteral nutrition using an FNJ in two cases and a nasoduodenal tube in one case.

CASE REPORTS

Case 1

A 62-year-old male patient underwent gastric resection for a gastrointestinal stroma tumor. There were no preexisting comorbidities. After total gastrectomy and cholecystectomy, a Roux-en-Y reconstruction with end-to-side esophagojejunal pouch

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anastomosis and jejunojejunal anastomosis was performed. The FNJ was inserted into the jejunum as described by Delany[8] around 50 cm distally to the jejunojejunal anastomosis. As usual, localization and function of the FNJ were intraoperatively controlled by injecting clear fluid. The operative course was completely uneventful.

Early enteral nutrition using a standard formula containing 22 g fiber per liter (Novasource; Novartis Nutrition, Switzerland) was started 6 hours postoperatively with a flow rate of 20 ml/hr. From postoperative day one to 5, the flow rate could stepwise be increased from 20 ml/hr to 30 ml/hr, thus increasing the daily volume from 100 ml to 550 ml, respectively. The clinical course remained uneventful until postoperative day 7, when the patient developed acute pain and abdominal distention. The computed tomography scan confirmed the clinical suspicion of a mechanical ileus and revealed an acute small bowel obstruction with subsequent dilatation of the proximal jejunum. There were no pathologic findings reported relating to the FNJ.

Intraoperatively, we found a small bowel obstruction proximal to the insertion of the FNJ (Fig. 1). The jejunal lumen was completely obstructed by denaturated enteral nutrition formula. The feeding tube was firmly stuck in that intraluminal plug. After removal of the FNJ, the denaturated mass was evacuated through a longitudinal incision of the jejunum. The patient recovered without further problems, whereby oral food intake was completely normalized when he was discharged from the hospital at postoperative day 18.

Case 2

A 36-year-old pregnant female patient (23rd week of gestation) was admitted with increasing abdominal pain, nausea, and emesis. Ultrasonography showed a large ovarian tumor on the left side measuring 23 cm × 11 cm × 15 cm, whereas no pathologic findings of the pregnancy or other intra-abdominal lesions could be detected. The tumor was resected through a midline laparotomy. Histologic examination of the 2.5-kg specimen revealed a metastasis of a gastric cancer (Krukenberg tumor). The primary tumor could be confirmed by gastroscopy but no further metastasis was detected. The patient was then reoperated with abortive cesarean section, total gastrectomy with D2-lymphadenectomy, and cholecystectomy. A Roux-en-Y reconstruction with end-to-side esophagojejunal pouch anastomosis and jejunojejunal anastomosis was performed. Finally, the FNJ was inserted into the jejunum 50 cm distal to the jejunojejunal anastomosis.

Enteral nutrition was started 6 hours postoperatively using a standard formula containing 22 g fiber per liter (Novasource; Novartis Nutrition) with flow rate of 20 ml/hr (480 ml/day). The flow rate was steadily increased up to 40 ml/hr without any clinical disturbances (1000 ml/day) in the following days. On

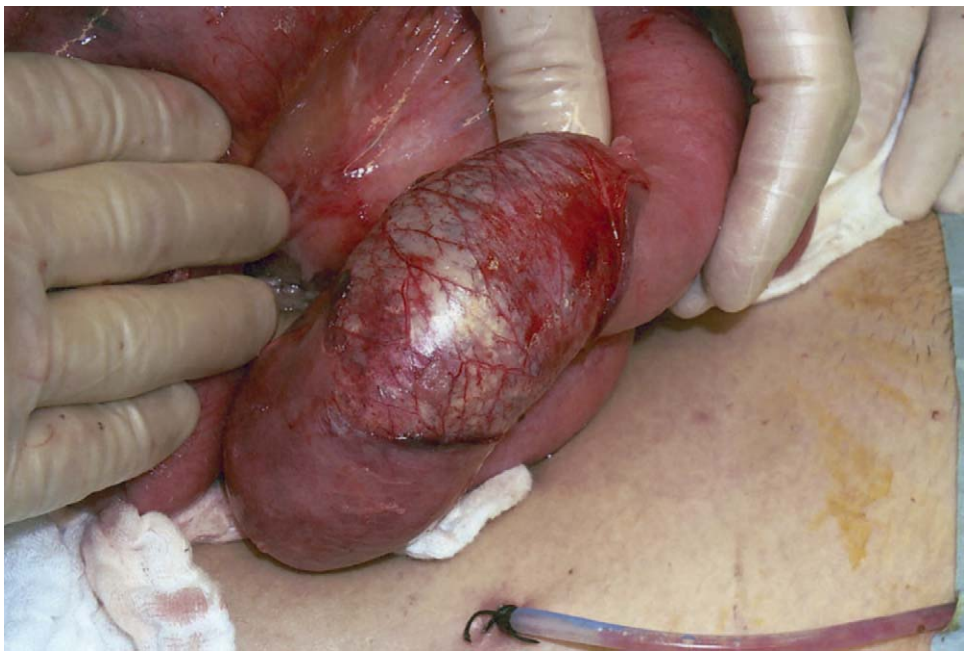

Fig. 1. Complete obstruction of the jejunal lumen by denaturated enteral nutrition formula. The feeding tube is firmly stuck in the intraluminal plug.

postoperative day 4, the patient developed acute abdominal pain and peritoneal signs. Without further investigations, the patient underwent re-laparotomy at the same day. Intraoperatively, a distended and hemorrhagic small bowel was found that originated from a mechanical obstruction at the FNJ. The small bowel was paved with denaturated nutrition formula forming a firm intraluminal plug of 80 cm in length. The feeding tube could be removed and the proximal small bowel was cleared through a jejunotomy (Fig. 2). The postoperative course was uneventful, and the patient was discharged on postoperative day 20.

Case 3

A 74-year-old male patient was referred with acute necrotizing cholecystitis and sepsis. A radical restorative cystectomy for bladder cancer T3 N0 with creation of a gastric pouch had been performed several years before. Except for chronic obstructive pulmonary disease, he had no other underlying diseases. Open cholecystectomy was performed immediately after admission. The postoperative course was complicated by cardiac and renal insufficiency. On the third postoperative day, parenteral nutrition was started (Nutriflex; B. Braun Medical AG, Sempach-Station, Switzerland). On postoperative day 8, a duodenal tube (16/9 French; Freka Trelumina; Fresenius Kabi GmbH) was inserted, and enteral feeding with a non–fiber-containing formula for renal insufficient patients (Nepro; Abbott Nutrition, Baar, Switzerland) was started at 10 ml/hr. Flow rate was increased to 30 ml/hr the next day (800 ml/d). On postoperative day 15, the patient developed acute abdominal pain and peritoneal signs. Enteral nutrition was discontinued immediately, and computed tomography scan revealed a mechanical obstruction of the small bowel. The patient underwent re-laparotomy at the same day. Intraoperatively, a distended and hemorrhagic small bowel was found that originated from a mechanical obstruction distal to the duodenal tube. Through enterotomy, denaturated nutritional formula was evacuated. Unfortunately, the patient did not recover and died on postoperative day 38.

DISCUSSION AND REVIEW OF THE LITERATURE

Early postoperative enteral nutrition is usually well tolerated and has significant benefits by reducing infectious complications. Different access for enteral nutrition can be used including nasogastric or nasoduodenal feeding tubes, percutaneous catheter feeding jejunostomy, and percutaneous endoscopic or surgical tube gastrostomy. Although tube gastrostomies are predominantly used for long-term nutritional support in patients with impaired swallowing, FNJ and nasoduodenal tubes are rather restricted to perioperative nutrition after major upper GI and pancreatic surgery. Intraoperatively, FNJ is placed through the abdominal wall and then inserted into a jejunal loop that has been attached to the abdominal wall. The reported morbidity in the literature for

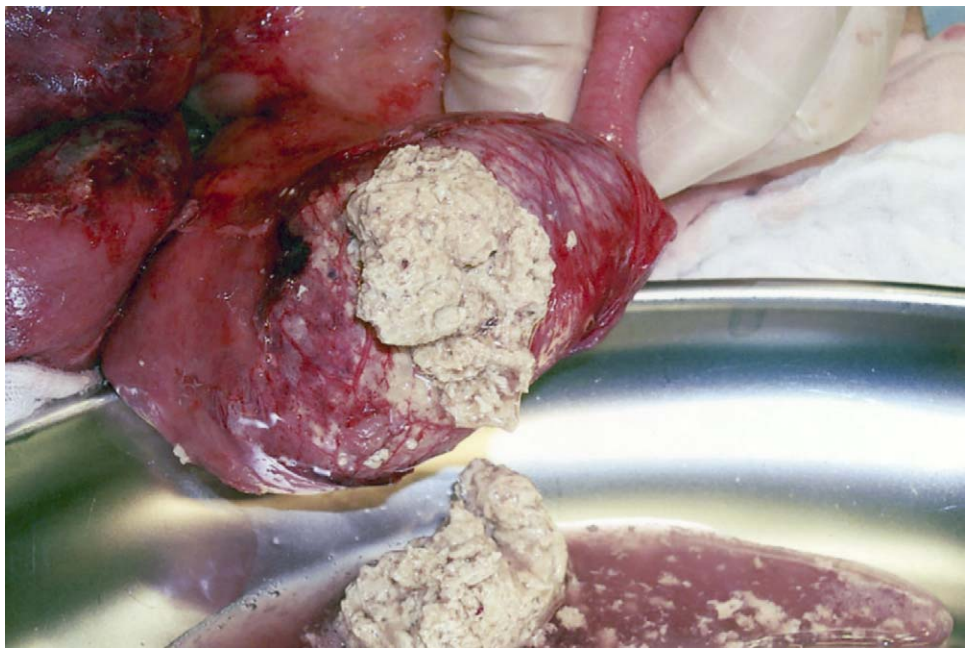

Fig. 2. Evacuation of the intraluminal plug through a jejunotomy.

major complication ranges from 1.6% to 2.7%.[5–7] The most common complications are phlegmatous infections at the entry site of the FNJ at the abdominal wall, which are usually treated with antibiotics and local disinfection. Catheter obstruction can often be managed conservatively by flushing with liquid including antioxidants (e.g., vitamin C). Catheter dislodgment with subsequent infusion of nutrition into the abdominal cavity is a rare complication (1%) and requires reoperation. Mechanical bowel obstruction due to bowel necrosis and pneumatosis intestinalis have been reported only rarely.

By thoroughly reviewing the literature, we identified only four patients with small bowel obstruction due to bezoar formation after enteral feeding.[9–11] The incidence of this rare complication is unknown, because only few cases are reported. O'Neil et al.[10] reported a 79-year-old woman with gastric cancer undergoing subtotal gastrectomy with Roux-en-Y reconstruction. Isocaloric non–fiber-containing enteral nutrition formula was administered through a nasogastric tube with the tip distal to the gastrojejunal anastomosis. Enteral feeding was started on the first postoperative day with 10 ml/hr and gradually increased to 80 ml/hr over the next 48 hours. She developed acute crampy abdominal pain on postoperative day 7. Plain abdominal radiography revealed a complete small bowel ileus caused by a bezoar in the efferent limb of the jejunum. Enteral feeding was immediately stopped. The bezoar was managed conservatively by intraluminal filling of 5 0 ml papain containing normal saline every 6 hours. O'Malley et al.[9] reported a 39-year-old man who underwent subtotal gastrectomy for bleeding gastric ulcer. A feeding catheter jejunostomy was placed for postoperative enteral nutrition using isocaloric non–fiber-containing formula. Flow rate was started at 6 ml/hr and increased to 125 ml/hr by the fifth postoperative day. On day 7, he developed fever and acute abdominal pain. Radiology showed an intestinal mass obstructing the small bowel lumen. The patient was reoperated and precipitated nutrition formula that stuck in the jejunum lumen was found. In addition, the small bowel wall was necrotic, and a segmental resection was performed with an end-to-end anastomosis. McIvor et al.[12] reported a 45-year-old man with a serious thrombotic thrombocytopenic purpura. The patient needed prolonged mechanical ventilation due to respiratory failure, and enteral nutrition was started by nasogastric tube using a fiber-containing formula at a rate of 25 ml/hr and increased to 125 ml/hr within 10 hours. On the sixth day the abdomen became distended. Enteral nutrition was stopped and parenteral nutrition started. Surgical exploration 3 days later revealed a dilated cecum and terminal ileum with inspissated stool. A right hemicolectomy and ileostomy were performed. Finally, Date et al.[11] described one patient with small bowel obstruction after gastrectomy as a result of precipitation of enteral feeding formula, but no further details were published.

In our patients, bezoar formation occurred after enteral nutrition with fiber-containing nutritional formula using an FNJ and nasoduodenal tube. This represents an incidence of 1% in our department; since we have used 200 FNJs during the four recent years. Similar to three of the four published cases, two of our patients also underwent gastrectomy, whereas the third patient had gastric pouch creation as urinary bladder replacement, and small bowel obstruction became clinically present after several days of enteral feeding. The pathogenesis of bezoar formation as a complication of enteral nutrition remains unclear. It has been assumed that both an impaired postoperative bowel motility and simultaneous overload with fiber-containing enteral nutrition are related to bezoar formation.[10,12] Disturbances of intraluminal pH levels may occur after gastrectomy due to the lack of acid secretion and could contribute to precipitation of fibers at the tip of the feeding tube. Furthermore, an increased flow rate may lead to intraluminal accumulation of enteral nutrition, and precipitation may then occur in the absence of intestinal fluid. The careful review of our cases failed to demonstrate any risk factors, such as use of opioids and diuretics, fluid substitution, and flow rate of enteral nutrition. We assume that bezoar formation might be attributed to intestinal acid-base levels. A suggested prevention could be dilution of the formula initially with water.[7] This might have a positive effect on concentration of fibers and the acid-base level inside the intestinal lumen.

In conclusion, bezoar formation represents a rare but serious complication of postoperative enteral feeding that may be underestimated. Acute onset of abdominal pain and the development of small bowel obstruction require immediate discontinuation of the enteral feeding and further investigations to rule out severe complications, such as bezoar formation. Due to its unknown pathogenesis, it remains unclear how this complication can be avoided.

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Thrombosis of a Large Portal Vein Aneurysm: Treatment by Thrombectomy, Aneurysmorrhaphy, and Portocaval Shunt

Martin Wolff, M.D., Nico Schaefer, M.D., Joachim Schmidt, M.D., Andreas Hirner, M.D.

An otherwise healthy 32-year-old woman had unspecific upper abdominal complaints. Diagnostic work-up, including a helical computed tomography (CT) scan and indirect splenoportography, revealed a giant extrahepatic portal vein aneurysm (PVA) extending to the central part of the splenic vein. On laparotomy, a thrombectomy and creation of a portocaval side-to-side shunt were performed. Thirteen days later, she was readmitted for re-thrombosis of the aneurysm. She underwent another laparotomy with thrombectomy and tapering of the portal venous wall (aneurysmorrhaphy) by vascular staplers. On follow-up 25 months after the operation, full relief of symptoms was noted. She was on warfarin therapy. Her portal venous system was patent. (J GASTROINTEST SURG 2006;10:128–131)

KEY WORDS: Portal vein aneurysm, aneurysmorrhaphy, portocaval shunt

CASE REPORT

A 32-year-old female patient was admitted to a community hospital because of 3 days of progressive epigastric pain and nausea. She had no previous illness and no history of liver or pancreatic disease. Physical examination showed tenderness of the upper abdomen and a low-grade fever of 38.2°C. Peripheral blood count and biochemistry were normal, apart from a bilirubin of 1.4 mg/dl. Upper gastrointestinal endoscopy showed mild gastritis without gastroesophageal varices. Ultrasonography revealed a heterogeneous echogenic mass at the porta hepatis. On CT scan, a large blood-equivalent mass with compression of the pancreatic head and the hepatic hilum was demonstrated.

She was transferred to our hospital for further treatment. A helical CT scan and indirect splenoportography revealed complete thrombosis of an 8 × 6-cm extrahepatic PVA extending to an aneurysmatic splenic vein of 5 cm in diameter (Fig. 1).

The patient underwent a laparotomy, which showed congested bowel and pancreas, a normal liver, and 2.5 L of clear ascites. On opening the gastrocolic ligaments, there was an impressive protrusion of the thrombosed and ectatic central part of the portal and superior mesenteric vein and the splenic vein underneath the body and head of the pancreas (Fig. 2). There was no arterioportal fistula. The portal aneurysm was mobilized from the hepatoduodenal ligament by retracting the common bile duct to the left. In order to obtain better access to the giant aneurysm, the gallbladder, which contained stones, was removed. The aneurysm was opened laterally at the supraduodenal portion of the portal vein, and the protruding thrombotic material was removed by using Fogarty catheters and suction until good inflow from the mesentery and backflow from the liver were obtained. A cell saver and systemic heparinization were used. Closure of the aneurysm was achieved by resecting a part of the wall longitudinally in order to reduce the diameter. A pressure measurement showed 23 mm Hg in the portal vein and 8 mm Hg in the infrahepatic vena cava and a central venous pressure of 6 mm Hg. Assuming a still existing elevated resistance within portal branches of the liver, the decision was taken to create a side-to-side portocaval shunt in order to facilitate outflow from the ectatic venous system. Following mobilization of the suprarenal vena cava, a tension-free anastomosis

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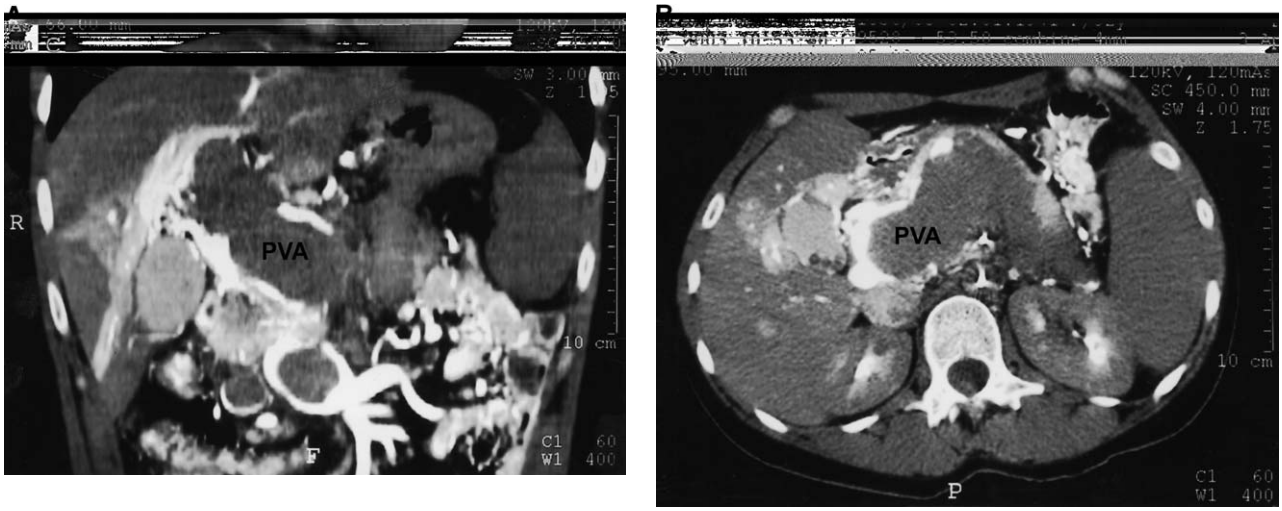

Fig. 1. Preoperative helical computed tomography scan with contrast enhancement during the portal phase. **A**, Portal vein aneurysm (PVA) with acute complete thrombosis. **B**, Extension of the portal vein thrombosis into the aneurysmatic splenic vein and gallbladder with stones.

could be achieved. Histologic examination of a liver biopsy and of the portal vein wall showed no abnormalities.

On postoperative day 3, a hematoma in the right subhepatic space was evacuated, which was attributed to anticoagulation. Thereafter, a helical CT scan, indirect splenoportography, and color flow ultrasound demonstrated a patent portal system and orthograde flow within the portal vein (Fig. 3). The patient was discharged on postoperative day 11 on a therapeutic dosage of low-molecular-weight heparin.

Two days later, the patient was readmitted for a recurrent thrombosis of the portal system, which was demonstrated on another CT scan. She underwent emergency laparotomy and another thrombectomy of the portal system. Transient clamping of the portocaval shunt was performed. This time, the thrombectomy was carried out by opening the aneurysmatic

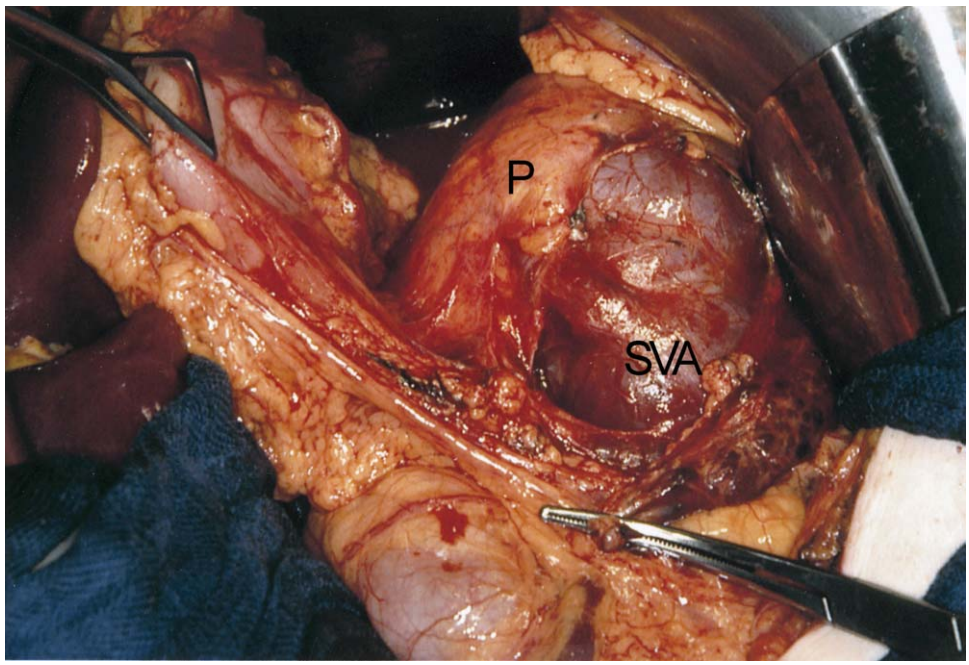

Fig. 2. Operative view into the lesser sac from the right. The stomach is reflected cephalad. The splenic part of the venous aneurysm (SVA) is shown at the inferior border of the pancreas (P).

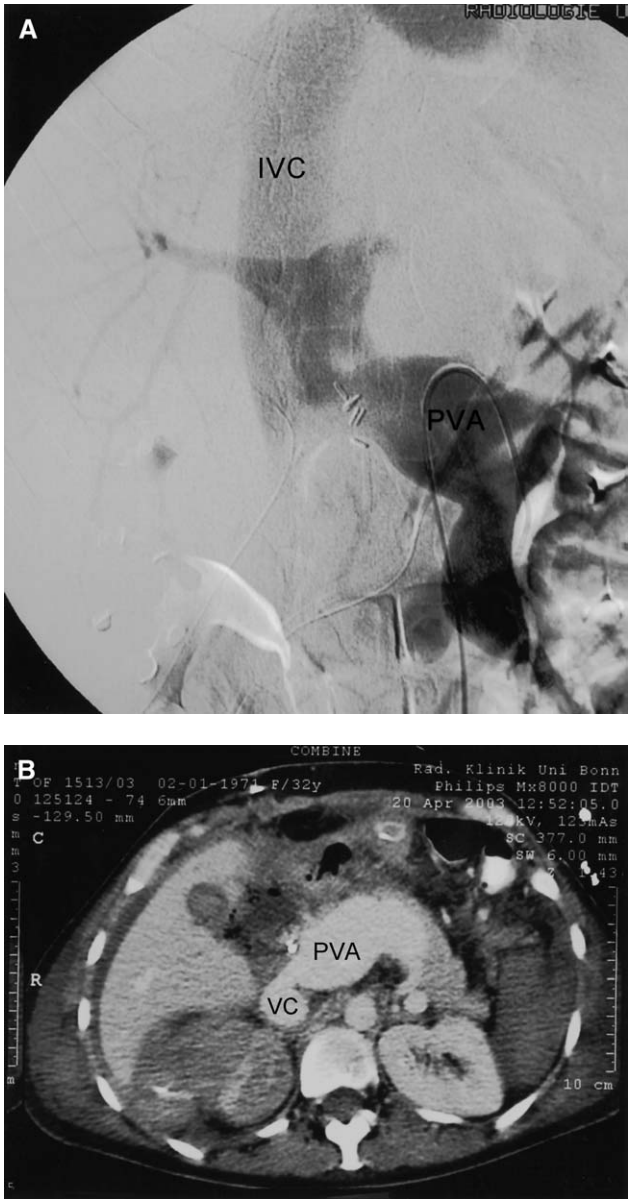

Fig. 3. Postoperative imaging on day 5 after the operation. **A**, Indirect splenoportography depicts the patency of the portal system with orthograde flow into the liver and patency of the portocaval shunt by opacification of the inferior vena cava (VC). **B**, Helical computed tomography scan with contrast enhancement of the portal venous phase showing the still enlarged portal vein (PVA) and the patency of the portocaval shunt as evidenced by contrast media in the inferior VC.

splenic vein as well as the previous venotomy at the portal vein. Both the splenic and portal veins were thoroughly mobilized. Tapering of the vessel diameters (aneurysmorrhaphy) was achieved by using multiple vascular stapler lines (30-mm Endo-GIA USS; Tyco Healthcare, Mansfield, MA). The patient recovered uneventfully and was discharged after adjustment of the dosage of phenprocoumon.

On follow-up 25 months after the operation, the patient presented without complaints and has continued working as a music teacher. Color Doppler ultrasonography revealed a patent portal system, orthograde flow in the intrahepatic portal vein with a patent portocaval shunt, and a normal spleen size. Blood cell counts and biochemical tests of liver function were normal.

DISCUSSION

PVAs are rare. However, asymptomatic aneurysms are described with increasing frequency due to the wide use of ultrasound and CT.[1] Most extrahepatic and intrahepatic PVAs have been described in association with liver disease, portal hypertension, and arterioportal fistulas.[1,2] A PVA at the umbilical portion of the portal vein may be associated with a portohepatic venous shunt and encephalopathy. In our present case, the etiology of the large fusiform aneurysm involving the central part of the portal vein and the splenic vein remains unclear. This entity could be also referred to as a giant central ectasia of the portal system, which is of congenital origin, probably.

In most reports, asymptomatic PVAs have been managed by observation.[1] However, in contrast to fusiform aneurysms, a saccular aneurysm can be resected with relative ease.[2] Complications of large PVAs include compression of the bile duct and rupture or thrombosis of the aneurysm with subsequent development of portal hypertension.[1,2] When acute thrombosis of the aneurysmatic portal vein occurs, it may mimic a pancreatic or hepatic mass on ultrasound.[3,4] Color Doppler sonography may be helpful, but the extent of the thrombosis can be investigated best by contrast-enhanced helical CT or magnetic resonance imaging.[5]

Acute thrombosis of the aneurysm can be managed nonoperatively.[3,5] However, cavernous transformation of the porta hepatis, the development of portal hypertension with the risk of variceal bleeding, and a possible extension of the thrombosis into mesenteric vein branches causing venous infarction remain an imminent problem.[1]

Therefore, we decided in this young patient to thrombectomize the portal system, reduce the resistance to portal flow by a portocaval shunt, improve laminar flow by aneurysmorrhaphy, and maintain patency by anticoagulation. This case is unusual because of the large size of the PVA, the extension into the splenic vein, and the absence of an underlying cause.

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Predictive Factors for Pancreatic Fistula After Pancreaticosplenectomy for Advanced Gastric Cancer in the Upper Third of the Stomach

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This study aimed to retrospectively investigate the predictive factors for pancreatic fistula following pancreaticosplenectomy. Pancreatic fistula is a major lethal complication of pancreaticosplenectomy. However, predictive factors for this condition have not yet been established. Between April 1992 and March 2000, 147 patients with advanced gastric cancer that was located predominantly in the upper third of the stomach were enrolled in this study. Predictive factors for pancreatic fistula were investigated using univariate and multivariate analyses. Pancreatic fistula, as defined according to our criteria, was observed in 73 (49.7%) patients. In the univariate analysis, age, body mass index, serum zinc level, hyperlipidemia, and comorbid disease all significantly affected the incidence of pancreatic fistula. In the multivariate analysis, body mass index, hyperlipidemia, and comorbid disease independently predicted the occurrence of pancreatic fistula. By contrast, the experience of the operating surgeon had no significant effect on the frequency of this condition. Our results suggest that pancreaticosplenectomy, the surgical merit of which is not apparent, should be avoided whenever possible. If this operative procedure must be used (e.g., in patients with extensive tumor presence), careful manipulation and appropriate drainage are essential, particularly in cases showing predictive factors of pancreatic fistula. (J GASTROINTEST SURG 2006;10:132–137)

KEY WORDS: Gastric cancer, pancreatic fistula, pancreaticosplenectomy, upper third of the stomach

In Japan, D2 gastrectomy is considered to be an established and reliable procedure. However, the use of this method has been discouraged in routine clinical practice in Western countries due to the relatively high operative mortality and the lack of apparent survival benefit.[1,2] In Japan, pancreaticosplenectomy or splenectomy for advanced gastric cancer located in the upper third of the stomach was previously used to achieve a more complete D2 gastrectomy,[3,4] but this procedure appeared to have no survival benefits[5,6] and a higher incidence of complications after pancreaticosplenectomy was reported by many clinicians.[7,8] Although a surgical approach has great potential in the treatment of gastric cancer, locoregional control with extended lymph node dissection is sometimes offset by higher morbidity and mortality rates. A subset analysis of the data from the Medical Research Council (MRC) Gastric Cancer Surgical Trial[1] and the Dutch Gastric Cancer Group Trial[2] revealed that the higher morbidity was caused by pancreaticosplenectomy rather than by extended lymph node dissection. This suggested that the higher postoperative mortality offset any long-term survival benefits of the treatment. Furthermore, pancreaticosplenectomy followed by D2 gastrectomy sometimes caused adverse complications, such as overt pancreatic fistula resulting in reconstructive anastomotic leakage. However, the Japan Clinical Oncology Group Study reported that specialized surgeons could safely perform not only D2 but also D3 gastrectomy with acceptable levels of complications.[9] Although many recent studies have reported adverse effects or no survival benefits of pancreaticosplenectomy for gastric cancer in the upper third of the stomach, we have clinically encountered cases of gastric tumor invading

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the pancreas body or tail in which pancreaticosplenectomy has sometimes been used. Therefore, it remains necessary to evaluate the predictive factors for the occurrence of pancreatic fistula after pancreaticosplenectomy, followed by D2 or more extended D3 gastrectomy for advanced gastric cancer located mainly in the upper third of the stomach.

MATERIAL AND METHODS

A series of 147 patients with advanced gastric cancer, in which the invasion penetrated deeper than the muscularis propria and the tumor was located predominantly in the upper third of the stomach, were enrolled in this study between April 1992 and March 2000. All of the subjects were preoperatively confirmed to have gastric adenocarcinoma by analysis of endoscopic biopsy specimens. The eligible patients comprised 107 men and 40 women with an average age of 60.7 years. A preoperative evaluation was performed for all patients consisting of a barium swallow study, an endoscopic examination with a biopsy, and computed tomography (CT) scans. Ultrasonography of the abdomen and endoscopic ultrasonography were also optionally used. Patients with distant metastasis (peritoneal, hematogenous, and nonregional lymph node metastases) were excluded from the study. Staging was based on the Japanese Classification of Gastric Carcinoma.[10] A well-defined tumor was macroscopically observed in 31 patients, and an ill-defined type was seen in the remaining 116 patients. The mean tumor diameter $\pm$ SD was 80.0 $\pm$ 39.6 mm. The depths of invasion were as follows: T2 (muscularis propria or subserosa) was observed in 64 patients, and either T3 (serosa penetrated) or T4 (adjacent organs) was detected in 83 patients. A differentiated tumor was histologically observed in 56 patients and an undifferentiated type was seen in 91 patients. Lymph node metastasis was observed in 33 patients. D2 gastrectomy (defined as complete lymph node dissection of group 1 and 2 nodes) was used in 21 patients, and D3 gastrectomy (defined as complete lymph node dissection of group 1, group 2, and para-aortic lymph nodes according to the Japanese Classification of Gastric Carcinoma) was performed in 126 patients. The latter procedure was only adopted in patients in whom the invasion penetrated deeper than the subserosa according to preoperative imaging modalities and who gave prior informed consent. The pathological stages were as follows: IA (6 patients), IB (11 patients), II (39 patients), IIIA (27 patients), IIIB (22 patients), and IV (42 patients). The majority (135 patients; 91.8%) of the cases were treated with curative gastrectomy, with the remaining subjects undergoing noncurative surgery.

Surgical Method for the Pancreatic Stump

After ligating and cutting the splenic artery and vein, we resected the pancreatic parenchyma and carefully searched for the main pancreatic duct. Once it was identified, we ligated and cut this duct. Bleeding from the microvessels in the pancreas parenchyma was generally stopped by a transfixing suture. After these operative procedures, we used two methods for the treatment of the pancreatic parenchymal stump: mattress suture (suture group) or no suture (open group).

Site of Ligation and Cutting of the Splenic Artery

During the first 6 years of performing this procedure, the splenic artery was ligated and cut at its root without preservation of the dorsal pancreatic artery (108 patients). During the last 2 years, the splenic artery was cut at the same resection site in the pancreas parenchyma, so as to preserve the dorsal pancreatic artery (39 patients). The splenic vein was ligated and resected at the same site in the pancreas parenchyma in all patients.

Definition of Pancreatic Fistula

According to our definition, a case of pancreatic fistula must satisfy three or more of the following five criteria: dirty-appearing discharge (of a yellowish-green, pulpy appearance) from the drain; skin redness around the drain due to amylase; an amylase concentration of 1000 U/L or greater in the discharge from the drain; evidence of bacterial infection; and enhancement of an abscess cavity around the pancreatic stump or the main pancreatic duct. Of the 147 patients, pancreatic fistula was diagnosed in 73 individuals (49.7%). Of these, skin redness and dirty-appearing discharge were observed in all 73 patients, fungal infections were detected in 29 patients, and various other bacterial infections in an additional 30 patients. In addition, nine patients showed elevated amylase levels in the discharge, and an abscess cavity or enhancement of the pancreatic duct was seen in five patients.

There was no postoperative death due to pancreatic fistula within 30 days or during the initial hospitalization period. Seven different surgeons operated on patients within the study group.

Statistical Analysis

The SPSS program version 9.0 for Windows (SPSS Inc., Chicago, IL) was used for all statistical

analyses. The χ^2 test was applied to evaluate the difference in proportions. The Student's *t* test was used to evaluate the continuous variables and the data were expressed as the mean ± SD. Logistic-regression analysis was used to test for interactions between the predictive factors and the incidence of pancreatic fistula. The following preoperative factors were evaluated: gender (male or female), age (years; <60 or ⩾60), body mass index (BMI) (kg/m^2; <25 or ⩾25), serum zinc (Zn) level (μg/dl; <70 or ⩾70), serum total protein level (g/dl; <7.0 or ⩾7.0), serum albumin level (g/dl; <3.0 or ⩾3.0), serum total cholesterol (T. Chol) level (U/L; <210 or ⩾210), serum hemoglobin level (g/dl; <10 or ⩾10), and comorbid disease (absence or presence). The intraoperative factors investigated were as follows: treatment of the pancreatic stump (sutured or open), site of resection of the pancreas (left or right side of the inferior mesenteric vein), preservation of the dorsal pancreatic artery (preserved or nonpreserved), operation time (minutes; <600 or ⩾600), and volume of bleeding (ml; <1000, ⩾1000 but <2000, or ⩾2,000). In addition, two postoperative factors were evaluated: pathologic stage (I/II or III/IV) and curability (curative or noncurative). All of the factors that were significant in the univariate analysis were included in the logistic-regression analysis. A probability (*P*) value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The incidence of pancreatic fistula was significantly higher among older patients and was significantly positively associated with BMI and serum levels of Zn and T. Chol. High BMI and high levels of zinc and cholesterol significantly induced pancreatic fistula. Moreover, the incidence of pancreatic fistula was significantly higher in patients with comorbid diseases for which treatments were necessary than in patients without these conditions. Hypertension was the most frequent comorbidity seen among the study group (28 cases), followed by cardiac dysfunction (17 cases), diabetes mellitus (13 cases), gout (3 cases), hypothyroidism (2 cases), renal failure (1 case), bronchial asthma (1 case), Addison's disease (1 case), and Bechet's disease (1 case). However, there was no significant difference in the frequency of occurrence between the two sexes and no significant association with serum levels of total protein, albumin, and hemoglobin (Hb) (Table 1).

Clinicopathologic Factors

There was a significant difference in the macroscopic appearance of the tumor between patients with and without pancreatic fistula. Pancreatic fistula was frequently observed in patients with well-defined macroscopic-type tumors. However, there were no significant differences in tumor diameter, depth of invasion, histological type, and lymph node metastasis or dissection (D2 or D3) between the two groups (Table 2).

Intraoperative Factors

None of the intraoperative factors evaluated had a significant effect on the incidence of pancreatic fistula (Table 3). Similarly, neither of the two postoperative factors examined (pathologic stage and curability) was significantly associated with the occurrence of pancreatic fistula. Stage I/II was seen in 29 patients with and 27 patients without pancreatic fistula, whereas the respective figures for stage III/IV were 44 and 47 ($P = 0.6859$). Curability was achieved in 67 patients with and 68 patients without pancreatic fistula ($P = 0.9804$).

Logistic-Regression Analysis

All five of the factors that showed a significant association with the incidence of pancreatic fistula in the univariate analysis were included in the logistic-regression analysis. The results revealed that BMI, serum level of T. Chol, and comorbid disease could all independently predict the occurrence of pancreatic fistula after pancreaticosplenectomy in patients with advanced gastric cancer located in the upper third of the stomach (Table 4).

Incidence of Pancreatic Fistula According to the Experience of the Surgeon

The duration of experience of the operating surgeon (<10 or ⩾10 years) had no significant effect on the frequency of occurrence of pancreatic fistula after pancreaticosplenectomy; it was observed in 16 patients who underwent surgery with less-experienced surgeons (<10 years) and in 57 patients who underwent surgery with more-experienced surgeons (⩾10 years) ($P = 0.5075$). Similarly, when considering the numbers of previous gastric surgeries combined with pancreaticosplenectomy performed by each surgeon (<50 or ⩾50 cases), there was no significant difference in the incidence of pancreatic fistula; it was observed in 39 patients who underwent surgery with less experienced surgeons (<50 cases) and in 37 patients who underwent surgery with experienced surgeons (⩾50 cases) ($P = 0.8066$).

Postoperative Course

There was no significant difference in the start time of oral intake (postoperative day 9.9 ± 2.9 versus

Table 1. Patient characteristics

	Pancreatic Fistula (+)	Pancreatic Fistula (−)	*P* Value
Age (yr), <60/≥60	24/49	42/32	.0036
Body mass index (kg/m^2), <25/≥25	48/25	68/6	.0001
Zn (μg/dl), <70/≥70	24/49	42/32	.0036
Total cholesterol (mg/dl), <220/≥220	47/26	64/10	.0018
Hemoglobin (g/dl), <10/≥10	14/59	7/67	.0923
Comorbid disease (n), absent/present	34/39	57/17	.0001

7.8 ± 0.8, $P = 0.3322$) between patients with and without pancreatic fistula. However, there was a significant difference in the length of hospital stay between these two groups (postoperative day 47.8 ± 8.9 versus 29.8 ± 6.8, $P < 0.0001$).

DISCUSSION

Our results revealed that BMI, serum level of T. Chol, and the presence of comorbid disease all independently predicted the occurrence of pancreatic fistula after pancreaticosplenectomy in cases of advanced gastric cancer located in the upper third of the stomach.

Pancreatic fistula is the main complication of extended (D2) or superextended (D3) gastrectomy accompanied by pancreaticosplenectomy.[7,8] Both the MRC and Dutch Gastric Cancer Group trials documented increased postoperative morbidity and mortality, and reduced long-term survival, as a result of the occurrence of pancreatic fistula after pancreaticosplenectomy. It has therefore been argued that pancreaticosplenectomy should only be used in D2 gastrectomy if there is a direct extension of the disease to the pancreas from posteriorly situated tumors. D2 gastrectomy with preservation of the pancreas is now recommended in Japan.[11] In the present study, a higher incidence of pancreatic fistula was observed after both D2 and D3 gastrectomy and no mortality was caused by this condition, indicating that this method should not influence the survival rate. However, the occurrence of pancreatic fistula undoubtedly has an adverse effect on the cost of treatment, as a longer period of hospitalization is required, as shown in the current study. Therefore, strict criteria should be applied for the indication of extended gastrectomy with pancreaticosplenectomy.

In the current study, the incidence of pancreatic fistula was higher than in the previous Japanese randomized trial.[9] However, the definition of pancreatic fistula was notably different. Most patients diagnosed with pancreatic fistula in the present study satisfied the criteria of skin reddening, dirty-appearing discharge, and bacterial infection, whereas elevation of amylase concentration in the discharge and enhancement of the cavity around the pancreatic stump were less frequent. Therefore, in the present study, the definition of pancreatic fistula was broader than those used in previous reports. Although the results shown in this study were based on this broad definition, they might be useful clinically. In a previous Japanese randomized trial, pancreatic fistula was defined only by elevation of the amylase concentration in the discharge. Therefore, the incidence of pancreatic fistula was lower (5.3%−6.2%). Adopting the same definition as the Japanese randomized trial, the incidence of pancreatic fistula in the present study group was 6.1%.

Our study confirmed that BMI independently predicted the occurrence of pancreatic fistula. Several previous reports have discussed postoperative morbidity from the viewpoint of BMI. However, although some authors found that BMI did not affect postoperative morbidity after D2 gastrectomy,[12,13] others

Table 2. Clinicopathological factors for pancreatic fistula after pancreaticosplenectomy assessed by univariate analysis

	Pancreatic Fistula (+)	Pancreatic Fistula (−)	*P* Value
Macroscopic appearance			
Well-defined	21	10	
Ill-defined	52	64	.0234
Lymph-node metastasis			
Present	12	21	
Absent	61	53	.0828

Table 3. Intraoperative predictive factors for pancreatic fistula after pancreaticosplenectomy assessed by univariate analysis

	Pancreatic Fistula (+)	Pancreatic Fistula (−)	*P* Value
Pancreatic stump (n), suture/open	58/15	64/10	.2564
Site of resection of pancreas (n), left side of IMV/right side of IMV*	68/5	71/3	.4551
Preservation of dorsal pancreatic artery (n), preservation/nonpreservation	17/56	22/52	.3764
Operation time (min), <600/≥600	41/32	40/34	.7970
Bleeding volume (ml), <1000/≥1000, <2000/≥2000	15/41/17	24/35/15	.2633

*IMV = inferior mesenteric vein.

reported a significant association between these factors.[14,15] Few previous studies have evaluated the potential correlation between BMI and the incidence of pancreatic fistula after pancreaticosplenectomy. It is clearly more difficult to accurately dissect the lymph nodes and to distinguish normal pancreatic tissue from fatty tissue in patients with a higher BMI, but the level of experience of the operating surgeon did not affect the incidence of pancreatic fistula in our dataset. Therefore, the skill of the surgeon does not appear to be a major contributory factor to the occurrence of pancreatic fistula. However, long operative periods and large volumes of bleeding were observed for some obese patients who underwent D3 gastrectomy according to our criteria. A higher BMI might be a risk factor for postoperative morbidity, including pancreatic fistula, after superextended gastrectomy. Fat accumulation frequently induces hyperlipidemia,[16] which in turn can lead to intrapancreatic arteriosclerosis of the pancreatic tissue and other organs.[17] Consequently, the fragility of the pancreas parenchyma might increase, resulting in pancreatic fistula. The elevated BMI and serum cholesterol levels might simply be correlated with obesity. Randomized controlled trials in the West have reported a higher incidence of pancreatic fistula after pancreaticosplenectomy than that observed in Japan. This might be attributable to the greater tendency toward obesity among Western populations. Comorbid diseases, such as hypertension and diabetes mellitus, might predispose patients to these conditions. Our analyses confirmed that high BMI, hyperlipidemia, and the presence of comorbid disease all independently predicted the occurrence of pancreatic fistula after pancreaticosplenectomy.

In the univariate analysis, pancreatic fistula was frequently observed in older patients, although age was not an independent predictive factor. Fatty infiltration, a reduced mass of acinar cells and interstitial tissues, arteriosclerosis of the microvessels, and dilation of the microduct of exocrine pancreatic tissue are all associated with aging.[18] These degenerative changes are likely to encourage and aggravate pancreatic fistula.

In the current study, the serum level of Zn was higher in patients with pancreatic fistula. Previous reports have shown that the serum level of Zn in patients with upper gastrointestinal cancer is correlated with their nutritional status.[19,20] Our present results also revealed that the serum level of Zn and the BMI were significantly positively correlated ($P = 0.0145$). These findings suggest that the serum level of Zn was positively correlated with the presence of pancreatic fistula.

The method of treatment of the pancreatic stump, the site of resection of the pancreas, and preservation of the dorsal pancreatic artery all failed to show a significant effect on the incidence of pancreatic fistula. Closure of the pancreatic stump did not prevent pancreatic fistula, and there was no correlation between the residual pancreas size and the incidence of this complication. Moreover, resection of the dorsal pancreatic artery did not influence the major blood supply at the pancreatic stump and, therefore,

Table 4. Predictive factors for pancreatic fistula following pancreaticosplenectomy assessed by logistic-regression analysis

	Odds Ratio (95% Confidence Interval)	*P* Value
Body mass index (kg/m^2), <25/≥25	5.4673 (1.9549–15.2904)	.0012
Total cholesterol (mg/dl), <220/≥220	3.4930 (1.4119–8.6417)	.0068
Comorbid disease (n), present/absent	4.3129 (1.9867–9.3628)	.0002

had no significant effect on the occurrence of pancreatic fistula. Despite these findings, meticulous attention remains essential during pancreatic surgery in order to decrease the complications.

Several previous reports have questioned the surgical value of pancreaticosplenectomy for advanced gastric cancer located in the upper third of the stomach.[5,6] Most retrospective reports have also indicated that pancreaticosplenectomy had no obvious survival benefits and could lead to severe complications, resulting in longer hospital stays, as shown in the current study.[7,8] We therefore suggest that this method should be used only when the tumor directly invades the pancreas; it should not be regarded as a standard surgical procedure for advanced gastric cancer without direct invasion into the pancreas located in the upper third of the stomach. Accordingly, we now use pancreas-preserving total gastrectomy as the treatment of choice.

In conclusion, our results revealed a relatively high incidence of pancreatic fistula after pancreaticosplenectomy. Furthermore, high BMI, hyperlipidemia, and the presence of comorbid disease in patients with advanced gastric cancer located in the upper third of the stomach were all independent predictive factors for pancreatic fistula. This operative method should only be indicated in patients whose tumor has invaded the pancreas or who have substantial lymph node metastasis at the distal splenic artery and splenic hilum. In patients with predictive factors for pancreatic fistula, delicate handling and adequate drainage are essential in order to minimize the risk of pancreatic fistula after pancreaticosplenectomy.

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Differences in Survival for Patients With Resectable Versus Unresectable Metastases From Pancreatic Islet Cell Cancer

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Well-differentiated islet cell tumors can be associated with aggressive biology, resulting in early metastases to the liver. This study was carried out to determine whether survival for patients with malignant islet cell tumors and synchronous liver metastases is affected by complete surgical resection. Thirty-one patients with synchronous liver metastases from islet cell cancer underwent surgical exploration with the intent for complete tumor resection, and all patients underwent resection of the pancreatic primary. The patients were divided into two groups, those with resectable versus unresectable liver metastases. Twenty-six of 31 (84%) patients underwent complete resection of both the primary tumor and all liver metastases, and 5 (16%) patients underwent only complete resection of the pancreatic primary without liver resection. To extirpate the primary tumor, a pancreaticoduodenectomy was performed in 11 of the 26 (42%) completely resected patients and in 4 of the 5 (80%) incompletely resected patients, P = NS. The remainder of the patients underwent distal pancreatectomy. There were no statistical differences in primary tumor size, lymph node metastases, or adjuvant treatments between patients with resected and unresected liver metastases. The median overall survival for the completely resected group was 78 months, longer than the 17 months for the group with unresectable liver metastases (P = 0.06). Complete tumor resection (or the tumor biology that allows such complete resection) affords a survival advantage to patients with metastatic islet cell tumors of the pancreas. Patterns of liver metastases from islet cell tumors, specifically multiple bilobar metastases that are not amenable to resection and/or ablation, predict a poor outcome despite resection of the primary pancreatic tumor. (J GASTROINTEST SURG 2006;10:138–145)

KEY WORDS: Pancreas, islet cell tumors, liver metastases

Pancreatic endocrine neoplasms, commonly referred to as islet cell tumors, are a distinct group of neoplasms characterized by indolent growth and, at times, unique clinical features attributable to the overproduction of endocrine hormones. Approximately 2500 new islet cell tumors are diagnosed in the United States each year, and the majority of these neoplasms display malignant behavior defined by local invasion into adjacent organs, regional lymph node spread, or metastases to the liver and beyond.[1] At least one third of patients with malignant islet cell cancers present with synchronous liver metastases at the time of diagnosis; however, even in the setting of such advanced metastatic disease, some patients may remain asymptomatic and experience prolonged survival without aggressive intervention.[2] In contrast to liver metastases from cancers arising from the exocrine pancreas, hepatic metastases from islet cell cancers rarely lead to rapid hepatic dysfunction and hepatic failure or tumor-associated cachexia, even in the presence of extensive liver replacement by tumor.

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Due to the relatively low incidence of islet cell cancer and the heterogeneous phenotypes associated with neuroendocrine tumors in general, it is difficult to conduct prospective clinical trials comparing the efficacy of medical and surgical therapies aimed at controlling metastatic islet cell cancers. Whereas major hepatic resection with curative intent has been shown to afford a survival benefit to patients with completely resected metastatic disease from various primary sites, most notably from the colon and rectum, there are no prospective studies demonstrating an advantage with aggressive interventions for metastatic islet cell cancer.[3,4] As a consequence, the management of liver metastases from islet cell carcinoma reflects the observations from small retrospective reviews of patients with metastatic neuroendocrine tumors of the gastrointestinal tract, usually combining abdominal carcinoids with pancreatic islet cell tumors.[5–10] Hepatic-directed treatments for metastatic neuroendocrine tumors include cytoreductive surgery or ablation, systemic or catheter-directed chemotherapy, syndrome-specific hormonal therapy, and liver transplantation.[2,11–17] Unfortunately, only a few studies have aimed to identify the patient- or tumor-related factors that potentially favor one intervention over another with regards to curative or palliative success.[5,18–20]

Clinical experience from high-volume centers has clearly demonstrated successful palliation of systemic endocrinopathies, and even cure, after complete resection of metastatic islet cell cancers.[17–20] Despite the shortcomings of retrospective studies, we performed this review to determine if survival for patients with malignant islet cell tumors and synchronous liver metastases is affected by complete resection of all gross disease at the time of initial surgical exploration.

METHODS

Patient Selection

From 207 patients who underwent resection of a pancreatic endocrine neoplasm at The Johns Hopkins Hospital between 1988 and 2003, we identified 31 patients who were found to have synchronous liver-only metastases at the time of initial presentation and who underwent exploration with intent for complete tumor resection (primary and hepatic metastatic disease). Patients with evidence of extrahepatic systemic metastases were excluded, as well as those who did not undergo surgical resection of their pancreatic primary in the setting of metastatic disease. After permission from the Johns Hopkins University Joint Committee on Clinical Investigation, information regarding tumor and patient characteristics, as well as clinical follow-up, was collected retrospectively from a prospective pancreatic tumor database combined with the hospital's electronic patient record system. Of the 31 patients who presented with islet cell cancer and synchronous liver metastases, 26 underwent complete resection of the pancreatic primary and all known metastatic disease within the liver. These 26 patients were compared to the remaining five patients who underwent pancreatic resection alone without concomitant surgical resection or ablation of liver metastases. Unresectability of metastatic disease within the liver was determined by the surgeon at the time of exploration, and no patients in this report underwent incomplete palliative debulking of liver metastases. A margin-negative resection of the primary pancreatic tumor was accomplished in all patients.

Statistical Analyses

Differences in patient and tumor characteristics between the resected and unresected groups were analyzed with the Fisher exact probability test, or Student's *t*-test when appropriate. A two-tailed *P* value of < 0.05 was considered statistically significant (Stata Release 6, College Station, TX). Survival was measured from the time of surgical resection to the time of death or last follow-up. Survival probability was calculated and displayed graphically by the Kaplan-Meier method, and the log rank test was used to compare differences in survival rates. Statistical significance was defined as *P* value of <0.05.

RESULTS

Patient and Tumor Characteristics

Age and gender were compared between patients with resected liver metastases and those with unresectable metastatic disease (Table 1). The average age of individuals in the resected group was 52 years (range, 31–71 years) compared to 41 years for the patients with unresected liver metastases. Roughly, half of the patients in each group were male, and over 90% of all patients were Caucasian.

The mean diameter of the primary pancreatic islet cell tumors in this study was 4.9 cm (range, 2.5–8.0 cm), and 19 of the 31 (61%) tumors arose from the head of the pancreas. All neoplasms were associated with histopathologically proven regional lymph node spread and synchronous liver-only metastases. Standardized immunohistochemistry for synaptophysin

Table 1. Patient data

	Resected	Unresected	*P* value
Number of patients	26	5	—
Mean age (yr) (range)	52 (31—71)	41 (31–52)	0.35
Gender			0.53
Male	13	2	
Female	13	3	
Mean follow-up (range)	44 mo (2–120)	29 mo (8–66)	—

and chromogranin A was performed on each of the tumors (primary and metastatic) to confirm neuroendocrine differentiation, and selective immunostaining was performed when a functional neuroendocrine tumor was suspected. Overall, there were eight functional islet cell tumors in this study. As shown in Table 2, there were no significant tumor characteristic differences between the groups with resectable or unresectable liver metastases; however, liver metastases in the unresectable group were more likely to be small, multiple, and bilobar. Because computed tomography or another uniform radiologic study was not available to calculate the total percentage of liver replacement by tumor in all cases, we did not compare the measurable extent of metastatic disease between the resectable and unresectable groups.

Surgical and Oncologic Management

Open liver metastasectomy, which was combined with radiofrequency ablation (RFA) in two patients, was performed synchronously with pancreatic resection in 26 of the 31 patients at the time of initial exploration. Fifteen of the 26 patients who underwent complete resection of all disease with curative intent were treated with pancreaticoduodenectomy, and 11 patients underwent synchronous liver resection with distal pancreatectomy and splenectomy. Nearly 80% of the liver resections involved a nonanatomic wedge resection or segmentectomy for one or several metastases (maximum four), and two of these patients received intraoperative, ultrasound-guided RFA of one or more (maximum two) metastatic deposits within the liver (Fig. 1, *A*). A formal hepatic lobectomy or trisegmentectomy was performed in addition to a pancreatic resection to achieve complete tumor removal in six patients (Table 3). Despite extensive tumor extirpation from the pancreas and liver, there were no operative or perioperative deaths, and early postoperative complications were encountered in just one quarter of these patients. One patient, treated via pancreaticoduodenectomy, required reexploration for hemorrhage from a branch vessel of the superior mesenteric artery. Three patients experienced delayed gastric emptying. Other major operative complications included one bile leak and one pancreatic fistula. None of the operative complications were directly attributable to liver resection or radiofrequency ablation.

Five patients in this study, who were discovered to have unresectable liver metastases at the time of surgical exploration, underwent palliative pancreatic resection only. Four patients with unresectable metastases harbored tumors within the head of the pancreas and were managed with pancreaticoduodenectomy to palliate existing or imminent symptoms of biliary or duodenal obstruction (Table 3). One patient with unresectable metastatic disease from a functional glucagonoma underwent distal pancreatectomy combined with postoperative systemic hormonal and chemotherapy for palliation of neuroendocrine symptoms (Fig. 1, *B*). One patient undergoing palliative pancreaticoduodenectomy experienced a bile leak during the early postoperative period, which was managed successfully via percutaneous biliary drainage without operative intervention.

Postoperative adjuvant systemic chemotherapy in the form of combinational streptozocin and doxorubicin was administered to three patients who underwent complete resection of all gross neoplastic disease at the time of surgical exploration. One patient who underwent a palliative distal pancreatic resection received systemic chemotherapy, and one other patient with unresectable liver metastases received chemoembolization directed at the residual tumor within the liver.

Table 2. Tumor characteristics

	Resected (n = 26)	Unresected (n = 5)	*P* value
Primary tumor size			
Mean (range)	4.7 cm (2.5–8.0)	5.2 cm (3.5–7.0)	0.89
Nonfunctional tumors	20	3	0.58
Functional tumors	6	2	
Gastrinoma	2	0	
Insulinoma	1	0	
VIPoma	3	0	
Glucagonoma	0	2	
Mean number of liver metastases (range)	1.8 (1–6)	10 (8–20)	0.15

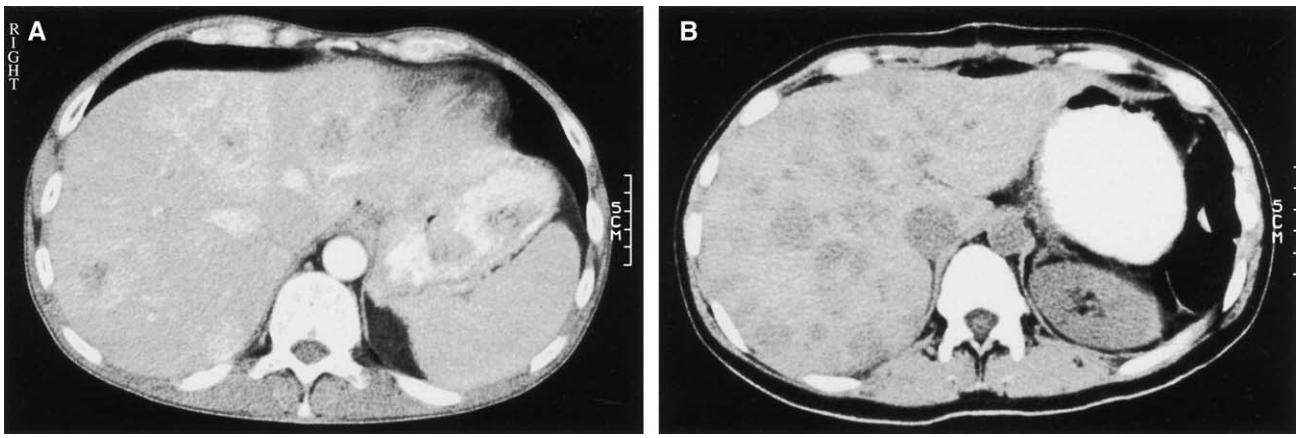

Fig. 1. (**A**) Preoperative contrast-enhanced computed tomographic scan of the liver in a 36-year-old man with four bilobar metastases that were confirmed by intraoperative ultrasound. This patient underwent left lobectomy combined with wedge resection and radiofrequency ablation of metastatic deposits in segments 5 and 6, respectively. (**B**) A patient with unresectable liver metastases from a glucagonoma, who was treated with palliative distal pancreatic resection in an attempt to control neuroendocrine symptoms.

Clinical Outcome

Complete follow-up for tumor recurrence and survival was achieved in 84% of all patients in this study and for all patients with unresectable metastases. The mean follow-up period was 44 months for the patients undergoing synchronous pancreatic and liver resections. As shown in Fig. 2, the median survival for patients who underwent complete resection was 78 months, compared to 17 months for patients who were determined to have unresectable liver metastases and were treated surgically with a palliative pancreatic resection alone. Due to the small number of patients with unresectable hepatic metastatic disease in this study, this survival difference did not reach statistical significance ($P = 0.06$). No patient with unresectable metastases survived beyond six years after the time of initial diagnosis. The 5-year survival rate for the patients who underwent surgical resection with curative intent was 65%. Three long-term (>10 years) survivors were identified in this study, but only two of these individuals are currently alive and without evidence of recurrent disease.

Table 3. Treatment differences

	Resected (n = 26)	Unresected (n = 5)	*P* value
Management of pancreatic primary			0.62
Pancreaticoduodenectomy	15	4	
Distal pancreatectomy	11	1	
Management of liver metastases	26	—	
Lobectomy	5		
Nonanatomic wedge resection(s)	20		
Trisegmentectomy	1		
RFA (combined with wedge resection)	2		
Postoperative chemotherapy	3	1	0.99

During follow-up, islet cell tumor recurrences were detected in 16 of the 26 patients who underwent synchronous pancreatic and hepatic resections (Table 4). Complete follow-up data were available for 21 patients with resected metastases; therefore, the tumor recurrence rate in patients who underwent resection with curative intent can be estimated at 76%. Half of these recurrences occurred within 2 years of initial resection, and the longest disease-free interval for a patient who developed a recurrence was 36 months. Three quarters of the tumor recurrences were isolated to the liver, and only one local recurrence within the pancreas was detected (Table 4). Fifty percent of patients died with disease within 3 years after the detection of tumor recurrence; however, one patient survived nearly 9 years with evidence of recurrent cancer. Only half (8 of 16) of the patients with recurrent disease received palliative therapy, ranging from repeat hepatic resection (n = 5) or RFA (n = 3), combined with either chemoembolization (n = 3) or systemic hormonal and/or chemotherapy (n = 5).

DISCUSSION

Similar to previous studies examining the role of aggressive surgical therapy for metastatic

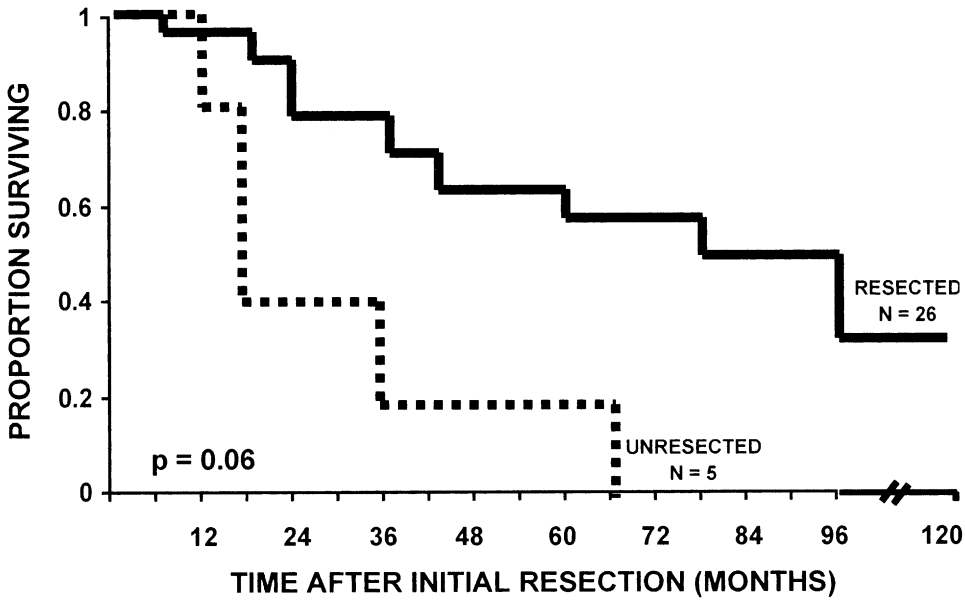

Fig. 2. Overall survival for patients who underwent complete resection of all primary and metastatic disease (solid) compared to survival for patients who were found to have unresectable liver metastases at the time of exploration and received palliative pancreatic resection only (broken). Statistical significance between the two groups was analyzed with the log rank test ($P = 0.06$).

neuroendocrine tumors, this review suggests that complete resection of primary pancreatic islet cell carcinoma along with synchronous liver metastases affords a survival benefit as compared to those patients with unresectable hepatic metastases.[5,6,9] In this study, the overall 5-year survival for patients who were found to have unresectable liver metastases at the time of palliative resection for a pancreatic islet cell cancer was estimated at 20% by Kaplan-Meier analysis, and no patient survived beyond 6 years from the time of diagnosis. These survival rates are somewhat lower than those reported in prior retrospective studies that examined the potential benefits of treating liver metastases from carcinoids or islet cell tumors.[2,6–8,10,17,19,20] Unlike most other prior studies, our review focused on a uniform group of malignant pancreatic neuroendocrine tumors and did not include gastrointestinal carcinoids. The functional status of tumors associated with unresectable metastases did not have an impact on outcome, and all patients who underwent palliative resection of the pancreatic primary remained free of biliary and duodenal obstruction.

Table 4. Outcomes in patients with resected metastases

Number of patients	26
Number of tumor recurrences	16
Liver-only recurrences	12
Liver and local recurrences	1
Widely systemic recurrences	3
Median time to tumor recurrence (range)	20 mo (7–36)
Treatment for tumor recurrences	8
Repeat wedge resection(s) of liver	5
RFA	3
Hepatic artery chemoembolization	3
Combinational cytoreductive therapy	5
Systemic chemo/hormonal therapy	4
Median time from recurrence to death (range)	33 mo (3–102)

Symptomatic palliation, by itself, was not responsible for the improved survival observed in the patients who underwent complete resection. The 5-year survival for patients who were cleared of pancreatic and liver disease was 65%. Whereas the addition of hepatic resection for synchronous metastases seems to offer a survival benefit, we estimated that tumor recurrences occurred in roughly three quarters of patients who underwent resection with curative intent, and most of these recurrences were detected within 2 years. Thus, we must assume that the beneficial effects of aggressive surgery take advantage, at least to some extent, of a favorable biology inherent to metastatic islet cell carcinomas that are amenable to complete surgical resection. The pattern of hepatic metastases in the unresectable group typically involved multiple, small-volume, bilobar deposits. This pattern of metastatic disease, which renders itself unresectable

by current surgical techniques, may reflect a more aggressive nature of islet cell carcinoma in this setting and is associated with a poor prognosis.

In the presence of multiple, bilobar liver metastases not amenable to cytoreductive therapy, decisions regarding operative palliation for obstruction related to the primary pancreatic neoplasm require careful consideration. In the past pancreaticoduodenectomy for cancer of the head of pancreas has been reserved for patients who are candidates for a potentially curative resection. As postoperative morbidity continues to improve after pancreaticoduodenectomy in high-volume centers, there is growing interest in this procedure as a palliative treatment for pancreatic neoplasia that cannot be resected completely. In the presence of liver and/or systemic metastases, pancreaticoduodenectomy is still not considered an appropriate palliative procedure for pancreatic adenocarcinoma, but it may have a role in palliating symptoms related to advanced pancreatic endocrine neoplasms. In this retrospective study, we identified four patients who presented with obstructive jaundice, abdominal pain, and unresectable synchronous liver metastases from islet cell tumors, who were successfully palliated with pancreaticoduodenectomy, without the need for further palliative procedures. Recognizing that the median survival for these patients was 17 months in this study, we have not proven that pancreaticoduodenectomy offers superior advantages over double bypass (gastrojejunostomy and hepaticojejunostomy) or endoscopic palliative procedures in this setting. The 5-year survival rate for our small group of five patients with unresectable metastases who received palliative pancreatic resection (four pancreaticoduodenectomy, one distal pancreatectomy) was 20%; whereas, prior studies have not consistently reported long-term survivors receiving medical therapy alone.[5] Whereas this one long-term survivor after palliative pancreaticoduodenectomy may lend support for aggressive surgical palliation in select patients with unresectable disease from islet cell cancer, we do not propose this strategy for all patients.

Even though liver metastases develop in a large proportion of all malignant islet cell cancers, patients typically remain asymptomatic for several months or even years unless a functional neuroendocrine syndrome is present or aggressive local tumor progression within the pancreas leads to biliary or gastroduodenal obstruction or tumor-associated pain. Similar to prior reports, our data support the aggressive concurrent resection of pancreatic islet cell tumors and synchronous hepatic metastases when this is technically feasible.[10,20] However, in the absence of symptoms, there is controversy regarding appropriate interventions and the timing of such for individual patients with metastatic disease. Even with extensive resections, tumor recurrence and progression occur frequently and ultimately contribute to death in most patients with metastatic islet cell tumors. Accordingly, our treatment philosophy toward these patients aims to control their disease over time with the consideration of multiple available modalities for tumor ablation and growth inhibition. Several nonresectional alternatives are available for patients who present with synchronous or metachronous liver metastases from islet cell carcinoma, including systemic chemotherapy or hormonal therapy, transcutaneous arterial chemoembolization (TACE), RFA, and liver transplantation. Systemic therapy with doxorubicin and streptozocin can achieve partial response rates in nearly two thirds of patients with metastatic islet cell carcinoma; however, these responses tend to be brief, at the cost of significant chemotoxicity.[2] Whereas octreotide is effective at controlling symptoms related to functional neuroendocrine tumors, it has not been proven to prolong survival significantly.[13,21] Likewise, TACE can offer symptomatic palliation by reducing liver tumor burden in some patients; it also has not been shown to improve survival.[14,22] Although orthotopic liver transplantation has afforded long-term survival to highly selected patients with metastatic carcinoids, transplant outcomes for patients with metastatic islet cell carcinoma have been disappointing.[18,23]

Whereas several therapeutic options are available for palliation of symptoms in patients with metastatic islet cell carcinoma, medical therapy alone has not been shown to consistently improve survival.[2,18,24,25] In an attempt to identify which patients are most likely to benefit from aggressive surgical resection of metastatic neuroendocrine tumors, Chamberlain and associates developed a prognostic scoring system based on functional status of the primary tumor, presence of extrahepatic metastases, extent of liver replacement with tumor, and the presence of bilobar hepatic metastases.[5] The presence of any two of these factors, when examined retrospectively, was associated with lower rates of both complete resectability and survival.

Our retrospective study suggests that there is a survival benefit from complete surgical resection of metastatic islet cell tumors originating from the pancreas; however, our results are based on a select patient population. Two clear limitations of this study are the small number of patients with unresectable metastases and the lack of volumetric comparisons of the extent of liver tumor burden

between the resectable and unresectable groups. Also, the patients with unresectable metastases were a highly selected group with extensive bilobar liver metastases that were not amenable to surgical resection or alternative forms of cytoreductive therapy. Obviously, the outcomes in this group, compared to patients with completely resectable disease, would be expectedly poor.

In a selective retrospective review from Memorial Sloan-Kettering Cancer Center, the median survival of 18 patients with metastatic neuroendocrine tumors who received medical therapy alone was 24 months; however, there was no report of the number of interventions (or the complications therein) that were required to palliate these patients sufficiently.[5] In the current study, the 4 patients with unresectable liver metastases who underwent pancreaticoduodenectomy for their primary tumor did not require any further palliative procedures beyond their initial operation, and their median survival was 17 months. Unfortunately, we were not able to compare their survival to patients with unresectable islet cell tumor metastases who did not receive palliative resection of their primary tumor.

The overall 5-year survival for patients undergoing complete surgical resection was 65%, and two of these patients were long-term, cancer-free survivors. Based on these results, we continue to offer synchronous pancreatic and hepatic resections to patients with metastatic islet cell carcinoma as long as all gross disease can be removed with acceptable operative morbidity and mortality. The high tumor recurrence rate in the completely resected patients, predominantly involving the liver, demonstrates either our limited ability to identify all metastatic disease during preoperative and perioperative assessment or the underlying tumor biology in select individuals. Previously our group has identified several biological markers that have been useful in predicting outcomes in patients who received curative resections for malignant pancreatic endocrine neoplasms.[26–29] The continued development of tumor and clinical markers that predict outcomes in patients with metastatic islet cell carcinoma will improve decision making for patients who are potential candidates for surgical, medical, or combined therapy.

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Mediastinal Pancreatic Pseudocyst With Acute Airway Obstruction

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Pancreatic pseudocysts are usually located in the peripancreatic area, but on rare occasion a pseudocyst can reach the mediastinum. The natural history of mediastinal pseudocysts is poorly understood and seldom reported in the literature. We treated a patient who presented with an acute airway obstruction from a mediastinal pancreatic pseudocyst. Initial acute airway management and stabilization proved successful. A staged cyst decompression via a cervical and abdominal transhiatal approach was ultimately required. The natural history, potential complications, and management of pancreatic mediastinal pseudocysts are reviewed. (J GASTROINTEST SURG 2006;10:146–150)

KEY WORDS: Mediastinum, pseudocysts, complications, bronchial obstruction, pancreatitis

Pancreatic pseudocysts are generally benign and rarely present as acute life-threatening emergencies.[1–3] Most pseudocysts develop in the peripancreatic area, but on rare occasions can occur in the mediastinum.[4–8] However, very little is known about pseudocysts presenting in atypical anatomic locations, both in terms of spontaneous resolution and complications. We could not find any report in the literature of a mediastinal pseudocyst causing airway obstruction. Understanding the natural history of pancreatic pseudocysts and potential complications is important when atypical presentations occur.

We describe a patient who developed sudden airway obstruction and respiratory arrest secondary to acute enlargement of a chronic mediastinal pseudocyst. We suspect spontaneous hemorrhage was the precipitating event. The natural history, potential complications, and management of pancreatic mediastinal pseudocysts are reviewed.

CASE REPORT

A 57-year-old female presented to an outside hospital with recurrent pancreatitis. CT scan of the abdomen and pelvis at this time revealed multiple pancreatic pseudocysts. A 2.9 × 2.6 cm cyst was located at the gastroesophageal junction, and multiple other intra-abdominal pseudocysts were within the peripancreatic region. During her hospital admission, she received supportive care and was ultimately discharged on a low-fat diet. During a subsequent admission, an endoscopic retrograde cholangiopancreatography (ERCP) was done. The pancreatic duct drained directly into the distal common bile duct, and this anatomical variant was determined to be the etiology of the patient's pancreatitis. Biliary sphincterotomy was performed, and the patient was discharged pain-free.

The patient was asymptomatic for approximately 7 months when she presented to an outside hospital with a new onset of symptoms that included a "grinding chest pain," and a "lumpy feeling" when swallowing liquids. She was transferred in a stable condition with symptoms of dysphagia, regurgitation, and chest pain. She deteriorated acutely. A witnessed respiratory arrest occurred as she experienced swelling of her throat and tongue, accompanied by cyanosis. An emergent airway was obtained with endotracheal intubation. Once the airway was controlled, she became hemodynamically stable. CT scan of the neck, chest, and abdomen showed mass effect compressing the retropharyngeal space, trachea, and posterior mediastinum (Fig. 1). We suspected that acute bleed into chronic mediastinal pseudocyst with rapid expansion caused the airway compromise.

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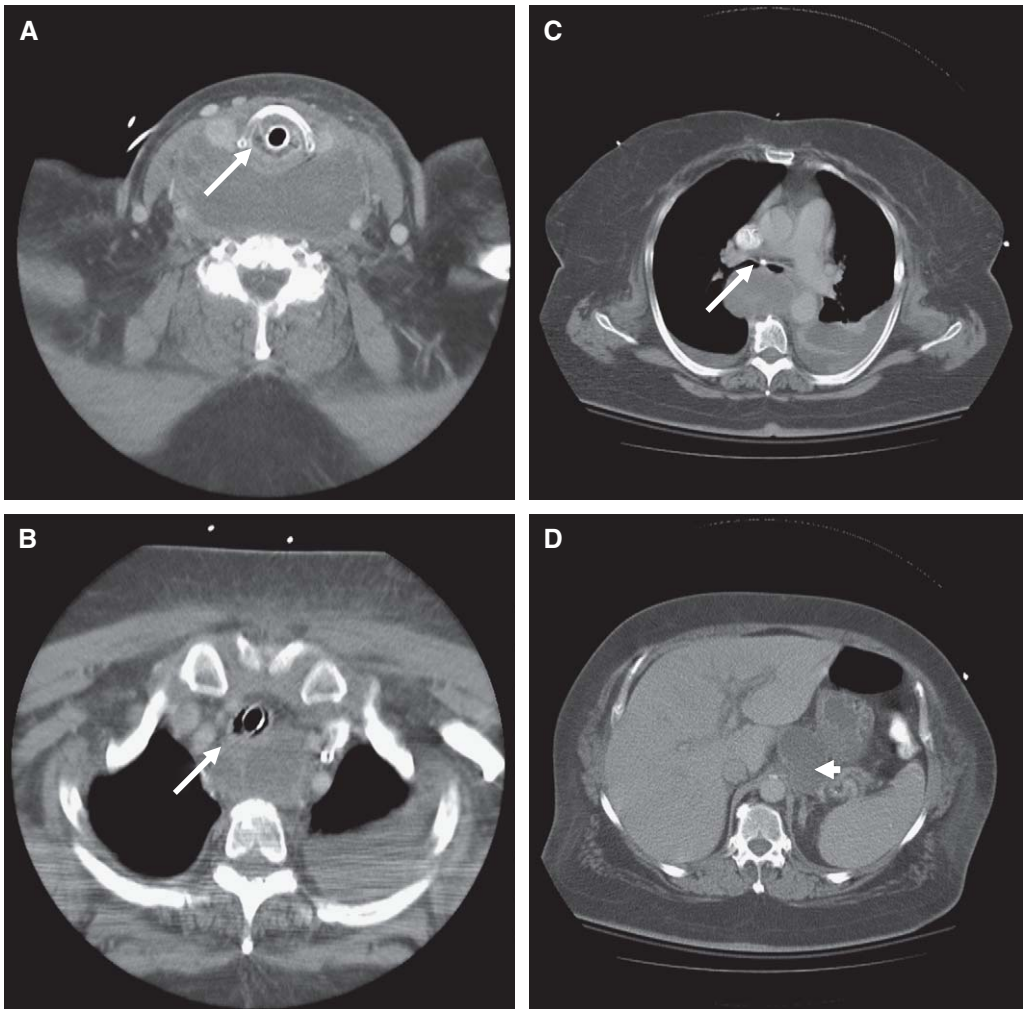

Fig. 1. Computed tomographic scans show airway compromise in a patient with a history of a chronic mediastinal pseudocyst. Compression of the airway by the cyst (*arrows*) is seen from the retropharyngeal space (**A**), to the thoracic inlet (**B**) to the carina (**C**). The pseudocyst encroaching on the left crus is seen at the diaphragmatic opening of the esophagus (*arrow head*) (**D**).

Investigations into the cause of the acute expansion were undertaken. Aspiration of the cervical component of the cyst (not drainage) was done to evaluate for active infection. Only sterile bloody cyst material was aspirated. A CT with arterial contrast was done to evaluate for active bleeding and/or formation of pseudoaneurysm. No signs of active bleeding or major vascular injury were seen. She was managed conservatively with airway support to further evaluate her possible anoxic central nervous system insult during her respiratory arrest.

The patient was taken to the operating room electively on hospital day 10 for mediastinal decompression. Through a left cervical and upper abdominal incision, wide mediastinal drainage and decompression of the airway was achieved (Fig. 2). The technique used most closely approximated that used for tranhiatal esophagectomy (the esophagus was mobilized but not injured or removed). Tracheostomy, open gastrostomy, and feeding jejunostomy were also placed for airway and nutritional access. The pancreatic pseudocysts in the abdomen were decompressed and drained. Neither active bleeding nor infection was encountered, and no pancreatic fistula resulted. She had a prolonged recovery secondary to anoxic brain injury and seizures. The patient was discharged after a two-month stay in stable condition on tube feeds to a skilled nursing facility.

DISCUSSION

Pancreatic pseudocysts are localized collections of pancreatic secretions in a cystic structure that lack an

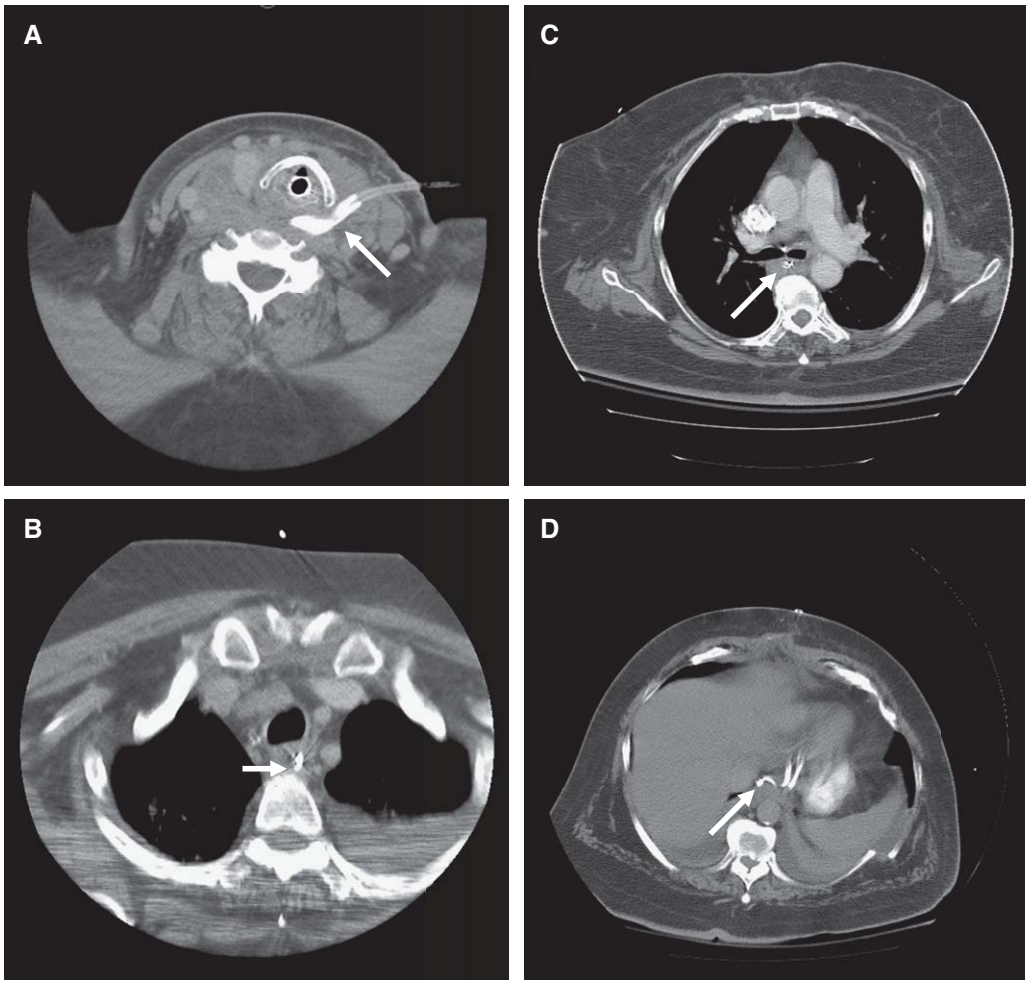

Fig. 2. Computed tomographic scan after transhiatal decompression. Drains (*arrows*) placed via (**A**) the left cervical and an upper abdominal incision are seen traversing the mediastinum: cervical (**A**), thoracic inlet (**B**), carina (**C**), and diaphragm (**D**) (all drains were extraluminal within mediastinum).

epithelial lining (and hence a pseudocyst). They occur when the disruption of a pancreatic duct is walled by surrounding tissues. They usually are located adjacent to the pancreas in one of the potential spaces around the pancreas.[9] The most common signs and symptoms include abdominal pain, nausea and vomiting (due to compression of the stomach or duodenum), jaundice (due to compression of the bile duct), or bleeding.[10,11] Although previous reports suggested that spontaneous resolution of pseudocysts occurred in about 25% of patients, the advent of CT scanning for patients suspected of having pancreatic pseudocysts has allowed precise documentation of the natural history of these lesions. It is now known that spontaneous resolution occurs in more than 50% of cases[11,12] and complications occur in 5% to 41% of cases.[11,13] Common complications include infection, intracyst hemorrhage, enlargement and mass effect causing common bile duct or bowel obstruction, and formation of fistulas, both internal and external.[10,11] Currently, conservative management of pancreatic pseudocysts is favored, reserving surgical, endoscopic, or interventional management for symptomatic, complicated, or enlarging pseudocysts.[10,11,14] Studies by Vitas and Sarr[11] from the Mayo Clinic and by Yeo et al.[15] at The Johns Hopkins Hospital suggest that strict size criteria alone are not sufficient to determine the need for operative versus nonoperative management.

The natural history and rate of complications of mediastinal pancreatic pseudocysts are not well known, as they are rare and have mainly been reported as case reports.[4–8] These pseudocysts occur when the pancreatic fluid tracks up through the diaphragmatic hiatus into the mediastinum. The most common sites of entry are the diaphragmatic openings for the esophagus and the aorta, and hence the cysts are usually located in the posterior

mediastinum.[4,7,16] The predominant cause cited in adults is alcoholic pancreatitis (75–90%), whereas in children trauma is more frequent.[17] Common presentations include pleural effusion, hemothorax, chest pain, pancreatic-thoracic fistula, dysphagia, and esophagobronchial fistula.[3,7,8,18,19] Unlike peripancreatic pseudocysts, spontaneous regression of mediastinal pancreatic pseudocysts is rare.[4,20] This clearly may be a result of preferential reporting of complicated cases of mediastinal pseudocysts.

There are several ways to manage stable and chronic mediastinal pseudocysts. Whereas there have been case reports of resolution with total parenteral nutrition and octreotide, in most cases some form of intervention is needed.[4,8,21] Less invasive options include percutaneous or endoscopic drainage. Although internal drainage may be appropriate for uncomplicated abdominal pseudocysts, mediastinal pseudocysts usually require external drainage. Percutaneous external drainage, including CT-guided placement, has been successfully reported for drainage of mediastinal pseudocysts.[5,6,22] Catheter drainage is preferred, as needle drainage has a very high rate of recurrence.[23,24] A cutaneous fistula usually occurs after external drainage but closes spontaneously in most cases.[23] Transcutaneous drainage, in general, has a recurrence rate of less than 20% and a complication rate of about 15%.[25] Complications include bleeding, infection, clogging of catheters, permanent fistula formation, and cyst recurrence.[9,22] Endoscopic interventions include transmural drainage and transpapillary stent placement. These procedures have gained favor as they are highly successful; however, more data is needed about their efficacy and safety.[7] Endoscopic drainage, in general, has a recurrence rate of less than 5% to 30% and a complication rate of about 10%.[26] Complications include hemorrhage, infection, post procedure pancreatitis, stent occlusion, migration of the drainage tube into the pancreas, stricture, retroperitoneal perforation, and duodenal erosion.[26,27] Finally, surgical treatment, including laparoscopic operations, is usually reserved for cases that fail to resolve by other measures.[20] The operation may consist of external drainage, internal drainage, or excision depending upon the case. Surgical options are highly successful, with recurrence rates of less than 10%[11,28,29] and mortality rates of less than 5%.[11,28,29]

Regardless of the location of a pseudocyst, one of the most dreaded complications of a pancreatic pseudocyst is hemorrhage, which carries a mortality rate of over 40%.[13,19] Whereas death from a pseudocyst is rare, more than half of the overall mortality from pseudocysts is due to hemorrhage.[30] Common presentations of bleeding from a pseudocyst include abdominal pain (due to the gradual enlargement of the pseudocyst), unexplained anemia, or gastrointestinal bleeding (the blood can reach the gut lumen through the pseudocyst or via the pancreatic duct).[11,30] In rare cases, the pseudocyst rapidly expands, causing obstruction of adjacent organs. We suspect the case described herein resulted from intracystic expansion from a contained, yet significant, bleed. Pseudocyst bleeding commonly arises from erosion of a small vessel in the wall of a pseudocyst or is due to a pseudoaneurysm formation. Bleeding from the wall is generally of low volume and can lead to expansion of the pseudocyst and further rupture of these small vessels.[30] The blood may remain in the pseudocyst, it may decompress spontaneously into the gut, or it may reach the duodenum through the pancreatic duct (hemosuccus pancreaticus).[31] Pseudoaneurysms, on the other hand, may cause more rapid and high-volume bleeding. They arise from the enzymatic destruction of the muscular wall of an artery released in response to the inflammation of the pancreas.[32] Bleeding may be massive and the mortality rate significant if the bleeding is not identified and treated urgently.

In summary, we describe our management of a patient with a complicated mediastinal pancreatic pseudocyst. Acute airway management and stabilization was successful. After evaluating the patient for active infection, which would require surgical drainage, and ongoing bleeding, which would require either angiographic embolization or surgical control, we opted to treat her conservatively while her anoxic insult was evaluated. Elective surgical cyst drainage was required to decompress the airway. The cervical and abdominal transhiatal technique of drainage proved safe and successful without the morbidity of thoracotomy.

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