The Impact of Reflux Composition on Mucosal Injury and Esophageal Function

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The components of refluxed gastric juice are known to cause mucosal injury, but their effect on esophageal function is less appreciated. Our aim was to determine the effect of acid and/or bile on mucosal injury and esophageal function. From 1993–2004, 402 patients with reflux symptoms had 24-hour pH and Bilitec monitoring, manometry, and endoscopy with biopsies. Mucosal injury (esophagitis or Barrett's esophagus) and esophageal function (lower esophageal sphincter [LES] characteristics and body contractility) in patients with acid reflux, bile reflux, or both were compared with patients without reflux. Reflux was present in 273/402 patients; of these, 37 (13.5%) had increased exposure to bile, 82 (30.0%) had increased exposure to acid, and 154 (56.4%) had increased exposure to both. Mucosal injury was most common with increased mixed acid and bile exposure, followed by acid alone, and was uncommon with bile alone ($P < 0.0001$). Functional deterioration paralleled mucosal injury ($P < 0.0001$). Mixed acid and bile exposure was present in more than half of patients with reflux and was associated with the most severe mucosal injury and the greatest deterioration of esophageal function. This suggests that composition of gastric juice is the primary determinant of inflammatory mucosal injury and subsequent loss of esophageal function. (J GASTROINTEST SURG 2006;10:787–797)

KEY WORDS: Gastroesophageal reflux disease, Barrett's esophagus, erosive esophagitis, Bilitec monitoring, pH monitoring

Gastroesophageal reflux disease (GERD) is a common ailment that affects 20% of Americans and imposes a serious burden on health care expenditure with the highest annual direct costs of any gastrointestinal disorder.[1,2] In 1998, more than half of the direct costs associated with treating GERD in the United States was spent on acid suppression medication ($5.8 billion).[2] In 2004, worldwide sales for acid suppression medication exceeded $25 billion.[3]

This emphasis on acid suppression has resulted in the misconception that GERD is associated with increased esophageal exposure to only gastric acid, whereas other components of refluxed gastric juice have been ignored. This has led to the hypothesis that an improvement in the potency of acid suppression therapy will reduce the incidence of mucosal damage. Indeed, clinical experience has shown a marked reduction in acid-related complications such as esophagitis and strictures with acid suppression.[4] Paradoxically, the incidence of Barrett's esophagus and esophageal adenocarcinoma has increased.[5–8] This implies that abnormal acid exposure in the distal esophagus is only part of the problem in GERD.

Bile has been implicated in the pathogenesis of reflux disease for decades.[9,10] However, the measurement of esophageal exposure to bile was problematic until the mid-1990s, when ambulatory monitoring

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for bilirubin was introduced (Bilitec 2000; Medtronic Inc., Minneapolis, Minnesota).[11,12] Early studies with the Bilitec probe suggested that the presence of bile in the refluxed gastric juice may be important in the pathophysiology of GERD.[12–14] Our experience over the past decade with a large number of patients who had both ambulatory esophageal pH and bilirubin monitoring allowed us the opportunity to study the effect of the composition of the refluxed gastric juice on the mucosa and function of the esophagus. We hypothesize that the effects of bile are synergistic with acid in causing greater inflammatory injury to the mucosa and loss of esophageal function than either acid or bile alone.

MATERIAL AND METHODS

Study Population

From June 1993 to December 2004, 460 patients with reflux symptoms underwent a comprehensive evaluation at the University of Southern California and had results available for review, including ambulatory 24-hour monitoring for both acid and bilirubin exposure in the distal esophagus, upper endoscopy with biopsies, and esophageal manometry. Fifty-eight patients were excluded from the study due to previous foregut surgery or a named motility disorder, leaving a total of 402 patients. The male: female ratio was 60:40, and the median age was 52.0 years (IQR [interquartile range], 42–63 years). The study was approved by the Institutional Review Board of the Keck School of Medicine, University of Southern California.

Ambulatory 24-Hour pH Monitoring

Ambulatory 24-hour pH monitoring of the distal esophagus was performed using a catheter-based antimony electrode (Slimline catheter, Medtronic Inc., Minneapolis, MN) that was passed transnasally and placed 5 cm above the upper border of the manometrically determined lower esophageal sphincter (LES). Data was stored in a portable data logger and downloaded to a computer for analysis with standard software (Polygram, Medtronic Inc.). All patients were studied off acid suppression medications (proton pump inhibitors for 2 weeks, H2 blockers for 2 days). The patients were instructed to carry out their usual daily activities and to use a diary to document the time of their meals, symptoms experienced, and time spent in the upright and supine positions. Patients were classified as having increased esophageal acid exposure if the composite DeMeester score was greater than 14.7.[15]

Ambulatory 24-Hour Bile Monitoring

Esophageal bile exposure was measured using the Bilitec 2000 (Medtronic Inc.). The Bilitec 2000 is a spectrophotometric device that measures bilirubin exposure based on its light absorption properties at a wavelength of 453 nm, as a surrogate marker for bile.[11] The catheter was passed transnasally and positioned 5 cm above the upper border of the manometrically determined LES. Patients were instructed to follow a special diet, previously described, to prevent interference with the spectrophotometer.[12] Data was stored in a portable data logger and downloaded to a computer for analysis with standard software (Esophogram 5.7, Medtronic Inc.). Increased bile exposure in the distal esophagus was defined as bilirubin absorbance greater than 0.2 for more than 1.7% of the total time of the 24-hour test period.[14]

Upper Endoscopy with Biopsies

All patients underwent upper gastrointestinal endoscopy under conscious sedation. The locations of the crural impression, the gastroesophageal junction, and the squamocolumnar junction were determined. The distance between the diaphragmatic crural impression and the gastroesophageal junction, defined by the top of the gastric rugal folds, was used to define the size of a hiatal hernia when present.

Endoscopic mucosal injury was defined by the presence of erosive esophagitis or Barrett's esophagus. The latter condition was identified by the presence of a visible columnar segment of any length that contained specialized intestinal metaplasia in cardiac mucosa on biopsy.[16] The presence of specialized intestinal metaplasia in cardiac mucosa from a normal appearing gastroesophageal (GEJ) (cardia intestinal metaplasia) was not considered to be Barrett's esophagus.

In patients who were endoscopically normal, the squamous epithelium was biopsied within 3 cm of the squamocolumnar junction. Histologic injury was defined as the presence of inflammatory cells (neutrophils and/or eosinophils). In 13 endoscopically normal patients, biopsies were not obtained.

Esophageal Manometry

Esophageal manometry was performed after an overnight fast by using an 8-channel water-perfused catheter inserted through the anesthetized nostril. Data was acquired using commercially available software (Polygram, Medtronic Inc.). A stationary pull-through procedure was performed to assess the LES by measuring its total length, abdominal length,

and the resting pressure at the midrespiratory inversion point.[17] The esophageal body was assessed by having the patient take 10 swallows of 5 ml of water, with the catheter positioned so that the proximal channel was 1 cm below the upper esophageal sphincter. Measurements from individual patients were compared with normal values obtained in a previously published series of 50 asymptomatic volunteers (total length ⩾2.0 cm, abdominal length ⩾1.0 cm, resting pressure 6–26 mm Hg, and distal esophageal contraction amplitudes 30–180 mm Hg).[18]

Statistical Analysis

Continuous variables were compared using the Kruskal-Wallis test, and the Mann-Whitney *U* test was used to identify differences between individual groups. The chi-square test was used to compare proportions among multiple groups, and the Fisher exact test was used to identify differences between individual groups. Statistical significance was defined by a *P* value of 0.05. All results are reported as median (IQR) unless otherwise noted.

RESULTS

Of the 402 patients studied, 129 (32%) had normal esophageal acid and bile exposure. Of the 273 who had increased esophageal exposure to acid and/or bile, more than half (154, 56.4%) had increased exposure to a mixture of acid and bile, whereas only 82 (30.0%) had increased esophageal exposure to acid alone and 37 (13.6%) to bile alone. Demographic data of patients are shown in Table 1.

Relationship of Reflux Composition to Mucosal Injury

Patients with increased esophageal exposure to a mixture of acid and bile had the highest prevalence of endoscopic mucosal injury ($P < 0.0001$ vs. all groups; Fig. 1). The prevalence of esophagitis was similar with increased esophageal exposure to acid or a mixture of acid and bile (22% vs. 27% respectively, $P = 0.43$), whereas the prevalence of Barrett's esophagus was greater with a mixture of acid and bile ($P \leqslant 0.0007$ vs. all groups).

The risk for erosive esophagitis and Barrett's esophagus for specific reflux compositions is detailed in Table 2. Compared with increased exposure to acid alone, the exposure to a mixture of acid and bile did not change the risk for esophagitis (OR 1.2; 95% CI, 0.8–2.0; $P = 0.43$) but tripled the risk for Barrett's esophagus (OR 3.0; 95% CI, 1.3–3.8; $P = 0.0007$).

One hundred twenty-two patients were endoscopically normal and were assessed for histological injury of their mucosa by biopsy of their squamous epithelium within 3 cm of the squamocolumnar junction. Of these patients, 27 had increased bile exposure, 45 had increased acid exposure, and 50 had increased exposure to both bile and acid. Biopsies showed histological evidence of inflammatory injury in 44 of the 122 patients (36%). Histological injury was most commonly associated with increased exposure to a combination of acid and bile (46%), followed by acid alone (33%), and bile alone (22%).

Relationship of Reflux Composition to Esophageal Shortening

The effect of reflux composition on esophageal shortening, another indicator of inflammatory esophageal injury, was assessed by measuring the distance between the diaphragmatic crura and the gastroesophageal junction identified by the proximal extent of the gastric rugal folds at endoscopy (Fig. 2). Increased bile exposure alone did not result in esophageal shortening, whereas exposure to acid alone significantly shortened the esophagus ($P \leqslant 0.005$), with the greatest shortening occurring with exposure to a mixture of acid and bile ($P \leqslant 0.036$ vs. all other groups).

Relationship of Reflux Composition to Esophageal Function

The relationship of reflux composition to the components of the LES is shown in Fig. 3, *A–C*. Increased exposure to acid and bile was associated with the greatest reduction in LES pressure, overall

Table 1. Patient characteristics

	All patients	Normal acid+bile	Increased bile only	Increased acid only	Increased acid+bile
Number	402	129	37	82	154
M:F ratio	60:40	50:50	38:62	65:35	73:27
Age	52.0 (42–63)	51.0 (40.5–63)	49.0 (42.5–64)	52.5 (40.5–65.5)	53 (43–62)

M = male; F = female.

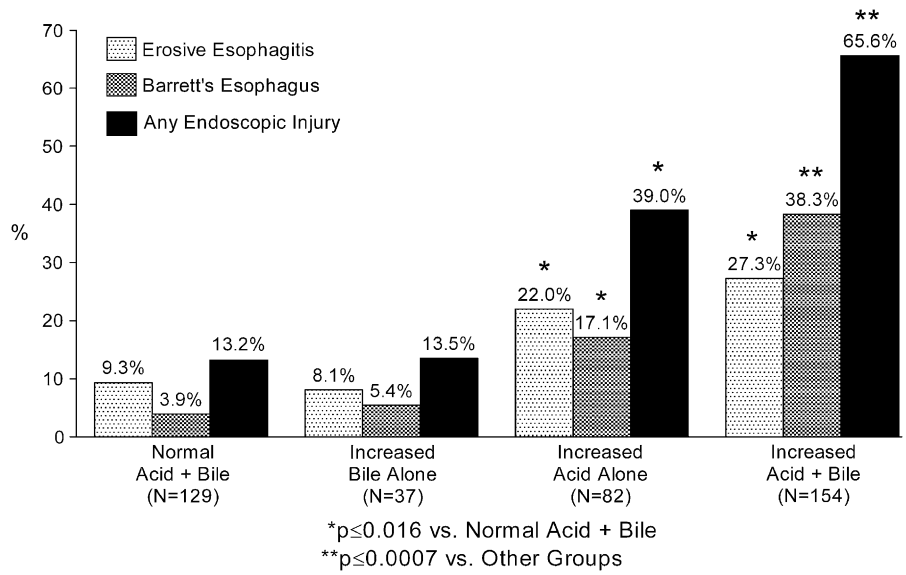

Fig. 1. Prevalence of erosive esophagitis, Barrett's esophagus, and endoscopic mucosal injury in patients with normal esophageal exposure to acid and bile and those with increased exposure to bile, acid, or both on 24-hour monitoring.

length, and abdominal length, followed by acid alone. Increased bile exposure had no effect. The relationship of reflux composition to distal esophageal contraction amplitude is shown in Fig. 3, *D*. Again, similar to the LES, increased exposure to acid or to a mixture of acid and bile was associated with significantly lower contraction amplitudes.

The risk for deterioration of the individual LES components and the presence of an overall defective LES for specific reflux compositions are shown in Table 3. A defective LES was three times more likely in patients with increased acid exposure and five times more likely with an increased exposure to a mixture of acid and bile.

Relationship of Mucosal Injury to Esophageal Function in Patients With Increased Esophageal Exposure to Acid and/or Bile

Mucosal injury was associated with functional deterioration of all LES components (Fig. 4). Endoscopic mucosal injury compared with histologic mucosal injury was associated with a greater deterioration of the LES pressure. Surprisingly, histologic mucosal injury had a similar effect on LES overall and abdominal lengths, as did endoscopic mucosal injury. A decrease in esophageal body contractility was seen only with endoscopic mucosal injury.

A pertinent observation is that histologic mucosal injury was associated with a similar prevalence of a defective LES as endoscopic mucosal injury (35/44 [79.5%] vs. 118/138 [85.5%], respectively; $P = 0.35$). Further, the prevalence of a defective LES was independent of the type of endoscopic mucosal injury (erosive esophagitis 54/63 [85.7%]) vs. Barrett's esophagus 64/75 [85.3%], $P = 1.0$).

DISCUSSION

This study shows that only 68% of patients with symptoms suggestive of GERD have an increased esophageal exposure to acid and/or bile. In the remaining 32% who have normal acid and bile

Table 2. Prevalence of mucosal injury and respective odds ratios by reflux composition

	Endoscopic esophagitis	OR (95% CI)	Barrett's esophagus	OR (95% CI)
Normal acid+bile	12/129 (9.3%)	—	5/129 (3.9%)	—
Increased bile only	3/37 (8.1%)	0.8 (0.2–3.1) $P = 1.0$	2/37 (5.4%)	1.4 (0.3–7.6) $P = 0.6$
Increased acid only	18/82 (22.0%)	2.7 (1.2–6.1) $P = 0.01$	14/82 (17.1%)	5.1 (1.7–11.8) $P = 0.002$
Increased acid+bile	42/154 (27.3%)	3.7 (1.8–7.3) $P = 0.0001$	59/154 (38.3%)	15.4 (6.0–39.9) $P < 0.0001$

Odds ratios were calculated using patients with normal esophageal exposure to acid and bite as the baseline group, and *P* values reflect comparison with these patients. OR = odds ratio; CI = confidence interval.

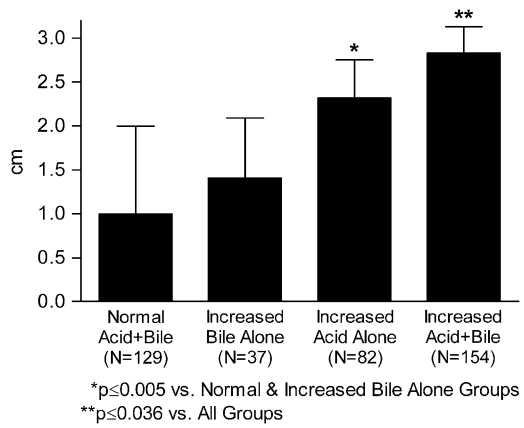

Fig. 2. Distance from the crural impression to the gastroesophageal junction (as defined by the proximal extent of the gastric rugal folds) determined at endoscopy in patients with normal esophageal exposure to acid and bile and those with increased exposure to bile, acid, or both on 24-hour monitoring. Bars represent median values, lines represent the upper quartile.

exposure, there are likely to be daily variations in the degree of exposure or increased exposure only during periods when the sphincter is challenged, such as after a meal. In the latter situation, the degree of exposure during the postprandial period is not sufficient to make the exposure over the 24-hour period abnormal. When there is increased esophageal exposure, the most common composition of gastric juice refluxed is a mixture of acid and bile. To date, this high prevalence of mixed reflux has not been appreciated, and the finding draws attention to the effect of bile on the pathophysiology of reflux disease. Further, the finding questions the exclusive focus of medical therapy on the control of gastric acid output. Our observation that increased esophageal exposure to a mixture of acid and bile is associated strongly with erosive esophagitis, Barrett's esophagus, and esophageal shortening emphasizes that the composition of the gastric juice refluxed has a major influence on the natural history of GERD.

The control of mucosal injury is an important goal in the management of patients with GERD. Injury is most commonly defined by the endoscopic evidence of erosive esophagitis or Barrett's esophagus. Our findings indicate that increased exposure to acid alone, or a mixture of acid and bile, is associated with a high prevalence of both types of mucosal injury. Patients with an increased esophageal exposure to acid alone or a mixture of acid and bile had a similar risk for erosive esophagitis. In contrast, an increased exposure to a mixture of acid and bile had a three times greater risk for Barrett's metaplasia than acid alone. This finding emphasizes the profound influence of bile when mixed with acid in the pathogenesis of Barrett's metaplasia.

Further, the composition of the refluxed gastric juice was associated with deterioration in esophageal function. Increased esophageal exposure to acid alone or acid and bile was associated with a significant reduction in the resting pressure, overall length, and abdominal length of the LES, and a reduction in the contraction amplitude of the esophageal body. The alterations in the LES were most severe with increased exposure to a mixture of acid and bile.

More than a third of patients without endoscopic evidence of injury had histological evidence of injury in the form of an intraepithelial inflammatory infiltrate. The association between reflux composition and histologic injury parallels that observed for endoscopic injury. Further, histologic injury was associated with a deterioration of LES function as with endoscopic mucosal injury. This finding indicates that for complete evaluation of patients with suspected GERD and no evidence of endoscopic injury, the squamous mucosa near the gastroesophageal junction should be biopsied.

In the practice of gastroenterology, it is accepted that endoscopic evidence of healing is the end point of successful medical therapy. Our results question this practice. We have shown that esophageal function can be destroyed even when the esophageal mucosa seems normal on endoscopy. When patients without evidence of injury on endoscopy are biopsied, over one third will have evidence of inflammation on histology, and of these, 80% will have a significant loss of LES resting pressure, overall length, and/or abdominal length. The prevalence of functional deterioration does not increase when mucosal injury can be seen on endoscopy; 85% of such patients in our study also had a defective LES. Consequently, the presence and not the degree of inflammatory injury, that is, histologic or endoscopic, seems to be the important factor related to functional deterioration. This finding implies that the focus of successful therapy for GERD should be resolution of inflammation at the cellular level. This requires that the effectiveness of therapy be assessed not only by endoscopic appearance, but histologically with biopsies of the distal esophagus.

The association of the loss of esophageal function with both the composition of the gastric juice refluxed and mucosal injury raises the question as to which event is primary. In animal studies, the loss of function has been shown to be a direct consequence of inflammatory injury.[19–22] In these studies, esophageal exposure to acid and bile resulted in a mucosal inflammatory reaction that extended into the muscularis propria, resulting in decreased muscle

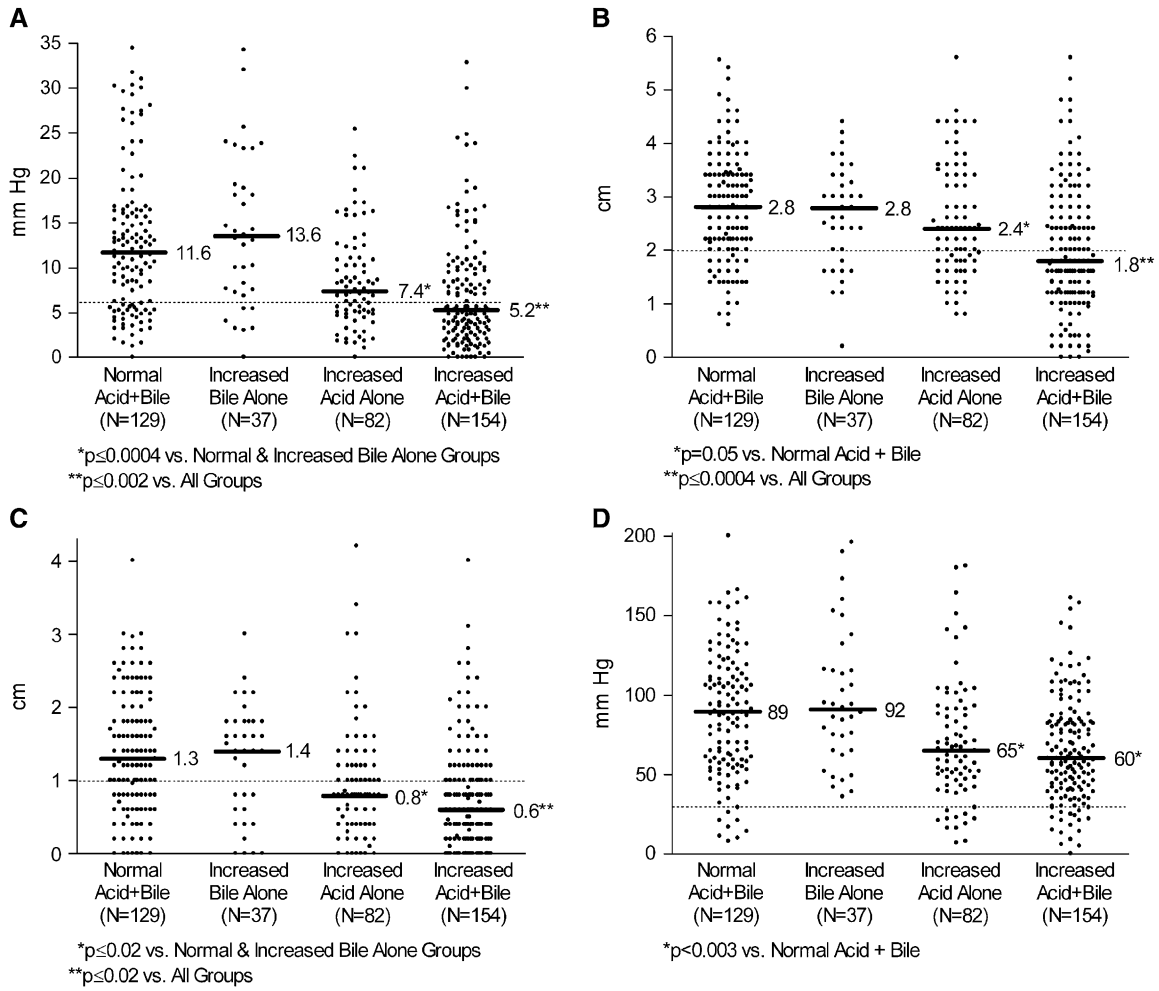

Fig. 3. LES characteristics and distal esophageal contraction amplitude in patients with normal esophageal exposure to acid and bile and those with increased exposure to bile, acid, or both on 24-hour monitoring. (**A**) Pressure of the LES. (**B**) Overall length of the LES. (**C**) Abdominal length of the LES. (**D**) Contraction amplitude of the distal esophageal body. The solid line represents the median value. The dashed line is the fifth percentile of normal, based on a study of 50 normal volunteer subjects.[18]

tone, contraction amplitude, and esophageal shortening. These observations imply that the primary event is the increased esophageal exposure to gastric juice. Based on our studies, the most potent composition is a mixture of acid and bile. The composition of gastric juice is determined by the degree of duodenogastric reflux.[23–25] Patients with GERD have been shown to have a higher concentration of bile acids in their gastric juice, accounting for the high prevalence of esophageal exposure to a mixture of acid and bile observed in our study.[26] A vicious cycle occurs when inflammatory injury causes a loss of the esophageal barrier, leading to greater esophageal exposure to gastric juice and more inflammation. Consequently, patients who reflux the most noxious composition, a mixture of acid and bile, should be treated more aggressively.

An alternative explanation is that functional deterioration is the primary event that allows increased esophageal exposure to gastric juice, resulting in inflammatory injury. This explanation is unlikely; in our observations, functional deterioration is uncommon in the absence of endoscopic or histologic mucosal injury, and is very common in the presence of injury. Further, if functional deterioration were the primary event, it becomes difficult to explain the observation that inflammatory injury can occur in the absence of functional deterioration. The most consistent explanation of the data is that inflammatory injury precedes functional deterioration.

The observation that increased esophageal exposure to bile alone is not associated with mucosal injury is likely explained by the chemical properties of bile acids.[27] At a pH above their pKa (≥6), bile acids

Table 3. Prevalence of abnormal lower esophageal sphincter components and respective odds ratios by reflux composition

	Abnormal overall length	OR (95% CI)	Abnormal abdominal length	OR (95% CI)	Abnormal resting pressure	OR (95% CI)	Defective LES	OR (95% CI)
Normal acid+bile	25/129 (19.4%)	—	41/129 (31.8%)	—	33/129 (25.6%)	—	58/129 (45.0%)	—
Increased bile only	9/37 (24.3%)	1.3 (0.6–3.2) $P = 0.5$	13/37 (35.1%)	1.2 (0.5–2.5) $P = 0.69$	7/37 (18.9%)	0.7 (0.3–1.7) $P = 0.51$	15/37 (40.5%)	0.8 (0.4–1.8) $P = 0.71$
Increased acid only	28/82 (34.1%)	2.2 (1.1–4.1) $P = 0.02$	44/82 (53.7%)	2.5 (1.4–4.4) $P = 0.002$	30/82 (36.6%)	1.7 (0.9–3.1) $P = 0.09$	60/82 (73.2%)	3.3 (1.8–6.1) $P < 0.0001$
Increased acid+bile	84/154 (54.5%)	5.0 (2.9–8.6) $P < 0.0001$	101/154 (65.6%)	4.1 (2.5–6.7) $P < 0.0001$	91/154 (59.1%)	4.2 (2.5–7.0) $P < 0.0001$	124/154 (80.5%)	5.1 (3.0–8.6) $P < 0.0001$

Odds ratios were calculated using patients with normal esophageal exposure to acid and bile as the baseline group. A defective LES was defined as an abnormality in at least one parameter of LES function: overall length, abdominal length, or resting pressure. OR = odds ratio; CI = confidence interval; LES = lower esophageal sphincter.

dissociate to hydrogen ions and bile salts that are unable to penetrate the cell membrane due to their polarity.[28] In a weak acid environment where the pH range is between 3 and 5, significant quantities of bile acids exist in the un-ionized, nonpolar form and can traverse the cell membrane, leading to cellular injury by the induction of reactive oxygen species and direct DNA damage.[29–32] In a strong acid environment where the pH level is less than 3, bile acids precipitate out of solution, resulting in esophageal exposure to only acid.[27] This chemical property likely explains the observation that increased esophageal exposure to bile alone at a pH ⩾6 is innocuous, but in a weak acid environment (pH 3–5), injury is severe.[13,33] The importance of an acid environment on the effect of bile was demonstrated by Ireland et al.[34] using a rat reflux model. In this study, surgically induced bile reflux was combined with various acid environments by altering the degree of gastrectomy. Bile in a mildly acid environment led to increased columnarization of the esophagus and the development of adenocarcinoma. In a strong acid environment, the development of columnar mucosa and adenocarcinoma was less common. These findings suggested that strong acid conditions protected the esophagus by causing the precipitation of bile acids.

It is tempting to conclude that high doses of acid suppression medication can raise the pH environment to a level at which bile acids are completely dissociated and protect the patient from injury. Based on the physical-chemical properties of bile acids, this would require that the pH be consistently maintained at a level ⩾6. The efficacy of antisecretory medications in clinical trials has shown that this is an extremely difficult goal to achieve.[35] In a randomized study that examined the efficacy of proton pump inhibitors, pH monitoring showed that gastric pH was maintained above 4 for only about half of the day (48%–63%), depending on the dose.[36] The end point of a pH greater than 4 is well below the pH of 6–7 required for complete bile acid dissociation. Further studies have shown that control of gastric pH is inconsistent, even with the newer and more potent acid suppression medications.[35] Of concern is that proton pump inhibitor therapy can relieve symptoms while allowing the reflux of weak acid and bile with the potential for ongoing tissue injury.[37] Indeed, studies have confirmed that proton pump inhibitors merely change the pH of the refluxed gastric juice but do not reduce reflux itself.[38]

A more physiological approach to the treatment of GERD is to surgically reestablish the gastroesophageal barrier and restore the esophageal luminal pH environment to its normal state. It has been

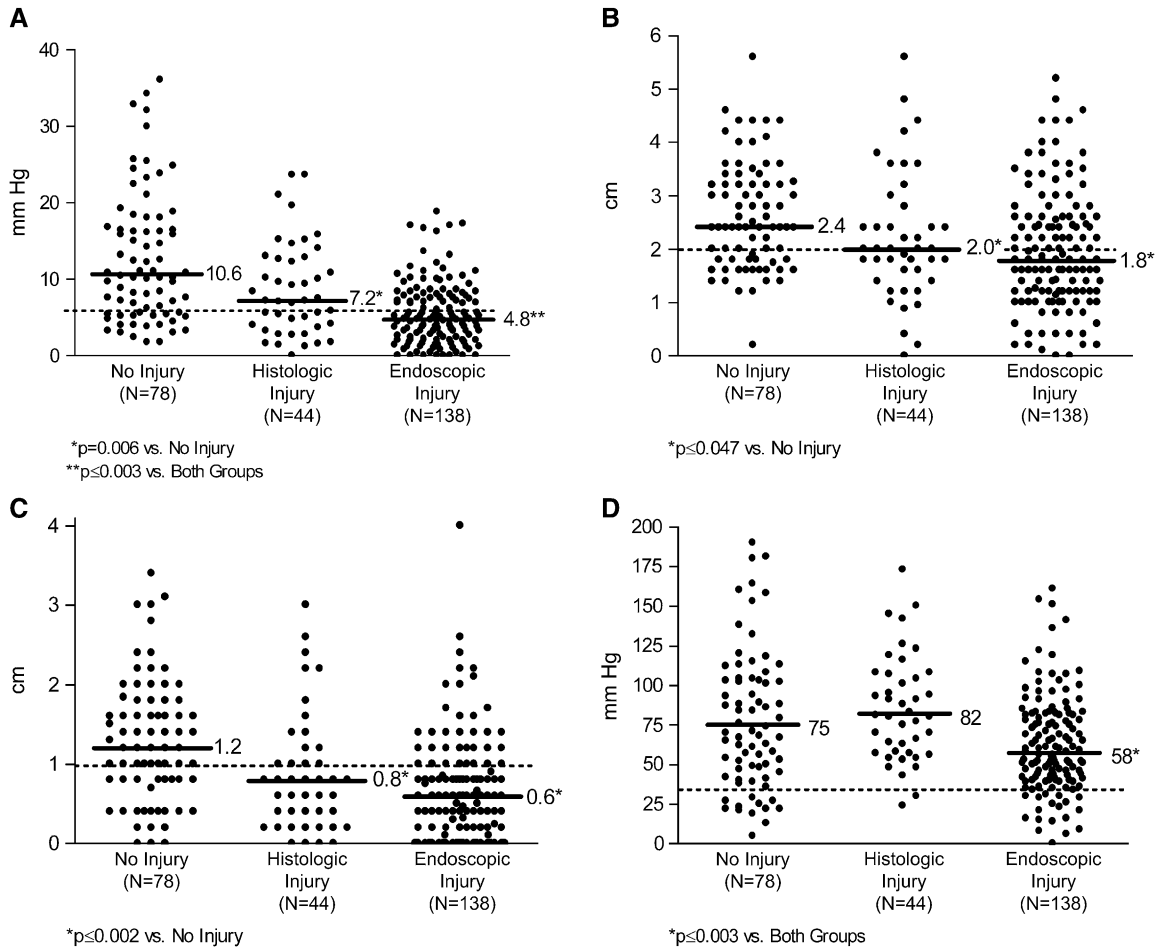

Fig. 4. LES characteristics and distal esophageal contraction amplitudes in patients with normal endoscopy and histology, histologic mucosal inflammatory injury, or endoscopic mucosal injury. All patients had increased esophageal exposure to acid and/or bile. (**A**) Pressure of the LES. (**B**) Overall length of the LES. (**C**) Abdominal length of the LES. (**D**) Contraction amplitude of the distal esophageal body. The solid line represents the median value. The dashed line indicates the fifth percentile level of normal, based on a study of 50 normal volunteer subjects.[18]

shown repeatedly that an effective Nissen fundoplication prevents the reflux of all gastric juice, regardless of its composition.[39] A comparison between medical and surgical therapy demonstrated that proton pump inhibitors could not match the results of laparoscopic Nissen fundoplication in normalizing esophageal exposure to both acid and bile.[40] Protection of the esophageal mucosa by a Nissen fundoplication prevents injury and maintains, or to some degree, improves esophageal function.[41–44]

CONCLUSION

Increased esophageal exposure to a mixture of acid and bile is the predominant composition of reflux in patients with GERD. This mixed reflux is associated with the greatest degree of mucosal injury by both endoscopic and histologic criteria. Increased esophageal exposure to a combination of acid and bile also results in the highest degree of functional loss. The common association of functional loss with mucosal injury, and the unlikelihood of functional loss in the absence of mucosal injury, suggests that the loss is due to the consequence of inflammatory injury. The frequent finding of functional deterioration in patients with a normal esophagus on endoscopy but with histologic evidence of inflammation calls into question the use of endoscopic healing of esophagitis as the end point in managing GERD. It is difficult for acid suppression therapy to adequately control mixed acid and bile reflux. In contrast, surgical reconstruction of the gastroesophageal barrier prevents all forms of reflux and is

encouraged for the therapy of mixed bile and acid reflux.

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Discussion

Dr. Keith Lillemoe (Indianapolis, IN) : I would like to thank the authors for providing me with the manuscript and the opportunity to discuss the paper, and acknowledge that Dr. DeMeester is one of the few people in the room that knows that I ever did anything with the esophagus, and so that is why he asked me, I think.

This is an interesting study and it does my heart good to see you now have the technology to confirm some of the things that Barbara Bass and I looked at well over 20 years ago in John Harmon's laboratory, that the combination of bile acids and acid is the worst combination of bile up into the esophagus, and clearly, there has got to be more than our standard belief that this is all a lower esophageal sphincter abnormality that is leading to his. So, I would like to ask you to hypothesize a little bit about how you think the bile gets up there, and what mechanism actually leads to this taking place. Clearly, some of the findings that you have seen are somewhat of a chicken and egg process; is it the loss of motility factors secondary to the inflammation? It would appear from the results that you have shown, but again, does that contribute at all to the bile reaching the esophagus and causing the damage?

And probably the most interesting question is what you had on your conclusion, and that relates to what are we doing to these patients by treating them with acid suppression along? And is this why we are seeing, despite adequate treatment of symptoms or even patients who are asymptomatic going on to develop Barrett's esophagus, Barrett's cancer in the face of what would appear not to be an acid-related problem, and perhaps is it silent reflux of bile acids that is really the damaging agent, which would certainly fit in some of the things that we see, choledochocysts?

The malignancies associated with choledochocysts are thought to be the reflux of contents, a mixture of pancreatic juice and bile in those cysts, and is the perhaps the problem? So, again, maybe you could hypothesize a little bit on the mechanism of where we are seeing the Barrett's develop.

It is a very nice paper.

Dr. Oh: Your first question on why bile gets into the stomach and up into the esophagus is an interesting one. Unfortunately, not many studies have been performed looking at this phenomenon.

Doing a literature search for our paper, I could find only a handful of papers looking at this problem. We do know from a paper from the Mayo Clinic published in *Gastroenterolgoy* in the early '80s looking at this issue in normal volunteers [Keane KB, DiMagno EP, Malagelada JR. Gastroenterology 1981;81:726–731], that there is duodenal dysmotility, random dysmotility, and they hypothesize that these conditions set the stage for duodeno-gastric reflux, thereby exposing, or having the potential to expose, the lower esophageal sphincter to these components. But again, not many studies have been looking into this.

Dr. Kauer has looked at aspiration studies in normal volunteers looking at bile, and they have documented exposure of the normal esophagus, in volunteers, to bile acids [Kauer WK, Peters JH, DeMeester TR, et al. Surgery 1997; 122: 87–881]. So, it is just the degree of the concentration and exposure present in these reflux patients that differs from a physiologic phenomenon.

Secondly, regarding whether it is a chicken or egg issue, that is the timeless question. I think we can take a lot of the work that was done in animal models by you and Dr. Bass and worked on at Walter Reed Army Hospital in the early '80s, and we can kind of put it in perspective with our clinical observations. We know that if you perfuse an animal esophagus with acid or bile, or a combination, you do get functional loss. This was shown by Dr. Shirazi as well as by Dr. Paterson in Canada. The researchers at Walter Reed have shown that a combination of bile and acid are the most harmful.

The question of what the mechanism by which this occurs is interesting. The hypothesis currently is that in order for bile acids to be harmful, it is based on the pH of the environment in which the bile acid exists relative to the pKa of that specific bile acid. We know that when the pH is elevated above the pKa, bile acids are ionized and can't cross the phospholipid membrane to injure cells. At a pH greatly below their pKa, they precipitate out of solution. So, there is a pH range around their pKa whereby bile acids are in solution and unionized, and it is thought that these bile acids are then able to cause cellular injury. There is evidence that bile acids are mutagenic and they induce reactive oxygen species.

Finally, your questions on PPI's effects, I think, directly tie into this. We are converting strong acid conditions into a weak acid environment, a pH of 3 to 5, allowing the presence of these soluble unionized bile acids to do their harmful effect.

Dr. John Hunter (Portland, OR): I was very interested in your motor findings in those who were endoscopically normal. It is hard to find people who haven't been treated with PPI, and therefore may have healed before you had a chance to endoscope them. Did you endoscope any people and find the normal endoscopy, abnormal motility in patients who had never been on PPIs?

Dr. Oh: Almost all of the patients who are in our study had been referred from outside institutions, so they all had a history of prior use of PPIs or some kind of antisecretory agent. However, all of the patients were off PPIs for 2 weeks prior to being evaluated, and off H2 blockers for 2 days. So these findings on histology are in the absence of active antisecretory agents.

Self-Expanding Metallic Stent as a Bridge to Surgery Versus Emergency Resection for Obstructing Left-Sided Colorectal Cancer: A Case-Matched Study

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This study aimed to compare the outcomes of patients who suffered from obstructing left-sided colorectal cancer, treated with self-expanding metallic stent (SEMS) as a bridge to surgery, with those who underwent emergency operation. Twenty patients who had acute obstruction due to left-sided colorectal cancer underwent surgical resection after insertion of SEMS (group I) were matched to 40 patients with emergency colonic resection (group II). The two groups were compared for the incidence of primary anastomosis, stoma rate, hospital stay, duration of intensive care, postoperative morbidity, and mortality. Both groups had similar preoperative comorbidity and stage of disease, but the tumors in group I were more distally located ($P < 0.001$). In group I, one patient developed colon perforation and required Hartmann's operation. All the other patients underwent elective operation with primary anastomosis. In group II, primary anastomosis was performed in 29 patients (72.5%; $P = 0.047$). The operative mortality of group I and group II was 5% and 12.5%, respectively ($P = 0.653$). Significantly shorter median postoperative hospital stay and median stay in the intensive care unit (ICU) were observed in group I (9 days [range, 5–39 days] vs. 12 days [range, 8–49 days], $P = 0.015$ and 0 day [range, 0–17 days] vs. 0.5 day [range, 0–18 days], $P = 0.022$, respectively). There were no differences in hospital mortality ($P = 0.653$) or 30-day mortality ($P = 0.653$). Both groups had similar reoperation rates, surgical complications, and medical complications. When compared with emergency resection, insertion of SEMS as a bridge to surgery for obstructing left-sided colorectal cancer is associated with a higher rate of primary anastomosis as well as a better outcome in terms of hospital stay and stay in the ICU. The wider application of this treatment option for obstructing colorectal cancer warranted further studies. (J GASTROINTEST SURG 2006;10:798–803)

KEY WORDS: Colorectal cancer, metallic stent

Colorectal carcinoma is one of the most common malignancies in developed countries. Acute obstruction is the initial presentation in 10%–30% of patients who suffer from colorectal cancer,[1–4] and 70% of all malignant large bowel obstruction occurs in the left-sided colon.[3,5,6] Emergency colorectal surgery for acute obstruction is associated with a mortality rate of 15%–20% and a morbidity rate of 40%–50%,[7,8] which are much higher when compared with resection on an elective setting with optimal bowel preparation. Moreover, there is no consensus as to the management of left-sided colonic obstruction. Although primary resection and primary anastomosis has been recommended by some authors,[9–11] it is still regarded as a risky procedure by most general surgeons.

Dohmoto[12] first described the use of a metallic stent as a palliative treatment for obstructive carcinoma of the rectum in 1991; since then, the self-expanding metallic stent (SEMS) has become an option in the management of left-sided colonic obstruction. Its role in the palliation of large bowel obstruction in the presence of advanced local or distant disease has been widely accepted.[13,14] As a temporary measure to relieve the bowel obstruction, it has been shown that operations could be performed on an elective

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setting with adequate bowel preparation.[13,15,16] The surgical outcome of using SEMS as a bridge to surgery compared with emergency resection has rarely been assessed. We conducted this case-matched study to compare the outcomes of patients who were treated with SEMS as a bridge to surgery with those who underwent emergency resection.

METHODS

During the study period, from February 1998 to May 2004, 20 patients who suffered from acute obstruction due to left-sided colorectal cancers (distal to the splenic flexure) were treated initially with the insertion of SEMS and were planned to undergo elective resection (group I). All the patients had clinical and radiological evidence of acute colonic obstruction. Insertion of SEMS was performed as an urgent procedure, and the details of the placement of the SEMS were described in our previous publication.[15] The insertion was performed under endoscopic and fluoroscopic guidance, and Enteral Wallstent (Boston Scientific Corporation, Natick, MA) was used in the majority of the patients. The success of the procedure was documented by the return of bowel movement as well as radiological evidence of resolution of the obstruction. Surgery was then scheduled on an elective setting after adequate optimization of the medical conditions.

The patient received mechanical bowel preparation with polyethylene glycol solution the day before surgery. Prophylactic antibiotics were administrated at the induction of anesthesia. Operation was performed by a midline laparotomy in the early stage of the study. Resection of the tumor-bearing segment, which contained the stent across the obstructing tumor, was performed and primary anastomosis was constructed. In case of a mid and distal rectal cancer, total mesorectal excision was performed and diversion stoma was constructed if the anastomosis was within 5 cm from the anal verge. From 2001, some patients underwent laparoscopically assisted colectomy after the insertion of the stent. The extent of resection was similar to an open procedure. All the operations in group I and group II were performed or supervised by colorectal surgeons who were capable of performing primary resection and anastomosis for left-sided colonic obstruction.

Patients in the treatment group (group I) were matched for age, gender, year of operation, and duration of obstruction to those who underwent emergency resection for left-sided colonic cancer (group II) in a ratio of 1:2. The operations were performed by colorectal specialists, and primary resection with primary anastomosis was performed if the condition of the patient was stable and the condition of the bowel was healthy.

Data on the patients' demographics, operative details, and postoperative outcomes were collected prospectively. The assessment of the American Society of Anesthesiologist class was performed before the operations. The two groups were compared for the incidence of primary anastomosis, incidence of stoma creation, postoperative hospital stay and length of stay in the intensive care unit (ICU), postoperative morbidity, and mortality. Hospital mortality was defined as death that occurred during the same admission.

Continuous variables were expressed as median values with range and were evaluated with the Mann-Whitney U test. The χ^2 test with Yates' correction or the Fisher exact test was used for nominal variables when appropriate. A two-sided P value of less than 0.05 was considered statistically significant.

RESULTS

The demographics of the patients, concomitant medical conditions, the American Society of Anesthesiology (ASA) class, the location, and the stage of the cancer are shown in Table 1. Those patients who underwent insertion of SEMS as a bridge of surgery had the tumors more distally located, and half of the tumors were at the rectum or rectosigmoid junction. There was a tendency of lower ASA class in patients in group I, although this did not reach statistical significance. Other parameters were similar in the two groups.

The types of operations are shown in Table 2. In group I, one patient underwent emergency Hartmann's operation because of colonic perforation after insertion of the SEMS. All the other patients could be treated with primary anastomosis after resection of the tumor. Six patients who suffered from rectal cancer required proximal diversion because they underwent total mesorectal excision with a low rectal anastomosis (below 5 cm from the anal verge). The resections were performed either by laparotomy (n = 13, including the patient with emergency Hartmann's operation) or laparoscopy (n = 7). In those with laparoscopic resection, one required conversion, whereas the other six patients had successful laparoscopic procedures.

Twenty-nine of the 40 (72.5%) patients in the control group (group II) underwent primary anastomosis after primary resection. The rate of primary anastomosis was significantly lower in group II (P = 0.047). Three patients in group II required proximal diversion (7.5%), whereas 11 had an end stoma (27.5%). There was no statistical difference in

Table 1. Patients' demographic data and tumor characteristics

	Group I (n = 20)	Group II (n = 40)	*P*
Median (range) age (years)	74 (45–88)	73.5 (38–88)	0.919
Sex ratio (M:F)	17:3	29:11	0.347
Median duration (range) of obstruction (days)	1.0 (0–7)	1.0 (0–6)	0.197
Cardiac (%)	6 (30)	16 (40)	0.573
Respiratory (%)	1 (5)	3 (7.5)	1.0
Diabetes (%)	1 (5)	9 (22.5)	0.142
Neurological (%)	1 (5)	3 (7.5)	1.0
ASA (%)			0.068
I	4 (20)	6 (15)	
II	13 (65)	16 (40)	
III	3 (15)	18 (45)	
Site of tumor (%)			<0.001
Descending colon	3 (15)	12 (30)	
Sigmoid colon	7 (35)	28 (70)	
Rectosigmoid junction	3 (15)	0 (0)	
Rectum	7 (35)	0 (0)	
Stage (UICC/AJCC) (%)			0.415
II	5 (25)	15 (37.5)	
III	10 (50)	16 (40)	
IV	5 (25)	9 (22.5)	

AJCC = American Joint Committee on Cancer; UICC = Union Internationale Contre le Cancer.

stoma rate; however, significantly more patients in group II were treated with an end stoma ($P = 0.047$).

One patient in group I and five patients in group II died after the operation, and the operative mortality was 5% and 12.5%, respectively. The patient in group I died of multiorgan failure after a reoperation for a bleeding duodenal ulcer that developed 7 days after a laparoscopically assisted left hemicolectomy. In group II, three patients without anastomosis and two with primary anastomosis died after the operation. The causes of postoperative mortality were pneumonia (n = 2), heart failure (n = 1), pulmonary embolism (n = 1), and sepsis due to anastomotic leakage (n = 1).

Four patients in group I (20%) required postoperative stay in the ICU for a total of 22 days, whereas 20 patients (50%) in group II who underwent emergency operation spent a total of 108 days in the ICU. Patients having surgery after insertion of SEMS stayed for a median of 9 days (range, 5–39 days), whereas the median length of hospital stay of patients in group II was 12 days (range, 8–49 days; $P = 0.015$).

The overall complication rate was lower in group I, although it did not reach statistical significance (Table 3). There was no anastomotic leakage in patients in group I, whereas three patients developed anastomotic leakage and required reoperation in group II. Significantly fewer medical complications, however, occurred in patients after insertion of SEMS (Table 3).

Table 2. Types of operations

	Group I (n = 20)	Group II (n = 40)
With primary anastomosis		
Left hemicolectomy	3	2
Sigmoid colectomy	1	7
Anterior resection	8	3
Low anterior resection	7	0
Subtotal colectomy	0	17
Total (%)	19 (95)	29 (72.5)
Without anastomosis		
Hartmann's operation	1	7
Subtotal colectomy with ileostomy	0	2
Colectomy with colostomy & mucous fistula	0	2
Total (%)	1 (5)	11 (27.5)

DISCUSSION

Although intestinal obstruction is the initial presentation in up to 30% of patients with colorectal cancer,[1–3] there is no consensus regarding management of left-sided colonic obstruction. The conventional three-stage operation is seldom performed at the present time, and primary resection is accepted as the standard treatment.[17,18] However, the operative mortality and morbidity after Hartmann's operation and subsequent closure of colostomy have

Table 3. Outcomes of treatment

	Group I (n = 20)	Group II (n = 40)	*P*
Type of stoma (%)			
Diversion stoma	6 (30)	3 (7.5)	
End stoma	1 (5)	11 (27.5)	
Total	7 (35)	14 (35)	1.0
Primary anastomosis (%)	19 (95)	29 (72.5)	0.047
Patients required ICU care (%)	4 (20)	20 (50)	0.025
Median (range) ICU stay (days)	0 (0–17)	0.5 (0–18)	0.022
Median (range) hospital stay (days)	9 (5–39)	12 (8–49)	0.015
Hospital mortality (%)	1 (5)	5 (12.5)	0.653
Re-operation (%)	1 (5)	4 (10)	0.656
Overall complication (%)	6 (22)	22 (55)	0.067
Medical complication (%)	2 (10)	14 (35)	0.039
Cardiac (%)	0 (0)	5 (12.5)	0.159
Respiratory (%)	2 (10)	8 (20)	0.471
Renal (%)	0 (0)	1 (2.5)	1.0
Deep vein thrombosis (%)	0 (0)	1 (2.5)	1.0
Surgical complication (%)	1 (5)	7 (17.5)	0.179
Anastomotic leakage (%)	0 (0)	3 (7.5)	0.544
Ileus (%)	0 (0)	1 (2.5)	1.0
GI bleeding (%)	1 (5)	0 (0)	0.333
Wound infection (%)	0 (0)	3 (7.5)	0.544

remained high, and many patients cannot achieve closure of the colostomy.[1] Whether primary anastomosis should be performed in the emergency operation is controversial, and it can be achieved by segmental resection with on-table lavage or by subtotal colectomy with ileocolonic anastomosis. Single-stage operation has been performed in some centers with favorable results.[10,19,20] In our previous study, primary resection was performed in 91% and primary anastomosis was achieved in 73% of patients with left-sided obstruction.[21]

The mortality rate of patients with obstructing colorectal cancers requiring emergency operation is up to 15%–25%,[1,5,7,8] which is significantly higher than that of patients who undergo elective operation. The conversion of emergency resection to an elective operation will certainly improve the outcome of the patients, and this can now be achieved by the insertion of SEMS.

SEMS has been accepted as a palliative option for malignant colorectal obstruction in the presence of advanced or disseminated disease.[14,22,23] The success rate is high and the morbidity associated with the insertion of SEMS is acceptable.[13] As a procedure to temporarily relieve the obstruction, SEMS has been shown to enable elective resection to be performed with bowel preparation.[15,16,24–26] In this case-matched study, the patients with insertion of SEMS as a bridge to surgery had more distally located tumors. This reflected our preference to treat rectal and rectosigmoid obstruction with preoperative SEMS insertion. Pelvic dissection in the presence of bowel obstruction is usually difficult, and tumor clearance is suboptimal. Despite the more distally located tumors, resection and anastomosis could be achieved in all except one patient with preoperative decompression with the SEMS.

In our series, the mortality rate of emergency resection was 12.5%. This is comparable to other series with emergency colorectal surgery.[7] The high mortality is due to the advancing age, poor general condition, and the presence of concomitant medical conditions. Patients with primary anastomosis did not have higher mortality when compared with those with resection without anastomosis. We demonstrated that those with primary anastomosis had a lower predicted mortality by the P-POSSUM (Porthsmouth modification of Physiological and Operative Severity Score for the en Umeration of Mortality and Morbidity), and the premorbid status was better than those without primary anastomosis.[27] Successful decompression was observed in all patients after insertion of SEMS, and 95% of them underwent an elective operation after better preoperative optimization. Only one patient required emergency operation after stenting, due to sigmoid perforation 1 week after SEMS insertion. Perforation was a documented complication of SEMS insertion. The rate of perforation was 4% and was associated with predilatation with the balloon.[13]

Other common complications related to stent insertion, such as migration or tumor ingrowth, did not occur in this group of patients with stent as a bridge to surgery because the obstructions were high-grade and the stent was only kept for a short duration.

We did not show any difference in the stoma rate (including end and loop stoma) in the two groups of patients. This is because we adopted an aggressive approach in the emergency setting, with single-stage procedure in 65% of patients. Moreover, more patients in group I had rectal cancer, and diversion stoma was performed after total mesorectal excision to protect the very low anastomosis. Despite the similar stoma rate, the hospital stay and the intensive care stay were significantly shorter in patients treated with SEMS. Concerning the cost effectiveness of the procedure, stent insertion as a bridge to surgery was demonstrated to be less costly.[20,28]

In our study, there were significantly fewer nonsurgical complications in the patients having SEMS insertion before surgery. This accounted for the shorter hospital stay and the lower incidence of admission to the ICU. The incidences of surgical complications were similar in the two groups. One of the most dreadful complications was anastomotic leakage. In this study, there was no anastomotic leakage in patients with prior stent insertion, whereas three patients with emergency surgery developed anastomotic leakage that accounted for one postoperative death. Anastomotic leakage is a severe complication after colorectal operation, and emergency surgery is usually regarded as a risk factor associated with a higher leakage rate. The conversion of an emergency operation to an elective one can reduce the leakage rate. Improvement of the general condition of the patients could be reflected in the more favorable ASA class in group I, although this did not reach statistical significance. This also helped to reduce the operative morbidity and mortality. In some selected patients with preoperative stent insertion, laparoscopic resection was possible with decompression of the bowel. Recent randomized controlled trials demonstrated that laparoscopic resection for colonic malignancy was associated with favorable short-term results without compromising the oncologic outcome.[29,30] However, patients with obstructing cancer were excluded from these trials. We, as well as other authors, have reported the feasibility of laparoscopic resection for obstructing cancer with prior decompression with SEMS.[31,32] We included patients with laparoscopic surgery in group I, and this probably also helped to improve the outcome. The minimally invasive approach is only possible with prior decompression with metallic stents; thus, these patients were included, although perfect match of the surgical approach was not achieved in the study. With the exclusion of those with laparoscopic surgery, favorable outcome was still achieved with less need for ICU stay. In the current study, conversion was only required in one of the seven patients with attempted laparoscopic resection. Thus, preoperative decompression for obstructing cancer can extend the scope of laparoscopic surgery, and the adoption of the minimally invasive approach can certainly reduce the morbidity and hasten the recovery of patients who are usually of elderly age and suffer from concomitant diseases.

Whether insertion of a metallic stent to relieve obstruction of the more proximal colon is beneficial is obviously controversial. Stent insertion to the large bowel proximal to the splenic flexure is technically more difficult, although this had been reported.[33] Moreover, emergency right or extended right colectomy with ileocolonic anastomosis is the usual practice in most patients, even in an emergency setting. Thus stent insertion was not performed for right-sided obstruction in our institution.

Admittedly, there are limitations in this retrospective study, and selection bias to different procedures was inevitable and difficult to avoid. The decisions of patients to be admitted and discharged from the ICU were unblinded. Such decisions were made mainly by the surgeons, based on the condition of the patients. However, there was no deliberate intention to bias patients in either group in terms of ICU or hospital stay. Although we tried to match the demographics of the patients and the tumor characteristics, perfect match of all the factors, including the sites of the tumor and comorbidity, is not possible. However, within the limitations, we could demonstrate that the treatment option with prior insertion of metallic stent could improve the outcome of patients with colonic obstruction. A randomized controlled trial can certainly help to further study this treatment option in colonic obstruction.

In conclusion, when compared with emergency resection, insertion of SEMS as a bridge to surgery for obstructing left-sided colorectal cancer is associated with a higher rate of primary anastomosis as well as a better outcome in terms of a shorter postoperative hospital stay and reduction in need to stay in the ICU. Preoperative decompression can also render laparoscopic resection possible. The wider application of this treatment option for obstructing colorectal cancer warrants further studies.

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Central Pancreatectomy Revisited

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Central pancreatectomy is a surgical procedure that removes the middle segment of the pancreas and preserves the distal pancreas and spleen. This limited resection has the advantage of conserving normal, uninvolved pancreatic parenchyma, thus reducing the possibility of postoperative exocrine and endocrine dysfunction. While the incidence of postoperative endocrine insufficiency may be as low as 4%, procedural morbidity, specifically pancreatic fistula, appears to exceed the published rates for standard resections (i.e., distal/subtotal pancreatectomy or pancreaticoduodenectomy). We have reviewed our prospective pancreatic cancer database to determine the utilization of central pancreatectomy in a major cancer center with expertise in pancreatic surgery. We identified only 10 cases of central pancreatectomy over the past 13 years. Six (60%) had postoperative complications including three cases (30%) of pancreatic fistula. No patients died as a result of the procedure. At a median follow-up of 13.6 months (mean, 25.2 months), only one patient had mild endocrine insufficiency and no patients had clinically significant exocrine dysfunction. The associated morbidity of central pancreatectomy may outweigh any potential benefit in long-term pancreatic secretory function. We suggest that such a procedure be used selectively, where preservation of the pancreas appears essential. (J GASTROINTEST SURG 2006;10:804–812)

KEY WORDS: Central pancreatectomy, pancreatic cystic neoplasm

Over the past two decades, there has been a dramatic increase in the utilization of cross-sectional imaging in minimally symptomatic patients. Coincident with this trend has been an increase in the diagnosis of asymptomatic pancreatic cystic neoplasms and intraductal papillary mucinous neoplasms (IPMNs).[1–3] Although the surgical indications for these tumors have not been well defined, the combination of patient-driven surgical consultations and the medicolegal hazards inherent with a course of observation have led to more frequent pancreatic resections for these tumors.[1,2]

The standard surgical management of both benign and small, low-grade malignant pancreatic neoplasms is influenced by their location within the gland. Pancreatic head lesions have traditionally been treated by pancreaticoduodenectomy, while tumors in the neck or proximal body have been managed by distal or subtotal pancreatectomy. Recent reported use of central or medial pancreatectomy (CP) over the past two decades has questioned its place in our surgical management for cystic lesions of the pancreas.[4,5] Proponents suggest that CP allows surgeons to tailor the procedure to the extent of disease, theoretically limiting indiscriminate resection of uninvolved parenchyma that may predispose patients to postoperative exocrine and endocrine insufficiency. Technical considerations may limit its use. The combination of a nondilated pancreatic duct and a soft gland can make CP a challenging operation. Pancreatic fistula/leak (PF) rates up to 40% have been reported following CP.[6,7] Currently, even selective use of CP remains controversial.

We sought to determine the actual utilization of CP at a tertiary referral central with expertise in

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pancreatic surgery over the past two decades with emphasis on the indications for operation, postoperative morbidity, and development of endocrine insufficiency. In addition, we have summarized the existing literature on the use of CP for pancreatic neoplasms over this time period.

MATERIAL AND METHODS

After obtaining institutional review board approval (waiver of authorization WA0056-05), the Memorial Sloan-Kettering Cancer Center (MSKCC) prospective pancreatic cancer database was queried to identify patients who had a CP during the study period (January 1, 1993, through April 1, 2005). Since CP does not have a unique *CPT-4* procedure code, we identified all patients in the database who had a pancreatic resection exclusive of pancreaticoduodenectomy during that time period. To avoid omitting patients not captured by the pancreatic cancer database, we also searched the complementary MSKCC institutional database for patients having any pancreatic resection during the study period. Patients were identified from the institutional database by *CPT-4* codes (48140, 48145, 48146, 48180, and 48999), and a list of medical record numbers was generated. Confidential patient information was encrypted in a password-protected database and used to initiate a complementary chart review to identify any additional cases of CP. All complications were defined according to strict criteria set forth by surgical secondary events at MSKCC.

RESULTS

During the study period, staff surgeons performed over 1350 pancreatic resections. The choice of operation was independent of protocol and formulated by patient characteristics and tumor-related variables. Overall, we identified 10 patients (~0.8%) who had a CP (Fig. 1). Patient demographics are listed in Table 1. Surgical indications included three solid tumors and seven pancreatic cystic neoplasms located in the neck or proximal body of the pancreas. Reconstruction of the distal pancreatic remnant was accomplished with Roux-en-Y pancreaticojejunostomy (PJ) (Fig. 2) in nine patients and pancreaticogastrostomy (PG) (Fig. 3) in one patient. Final postoperative pathology included five cases of serous cystadenoma, three pancreatic islet cell tumors, one solid and pseudopapillary tumor, and one low-grade neuroendocrine neoplasm. CP was not used to treat pancreatic ductal adenocarcinoma. All resection margins were microscopically negative.

Patient clinicopathologic characteristics are summarized in Table 2. Six patients (60%) had a postoperative complication. Five of the six complications were severe and required invasive procedures (surgical or interventional radiology) for treatment; one patient had reoperative surgery for uncontrolled hemorrhage. Three patients (30%) had a pancreatic leak. All resolved with percutaneous drainage and short-term (<1 month) subcutaneous octreotide therapy. Two of the three leaks occurred in patients reconstructed with a Roux-en-Y PJ (patients 3 and 4); the other leak was in a patient with a pancreaticogastric anastomosis (patient 10). There were no postoperative deaths. One patient was persistently hyperglycemia postoperatively (patient 6). This patient required dietary modifications and administration of an oral hypoglycemic agent to maintain euglycemia. Another patient with preoperative type 1 diabetes mellitus (patient 3) did not require dose adjustment or additional medications postoperatively. The incidence of postoperative exocrine insufficiency was difficult to characterize, but no patients required pancreatic enzyme supplementation after their operation for symptomatic malabsorption or diarrhea.

All patients were alive at a median follow-up of 13.6 months (mean, 25.3 months; range, 1–92 months). The only recurrence was in patient 9, who presented with a 2.5-cm low-grade pancreatic neuroendocrine tumor with four distinct liver metastases. She had an uncomplicated CP and partial hepatectomy without clinical or radiologic evidence of residual disease. She had recurrence more than 8 months after her operation with diffuse hepatic metastases. She was treated with long-acting somatostatin depot subcutaneously and multiple hepatic arterial embolizations.

DISCUSSION

Recent use of cross-sectional imaging has led to an increased number of patients diagnosed with asymptomatic pancreatic neoplasms seeking surgical treatment. While the safety of traditional procedures has reached acceptable levels in centers of experience, a number of recent reports have advocated the use of CP as an alternative, less-radical procedure tailored to the anatomic specifications of centrally located pancreatic tumors.[8,9] While there appears to be a number of attributes to CP, such as preservation of normal pancreas and spleen and decreased risk of postoperative exocrine and endocrine insufficiency, technical considerations may contribute to increased postoperative morbidity.

At our institution, the use of CP is rare. We identified only 10 patients (~0.8%) who had a CP from

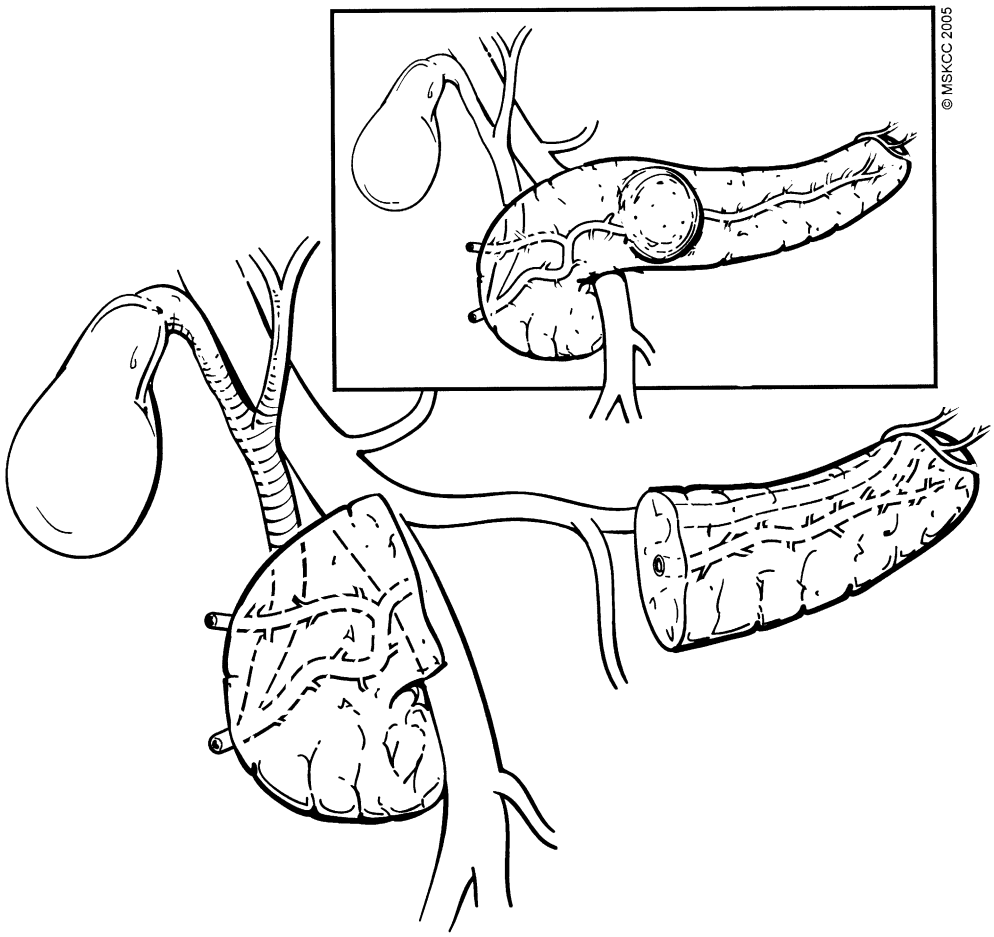

Fig. 1. Central pancreatic resection. This illustration shows the resection margins following central pancreatectomy. The distal transected pancreatic duct (*right*) can be reconstructed by either Roux-en-Y pancreaticojejunostomy or pancreaticogastrostomy. *Inset*, Typical pancreatic cystic neoplasm or intraductal papillary mucinous neoplasm located in the central pancreas prior to resection.

Table 1. Central pancreatectomy: Indications for operation and histopathology

Patient	Year of operation	Indication	Post-op pathology	Reconstruction	Margin	Status	Recurrence
1	1993	Solid mass	SPPT	RY PJ	R0	NED	No
2	1996	PCN	Islet cell	RY PJ	R0	NED	No
3	2000	PCN	Serous cystadenoma	RY PJ	R0	NED	No
4	2002	PCN	Serous cystadenoma	RY PJ	R0	NED	No
5	2002	PCN	Serous cystadenoma	RY PJ	R0	NED	No
6	2003	Solid mass	Islet cell	RY PJ	R0	NED	No
7	2003	PCN	Islet cell	RY PJ	R0	NED	No
8	2004	PCN	Serous cystadenoma	RY PJ	R0	NED	No
9	2004	Solid mass	Low-grade NET	RY PJ	R0	AWD	Yes
10	2005	PCN	Serous cystadenoma	PG	R0	NED	No

Tabulated summary of patients' surgical indications, methods of distal pancreatic segment reconstruction, and postoperative histopathology. PCN = pancreatic cystic neoplasm, SPPT = solid and pseudopapillary tumor of the pancreas, NET = neuroendocrine tumor. RY PJ = Roux-en-Y pancreaticojejunostomy, PG = end-to-side pancreaticogastrostomy, R0 = margin-negative resection, AWD = alive with disease, NED = no evidence of disease.

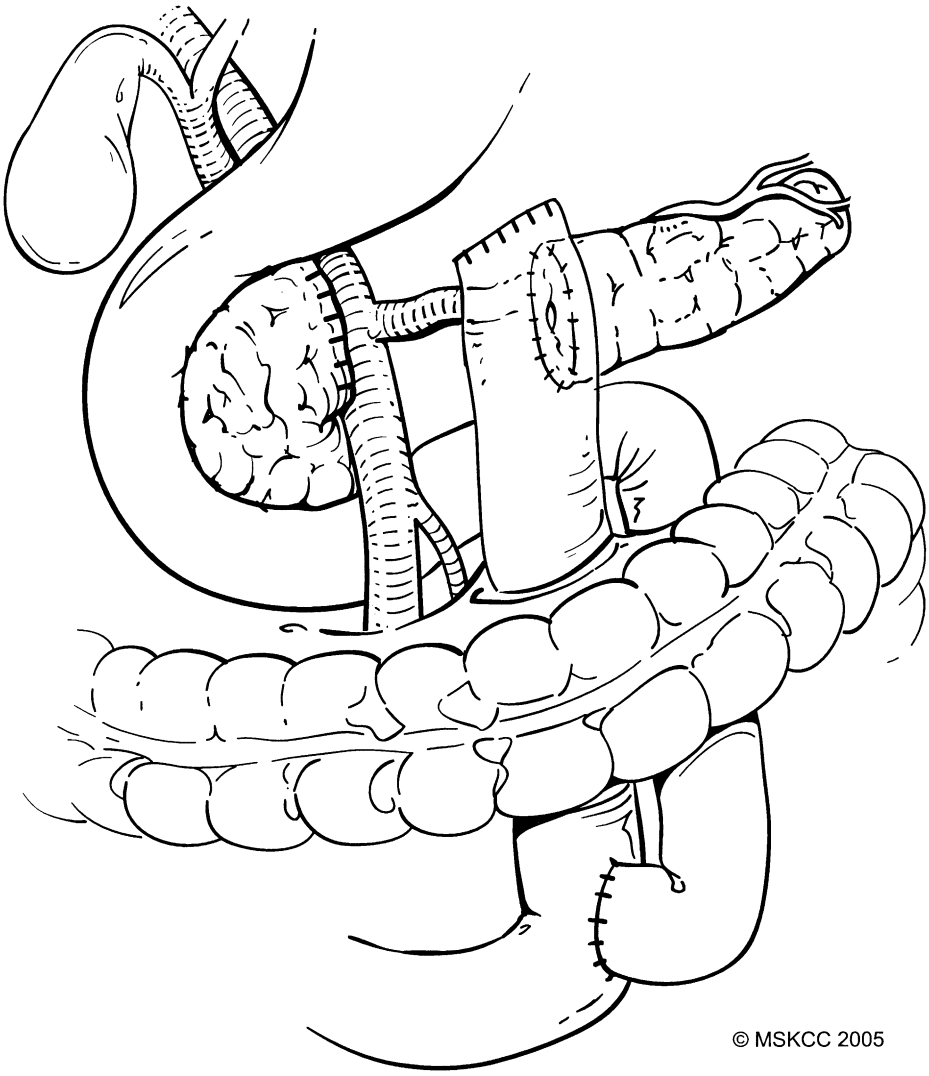

Fig. 2. Roux-en-Y pancreaticojejunostomy reconstruction following central pancreatectomy. A Roux limb of proximal jejunum is mobilized to reconstruct the distal pancreatic remnant. A two-layer closure is fashioned with an internal layer of bowel mucosa to pancreatic duct mucosa and an external layer between the pancreatic parenchyma and seromuscular layer of the jejunum.

over 1350 pancreatic procedures performed during the study period. These figures are similar to those of others who reported only three cases (2%) of CP from 136 resected IPMNs during a 16-year period.[1] Our postoperative complication rate of 60% is significantly higher than that described in the majority of previous studies examining more than 10 patients[5–7,10–15] (range, 12.5–71%; Table 3). This is consistent with our policy of having a prospective database that scrutinizes all complications on a weekly basis.[16] This prospective review of complications increases and probably more closely defines actual complication rates. There were no deaths in our series and only one fatality has been reported in the literature following CP (1 of 207, or 0.5%).[14]

The potential for leaks and fistulas arising from either the proximal pancreatic suture line or the pancreatic enterostomy site remains a major deterrent to widespread acceptance of CP. The combination of a soft gland, normal-caliber pancreatic duct, and the formation of two transected pancreatic surfaces (each with the potential for leak) leads us to speculate that this rate must exceed that following distal pancreatectomy. Three patients (30%) in our series had a postoperative PF following CP, and this rate is similar to previous reports.[13,14,17] Published rates of PF after pancreaticoduodenectomy and distal pancreatectomy range from 5% to 25%.[18–25] A recent cohort of 211 patients from our own institution had a PF rate of 7.6% (16/211) following distal

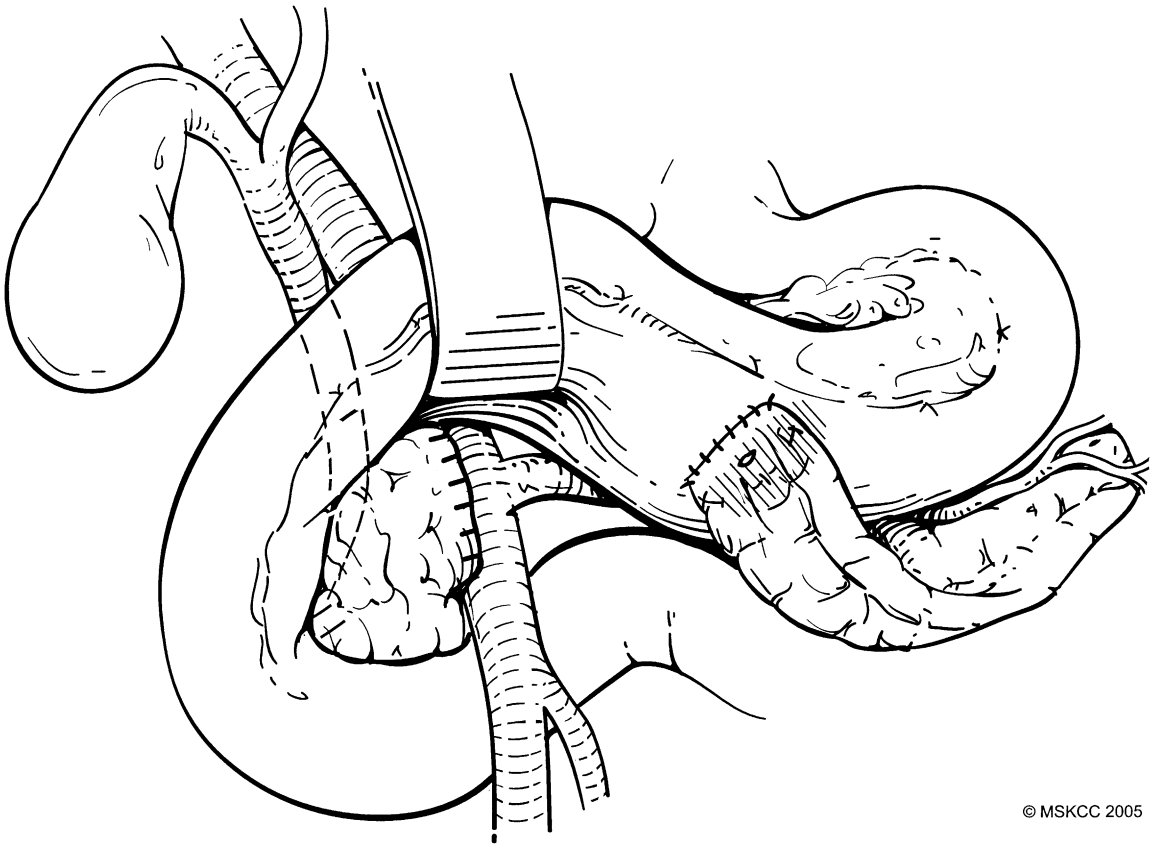

Fig. 3. Pancreaticogastrostomy reconstruction following central pancreatectomy. This anastomosis is created in two layers in a similar fashion to the Roux-en-Y pancreaticojejunostomy with the gastric mucosa and seromuscular tissues.

pancreatectomy.[23] Factors associated with the development of PF include gland texture, duct caliber, and the technical experience of the surgeon.[18–22] The actual incidence of PF is difficult to quantify in the absence of standard criteria for diagnosing and reporting this complication. Previous studies have shown that neither the type of pancreaticoenteric reconstruction nor the use of octreotide has been shown to be effective in prevention of PF after CP.[6,14,22] A randomized trial of PG versus PJ after pancreaticoduodenectomy did not show any significant difference in fistula rates.[26]

Preservation of postoperative endocrine and exocrine function has been the most frequently reported benefit of CP. Six previous reports have investigated the etiology and rate of postoperative endocrine and exocrine pancreatic insufficiency after CP.[5,10–13,15] Iacono et al.[5] studied six patients preoperatively and postoperatively with oral glucose tolerance testing (OGT), pancreolauryl, and fecal fat excretion testing and reported that no significant difference occurred before and after operation. Sperti et al.[13] performed exocrine and endocrine functional evaluation in 10 patients preoperatively and at least 6 months postoperatively after CP (mean follow-up, 25.5 months) by fecal chymotrypsin excretion measurements and OGT testing. OGT findings were normal in all but one patient, who had glucose intolerance before the operation. Postoperative fecal chymotrypsin measurements were normal in all patients. Ikeda et al.[11] tested 13 patients with a mean follow-up of 40 months after CP with OGT testing for endocrine insufficiency. None of the patients showed deterioration in their glucose homeostasis.[11] In one of the first series on CP, Rotman et al.[10] evaluated functional results after CP in all 14 patients with OGT testing and measurements of fecal fat excretion. At a mean follow-up of 36.3 months, all OGT levels were normal. The fat contents of all stool tests were normal in all patients except in one, in whom it was slightly increased. In the largest study on CP from the French Pancreas Club, 49 of 50 patients who were not reoperated on had their fasting blood glucose concentrations measured at least 12 months after CP.[14] Three (6%) of the 47 patients had abnormal glucose concentrations; one

Table 2. Central pancreatectomy: Postoperative morbidity

Patient	Morbidity	Highest grade complication	Reoperation	Pancreatic leak	Postoperative mortality	Preoperative DM	Postoperative DM
1	Yes	2	No	No	No	No	No
2	No	—	No	No	No	No	No
3	Yes	3	No	Yes	No	Yes	Yes
4	Yes	3	No	Yes	No	No	No
5	No	—	No	No	No	No	No
6	No	—	No	No	No	No	Yes
7	Yes	3	No	No	No	No	No
8	No	—	No	No	No	No	No
9	Yes	3	Yes	No	No	No	No
10	Yes	3	No	Yes	No	No	No
Total	6/10 (60%)	—	1/10 (10%)	3/10 (30%)	0	1/10 (10%)	2/10 (20%)

Detailed postoperative morbidity and mortality rates. Grading of postoperative complications was defined according to strict criteria set forth by surgical secondary events at MSKCC (scale 1–5). DM = diabetes mellitus.

developed diabetes soon after an extended CP for IPMN of the pancreas, and another developed diabetes after IPMN recurrence treated with pancreaticoduodenectomy. The third patient developed diabetes after severe acute pancreatitis. Goldstein et al.[15] reported two cases (2 of 20, or 10%) of postoperative endocrine insufficiency by abnormal serum glycosylated hemoglobin levels during a median follow-up of 18 months after CP. In the most recent report by Iacono et al.,[27] none of the 20 patients developed postoperative pancreatic dysfunction. Thus, the cumulative, published rate of exocrine and endocrine insufficiency after CP in 237 patients is less than 4% (Table 3).

Overall, these results compare favorably to postoperative endocrine and exocrine function after pancreaticoduodenectomy and distal pancreatectomy. The validity of comparisons is limited. (1) The incidence of exocrine and endocrine dysfunction is related to patient comorbidities as well as to the size

Table 3. Central pancreatectomy: Summary of case series in the literature

Series	Year	N	Median follow-up (months)	Morbidity N (%)	Reconstruction PG/PJ	Pancreatic fistula N (%)	# EXO (test)	# ENDO (test)
Fagniez[42]	1988	2	—	0	−/2	0	0	0
Asanuma[43]	1993	2	36	0	−/2	0	0 (PFD)	1 (OGT)
Rotman[10]	1993	14	36.3	4 (29%)	−/14	2 (14%)	0 (FFT)	0 (OGT)
Ikeda[11]	1995	24	40	3 (13%)	−/24	3 (13%)	2 (PFT)	0 (OGT)
Iacono[5]	1998	13	68	3 (23%)	−/13	3 (23%)	0 (FFT)	0 (OGT)
Warshaw[12]	1998	12	—	3 (25%)	−/12	2 (17%)	0	0 (OGT)
Partensky[7]	1998	10	31	4 (40%)	10/−	4 (40%)	—	—
Takeyoshi[44]	1999	3	—	0	−/3	0	0 (PFD)	0 (OGT)
Sperti[13]	2000	10	63	4 (40%)	−/10	3 (30%)	0 (FCT)	0 (OGT)
Celis[45]	2001	5	17	0	−/5	0	0	0
Sauvanet[14]	2002	53	26	22 (41%)	25/26 (2 oversewn)	16 (30%)	4	3 (OGT)
Christein[46]	2003	3	34	0	−/3	0	0	0 (RG)
Efron[6]	2004	14	12	10 (71%)	14/−	5 (36%)	0	0
Goldstein[15]	2004	12	18	3 (25%)	12/−	0	0	2 (HbAlc)
Iacono[27]	2005	20	—	7 (35%)	−/20	5 (25%)	0 (PFT)	0 (OGT)
MSKCC	2005	10	14	6 (60%)	1/9	3 (30%)	0	1 (RG)
Total		207	—	69/207 (33.3%)		46/207 (22.2%)	6/197 (3%)	7/197 (3.6%)

Recent published series of central pancreatectomy in the literature with rates of post-operative morbidity (exocrine/endocrine insufficiency), complications, and pancreatic leak/fistula. Abbreviations: (N/# = number of patients; PG = end-to-side pancreaticogastrostomy; PJ = roux-en-Y pancreaticojejunostomy; EXO = exocrine insufficiency; ENDO = endocrine insufficiency; PFD = pancreatic functional diagnostic tests; FFT = fecal fat excretion test; PFT = pancreo-lauryl fat excretion test; FCT = fecal chymotrypsin test; OGT = oral glucose tolerance test; RG = random serum glucose; HbAlc = hemoglobin Alc serum levels).

of the tumor and its location in the pancreas. (2) Accurate measurement of clinically significant exocrine and endocrine insufficiency is difficult to perform and varies by technique and assay type. (3) Most series emphasize outcome parameters of recurrence and survival, not hormone dysfunction. (4) Some studies include patients with chronic, progressive diseases (e.g., chronic pancreatitis), which may surreptitiously cause subsequent insufficiency. Since the vast majority of CP patients are on average younger and have fewer comorbidities than patients undergoing pancreaticoduodenectomy or distal pancreatectomy for pancreatic adenocarcinoma, Kendall's cohort of healthy donors of pancreatic grafts might represent the best matched control group.[28] Seven of the 28 donors in this study had abnormal glucose tolerance 1 year after hemipancreatectomy. Subsequent deterioration in insulin secretion was eventually noted in 17 of 28 donors. Although no overt diabetes occurred, the development of glucose intolerance in 25% of healthy donors raises concern for patients with a more limited pancreatic reserve. These data are similar to Lillemoe's retrospective review of 235 cases of distal pancreatectomy.[20] In this report, the mean age of the patients was 51 years and most distal pancreatectomies were performed for chronic pancreatitis (24%). New-onset insulin-dependent diabetes developed in 8% of cases. The rate of endocrine dysfunction was proportionally increased by subsequent resections and loss of viable insulin-producing pancreatic parenchyma.[29,30] Previous reports have shown that 72% of patients became insulin dependent after a subtotal left pancreatectomy, whereas 85–95% resection caused diabetes in all patients.[31,32] This positive correlation between the amounts of pancreatic parenchyma resected, as well as limitations of the remaining pancreatic reserve due to intrinsic disease and the risk of postoperative diabetes, is also seen in right-sided resections. When pancreaticoduodenectomy is performed on normal pancreatic parenchyma without preexisting diabetes, the incidence of postoperative diabetes ranges from 0% to 10%.[33–35] In a series of 253 patients operated on for periampullary cancer, Warren et al.[36] reported an incidence of diabetes of 15% after the operation. After pancreaticoduodenectomy for chronic pancreatitis, diabetes occurred in up to 40% of cases.[36] When the resection of pancreatic parenchyma was only 20–30%, as described by Beger et al.[37] in duodenum-preserving pancreatectomy, the glucose mechanism remained essentially unchanged but increased to 3.7% in patients operated on for chronic pancreatitis. Büchler et al. showed that duodenum-preserving pancreatic head resection (Beger procedure) is superior to pylorus-preserving pancreaticoduodenectomy with respect to glucose metabolism, suggesting that the integrity of the duodenum plays an important role in glucose homeostasis.[37,38]

Splenic preservation with CP is another major advantage of CP.[6,11,13,27] The theoretical benefit of immune preservation has largely been extrapolated from prior observations in gastric and colorectal surgery.[23,39–41] These studies showed a higher rate of infectious complications associated with splenectomy. This observation has been reported in a group of patients from our institution following distal pancreatectomy.[23] Patients with benign or low-grade malignant lesions undergoing distal pancreatectomy with splenectomy had a significantly higher perioperative morbidity, including grade III to V complications (11% versus 2%), infectious complications (28% versus 9%), and length of hospital stay (9 versus 7 days), than did patients in the splenic preservation group.[23] The value of splenic preservation has also been confirmed in patients undergoing laparoscopic distal pancreatectomy.[39]

CONCLUSION

Preservation of uninvolved pancreas and spleen and conservation of exocrine and endocrine function make CP an attractive alternative to more radical resections for centrally located benign and low-grade malignant neoplasms. However, based on our findings and subsequent literature review, we believe that the associated probability of early morbidity may outweigh the theoretical advantages of CP. At present, we do not advocate the routine use of CP. As is true with any infrequently used procedure, a significant learning curve exists. Although the current role of CP for IPMNs and pancreatic cystic neoplasms remains unclear, it may be clarified in parallel with our understanding of the biologic behavior of these tumors. Because these lesions may represent a pancreatic field defect, limited resections may ultimately evolve to be a more effective strategy than radical resection. It is necessary to determine the optimal method of pancreaticoenteric reconstruction, the most accurate diagnostic assays for evaluation of endocrine and exocrine insufficiency, and a cost-effective surveillance strategy for these tumors before CP can be accepted. We recommend that CP be used selectively, where preservation of the pancreas appears essential.

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Outcome after Pancreaticoduodenectomy for Cancer In Elderly Patients

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During the last decade, the outcome after pancreaticoduodenectomy (PD) for cancer showed a continuous improvement. Therefore, an increasing number of patients, especially elderly patients, have been considered for this procedure. However, the debate on the possible deleterious influence of patients' advanced age on their postoperative outcome after pancreaticoduodenectomy still continues. From June 1995 to October 2003, 70 elderly patients (range, 70–84 years) underwent pancreaticoduodenectomy with pancreatogastrostomy for cancer. Among them, 38 patients were 70–75 years old and 32 were ⩾75 years. Patients were identified from a prospective database of a single institution, and their records were reviewed retrospectively. Patient and tumor characteristics, postoperative morbidity and mortality, length of hospital stay, readmission rate, and overall survival were compared between the two groups. There were no statistical differences regarding the postoperative mortality ($P = 0.205$), overall morbidity ($P = 0.267$), mean length of hospital stay ($P = 0.345$), and readmission rate ($P = 1$) between both groups. Only delayed gastric emptying was significantly more frequent in patients ⩾75 years ($P = 0.039$). The median overall survival was 20 months. Survival was significantly influenced by the pathological type of the tumor, with worse results for patients with ductal pancreatic adenocarcinoma. In elderly patients, age does not seem to influence the postoperative outcome after pancreaticoduodenectomy with pancreatogastrostomy. (J GASTROINTEST SURG 2006;10:813–822)

KEY WORDS: Elderly patients, outcome, pancreaticoduodenectomy

Population over 65 years old represents the fastest growing group of overall population, and in this group, people over 80 years old have the highest demographic growth.[1] In 2003, life expectancy for the French population at age 70 was estimated at an additional 10.8 years for men and 15.6 years for women.[2] In the elderly, cancer is the second cause of death.[3] Pancreatic ductal adenocarcinoma has the highest incidence between the sixth and seventh decades of life, whereas 80% of periampullary malignant tumors (ampullary carcinoma, cholangiocarcinoma of the distal bile duct, and duodenal tumor) are diagnosed in patients between 60–80 years old.[4] Surgical therapy remains the only potentially curative treatment for pancreatic ductal adenocarcinoma and periampullary malignant tumors, because the effects on survival of adjuvant treatments are still under debate.[5]

Before the early 1990s, most authors emphasized that there was rarely any indication for performing a pancreaticoduodenectomy (PD) in patients over 70 years old because of prohibitively high mortality and morbidity rates and the short survival time.[6,7] Recently, increased surgical experience and advances in perioperative care, associated with better patient selection, reduced mortality rates—even in elderly patients—after major surgical procedures such as PD or hepatic resections.[8,9] Indeed, after PD, mortality and major complication rates declined in high-volume centers.[10–12] Therefore, an increasing number of surgeons consider that age is no longer a limiting factor for PD and that it could be performed safely in the elderly, with acceptable outcomes. Indeed, several studies have compared patients of 70 years of age to those younger than 70 years and found no difference between these

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two groups regarding early and late outcomes.[13,14] Currently the debate was extended to patients over 75 years old, and even to octogenarians.[15–17] However, until now there is no consensus about a limit of age for performing PD. Furthermore, some authors still consider that PD in elderly patients is less effective.[18,19]

This retrospective study analyzed the records of patients older than 70 years who underwent a PD to evaluate if there is an age limit beyond which PD should no longer be considered a safe procedure.

PATIENTS AND METHODS

This study was performed in a single institution. The medical data of 70 consecutive patients older than 70 years (range, 70–84) presenting with ductal adenocarcinoma of the head of the pancreas or periampullary malignant tumors, who underwent a PD between June 1995 and October 2003, were analyzed. During the same period of time, 165 patients younger than 70 years underwent PD. The clinical records from a prospective database were retrospectively reviewed. All patients underwent PD with pancreatogastrostomy (PG). The surgical technique has been previously reported.[20] Postoperatively, all the patients were admitted to the intensive care unit until the 6th postoperative day. During this period, they were kept under total parenteral nutrition, gastric antisecretory medication, and analgetics. All the patients received octreotide, 24 hours antibioprophylaxis, and thromboembolism prophylaxis by low-weight molecular heparin. Patients were discharged to the ward when they resumed an intestinal transit if there was no evidence of any major postoperative complications.

Postoperative complications were classified as surgical (pancreatic fistula, delayed gastric emptying, intra-abdominal collections, or pleural effusion requiring drainage) and medical (cardiac, pulmonary, neurologic, or urinary complications). Pancreatic fistula was defined according to Yeo's[21] definition as drainage greater than 50 ml of amylase-rich fluid (greater than threefold elevation above upper limit of normal in serum) through the operatively placed drains on or after postoperative day 10 or as pancreatic anastomotic disruption demonstrated radiographically. The delayed gastric emptying was defined as the inability to consume a regular diet by day 10 postoperatively as well as the need for a nasogastric drainage tube on or beyond day 10.[22] Close follow-up was provided for all patients, and data were updated by personal contacts with patients during follow-up consultations, letters, telephone calls to referring physicians and general practitioners, and telephone calls to the patients or their families. No patient was lost during follow-up. Postoperative mortality, morbidity, hospital stay, readmission rate, and overall survival were analyzed in two groups of patients: 70–75 years (group A, n = 38) and ⩾75 years (group B, n = 32).

Values are expressed as mean ± standard error of mean. The Mann-Whitney U test, χ^2, and Fisher exact tests were appropriately used. Cumulative survival was calculated, from the time of surgery to either death or most recent follow-up, by the Kaplan-Meier method. A log-rank comparison test for univariate survival analysis was used. A multivariate analysis of survival was performed using a stepwise Cox model. A value of $P < 0.05$ was considered statistically significant. All analyses were performed with the Statview Software (Abacus Concepts, Inc., Berkeley, CA).

RESULTS

Patient Characteristics and Comparability of Groups

There was no statistical difference between both groups of patients in terms of sex distribution, associated comorbidity, ASA score, preoperative hospital stay, clinical history, creatinine and total bilirubin blood levels, preoperative evaluation by endoscopic retrograde cholangiopancreatography (ERCP) and biliary drainage, pylorus preserving procedures, and mesenterico-portal vein resections (Table 1).[23] Among comorbidities, only arterial hypertension in group B was significantly more frequent compared with group A (56.2% vs. 28.9%; $P = 0.020$; Table 2). The mean number of associated comorbidities in each patient was 1.8 ± 0.7 (range, 1–3). The mean operative duration did not differ between group A and B (431 ± 94 vs. 434 ± 126 minutes, respectively; $P = 0.850$). During surgery, 50 patients (71.4%) received blood transfusions. The mean number of packed red blood cell units was lower in group A patients, but did not differ from that transfused in group B (3 ± 1 vs. 4 ± 4; $P = 0.987$). The annual distribution of the PD performed in the elderly is depicted in Fig. 1. More than half of patients in both groups underwent a PD in the second part of the study period, from 2000 to 2003 (Table 1).

Among patients with periampullary malignancies (n = 23), only two—one in each group—underwent adjuvant radiochemotherapy for distal bile duct cholangiocarcinoma. Among the 47 patients with pancreatic ductal adenocarcinoma, 25 received

Table 1. Patient and tumor characteristics

	Group A (n = 38)	Group B (n = 32)	*P* value
Study period			0.114
1995–1999	15	7	
2000–2003	23	25	
Sex			0.762
Male	18	14	
Female	20	18	
Comorbidity			0.147
No	13	6	
Yes	25	26	
ASA score			0.179
1 and 2	33	24	
3	5	8	
Preoperative history			
Weight loss	17	16	0.810
Abdominal pain	21	10	0.055
Preoperative blood tests			
Total bilirubin (μmol/L)			0.810
⩾100	17	13	
<100	21	19	
Creatinine (μmol/L)			0.493
⩾120	6	3	
<120	32	29	
Preoperative biliary drainage			0.745
Yes	6	4	
No	32	28	
Preoperative evaluation by ERCP			0.999
Yes	10	9	
No	28	23	
Pathology			0.654
Ductal adenocarcinoma	27	20	
Ampullary carcinoma	4	3	
Cholangiocarcinoma	3	3	
Other	4	6	
Type of pancreaticoduodenectomy			0.401
Standard Whipple procedure	36	28	
Pylorus preserving pancreaticoduodenectomy	2	4	
Mesenterico-portal vein resection			0.121
Yes	12	5	
No	26	27	
AJCC Stage[23,*]			0.514
1 and 2	15	13	
3 and 4	12	7	

*Only for the 47 patients with pancreatic ductal adenocarcinoma.

Table 2. Associated comorbidities

	Group A (n = 38)	Group B (n = 32)	*P* value
Number of comorbidity per patient			0.43
No comorbidity	13 (34.2)	6 (18.7)	
1 associated comorbidity	11 (28.9)	9 (28.1)	
2 associated comorbidity	8 (21.0)	11 (34.3)	
>2 associated comorbidity	6 (15.7)	6 (18.7)	
Mean number of comorbidity per patient	1.8 ± 0.8	1.9 ± 0.7	0.68
Diabetes mellitus	8 (21.0)	8 (25.0)	0.77
Hypertension	11 (28.9)	18 (56.2)	0.02
Cardiac disease	9 (23.6)	8 (25.0)	1
Renal insufficiency	1 (2.6)	2 (6.2)	0.58
Pulmonary disease	1 (2.6)	0 (0.0)	1
Neurologic disease	1 (2.6)	1 (3.1)	1
Others	14 (36.8)	12 (37.5)	1

Values in parentheses are percentages.

postoperative radiochemotherapy (21 in group A and 4 in group B). Adjuvant chemotherapy alone was administered to three patients in group A.

Surgical Outcome

Mortality and morbidity. Two in-hospital deaths occurred in group B, at postoperative day 14 after a stroke and at postoperative day 55 due to a fungus septicemia. There was no significant difference in the mortality rate between group A and group B (0% vs. 6.2%, respectively; $P = 0.205$). The mortality rate in patients younger than 70 years was 2.4% (4 out of 165 patients) and did differ from that observed in group A and B patients ($P = 0.251$).

The mean hospital stay for all patients was 18.5 ± 5.9 days. The hospital stay was longer in group B (19 ± 7 days) but did not significantly differ from that observed for patients in group A (17 ± 6 days; $P = 0.345$; Table 3).

Forty-three postoperative complications occurred in 30 patients (42.8%, Table 4). Among these patients, six (20.0%) developed surgical complications alone, 15 (50.0%) suffered from medical complications, and nine (30.0%) from surgical and medical complications. A single postoperative complication occurred in 18 patients (60.0%), two complications occurred in 11 (36.6%), and one patient (3.4%) presented three complications. The overall number of postoperative complications in group A (36.8%) was lower but did not significantly differ from that observed in group B (50.0%; $P = 0.267$). Moreover, surgical and medical complication rates did not differ between group A and B ($P = 0.735$; Table 3). Interestingly, the overall morbidity rate in patients younger than 70 years who underwent PD during the same period of time was 30.9% (51 out of 165 patients) and did not differ from that observed in group A and B patients ($P = 0.108$). In elderly patients, the most common postoperative complications were urinary infection (n = 11), pneumopathy and pleural effusion, (n = 5) and delayed gastric emptying (n = 4). Two pancreatic fistulas occurred, one in each group (2.6% vs. 3.1%; $P = 1$),

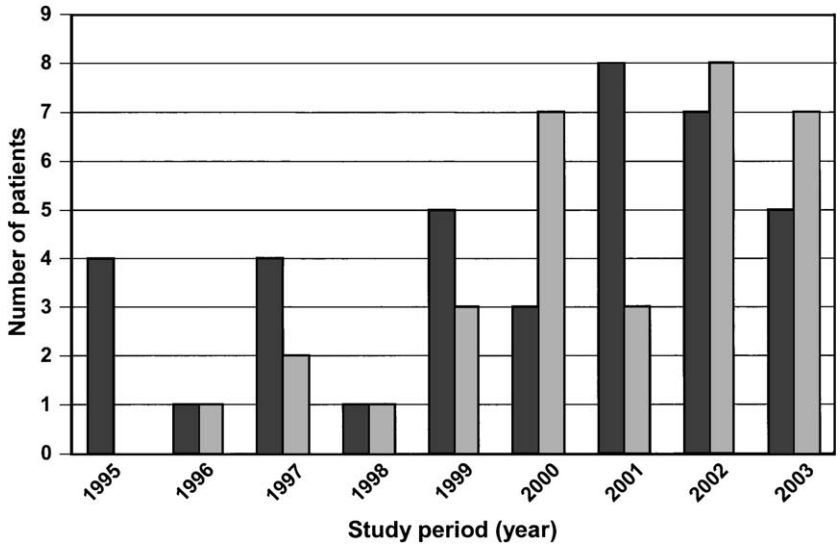

Fig. 1. Annual distribution of pancreaticoduodenectomies performed in elderly patients during the study period: (■) patients between 70 and 75 years old; (■) patients equal to or older than 75 years old.

with an overall rate of 2.8%; both could be treated conservatively. The rate of delayed gastric emptying was significantly higher in group B compared with group A (12.5% vs. 0%, respectively; $P = 0.039$). Two patients (one in each group) developed intra-abdominal collections, which were evacuated under ultrasound control. In none of these patients was a pancreatic fistula proved. There was no statistical difference for the remaining postoperative complications (Table 4). Two patients, one in each group, (2.8%) required relaparotomy (Table 3). The relaparotomy rate was lower in group A (2.6%) but did not significantly differ from that observed in group B (3.1%; $P = 1$). Relaparotomy was required for bleeding from the pancreatic cut edge in one patient of group B and for a stenosis of the hepaticojejunal anastomoses in one patient of group A.

Table 3. Outcome according to age of patients

	Group A (n = 38)	Group B (n = 32)	*P* value
Mortality	0	2 (6.2)	0.205
Morbidity	14 (36.8)	16 (50.0)	0.267
Medical	7 (18.4)	8 (25.0)	0.735
Surgical	3 (7.8)	3 (9.3)	
Surgical and medical	4 (10.5)	5 (15.6)	
Relaparotomy	1 (2.6)	1 (3.1)	1
Hospital stay (days), mean ± SD	17 ± 6	19 ± 7	0.345
range	7–41	13–55	
Transfused patients	24	26	0.095

Values in parenthesis are percentages.

Eleven patients (5 in group B and 6 in group A) were readmitted within 30 days of discharge. The readmission rate was similar in group A and B (15.7% vs. 15.6%; $P = 1$). Patients were readmitted mostly for postoperative diabetes (two patients from each group) or for poor general condition (one patient in group A and three patients in group B). One patient presented with cholangitis controlled by

Table 4. Postoperative complications

	Group A (n = 38)	Group B (n = 32)	*P* value
Surgical	8	10	0.168
Pancreatic fistula	1	1	1
Delayed gastric emptying	0	4	0.039
Bleeding	0	2	0.205
Intestinal occlusion	2	0	0.496
Intraabdominal collection	1	1	1
Abdominal wall sepsis	1	1	1
Stress ulcer	1	0	1
Biliary stenosis	1	0	1
Sepsis	1	1	1
Medical	12	13	0.219
Urinary infection	7	4	0.497
Pneumopathy and pleural effusion	2	3	0.654
Neurologic complications	0	3	0.090
Pulmonary embolism	1	0	1
Sepsis	0	1	0.457
Diarrhea	1	0	1
Thrombophlebitis	1	2	0.589

Values are number of complications.

antibiotherapy, another one with an infected lymphocele had to be drained percutaneously, whereas a third one presented with hepatic metastasis and was treated by palliative chemotherapy.

Survival

The median survival of the 70 patients was 20 months (mean: 27 ± 24; range, 0–120). Excluding the postoperative deaths, 48 patients died during the follow-up. The cause of death was tumor recurrence in 43 patients, aplastic anemia after adjuvant radiochemotherapy (n = 1), colonic adenocarcinoma (n = 1), and cancer unrelated deaths (n = 3). Twenty patients are still alive, and among them, three patients developed recurrences. The overall 1- and 3-year survival rates of patients in group A (63.2% and 33.1%, respectively) did not differ from those observed in group B (71.9% and 27.7%, respectively; $P = 0.603$; Fig. 2).

Patients with pancreatic ductal adenocarcinoma (n = 47). The mean follow up was 20 ± 20 months (median: 20; range, 0–108). The overall 1- and 3-year survival rates in group A (51.9% and 17.3%, respectively) and in group B (60.0% and 6.7%, respectively) did not differ ($P = 0.435$).

Patients with periampullary tumors (n = 23). Among the 23 patients with periampullary tumors, the mean follow up was 39 ± 27 months (median: 20; range, 2–120). The overall 1- and 3-year survival rates in group A patients (90.9% and 72.7%, respectively) were comparable with those recorded in group B (91.7% and 64.8%, respectively; $P = 0.500$).

Figs. 3 and 4 show that overall survival was influenced by the tumor pathology independently of the age of the patients. Indeed, in group A patients, the 5-year survival rate after PD for pancreatic duct adenocarcinoma significantly differs from that observed after PD for periampullary carcinoma (17.3% vs. 72.7%, respectively; $P = 0.002$). Moreover, in group B patients, the 3-year survival rate after PD for pancreatic duct adenocarcinoma significantly differs from that observed after PD for periampullary carcinoma (6.7% vs. 64.8%, respectively; $P = 0.002$).

DISCUSSION

This study provides further evidence that PD with PG in patients over 70 years old can be achieved safely. In patients over 75 years old, postoperative morbidity and mortality were higher than in patients

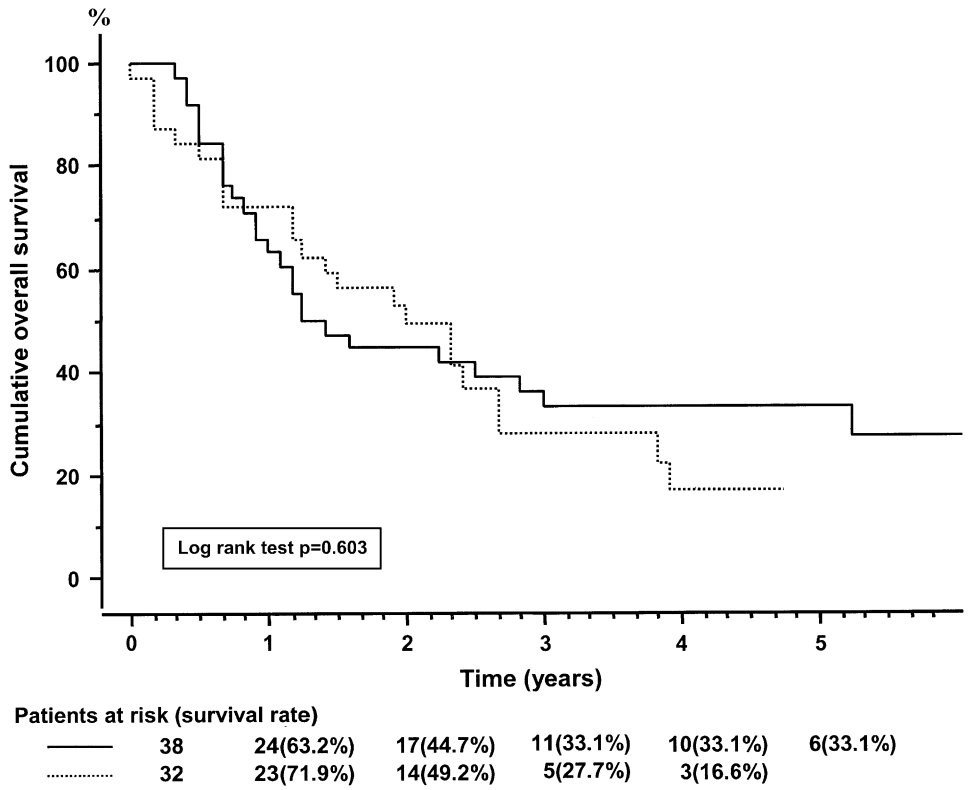

Fig. 2. Cumulative overall survival after PD according to the age of the patient: patients 70 to <75 years old (n = 38, solid line) and patients ≥75 years old (n = 32, dashed line).

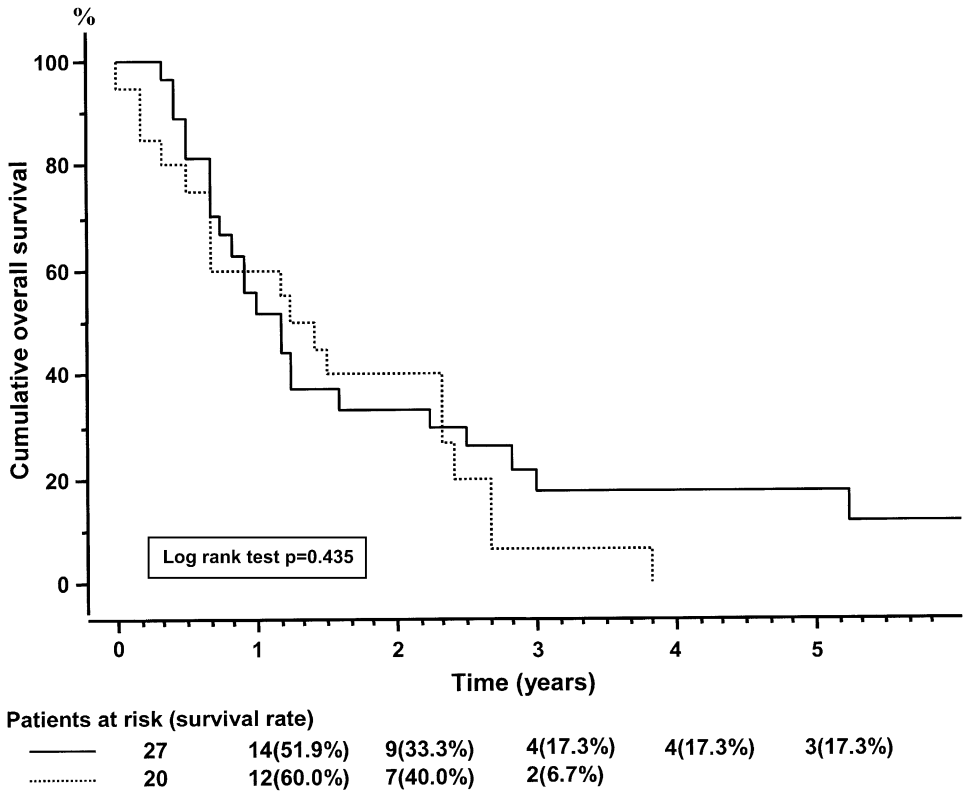

Fig. 3. Cumulative overall survival after PD for pancreatic duct adenocarcinoma according to the age of the patient: patients 70 to <75 years old (n = 27, solid line) and patients ⩾75 years old (n = 20, dashed line).

aged between 70 and 75 years, but there was no statistical difference between the postoperative outcomes in both groups of patients. These results suggest that PD is justified in the elderly—even over 75 years old—because it offers, like in younger patients, the only chance for cure, providing the procedure is carried out in a high-volume center.

Attempts to detect a limit of age for radical surgery became a matter of interest because of the continuous aging of the population. Furthermore, the incidence of digestive malignancies is very high in the western population over 65 years of age,[24] and among these tumors, the incidence of periampullary malignant tumors and of pancreatic ductal adenocarcinoma are one of the highest.[3] Therefore, an increasing number of patients are developing such tumors, making them potential candidates for PD. This trend was already observed by Hannoun et al.[25] in 1993 and later by Sohn et al.[16]; it is also recorded in our series. During the period of the present study, there has been a continuous increase in the number of PDs performed in the elderly, as shown in Fig. 1. Indeed, more than half (n = 48; 68.5%) of all the included patients have been operated on in the last 4 years of the study period, including the majority (n = 25) of patients older than 75 years (Table 1).

Pancreatic ductal adenocarcinoma is one of the 10 main causes of death from cancer in the western world.[3] Surgical resection remains the only potentially curative treatment and is proved to be the major predictor for overall survival.[26] However, until the early 1980s, operative mortality as high as 25% and 5-year survival rates as low as 0% have been reported, especially in the elderly. These results had a prohibitive influence in recommending PD for patients over 65 years old.[6,7,27] In the late 1990s, improved postoperative outcomes have generated an increased interest in the potential candidacy of older patients for PD.[10,28] As consequence, PD has been considered a safe procedure in selected patients over 70 years old, with a mortality rate ranging from 0%–5%.[4,13,14,25]

In the present study, the overall postoperative mortality rate (2.8%) was similar to that reported by others, regardless of the age of the patients.[12,19,28,29] There were two postoperative deaths, both in group B, of patients over 75 years of age. However, the postoperative mortality (6.2%) did not differ from that observed in group A patients and was similar to other

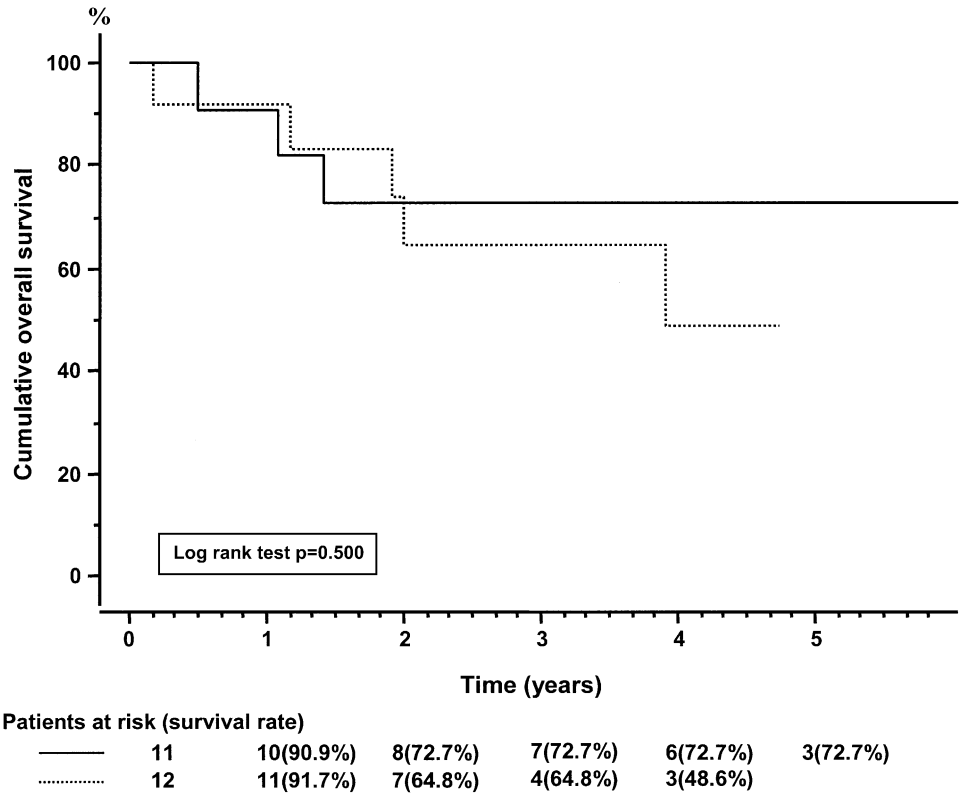

Fig. 4. Cumulative overall survival after PD for periampullary malignancies according to the age of the patient: 70 to <75 years old (n = 11, solid line) and patients ⩾75 years old (n = 12, dashed line).

reported results.[7,8,26] One of the postoperative deaths was directly related to an arterial hypertensive episode. Thomas and Ritchie[30] showed that arterial hypertension is the only associated morbidity that is more frequently encountered in the elderly than in younger patients. Our results support this finding, because the prevalence of arterial hypertension in group B was significantly higher than in group A, whereas the overall incidence of the associated diseases was not significantly different in both groups (Table 2).

Postoperative overall morbidity in the elderly has been reported to range from 14%–69%.[4,8,14–17] In the present series, postoperative morbidity rate in group B (50%) was higher but did not differ significantly from that observed in group A (36.8%).

Postoperative hemorrhages have been found to be more frequent in elderly patients, and it was suggested that early relaparotomy should be indicated whenever an internal hemorrhage is suspected, because elderly patients have limited reserves to overcome acute anemia.[13] In the particular case of PD with PG, careful hemostasis of the pancreatic cut edge and long-term postoperative administration of inhibitors of the proton pump seem useful. In the present study, one of the two relaparotomies was performed in a group B patient for bleeding from the pancreatic cut edge. This kind of complication was not registered during the last 5 years of the study.

Pancreatic fistula is the most severe complication after PD. In the present series, it occurred in two patients: one in each group, with an overall incidence of 2.8%. This favorable result could probably be achieved due to the use of a standardized surgical technique in performing the telescoped PG procedure as described by Delcore et al.[31] Indeed, several other authors have already reported lower rates of pancreatic fistula after PD with PG when compared with pancreatojejunostomy.[32,33] We also previously reported the same favorable results with PG.[20]

Riediger et al.[22] reported that age over 65 years and associated postoperative complications, sepsis in particular, were significantly associated with delayed gastric emptying, regardless of pylorus preservation. In our series, delayed gastric emptying was found to be significantly more frequent in group B, and this result seems to confirm the influence of age on the delayed gastric emptying incidence after PD. Among the four patients with postoperative delayed gastric emptying, all of them over 75 years old, just one had a pylorus preservation procedure, whereas none of them had another associated

Table 5. Results after PD in elderly

First author	No	Age	Morbidity (%)	Mortality (%)	PF (%)	DGE (%)	LOS (days)	Type of reconstruction after PD		Pylorus preservation	Portal vein resection
								PJ	PG		
Spencer, 1990[29]	31	>70	31	12	0	0	16	31	0	4	—
Delcore, 1991[4]	42	>70	14	5	0	—	—	13	25	—	—
Cameron, 1993[37]	37	>70	62	0	22	46	20	–	—	—	—
Hannoun, 1993[25]	44	>70	36	4.5	15.9	—	22	44	0	0	0
Kayahara, 1994[38]	28	>70	54	18							
Fong, 1995[8]	138	>70	45	6	5	—	20	—	—	—	—
Vickers, 1996[14]	21	>70	44	0	5	14	18.6	—	—	—	—
Di Carlo, 1998[13]	24	>70	39	6	6	12	17	—	—	—	—
Sohn, 1998[16]	46	>80	57	4.3	15	33	15	32 (71%)	13 (29%)	41 (89%)	2 (4%)
Magistrelli, 1998[39]	29	>70	31	0	3.4 (1)*	—	19.3	26	0	14 (48.3%)	—
Bathe, 2000[15]	16	>75	69	25	12.5	25	25	—	—	—	2 (12.5%)
Burcharth, 2001[40]	34	>70	47	12	15	—	22	32	0	0	3 (8.8%)
Chen, 2003[17]	16	>80	51	13	13	19	25	—	—	—	—
Present Study	32	⩾75	50	6.2	3	12.5	19	0	32	4 (12.5%)	5 (15.6%)

PF = pancreatic fistula; PJ = pancreatojejunostomy; PG = pancreatogastrostomy; DGE = delayed gastric emptyning, LOS = length of hospital stay (LOS is expressed as median).
*Number of patients.

postoperative complication. A similar result was found by Sohn et al.[16] in a series of patients older than 80 years, whereas other previous series, which also reported a higher incidence of delayed gastric emptying in elderly, have failed to prove any significant difference compared with younger patients.[13,17]

Brooks et al.[34] recently reported that age of the patient was an independent factor influencing the length of hospital stay. However, this result could have been influenced by the important number of patients operated on before 1992 (almost 50%), with more frequent postoperative complications and subsequently longer hospital stays. Moreover, their study showed a regular decrease in the length of hospital stay during the study period. At the opposite, our series did not show any significant difference in the overall hospital stay between the two groups of patients.

In the present series, one patient died of aplastic anemia after adjuvant radiochemotherapy. This could suggest that, in relatively fragile patients, the adjuvant treatment should be carefully adapted. However, the impact of the adjuvant treatment on survival was not analyzed in the present study because it was performed in less than half (30 patients) of the patients.

The reported median overall survival of elderly patients after PD for cancer ranged from 14–38 months.[4,13,15–17,25] In the present series, the median overall survival was 20 months. However, we have to stress that 19 patients (27%) with pancreatic adenocarcinoma were AJCC stages III and IV, and half of the patients included in the study and more than half of the patients over 75 years of age underwent a PD in the last study period, resulting in a shorter follow-up (Table 1). In the present series, the median survival of 20 months after PD in patients with pancreatic ductal adenocarcinoma was similar to that reported by Bathe et al.[15] (18 months) and is far better than a median survival of 8.9 months observed in patients treated by radiochemotherapy alone.[35]

To our knowledge the present series is the first European series investigating the outcome after PD in a group of elderly patients over 75 years old, and it is the second largest series on this topic. This study reports a lower postoperative mortality than that reported by Bathe et al.[15] and Chen et al.[17] and is comparable with that reported by Sohn et al.,[16] whereas it reports the lowest morbidity. Furthermore, this series includes the greatest number of mesentericoportal vein resections published until now in patients over 75 years old. As we previously reported, these results suggest that venous resection has no deleterious influence on the postoperative outcome.[36]

In accordance with all the referenced series[4,8,13–17,25,29,37–40] (Table 5), the results of the present series strongly suggest that age should not be considered as a contraindication for PD. At the opposite, the type of pathology significantly affects survival, with a better prognosis for patients with

periampullary malignant tumors compared with patients with pancreatic ductal adenocarcinoma (Figs. 3 and 4).[8,41]

CONCLUSION

Our data suggest that PD for pancreatic ductal adenocarcinoma should be performed independently of the age of the patients, provided that a curative resection can be safely achieved.

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Impact of Lymph Node Metastasis on Survival in Patients With Pathological T1 Carcinoma of the Ampulla of Vater

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To determine the prognostic factors for patients with pathological T1 (pT1) carcinoma of the ampulla of Vater, 36 consecutive patients with carcinoma of the ampulla of Vater who underwent surgery were retrospectively analyzed in terms of clinicopathological features. The overall 5-year Kaplan-Meier survival in all patients was 50.2%, and the median survival of all patients was 64.0 months. Factors favorably influencing a long-term outcome were the absence of lymph node metastasis ($P < 0.0001$), the absence of ulcer formation of the tumor ($P = 0.0062$), and the absence of tumor invasion into the duodenum ($P = 0.0025$) and the pancreas ($P = 0.0098$). In a multivariate analysis, lymph node metastasis was the only predictor of survival ($P = 0.0023$). In the pT1 stage patients, 20% of the patients had lymph node metastasis, and their survival was statistically poor compared to the pT1 patients without lymph node metastasis ($P = 0.017$). As for survival after the operation, there was no significant difference between pancreatoduodenectomy and pylorus-preserving pancreatoduodenectomy. (J GASTROINTEST SURG 2006;10:823–828)

KEY WORDS: Carcinoma of ampulla of Vater, prognostic factor, lymph node metastasis

The ampulla of Vater consists of the papilla, the common channel, the distal common bile duct, and the distal main pancreatic duct. The papilla is covered by intestinal mucosa.[1] Carcinoma of the ampulla of Vater is relatively rare and has a better prognosis after resection compared with pancreatic head carcinoma.[2–6] However, some percentage of patients have a poor prognosis because of distant metastases or a local recurrence even after an R0 resection. As for the prognostic factors for carcinoma of the ampulla of Vater, some reports have been published.[7–13] In these studies, lymph node metastasis,[7,8,10–13] tumor invasion into the pancreas or the duodenum,[12] ulcer formation of the tumor,[7,11] and tumor differentiation[8,12] were poor prognostic factors, but their importance has not been well established. Especially in pT1 stage carcinoma that has no invasion to the pancreas and the duodenum, it is unclear what the prognostic factors are after an R0 resection. Moreover, although local resection or pancreatoduodenectomy (PD) with lymphadenectomy[14–18] are commonly performed, no standard surgical strategy against carcinoma of the ampulla of Vater in the pT1 stage has been established. The present study was conducted to review the prognostic factors in 36 patients with carcinoma of the ampulla of Vater and to determine the appropriate surgical procedure, especially in stage pT1.

PATIENTS AND METHODS

From January 1993 to December 2003, 37 patients were operated on for carcinoma of the ampulla of Vater at Wakayama Medical University Hospital and its related teaching hospitals. Thirty-six patients underwent a PD or a pylorus-preserving pancreatoduodenectomy (PpPD) with regional lymphadenectomy that included lymph nodes in the hepatoduodenal ligament, along the superior

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mesenteric vessels, and on the surface of the pancreatic head. One patient underwent local resection of the ampulla of Vater because of her poor medical condition. Follow-up data were obtained through medical record review, which includes the background of the patients, surgical data, tumor characteristics, and survival time. The tumors were classified by the tumor-node-metastasis (TNM) classification criteria.[19] As tumor markers, the preoperative serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were measured. The cutoff levels for these markers were 5.0 ng/ml and 37 units/dl, respectively. Survival estimates were generated using the Kaplan-Meier method, and survival curves were compared using a log-rank test. A multivariate Cox proportional hazards model was established to evaluate which factors independently affected postoperative survival. Statistical significance was achieved at $P < 0.05$.

RESULTS

Patient Characteristics

The mean age of the patients was 65.3 years old. Fourteen were female and 22 were male. Patients were in TNM stage IA (33.3%), stage IB (16.7%), stage IIA (8.3%), and stage IIB (41.7%). No patients belonged in TNM stages III or IV. Fifteen, 12, and 9 patients had tumor stage pT1, pT2, and pT3, respectively, while 3 patients had lymph node metastasis in the pT1 stage and 7 patients had lymph node metastasis in the pT2 stage. Eleven patients (30.7%) underwent PD, and 25 patients (69.8%) underwent PpPD (Table 1).

Overall Actuarial Survival for Patients

The overall 5-year survival rates of TNM stages IA, IB, IIA, and IIB were 83.3%, 75.0%, 66.7%, and 17.8%, respectively. Patients with TNM stage IIB had a statistically poor prognosis, compared to the other stages ($P < 0.01$) (Fig. 1).

Table 1. Background of the patients

Mean age (yr)	65.3
Gender (male:female)	22:14
TNM stage	
IA (%)	12 (33.3)
IB	6 (16.7)
IIA	3 (8.3)
IIB	15 (41.7)
Operative procedure	
Pancreatic head resection	
PD (%)	11 (30.7)
PpPD	25 (69.5)
Local resection	1 (2.8)

PD = pancreatoduodenectomy; PpPD = pylorus-preserving pancreatoduodenectomy; TMN = tumor, metastasis, lymph node.

Univariate Analysis of Predictors of Survival

Lymph node metastasis ($P < 0.0001$), ulcer formation of the tumor ($P = 0.0062$), and tumor invasion to the duodenum ($P = 0.0254$) or the pancreas ($P = 0.0098$) had a negative impact on survival following a resection in univariate analysis (Table 2). Operation procedure (PD versus PpPD) and preoperative serum levels of CEA or CA19-9 had no influence on survival.

Multivariate Analysis of Predictors of Survival

Multivariate analysis showed that the presence of lymph node metastasis was associated with a poor prognosis and was an independent predictive factor for survival ($P = 0.0023$) (Table 3).

Survival for Patients According to TMN Stage

Together with the pT1 and pT2 stage carcinoma, patients with lymph node metastasis (N1) had a poor prognosis compared to patients without lymph node metastasis (N0) ($P = 0.001$) (Fig. 2).

Location of the Metastatic Lymph Nodes

Fifteen patients had lymph node metastasis. The locations of the metastatic lymph nodes were on the posterior surface of the pancreatic head (80%), along the superior mesenteric vein (33.3%), along the common hepatic artery (13.3%), and on the superior surface of the pancreatic head (6.7%) (Table 4).

DISCUSSION

Carcinoma of the ampulla of Vater has a more favorable prognosis than other malignant tumors of the periampullary region.[2–6] Tumors of the ampulla of Vater tend to obstruct the common bile duct early in the disease process compared with tumors of the pancreas head, and, thus, are diagnosed earlier in the course of the disease. As for the prognostic factors of carcinoma of the ampulla of Vater, some reports have been published.[7–13] Lymph node metastasis,[7,8,10–13] tumor invasion into the pancreas or the duodenum,[11] ulcer formation of the tumor,[7,11] and tumor differentiation[8,12] have been reported as poor prognostic factors. In particular, lymph node metastasis is probably the most common prognostic factor, but it has not been well established and it is

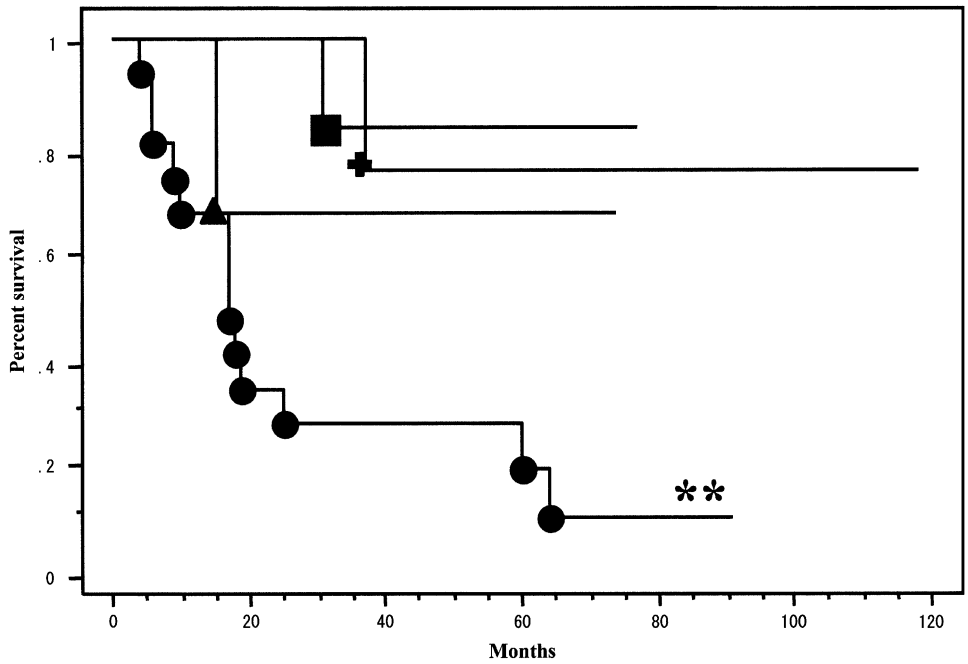

Fig. 1. Overall percent survival (1 = 100%) for patients with carcinoma of the ampulla of Vater (n = 36) stratified for UICC stage. ■, Stage IA; +, stage IB; ▲, stage IIA; ●, stage IIB. $^{**}P < 0.01$, compared with other stages.

unclear whether this factor fits as a predictor of long-term survival in patients with pT1 stage carcinoma. However, if lymph node metastasis is the prognostic factor for pT1 stage carcinoma, this factor might have an impact on the decision of surgical procedure for pT1 stage carcinoma. Therefore, the choice of surgical procedures (for example, a PpPD with standard lymph node resection versus local resection) is not clear for patients with pT1 stage carcinoma.[14–18]

In this study, lymph node metastasis, ulcer formation of the tumor, and tumor invasion to the duodenum or the pancreas had a negative impact on the survival in the univariate analysis. Previously, it has been shown that submucosal invasion is not associated with lymph node metastasis, but deeper invasion than submucosal is associated.[11] It has been reported that the preoperative serum CEA level influenced the postoperative survival of carcinoma of the ampulla of Vater.[7] In our study, serum CEA and CA19-9 levels were not predictors of survival after operation.

The final results of multivariate analysis show that lymph node metastasis was associated with a poor prognosis and was an independent predictive factor for survival. We herein reported that 20% of pT1 stage tumors and 58.8% of pT2 stage tumors had lymph node metastasis. We again analyzed the influence of the nodal status on survival of pT1 and pT2 stage patients. The survival of pT1 and pT2 patients with lymph node metastasis was statistically poor compared to pT1 and pT2 patients without lymph node metastasis.

Several reports suggested that a PD with regional lymphadenectomy should be a curative resection of carcinoma of the ampulla of Vater.[7–13] However, regarding pT1 or pT2 stage carcinoma, a surgical strategy is not fully clarified. Mehrdad et al.[17] reported that local resection is a suitable alternative to PD in patients with pT1 and pT2 stage carcinomas. Asbun et al.[18] reported that local resection has been advocated as being equal to PD in patients with pT1 stage. On the other hand, Castro et al.[15] reported that PD is recommended even for pT1 stage carcinomas because 28% of the patients with pT1 stage had lymph node metastasis. Mu et al.[20] retrospectively investigated the frequency of lymph node involvement in perigastric lesions for 41 patients with carcinoma of the ampulla of Vater and the frequency was 2.5%. In our study, pT1 stage carcinomas resulted in lymph node metastases, so we recommend PD with lymphadenectomy. Indeed, the only patient who underwent local resection in this study later developed clinically obvious lymph node metastasis after operation.

With the recent tendency toward preservation of functions, PpPD has become common for the

Table 2. Clinicopathological characteristics and univariate analysis for survival

Characteristics	Survival			*P* value
	1 year	3 years	5 years	
Ulcer formation				
Negative (n = 9)	96.2%	70.2%	57.9%	0.0062
Positive (n = 27)	55.6%	22.2%	22.2%	
Tumor differentiation				
Papillary (n = 16)	93.3%	74.2%	74.2%	0.0954
Well (n = 5)	80.0%	80.0%	80.0%	
Moderately (n = 11)	72.7%	41.6%	31.2%	
Tumor invasion				
Duodenum				
Negative (n = 27)	88.5%	72.2%	59.5%	0.0254
Positive (n = 9)	77.8%	22.2%	22.2%	
Pancreas				
Negative (n = 15)	93.3%	74.2%	74.2%	0.0098
Positive (n = 21)	80.2%	42.8%	31.2%	
Vein				
Negative (n = 27)	88.5%	61.6%	55.5%	0.272
Positive (n = 9)	77.8%	44.4%	33.3%	
Lymphatic vessel				
Negative (n = 12)	90.9%	72.7%	72.7%	0.137
Positive (n = 24)	83.3%	50.9%	41.2%	
Nerve				
Negative (n = 28)	89.0%	63.6%	51.4%	0.458
Positive (n = 8)	75.0%	37.5%	37.5%	
Lymph node metastasis				
Negative (n = 21)	100%	85.1%	76.6%	<0.0001
Positive (n = 15	66.7%	26.7%	17.8%	
Tumor marker				
CEA				
Normal range (n = 27)	84.7%	56.3%	48.3%	0.543
High (n = 6)	83.3%	66.7%	66.7%	
CA19-9				
Normal range (n = 22)	90.5%	65.8%	65.8%	0.111
High (n = 11)	72.7%	45.5%	30.3%	
Operation procedure				
PD (n = 11)	90.9%	50.5%	40.4%	0.414
PpPD (n = 25)	83.5%	66.3%	59.0%	

surgical treatment of tumors in the pancreatic head region. In our study, we compared PpPD to PD in terms of survival time after resection. We found that these two procedures resulted in similar postoperative survival. PpPD generally does not remove peripyloric lymph nodes. However, locations of the metastatic lymph nodes in out study were 80% on the posterior surface of the pancreatic head, 33.3% along the superior mesenteric vein, and 6.7% on the superior surface of the pancreatic head. There was no peripyloric lymph node metastasis in the present study. Therefore, we strongly suggest that PpPD is a suitable procedure for patients with carcinoma of the ampulla of Vater even if the preoperative stage was stage T1 using endoscopic ultrasonography and thin-cut computed tomography.

Table 3. Multivariate analysis for survival

	95% Confidence interval	Relative risk	*P* value
Tumor invasion			
Pancreas	0.306–5.057	1.244	0.766
Duodenum	0.342–8.412	1.696	0.518
Lymph node etastasis	2.184–36.11	8.880	0.002
Ulcer formation	0.869–14.94	3.604	0.078

As for adjuvant therapy, the effect of chemoradiotherapy on the survival is not yet established in

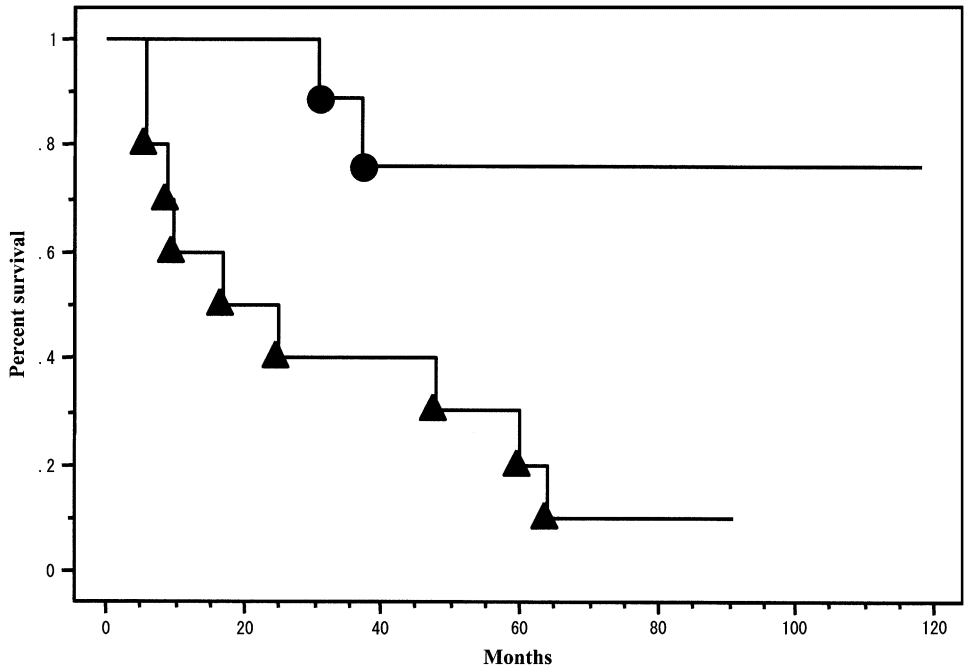

Fig. 2. Percent survival (1 = 100%) for patients with carcinoma of the ampulla of Vater, stratified for UICC T1 and T2 stage and lymph node status ($P = 0.001$). ●, N0; ▲, N1.

carcinoma of the ampulla of Vater. It has been reported that adjuvant chemoradiotherapy for carcinoma of the ampulla of Vater is well tolerated and might improve the survival.[21] On the other hand, Sikora et al.[22] reported that adjuvant chemoradiotherapy did not improve the long-term survival or decrease recurrence rates in patients with carcinoma of the ampulla of Vater who had undergone pancreaticoduodenectomy. In the present study, 11 patients with advanced stage disease had adjuvant chemotherapy with 5-fluorouracil. The number of patients who received adjuvant chemotherapy was too small to draw any conclusion in terms of the efficacy of the chemotherapy.

CONCLUSION

The presence of lymph node metastases was a negative predictive factor for survival of carcinoma of the ampulla of Vater after operation. Judging from the frequency and locations of lymph node metastasis, PpPD is the best choice of operation for carcinoma of the ampulla of Vater even for patients with pT1 stage tumors.

Table 4. Location of the metastatic lymph nodes (n = 15)

On the posterior surface of the pancreatic head	12 (80.0%)*
Along the superior mesenteric vein	5 (33.3%)*
Along the common hepatic artery	2 (13.3%)*
On the superior surface of the pancreatic head	1 (6.7%)*

*Three patients are overlapped with two or three locations.

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Pancreatoblastoma in an Adult: Case Report and Review of the Literature

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A 50-year-old man presented with progressive gastrointestinal symptoms. An abdominal computed tomography scan demonstrated a 12 × 12-cm pancreatic mass involving the greater curvature of the stomach and multiple hypervascular hepatic metastases. An initial fine needle aspiration of the pancreatic mass was nondiagnostic, and a subsequent fine needle aspiration of a liver mass was read as metastatic acinar cell carcinoma. The patient underwent a palliative resection for tumor-associated pain and gastrointestinal hemorrhage that revealed a large pancreatic tumor invading through the full thickness of the colon at the splenic flexure and adherent to the posterior gastric wall. The pathology from the distal pancreatectomy, splenectomy, partial gastrectomy, partial colectomy, and cholecystectomy unexpectedly supported a diagnosis of pancreatoblastoma with evidence for squamoid corpuscles as well as areas of acinar formation. Despite multiple chemotherapy regimens, the patient's disease continued to progress in the liver and the lungs. During the course of his therapy, the patient's serum α-fetoprotein levels and serum lipase levels rose concurrently, suggesting tumor-associated production of both of these factors. Seventeen months after the diagnosis of metastatic pancreatoblastoma, the patient died from his disease. Our case illustrates the fact that pancreatoblastomas are extremely difficult to diagnosis preoperatively. In addition, our case demonstrates that pancreatoblastomas can be α-fetoprotein producing, hormone producing, and enzyme producing when it occurs in adults. (J GASTROINTEST SURG 2006;10:829–836)

KEY WORDS: Pancreatoblastoma, pancreatic cancer, treatment, review

CASE REPORT

A 50-year-old man presented with a 6-month history of progressive epigastric discomfort, nausea, vomiting, and early satiety and a 15-pound weight loss. An avid athlete, the subject also noted the development of lightheadedness during his regular 5-mile runs. Treatment with a proton pump inhibitor failed to alleviate his symptoms. An initial physical examination was remarkable for epigastric tenderness. An abdominal computed tomography scan demonstrated a 12 × 12-cm mass in the tail of the pancreas involving the greater curvature of the stomach, multiple hypervascular liver metastases, and splenic vein compression with associated venous collaterals (Fig. 1). An extensive laboratory work-up was significant for a mild normocytic anemia (hemoglobin = 12.2 g/dl, mean cell volume = 83 fl) and elevated serum lipase (207 units/L, normal=17−57) and proinsulin (147 ng/ml, normal <17.4) levels. His other laboratory tests were normal, including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, amylase, fasting insulin, gastrin, glucagon, chromogranin A, CA19-9, CEA, α-fetoprotein (AFP), β-human chorionic gonadotrophin, and lactate dehydrogenase. A fine needle aspiration (FNA) of the pancreatic mass was read as normal pancreatic tissue. An FNA of a liver mass revealed small, monotonous-appearing, minimally atypical cells organized in an acinar pattern mimicking normal pancreas but without an associated ductal component (Fig. 2). These findings were consistent with a diagnosis of metastatic acinar cell carcinoma (ACC).

While considering treatment options including radiation and chemotherapy,[1] the patient developed

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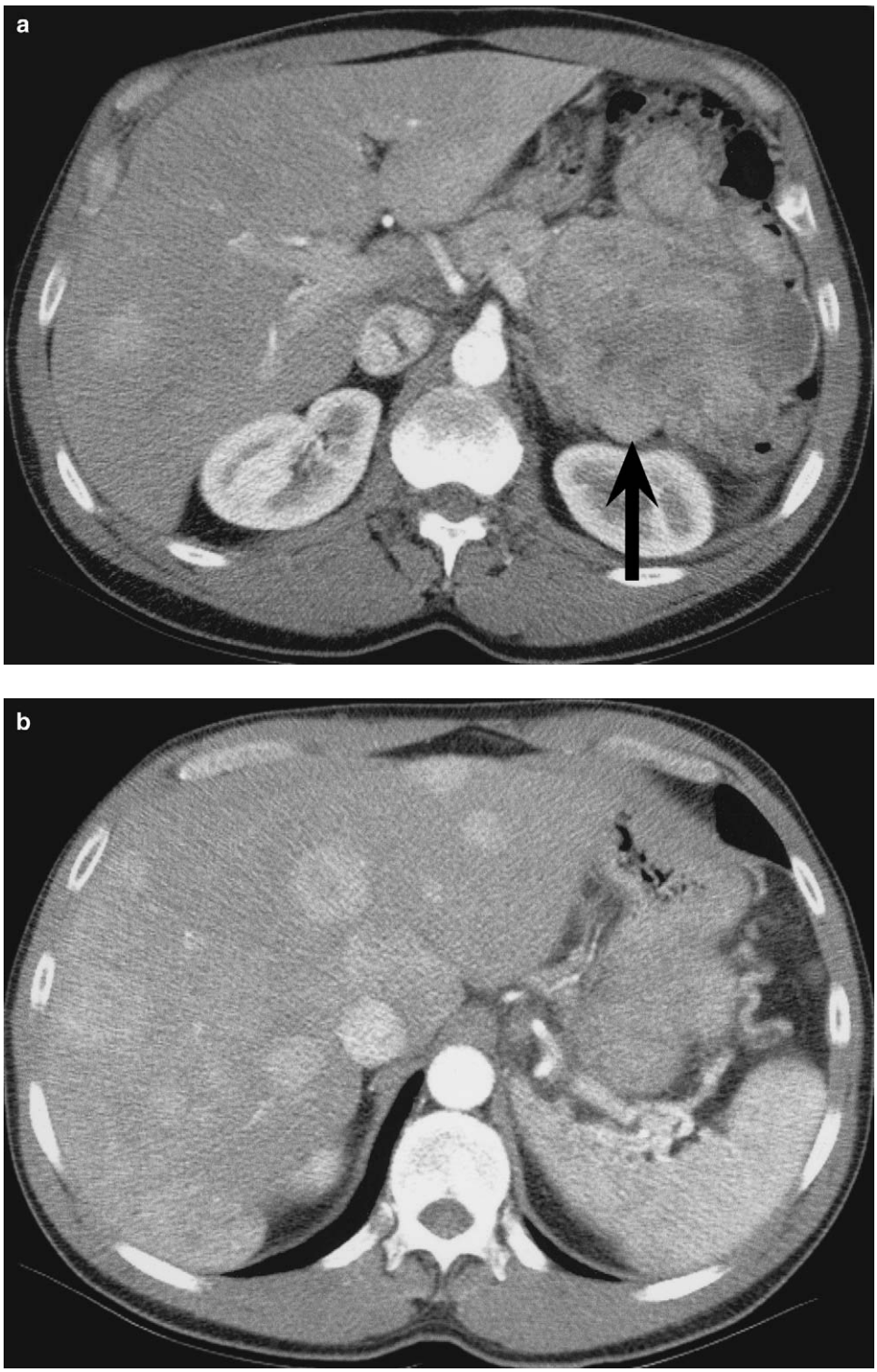

Fig. 1. (**a**) Abdominal computed tomography scan with lobular mass in the tail of the pancreas involving the greater curvature of the stomach and invading the splenic vein. (**b**) Abdominal computed tomography scan with numerous hypervascular masses throughout the liver.

gastrointestinal bleeding requiring red blood cell transfusions (hemoglobin, 7.3 g/dl), progressive abdominal pain, and early satiety. An endoscopic ultrasound identified tumor invasion of the gastric wall. A decision was made to perform a palliative resection of the primary tumor in this otherwise fit

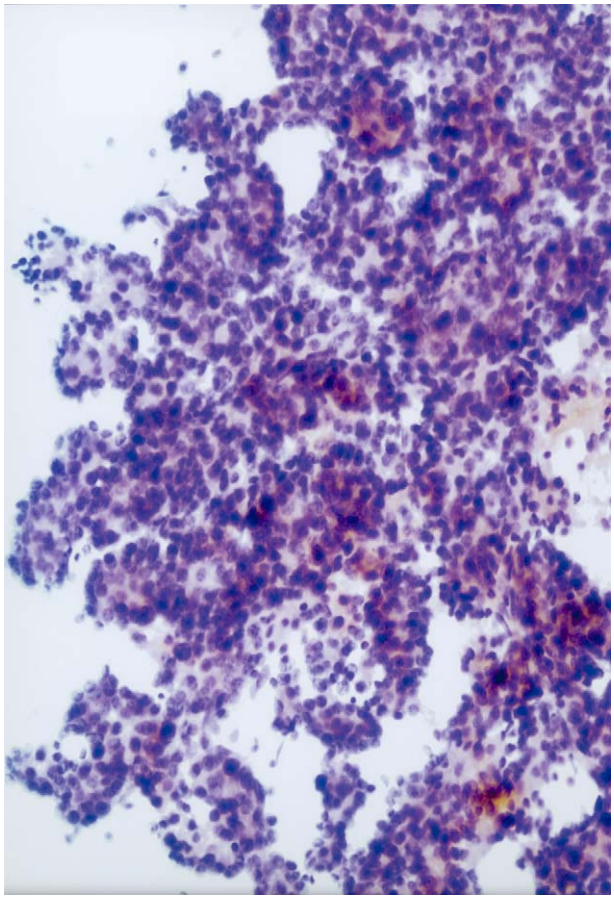

Fig. 2. Fine needle aspiration of a liver mass with small, monotonous appearing, minimally atypical cells organized in an acinar pattern mimicking normal pancreas but without an associated ductal component.

patient with tumor-associated pain and gastrointestinal hemorrhage. Intraoperatively, the patient was found to have a large pancreatic tumor invading through the full thickness of the colon at the splenic flexure (Fig. 3, *a*) and adherent to the posterior gastric wall (Fig. 3, *b*). Multiple hepatic metastases were noted. The patient underwent a distal pancreatectomy, splenectomy, partial gastrectomy, partial colectomy, and cholecystectomy. His postoperative course was complicated by a fever on postoperative day 3 related to an enterococcal bacteremia. He was treated with intravenous ampicillin and defervesced by postoperative day 5. The patient was discharged on a regular diet on postoperative day 8 and completed a course of oral ampicillin as an outpatient.

Unexpectedly, the histopathologic features supported a diagnosis of pancreatoblastoma (PB) with evidence for squamoid corpuscles (Fig. 4, *a*) as well as areas of acinar formation (Fig. 4, *b*) reminiscent of the findings from the FNA. Additional immunohistochemical studies showed that the tumor exhibited weak staining for CD7 and moderate to strong staining for trypsin. Immunohistochemical tests for CK20, CK5/6, CK17, CD99, high molecular weight keratin, vimentin, insulin, chromogranin A, synaptophysin, p53, and AFP were all negative. The tumor was 13 cm in greatest diameter and showed transmural invasion of the colon (the probable source of the hemorrhage) but not the stomach or the spleen. No lymph node involvement was seen (26 lymph nodes were tested); although liver metastases were confirmed histologically. The surgical margins of the primary tumor resection were negative.

Postoperatively, the patient received cisplatin and doxorubicin, resulting in a mixed radiographic response. Within 3 months of starting therapy, however, there was evidence for disease progression in both the liver and the lungs. The patient's chemotherapy regimen was changed to docetaxel and gemcitabine without obvious benefit. The patient subsequently showed evidence of a modest radiographic response to capecitabine with oxaliplatin; however, after 4 months of therapy, the patient discontinued oxaliplatin due to an associated debilitating neuropathy. Capecitabine alone proved ineffective; the patient experienced progressive fatigue, weight loss, and right-upper-quadrant abdominal pain. During the course of his therapy, the patient's serum AFP level rose from 7.6 ng/ml at baseline (normal <10.9) to 514 ng/ml as his disease progressed. In addition, his serum lipase rose concurrently to 2964 units/L (normal <57) from 207 units/L, suggesting tumor-associated production of both of these factors. Seventeen months after the diagnosis of metastatic PB, the patient died from his disease.

DISCUSSION

PB is an unusual malignant neoplasm of the pediatric pancreas that is rarely seen in adults. Since Becker described the first case of infantile PB in 1957, over 200 cases have been reported in children.[2] In contrast, only 14 cases have been confirmed in adults (Table 1).[3–12] PBs must be differentiated from other tumor types, including pancreatic carcinomas (particularly ACC), solid and papillary tumors, and islet cell tumors.[13] Patients typically present with nonspecific gastrointestinal symptoms such as abdominal pain and weight loss.[3] Radiographically, the tumors usually appear as large (>8 cm), enhancing masses with cystic or necrotic components.[14] Grossly, the lesions are often large,

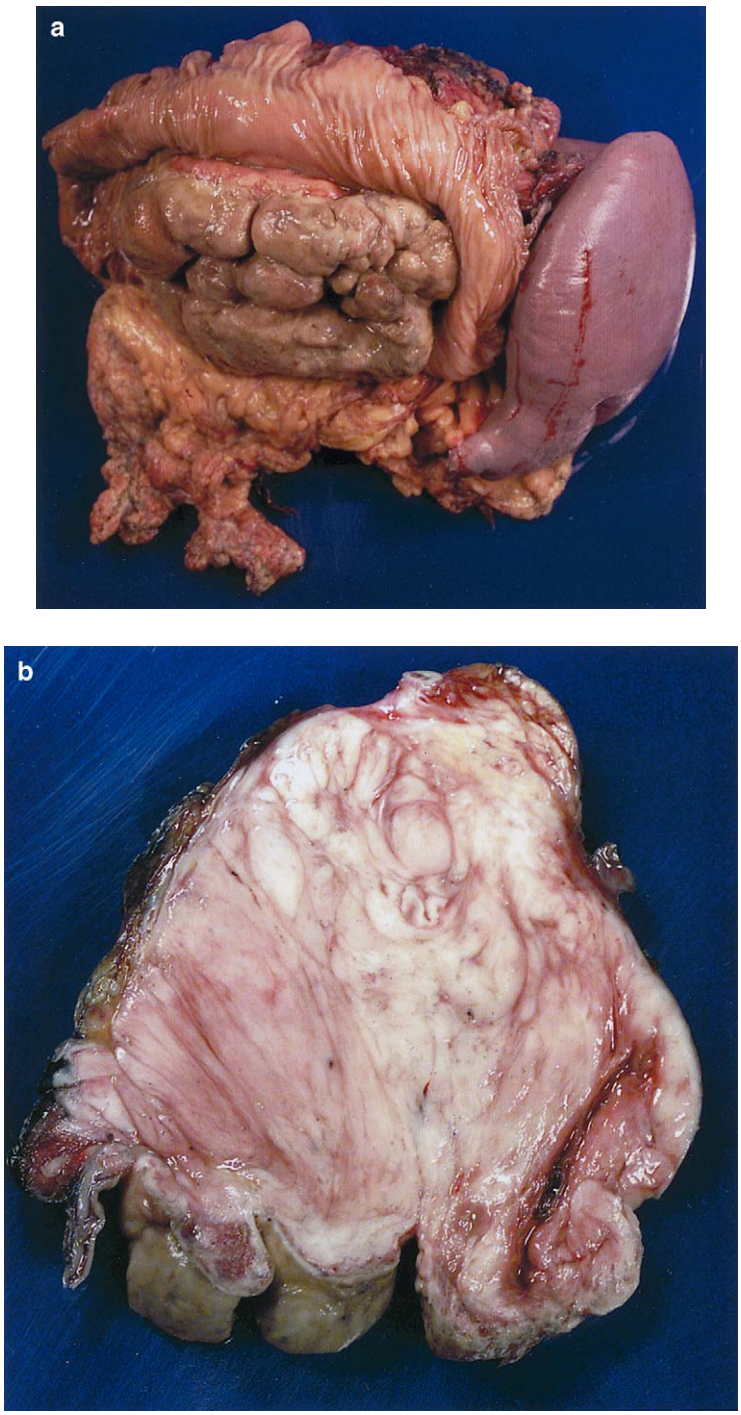

Fig. 3. (**a**) Gross pancreatic tumor involving the splenic flexure of the colon and adherent to the stomach. (**b**) Gross cross section of tumor.

globular, discrete masses with pseudocapsules of compressed tissue, arising from the head or tail of the pancreas.[3]

Histologically, the tumors resemble fetal tissue with foci of epithelial, mesenchymal, exocrine, squamous, or endocrine differentiation.[3] PBs are distinguished from ACCs and neuroendocrine tumors by their distinct sheets of malignant cells, nesting growth pattern, acinar formation, squamoid corpuscles, and cellular stroma (Fig. 4).[13] Immunohistochemical evidence for acinar differentiation (e.g., staining for trypsin, chymotrypsin, and/or lipase) is typical, although regional variability is common. Neuroendocrine differentiation (as evidenced by

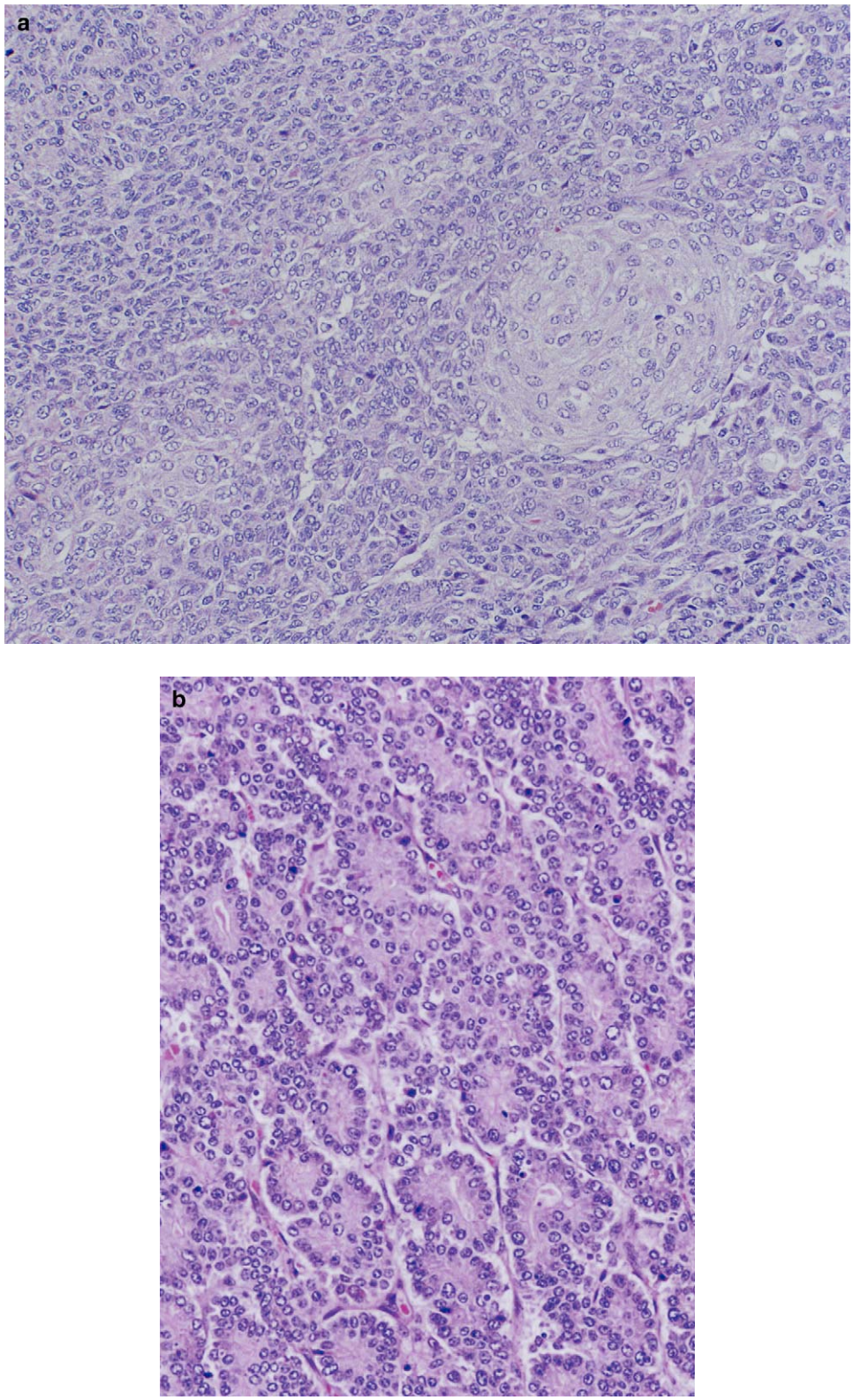

Fig. 4. (**a**) Representative histologic section of tumor containing scattered islands of squamoid differentiation termed "squamoid corpuscles." The squamoid cells have abundant, pale, eosinophilic cytoplasm, and larger, pale nuclei. The squamoid corpuscles have a subtle, whorling growth pattern that helps differentiate them from the surrounding solid growth areas. (**b**) Representative histologic section of tumor composed predominantly of acinar cells with basally located, round nuclei and fairly abundant, amphophilic cytoplasm arranged around a central lumen. Nuclear chromatin is mainly vesicular, but some cells show a finely granular pattern. Nucleoli are occasionally prominent. The cytoplasm contains fine, refractile, eosinophilic granules and shows faint, diastase-resistant PAS staining.

Table 1. Case reports of adult pancreatoblastoma

Case	Presentation	Tumor	Therapy	Outcome
Palosarri[6]	37y M w/abd pain, diarrhea, wt loss	8-cm head, +LN, encasing CBD, SMA, SMV, PV	Incomplete resection → adj 5-fluorouracil/ doxorubicin/mitomycin ×3 → no response → intraop XRT 15 Gy + EBXRT 45 Gy → significant tumor shrinkage ×10 mo → new liver mets	Liver mets at 15 mo
Hoorens[7]	39y F w/abd mass	13-cm tail	Resection	NED at 30 mo
Dunn[8]	61y M w/splenomegaly	9-cm tail, spleen invasion—postmortem diagnosis (original diagnosis—microadenoma)	Resection → adj 5-fluorouracil/ doxorubicin/mitomycin	Died at 11 mo of cerebral hemorrhage, NED at autopsy
Klimstra[5]	19y M w/incidental mass	15 cm head, +LN, mets to lungs, liver, adrenals, spleen, kidney	Resection	Died at 10 mo of advanced disease
	36y M w/obstructive jaundice	"large" head, +LN, liver mets—postmortem diagnosis	None	Died at 5 mo of advanced disease
	37y M w/abd mass, wt loss	12-cm head, liver mets	Chemotherapy/XRT	Died at 38 mo of advanced disease
	54y M w/abd pain	20-cm tail	Resection	NED at 15 mo
	56y M/abd mass	20-cm tail	Resection	NED at 5 mo
Levey[3]	68y F w/diarrhea, wt loss	12-cm tail, spleen and stomach invasion	Resection	Died at 4 mo of liver mets
Robin[9]	20y M w/abd mass	9-cm head, no mets	Resection → adj chemo	Died at 7 mo of liver mets
Mumme[10]	22y F w/abd pain, abd mass, wt loss	9-cm tail, no mets	Resection + intraop XRT 15 Gy → adj doxorubicin/carboplatin ×2 + EBXRT 36 Gy	Died at 9 mo
Benoist[11]	48y F w/abd pain, melena	10-cm body/tail extending from splenic hilum to PV, gastric varices, –LN, 2 liver mets	Resection w/metasectomy → adj cisplatin/levimasole/5-fluorouracil/ etoposide ×6	NED at 36 mo
Gruppioni[12]	30y M w/abd pain	8-cm head	Resection	NED at 10 mo
Du[4]	78y F w/painless jaundice	2.7-cm ampulla of Vater	Resection	NED at 6 mo
Rajpal	50y M w/abd pain, wt loss	13-cm tail, colon invasion, liver mets	Resection → multiple chemo regimens	Died at 17 mo

abd = abdominal; adj = adjuvant; CBD = common bile duct; EBXRT = external beam radiation therapy; F = female; intraop = intraoperative; IN = lymph nodes; M = male; mets = metastases; PV = portal vein; SMA = superior mesenteric artery; SMV = superior mesenteric vein; w/ = with; wt = weight; XRT = radiation therapy.

expression of chromogranin, synaptophysin, and/or neuron-specific enolase) is evident in more than 50% of tumors, but staining is usually multifocal and a significant endocrine component (>10% of neoplastic population) is unusual. Expression of specific hormones like insulin and glucagon is rarely seen.[5] Electron microscopy can be used to demonstrate the presence of electron-dense zymogen granules suggestive of acinar differentiation; neurosecretory granules are seen less frequently. Evidence for ductal differentiation (mucin production or CA19-9 expression) is common, although well-formed ductal structures are not typically present.[5] Despite the admixture of cells with exocrine and endocrine differentiation within PBs, reports of patients with hormone- or enzyme-secreting tumors are rare.[5]

As in the case we presented, PB is extremely difficult to diagnose by percutaneous biopsy because (1) its histologic features overlap those of ACC, which is far more common, (2) it is so rare that it is often not considered in the differential diagnosis, and (3) squamoid corpuscles may not be visualized simply due to sampling error, thus compromising one's ability to make the correct diagnosis. As a result, the correct diagnosis is often only made post mortem or after gross resection. PBs can invade adjacent structures, including the duodenum, stomach, transverse colon, and spleen.[3,4] Dissemination by the bloodstream or lymphatics results in metastases to the liver, regional lymph nodes, lungs, and bone.[5] In approximately 50% of pediatric cases, long-term survival is achieved with surgical resection alone.[3] Because of the rarity of this tumor in adults, the natural history and prognosis of this disease cannot be accurately predicted, although the vast majority of patients appear to have died from their disease.[3,5,6,9,10] The longest documented survival after diagnosis in an adult is 38 months.[5]

The pathogenesis of this disease process is still under investigation. Abraham et al.[13] analyzed a series of nine PBs (seven children and two adults) for genetic mutations. Allelic loss on chromosome 11p was the most common genetic alteration (six of seven infantile cases).[13] This finding supports a potential link between Beckwith-Wiedemann syndrome and PB.[13] In fact, there have been four documented cases of PB in infants with Beckwith-Wiedmann syndrome.[13] Abraham et al. also discovered molecular alterations in the adenomatous polyposis coli/β-catenin pathway in 67% of their cases of PB.[13] Abnormalities typically found in pancreatic ductal adenocarcinomas in adults were not identified (such as mutations in the *k-ras* gene and *p53* accumulation).[13] These provocative findings suggest that PBs are genetically distinct from pancreatic ductal adenocarcinomas but may share certain molecular features with other infantile embryonal tumors such as hepatoblastoma.[13]

To our knowledge, only one example of serum tumor marker production by an adult PB has been recorded.[4] Du et al. observed an elevated CA19-9 in their patient who presented with an ampulla of Vater PB.[4] In contrast, 30−50% of pediatric cases of PB are associated with markedly elevated serum levels of CEA and/or AFP (yolk sac type).[3,4] Presumably, like hepatoblastomas, tumor-associated AFP production in this setting reflects the embryonal nature of this neoplasm. Tumor markers typically normalize after tumor resection and serve as potential indicators of subsequent tumor recurrence.[3,5] Despite the fact that our patient's primary tumor did not express AFP by immunohistochemistry, his serum AFP level rose from normal to 514 ng/ml as his disease progressed. In addition, our patient's serum lipase and proinsulin levels were elevated on presentation, suggesting tumor-associated production of these factors. As the patient's disease progressed, his serum lipase rose accordingly. We do not have follow-up serum proinsulin levels, but the patient did not develop laboratory evidence for hypoglycemia. As far as we can tell, this case is the first report of an enzyme- and hormone-producing PB in an adult.[3,6,11]

As described, the preoperative diagnosis in our patient was ACC of the pancreas, and distinguishing between ACC and PB can be difficult when limited to material obtained from a percutaneous biopsy. ACC is another rare pancreatic neoplasm that accounts for only 1−2% of pancreatic exocrine tumors. Clinically, ACCs are aggressive neoplasms that may present with a characteristic syndrome of disseminated fat necrosis marked by panniculitis and polyarthritis.[15] In contrast to PB, ACC typically occurs in adults, is composed of a single population of cells with solid and acinar areas, and lacks squamoid corpuscles.[5] Like PB, AFP overexpression is sometimes seen, and the presence of mixed ductal and endocrine components has been described.[16,17] However, compared to PB, ACC is generally associated with more intense and diffusely positive immunohistochemical staining for pancreatic digestive enzymes (e.g., lipase, trypsinogen, chymotrysinogen, and alpha-1-antitrypsin), and elevated serum levels are more commonly seen.[16] In addition, clinical manifestations related to tumor-associated elaboration of hormones occur more frequently.[18]

Optimal treatment for PB remains to be defined due to the paucity of cases in adults. The mainstay of treatment is complete surgical resection, as the only reports of long-term survival are in patients

who had their primary tumors resected.[2] The role of adjuvant therapy is less clear and is largely based on anecdotal experience. In children with locally unresectable, recurrent, or metastatic disease, the most commonly used chemotherapy regimen is doxorubicin and cisplatin.[2,19] Other chemotherapy combinations that have been used in children with advanced disease include ifosfamide/vincristine/dactinomycin, cisplatin/doxorubicin, cisplatin/vinblastine/bleomycin, cyclophosphamide/dactinomycin, vincristine/cyclophosphamide/doxorubicin, vincristine/cyclophosphamide/cisplatin/etoposide, and vincristine/actinomycin d/cyclophosphamide.[2] In adults, 5-fluorouracil/doxorubicin/mitomycin has been used in two cases for locally advanced disease.[6,8] Doxorubicin/carboplatin has been given as adjuvant therapy to 1 patient.[10] An adult with metastatic disease received cisplatin/levimasole/5-fluorouracil/etoposide following gross resection with metastectomy for synchronous liver metastases.[11] Chemotherapy-resistant disease in both children and adults occasionally responds to radiation therapy.[2,6] Metastectomies are performed when possible.[11,20,21] Unlike adults, however, children often present with encapsulated tumors and are more likely to achieve long-term survival with surgery alone.

Our case illustrates a number of important features of adult PB, including the fact that it is an extremely difficult tumor to diagnosis correctly preoperatively. In addition, we demonstrated that PB can be AFP producing, hormone producing, and enzyme producing when it occurs in adults. Thus, there is potential overlap in clinical, as well as histopathologic, features between ACC and PB. Finally, our patient's metastatic disease quickly proved refractory to first-line treatment with doxorubicin and cisplatin, underscoring the fact that PBs present significant therapeutic, as well as diagnostic, challenges when they occur in adults.

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The Role of p65 NF-κB/RelA in Pancreatitis-Induced Kupffer Cell Apoptosis

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Acute pancreatitis induces liver injury by upregulating Kupffer cell-derived Fas/FasL; on the other hand, acute pancreatitis induces apoptosis of Kupffer cells via NF-κB-dependent pathways. The balance between upregulation of Fas/FasL and Fas/FasL-induced apoptosis of its originator cell may determine the severity of pancreatitis-related liver injury. The aim of our study was to determine the role of p65 NF-κB/RelA in pancreatitis-induced Kupffer cell apoptosis. Acute pancreatitis was induced in NIH Swiss mice by a choline-deficient ethionine-supplement (CDE) diet. In vitro mouse Kupffer cell line was transfected with p65 siRNA and treated with pancreatic elastase to mimic pancreatitis. CDE pancreatitis upregulated nuclear translocation of p65 NF-κB/RelA, Fas/FasL, caspase-3, and DNA fragmentation in mice livers (all $P < 0.001$). In vitro, pancreatic elastase mimicked CDE-pancreatitis by upregulating nuclear translocation of p65 NF-κB/RelA, Fas/FasL, caspase-3, DNA fragmentation, and apoptosis in Kupffer cells (all $P < 0.001$). Transfection with p65 siRNA attenuated the elastase-induced nuclear translocation of p65 NF-κB/RelA, upregulation of Fas/FasL, caspase-3, DNA fragmentation, and apoptosis in Kupffer cells (all $P < 0.001$). Acute pancreatitis activates p65 NF-κB/RelA and induces apoptosis of Kupffer cells. Inhibition of p65NF-κB/RelA attenuates elastase-induced upregulation of proapoptotic pathways and apoptosis in Kupffer cells. The ability of Kupffer cells to autoregulate their stress response by inducing self-apoptosis warrants further investigation. (J GASTROINTEST SURG 2006;10:837–847)

KEY WORDS: Acute pancreatitis, Kupffer cells, NF-κB, RelA/p65, Fas/FasL, apoptosis

Kupffer cells, the liver resident macrophages, play a central role in the pathogenesis of acute pancreatitis as well as sepsis and alcohol-induced liver injury.[1] The maintenance of cell homeostasis by apoptosis is a critical regulatory mechanism in the normal immune system. The Fas/FasL death pathway and tumor necrosis factor receptor super family are involved in various forms of physiological and pathological cell death.[2,3] We have previously demonstrated that Kupffer cell-derived tumor necrosis factor and Fas/FasL mediate liver injury and hepatocyte apoptosis in an experimental model of acute pancreatitis.[2] Furthermore, we demonstrated that Fas, the cell surface receptor for FasL, was upregulated in Kupffer cells during acute pancreatitis.[2] Recently, we demonstrated that Kupffer cells undergo accelerated apoptosis during experimental pancreatitis and that inhibiting IκBα by overexpressing a mutant form of IκBα, attenuates pancreatitis-induced pancreatitis in Kupffer cells through NF-κB transcriptional regulation of Fas/FasL.[4,5] These data suggest that Kupffer cells may truncate their stress response by upregulating their own death receptor/ligand pathways.

The mammalian NF-κB family consists of five members, RelA (p65), RelB, c-Rel, p105/p50, and p100/p52, all of which contain homologous N-terminal RHDs (Rel homology domains). NF-κB is a homodimer or heterodimer of these subunits where the RHD mediates dimerization, DNA binding, nuclear localization, and interaction with inhibitors of NF-κB (IκB proteins).[6,7]

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NF-κB is activated in response to many stimuli, and in turn it activates a large number of diverse target genes; some of these genes are known to trigger antiapoptotic pathways, whereas others activate NF-κB-dependent apoptosis. Recently, it has been shown that NF-κB induces cell death after T-cell receptor engagement or exposure to DNA-damaging agents.[8] Others have shown that NF-κB activation is required for the onset of apoptosis induced by kainic acid,[9] whereas in the same cell type, inhibition of NF-κB by glucocorticoids promotes apoptosis. These findings suggest that the proapoptotic or antiapoptotic properties of NF-κB in a given cell depend on the cell type, extent of NF-κB activation or inhibition, and the nature of the stimulus.

Whether NF-κB activation results in antiapoptotic or proapoptotic effects suggests functional complexity greater than just structural changes from distinct NF-κB dimmer combinations. Nonetheless, the RelA (p65) subunit has an important role in the context of inflammatory conditions and cytokine production.

Acute pancreatitis can evolve from localized inflammation (in the pancreas) to severe systemic inflammation and distant organ injury. Pancreatic enzymes that may gain access to the systemic circulation-induced production of extrapancreatic, macrophage-derived cytokines and inflammatory mediators that precipitate histomorphologic injury in the liver and lung.[2,3] Specifically, we have demonstrated that Kupffer cell-derived Fas/FasL induces hepatocyte apoptosis. Furthermore, Fas/FasL mediates apoptosis of its originator cells (Kupffer cells) by NF-κB dependent pathways.[5] The objective of this study is to examine the role of p65 NF-κB/ RelA in pancreatitis-induced Kupffer cell apoptosis.

MATERIAL AND METHODS

All experiments were conducted with the prior approval of the Institutional Animal Care and Use Committee at the University of South Florida College of Medicine.

CDE Diet-Induced Pancreatitis

Acute pancreatitis was induced (n = 3 for all experiments) in female NIH Swiss mice (10–15 g) by using a choline-deficient ethionine-supplement diet (CDE). CDE diet induces severe acute hemorrhagic and necrotizing pancreatitis, with approximately 70% mortality over 5 days. Briefly, mice were fasted overnight with free access to water before beginning the CDE diet. The special laboratory mouse food (Harlan Taklad, Madison, WI) was mixed with 5% ethionine (Sigma, St. Louis, MO) and given to mice with a special "J" feeder. The feeder was changed every 4 to 6 hours, or sooner if found to be contaminated by animal excrement, to ensure sanitary conditions. Livers were harvested 48 hours after initiation of the CDE diet for protein analysis.

Murine Kupffer Cells

A cell line of murine Kupffer cells, KCL3-2 was established in the laboratory of one of the coauthors (R.L.), and was generated from H-2Kb-tsA58 mice.[10,11] These cells are derived from large size Kupffer cells and express the thermo labile mutant tsA58 of the Simian virus 40 large T antigen under the control the H-2K promoter. Similar to primary Kupffer cells, this cell line expresses scavenger receptor A, CD14, Toll-like receptor-4, the antigen-presenting molecules CD-40, CD-80, CD-1, endocytosed dextran-fluorescein isothiocyanate, and retains the capacity of clearing bacteria.

Cultures of Kupffer Cells

Mouse KCL3-2 cells were grown in RPMI 1640 with 10% fetal calf serum, 1% Na-pyruvate, 1% nonessential amino acids, 0.15% HEPES, 0.03% glutamax, and 1/5 volume condition medium that was collected from grown HepG2 and EAhy926 cell lines. Mouse KCL3-2 cells were subcultured at 33° C, and then at 37° C 1 day before experiments.[11]

Design and Transfection of siRNA

To design specific siRNAs that target the mouse NF-κB/p65 subunit, DNA sequences of the type AA (N19) were selected using siRNA target finder.[12] siRNA sequence UUGGUGACCCGUAAGAGUUU3′ was also used as negative control, as it does not match any mammalian sequences currently available on databases. The Mix siRNA for p65 sequences are: (5′ UGUGUCCAUUGUCUCACUC 3′) and (5′AGUC CCUGUCUGCACCUGU 3′).

p65 siRNA pool and nonspecific siRNA control were transfected into KCL3-2 cells by using a transfection reagent kit (Imgenex, San Diego, CA) according to the manufacturer's protocol; nontargeted p42-MAPK was used as a control. Twenty-four to 48 hours after siRNA transfection, 1×10^7 KCL3-2 cells were treated with pancreatic elastase (1U/ml, Sigma) for 4 hours to induce conditions that mimic acute pancreatitis. The dose of elastase had been validated in our lab in human mononuclear cells, lung macrophages, and Kupffer cells.[2–5] In addition, the role of elastase in the sepsis syndrome had been recently elucidated.[13] The experiments were grouped as follows: (1)

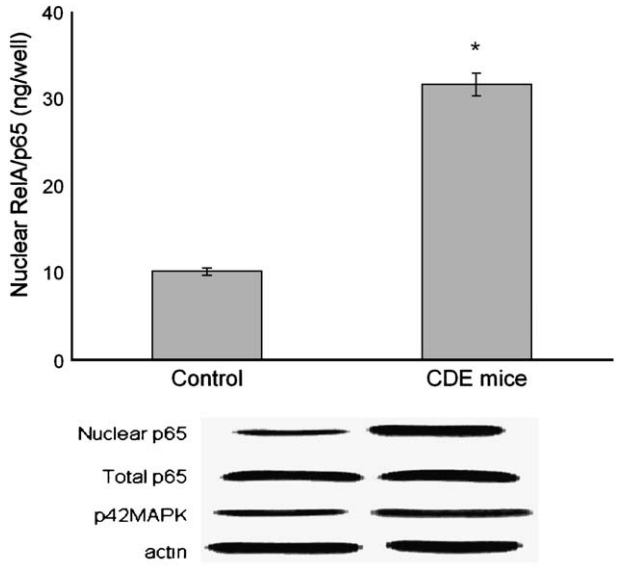


Fig. 1. Nuclear translocation of p65/RelA is dramatically increased in NIH mice livers by CDE pancreatitis (*$P < 0.001$ vs. control mice), whereas total cell p65 did not increase. p42 MAPK serves as control.

KCL3-2 + no treatment, (2) KCL3-2 + elastase, (3) KCL3-2 + control siRNA, (4) KCL3-2 + control siRNA + elastase, (5) KCL3-2 + p65 siRNA, and (6) KCL3-2 + p65 siRNA + elastase.

Reverse Transcription-Polymerase Chain Reaction

Briefly, total cells mRNA were isolated by Trizol solution (Invitrogen, Carlsbad, CA). One μg of RNA was primed by using oligo(dT) (Gibco, Gaithersburg, MD) and subsequently reverse transcribed with reverse transcriptase (SuperscriptII, Gibco). cDNA production was amplified in the presence of specific mp65 and βMG primers for 30 cycles of PCR in an UNO-Thermo block (Biometra, Tampa, FL). The mouse p65 primers were: sense 5′AAAGAAGACAT TGAGGTGTA3′, antisense 5′AGGTACCATGG CTGTGGAAC3′ (Invitrogen). The βMG primers were: sense 5′CTCCCCAAATTCAAGTGTACTC TCG3′, antisense 5′GAGTGACGTGTTTAACTC TGCAAGC3′. The polymerase chain reaction products were separated with electrophoresis in 4% low melting temperature agarose gel containing ethidium bromide and photographed digitally under UV light with the gel documentation system (UVP, Upland, CA). Band intensity of each sample was determined by using GDS image analysis software (UVP, Upland, CA) and quantified using densitometry.

Immunoblot Analysis (Total p65, Fas/FasL, and Activated Caspase-3)

Cells were lysed in RIPA buffer (1 × PBS, 0.1% SDS, 1%NP40, 0.5% sodium deoxycholate); 50–100 μg

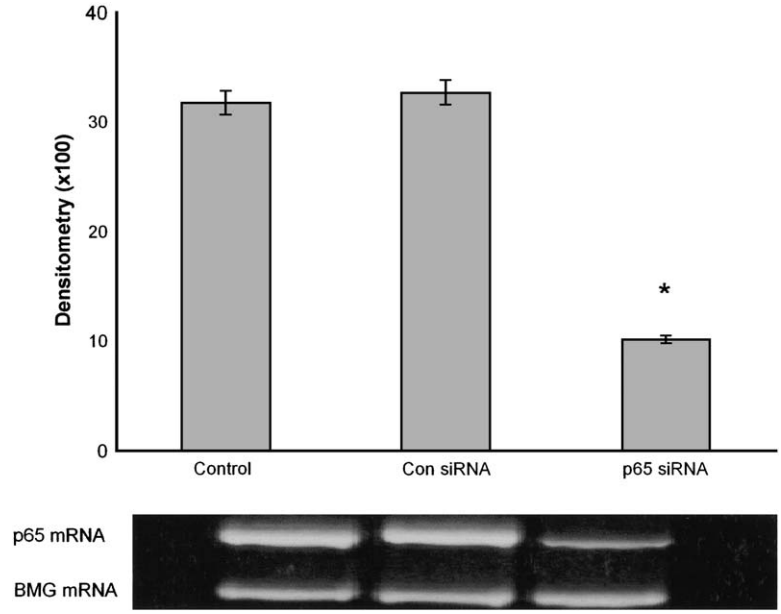
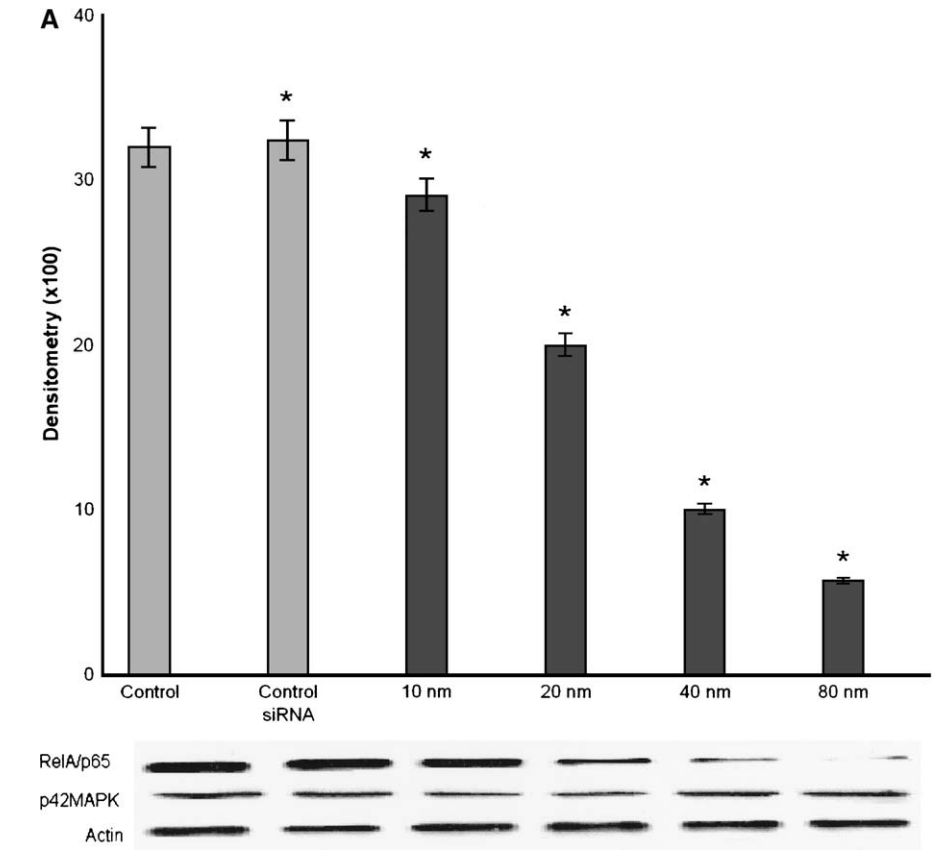


Fig. 2. Transfection of mice Kupffer cells KCL3-2 with p65 siRNA inhibits mRNA transcription of p65 as compared with untransfected cells or cells transfected with nontargeted control siRNA (*$P < 0.001$ p65 siRNA vs. control siRNA or untransfected controls). The bar graph represents densitometric quantification of n = 3 agarose gels of reverse transcription-polymerase chain reaction samples. Con = control; BMG = Beta-2 microglobulin, a housekeeping gene.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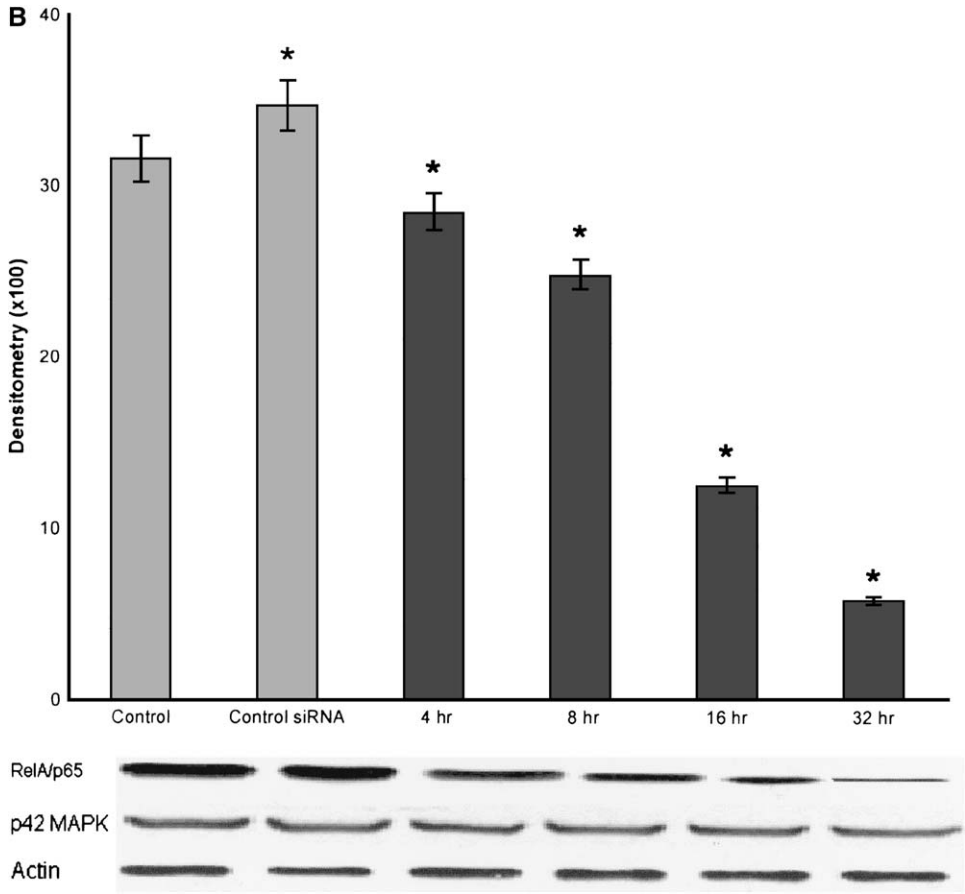
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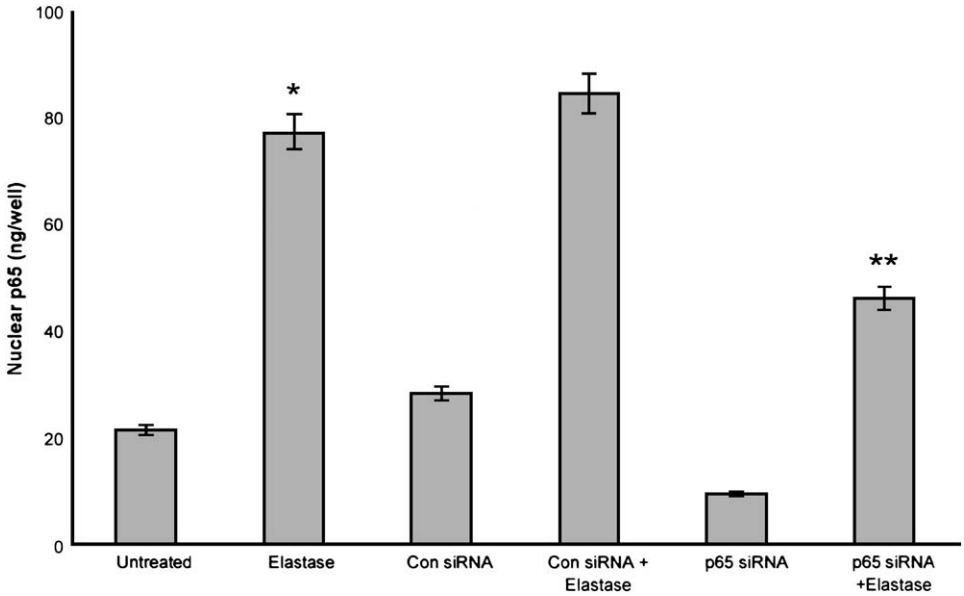

Fig. 4. p65/RelA siRNA transfection dramatically inhibits elastase-induced nuclear translocation of p65 in mice Kupffer cells KCL-3-2. (All $P < 0.001$; *elastase vs. control; **p65 siRNA + elastase vs control siRNA + elastase).

protein was fractionated by 10% SDS-PAGE, and transferred to nitrocellulose membrane (Amersham Pharmacia Biotech, Buckinghamshire, England), blocked for 1 hour in blocking buffer with phosphate buffer system BS containing 5% instant nonfat dry milk, and 0.1% Tween-20, then incubated for 2 hours in blocking buffer containing either Fas, FasL (BD, Biosciences, San Diego, CA) activated caspase-3, RelA/p65, or β-actin (Cell Signaling Technology, Beverly, MA) antibodies. Bound primary antibody was detected by incubating with horseradish peroxide goat anti-mouse IgG. The membranes were developed using Super signal (Pierce, Rockford, ILL) ECL reagent and quantified using densitometry (UVP).

Enzyme-Linked Immunosorbent Assay for Nuclear Translocation of p65/Rel A

Kupffer cell pellets were lysed in 400 μL hypotonic lysis buffer with 10% NP-40, after centrifugation for 30 seconds at 14000 rpm. The supernatant (cytoplasmic extracts) was removed and 220 μL of ice cold nuclear extraction buffer was added to the remaining pellet. Nuclear extracts were used for determination of protein concentration and ELISA (Imgenex, San Diego, CA), using colorimetry at 405 nm.

DNA Fragmentation

10^4 cells were lysed, transferred to a 96-well plate, and incubated with 80 μL of immunoreagent for 2–4 hours at room temperature or 4° C for overnight. After adding ABTS, the plates were left on a plate shaker at 250 rpm until color development was sufficient for photometric analysis at 405 nm against ABTS solution as a blank.

Flow Cytometry

Apoptosis was determined by two-color flow cytometric analysis using Annexin V-FITC reagent and 7-AAD (BD PharMingen, San Diego, CA). The FACS flow cytometer was equipped with a 488 nm laser excitation source. Forward scatter and side scatter plots were used to identify Kupffer cell populations. Measurements for fluorescein were carried

Fig. 3. (**A**) Transfection of mice Kupffer cells KCL3-2 with p65 siRNA decreased p65/RelA protein expression in whole cell extracts in a dose-dependent manner (10–80 nm; *$P < 0.001$ p65 siRNA vs. control siRNA). Nontargeted protein p42 MAPK was not changed. The bar graph represents densitometric quantification of n = 3 immunoblots. (**B**) Transfection of mice Kupffer cells KCL3-2 with p65 siRNA inhibits p65/RelA protein expression in whole cell extracts in a time-dependent manner (4–32 hours; *$P < 0.001$ p65 siRNA vs. control siRNA). Nontargeted protein p42 MAPK was not changed. The bar graph represents densitometric quantification of n = 3 immunoblots.

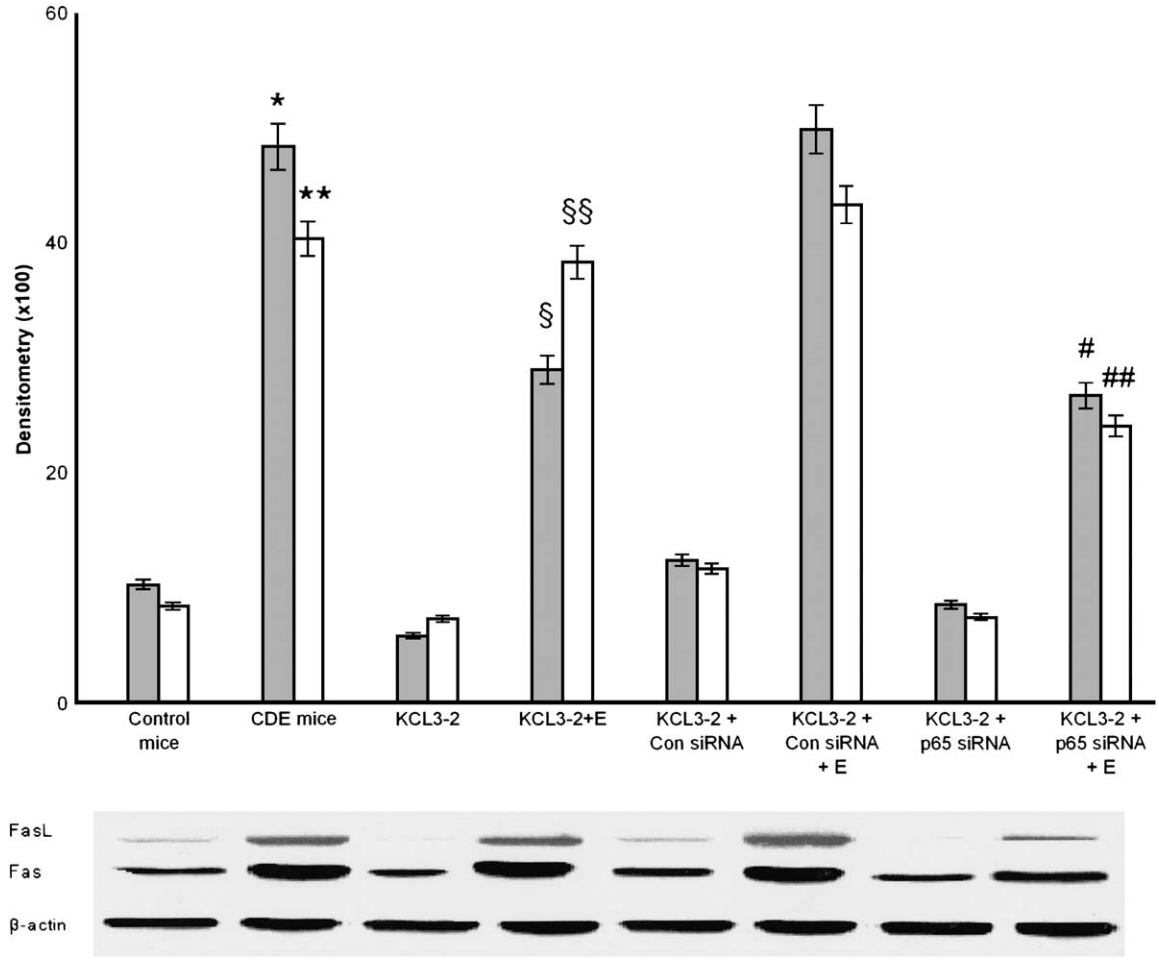

Fig. 5. CDE pancreatitis upregulates expression of Fas (full bars) and FasL (empty bars) in mice livers (*, **$P < 0.001$; CDE vs. control mice). Transfection of p65 siRNA significantly inhibits elastase-induced Fas (full bars) and FasL (empty bars) expression within mice Kupffer cells KCL3-2. (All $P < 0.001$; §, §§ elastase vs. untreated cells; #, ## p65 siRNA + elastase vs. control siRNA + elastase). The bar graph represents densitometric quantification of n = 4 immunoblots. E = elastase; con = control.

out using fluorescein detector (530/30 nm); the nucleic acid dye was detected using the FL2 detector (585/42 nm). A total of 1×10^5 events were collected for each data set, and the percentages of dual-labeled cells were determined.[14]

DATA ANALYSIS

All experiments were repeated in triplicate. ANOVA was used to compare means of different experimental groups; if $P < 0.05$ then a t test was used to compare means of two different arms; for example, control versus elastase. A Bonferroni's correction was used to correct for multiple comparisons. Generally, we used six different controls or treatment arms per experiment, therefore the corrected P value for statistical significance should be $P = .05/6 = 0.008$.

RESULTS

Enhancement of p65 Nuclear Translocation by CDE-Induced Pancreatitis

Total p65 protein levels in whole cells were not different among control mice and mice with CDE pancreatitis (3301 ± 152 vs. 3204 ± 160; P = NS); however, nontargeted control protein p42 MAPK increased significantly (5010 ± 205 vs. 2501 ± 112; CDE pancreatitis vs. control; $P < 0.001$; Fig. 1). Moreover, nuclear p65 protein increased dramatically in mice with CDE pancreatitis (32 ± 2 vs. 10 ± 1 ng/well; $P < 0.001$, CDE pancreatitis vs. control; Fig. 1).

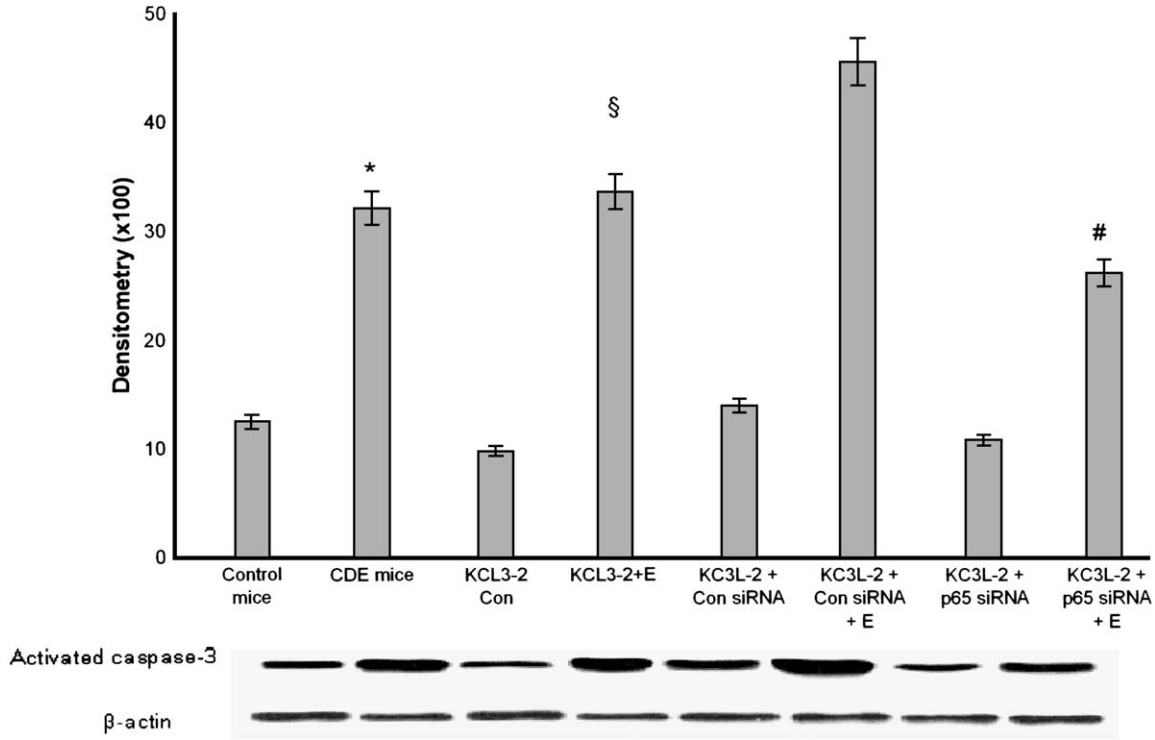

Fig. 6. CDE pancreatitis upregulates activation of caspase-3 in mice livers; (*$P < 0.001$; CDE vs. control mice). Transfection with p65 siRNA significantly inhibits elastase-induced activation of caspase-3 within mice Kupffer cells KCL3-2. (All $P < 0.001$; § elastase vs. untreated cells; # p65 siRNA + elastase vs. control siRNA + elastase). The bar graph represents densitometric quantification of n = 4 immunoblots. E = elastase; con = control.

These results suggest that CDE pancreatitis promotes nuclear translocation of RelA/p65.

In Vitro Reduction of p65 Gene Expression in KCL3-2 Mouse Kupffer Cells

To determine the efficacy and specificity of p65 siRNA, KCL3-2 cells were transfected with p65 siRNA. Transfection with p65 siRNA significantly attenuated the transcription of p65 mRNA (3286 ± 124 vs. 1175 ± 40; $P < 0.001$, p65 siRNA vs. control siRNA or vs. control; Fig. 2).

Moreover, whole cell p65 protein is significantly reduced by p65 siRNA transfection in a dose and time-dependent manner. Whole cell extracts of p65 protein decreased with increasing doses of p65 siRNA from 10–80 nm (5.7 ± 0.2 vs. 32.4 ± 1.0; 80 nm p65 siRNA vs. control siRNA, $P < 0.001$; Fig. 3, *A*) and with increasing duration of siRNA transfection from 4–32 hours (5.8 ± 0.1 vs. 34.7 ± 1.1; 32 hours p65 siRNA vs. control siRNA; $P < 0.001$, Fig. 3, *B*). Nontargeted protein p42 MAPK levels were not changed, indicating that transfection with siRNA is specific and effective (Fig. 3, *A*, *B*).

In Vitro Inhibition of Elastase-Induced Nuclear Translocation of p65/RelA

Elastase-induced nuclear translocation of p65 in KCL3-2 cells (77.5 ± 3.1 vs. 21.6 ± 1.1 ng/well; elastase vs. untreated; $P < 0.001$; Fig. 4). Transfection of KCL3-2 cells with p65 siRNA dramatically attenuated the elastase-induced nuclear translocation of p65 (46.9 ± 2.0 vs. 84.9 ± 4.2; $P < 0.001$; p65 siRNA + elasatse vs. control siRNA + elastase; Fig. 4). These data suggest that stress (elastase-induced) upregulates p65/RelA and transfection with p65 siRNA attenuates that response in Kupffer cells.

Inhibition of RelA/p65 Reduces Fas/FasL Expression

Both in vivo (CDE-induced pancreatitis) and in vitro (elastase treatment) significantly upregulate the expression of Fas/FasL: In vivo: Fas: 4824 ± 150 vs. 1025 ± 31; $P < 0.001$, CDE mice vs. control mice; FasL: 4024 ± 124 vs. 834 ± 28; $P < 0.001$, CDE mice vs. control mice; Fig. 5. In vitro: Fas: 2889 ± 92 vs. 575 ± 25; $P < 0.001$; elastase vs.

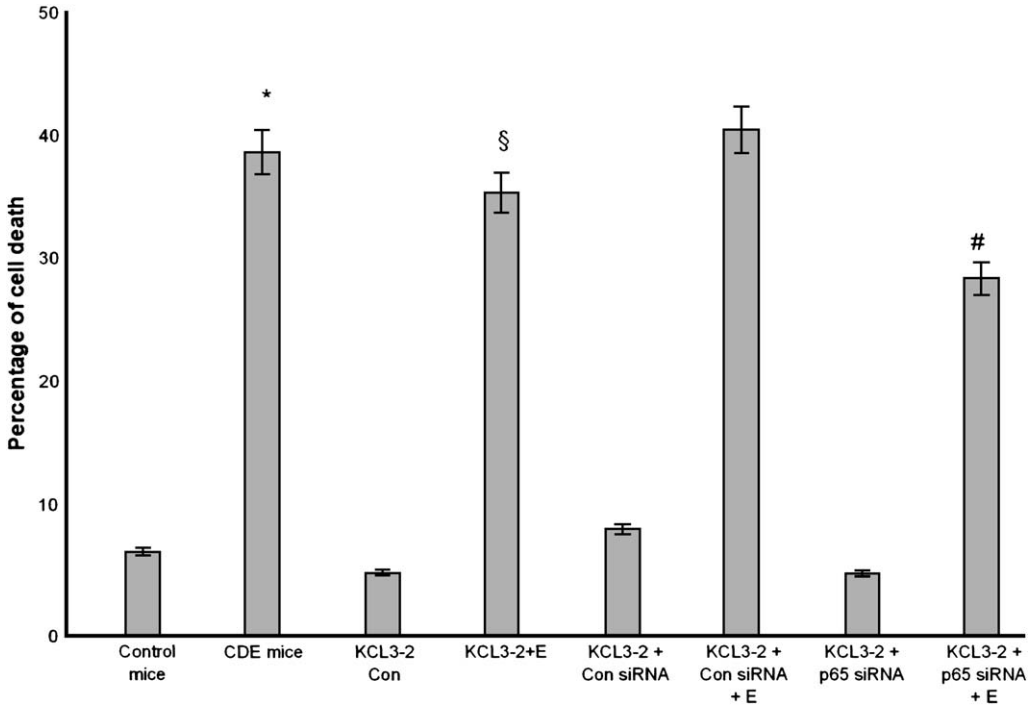

Fig. 7. CDE pancreatitis significantly increases the percentage of DNA fragmentation and cell death in mice livers; (*$P < 0.001$; CDE vs. control mice). Transfection with p65 siRNA significantly inhibits elastase-induced increase in DNA fragmentation and cell death in KCL3-2 cells. (All $P < 0.001$; § elastase vs. untreated cells; # p65siRNA + elastase vs. control siRNA + elastase). E = elastase; con = control.

control; FasL: 3821 ± 119 vs. 740 ± 28; $P < 0.001$; elastase vs. control; Fig. 5.

Transfection of KCL3-2 cells with p65 siRNA significantly attenuated the elastase-induced upregulation of Fas/FasL: Fas: 2670 ± 95 vs. 4980 ± 174; $P < 0.001$; p65 siRNA + elastase vs. control siRNA + elastase. FasL: 2401 ± 79 vs. 4321 ± 154; $P < 0.001$; p65siRNA + elastase vs. control siRNA + elastase; Fig. 5. These data suggest that nuclear translocation of p65/RelA is critical to the stress-induced upregulation of Fas/FasL in Kupffer cells.

Inhibition of p65/RelA Reduces Caspase-3 Activation

Similarly, CDE-induced pancreatitis and elastase treatment significantly increased activated caspase-3 (19KD form, caspase-3 cleaved large fragment) in mice livers (3201 ± 101 vs. 1254 ± 38; $P < 0.001$, CDE vs. control; Fig. 6) and in KCL 3-2 mouse Kupffer cells (3327 ± 104 vs. 964 ± 33; $P < 0.001$; elastase vs. control; Fig. 6), respectively. Transfection with p65 siRNA significantly attenuated the elastase-induced activation of caspase-3 in KCL3-2 mouse Kupffer cells (2542 ± 78 vs. 4503 ± 139; $P < 0.001$, p65 siRNA + elastase vs. control siRNA + elastase; Fig. 6).

Inhibition of p65/RelA Reduces Apoptosis

CDE-induced pancreatitis significantly increased DNA fragmentation in mice livers (38.8 ± 1.2 vs. 6.8 ± 0.21, $P < 0.001$; CDE vs. control mice, Fig. 7). Similarly, elastase increased DNA fragmentation in KCL3-2 mouse Kupffer cells (35.5 ± 1.1 vs. 5 ± 0.2; $P < 0.001$; elastase vs. control, Fig. 7).

Inhibition of RelA/p65 by p65 siRNA attenuated the elastase-induced DNA fragmentation in KCL3-2 mouse Kupffer cells (28.5 ± 0.9 vs. 40.5 ± 1.4; $P < 0.001$; p65 siRNA + elastase vs. control siRNA + elastase; Fig. 7).

Similarly, transfection of p65 siRNA significantly attenuated the percentage of dual-labeled cells (nonviable) in elastase-treated KCL3-2 mouse Kupffer cells by flow cytometry (28.7 ± 0.9 vs. 51.2 ± 1.6; $P < 0.001$; p65 siRNA + elastase vs. control siRNA + elastase, Fig. 8).

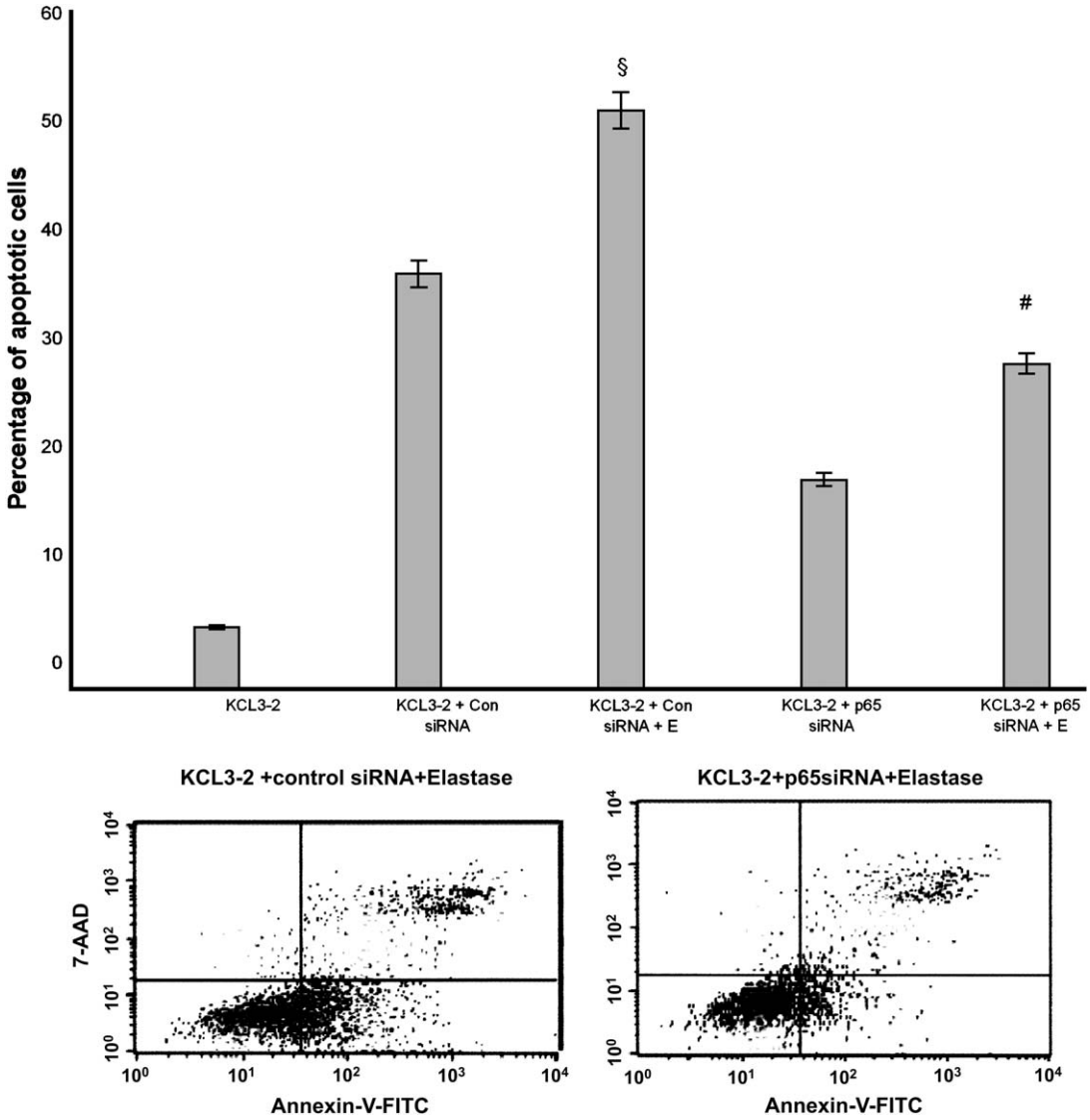

Fig. 8. Transfection with p65 siRNA significantly inhibits elastase-induced increase in dual-labeled KCL3-2 cells. (All $P < 0.001$; § elastase vs. untreated cells; # p65siRNA + elastase vs. control siRNA + elastase). E = elastase; con = control. Bar graphs are n = 4; lower panels are representative samples of dual-labeling flow cytometry.

DISCUSSION

Acute pancreatitis is characterized by superinflammation, overproduction of inflammatory mediators, and distant organ injury such as liver, lung, and kidney. Those systemic manifestations of acute pancreatitis are mediated by extrapancreatic and resident macrophage-derived production of proinflammatory cytokines that induce biochemical and histomorphologic organ injury. Specifically, in both in vivo and in vitro models of acute pancreatitis, we demonstrated that Kupffer cell-derived tumor necrosis factor and Fas/FasL induce liver injury and hepatocyte apoptosis via NF-κB dependent pathways.[3,4]

More recently, we described a novel finding; in addition to producing FasL, Kupffer cells upregulate Fas (the FasL receptor)[15] and undergo accelerated apoptosis during experimental acute pancreatitis. Inhibiting NF-κB transcriptional activation by overexpression of mutant IκBα attenuates upregulation of Fas/FasL and attenuates Kupffer cells apoptosis, thereby suggesting that Kupffer cells may modulate their stress response by upregulating their cell death ligand/receptors. We therefore hypothesized that NF-κB plays a central role in Kupffer cells' apoptosis and undertook this study to characterize the role of its p65/RelA subunit.

Nuclear Translocation of p65/RelA in Acute Pancreatitis-Induced Injury Liver

NF-κB is a ubiquitous transcription factor that belongs to a family of five subunits. The role of its most common active form, p65/RelA, has not been established in Kupffer cells, which are believed to critically regulate survival, proliferation, and apoptosis of hepatocytes and other types of liver cells.

Our data demonstrates that CDE-induced pancreatitis dramatically upregulates nuclear translocation of RelA/p65 in mice livers (Fig. 1). We further confirmed these findings in a mouse Kupffer cell line (KCL3-2) by using pancreatic elastase as a surrogate for pancreatitis. Treatment with elastase upregulated nuclear translocation of p65/RelA within Kupffer cells (Fig. 4).

Inhibition of p65/RelA by siRNA

Transfection of mammalian cells with synthetic small interfering RNAs (siRNA; 21–23nt in length) specifically suppresses expression of endogenous genes by RNA interference in cell cultures. Recently, few reports suggested that siRNAs against caspase-8,[16] and Fas[17] could be delivered effectively into hepatocytes; however, similar data on Kupffer cells is scant. Therefore, we conducted dose-response and time-course experiments to document the efficacy and specificity of p65 siRNA. Our data demonstrates that p65 siRNA attenuates the expression of Kupffer cell p65/RelA in a dose and time-dependent manner (Figs. 2, 3, and 4). In addition to reducing nuclear translocation of p65/RelA in untreated (no elastase) KCL3-2 cells (Fig. 3), p65 siRNA significantly attenuated the elastase-induced nuclear translocation of p65/RelA (Fig. 4), thereby suggesting that the depletion or reduction of baseline level of RelA/p65 may further reduce its nuclear translocation.

Inhibition of Nuclear Translocation of p65/RelA Reduces Kupffer Cell Apoptosis

We investigated changes in cell-death pathways to determine the role of p65/RelA in pancreatitis-induced Kupffer cell apoptosis. CDE-induced pancreatitis and elastase upregulated Fas/FasL, caspase-3, and percentage of cell death (DNA fragmentation and dual labeling with Annexin/7-AAD; Figs. 5, 6, 7, and 8). Inhibition of nuclear translocation of p65/RelA by p65 siRNA protected Kupffer cells from elastase-induced cell death and apoptosis, and downregulated Fas/FasL, caspase-3, DNA fragmentation, and percentage of apoptotic cells (Figs. 5, 6, 7, and 8).

Nuclear translocation of p65/RelA upregulates NF-κB dependent gene transcription of Fas/FasL; however, transfection with p65/RelA siRNA did not completely eliminate nuclear translocation of p65/RelA. This may be consistent with recent data that suggest that post-translational modification of p65/RelA NF-κB may regulate gene expression, too. Mechanistically, this NF-κB transcription independent event may result from p65/RelA deacetylation of specific promoters that are important in cell survival and cell apoptosis.[18]

Our current findings implicating p65/RelA in pancreatitis-induced upregulation of Fas/FasL and Kupffer cell apoptosis are consistent with our previous observations. We have demonstrated that Kupffer cell-derived Fas/FasL induces hepatocyte apoptosis in experimental pancreatitis.[3,4] Concomitant upregulation of Fas within Kupffer cells induces apoptosis of the originator cell (Kupffer cell) and thereby abrogates its stress response. The ability of Kupffer cells to autoregulate their stress response warrants further investigation.

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Predictors of Long-term Survival in Patients with Gallbladder Cancer

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The aim of this study was to examine the predictors of long-term survival (> 24 months) in patients with gall bladder cancer. A retrospective review of 117 cases of gall bladder cancer resected between 1989 and 2000. The resections included 80 simple cholecystectomies and 37 extended procedures. Patients with survival > 24 months (n = 44) were compared with those having survival < 24 months (n = 73) for 17 prognostic factors. Overall median survival was 16 months with a 5-year survival of 27%. T status (P = .000) and adjuvant chemoradiotherapy (P = .001) were independent predictors of long-term survival. Survival advantage was seen in T3N+ve disease (P = .007) with extended procedures. Complete (R0) resection was attained in 30 patients with a 5-year survival advantage of 30% as compared with incomplete (R1) resection (P = .0002). Adjuvant chemoradiotherapy improved survival in simple cholecystectomy group (P = .0008) but no advantage was seen after extended procedures. Stage III (P = .001) and node-positive disease (P = .0005) had significant benefit with adjuvant therapy. Poor differentiation and vascular invasion were associated with poor long-term survival. R0 resection was associated with prolonged survival. Extended procedures improved survival in patients with T3N+ve disease. Addition of chemoradiotherapy made significant improvement in long-term survival in stage III and node-positive lesions and in patients undergoing simple cholecystectomy. R0 resection predicted long-term survival in gall bladder cancer. T3 N+ve disease had better survival after extended procedures. Adjuvant chemoradiotherapy improved survival in stage III and node-positive disease. Poor differentiation and vascular invasion were adverse predictors of survival. (J GASTROINTEST SURG 2006;10:848–854)

KEY WORDS: Gall bladder neoplasms, survival, cholecystectomy, radiotherapy, chemotherapy

Gallbladder cancer (GBC) is the most common biliary tract malignancy. Approximately 1%–3% of patients undergoing cholecystectomy have GBC.[1,2] It is the fifth most common gastrointestinal malignancy in Western countries.[3] The incidence is extremely variable by geographical region and racial ethnic group. Recently, hospital-based cancer registries in north India have reported a very high incidence rate of GBC.[4] In fact, GBC is the most common gastrointestinal malignancy in females in north India, the age-adjusted rate being 8.9/100,000; this incidence is next only to New Mexico American Indians (12.5/100,000). The actual volume of GBC in north India may be much more as there is no population based study in this high-incidence zone.

GBC is an aggressive and lethal cancer, with overall 5-year survival being only 5%–10%. Survival following resection, especially in early stages, has shown some improvement due to advances in surgical treatment. Advanced stages, however, continue to have dismal outcome with only anecdotal long-term survival. The majority of patients with GBC have advanced disease and dismal outcome reported in various studies has led to a general pessimism about cure in GBC. This article aims to identify clinical, operative, macroscopic, and microscopic factors that influence the 2-year survival after resection of the tumor in patients with GBC.

PATIENTS AND METHODS

Four hundred and one patients with GBC were operated on between January 1989 and December 2000 in the Department of Surgical Gastroenterology

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at the Sanjay Gandhi Post-Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, a tertiary level referral hospital in northern India. One hundred fifty nine of these 401 patients (40%) underwent surgical resection of which 47 patients underwent extended procedures and 112 had simple cholecystectomy. Prospectively maintained records of these 159 patients were analyzed retrospectively to assess predictors of long-term survival. Follow-up was obtained from hospital visits or by postal questionnaires at regular intervals. Follow-up was completed throughout June 2003.

Patients who survived more than 24 months were compared with those who died within 24 months of resection to identify predictors of long-term survival. Forty-two patients were excluded from the study—they included 5 in-hospital deaths, 14 patients lost to follow-up immediately after hospital discharge and 23 further patients lost to follow-up during first 24 months. One hundred seventeen of the remaining patients who either died within 24 months or had a follow-up of at least 24 months were included for further analysis. 80 of these 117 patients had simple cholecystectomy and 37 had undergone extended procedures.

All resected gallbladder specimens were subjected to review of histopathology and staged as per American Joint Committee on Cancer TNM classification 1997. Extended procedures were considered complete (R0) if resection margins were free of tumor and excised negative lymph nodes were a level beyond microscopic spread. If the resection margins were positive and/or extent of lymph node dissection did not include uninvolved nodes one level beyond involved nodes it was labeled as incomplete (R1) resection.

In patients undergoing simple cholecystectomy, presence of positive nodes in the specimen or significantly enlarged nodes detected during surgery was taken as node-positive disease (n = 40), the remaining patients were considered Nx (n = 40). The patients with T1 disease who underwent simple cholecystectomy were assigned stage I and R0 status. Patients with T2 and T3 lesions and no detectable nodes during surgery were assigned stage II and III, respectively.

Statistical analysis was done by using SPSS Version 9. Factors, which were found to be significant on univariate analysis by chi-square analysis, were chosen for multivariate analysis. The odds ratio (OR) and *P* value were calculated. A *P* value of <0.05 was considered significant.

RESULTS

Median age of the 117 patients included in this analysis was 53 years; mean age was 53 ± 13 years (23–80 years). 37 patients (32%) were male and 80 (68%) were female. Median hemoglobin was 11 (4-15) gm% and median albumin 3.6 (2.0–5.4) gm%. Total bilirubin was > 2 mg% in 29 patients (25%) – the cause was concomitant CBD stones in 12 patients (41%) and tumor infiltration of CBD in 17 patients (59%). 80 patients (68%) had gallstones; they were present in 20/37 males (54%) and in 60/80 females (75%). Forty-six patients (39%) underwent US-guided fine needle aspiration cytology, which was positive for malignancy in 35/46 (76%) patients. All 117 patients had evidence of malignancy in the final histopathology specimen of resected gallbladder.

Simple Cholecystectomy

Simple cholecystectomy was done in 80 patients. T1 lesion was seen in 12 patients (15%), T2 in 19 (24%), T3 in 39 (49%) and T4 in 10 patients (12%). At operation, 40 of these patients (50%) had significantly enlarged lymph nodes or had positive nodes in the final histopathology specimen. Simple cholecystectomy was carried out as a palliative tumor debulking measure in these patients. Forty patients (50%) in whom nodal status was unknown were taken as Nx disease. Overall stage distribution was stage I (n = 12), II (n = 12), III (n = 43), and IV (n = 13).

Extended Procedures

An extended procedure was performed in 37 patients. Twenty-eight patients underwent extended cholecystectomy (cholecystectomy with en-bloc resection of a nonanatomical 2 cm wedge of liver + pericholedochal, hepatoduodenal, suprapancreatic, and retropancreatic nodal clearance); 2 of these 28 patients underwent right hepatectomy and in 6 of these 28 patients common bile duct (CBD) excision was also performed because the tumor was involving the neck of the GB or the cystic duct with infiltration of the CBD. Only cholecystectomy and nodal clearance (without any liver resection) was done in 6 patients with disease on the peritoneal aspect of the GB without liver infiltration. Three patients, who were diagnosed to have GBC after cholecystectomy for stone disease, underwent completion surgery with lymph node clearance and wedge excision of liver as a second stage procedure.

Only 18/37 patients (49%) had an R0 resection. All 6 patients with T1 (n = 2) and T2 (n = 4) lesion and only 12/29 patients (41%) with T3 lesion had an R0 resection; no patient with T4 lesion achieved an R0 resection. R0 status was attained in 15/18 patients (82%) with node-negative disease while only 3/16 (19%) with node-positive disease had R0

resection. Overall stage distribution was stage I (n = 2), II (n = 4), III (n = 29), and IV (n = 2).

Survival

Overall median survival of 117 patients was 16 months with 5-year actuarial survival of 27%. Overall median and actuarial survival in various T, N, and TNM stages is shown in Figs. 1, 2, and 3, respectively.

Univariate analysis revealed the following factors to have a significant bearing on long-term survival: R0 resection status (P = .001, OR: 4.28), T stage (P = .0001, OR: 3.02), grade of differentiation (P = .008, OR: 3.00), vascular invasion (P = .006, OR: 4.06), and adjuvant chemoradiotherapy (P = .0001, OR: 5.43) (Table 1).

Multivariate analysis of factors found significant on univariate analysis showed T status (P = .000, OR: 2.973) and adjuvant chemoradiotherapy (P = .001, OR: 5.540) as independent significant factors for long-term survival (Table 2).

There was no survival advantage of extended resections over simple cholecystectomy in the overall group, but on subanalysis, survival benefit (P = .007) was observed with extended resections in T3N+ve disease (Table 3).

Patients with R0 resection status had a significant survival advantage (P = .0002) as compared with those with R1 resection. Benefit (P = .05) was seen with R0 resection for T3 disease. All patients with T1 tumor had R0 resection. R0 resection was achieved in only 4 patients with T2 lesions and it was too small a group for any subanalysis. R0 resection could not be achieved in any patient with T4 lesion (Table 4).

Addition of adjuvant chemoradiotherapy showed significant survival advantage for stage III (P = .0001) and node-positive (P = .0005) lesions. Patients undergoing simple cholecystectomy also benefited (P = .0008) by addition of adjuvant chemoradiotherapy (Table 5).

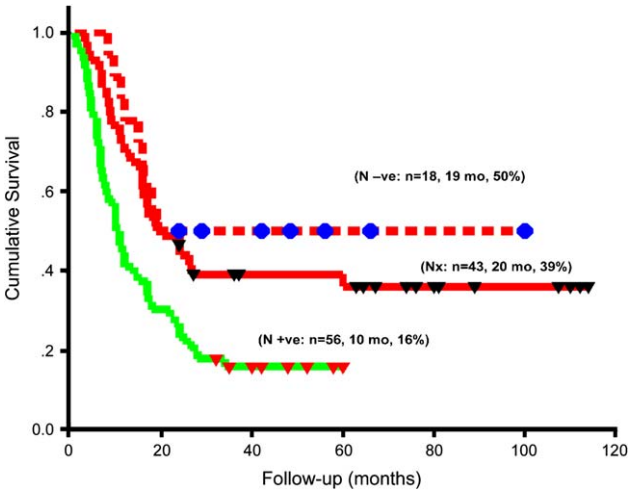

Fig. 2. N stage and survival.

DISCUSSION

Prognosis in patients with GBC is dismal, with 5-year survival rates varying between 5%–10%.[2,5] Only 10%–35% lesions are resectable[6–8]; our resectability rate has also been only 40%.

This experience is from an area where gallbladder cancer is common.[4] We had reported earlier[9] that age > 60 years (P = .005) and palpable mass (P = .001) adversely affected survival. In another recent publication including only those patients who underwent extended resection, we reported male sex,

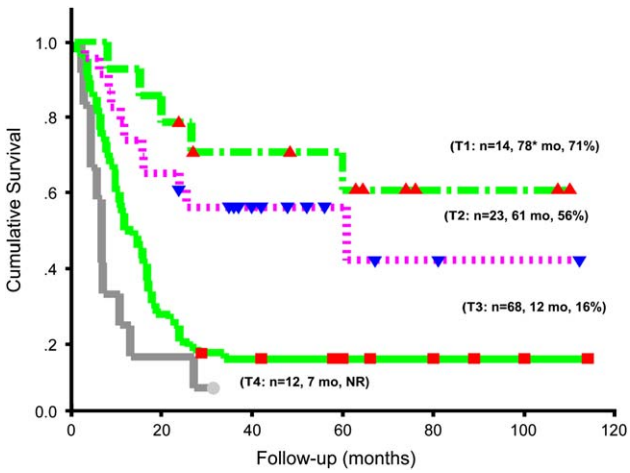

Fig. 1. T stage and survival. *Mean survival (median survival not reached); NR = not reached.

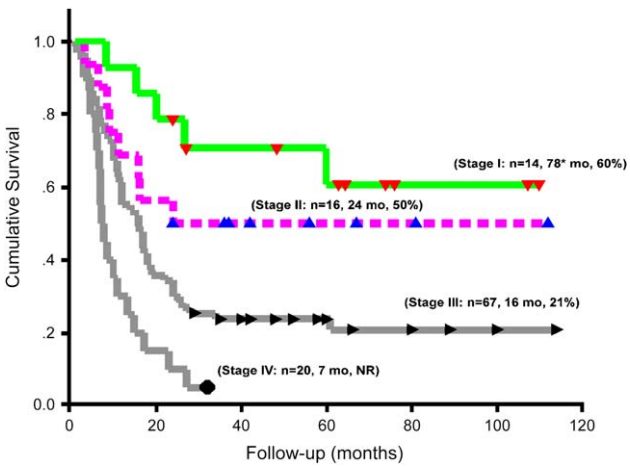

Fig. 3. Stage and survival. *Mean survival (median survival not reached); NR = not reached.

Table 1. Univariate analysis of predictors of long-term survival (survival ⩾ 24 months)

Factor		No.	⩾2-year survival	<2-year survival	*P* value	Odds ratio
Age (yrs)	⩽60	87	30	57	0.23	0.60
	>60	30	14	16		
Sex	Male	37	13	24	0.7	0.85
	Female	80	31	49		
Jaundice	Yes	29	9	20	0.43	0.70
	No	87	34	53		
Hemoglobin (gm%)	⩽10	32	13	19	0.55	1.30
	>10	81	28	53		
Serum bilirubin (mg%)	⩽10	98	40	61	0.26	1.97
	>10	8	4	12		
Serum albumin (gm%)	⩾3.5	63	23	40	0.79	0.90
	<3.5	53	21	33		
Gallstones	Yes	80	28	52	0.39	0.71
	No	37	16	21		
Resection	Simple Ccx	80	29	51	0.66	1.20
	Extended Ccx	37	15	22		
Liver wedge resection	No	88	33	55	0.97	1.02
	Yes	29	11	18		
Grade of differentiation	1	69	33	36	0.008*	3.00
	2–4	48	11	37		
Neural invasion	No	91	37	54	0.20	0.54
	Yes	26	7	19		
Vascular invasion	No	87	39	48	0.006*	4.06
	Yes	30	5	25		
T stage	T1	14	10	4	0.0001*	3.02
	T2	23	15	8		
	T3	68	17	51		
	T4	12	2	10		
N stage	N0	18	9	9	0.06	2.39
	N1	56	15	41		
	Nx	43	20	23		
Chemoradiotherapy	Yes	73	37	36	0.0001*	5.43
	No	44	7	37		
Resection status	R0	30	19	11	0.001*	4.28
	R1	87	25	62		
XGC	Yes	13	5	8	0.95	1.04
	No	104	39	65		

Ccx = cholecystectomy; XGC = xanthogranulomatous cholecystitis.
*Significant.

absence of gallstones, complete resection (R0 status), and absence of nodal involvement as the predictors of long-term survival.[10]

In the current analysis of all patients undergoing resection, univariate analysis showed that long-term survival (> 24 months) was associated with early T stage, better grade of differentiation, absence of vascular invasion, complete resection (R0) status, and use of adjuvant chemoradiotherapy. Multivariate analysis showed only T status and adjuvant chemoradiotherapy as the independent predictors of survival. Bartlett et al.[11] reported N stage as the only significant predictor of survival on multivariate analysis. Yamaguchi et al.,[12] on retrospective analysis of 68 resected patients, found lymph node metastasis and perineural invasion to be significant prognostic variables. Fong et al.[13] found T and N status as independent predictors of survival. Ouchi et al.[14] found venous, lymphatic, or neural infiltration or a combination thereof and serosal infiltration to be associated with poorer survival; long-term survival was noted with papillary and well-differentiated growths.

T1a (mucosal) lesions have good survival results after simple cholecystectomy. T1b (muscle) lesions, however, require an extended resection as shown by us earlier.[15]

Table 2. Multivariate analysis of predictors of long-term survival (survival ⩾ 24 months)

Variable	*P* value	Exp (B)	95% CI for Exp (B)	
			Lower	Upper
Tumor (T) status	0.000*	2.973	1.662	5.318
Chemoradiotherapy	0.001*	5.540	1.983	15.476
Constant	0.000	0.010		

*Significant.

Lymph nodes are involved in 46% of T2 and 92% of T3/ T4 lesions, respectively; extended resection is, therefore, imperative in these groups.[11,16] Shirai et al.[17] reported 5-year survival of 90% after extended resections as compared with 40% after simple cholecystectomy for T2 and T3 lesions. Yamaguchi et al. reported 3-year survival of 91% after extended resections and 28% after simple cholecystectomy for T2 lesions.[18] Prolonged survival after resection for even T4 lesions has been reported by Todoroki et al.[19] and Kondo et al.[20] These studies, though associated with higher postoperative mortality of about 20%,[20,21] have shown a lower failure rate with extended resections even in patients with locally advanced disease.

In our experience, early (T1) disease did not benefit from extended resection. The number of patients with T2 disease undergoing extended resection was very small for any meaningful conclusion. Significant survival advantage was seen for T3N+ve lesions after extended cholecystectomy. Patients with T4 lesions did not show any survival benefit with extended resection because R0 status could not be attained in any of our T4 patients.

Lymph node metastasis has been consistently shown to be an indicator of poor prognosis.[11,12,13] Series from western countries[6,11,22] have reported no 5-year survival among node-positive patients. Bartlett et al.[11] reported that none of their node-positive patients lived beyond 2 years. Japanese surgeons have shown much better 5-year survivals after R0 resection for node-positive disease: Shirai et al.[17] (45%), Todoroki et al.[19] (49% for N1 nodes and 6% for N2 nodes), Chijiwa et al.[23] (50% for T2 node-positive disease), and Onoyama et al.[24] (60%). Consistently poor results have been seen with involvement of celiac, superior mesenteric, para-aortic and aortocaval nodes with only anecdotal long-term survivors. Our 5-year survival of 16% for node-positive patients is intermediate between western series reporting no 5-year survival but not as high as that reported by the Japanese groups.

R0 resection status was associated with prolonged survival in our study. Similar results were shown by Aretxabala et al.[8] and Fong et al.[14] Todoroki et al.[19,25] performed extensive resections for even advanced disease and achieved 5-year survival of 73% after R0 resection but it was only 15% when R0 resection could not be achieved. Small numbers of R0 resection in T2 disease in our group prevent any meaningful subanalysis. In T4 lesions, no R0 resection could be achieved by us because of our management philosophy, which did not include supraradical resections. In T3 node-positive disease, only 3

Table 3. Survival analysis for simple cholecystectomy and extended procedures

T and N stage	Simple cholecystectomy			Extended procedures			*P* value
	No.	Median survival (mo)	5-year survival (%)	No.	Median survival (mo)	5-year survival (%)	
Overall	80	16	28	37	18	29	0.5
T1	12	82*	63	2	8	50	0.32
T2	19	53	61	4	46	75	0.42
T3	39	10	10	29	18	23	0.01
T3N0	0	—	—	12	18	42	—
T3 N + ve	24	8	—	15	18	—	—
T3Nx	15	16	—	2	7	—	0.42
T4	10	7	—	2	6	—	0.5
N0	—	—	—	18	19	50	—
N + ve	40	9	17	16	15	—	0.4
Stage I	12	81*	66	2	8	—	0.32
Stage II	12	16	42	4	46	—	0.24
Stage III	43	12	21	24	18	28	0.13
Stage IV	13	7	—	7	10	—	0.25

Forty patients in the simple cholecystectomy group and three patients in the extended procedures group had Nx disease.
*Mean survival (median not reached as yet).

Table 4. Effect of resection status on survival

	R0 resection			R1 resection			
T and N stage	No.	Median survival (mo)	5-year survival (%)	No.	Median survival (mo)	5-year survival (%)	*P* value
Overall	30	66*	51	87	12	20	0.0002
Survival							
T1	14	78*	71	0	—	—	—
T2	4	46	—	19	61	52	0.42
T3	12	18	33	56	11	12	0.05
T4	0	—	—	12	7	—	—
N−ve	15	59	53	3	19	—	0.76
N+ve	3	24	—	53	10	17	0.68
Extended procedures	18	24	44	19	14	—	0.04
Stage I	14	78*	71	0	—	—	—
Stage II	4	46	—	12	16	42	0.24
Stage III	12	18	33	55	15	16	0.19
Stage IV	0	—	—	20	7	—	—

Forty-three patients had Nx disease.
*Mean survival (median not reached as yet).

patients could attain R0 status as our lymph node dissection was limited to hepatoduodenal ligament and the retropancreatic region; these patients had a median survival of 24 months as compared with 10 months when R0 status was not attained.

Chemoradiotherapy has been found to be effective for palliation of jaundice and pain.[26,27] Vattinen[28] and Oswalt and Cruz[29] showed benefit with chemoradiotherapy after resection, although the results did not attain statistical significance due to small number of patients. In 21 patients with stage III/ IV GBC, Mehta et al.[30] showed a 6-month survival of 67%, 1-year survival of 33%, and 5-year survival of 23% with adjuvant therapy; patients with residual disease had no improvement in survival. Todoroki et al.[31] in a retrospective analysis of collected series, showed that radiotherapy significantly prolonged survival in patients with microscopic residual disease. They had earlier reported a 9% 5-year survival rate after surgery and radiotherapy as compared with 3% after surgery alone for stage IV disease.[25] We had an overall 5-year survival of 35% with surgery and adjuvant chemoradiotherapy as compared with 16% after surgery alone. Addition of adjuvant therapy made no survival difference in early lesions. Maximum benefit of adding

Table 5. Adjuvant therapy and survival

	Adjuvant therapy			No adjuvant therapy			
T and N stage	No.	Median survival (mo)	5-year survival (%)	No.	Median survival (mo)	5-year survival (%)	*P* value
Overall	73	24	35	44	11	16	0.001
T1	8	75*	62	6	56*	56	0.84
T2	20	61	60	3	16	33	0.52
T3	42	17	24	26	10	—	0.0002
T4	3	7	—	9	6	—	0.2
N−ve	13	66	62	5	16	—	0.24
N+ve	31	18	25	25	7	—	0.0005
Nx	29	24	41	14	13	27	0.26
Extended proceudres	26	23	33	11	15	18	0.12
Simple Ccx	47	24	40	33	10	11	0.0008
Stage I	8	75	62	6	56	55	0.84
Stage II	13	66	54	3	16	33	0.53
Stage III	46	18	28	21	10	—	0.001
Stage IV	6	8	—	14	7	—	0.09

*Mean survival (median not reached as yet). Ccx = cholecystectomy.

chemoradiotherapy was seen in stage III disease. Positive benefit was also seen for stage IV disease but it did not attain statistical significance.

We observed poor survival with lower levels of differentiation and presence of vascular invasion on histology; neural invasion, however, had no significant impact on survival. Similar results of poor survival with lower levels of differentiation were documented by Ouchi et al.[6] and Yamaguchi et al.[12] Vascular invasion, especially venous, has also been documented as a negative prognostic factor by Ouchi et al.[7]

CONCLUSIONS

Early lesions (T1 and T2) have a good prognosis; locally advanced lesions (T3) also do well if extended cholecystectomy is performed and R0 resection status can be achieved. Addition of chemoradiotherapy can make significant influence on long-term survival in patients with stage III (T3 and node-positive) lesions and can improve the overall survival after simple cholecystectomy. Poor tumor differentiation and vascular invasion on histology are predictors of poor long-term survival.

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Resection of Hepatocellular Carcinoma with Tumor Thrombus in the Major Vasculature. A European Case-Control Series

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Tumor thrombus in major vasculature is a frequent finding with a poor long-term prognosis in patients with hepatocellular carcinoma (HCC). The utility of surgical resection is still controversial. This study compared morbidity and survival after resection for HCC with and without tumor thrombus. Data of 108 patients who underwent major hepatic resection for HCC were prospectively recorded. Patients were divided into two groups. The venous thrombectomy (VT) group included 26 patients who had HCC with tumor thrombus in the portal or hepatic veins. The matched control group included 82 patients who had HCC without tumor thrombus. Surgical technique, early outcome, and late survival were analyzed in each group. Multivariate analysis was performed to assess the prognostic value of this feature. Surgical technique was comparable in the VT and control group with regard to extent of hepatectomy, procedure duration, and transfusion requirements. Early postoperative outcome was also comparable. Actuarial survival at 1, 3, and 5 years was 38%, 20%, and 13%, respectively, in the VT group (median: 9 months) versus 74%, 56%, and 33%, respectively, in the control group (median: 41 months). In the subgroup of patients with tumor thrombus limited to the portal vein, actuarial survival at 1, 3, and 5 years was 50%, 26%, and 17%, respectively, (median: 12 months) and two patients lived longer than 5 years. Multivariate analysis showed that incomplete resection, alphafetoprotein level greater than 100 N, more than two tumor nodules, and tumor thrombus in major vasculature were independent factors of poor prognosis. Survival after resection for HCC with tumor thrombus in the major vasculature is poorer than after resection for HCC without tumor thrombus. However, an aggressive surgical strategy can provide significant survival with comparable morbidity in selected cases, that is, tumor thrombus located in the portal vein only and expected complete resection of the lesions. (J GASTROINTEST SURG 2006;10:855–862)

KEY WORDS: Hepatocellular carcinoma, tumor thrombus, venous invasion, surgical resection

Venous invasion is a characteristic mode of extension for hepatocellular carcinoma (HCC). In one autopsy series, invasion of the portal vein and its main branches was noted in 65% of cases, and invasion of hepatic veins, always in association with portal vein invasion, was noted in 23% of cases.[1] In clinical practice, median survival of patients presenting macroscopic venous invasion (TNM classification, stage IVA) is less than 3 months without treatment,[2] and only slightly longer after systemic chemotherapy.[3] Because of poor survival, some practitioners consider venous invasion as a contraindication for resection,[4] whereas others consider that resection is justified as the last chance.[5] Tumor thrombus in the major portal or hepatic vein has implications for surgical strategy. However, postoperative morbidity/mortality and long-term survival after resections in such cases has not been well evaluated. This European case-control series was undertaken to assess the outcome of surgical treatment of cases involving tumor thrombus in the major vasculature.

PATIENTS AND METHODS

Patients

Between January 1988 and March 2004, we performed surgery for HCC in 370 patients. The procedure consisted of partial hepatectomy in 234 patients, including 26 patients presenting HCC with vascular invasion of a major vein, liver transplantation in 91 patients, intraoperative

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radiofrequency thermal ablation in 6 patients, and exploratory laparotomy in 39 patients. This study focuses on the 26 patients who underwent major hepatectomy, that is, resection of at least three contiguous Couinaud segments, in association with venous thrombectomy (VT). The VT group was compared with 82 control patients who underwent major hepatectomy for HCC during the same period.

Venous Invasion

Preoperative diagnosis of tumor thrombus was achieved in all cases by Doppler ultrasound, CT scan with injection, or MRI. Portography or cavography was also performed in some cases. Tumor thrombus in the portal vein was considered as resectable if residual hepatopetal flow around the thrombus could be observed contralateral to the planned resection site (Figs. 1 and 2). Tumor thrombus in the hepatic veins or inferior vena cava (IVC) was considered as resectable if the IVC was not completely obstructed, except in patients with Budd Chiari syndrome.

Indication for Major Hepatectomy for HCC

Most patients undergoing major hepatectomy were noncirrhotic. Only cirrhotic patients classified Pugh-Child A without portal hypertension were considered as eligible for major hepatectomy. The indocyanine green (ICG) clearance test has been used to evaluate liver function in most patients since 1996. Major hepatectomy was considered feasible if ICG values were 12% or less at 15 minutes (laboratory normal value). However, higher values were not considered as an absolute contraindication, especially for patients who had tumor-related vascular obstruction that could impair ICG clearance. Embolization of the portal vein was performed before major hepatectomy in four cirrhotic patients in the control group.

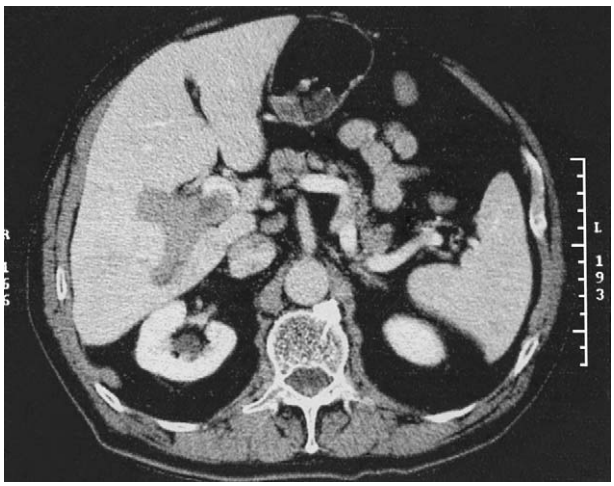

Fig. 1. CT scan showing solitary HCC located in segment VI, with tumor thrombus in the right portal vein almost completely obstructing the portal bifurcation.

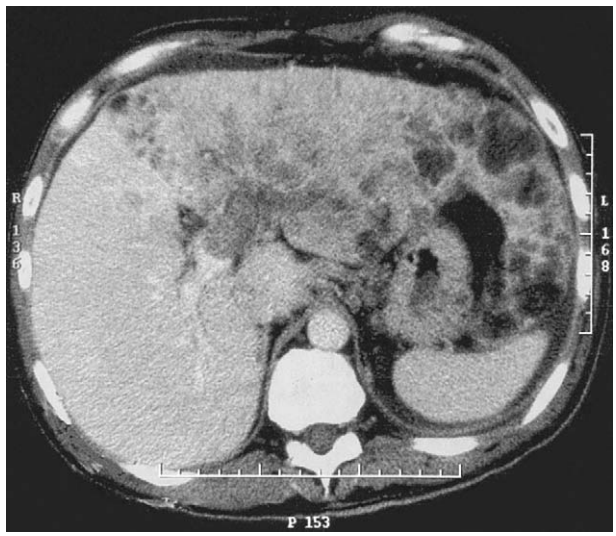

Fig. 2. CT scan showing multinodular HCC of the left liver with tumor thrombus narrowing the portal bifurcation.

Surgical Technique

The abdominal approach was used in all but four patients. Intraoperative ultrasound imaging was performed to assess the extent of thrombus (Fig. 3). Transsection of the liver was carried out using continuous or intermittent clamping of the hepatic pedicle (Pringle maneuver). Hepatic vascular exclusion (HVE) was used only if necessary and as briefly as possible. Mobilization of the liver and dissection of the IVC and hepatic veins was performed first except in cases involving large right-sided tumors treated by an anterior approach.[6] The portal pedicles were exposed by the scissural or suprahilar approach without hilar dissection. For portal vein tumor thrombus extending to the bifurcation, the sheath of the portal pedicle and then the portal vein were opened to allow extraction of the tip of the thrombus by using a forceps or Fogarty catheter. The vein was purged by portal flow before suture of the venous stump, and complete patency was checked by Doppler ultrasound. For hepatic vein tumor thrombus limited to the IVC (Fig. 4), the tip of the thrombus was extracted either by side clamping the IVC or by brief HVE. In case of atrial extension, the intracardiac tumor thrombus was removed in a first stage procedure with cardiopulmonary bypass before

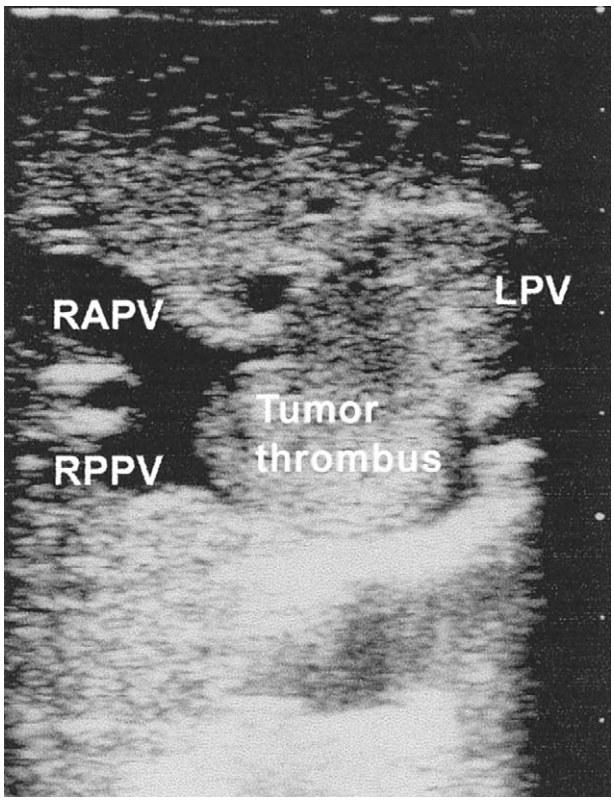

Fig. 3. Intraoperative ultrasound showing tumor thrombus of the left portal vein, almost completely obstructing the bifurcation. LPV = left portal vein; RAPV = right anterior portal vein; RPPV = right posterior portal vein.

hepatectomy.[7] Transfusion was performed if the hemoglobin level was less than 80 g/L. Anticoagulation therapy was not administered systematically. In the VT group (Table 1), thrombus was located in the portal vein in 20 patients, and in the hepatic veins in six patients, including two with extensions into the right atrium leading to acute Budd-Chiari syndrome. These two cases have been described in detail elsewhere.[7]

The VT and control groups were comparable (Table 2) with regard to age, sex, incidence of hepatitis virus B or C infection, tumor size, prothrombin time, bilirubinemia, and albuminemia. However, HCC was associated with cirrhosis or severe fibrosis (Metavir grade F4 and F3) in twice as many patients in the VT group, and the proportion of cirrhotic patients whose ICG was less than or equal to 12% at the time of surgery was significantly lower in the VT group. The alphafetoprotein (AFP) level was significantly higher in the VT group than in the control group.

Operative mortality was defined as death that occurred during hospitalization after surgery. Morbidity included any complication that required specific

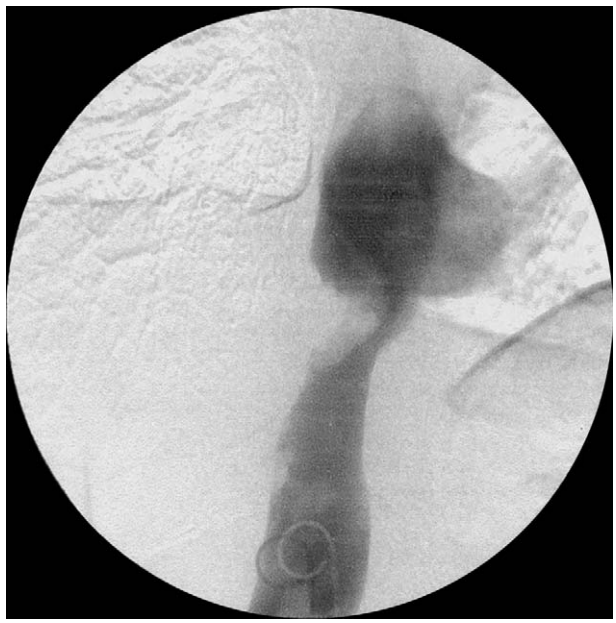

Fig. 4. Cavography showing thrombus in the right hepatic vein, extending into the lumen of the inferior vena cava.

treatment, affected outcome, or lengthened hospital stay as defined in a previous study.[8]

Statistical Analysis

Data for this case-control study was prospectively collected from a database. Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test. No patient was lost from follow-up. Survival was calculated using the Kaplan-Meier method from the time of operation to December 31, 2004. Differences between survival curves were compared using the log-rank test. Cox regression analysis was used on prognostic variables that were significantly different between groups in univariate analysis. Statistical analysis was performed with SPSS 10.0 software (SPSS Inc., Chicago, IL). A P value < 0.05 was considered significant.

RESULTS

Surgical Procedures

In the VT group, the surgical procedure consisted of right or extended right hepatectomy in 15 cases and left or extended left hepatectomy in 11 cases. In addition to extraction of thrombus, extrahepatic resection was performed in nine cases, that is, resection or ablation of a contralateral tumor in three cases, lymphadenectomy in three cases, diaphragmatic resection in one case, segmental colonic

Table 1. Location of tumor thrombus in 26 patients treated for hepatocellular carcinoma with venous invasion

Location and extension of the tumor thrombus	No. of patients
Right portal vein	
with partial obstruction of the bifurcation	8
with no obstruction of the bifurcation	3
Left portal vein	
with partial obstruction of the bifurcation	6
with no obstruction of the bifurcation	3
Right hepatic vein	
with IVC extension	2*
with IVC and atrial extension	2
Left hepatic vein	
with IVC extension	2*

IVC = inferior vena cava.
*Including one case with ipsilateral portal vein thrombus.

resection in one case, and splenectomy in one case. The extent of resection, specimen weight, Pringle maneuver duration, number of HVEs, procedure duration, and percentage of patients requiring transfusion were comparable in the VT and control groups. The proportion of patients with single or double tumors and the rate of complete resection were significantly lower in the VT group. In the VT group, 10 resections were considered as incomplete due to residual tumor nodules or emboli on the hepatectomy margin (eight cases), tumor nodules remaining in the contralateral liver (one case), or incomplete resection of lymph nodes (one case). In the control group, six resections were classified as incomplete due to contralateral tumor nodules (four cases) or tumor emboli on the resection margin (two cases). Surgical procedures and pathological data are presented in Table 3.

Early Outcome

Mortality and morbidity rates were the same in the VT and control groups (Table 4). However the incidence of postoperative ascites was three times higher in the VT group (27% vs. 9%; $P < 0.02$). No difference was observed between groups for other complications. Causes of death in the VT group were heart failure in one case and hepatic insufficiency in two cases, including one after intraoperative hemorrhage and the other related to cytomegalovirus infection in a patient who underwent cavoatrial disobstruction. The causes of death in the control group were hepatic failure in six cases, including two cases after intraoperative hemorrhage, cardiac complication in one case, and digestive tract perforation in one case.

Survival

Actuarial survival in the VT group was 38% at 1 year, 20% at 3 years, and 13% at 5 years (Fig. 5). Median survival was 9 months. The respective actuarial rates for the 20 patients who presented portal vein thrombus alone were 50%, 26%, and 17% with a median survival of 12 months. The duration of survival in the six patients who had hepatic vein tumor thrombus was 0.5, 0.5, 2, 6, 9, and 11 months (median, 4 months). In the VT group 3 of the 10 patients in whom resection was incomplete died

Table 2. Preoperative findings

Preoperative findings	VT group (n = 26)	Control group (n = 82)	*P*
Age	63 years (21–79)	66 years (26–81)	NS
Male sex	22 (84%)	68 (80%)	NS
Hepatitis virus B or C	12 (46%)	25 (30%)	NS
Tumor size	9 cm (3–24)	10 cm (3–25)	NS
Protrombin time ratio	91% (60–100)	100% (55–100)	NS
Bilirubin	17 μmoles/1 (7–45)	14 μmoles/1 (4–520)	NS
Albumin	38 g/1 (18–45)	41 g/1 (32–52)	NS
ICG test ⩽ 12%*	8/16 (50%)	26/37 (76%)	NS
Cirrhosis or severe fibrosis	17 (65%)	26 (32%)	<0.01
ICG test ⩽ 12% (cirrhosis/fibrosis)	4/12 (33%)	12/17 (71%)	<0.05
AFP ⩽ 3 N	9 (35%)	52 (63%)	<0.01
AFP > 100 N	14 (54%)	14 (17%)	<0.001

Data presented as median (range), and n (%).
VT = venous thrombectomy; ICG = indocyanine green; AFP = alpha fetoprotein; N = superior limit of normal value.
*53 patients were tested.

Table 3. Surgical procedures and pathological data

	VT group (n = 26)	Control group (n = 82)	*P*
Complete resection	16 (62%)	76 (93%)	<0.001
Number of tumors			
Single or double tumor	7 (27%)	42 (51%)	<0.001
Single tumor with satellite nodules	8 (31%)	31 (38%)	
Multiple tumors	11 (42%)	9 (11%)	
Number of resected segments: 3/4/5–6	8/13/5	35/36/11	NS
Pringle maneuver duration	37 min (15–80)	31 min (0–60)	NS
Number of HVE	5 (19%)	4 (5%)	NS
Procedure duration	180 min (120–420)	170 min (75–450)	NS
Patients requiring transfusion	11 (42%)	22 (28%)	NS
Weight of surgical specimen	947 g (322–2140)	965 (269–3250)	NS

Data presented as median (range), and n (%). VT = venous thrombectomy; HVE = hepatic vascular exclusion.

postoperatively. Median survival after incomplete resection was 2 months overall, and 6 months for the seven survivors. Median survival after complete resection (n = 16) was 10 months. Two patients lived longer than 5 years. One of these two long-term survivors died 73 months after the procedure with no sign of recurrence. The second long-term survivor was still alive with a follow-up of 90 months.

Actuarial survival in the control group was 74% at 1 year, 56% at 3 years, and 33% at 5 years ($P < 0.001$ with VT group). Median survival was 41 months. Fourteen patients in the control group lived longer than 5 years. Multivariate analysis (Table 5) showed that incomplete resection, AFP level greater than 100 N, number of tumor nodules greater than two, and presence of tumor thrombus in the major vasculature were independent factors of shorter survival.

Table 4. Early outcome after surgical treatment

Early outcome	VT group (n = 26)	Control group (n = 82)	*P*
Postoperative mortality	3 (11, 5%)	7 (8.5%)	NS
Postoperative morbidity	10 (38, 5%)	34 (41.5%)	NS
Uneventful recovery	16 (62%)	48 (59%)	NS
Duration of postoperative hospitalization (days)	14 (8–30)	12 (2–52)	NS

Data presented as n (%), and median (range). VT = venous thrombectomy.

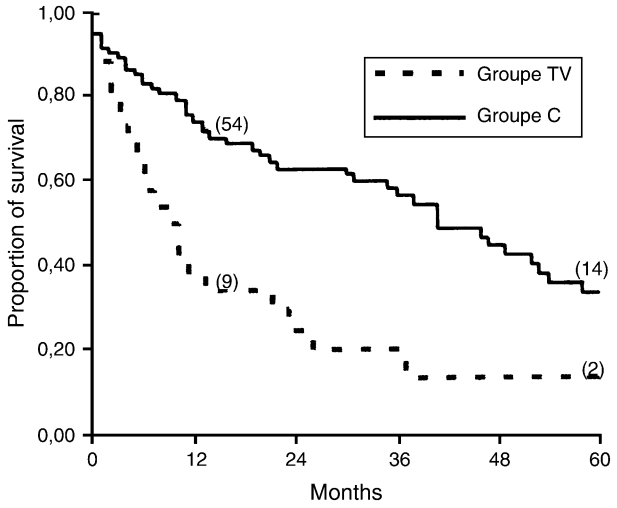

Fig. 5. Actuarial survival. The difference between curves is highly significant. $P < 0.001$.

DISCUSSION

This series showed that the risks of major hepatectomy undertaken with intent to cure HCC were comparable in patients with or without associated tumor thrombus. However, median survival was four to five times shorter after major hepatectomy for HCC with than without tumor thrombus, and that tumor thrombus was an independent predictor of short survival. Most cases in this series were associated with factors shown to adversely impact survival,[9] including large, often multinodular tumors (Fig. 2), hepatic vein tumor thrombus, or incomplete resection. However, patients in whom venous invasion was located exclusively in the portal vein had a postoperative mortality of 5%, median survival of 12 months, and a 5-year survival rate of 17%.

Mortality in both the VT and control group in this series was around 10%. Although some recent investigators from the Far East have reported zero mortality rates,[10,11] most series describing surgical treatment of HCC have reported rates ranging from 5% to 7%.[12–14] In a multicentric European series that included 1647 cases, Jaeck et al.[15] reported a mortality rate of 10.6 ± 6% at 30 days and identified cirrhosis, extent of resection (minor in 77% of cases), and time of study period as the main risk factors for mortality. Our series is consistent with these findings because 40% of patients had cirrhosis, the study period lasted 15 years, and all resections were major. In their series

Table 5. Multivariate analysis of prognostic factors

Variables	Adjusted OR	*P*	95% CI
Incomplete resection	3.09	0.05	[1.4–6.8]
AFP > 100N	2.52	0.016	[1.2–5.4]
Tumor number > 2	2.09	0.016	[1.1–3.8]
Tumor thrombus	2.08	0.026	[1.1–3.9]
Cirrhosis/fibrosis	1.56	0.16	[0.83–2.91]

OR = odds ratio; CI = confidence interval; N = superior limit of normal value.

of major hepatectomies for HCC associated with cirrhosis, Capussotti et al.[16] observed a mortality rate of only 5.6% by using strict selection criteria, that is, residual hepatic volume ⩾35% and ICG test less than or equal to 10%.

Cirrhotic patients in our VT group rarely presented normal ICG test values (33% vs. 71%; $P < 0.05$). Some investigators contraindicate major hepatectomy in patients with ICG test values exceeding 14%[5] or even 10%.[16–18] However, current experience suggests that the cutoff can be raised to 20% in low-risk cases in terms of residual liver volume and severity of cirrhosis,[5] and up to 30% for hepatectomy involving three segments.[19] To further extend the limit, some investigators have advocated preoperative portal vein embolization for patients requiring more extensive resection than compatible with ICG test values.[17] The efficacy of embolization has been demonstrated in patients with severe fibrosis or cirrhosis.[18,20,21] Tumor obstruction of a main branch of the portal vein may simulate the effects of preoperative embolization. This could account for the absence of a significant difference in mortality or morbidity between the two groups in our series, despite the twofold higher incidence of cirrhosis in the VT group than in the control group.

Most investigators have advocated simple operative techniques for treatment of thrombus associated with HCC, such as en bloc removal with the liver specimen. If thrombus extends beyond the portal bifurcation, extraction via venotomy requires proximal clamping. Balloon catheter occlusion of the contralateral portal vein may be used to limit the hypothetical risk of tumor dissemination from the tip of the thrombus.[22,23] Segmental resection of the portal vein is seldom necessary.[22,24] Extraction of tumor thrombus from the hepatic veins is more difficult. If thrombus extends only slightly into the lumen of the IVC, extraction can be performed after side clamping the IVC. For more extensive thrombus, HVE is necessary with or without venovenous bypass.[19,24] For thrombus extending into the right atrium, cardiopulmonary bypass is mandatory.[7,24]

Table 6. Review of the literature about surgical treatment of HCC with venous invasion

First author, year	Number of resections	Postoperative mortality	One-year survival	Three-year survival	Median survival
Yamaoka, 1992[22]	29	3 (11%)	52%	12%	14 mo
Tanaka, 1996[26]	62		47%	20%	7 mo
Asahara, 1999[24]	17*	1 (6%)			8 mo
Ohkubo, 2000[23]	47†	1 (2%)	54%	33%	14 mo
Konishi, 2001[28]	18	0 (0%)	48%		9 mo
Minagawa, 2001[27]	18	1 (6%)	82%	42%	24 mo
Fukuda, 2002[19]	19‡	0 (0%)	—	48.5%	22 mo
Poon, 2003[30]	20	1 (5%)	30%	13%	6 mo
Capussotti, 2004[16]	13	1 (7%)	45%	18%	11 mo
Present series	26	3 (11.5%)	38%	20%	9 mo
	20§	1 (5%)	50%	26%	12 mo

*Including 13 hepatectomies with venous disobstruction.
†Including 33 cases with tumor thrombus limited to second-order portal vein branches.
‡Including seven cases with endobiliary thrombus.
§Cases with portal vein tumor thrombus.

Table 6 presents early and late results, after hepatectomy with tumor thrombus extraction in patients with HCC, reported in the literature. Mortality has been acceptable, that is, 0% to 11%. In our series, overall mortality was 11.5%, but it dropped to 5% in cases involving thrombus located exclusively in the portal vein. In comparison, reported postoperative mortality associated with major hepatectomy after portal vein embolization has ranged from 0% to 6.5% in noncirrhotic patients, and from 6% to 7% in cirrhotic patients.[25] Late results have been poor, with median survival ranging from 6 to 14 months and 3-year survival from 10% to 20% (Table 6). However, it should be noted that indications and selection criteria for resection have varied widely in different series. Yamaoka et al.[22] performed tumor thrombectomy to delay rupture of esophageal varices, resulting from occlusion of the portal vein, and to allow transarterial chemoembolization (TACE). Some series like ours have included tumor thrombus involving the hepatic veins, IVC, or the right atrium,[19,24,26] which has a worse prognosis than portal vein tumor thrombus. Other series have included

endobiliary tumor thrombus that has a less severe prognosis.[19] In the series of Ohkubo et al.,[23] most thrombus (70%) was confined to second-order branches of the portal vein so that complete resection was easier. Use of the recommended selection criteria used in one series, that is, no contralateral metastasis, no cirrhosis, relatively small main tumor, and thrombus limited to the first contralateral branch or splenomesenteric junction,[26] would have excluded most of patients from one other series.[24]

Two series stand out from all the others in the literature.[19,27] Minagawa et al.[27] reported a survival of 82% at 1 year and 42% at 3 years due to strict patient selection criteria, that is, no more than two tumor nodules, involvement of fewer than four hepatic segments, absence of portal vein obstruction, and ICG test values less than 20%. They also attributed their results to the use of preoperative TACE to stop thrombus progression and to induce further atrophy of the segment to be resected. This approach achieved good results, but stringent selection limited treatment to a small proportion of patients (18 of 45, i.e., 40%), and survival in patients that did not undergo resection was 7% at 1 year with a median survival of approximately 3 months. Fukuda et al.[19] reported 48.5% survival at 3 years and emphasized the role of postoperative TACE or intra-arterial chemotherapy that is facilitated after clearing the portal vein. However, other series have reported less convincing results in patients who underwent preoperative[24] or postoperative TACE,[22,26] suggesting that selection criteria was more important than TACE in the aforementioned results.[19,27]

Achieving complete resection is considered to be the main prognostic factor by all investigators.[5,17,19,22,23,26] Incomplete resection was the worst independent prognostic factor in our study. Various techniques can be used to improve tumor clearance. First, complete venous disobstruction must be achieved to rapidly prevent fatal tumor recurrence.[28] The limit of portal vein thrombus extension compatible with complete resection seems to be the first contralateral branch and the splenoportal junction.[26,28] If complete disobstruction cannot be achieved, portal vein stent placement under radiologic guidance is an acceptable alternative[29] that is probably preferable to incomplete resection. Regarding complete resection, preoperative TACE can be useful to ensure elimination of any tumor site in the contralateral liver before resection; patients with intrahepatic metastasis enhanced by iodized oil should be excluded. However, we consider that selection based on other prognostic factors such as AFP level or number of tumors sets aside many patients who may benefit from surgery.

In conclusion, the results of this series suggest that although HCC with tumor thrombus in the major vasculature has the poorest prognosis of the TNM stage IVA classification,[30] an aggressive surgical strategy can improve survival for selected patients with portal vein tumor thrombus in whom complete resection can be achieved. Due to the complexity of the procedure and poor results, resection of HCC with hepatic vein tumor thrombus must be attempted only in young, highly symptomatic patients (i.e., acute Budd Chiari syndrome). In cases of HCC with asymptomatic IVC or atrial tumor thrombus, we currently agree with other investigators[17,24] that these procedures are futile. Nevertheless, our policy is designed to identify as many patients as possible who could benefit from surgical treatment.

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Long-term Control of Gastroesophageal Reflux Disease Symptoms After Laparoscopic Nissen-Rosetti Fundoplication

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Laparoscopic fundoplication is the gold standard surgical treatment for gastroesophageal reflux disease, although some patients develop recurrence or collateral symptoms related to surgery. The aims of this study were to describe the long-term symptoms control in patients undergoing laparoscopic fundoplication, to analyze the patterns of failure and to correlate postoperative symptoms with anatomic and physiologic findings. Extensive preoperative and postoperative work-up including symptom questionnaire, barium meal, endoscopy, manometry, and 24-hour pH-metry were performed in 130 consecutive patients undergoing laparoscopic fundoplication. Mean follow-up was 52 months. After laparoscopic fundoplication, 117 patients (90%) were asymptomatic with Visick grade I and II symptoms reported by 124 patients (95%). On evaluation, 119 (92%) patients were satisfied and willing to repeat surgery. Two failure patterns, anatomic abnormalities (wrap migration into the chest or down onto the stomach with or without repair disruption) and functional (incompetence of antireflux mechanism), were reported in 17 patients. Reflux can be controlled in up to 90% of patients with gastroesophageal reflux disease with relatively few complications and a high degree of patient satisfaction. The most common cause of recurrent symptoms is an anatomic failure of the fundoplication. (J GASTROINTEST SURG 2006;10:863–869)

KEY WORDS: Gastroesophageal reflux disease, surgical procedures, fundoplication, laparoscopy

Laparoscopic fundoplication has become the gold standard surgical treatment to control gastroesophageal reflux disease (GERD).[1–13] Surgical series have shown an 80–90% success rate.[1–3,6,8,9,14–16] On the other hand, 10–20% of patients develop recurrence of GERD or collateral symptoms related to the surgical procedure,[16–23] although the mechanisms of failure remain unclear. Identification of the cause of failure and the management of these patients are challenging problems.

Most reports describe the preoperative work-up of the patients but few perform anatomic and physiologic studies (barium meal, upper gastrointestinal endoscopy,[16,22,23] manometry, and/or 24-hour pH recordings[17,22–27]) undertaken on a regular basis during follow-up that could explain the causes of failure.

The aims of this study, therefore, were to describe the long-term symptoms control in a group of 130 patients undergoing laparoscopic Nissen-Rosetti fundoplication (LNRF) for GERD, to analyze the patterns of failure, and to correlate postoperative symptoms with anatomic and physiologic findings.

MATERIAL AND METHODS

From September 1995 to December 2002, 130 consecutive patients undergoing LNRF for GERD were included in the study. All the patients had symptomatic GERD. The indications for surgery were (1) GERD that was refractory or incompletely controlled with medical therapy and (2) GERD that was medically controlled but patients expressed the wish to avoid life-long therapy. Patients with previous antireflux surgery or with esophageal stricture <10 mm were excluded.

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Clinical and Functional Evaluation

Symptoms. A standard questionnaire was used to collect data assessing the presence of GERD (heartburn, regurgitation, or dysphagia). Symptoms were rated on a scale (Table 1) with a maximum severity score of 17. At the postoperative follow-up, questions concerning side effects (persistent difficulty in swallowing, fullness, bloating, diarrhea, inability to belch or vomit) were also registered.

Barium Meal. Barium esophagogastrography was performed to obtain information about the anatomy of the gastroesophageal junction and esophageal emptying.

Endoscopy. Upper gastrointestinal endoscopy was performed using Olympus panendoscopes (models GIF 100, 140, and 160). Endoscopic findings were graded according to the MUSE (metaplasia, ulcer, stenosis, erosion) classification reported by Armstrong et al.[28]

Esophageal Function Tests. Esophageal function tests were performed in all patients as described elsewhere.[24,29] Esophageal manometry was performed using a continuously perfused three-lumen catheter. Basal lower esophageal sphincter pressure was determined by the station pull-through technique. The presence and amplitude of peristalsis in the body of the esophagus were evaluated after wet swallows. The diagnostic criteria for motility disorders were based on the lower and upper limits (5th and 95th percentiles, respectively) of motor variables obtained in 79 control subjects studied in our laboratory.[24]

Ambulatory 24-hour intraesophageal pH-metry was performed after manometric location of the lower esophageal sphincter, with an antimony pH electrode (Zinetics 24ME multiuse pH Catheter, model 91-9011; Medtronic, Copenhagen, Denmark) connected to a portable pH-meter (Digitrapper MK III; Synectics Medical, Sweden). All pH recordings were analyzed by computer using the Esophagogram software program, version 5.70C2 (Synectics Medical, Stockholm Sweden). The 24-hour pH results were considered diagnostic of GERD if one of the three indices for percent time of esophageal exposure to acid during the overall 24-hour, upright, and recumbent periods exceeded the 95th percentile values ($pH < 4$ for more than 4.6%, 6.0%, and 1.9% of the time, respectively) derived from previous studies in 39 healthy controls.[29] An overall assessment of the procedure was obtained with the DeMeester score.

Table 1. Symptom scoring

Symptom	Score
Heartburn	
Never	0
Occasionally	1
Seasonally	2
Daily (daytime)	3
Daily (daytime/nighttime ⩽1 day/week)	4
Daily (daytime/nighttime >1 day/week)	5
Daily (daytime/nighttime)	6
Regurgitation	
Never	0
Occasionally	1
Daily (daytime)	2
Daily (daytime/nighttime ⩽1 day/week)	3
Daily (daytime/nighttime >1 day/week)	4
Daily (daytime/nighttime), cough, and/or dyspnea	5
Dysphagia	
Never	0
<1 day/week	1
>1 day/week	2
Daily	3
Every Meal	4
Every swallow	5
Unable to eat	6

Surgical Procedure

The same group of surgeons using a standardized technique performed all procedures. After incision of the phrenoesophageal ligament, the distal esophagus was completely mobilized and a wide retroesophageal window was made. A crural repair, posterior to the esophagus, using two or three nonabsorbable sutures, was made. Short gastric vessels were divided in all patients, except in 16, allowing full fundus mobilization. A 360° tension-free, 2-cm-long wrap was created using the anterior wall of the gastric fundus (Rosetti modification). The wrap was fixed with three nonabsorbable sutures that included the anterior esophageal wall. In all patients, the fundoplication was constructed around a 56 F Maloney dilator.

Follow-up. A physician not participating in the diagnosis or treatment of GERD carried out the clinical evaluation, using the questionnaire described above every 3 months during the first year, every 6 months for 3 years, and yearly thereafter. The most recent evaluation was used for data analysis except when symptomatic recurrence had occurred earlier. A modified Visick grading scheme assessed clinical results. Patients were also asked for a personal assessment of the operation. In patients who did not attend the clinical controls, the questionnaire was undertaken by telephone.

Patients were invited to undergo full postoperative testing, including barium meal, endoscopy, esophageal manometry, and 24-hour pH recording, 12 months after surgery. The same work-up was proposed when recurrence of GERD was suspected.

Statistical Analysis

After validation of the data and a consistency analysis, the analysis of variance or nonparametric test (Wilcoxon) was used for statistical comparison of continuous variables. The χ^2 or Fisher exact test was used to compare categorical variables. The two-tailed Student's *t*-test was used to compare mean and standard deviation values. All tests were performed using the statistical software package SPSS 10.0 for Windows (SPSS, Chicago, IL). The significance level was set at $P < 0.05$.

RESULTS

One hundred thirty patients (66 men and 64 women; mean age, 49 years) were included. Nineteen patients (15%) had previous abdominal surgery, but no patient had undergone prior antireflux surgery.

The mean postoperative follow-up of the series was 52 months. The number of patients at risk included in the study at 12, 36, and 60 postoperative months was 130, 102, and 70, respectively. Data were available for 128, 93, and 58 patients in each postoperative period (99%, 92%, and 83%, respectively).

Preoperative Findings

In addition to clinical evaluation, and as part of the preoperative work-up, a barium meal was carried out in all patients. Moreover, endoscopy was performed in 126 (97%), and esophageal manometry and 24-hour pH-metry were carried out in 111 (85%) patients.

On preoperative evaluation, all patients (100%) had heartburn, 91 (70%) had referred regurgitation episodes, and 20 (15%) had a varying degree of nonobstructive dysphagia.

Preoperative barium meal showed 104 patients (80%) with type I hiatus hernia, 8 (6%) with type II, and 14 (11%) with type III. In four patients, no hernia was found.

At the preoperative upper endoscopy, 58 patients (46%) had erosive esophagitis. Barrett's esophagus, esophageal ulcers, and mild stenosis were observed in eight, four, and four patients, respectively.

The main preoperative manometric and pH-metric values are depicted in Table 2.

Surgical Complications

Fundoplication was completed laparoscopically in all except four patients (conversion rate to open operation, 3%) with extensive adhesions from previous operations.

No postoperative mortality occurred. Complications developed in 16 (12.5%) patients. Two patients developed pneumothorax during hiatus dissection, both treated with pleural drainage. There were two bleeds in the early postoperative period, one intra-

Table 2. Results of manometry and 24-hour pH-metry in the whole series and in patients in whom both studies were available in preoperative and postoperative periods

		Series with preoperative and postoperative data (n = 79)		
Parameter	**Overall series (n = 111)**	**Preoperative**	**Postoperative**	***P***
Manometric data				
LES_P* (mm Hg)	12 ± 1	12.1 ± 1	17.8 ± 1	<0.05
Peristalsis amplitude (mm Hg)				
Upper third	55 ± 3	54 ± 3	48 ± 3	NS
Middle third	48 ± 3	48 ± 3	55 ± 3	NS
Lower third	67 ± 3	66 ± 3	80 ± 5	<0.05
Primary peristalsis (%)	90	90	90	NS
Simultaneous waves (%)	17	15	16	NS
pHmetric data				
Reflux time (%)	9.5 ± 1	9.4 ± 1	0.7 ± 1	<0.05
DeMeester score (n)	30 ± 4	30 ± 4	2 ± 3	<0.05

Values given as mean ± SEM.
LESp = lower esophageal sphincter pressure.
**P* values between preoperative and postoperative values.

abdominal and one incisional treated conservatively. One patient had early migration of the wrap requiring reoperation. There were four wound infections. One patient developed atelectasia, and one had urinary infection. During follow-up, five patients were found to have incisional hernias in the port orifices.

Postoperative Findings

Symptoms. LNRF was associated with a statistically significant decrease in the heartburn, dysphagia, and regurgitation scores at 12, 36, and 60 months of follow-up (Fig. 1). After the surgical procedure, 117 patients (90%) were completely asymptomatic regarding their primary GERD symptoms on the last follow-up.

On the other hand, 13 (10%) patients had persistent or recurrent symptoms related to GERD after LNRF: heartburn in eight (6%) patients (two associated with regurgitation episodes) and persistent or newly developed dysphagia in five (4%) patients (Table 3). Heartburn had recurred in two patients at 6 months of follow-up, in one patient at 9 months, in one patient at 12 months, and in four patients at 36 months.

All patients in this series presented with varying degrees of dysphagia in the early postoperative (<4 weeks) period, but no specific treatment was needed. In five (4%) patients, the dysphagia episodes persisted or reappeared during follow-up.

Symptoms probably related to the surgical procedure included diarrhea in 10 patients (8%; transient in 9 and permanent in 1), postprandial fullness or bloating in 19 (15%) patients, and inability to belch or vomit in 59 (45%) patients.

Barium Meal. At the 12-month postoperative follow-up, 105 (81%) patients agreed to undergo a barium meal. We found anatomic abnormalities in nine (9%) patients: in four (4%), the fundoplication had migrated to the thorax (in one, this anomaly was associated with a gastric volvulus), in three (3%) patients a slipped fundoplication was observed, in one (1%) patient there was a wrap malposition with esophageal torsion, and one (1%) patient had early disruption of the fundoplication (Table 3).

Upper Endoscopy. Forty-six of our 130 patients had repeated endoscopy at 12 months. Before operation, 23 (50%) of these had esophagitis. On the following examinations, four (9%) had esophagitis. One of these patients did not have esophagitis before operation.

Esophageal Function Tests. Esophageal manometry and 24-hour pH-metry were carried out in 79 (71%) of 111 patients during the follow-up. Results are shown in Table 2. The mean lower esophageal sphincter pressure increased from 12.1 ± 1 mm Hg before operation to 17.8 ± 1 mm Hg, and 24-hour pH reflux time decreased from 9.4 ± 1% to 0.7 ± 1%. In six patients, a pathologic reflux (>4.6% of recording time) was found within 12 months. In three additional patients, GERD

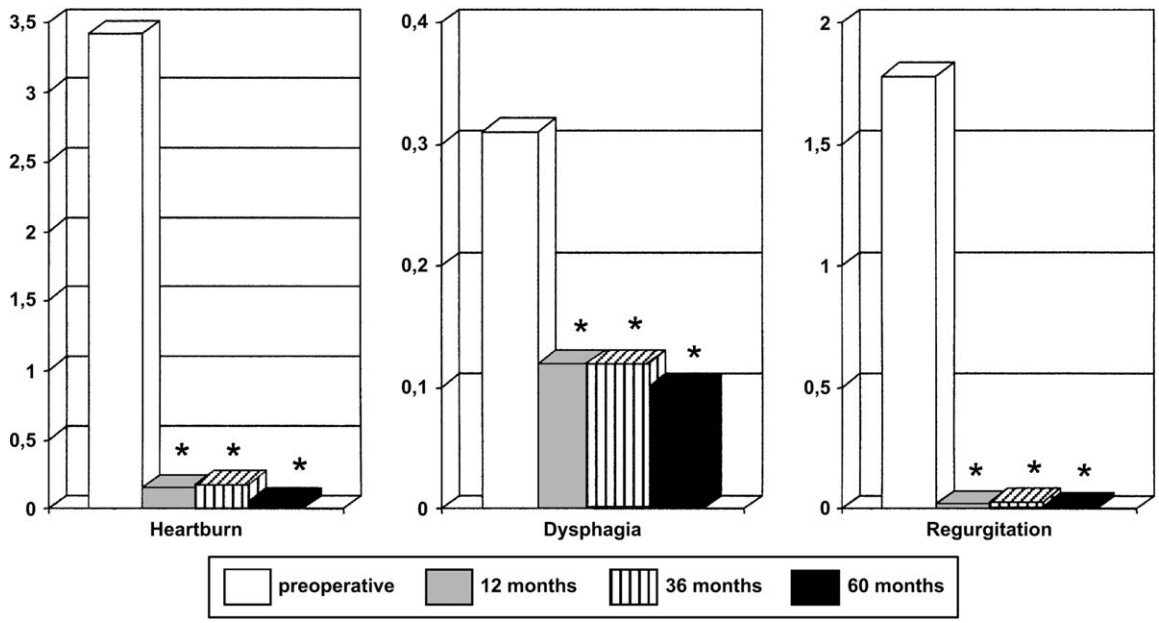

Fig. 1. Preoperative and postoperative symptom scores for heartburn, dysphagia, and regurgitation (*$P < 0.05$ versus preoperative values).

Table 3. Characteristics of 17 patients with some clinical, radiological, or functional alteration on follow-up

Patient	Symptom	Follow-up (mo)	Barium meal	Endoscopy	Manometry	pHmetry	Outcome
1	Heartburn*	6	Slippage	Esophagitis	Normal	Reflux	Reoperation
2	Heartburn	6	Migration	Normal	Normal	Normal	Reoperation
3	Heartburn*	9	Normal	Esophagitis	Normal	Reflux	PPI
4	Heartburn	12	Migration	Normal	Normal	Normal	Reoperation
5	Heartburn	36	Normal	Esophagitis	Normal	Reflux	PPI
6	Heartburn	36	Migration	Normal	Normal	Normal	PPI
7	Heartburn	36	Normal	Normal	IEM	Reflux	PPI
8	Heartburn	36	Slippage	Normal	IEM	Reflux	Reoperation
9	Dysphagia	0	Normal	Normal	IEM	Normal	CIS + RN
10	Dysphagia	1	Torsion	Normal	Normal	Normal	Reoperation
11	Dysphagia	3	Disruption	Normal	Normal	Normal	Reoperation
12	Dysphagia	12	Normal	Normal	Normal	Normal	CIS + RN
13	Dysphagia	36	Migration + volvulus	Normal	Normal	Normal	Reoperation
14	No	12	Slippage	Normal	Normal	Reflux	PPI
15	No	12	Normal	Esophagitis	Normal	Reflux	PPI
16	No	12	Normal	Normal	Normal	Reflux	PPI
17	No	12	Normal	Normal	Normal	Reflux	PPI

PPI = proton pump inhibitors, IEM = ineffective esophageal motility, CIS + RN = cisapride + ranitidine.
*Regurgitation associated.

symptoms recurred later and the 24-hour pH recording was then abnormal.

Correlations Between Postoperative Symptoms and Tests

Table 3 shows the correlation between symptoms (heartburn, dysphagia, or none) related to GERD and functional abnormalities detected after fundoplication.

All patients with heartburn had at least one radiologic, endoscopic, or functional abnormality. In five patients, the barium meal showed a fundoplication defect (migration of the wrap into the chest in three patients, and in two, a slippage down onto the stomach). Reflux was present by 24-hour pH-metry in five patients (in two, motility disorders were also observed). In addition, three patients had erosive esophagitis on endoscopy. Two patients with heartburn also reported regurgitation (1.5%). Four of eight patients with heartburn needed reoperation to restore normal anatomy, whereas in the other four, symptoms were controlled with acid suppression medication.

In three of the five patients with postoperative dysphagia, an anatomic failure was detected in the postoperative barium meal and a redo procedure was performed (Table 3). One further patient with dysphagia had a persistent motility disorder.

Four asymptomatic patients had pathologic reflux on 24-hour pH-metry. One of these had erosive esophagitis, and one, a slippage of the fundoplication.

At the last follow-up, 20 patients (15%) were on antisecretory treatment: 10 (8%) because of GERD and 10 (8%) because they were taking nonsteroidal anti-inflammatory drugs.

Degree of Satisfaction

A functional status of Visick grades I and II, asymptomatic or mild symptoms only, was reported by 124 patients (95%). Minor symptoms were rarely volunteered by the patients and were discovered only by specific leading questions. At the time of evaluation, 119 patients (92%) were satisfied with the surgical results and would be willing to undergo the same surgery again.

DISCUSSION

The present study reports a high frequency of symptomatic cure of GERD after laparoscopic fundoplication and a high degree of patient satisfaction with relatively few collateral effects. Although conservative treatment continues to be the gold standard for patients with nonerosive GERD, the introduction of laparoscopic techniques has led to resurgence in the use of antireflux surgery.[3,8,9] Many centers that have introduced this procedure over the past 15 years have reported an increase in the referral of patients controlled by maintenance antisecretory therapy who want to avoid long-term medication and choose to undergo laparoscopic surgery because

of the significant reduction in morbidity, postoperative pain, hospital stay, and earlier return to normal activity compared with open surgery.[7,10,11]

Studies with long-term follow-up (more than 10 years) have shown success rates of 80–90% with open fundoplication in the treatment of GERD.[27,30] In our experience, symptomatic control and satisfaction degree after open surgery was 92% at 20 years.[30] The success rate of the laparoscopic procedure, which differs only in its surgical approach, should be similar, but there are few reports objectively documenting the medium-/long-term results.[2,6,9,14,15,31] As in other series, our study reports good clinical results after laparoscopic fundoplication,[2,5–7,10,12] despite recurrent heartburn in 6% of the patients and dysphagia in 4%. Eight percent of our patients reported diarrhea and 45% were unable to belch or vomit. Despite these symptoms, 95% of our patients were satisfied with the outcome and would make the same decision again, even in the patients requiring reoperation. Similar results have been reported by other authors.[14,15,19,30]

A controversial issue is the use of extensive esophageal tests in preoperative and postoperative evaluation. Some authors have demonstrated that preoperative esophageal studies, other than those required to make an accurate diagnosis, were of no value in deciding the suitability of patients for surgical correction of reflux.[30] Postoperative studies are not performed on a regular basis because of patient refusal, particularly when symptom free, and because their utility has not been proved.[2,17,19,21,24] However, these studies are mandatory when untoward symptoms appear. Nonetheless, despite our efforts to carry out an extensive follow-up of all patients, 40% of the patients refused to undergo the tests, particularly when free of symptoms.

As in other studies, endoscopic improvement was significant.[27,32,33] Erosive esophagitis disappeared in the majority of patients. Regarding esophageal manometry, the present data corroborate earlier reports of an increase in lower esophageal sphincter pressure and esophageal contraction amplitude following antireflux surgery.[2,24,27,34] Moreover, 24-hour pH monitoring demonstrated normalization of acid exposure in 89% of patients tested. Four patients without GERD symptoms still had pathologic reflux but not as severe as before operation. The reduced reflux may explain the resolution of symptoms, although one of the four still had esophagitis.

Analysis of the 13 patients who had recurrent or persistent symptoms indicated two patterns of failure.[35] The most common cause of anatomic abnormality was the migration of the wrap into the chest or down onto the stomach (slippage) with or without disruption of the repair. The second was a functional failure, the incompetence of the antireflux mechanisms despite a satisfactory appearing wrap. In this scenario, a careful barium study should be first performed on reappearance of symptoms. Endoscopy can be complementary to esophagogram in identifying anatomic reasons for failed fundoplication.[33] Ambulatory 24-hour pH-metry is essential for documenting the presence of reflux when there is no evidence of anatomic failure on barium study and/or endoscopy.[2,5,6,14,27] Manometry is also essential in patients with persistent dysphagia.[17,19,24,25]

CONCLUSION

If patients with GERD are properly selected and have been thoroughly informed about the operation and the possible side effects and the wrap is loosely fashioned, control of the reflux can be achieved in up to 90% of the patients with relatively few complications and a high degree of patient satisfaction. The most common cause of recurrent symptoms is anatomic failure of the fundoplication.

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Response of the Lower Esophageal Sphincter to Gastric Distention by Carbonated Beverages

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Gastroesophageal reflux disease often occurs in patients with normal resting pressure and length of the lower esophageal sphincter. Such patients often have postprandial reflux. The mechanism of postprandial reflux remains controversial. To further clarify this, we studied the effect of carbonated beverages on the resting parameters of the lower esophageal sphincter. Nine asymptomatic healthy volunteers underwent lower esophageal sphincter manometry using a slow motorized pull through technique after ingestion of tap water and carbonated beverages. Resting pressure, overall length, and abdominal length of the lower esophageal sphincter were measured. All carbonated beverages produced sustained (20 minutes) reduction of 30−50% in all three parameters of the lower esophageal sphincter. In 62%, the reduction was of sufficient magnitude to cause the lower esophageal sphincter to reach a level normally diagnostic of incompetence. Tap water caused no reduction in sphincter parameters. Carbonated beverages, but not tap water, reduce the strength of the lower esophageal sphincter. This may be relevant to the pathogenesis of gastroesophageal reflux disease, especially in Western society. (J GASTROINTEST SURG 2006;10:870–877)

KEY WORDS: Lower esophageal sphincter, gastroesophageal reflux, carbonated beverages

The lower esophageal sphincter (LES) is the major barrier that protects the esophagus from reflux of gastric juice. The mechanisms whereby this protective function may be lost during the development of gastroesophageal reflux disease (GERD) are the subject of much controversy. Intuitively, it seems clear that profound LES hypotonia can lead to increased exposure of the esophagus to gastric juice, a state often observed in advanced GERD. Loss of the length over which this pressure is exerted, especially the length exposed to intra-abdominal pressure, is also associated with decreased reflux protection.[1] Increasingly, patients with symptoms suggestive of GERD referred for motility studies are found to have normal parameters of the LES. In these patients, the prevailing view attributes GER to transient episodes of LES relaxation, in which the LES pressure transiently approaches zero. During such moments acid reflux into the esophagus may occur.[2] The current emphasis on this mechanism has the tendency to minimize the importance of the resting parameters of the LES. It is known that most episodes of reflux, especially in patients with uncomplicated GERD, tend to be concentrated in the immediate postprandial period.[3] Early studies of LES pressure using the less sophisticated technology available in the 1960s and 1970s noted that many common dietary substances reduced LES pressure.[4–7] Little attention has been paid to the effect of dietary substances on other parameters of the LES such as its overall length and intra-abdominal length. The recent development of slow motorized pull through manometry (SMPT) of the LES has facilitated the study of this phenomenon. It is ideally suited to detecting changes in the resting parameters of the LES since it can be conducted relatively quickly, allowing for frequent repetition, and its analysis has been shown to be reproducible.[8] We hypothesized that the resting characteristics of the normal LES may decline into the abnormal range in response to a gastric challenge containing materials typically found in a Western diet. Consumption of carbonated beverages has greatly increased in a time frame comparable to that associated with

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the recognition of GERD as a major health issue. We wished to study the physiological effect of these substances on the LES. We therefore assessed the effect of various kinds of carbonated beverages on the resting parameters of the LES using SMPT.

MATERIAL AND METHODS

Nine healthy volunteers (six men and three women; age range, 25−45 years) with no or minimal symptoms of heartburn (never requiring medical treatment) had manometry of the LES carried out by SMPT. After a 5-hour fast, a catheter with four recording sites spaced 90° apart at the same level was pulled through the LES at a constant rate of 1 mm/sec while the subject breathed normally. This rate of catheter movement was imperceptible to the subject and gave clear artifact-free tracings. Three ports located 5, 10, and 15 cm proximal to the LES were used to monitor esophageal body activity. Any tracings in which either swallow-induced or secondary peristalsis was observed were discarded. A single port 5 cm distal to the above sites recorded intragastric pressure and was used to flag respirations.

The catheters were perfused with distilled water at a constant rate of 0.6 ml/min using a pneumohydraulic low compliance perfusion pump (Arndorfer Medical Specialties Inc., Greendale, WI). For each of the four LES channels recorded by the catheter, the distal limit was defined as the point when the end-expiratory pressure exceeded gastric baseline by 2 mm Hg, the proximal limit as the last breath in which the end-expiratory pressure was above the gastric baseline, and the respiratory inversion point was the first inspiration that caused a negative pressure deflection (Fig. 1). In cases where the LES showed asymmetry, the *respiratory inversion point* was defined as the first inspiration in which three of the four channels showed a downward deflection.

For each channel, the *overall length* was defined as the distance between the proximal and distal limits of the LES, and the *abdominal length* was defined as the distance from the distal limit to the respiratory inversion point. The resting pressure used was the end-expiratory pressure at the respiratory inversion point, which was defined as the average of the end-expiratory values from the breath immediately preceding, and the breath immediately following, the respiratory inversion point. All values were

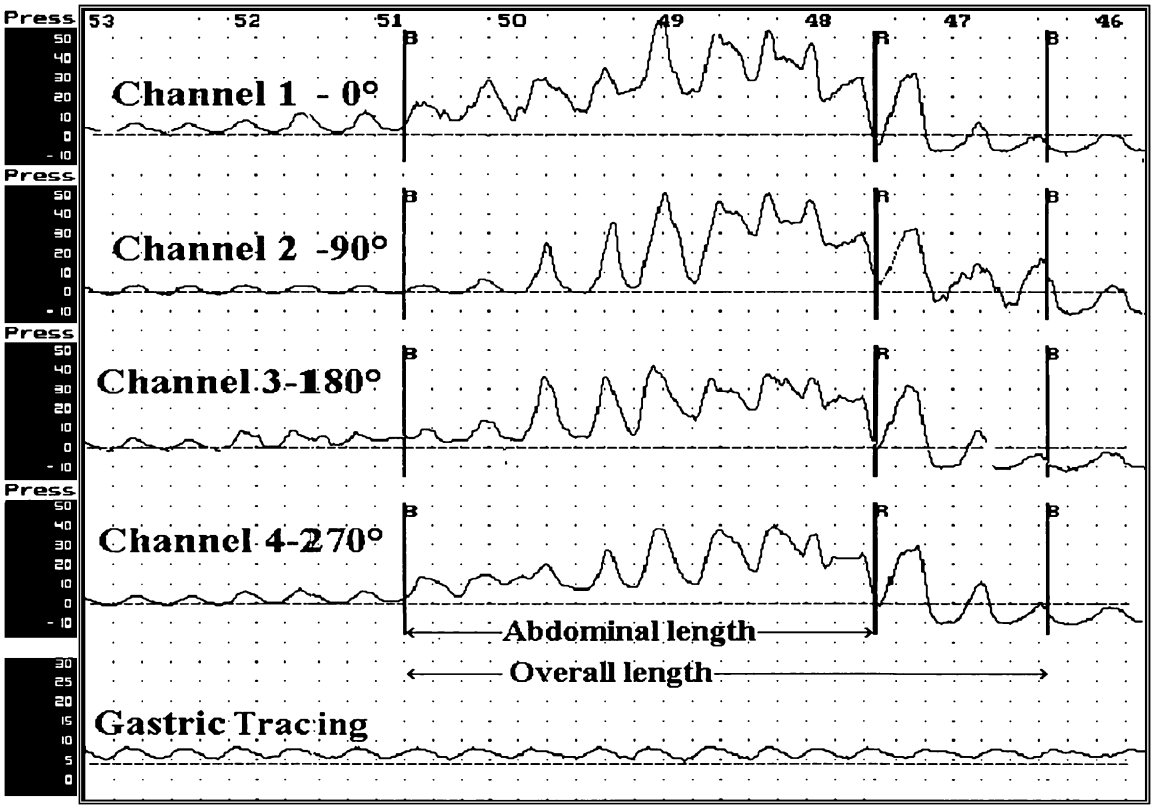

Fig. 1. Normal baseline tracing in fasting subject showing motorized pull through of lower esophageal sphincter.

calculated for each of the four channels at 90° and averaged.

To perform the analysis, the analyst was required to mark only the beginning, end, and the respiratory inversion point of the LES. All manometric analyses were confirmed by the senior author, who was blinded to the nature of the beverage consumed. A custom-written computer program (Medtronic, Minneapolis, MN) was used to calculate all of the above values as previously described.[8]

Study Design

All manometry was performed with the subject supine. A fasting SMPT was first performed. With the catheter still in situ, the subjects drank 355 ml of tap water (the volume of a standard can of soda) at room temperature. A further pull through was performed 5 minutes and 10 minutes later. After a recovery period of 20 minutes, the subjects then drank 355 ml of a carbonated beverage refrigerated at 4 °C, either caffeinated Pepsi, decaffeinated Pepsi, or sparkling water. A further SMPT was performed after 5 minutes and again after 20 minutes. The timing of the repeated manometric studies was chosen because there was no perceptible alteration with tap water after 5 minutes, whereas there was a very marked alteration with the carbonated beverages and we wished to see if its duration was prolonged.

In order to observe LES pressure over a sustained period, one subject underwent an additional study using a modified protocol. The reason was to confirm whether or not the LES experienced a sustained reduction or if there were clearly definable episodes of transient LES relaxations. After a 5-hour fast, a catheter with eight recording sites spaced 1 cm apart was placed so as to straddle the LES and the baseline pressure was recorded. The subject then drank 355 ml of Pepsi with the catheter still in place. The pressure was continuously recorded for a 10-minute period.

All subjects gave informed consent, and the protocol was approved by the institutional review board.

Data Analysis

To assess the effect of each beverage, each subject acted as his or her own control. A new baseline SMPT was performed each time a subject participated in the study, in order to eliminate error arising from fluctuations in resting LES parameters on different days.

For each parameter (pressure, overall length, and abdominal length), the median change from baseline was calculated. Results were expressed as percentages and compared using the Wilcoxon signed ranks test for paired samples. Statistical calculations were performed using Minitab for Windows. A P-value of <0.05 was accepted as significant.

For each subject, the sphincter was classified as either normal or defective based on whether the resting parameters fell within the normal range (LES pressure >6 mm Hg, overall length >2 cm, abdominal length >1 cm). The proportion of normal subjects whose lower esophageal sphincters fell into the abnormal range in response to the ingestion of carbonated beverages was calculated.

RESULTS

Median values of the LES overall length, abdominal length, and pressure in response to ingestion of all beverages are presented in Tables 1–3. All carbonated beverages produced reductions of 20−50% in the resting parameters of the LES. Typical baseline and post-Pepsi ingestion tracings are shown (Figs. 1 and 2). The duration of the effect was variable, as abdominal length tended to recover after Pepsi ingestion, but the reduction was more sustained after sparkling water (Figs. 3 and 4). The magnitude of the reduction was not significantly different between any of the three carbonated beverages, presumably because of the small numbers in each group. By contrast with the carbonated beverages, plain tap water caused only minimal changes in overall and abdominal length and the pressure actually increased (Fig. 5).

In the subject who underwent continuous monitoring of LES pressure following ingestion of 355 ml of Pepsi, an immediate reduction in LES pressure occurred, which was sustained over a 10-minute time period (Fig. 6). No belches were observed during this period.

In 8 of 13 studies (62%) performed in subjects with normal baseline LES parameters, the LES parameters fell in the range normally categorized as defective. This was due to reductions in LES pressure into the abnormal range in only two cases; in the remaining six studies, the sphincter became defective because of a decrease in either overall or abdominal length.

Table 1. Median and IQ range of LES overall length, abdominal length, and pressure following ingestion of regular Pepsi

Parameter	Baseline	Pepsi early	Pepsi late
Overall length (cm)	3.3 ± 1.1	2.1 ± 0.65	2.8 ± 0.9
Abdominal length (cm)	2.2 ± 0.75	1.5 ± 0.90	1.7 ± 1.4
LES pressure (mm Hg)	16 ± 11	12 ± 14	12 ± 6

Table 2. Median and IQ range of LES overall length, abdominal length, and pressure following ingestion of caffeine-free Pepsi

Parameter	Baseline	Caffeine-free Pepsi early	Caffeine-free Pepsi late
Overall length (cm)	2.4 ± 2.0	1.6 ± 1.5	1.6 ± 0.95
Abdominal length (cm)	1.3 ± 1.6	0.6 ± 1.7	1.2 ± 1.5
LES pressure (mm Hg)	11 ± 16	10 ± 4.5	8 ± 9.0

DISCUSSION

The most striking finding of this study was that both LES pressure and length were significantly reduced after drinking carbonated beverages but not after plain tap water. Earlier studies done in the 1970s using less sophisticated manometric techniques have demonstrated a decrease in LES pressure following ingestion of a wide variety of substances including chocolate, foods rich in fat, and tobacco smoke.[4–7,9] Other studies have shown an increase in gastric acid secretion in response to substances such as chocolate, raw onions, Coke, Tab, 7-Up, instant coffee, tea, milk, and beer.[10–13] The effect of coffee on LES pressure is more controversial, with some studies reporting a decrease of pressure after ingestion of coffee and some reporting no effect.[14,15] In these early studies, the effect was believed to be chiefly mediated by changes in the concentration of gastrin brought about by the effect of the ingested material on acid secretion. However, alterations in the anatomic configuration of the LES length in response to dietary substances have not been hitherto described. The ease with which the SMPT technique rapidly identifies changes in LES configuration has made this more detailed study of the LES possible.

Another potential effect of ingesting carbonated beverages is an increase in the rate of transient LES relaxations.[2] It is important to emphasize that our study was not designed to assess the effect of carbonated beverages on transient episodes of LES relaxations. Such episodes of LES loss of tone typically occur in the upright position after meals and presumably are responsible for the postprandial reflux seen in normal subjects and patients with milder forms of GERD. It may be suspected that this phenomenon occurred in our subjects. In order to exclude the possibility that this mechanism was the cause of the observed reduction in LES length and pressure in this study, the LES pressure at multiple sites along its length was monitored continuously for 10 minutes following ingestion of 355 ml of Pepsi. LES pressure was characterized by sustained rather than episodic reduction from baseline over this time period. It was also observed in all the subjects that belching was highly uncommon while the subjects were undergoing the study in the supine position, but after the completion of the measurements when they assumed the upright posture, belching was very common.

Table 3. Median and IQ range of LES overall length, abdominal length, and pressure following ingestion of sparkling water

Parameter	Baseline	Sparkling water early	Sparkling water late
Overall length (cm)	3.1 ± 1.7	2.2 ± 0.55	2.2 ± 1.3
Abdominal length (cm)	2 ± 1.1	0.9 ± 1.1	1.8 ± 2.3
LES pressure (mm Hg)	24 ± 16	12 ± 18	12 ± 9.5

In the normal physiologic state, consumption of carbonated beverages in the upright position might be expected to induce reflux by this additional mechanism. The intraesophageal pH was not measured in this study, so it cannot be unequivocally asserted that episodes of reflux did not occur. However, the focus of the study was to assess the alterations in resting LES configuration produced by carbonated beverages. There is evidence from the studies of Kahrilas et al.[16] that induction of gastric distention by insufflation with air causes an increase in the rate of transient LES relaxation. The changes we observed may be thought of as a change in the static function of the LES and may be additive to those dynamic changes observed by Kahrilas et al.

The mechanism of this effect appears to be a consequence of gaseous distention of the stomach, because the three carbonated beverages had a similar effect despite differing chemical composition. It is possible that, with a larger number of subjects, a significant difference between sparkling water and Pepsi would have been found. Although the manufacturers were understandably reluctant to reveal the precise gas content of their beverages, both Pepsi and sparkling water were reported to contain roughly three times their volume in gas. However, the pH values of Pepsi and sparkling water were different, with Pepsi having a pH of 2.9 and sparkling water having a pH of 5.0.

Gastric distention is a well-recognized factor in the production of GER.[17] However, it is possible that the effect of gas on the LES is distinct from that produced by distention of the stomach with liquids or solids, perhaps because gas tends to be concentrated in the fundus. This is indirectly consistent with the epidemiologic observation that in African populations GERD and its complications

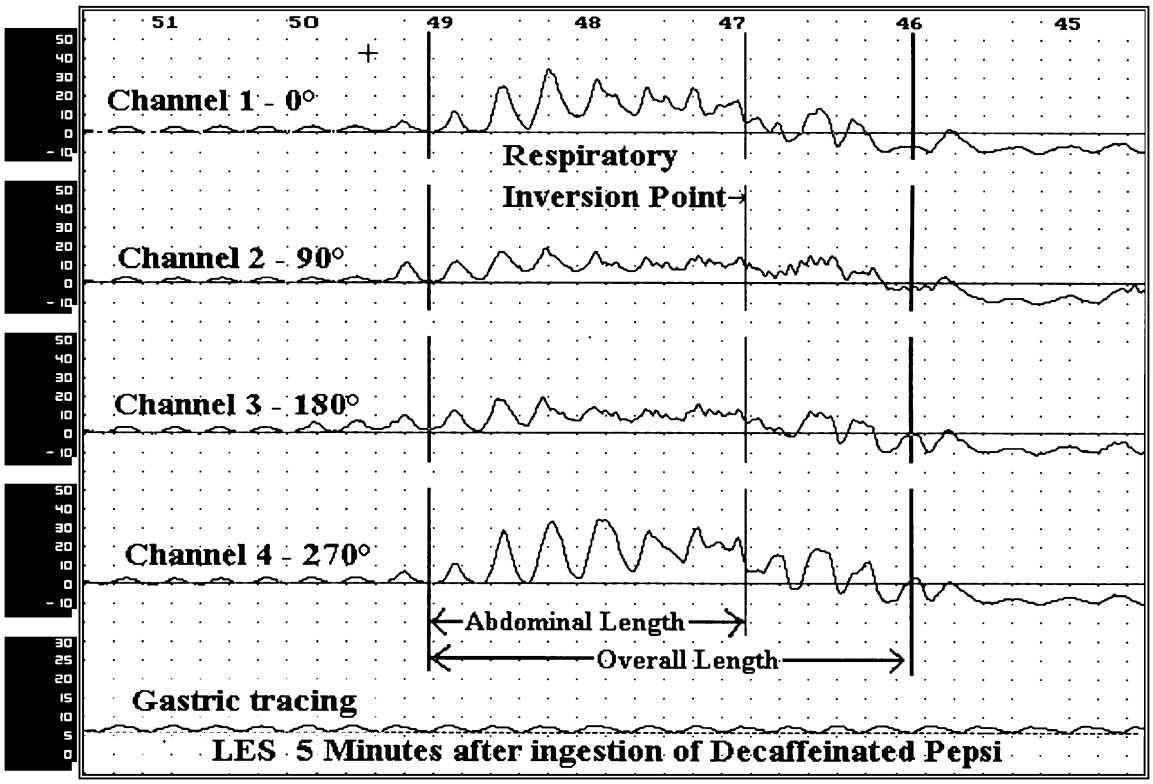

Fig. 2. Motorized pull through of the lower esophageal sphincter in the same subject 5 minutes after ingestion of Pepsi.

are much more rare than in Western patients, despite the fact that the typical diet in these countries is much greater in bulk than that consumed in the more industrialized nations.[18]

It may be objected that length and pressure are not independent phenomena in the LES and that, if the pressure at all points along the sphincter were globally reduced by a given fraction, the length would necessarily be reduced. If this were the only explanation of our observations, one would have expected the alterations in LES pressure and length to change by comparable magnitude and over the same

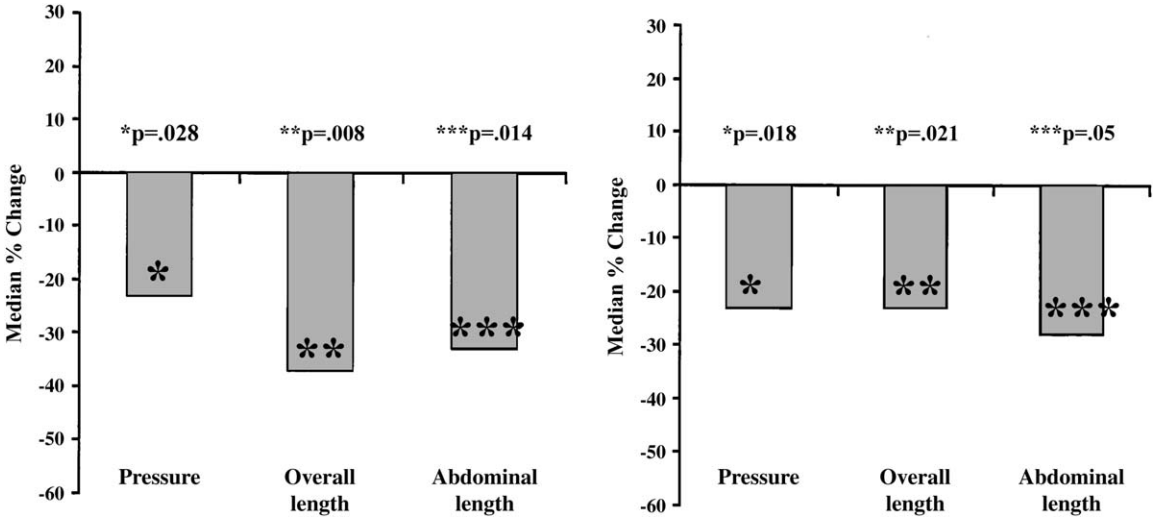

Fig. 3. Median percentage change of lower esophageal sphincter parameters 5 and 20 minutes after ingestion of Pepsi (regular and decaffeinated combined).

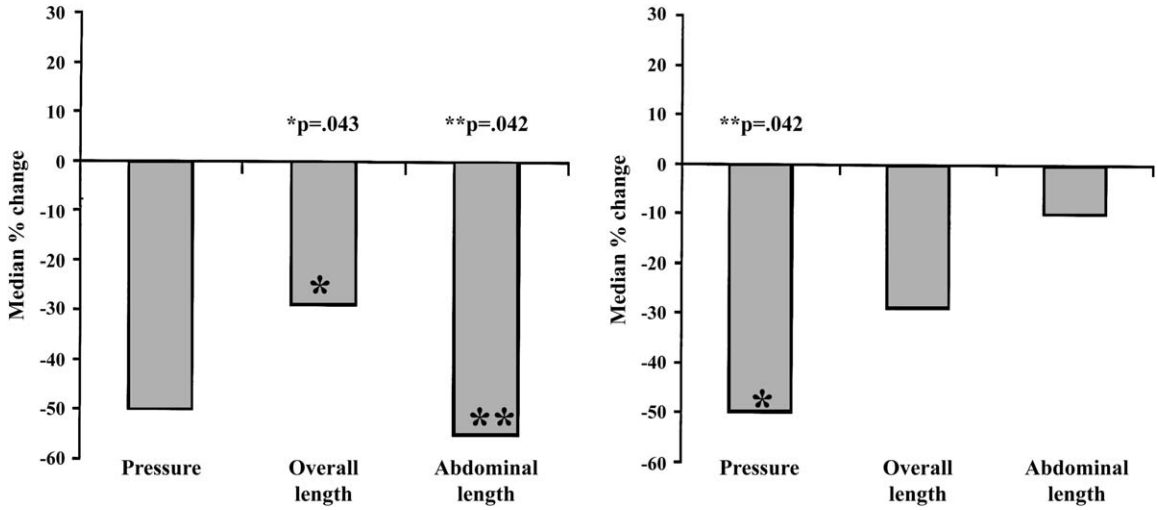

Fig. 4. Median percentage change of lower esophageal sphincter parameters 5 and 20 minutes after ingestion of sparkling water.

time scale, whereas the reduction in length was the earliest change and the change in pressure was more significant in the later measurements. This phenomenon also makes it unlikely that the temperature of the cold beverage was a significant factor. Although cold materials such as ice cream can produce loss of esophageal peristalsis,[19] it is likely that any sphincter hypotonia produced by ingestion of cold substances would tend to diminish as the temperature of the beverage equilibrated, whereas the reduction in LES pressure was found to be even more pronounced in the later measurements.

The potential clinical significance of these observations can be inferred from the magnitude of the changes: in 62% of the studies performed, the LES, although normal in the baseline state, deteriorated into the range that would have been characteristic of a defective sphincter if it had been found in a fasting patient. In both asymptomatic people and patients with mild GERD, acid reflux tends to be concentrated in the postprandial period. In patients with mild GERD, the resting LES characteristics are often normal. We speculate that gastric distention leads to a reduction in the resting pressure and length of the LES, and this may alter the threshold for reflux events. Although previous investigations failed to find a relationship between the resting pressure of the LES and the occurrence of reflux episodes in normal subjects, the Dent sleeve used in these studies makes it impossible to record

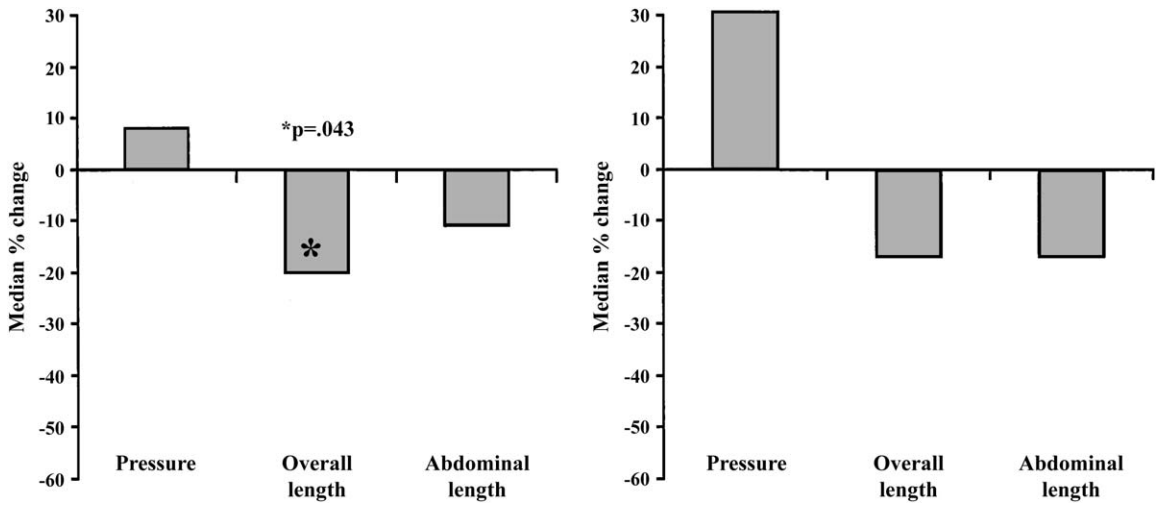

Fig. 5. Median percentage change of lower esophageal sphincter parameters 5 and 10 minutes after ingestion of regular tap water.

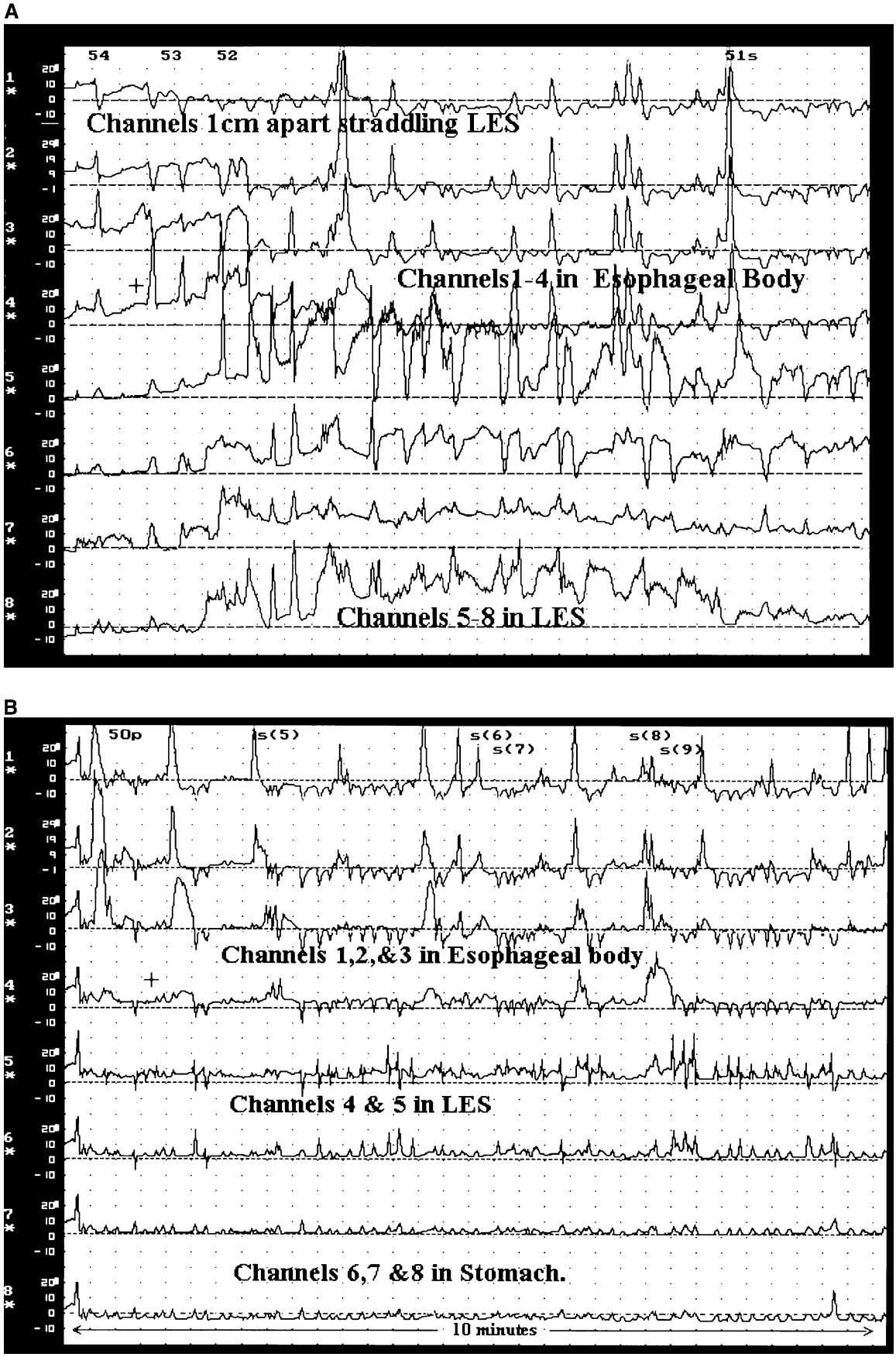

Fig. 6. Ten minute recording of a subject using a catheter with eight closely spaced transducers straddling the LES (**A**) fasting and (**B**) immediately after ingestion of Pepsi. Note the sustained reduction in LES pressure during the ten-minute time interval.

Table 4. Median and IQ range of LES overall length, abdominal length, and pressure following ingestion of tap water

Parameter	Baseline	Tap water early	Tap water late
Overall length (cm)	3.0 ± 1.8	2.4 ± 1.5	2.5 ± 1.5
Abdominal length (cm)	1.8 ± 1.3	1.4 ± 1.6	1.5 ± 1.5
LES pressure (mm Hg)	13 ± 8	14 ± 17	17 ± 12

changes in LES length.[2] In support of this view, Mason et al.[20] found that increasing the intragastric pressure in anesthetized baboons caused a proportional decrease in LES length and an increased rate of common cavity episodes. The same study showed that the changes in LES parameters induced by gastric distension were prevented by Nissen fundoplication. This is also consistent with recent clinical evidence that outcome after Nissen fundoplication for GERD was equally good regardless of the status of the LES preoperatively.[21] Fundoplication appears to work by correcting both defective resting LES parameters and postprandial deterioration. In a patient with GERD with normal LES parameters on fasting manometry, it is possible that assessing the same parameters after ingestion of a standardized volume of gas may be a more sensitive method of identifying a subtle defect in LES function. LES decompensation in response to a gaseous challenge may be an important mechanism in early GERD and may precede the development of frank mechanical incompetence.

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Patient Perception of a Clinical Pathway for Laparoscopic Foregut Surgery

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Clinical pathways have been implemented for a number of surgical procedures, yet few data are available that explore the patients' perception of these changes in clinical practice. A clinical pathway was developed for laparoscopic fundoplication, Heller myotomy, and paraesophageal hernia repair. Data collected from a cohort of patients undergoing surgery with the pathway over a 12-month period was compared with a group of patients operated on in the 12 months prior to pathway implementation. A questionnaire examining patient-based outcomes and perceptions was completed 6 weeks after surgery. From November 2001 through November 2003, 49 patients underwent primary laparoscopic foregut surgery, 27 before and 22 after pathway implementation. There were no differences in age, gender, procedure, or ASA Class. Parenteral opioid use diminished significantly without compromising the patients' perceived pain control. The number of patients undergoing postoperative investigations diminished, as did length of stay. Of the 20 postpathway patients completing satisfaction questionnaires, 95% were satisfied or very satisfied with their care during admission. Pathway implementation resulted in a significant reduction in direct postoperative hospital costs. A clinical pathway for laparoscopic foregut surgery was successfully implemented in a single-payer system, resulting in decreased utilization of hospital resources while maintaining high patient satisfaction. (J GASTROINTEST SURG 2006;10:878–882)

KEY WORDS: Clinical pathway, laparoscopy, fundoplication, hiatal hernia, achalasia, myotomy, esophageal surgery

The prevalence of managed care in the United States and limited health care dollars in single-payer systems such as in Canada have provided incentive for identifying methods to reduce costs. Clinical pathways have been demonstrated as effective cost-containment measures for a variety of conditions and operative procedures.[1–4] However, few studies have examined the impact of clinical pathways in laparoscopic hiatal surgery or assessed the patient perception of these protocols. In addition, little data exist on the benefit of clinical pathways on health care resource utilization in a single-payer system.

Length of stay after laparoscopic hiatal surgery (Nissen fundoplication, Heller myotomy, paraesophageal hernia repair) ranges from 2 to 5 days depending on the specific procedure, the surgical practice and local norms, and the health care system.[5–10] Therefore, given this relatively short postoperative period, the opportunity for further reduction in length of stay in these cases is limited. Nonetheless, we believed that a standardized approach to the postoperative care for patients undergoing laparoscopic hiatal surgery could further improve these outcomes. We sought to determine the impact of a clinical pathway on laparoscopic surgery for achalasia, gastroesophageal reflux disease, and paraesophageal hernias from the patients' perspective.

METHODS

A clinical pathway was developed for all patients undergoing laparoscopic hiatal surgery including Heller myotomy, Nissen fundoplication, and paraesophageal repair. In its design, input was obtained from surgeons, nurses, dietitians, pharmacists, and anesthetists. The clinical pathway outlined

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all preoperative, immediate postoperative, and discharge care from a nursing, activity, medication, diet, and medical intervention perspective. Nursing instructions involved preoperative teaching and postoperative care. All postoperative investigations (e.g., chest or contrast radiography, laboratory investigations) were omitted unless the patient clinical status deviated significantly from the expected postoperative course. Analgesia was controlled primarily with acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs), with a significant reduction of opioids. Patients were allowed sips of water immediately postoperatively, and a liquid diet was started on the first postoperative day, after instructions on a posthiatal surgery diet provided by the ward nutritionist. Ambulation was required on the evening of surgery and most patients were expected to meet discharge criteria (absence of fever, control of pain with oral analgesics, and ability to tolerate liquid oral intake) by the afternoon of the first postoperative day. All members of the treating team were educated about the pathway at informal sessions on participating clinical units.

The pathway was implemented November 2000 and applied to all patients undergoing primary laparoscopic foregut surgery. Patients undergoing reoperative surgery were excluded. The cohort of patients operated over a 12-month period under the clinical pathway was compared with those who had undergone laparoscopic foregut surgery in the 12-month period immediately prior to clinical pathway implementation. Patient characteristics, postoperative course (complications, length of stay, opioid use), resource utilization (investigations, postoperative direct hospital cost), and quality of life (Short Form-12 Mental and Physical) were prospectively collected in the postimplementation group and compared with outcomes in the preimplementation group. Readmissions and reasons for deviation from the pathway were also documented. A questionnaire examining patient-based outcomes and perceptions (satisfaction, pain control, timing of discharge from hospital) was completed 6 weeks after surgery in the postimplementation group. Direct hospital costs were compiled for both study groups. Given that the primary goal of the clinical pathway is to impact the postoperative course, only direct costs in this period (nursing, investigation, and hotel costs) were analyzed. Data are presented as mean ± standard error of the mean, or median (range). The two groups were analyzed and compared using Student's *t*-test or χ^2 test. Differences with a *P*-value of ≤ 0.05 were considered to be significant.

RESULTS

From November 2001 to November 2003, a total of 55 patients underwent laparoscopic foregut surgery (Heller myotomy, Nissen fundoplication, or paraesophageal hernia repair). Of these, six had undergone prior open or laparoscopic foregut surgery and were not included in the study. Therefore, 49 patients were assessed, 27 before and 22 after implementation of the clinical pathway. Patient characteristics are displayed in Table 1. There was a slight trend for more advanced age and significantly more male patients in those being managed by the clinical pathway. Surgery for paraesophageal hernia repair represented 30% of cases in the prepathway group and 45% in the postpathway group (NS).

A significant reduction in length of stay (from 2.7 to 1.6 days) was achieved after implementation of the clinical pathway. Standardized postoperative orders also resulted in a substantial reduction in the use of parenteral opioids (from 36 to 7.5 mg morphine equivalents) (Table 2). One patient was readmitted in the prepathway group for severe dysphagia. No patients required readmission after introduction of the clinical pathway. Although more postoperative complications occurred in the prepathway cohort, the difference was not significant and the complications were generally minor (Clavien Classes I and II).

The majority (18 of 27) of the prepathway cohort had some postoperative investigation. These were mostly laboratory tests including complete blood count (14 of 27) and electrolytes/renal function tests (11 of 27), usually performed in the postanesthesia care unit and on the first postoperative day. Radiographic tests were performed in nine prepathway patients (four chest radiographs and five contrast studies). Conversely, only five (23%) of the postpathway patients had received postoperative investigations ($P < 0.05$). These included two chest radiographs and three blood tests (complete blood

Table 1. Characteristics of patients undergoing laparoscopic foregut surgery prior to and after clinical pathway implementation

	Prepathway	Postpathway	*P*-value
Number	27	22	
Age, median y (range)	53 (23–84)	58 (30–77)	0.56
Gender (% male)	11 (41%)	15 (68%)	0.06
ASA>2 (%)	6 (22%)	5 (23%)	0.92
Procedure			
Fundoplication	10	6	
Heller myotomy	9	6	
PEH repair	8	10	0.51

Table 2. Post operative outcomes pre- and post-clinical pathway implementation

	Prepathway	Postpathway	*P*-value
Time to oral intake	1.3 ± 0.8	1 .0 ± 0	0.98
Length of stay (days)	2.7 ± 1.2	1.6 ± 0.7	<0.01
Parenteral opioid (mg morphine equivalent)	36 (5–92)	7.5 (0–60)	<0.01
Complications	4/27 (14%) Dysphagia × 2 Diarrhea Pulmonary edema	1/22 (4.5%) Urinary retention	0.07

count and electrolytes), all performed in the recovery room and ordered by the anesthesia team.

The care of nine patients (41%) in the post cohort deviated from the clinical pathway, and the reasons for deviation were documented. Investigations ordered by the anesthesia team in the postanesthesia care unit accounted for more than half of these. An anesthetist unfamiliar with the pathway ordered patient-controlled anesthesia for two patients. A full diet was given to the first patient on the clinical pathway due to a miscommunication with nutrition services.

Implementation of the clinical pathway resulted in a 44% reduction in direct postoperative hospital costs. Significant decreases in nursing, hotel, and investigation costs were documented in the postpathway group (Table 3). A savings of 371.37 $C per case was demonstrated with implementation of the pathway.

Patient-based outcomes were assessed at 6 weeks in the postimplementation study group. Of the 22 patients in the postpathway cohort, 20 (91%) completed the questionnaire. Of respondents, 75% were very satisfied and 20% were satisfied. Only one patient was dissatisfied (5%). None of the respondents thought that they were discharged prematurely from the hospital; all (20 of 20) thought that the timing of discharge was appropriate. Despite a significant reduction in parenteral opioid use, 90% of the patients thought that pain was adequately controlled. General quality of life as assessed by the Short Form-12 at 6 weeks did not significantly differ between the prepathway and postpathway groups (Table 4). In addition, there was no difference between preoperative and postoperative scores within the two study groups.

Table 3. Postoperative hospital costs per patient pre- and post-clinical pathway implementation

	Prepathway	Postpathway	*P*-value
Nursing costs/case	677.47	384.93	<0.01
Hotel costs/case	138.07	78.45	<0.01
Investigation costs/case	25.54	6.33	<0.01
Total direct postoperative costs/case	841.08	469.71	<0.01

DISCUSSION

We have demonstrated not only that a clinical pathway for laparoscopic foregut surgery is feasible in a single-payer system but also that a significant (greater that 40%) reduction in postoperative direct costs is possible. Although this finding has been shown for a number of procedures, this present article is unique in that we have reported that clinical pathways are effective in reducing spending in a single-payer system. In addition, this is the first article to document the impact of these protocols on laparoscopic foregut surgery. We limited the analysis to postoperative costs, because the clinical pathway was directed primarily towards postoperative management. We elected not to include costs for medications, for we thought that patients' preoperative medications would add an additional variable for which we could not control. However, given that there was a three-fold increase in parenteral opioid use in the prepathway group, costs would clearly be increased for this medication alone.

Despite an already short length of stay in the prepathway cohort, we were able to further reduce hospital stay with implementation of the clinical pathway. The prepathway mean length of stay of 2.6 days is consistent with the majority of published series; however, some authors have reported successful outpatient laparoscopic Nissen fundoplication procedures.[11] The postpathway mean length of stay

Table 4. Preoperative and postoperative general quality of life prior to and after (6 weeks) clinical pathway implementation

	Prepathway	Postpathway	*P*-value
Short Form 12 Mental			
Preoperative	49.8 ± 11.2	53. 5 ± 7.9	0.21
Postoperative	54.4 ± 10.2	52.5 ± 8.9	0.53
Short Form 12 Physical			
Preoperative	44.1 ± 12.4	44.7 ± 12.1	0.87
Postoperative	46.0 ± 10.5	46.7 ± 11. 2	0.84

of 1.6 days, with a median of 1 day (1–3 days), is made more impressive by the greater proportion of patients with giant paraesophageal hernias in this cohort (45% versus 30%). Laparoscopic paraesophageal hernia repair tends to be a more extensive procedure than either laparoscopic Heller myotomy or fundoplication for gastroesophageal reflux, and accordingly, the reported hospital stays in large series are in the range of 3–4 days.[6,8] In the assessment of length of stay, it is important to document 30-day readmission rates. There was only one readmission after discharge, involving a prepathway patient with excessive dysphagia after a paraesophageal hernia repair. One weakness of the study is the use of historical controls rather than a contemporaneous nonpathway group. However, the benefits of the pathway were apparent very early in the design of this study, so we thought that all patients should undergo the protocol.

Pain control prior to the clinical pathway was not standardized. The majority of patients received patient-controlled analgesia, and there was an underuse of NSAIDs. Although not specifically tested in this study, it was our belief that excess opioids could potentially increase length of stay by their effects on the patients' level of consciousness, by decreasing bowel motility and increasing nausea, and by delaying ambulation. With the regular use of acetaminophen and NSAIDs in the clinical pathway, we were able to significantly diminish parenteral opioid use, without adversely affecting pain control. A weakness of the study is that adequacy of pain control was assessed at 6 weeks without a validated pain scale and only in the postpathway cohort. However, our primary concern was to determine the patients' perception of pain control, rather than to quantify the pain directly. Nonetheless, this patient population overwhelmingly perceived at 6 weeks that pain was well controlled in the postoperative period.

In the initial design of this clinical pathway, we sought not only to evaluate the feasibility of the protocol but also to assess the patients' perception. The vast majority of patients undergoing the clinical pathway in our study were satisfied or very satisfied with care during their hospital stay. This is consistent with another study examining patient-based outcome after clinical pathway implementation for outpatient cholecystectomy.[1] Although specific reasons for the high rate of satisfaction were not studied, it is possible that under the clinical pathway patients know exactly what to expect as they recover from surgery. This elimination of uncertainty may result in a reduction of patient anxiety about their care. In addition, all members of the health care system are working under the same protocol, resulting in less confusion between them.

Despite a successful implementation of the pathway with the desired reduction in length of stay, direct costs, and maintenance of satisfaction, there were numerous deviations (9 of 22) from the clinical pathway. The majority of these were minor and resulted from a breakdown in the lines of communication between the various health care workers involved in the care of these patients. This underscores the single most important key for a clinical pathway. Although patient education is vital for the success of a clinical pathway,[1,12] the information must also be effectively conveyed to all members of the treating team for it to work flawlessly. We have not only demonstrated the feasibility of a clinical pathway for laparoscopic foregut surgery but also shown that resource utilization may be reduced in single-payer system. More important, we have shown that patient perception of their hospital stay under a clinical pathway can remain favorable.

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Presence and Density of *Helicobacter pylori* Biofilms in Human Gastric Mucosa in Patients With Peptic Ulcer Disease

James M. Coticchia, M.D., Choichi Sugawa, M.D., Vivian R. Tran, B.S., Jose Gurrola, B.S., Evan Kowalski, Michael A. Carron, M.D.

Our purpose was to use endoscopically directed biopsies and scanning electron microscopy to quantify *Helicobacter pylori* biofilm density on the surface of human gastric mucosa in urease-positive and -negative patients. Participating patients underwent flexible esophagogastroduodenoscopies coupled with gastric mucosal biopsies. Rapid urease testing was performed on all specimens to determine the presence of *H. pylori*, followed by scanning electron microscopy to identify the existence of biofilms. Samples were then analyzed using Carnoy Image Analysis Software to determine percent biofilm coverage of the total surface area. These data were compared to control specimens that were urease negative. Of the patients who tested urease positive for *H. pylori*, the average percent of total surface area covered by biofilms was 97.3%. Those testing negative had an average surface area coverage of only 1.64%. These differences were determined to be statistically significant at the 0.0001 level. This study demonstrates that compared with controls, urease-positive specimens have significant biofilm formation, whereas urease-negative specimens have little to none. This was reflected in the significantly increased biofilm surface density in urease positive specimens compared with urease-negative controls. (J GASTROINTEST SURG 2006;10:883–889)

KEY WORDS: biofilms, *H. pylori*, scanning electron microscopy, image analysis, peptic ulcer disease

Helicobacter pylori is one of the most common microbial diseases in the world, infecting 50% of the world's populations.[1] It has long been associated in the pathogenesis of duodenal ulcers, gastric ulcers, chronic gastritis, and gastric carcinoma. The eradication of *H. pylori* can be difficult, usually requiring a multi-drug regimen and a lengthy treatment period.[2] There are currently several possible therapeutic options available to help eradicate this troublesome and potentially dangerous organism.[3] Despite aggressive antimicrobial therapy, 10–20% of infections manage to persist, which suggests that these infections have some unique propensity to withstand antimicrobial treatment.[4]

Since the 1970s, the term *biofilm* has been used to describe the structurally complex bacterial ecosystems that allow bacteria to function collectively in a coordinated fashion.[5] Costerton et al.[6] define biofilms as "matrix enclosed bacterial populations adherent to each other and to surfaces or interfaces." It has been demonstrated that biofilms have many characteristics unique from that of nonsessile, planktonic bacterium. Not only can they form in multiple steps, but they also have been shown to be involved in intercellular signaling and to exhibit gene transcription that is very distinct from their planktonic counterparts.[7] In response to quorum sensing signals, bacteria migrate and adhere to a surface, divide to form microcolonies, and expand laterally and vertically.[8]

What makes the biofilm so resilient is its ability to encase itself in an exopolysaccharide (EPS) matrix. The EPS matrix of a biofilm provides the bacteria with a significant degree of protection from host defense mechanisms as well as climatic and environmental changes. Through its capacity to alter the state of its microenvironment, the biofilm effectively eliminates the diffusion of antimicrobials, shields

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Table 1. Biofilm density (urease-positive specimens)

Sample	Surface area (μm^2)	Biofilm density (μm^2)	Percentage
1	42136.28989	40906.94671	0.97082
2	42106.84454	40734.93179	0.96742
3	42202.54191	42136.28989	0.99843
4	42231.83703	40840.39421	0.96705
5	42231.83703	40583.94928	0.96098
6	42298.23929	42106.84454	0.99548
7	42136.28989	40108.01635	0.95186

Table depicts gastric mucosa samples and biofilm density in *H.pylori*–positive patients.

Table 2. Biofilm density (urease-negative specimens)

Sample	Surface area (μm^2)	Biofilm density (μm^2)	Percentage
8	42231.83703	1102.24746	0.0261
9	42136.28989	1075.20582	0.02552
10	42136.28989	Minimal	0
11	42202.54191	1114.20047	0.0264
12	42298.23929	826.12223	0.01953
13	42231.83703	714.95102	0.01693
14	42298.23929	Minimal	0

Table depicts gastric mucosa samples and biofilm density in *H.pylori*–negative patients.

UV radiation, buffers pH shifts, and prevents dessication. Biofilms also exhibit decreased metabolic and growth rates (lowering their susceptibility to antimicrobials) and readily express and transmit genes involved in the resistance to certain antibiotics.[9] These sessile communities can "shed" free-floating, planktonic cells that can rapidly multiply, disperse, and infect. The temporary clinical improvement afforded by antibiotics will last for only a short period of time, resulting in an eventual relapse as planktonic cells are continuously shed. The only reliable mechanism to eradicate these recurrent infections is mechanical removal of the biofilm, destroying its ability to provide additional infectious organisms.[10]

The persistent nature of *H. pylori* infections has led investigators to postulate that biofilms may play a role in this clinical entity. Recently, our laboratory has shown that *H. pylori* also forms biofilms in vivo in

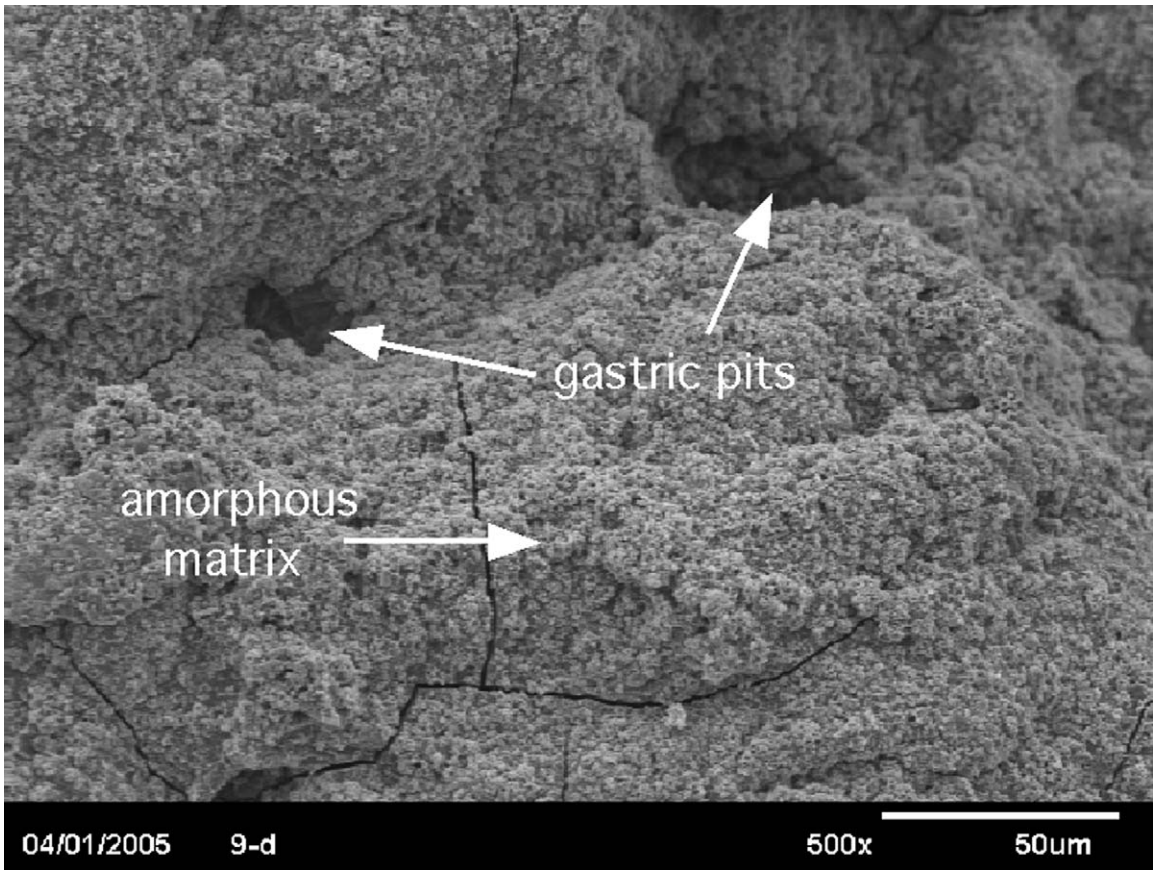

Fig. 1. Depicts an scanning electron micrograph at ×500 of human mucosal surface covered in a blanket of biofilm.

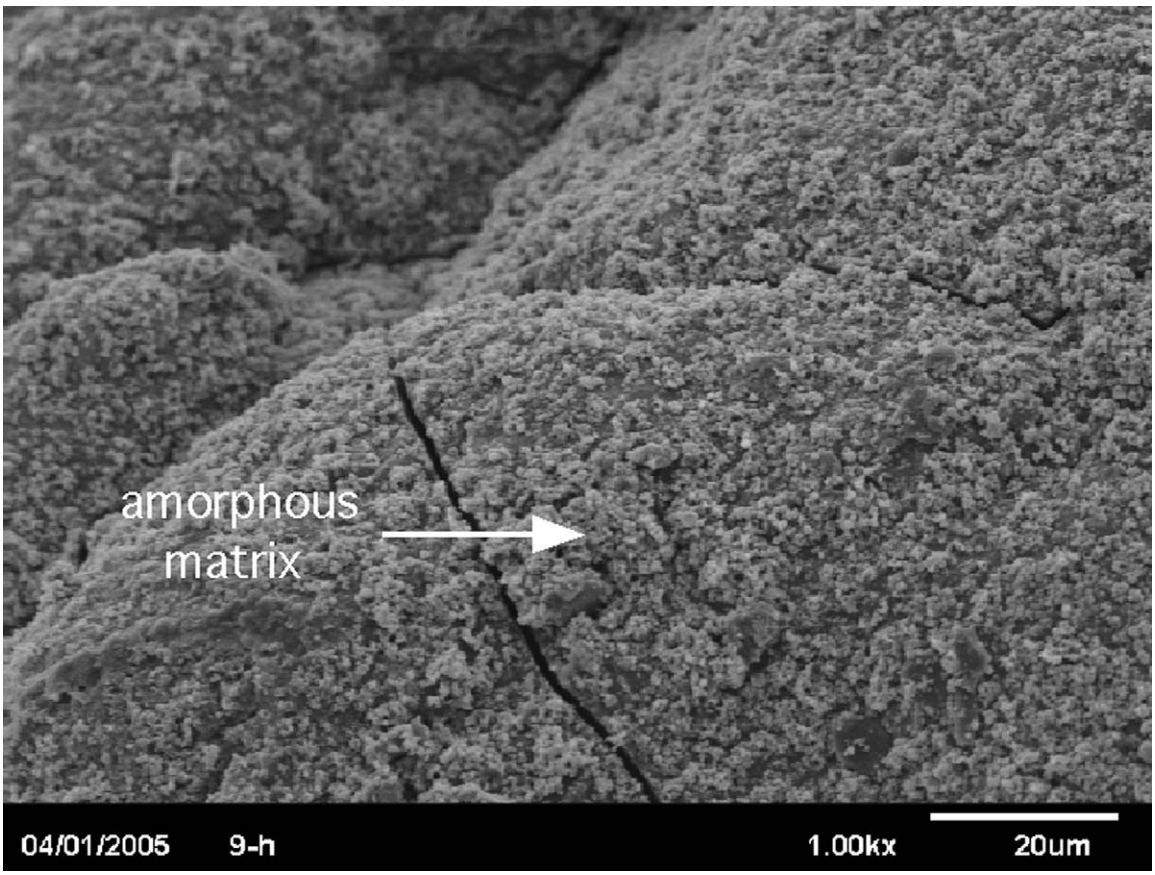

Fig. 2. Depicts an scanning electron micrograph at ×1000 of biofilm architecture on mucosal surface.

human gastric mucosa.[11] In this investigation, we use standard scanning electron microscopic (SEM) techniques to evaluate gastric mucosal surfaces of *H. pylori*–positive and *H. pylori*–negative specimens to determine any differences in biofilm coverage between the two sets using surface density analysis. We hypothesize that biofilm surface density will be significantly greater in *H. pylori*–positive specimens compared with urease-negative control specimens.

MATERIALS AND METHODS

Sample Collection

This study was done in accordance with our institutional review board. All samples were obtained from esophagogastroduodenoscopy performed at Detroit Receiving Hospital, Detroit, Michigan. Twenty-six patients underwent flexible esophagogastroduodenoscopies with three gastric mucosal biopsies. Rapid urease testing (Pyloritek Serim Research) was also performed to determine the presence of *H. pylori*. Seventeen specimens were urease positive and nine specimens were urease negative. Urease negative specimens were controls. All specimens were prepared and imaged with scanning electron microscopy. The ages of the patients ranged from 37 to 86 years; there were 15 male patients and 11 female patients.

SEM Preparation and Fixation

All samples were prepared for SEM with the following methodology. Tissue was initially fixed for 3 hours in 2.5% glutaraldehyde. Sorensen's phosphate buffer (0.2 M) was then used for washing. Four 15-minute washings were performed. Next, the samples were treated with 2% osmium tetroxide for 30 minutes. The tissue was then dehydrated with incremental concentrations of ethanol as follows: 30% for 15 minutes, 30% for 15 minutes, 50% for 15 minutes, 70% for 15 minutes, 90% for 15 minutes and 100% for 15 minutes. Finally, the tissue was washed with HMVS (Electron Microscopy Sciences, Fort Washington, PA) three times for 15 minutes. Three drops of HMVS were then placed on the samples, and they were left to dry overnight in a fume hood. Specimens were then mounted on SEM

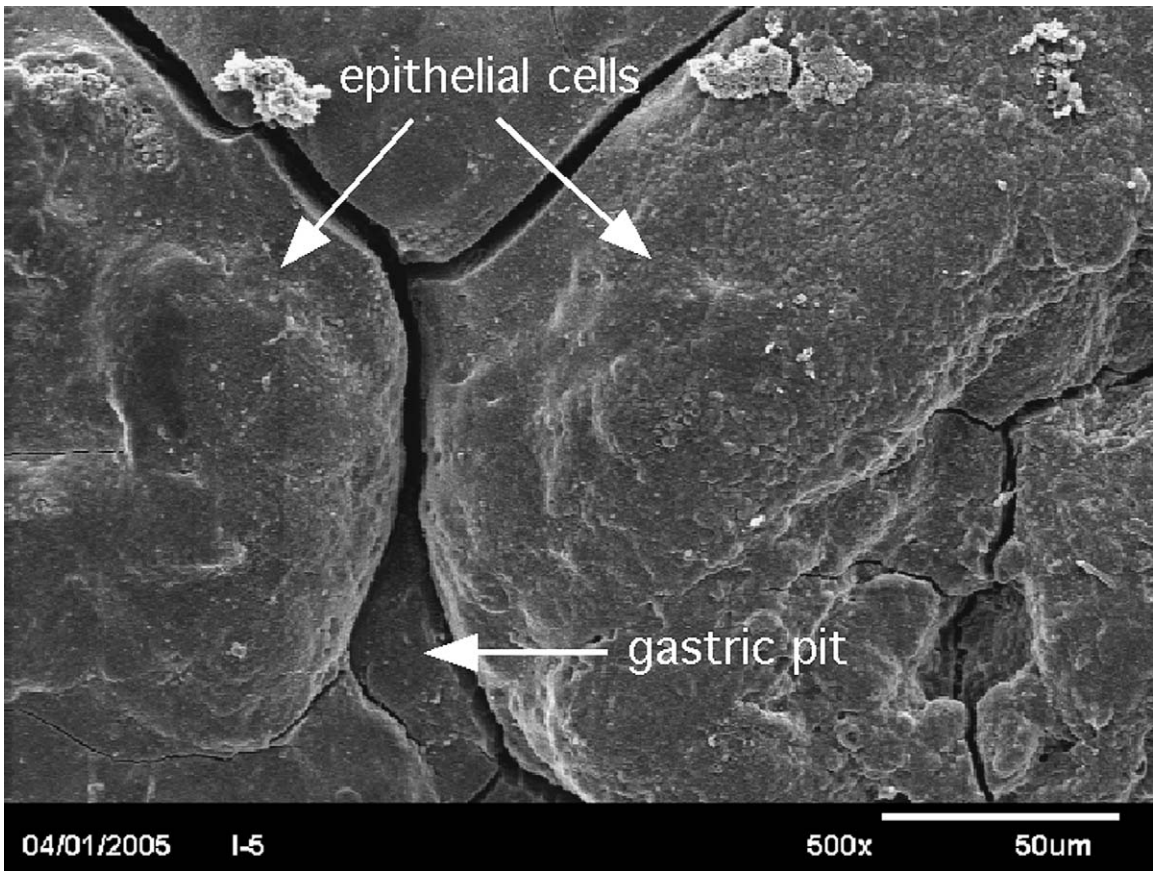

Fig. 3. Depicts an scanning electron image at ×500 of mucosal surface devoid of biofilms.

specimen pedestals and secured with a silver paste (Electron Microscopy Sciences, Fort Washington, PA). All specimens were gold-palladium sputter coated for two 90-second intervals (Ted Pella Incorporated, Redding, California).

SEM Imaging

Imaging was done at our SEM laboratory. The senior author was present at all imaging sessions. An AMRAY scanning electron microscope at 10 KV was used to take photomicrographs at ×1000 and ×500 magnification for each sample. Digital images were then captured and stored on CD-ROM for image analysis.

Surface Density Analysis

Seven urease-negative and seven urease-positive specimens were randomly selected for image analysis. Total surface area, biofilm density, and percent of total surface area covered by biofilm was calculated using Carnoy SEM image analysis software (analysis software for LM, SEM, and TEM images; Carnoy, Flanders, Belgium). The data were tabulated and statistically analyzed.

Statistical Analysis

To determine a statistically significant difference between the average biofilm surface area in *H. pylori*–positive and–negative patients, an independent Student *t*-test was performed. The average percent area covered by biofilm in urease-positive patients and urease-negative patients were determined by Carnoy Image Analysis to be 97.3% and 1.64%, respectively. Using the Student *t*-test, this difference was statistically significant with $P = 0.0001$.

RESULTS

We used the definition of previous investigators to define biofilm architecture—that of dense accumulations of bacteria within an amorphous matrix.[12,13] We compared our SEM images to existing SEM biofilm images from other investigators.[14,15] Digital image analysis of the seven SEM images taken from urease-positive specimens demonstrated

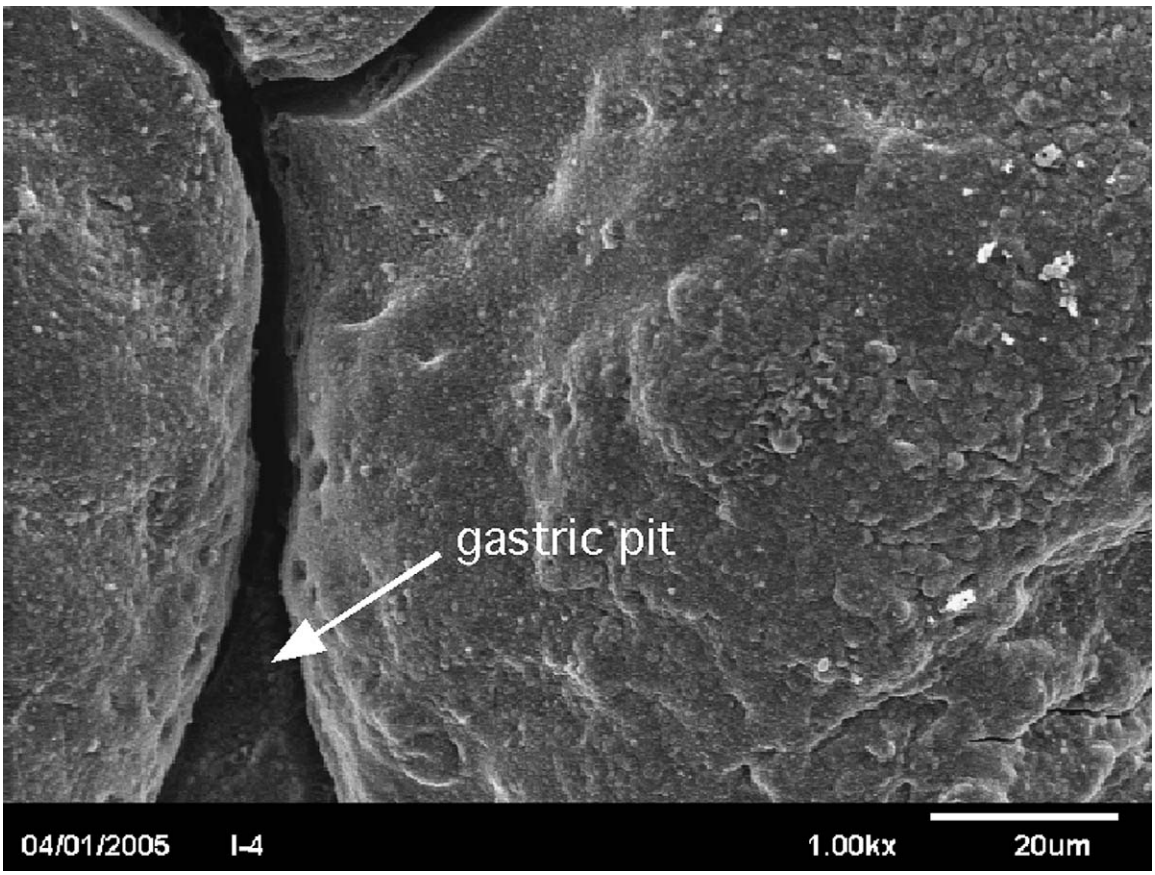

Fig. 4. Depicts a high-power scanning electron image, at ×1000, of a barren mucosal surface showing no biofilm.

mature confluent mucosal biofilms. The average total surface area of the urease-positive specimens was determined to be 42191.93 μm^2, of which an average of 41059.62 μm^2 was covered by dense mature biofilm, resulting in an average percent area coverage of 97.31% (Table 1). By contrast, in the seven urease-negative control specimens, the average total surface area, the average biofilm density, and the average percent of total surface area covered by biofilm values were 42219.32 μm^2, 690.39 μm^2, and 1.6354%, respectively (Table 2). This difference was statistically significant with $P = 0.0001$.

Figure 1 is an electron micrograph (×500) of human gastric mucosal surface demonstrating dense mature biofilm architecture. Figure 2 is an electron micrograph of the same patient but at a higher power (×l000). These two figures cleary depict dense biofilm coverage. Figure 3 is an electron micrograph (×500) of normal gastric mucosal surface epithelium and is devoid of biofilm. It has a smooth mucosal surface with epithelium and gastric pits. Figure 4 is a higher power electron micrograph (×1000) of the same specimen showing individual cells and numerous gastric pits.[16,17] Figure 5 is a bar graph showing the difference in biofilm surface area coverage for all urease-positive and urease-negative specimens.

DISCUSSION

Biofilms are known to play a role in dental disease, urinary catheter infections, endocarditis, bacterial prostatitis, osteomyelitis, otitis media, vascular grafts, IUDs, endotracheal tubes, penile prostheses, and biliary tract infections.[18] In our previous study by Carron et al.,[1] we provided photographic evidence of *H. pylori* existing in a biofilm complex in vivo. We found that gastric biopsy samples taken from urease-positive patients demonstrated surface structures composed of *H. pylori* microorganisms embedded in amorphous matrix. This cytoarchitecture covered almost the entire mucosal surface of the specimens. The unique morphological characteristics remained consistent with those identified in other disease states associated with biofilm formation. This previous study provided direct evidence that *H. pylori* forms

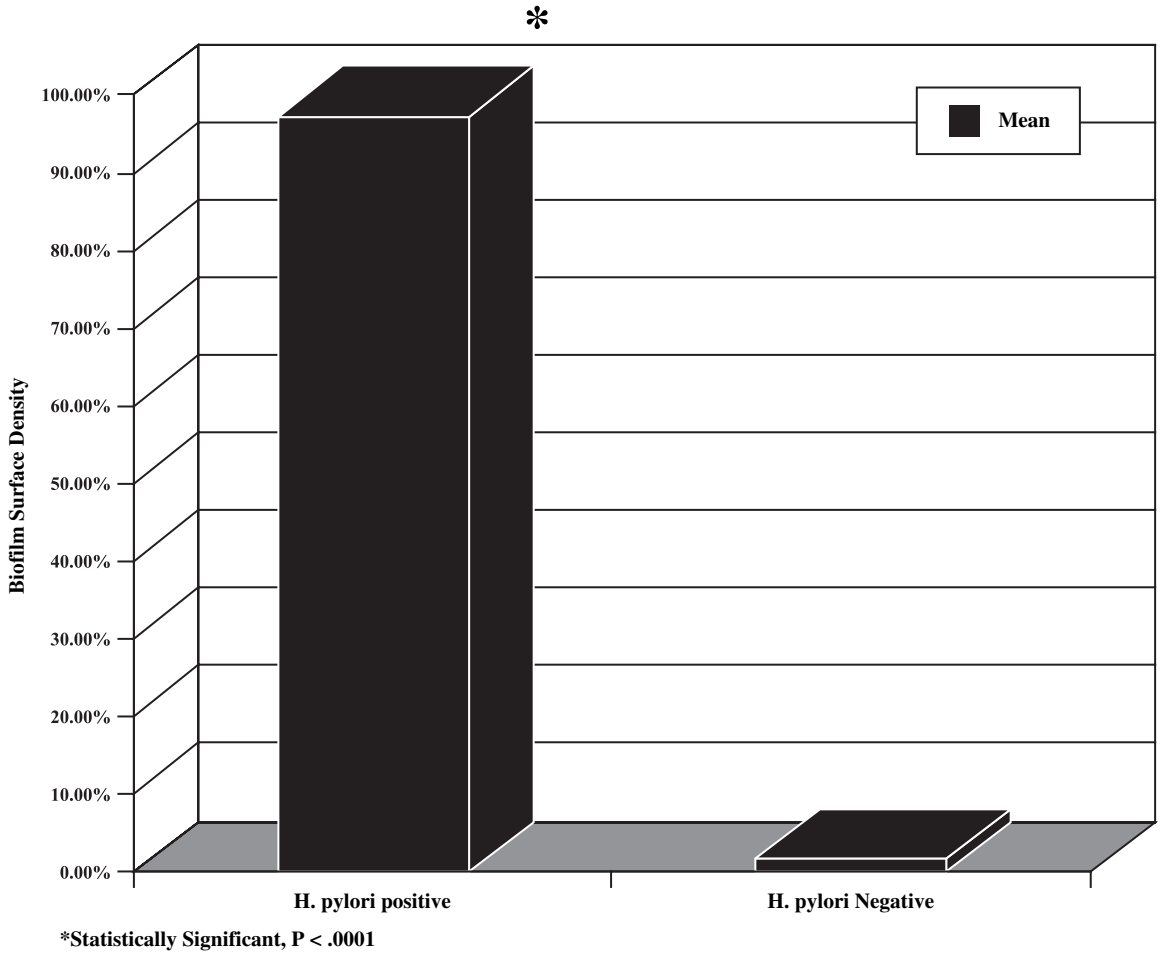

Fig. 5. Bar graph demonstrating the difference in total biofilm surface area coverage between urease-positive and-negative patients.

dense mature biofilm in urease-positive patients. In our current study, we determined surface area density and percent coverage by biofilm in urease-positive patients. These data were compared to mucosal biopsy samples taken from urease-negative controls. Using Carnoy image analysis software, we calculated significantly increased biofilm mucosal density and coverage in urease-positive patients.

Peptic ulcer disease (PUD) has a well-documented history of resistance to treatment and recurrence. While it is now known that *H. pylori* appears to be involved in the majority of cases of PUD, the overall pathogenesis is not fully understood. While triple therapy may be useful for some patients with PUD, 10–20% of cases still prove either resistant or recurrent. Because biofilms by their very nature are resistant to antimicrobial therapy, the documentation of *H. pylori* biofilms may contribute to the understanding of the pathophysiology of this organism and help explain observed treatment failures. Many have postulated the potential for *H. pylori* biofilm formation, and some have speculated on the effect it may have in the disease pathogenesis. As previously stated, our results demonstrate a high biofilm density (97.3% average surface coverage) in urease-positive patients and a relative paucity of biofilm (1.6% average surface coverage) in urease-negative patients. This was statistically significant at $p = 0.0001$. These data suggest that biofilm formation by *H. pylori* may be an important mechanism in the establishment and persistence of infection by this organism. By increasing our understanding of the various pathophysiological mechanisms in *H. pylori* infection, we hope novel treatment strategies to treat this clinical entity will be designed.

CONCLUSION

Our results show that patients with *H. pylori* infections had dense mature biofilm covering almost their entire mucosal surface which was not demonstrated in the control specimens. This is in accordance

with our hypothesis. The increased surface area coverage with biofilm in urease-positive specimens compared with urease-negative controls was statistically significant. Currently, the observed treatment failure rate in *H. pylori*–infected patients is 10–20%. Although additional studies need to be performed and no direct pathogenic mechanisms have been determined, the association dense *H. pylori* biofilm in *H. pylori*–infected patients should be considered as a potential contributing mechanism behind the pathogenesis of this organism.

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Benign Pneumatosis Intestinalis in the Setting of Celiac Disease

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Pneumatosis intestinalis is an uncommon finding that may indicate the presence of several alarming pathological conditions, including bowel ischemia, that require urgent surgical intervention. We report the case of a 51-year-old man with celiac disease who underwent resection of a large duodenal adenocarcinoma. Although he initially recovered rapidly from his procedure, he subsequently developed abdominal distention and leukocytosis. Abdominal imaging revealed extensive small bowel pneumatosis and pneumoperitoneum. Emergent surgical exploration revealed only bowel wall air cysts and dilated bowel but failed to demonstrate any intra-abdominal pathology. The patient recovered uneventfully and was discharged without any further complications or recurrence of symptoms. We review the current literature on the rare finding of pneumatosis intestinalis in the setting of celiac disease. In all reported cases, even when pneumatosis is accompanied by pneumoperitoneum, these alarming findings have proved to be of "benign" origin, that is with no evidence of bowel ischemia, perforation, or peritonitis. The available evidence suggests that pneumatosis in the setting of celiac disease may reflect the dissection of intraluminal gas into the inflamed bowel wall without accompanying intra-abdominal pathology. We conclude that pneumatosis intestinalis, even with accompanying pneumoperitoneum, does not uniformly mandate surgical exploration in patients with celiac disease. (J GASTROINTEST SURG 2006;10:890–894)

KEY WORDS: Celiac disease, pneumatosis intestinalis, pneumoperitoneum

Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is a malabsorptive syndrome of the small bowel characterized by mucosal inflammation in response to gluten ingestion.[1] The disease is strongly linked to specific human leukocyte antigen (HLA) haplotypes and has its highest prevalence (1 in 120–300 persons) in western Europe, North America, and Australia. Celiac disease most commonly presents with iron deficiency anemia, but patients often complain of diarrhea, flatulence, abdominal discomfort and bloating, and weight loss. Once the diagnosis is definitively established by biopsy, the mainstay of therapy is a gluten-free diet. Pneumatosis intestinalis refers to the finding of gas within the bowel wall, often but not invariably due to pathological conditions such as bowel wall ischemia. We present the case of a patient with celiac disease in whom pneumatosis intestinalis developed after an abdominal surgical procedure, and we review the literature on pneumatosis intestinalis in patients with celiac disease. The current knowledge on pneumatosis intestinalis in the setting of celiac disease suggests that the surgeon should potentially consider conservative management of these patients.

CASE PRESENTATION

A 51-year-old man with celiac disease presented with a 20-pound weight loss over several weeks. Abdominal imaging revealed a mass arising in the fourth portion of the duodenum and involving the body of the pancreas and the transverse colon. Upper endoscopy confirmed the diagnosis of adenocarcinoma.

The patient underwent resection of the third and fourth portions of the duodenum, distal pancreatectomy, splenectomy, and segmental transverse colectomy. Bowel continuity was reestablished with a hand-sewn end-to-side duodenojejunostomy and a hand-sewn end-to-end colocolostomy. His immediate postoperative course was complicated only by

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an ileus. He was managed conservatively without nasogastric tube decompression, and he remained afebrile with a white blood cell count within the normal range. A computed tomography (CT) scan on the fifth postoperative day (POD) demonstrated findings consistent with an ileus and minimal residual pneumoperitoneum. An abdominal plain film on POD 7 showed no evidence of intraperitoneal free air.

On POD 10, the patient developed abdominal pain that worsened over several hours. A repeat CT scan demonstrated extensive small bowel pneumatosis and pneumoperitoneum (Fig. 1). That day, his white blood cell count rose to 29,000/μL from 7000/μL on the previous day. Emergent surgical exploration revealed bowel wall air cysts and distended loops of small and large bowel but no evidence of ischemia or perforation. Intraoperative proctoscopy did not reveal pseudomembranes. Decompression was achieved through a small bowel enterotomy, which was primarily closed. He recovered uneventfully from his second operation, and a repeat CT scan 4 days later showed resolution of the pneumatosis and decreasing pneumoperitoneum. Fecal cultures remained persistently negative during his hospital stay, including assays for *Clostridium difficile*. By the time of discharge on POD 26 after his original operation, he was tolerating a solid diet with no return of his abdominal pain or leukocytosis.

Of note, histological examination of the original resection specimen revealed a 13.5-cm poorly differentiated adenocarcinoma. There were no lymph nodes positive for tumor. The nonneoplastic sections of duodenum demonstrated villous blunting, chronic inflammation, and increased intraepithelial lymphocytes consistent with celiac disease.

DISCUSSION

Pneumatosis intestinalis (PI), the presence of gas within the wall of the gastrointestinal tract, is an

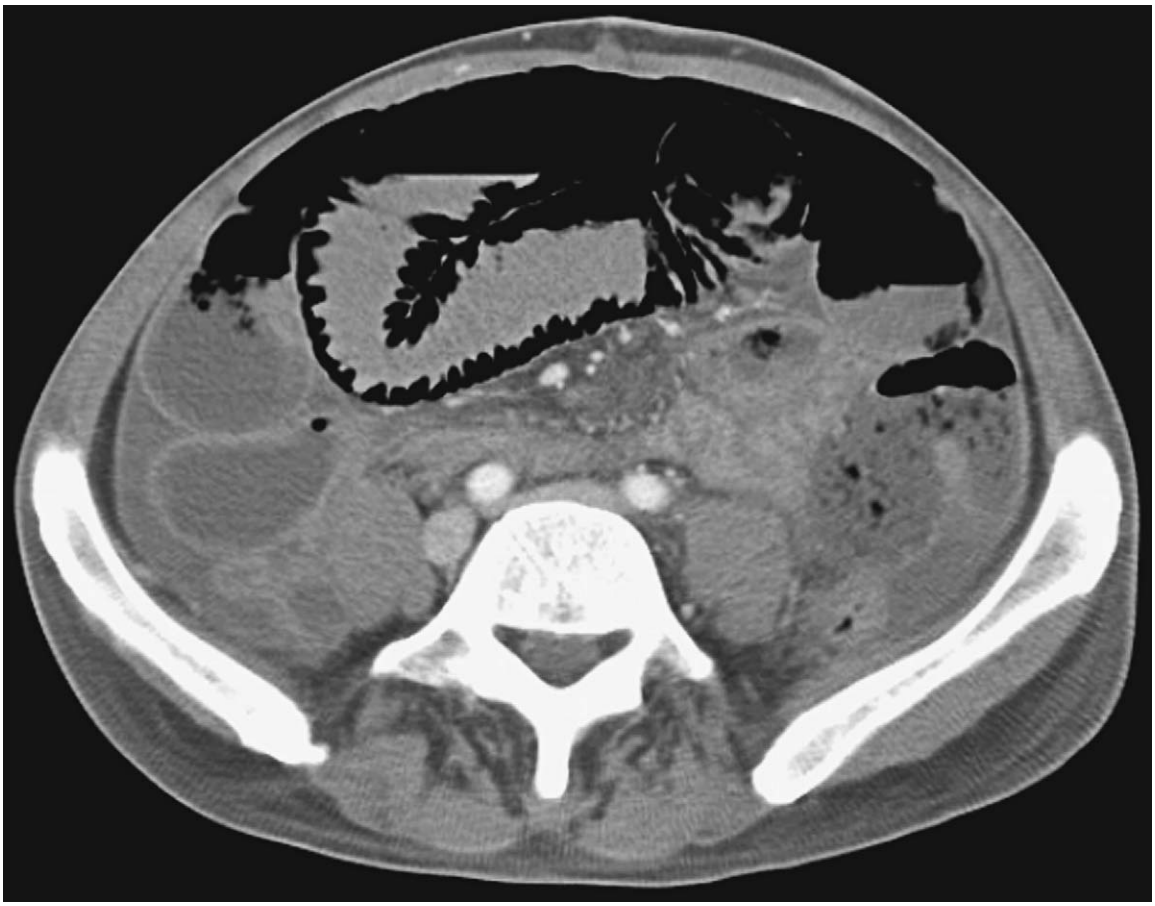

Fig. 1. CT scan demonstrating extensive small bowel pneumatosis and pneumoperitoneum.

uncommon finding that may suggest a broad spectrum of underlying pathophysiological processes. This sign, most often appreciated radiographically, may indicate the presence of disease processes as diverse as chronic obstructive pulmonary disease (COPD), immunocompromised states, and bowel ischemia and infarction. Less frequently, it may occur with no apparent associated disease ("primary" PI). For this reason, it is important to consider a patient's overall clinical status to discriminate between pathological and benign primary PI.

The most common symptoms found in patients with PI are diarrhea, bloody stools, abdominal pain, abdominal distention, constipation, weight loss, and tenesmus.[2] Radiographic investigation by plain film, ultrasound, or barium enema can detect PI, but the radiographic test of choice for detection of PI is CT, as it can differentiate PI from intraluminal gas and submucosal fat as well as survey the abdomen for associated pathology.[3] Occasionally, PI may also be detected by surgical exploration or endoscopy.

As the incidental discovery of PI increases due to the prevalence of high-resolution CT imaging, it becomes ever more important to emphasize that the significance of PI—as well the associated symptoms, appropriate treatment, and prognosis for patients who develop it—depends on the underlying disease process that underlies it, not on the presence of intramural gas itself. For example, PI may be associated with a sterile pneumoperitoneum in the absence of peritonitis, presumably caused by rupture of intramural gas-filled cysts without transmural perforation. This "benign pneumoperitoneum" occurs more commonly in small bowel PI, but it may occur in colonic PI as well.[2] In contrast, the presence of portal venous air together with PI suggests serious bowel infection or infarction and carries a grave prognosis.[4]

Three major theories seek to explain the pathogenesis of PI.[3] One theory suggests that intraluminal gas makes its way into the bowel wall, as a result of either increased intraluminal pressure (as with vomiting or obstruction), injury to the mucosa or its immune barrier (as with immunodeficiency states or therapy with corticosteroids or cytotoxic agents), or a combination of both increased pressure and mucosal compromise. A second explanation implicates gut bacteria as the source of the intramural gas. Bacteria may invade a compromised mucosal barrier and produce intramural gas, or intraluminal bacteria may create high local concentrations of hydrogen, which subsequently diffuse into the bowel wall. A third

Table 1. English-language case reports of pneumatosis intestinalis associated with celiac disease

Authors	Age (yr)/ gender	Symptoms	Pp	Bowel	Risk factors	Therapy and outcome	Resolution of PI
Frank and O'Connell, 1977[8]	48/F	Abdominal pain, distention	Yes	SB	Steroid use	Ileocolic intussusception, reduced via laparotomy; full recovery	Resolved by POD 14
Gefter et al., 1981[9]	61/F	Abdominal distention, nonbloody diarrhea	No	C	Gluten in diet	Gluten-free diet; full recovery	No follow-up imaging
Breiter et al., 1982[10]	57/F	Nonbloody diarrhea	Yes	SB	Gluten in diet	Gluten-free diet; eventual improvement on steroids	Resolved within 3 days
Sackier et al., 1988[11]	83/F	Abdominal pain, distension, vomiting	Yes	C	Gluten in diet, ibuprofen use	Negative laparotomy, gluten-free diet; full recovery	Resolved by POD 7
Khouri et al., 1989[12]	74/F	Abdominal distention, nonbloody diarrhea	Yes	SB	Gluten in diet	Gluten-free diet; full recovery	No follow-up imaging
Fred and Hariharan, 1977[13]	46/M	Abdominal discomfort, bloody bowel movements	Yes	C	None	Negative laparotomy; resolution of symptoms	Persistent at 1 year
Terzic et al., 2001[14]	66/M	Abdominal distention	Yes	SB	Mild COPD	Negative laparoscopy	Persistent at 2 weeks
Present study, 2005	51/M	Abdominal pain	Yes	SB	Ileus	Negative laparotomy; full recovery	Resolved by POD 4

Pp = pneumoperitoneum; COPD = chronic obstructive pulmonary disease; SB = small bowel; C = colon; POD = postoperative day.

theory postulates that ruptured alveoli allow air to track along the vasculature, but this explanation has met with skepticism due to the lack of interstitial air in the lung and mesentery of many patients with PI.

The pathogenesis of celiac disease involves T-cell–mediated inflammatory injury to the bowel wall. Over 95% of patients with celiac disease express either the HLA-DQ2 or HLA-DQ8 heterodimer, both of which preferentially present gluten-derived gliadin peptides to activate CD4 T cells in the lamina propria.[5] These T cells then secrete interferon γ, which mediates an inflammatory response in the mucosal epithelium. The characteristic histological findings of celiac disease are villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. Of note, celiac disease confers an increased risk of small bowel adenocarcinoma, esophageal and oropharyngeal squamous cell carcinoma, and non-Hodgkin lymphoma. The risk of small bowel adenocarcinoma in celiac disease patients is about 80-fold greater than that of the general population.[5]

Pneumatosis intestinalis in the setting of celiac disease occurs infrequently: our search of the literature yielded nine case reports, including seven English-language reports (Table 1) and two foreign language reports.[6,7] We found no reports prior to 1977. Most of the case reports involved female patients, perhaps reflecting the slight female preponderance of celiac disease itself.[1] The associated symptoms were generally nonspecific. In almost all cases, pneumatosis was accompanied by pneumoperitoneum. There were no cases of bowel perforation, implicating bowel wall air cyst rupture as the likely cause of the benign pneumoperitoneum.

Most of the seven patients had an identifiable, if theoretical, risk factor for the development of pneumatosis. In most cases, these risk factors suggest a breach of mucosal integrity as the primary mechanism by which pneumatosis developed. Steroid or nonsteroidal anti-inflammatory drug use, for example, could have compromised the mucosal barrier. Gluten ingestion, either because of noncompliance or because celiac disease was previously undiagnosed, was the most common risk factor. The enteritis and enterocyte damage that result from gluten exposure could allow the infiltration of intraluminal gas. The finding of pneumatosis exclusively in the colon in several patients, however, challenges this explanation. While it is possible that the pneumatosis in these patients was incidental and unrelated to their celiac disease, the resolution of pneumatosis on a gluten-free diet in two of the three suggests that a more complex relationship may be involved.

Despite gluten avoidance (and in fact complete bowel rest during most of his postoperative course), our patient's initial resection specimen did demonstrate evidence of active chronic inflammation. This is not surprising, given that one-half of adult celiac disease patients on gluten-free diets demonstrate only partial resolution of the characteristic histological changes.[1,5] We therefore propose that the mechanism of pneumatosis formation in our patient involved some degree of mucosal compromise resulting from his celiac disease. In the setting of this damaged mucosal barrier, the increased intraluminal pressure that resulted from his postoperative ileus likely caused intraluminal air to migrate intramurally, resulting in the finding of PI. Eventually, intramural air could have migrated into the peritoneal cavity by cyst rupture, resulting in pneumoperitoneum. The importance of increased intraluminal pressure due to an ileus is supported by the prompt resolution of pneumatosis with operative decompression.

Evaluation of the significance of PI remains challenging. Given the possibility of a potentially catastrophic reason for postoperative pneumatosis and pneumoperitoneum, we felt obligated to explore our patient. In four of seven reviewed cases, an operative procedure ruled out bowel perforation or infarction, while conservative measures were undertaken in the remaining three. With the exception of an ileocolic intussusception thought to be caused by an area of pneumatosis acting as a lead point,[8] there were no findings of intra-abdominal pathology aside from the celiac disease itself. Most patients experienced full resolution of their presenting symptoms, but even those who had persistent symptoms did eventually improve. This uniform clinical improvement contrasts with the variable radiographic resolution of pneumatosis. These outcomes emphasize that in PI associated with celiac disease, as in PI generally, the overall clinical picture and suspected underlying pathology should dictate the workup and intervention. Urgent surgical exploration should be considered if intra-abdominal catastrophe is suspected, but it is not uniformly indicated.

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Laparoscopic Versus Open Colostomy Reversal: A Comparative Analysis

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Open colostomy reversal carries significant rates of wound infection, anastomotic leak, and incisional hernia which often limit its acceptance. We hypothesized that the laparoscopic approach to the restoration of intestinal continuity may result in lower perioperative morbidity and faster postoperative recovery. Twenty-two cases of laparoscopic colostomy reversals performed at a single institution were identified and compared to 22 randomly selected open colostomy closures performed during the same time period. Patients were compared based on demographics, previous indications for colostomy procedures, and perioperative outcomes. A total of 152 patients underwent reversal of left-sided colostomies during the study period. The laparoscopic approach was successful in 20 of 22 cases; there were 2 conversions to open (9%) secondary to inability to adequately mobilize the rectal stump. The laparoscopic and open groups were comparable based on mean age (54 years versus 49 years; $P = 0.23$), BMI (26 kg/m^2 versus 27 kg/m^2; $P = 0.66$), gender (9% males versus 13% males; $P = 0.23$), ASA Class (2.6 versus 2.3; $P = 0.07$), and history of previous intra-abdominal sepsis (17 versus 16 cases). Operative times were similar (158 versus 189 minutes; $P = 0.16$), and estimated blood loss was significantly less in the laparoscopic group (113 versus 270 ml; $P = 0.01$). No intraoperative complications occurred in the laparoscopic group and two enterotomies occurred in the open group. The laparoscopic group had earlier passage of flatus (3.5 versus 5.0 days; $P = 0.001$) and shorter hospitalization (4.2 versus 7.3 days; $P = 0.001$). Perioperative complications occurred in 3 (14%) laparoscopic and 13 (59%) open cases ($P = 0.01$). There was no mortality in this series. The laparoscopic approach can be safely used in the restoration of intestinal continuity. It results in a decreased perioperative morbidity and faster recovery, and it offers distinct advantages over the open approach to colostomy reversal. (J GASTROINTEST SURG 2006;10:895–900)

KEY WORDS: Laparoscopy, colostomy reversal, comparative trial, colorectal surgery, Hartmann's procedure

The standard open approach for the closure of left sided colostomies carries significant morbidity with leakage rates ranging from 0% to 15% and an operative mortality reportedly as high as 10%.[1–4] This perceived morbidity results in almost half of patients electing to forego colostomy closure.[1,2] As a result, patients who retain their stomas are forced to face many physical and psychological challenges, including skin rashes, leakage, ballooning, lifestyle alterations, sexual dysfunction, and parastomal herniation.[5,6] In an attempt to reduce morbidity and mortality associated with the open colostomy reversal, several laparoscopic and hand assisted techniques have been described.

The initial small laparoscopic series report short lengths of hospitalization, low morbidity, and no mortality. Despite these seemingly favorable results, fewer than 100 cases have been described in the world literature.[7–14] Overall, technical demands of this procedure have limited the universal acceptance of a laparoscopic approach to the reversal of left-sided colostomies. Comparative trials evaluating the laparoscopic versus the open approach for the restoration of intestinal continuity after left-sided colostomy formation have not yet been reported. We hypothesized that the laparoscopic approach to left sided colostomy reversal may result in decreased perioperative morbidity and faster postoperative

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functional recovery compared with the conventional open approach.

METHODS

After obtaining institutional review board approval, a retrospective analysis was used to identify those patients undergoing colostomy reversal at a single institution. Records were identified using the *ICD-9* code 46.52 (colostomy reversal) and reviewing billing data to identify all patients undergoing colostomy reversal between July 1997 and January 2004. Patients less than 18 years old and those undergoing ileostomy closure were excluded. Using a computerized random number generator, a sample of 22 open cases was included for analysis. Eighteen attending surgeons were included in the study. Two surgeons with advanced laparoscopic training performed all of the laparoscopic colostomy takedowns. The remaining 16 surgeons performed the 22 open colostomy takedowns. These surgeons included general surgeons, trauma surgeons, and gynecology oncology surgeons. In order to avoid bias, surgeons performing laparoscopic colostomy reversal were excluded from open colostomy evaluations. Adhering to an intent-to-treat analysis, converted cases were maintained in the laparoscopic group for the purposes of statistical analysis.

Pertinent data collection included patient age, gender, body mass index, comorbidities, number of previous abdominal operations, indication for initial Hartmann's procedure, estimated blood loss, operating time, reason for conversion to an open procedure, mobilization of splenic flexure, intraoperative complications, length of post operative hospital stay, and early postoperative complications. Complications were reported as major and minor. Minor wound infections were defined as erythema or culture-proved wound drainage necessitating either oral antibiotic administration or local wound care intervention. Major complications included readmissions, enterotomies, wound infections requiring intravenous antibiotics or reexplorations, and anastomotic leakage. A clinically significant ileus was defined by the need for nasogastric decompression beyond postoperative day five. Short-term follow-up was obtained from office records.

Data were analyzed using standard statistical methods. Descriptive statistics including means and standard deviations, or counts and percentages, were used to describe the study population on all variables. Patients were grouped based on surgical technique (laparoscopic versus open approach). Demographic and baseline measures were compared to determine differences between groups. For continuous variables, the Shapiro-Wilk test of normality was used to test for normality, and comparisons were made between groups using either *t*-tests or Wilcoxon rank-sum tests. For categorical variables, χ^2 and Kruskal-Wallis tests were used to make comparisons between groups. The principal analysis involved comparing intraoperative and postoperative clinical outcomes for the two surgical approaches. The secondary analysis identified potential differences between groups in patient demographic characteristics as well as prevalence of specific comorbidities. A *P*-value of <0.05 was used for all significance determinations. The SAS System version 8.02 was used for all statistical analyses.

Surgical Technique

Our surgical technique for the laparoscopic reversal of left-sided colostomies has been previously reported. In brief, patients receive a preoperative bowel preparation and an enema to evacuate the rectal stump. The patients are placed in the modified lithotomy position, and a three-way Foley catheter is inserted.

Initial port placement is related to the location of the prior abdominal incisions. Either the colostomy site is used or an open cutdown technique is performed to access the peritoneum. If the prior midline incision extends to the epigastrium, the initial port is placed at the colostomy site. The colostomy is mobilized, and the colon is transected with a stapler at the mucocutaneous junction. The stapled colon is dropped back into the abdomen, and a 10-mm balloon trocar is placed in the previous colostomy site.

Alternatively, if a lower midline incision is present, access to the peritoneum is often gained with an open technique under direct vision in the left upper quadrant. A 5- or 10-mm port is placed in this incision. The completed port configuration is depicted in Figure 1. If the adhesions to the midline are extensive, the more medial port is moved to the left of the midline.

Sharp adhesiolysis is performed to mobilize the splenic flexure and left colon. Excessive adhesiolysis of the prior midline incision is avoided. Next, the rectal stump is identified. If polypropylene sutures were placed on the rectum at the initial operation, they can greatly aid in the localization of the rectal stump. An additional aid in delineating the rectum is to insert a rectal dilator transanally. Once the rectal stump is visualized, it is dissected as needed to enable a stapled anastomosis. With extensive adhesions in the pelvis and in women who have had

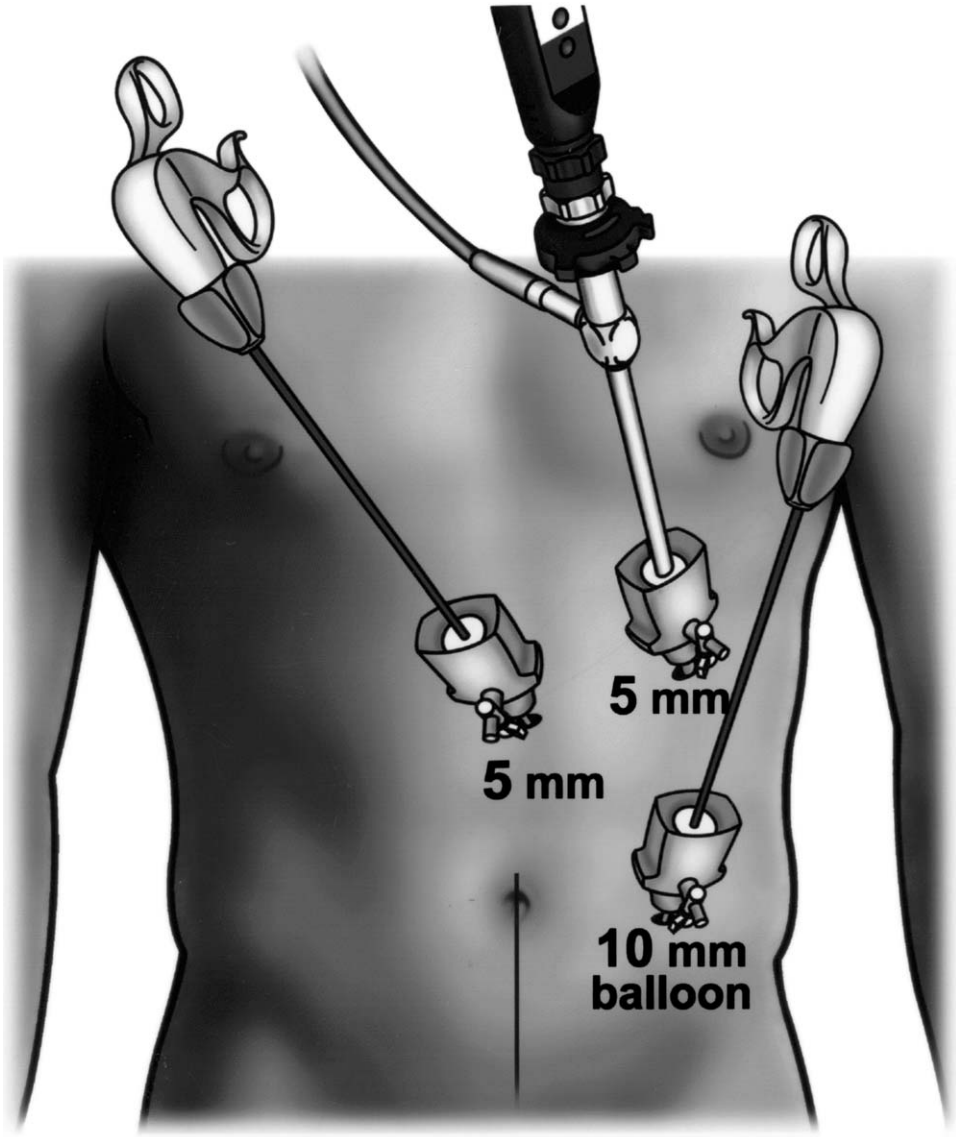

Fig. 1. Completed port configuration.

a hysterectomy, the bladder can be adherent to the rectum. This relationship can be difficult to interpret laparoscopically. At this point, 300–400 ml of saline is instilled through the three-way Foley catheter to accurately localize the bladder and to ensure that the rectum is safely freed from it. The stapled left colon is then brought out through the prior ostomy site after the 10-mm balloon port is removed. The anvil for the circular stapler is secured within the left colon lumen. The colon is then returned to the abdomen and the balloon port is replaced. The anvil is secured to the stapling device under direct laparoscopic visualization.

RESULTS

During the study period, 152 colostomy closure procedures were performed. Twenty-two laparoscopic colostomy closures were attempted. One case was performed using a hand-assisted technique in which a concomitant nephrectomy was performed for a known right-sided renal cancer. The remaining 21 cases were performed laparoscopically with a mean of three trocars. There were two patients (9%) converted to an open procedure secondary to inadequate visualization or mobilization of the rectal stump. Of the 130 open left-sided colostomy closure

Table 1. Comparison of demographic characteristics between the laparoscopic and open colostomy reversal patients

Variable	Laparoscopic	Open	*P* value
Mean age (range, yr)	54 (33–73)	49 (20–83)	0.23
Mean BMI (range, kg/m^2)	26.2 (19.6–34.4)	27.2 (19.5–43.8)	0.66
Male (%)	9 (41)	13 (59)	0.23
ASA score ⩾3 (%)	14 (64)	8 (36)	0.07
Hypertension (%)	9 (41)	6 (27)	0.34
Diabetes (%)	3 (14)	3 (14)	1.00
Pulmonary disease (%)	2 (9)	0 (0)	0.49
Cardiac disease	4 (18)	3 (14)	0.68
Cancer	2 (9)	6 (27)	0.24
Mean time to reversal (mo)	5.6 (3–12)	9.1 (3–24)	0.03

procedures performed during the study period, a random sample of 22 cases were identified.

Patient demographics were similar between the two groups except that the laparoscopic group underwent reversal of their colostomy on average 3 months earlier than the open group and they tended to have higher ASA scores, although this did not reach statistical significance (Table 1). Despite random selection, both groups were comparable based on comorbidities and previous indications for colostomy. Seventeen of the laparoscopic and 16 of the open procedures were performed after previous intra-abdominal sepsis (Table 2). There was no significant difference in average operative times between the laparoscopic and open procedures (158 versus 189 minutes; $P = 0.16$) (Table 3). However, the laparoscopic procedures were performed with less blood loss (113 versus 270 ml; $P = 0.01$). The splenic flexure was mobilized in all laparoscopic procedures, while only seven (33%) of the open procedures underwent splenic flexure mobilization ($P = 0.0001$). There were two enterotomies in the open group that were recognized intraoperatively and repaired primarily without further sequelae. No intraoperative complications occurred in the laparoscopic procedures. Seven additional procedures were performed during open colostomy reversal: primary ventral hernia repair (n = 4), incidental appendectomy (n = 1), omentectomy (n = 1), and planned splenectomy for lymphoma (n = 1).

Postoperatively, the laparoscopic patients had earlier return of bowel function as measured by passage of flatus (3.5 versus 5.0 days; $P = 0.001$) and shorter lengths of stay (4.2 versus 7.3 days; $P = 0.001$). Four (18%) of the laparoscopic patients had a nasogastric tube postoperatively for an average of 2 days, while 13 (59%) of the open group had a nasogastric tube in place for an average of 4 days. Postoperative complications occurred in three laparoscopic cases and 13 open cases ($P = 0.01$) (Table 4). In the laparoscopic group, there were three postoperative superficial wound infections at the previous colostomy site that were managed with antibiotics and/or wound packing. Sixteen complications occurred in 13 patients in the open group.

Table 2. Previous indication for left-sided colostomy

Indication	Laparoscopic	Open
Perforated sigmoid diverticulitis	15	8
Traumatic colon/rectal perforation	1	5
Prior anastomotic leak	1	2
Obstructing nonperforated cancer	2	4
Obstructing perforated cancer	0	1
Perineal necrotizing fascitis	2	2
Radiation colitis	1	0

Major complications included midline wound infections requiring readmission for intravenous antibiotics and wound care (n = 5), anastomotic leak with intra-abdominal abscess requiring percutaneous drainage (n = 1), pneumonia (n = 1), respiratory arrest after narcotic analgesia overdose (n = 1), postoperative hemorrhage requiring 3 units of blood transfusion (n = 1), and readmission for early postoperative small bowel obstruction (n = 1).

Minor complications in the open group included postoperative ileus (n = 4), urinary tract infection (n = 1), and midline wound infection treated with oral antibiotics as an outpatient (n = 1). There was no mortality in this series. Infectious complications or return of bowel function was not predicted by the method of bowel anastomosis in the open group. In the hand-sewn group, there were two wound infections, one pelvic abscess, and two cases of postoperative ileus. In the open group with a stapled anastomosis there were three major wound infections, one minor wound infection, one early postoperative bowel obstruction, and two cases of postoperative ileus. Likewise, patients in the open group who underwent splenic flexure mobilization had a 42% complication rate, while those in whom the splenic flexure was not mobilized had a 64% complication rate.

DISCUSSION

The standard second-stage colostomy reversal to reestablish intestinal continuity requires a major

Table 3. Intraoperative details of laparoscopic versus open colostomy reversals

Variable	Laparoscopic	Open	*P* value
Mean estimated blood loss (ml, range)	114 (30–250)	270 (50–800)	0.01
Mean operative time (min, range)	158 (84–356)	189 (90–308)	0.16
Splenic flexure mobilized (%)	22 (100)	7 (33)	0.0001
Stapled end-to-end anastomosis	22	12	—
Hand-sewn anastomosis	0	10	—
Additional procedures	1	7	—
Intraoperative complications	0	2	—

abdominal operation resulting in extended recovery, incisional discomfort, and prolonged hospital stays. These limitations coupled with associated morbidities have resulted in almost 50% of patients electing to forego colostomy reversal.[1,3] Our group has offered a laparoscopic approach for the reversal of colostomies with early success. Based on the current comparative evaluation with respect to the open technique, the laparoscopic approach affords patients the advantages of less morbidity, shorter hospital stays, and no mortality, which may result in wider acceptance of colostomy reversal in those patients with a prior left-sided colostomy.

There are certain advantages of the laparoscopic procedure that might reduce the morbidity associated with the operation. The laparoscopic technique allows excellent visualization of the splenic flexure for routine mobilization. In order to free the splenic flexure using open techniques, the midline incision often must be extended quite high, increasing the postoperative morbidity of the procedure. In this series, the splenic flexure was mobilized in only 33% of the open colostomy reversal procedures. Without adequate splenic flexure mobilization, excessive tension can result in anastomotic dehiscence or stricture formation. In the present series, the one anastomotic dehiscence resulting in pelvic sepsis occurred in the open group in a patient who did not undergo splenic flexure mobilization.

Table 4. Postoperative complications

Laparoscopic	Open
Major (n = 0)	Major (n = 10) Wound infection, n = 5 Anastomotic leak, n = 1 Respiratory arrest, n = 1 Blood transfusion, n = 1 Pneumonia, n = 1 SBO, n = 1
Minor (n = 3) Wound infection (n = 3)	Minor (n = 6) Ileus, n = 4 Urinary tract infection, n = 1 Wound infection, n = 1

Many patients with colostomies have significant intra-abdominal adhesions. As a result, gaining access to the peritoneal cavity carries risks of bowel injury. These adhesions tend to be centered under the previous midline incision and within the pelvis. Using the open approach, the midline incision is reentered, increasing the likelihood of bowel injury as these adhesions are approached. However, in the laparoscopic approach, the abdomen is typically entered at a site remote from previous intra-abdominal scarring. By using an open cutdown technique for initial trocar placement, we encountered no visceral injuries. Alternatively, in the open group, two enterotomies occurred. Eliminating the laparotomy incision can also limit postoperative wound complications. There were six wound infections in the open group, and five of them required readmission for wound care and intravenous antibiotics. Each of the three laparoscopic infections occurred at the colostomy site, which were partially closed at the time of surgery. In the majority of the open cases, the colostomy sites were left open and packed with gauze.

Regardless of the approach, the most technically challenging aspect of the reversal of a Hartmann's procedure is the identification and mobilization of the rectal stump within the reoperative pelvis. At the primary operation, we routinely place two polypropylene sutures with 6-cm tails at the rectal staple line. They can greatly aid in finding the proximal rectum. If polypropylene sutures have not been placed, the use of rectal dilators, rigid sigmoidoscopy, and three-way bladder catheters may provide assistance in safely identifying the rectal stump and avoiding injury to adjacent structures. The two conversions in the present series were performed after an inability to visualize or mobilize the rectal stump. Despite our low conversion rate (9%), we maintain a low threshold for conversion if the pelvic anatomy cannot be clearly identified.

In this series, cases were comparable based on previous indications for the colostomy procedure

with respect to prior intraperitoneal sepsis. In fact, 77% of the laparoscopic procedures and 72% of the open colostomy reversals were performed after prior intra-abdominal sepsis. In the laparoscopic approach, the small bowel adhesions in the midline are not regularly lysed; in fact, an effort is made not to manipulate the intestine other than the colon if possible. Unlike the laparoscopic approach, the open technique requires excessive bowel manipulation for dissection and retraction purposes that likely results in prolonged postoperative ileus. The increased use of postoperative nasogastric tubes in the open group is likely due to the higher incidence of postoperative ileus, which directly relates to the later return of gastrointestinal function. One might argue that nasogastric tube decompression is based on surgeon preference and therefore not a good outcome variable. However, this study does not include historical controls and therefore represents current practice patterns during the entire study period, which we believe makes the groups comparable.

The absence of a prospective randomized design is a limitation of this study. The laparoscopic procedures might induce bias as not all patients were offered the laparoscopic approach by those surgeons performing laparoscopic colostomy reversal. However, laparoscopic surgeons were not included in the open data in order to avoid this potential bias. In addition, seven additional procedures were performed in the open series. Closer inspection reveals that four of these were midline incisional hernia repairs that were closed primarily, which essentially involved opening and closing the prior incision. Furthermore, the design and inclusion of various surgeons without a uniform approach might lead to bias against the open procedure. Specifically, the 22 cases identified might not be a reasonable representation of the overall open colostomy reversal experience. A review of the current literature would not support this argument. In a compilation of almost 400 patients from several institutions' experience with open colostomy reversal, mortality rates of 0.6–8.3% are reported.[1–4] These authors reported anastomotic leakage rates of 4–16%, which is comparable to the current series rate of 5%. While the major complication rate in the present series of 45% may seem excessive, the current literature reports major morbidity rates of 30–40% for open colostomy reversal[1–4] In our series, the laparoscopic group and the open group were similar with respect to various demographics including age, body mass index, and preoperative comorbidities. The only significant preoperative difference between the laparoscopic group and the open group was that the laparoscopic group tended to undergo colostomy closure 3 months earlier than the open group. While this is statistically significant, most authors have found no difference in complications after waiting 6 months for colostomy reversal.[1]

CONCLUSIONS

The use of the laparoscopic technique for the reversal of colostomies appears to offer distinct advantages over the open approach. In our single-institution experience, this technique has resulted in less operative blood loss, decreased complications, quicker return of bowel function, and shorter hospital stays. Based on this study, the laparoscopic approach for the restoration of intestinal continuity may be the procedure of choice for select patients requiring closure of a left-sided colostomy.

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Abdominal Computed Tomography for Postoperative Abscess: Is It Useful During the First Week?

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While classic teaching dictates computed tomography (CT) for postoperative abdominal or pelvic abscess in the first week is of low yield, little evidence supports intentional delays in imaging for suspected abscess. This retrospective review examined all CT scans obtained for clinical suspicion of abscess between 3 and 30 days after abdominal or pelvic operation over a 3-year period. Scans were grouped into those obtained between 3 and 7 days after surgery (EARLY) and those obtained after day 7 (LATE). Diagnostic yield was compared between EARLY and LATE groups. Of 262 CT examinations (EARLY, n = 106; LATE, n = 156), 71 studies (27%) demonstrated abscess. There was no significant difference in the diagnostic yield of CT for abscess between EARLY and LATE groups (23% [24 of 106] versus 30% [47 of 156], $P = 0.18$). Of patients with an abscess, 63% (45 of 71) underwent percutaneous or operative drainage (EARLY 75% [18 of 24], LATE 57% [27 of 47], $P = 0.15$). Abdominal CT for postoperative abscess can be expected to be diagnostic in a substantial proportion of cases in the first week, the majority of which lead to percutaneous or operative drainage. Postoperative CT for intra-abdominal abscess should be obtained as clinically indicated, regardless of interval from surgery.
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KEY WORDS: Spiral computed tomography, abscess, postoperative complications, diagnostic techniques and procedures, diagnostic imaging

Computed tomography (CT) is the initial test of choice for suspected intra-abdominal abscess (IAA) after abdominal or pelvic surgery. In addition to providing important diagnostic information, CT often guides treatment. While CT is traditionally thought to be low yield for IAA in the early postoperative period, no recent studies have examined the efficacy of CT for abscess during the first week after operation. The objective of the current study is to compare the diagnostic utility of CT for IAA during the first postoperative week with that after day 7.

MATERIAL AND METHODS

For a 3-year period from January 1, 2000, to December 31, 2002, we retrospectively examined all CT studies of the abdomen and pelvis for suspected abscess between 3 and 30 days after an abdominal or pelvic surgical procedure. CT imaging was ordered on a case-by-case basis by the attending surgeon, as a result of pain, tenderness, fever, or leukocytosis out of proportion to expected postoperative findings. Prior to January 2001, patients with suspected abscess were imaged using a single-detector CT scanner (HiSpeed Advantage; General Electric Medical Systems, Milwaukee, WI). A four-detector CT (LightSpeed Plus; General Electric) was used for all tomographic imaging after January 2001. All studies were performed with 7-mm collimation cuts from the xiphoid to the symphysis pubis. Intravenous and oral contrast media was used for all studies unless specifically contraindicated. Rectal contrast was used selectively in cases of suspected pelvic abscess. An attending radiologist interpreted all studies prior to therapeutic interventions.

For each CT study, inpatient records were queried to determine the type of operation, interval from operation to imaging, CT results, and subsequent treatment. CT studies interpreted as equivocal for abscess were classified as negative. In addition to classifying each CT as positive or negative for

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abscess, other significant radiographic diagnoses were recorded. Alternative diagnoses were classified as significant if they potentially led to a substantial change in patient management, including operative or percutaneous drainage, anticoagulation, or the prolonged use of intravenous antibiotics. All treatments were recorded, and the results of all cultures were documented.

The yield of CT for IAA during postoperative days 3–7 (EARLY group) was compared to CT after day 7 (LATE group) using a χ^2 analysis (GraphPad Software, San Diego, CA). Yield for all significant diagnostic findings was similarly compared between groups, as was the rate of operative or percutaneous drainage after tomographic confirmation of a clinically suspected abscess. A pre-hoc power analysis predicted a minimum sample size of 95 in each group to demonstrate a 15% difference in yield with 80% statistical power and 95% confidence (DSS Research, Fort Worth, TX). The local investigative review board approved this study.

RESULTS

For the 3-year period, 262 CT scans were performed for suspected IAA in 227 patients between 3 and 30 days after an abdominal or a pelvic surgical procedure (EARLY, 106; LATE, 156). There were approximately 4500 abdominal or pelvic surgical cases over the study period, such that postoperative abdominal CT for suspected abscess was performed in 5% (227 of 4500) of cases. The mean interval between operation and imaging was significantly greater in the LATE group (5.6 days versus 15.0 days, $P < 0.001$). Procedures are listed in Table 1. The distribution of postoperative time interval for CT scans is depicted in Figure 1. The most common time period for CT was the seventh postoperative day (mean, 11.3 days; median, 9 days).

Table 1. Surgical procedures

Procedure type	No.
Appendectomy	51 (22%)
Colorectal	50 (22%)
Hysterectomy/gynecologic	27 (12%)
Small bowel/lysis of adhesions	21 (9%)
Gastric/esophageal	17 (7%)
Cesarean section	14 (6%)
Gallbladder/biliary tract/liver	14 (6%)
Genitourinary	9 (4%)
Pancreatic	8 (4%)
Hernia	5 (2%)
Other	11 (5%)

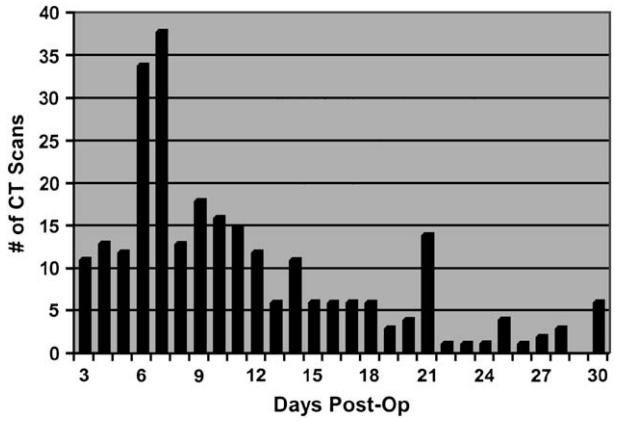

Fig. 1. Computed tomographic studies by postoperative interval.

CT in the postoperative period confirmed suspected IAA in 27% (71 of 262) of cases. When CT did not demonstrate abscess, it frequently revealed alternate diagnoses with important implications for patient management (Table 2). Overall, CT was diagnostic for significant findings in 43% (113 of 262) of cases. There were no significant differences in CT yield for IAA or other significant diagnostic findings between EARLY and LATE groups (Table 3). The highest diagnostic yield for abscess was on the fifth postoperative day, where 50% (6 of 12) of CT studies confirmed suspected abdominal or pelvic abscess. Figure 2 demonstrates a culture-positive pelvic abscess 4 days after small bowel lysis of adhesions, treated successfully with percutaneous drainage and antibiotics.

Of the 71 patients with IAA demonstrated by CT, 36 (51%) underwent percutaneous drainage as a direct result of radiographic findings. In an additional nine cases (13%), CT findings led to operative intervention. The remaining patients with IAA were

Table 2. Significant diagnostic findings

Finding	No.
Intra abdominal abscess	71
Hematoma or bleeding	10
Bowel obstruction	10
Gastrointestinal leak	8
Wound abscess	5
Mesenteric venous thrombosis	5
Hepatic abscess/infarct	4
Gastrointestinal fistula	4
Colitis	2
Pneumothorax	1
Biloma	1

Table 3. Comparison of diagnostic computed tomography findings and rates of drainage between EARLY and LATE groups

	EARLY days 3–7	LATE days 7–30	*P* value
Diagnostic for abscess	23% (16–31%) (24/106)	30% (23–37%) (47/156)	0.18
Significant diagnostic findings	36% (27–45%) (38/106)	47% (39–55%) (74/156)	0.06
Abscess drainage rate	75% (58–92%) (18/24)	57% (43–71%) (27/47)	0.15

successfully treated with antibiotics, observation, and serial imaging. Of the 38 abscesses with specimens submitted for culture, 35 (92%) grew at least one organism. The rate of percutaneous or operative abscess drainage did not differ significantly between EARLY and LATE groups (Table 3).

In 26 patients, CT scan for suspected postoperative IAA was repeated after an initial study was interpreted as negative. While 15 of such repeat studies remained negative, repeat CT diagnosed seven patients with IAA, two with fistulas, and two with gastrointestinal leak. In 6 of the 11 cases with a diagnostic repeat CT, the initial negative study was obtained more than 7 days after operation.

DISCUSSION

IAAs are localized collections of purulent inflammatory tissue caused by pyogenic mixed anaerobic and facultative bacteria.[1] Abscesses are characterized by a central collection of necrotic leukocytes and native tissue cells, seen tomographically as a central region of low density.[2,3] Outside this region, vascular dilation and parenchymal and fibroblastic

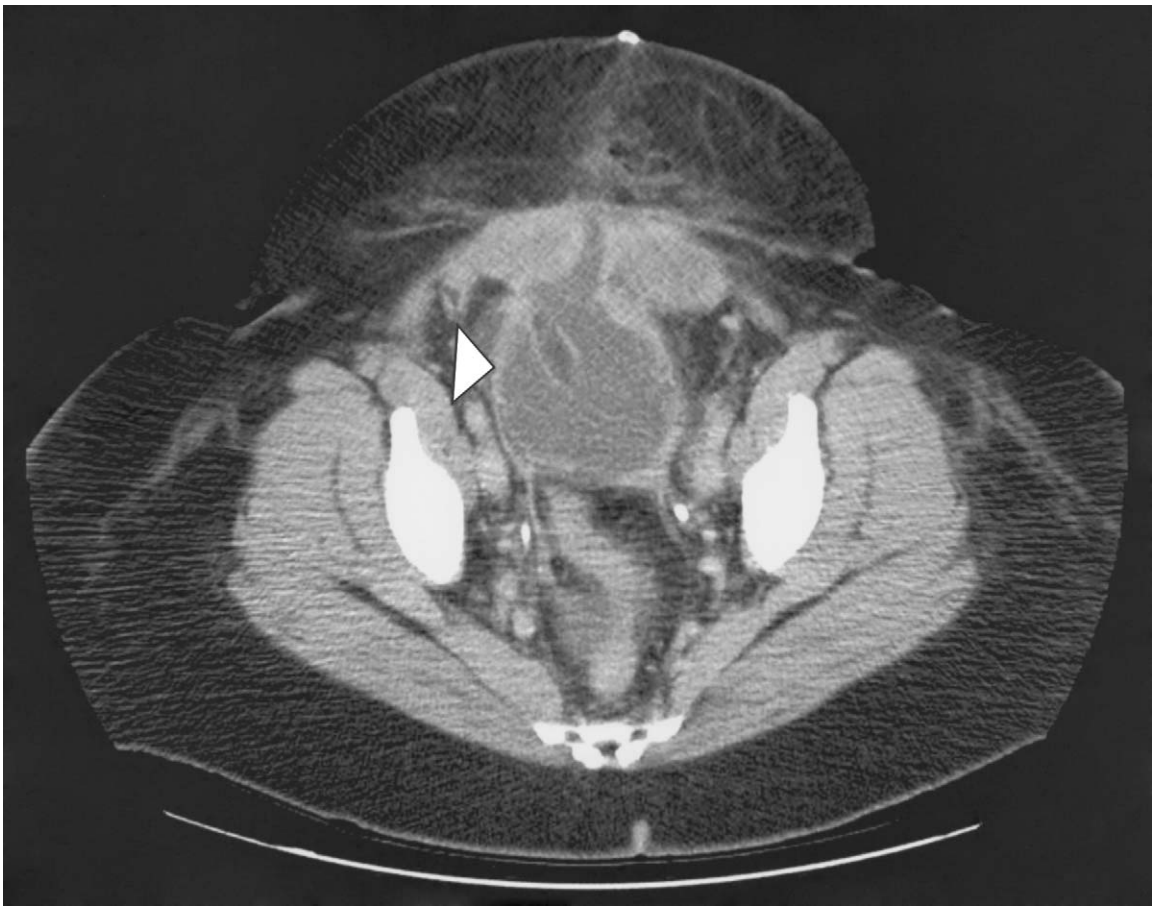

Fig. 2. Computed tomographic image demonstrating large pelvic abscess (*arrowhead*) 4 days after small bowel lysis of adhesions.

proliferation occur. This vascularized connective tissue appears on tomographic imaging as a defined rim, which generally enhances with the administration of intravenous contrast.[2] The most specific sign of abscess on CT is extraluminal air within a fluid collection resulting from bacterial gas formation,[2,4] although this finding is seen in only 50% of IAAs.

Surgery is the most common etiology of IAA,[5] which is best diagnosed with CT.[4,6,7] CT is also central to effective management, as image-guided percutaneous drainage has emerged as the treatment of choice for the vast majority of postoperative IAA.[8–11] Because the imaging features that differentiate an organized abscess from a simple fluid collection are time dependent, the utility of CT for IAA is thought to be low before the second postoperative week.[2,12] Patients undergoing major operative procedures will presumably have nonsuppurative fluid collections from old blood, serum, and irrigant.[12] In addition to allowing time for abscess maturation, deferring CT until after the first postoperative week is intended to allow time for these benign fluid collections to resolve.

In describing their experience with CT for postoperative abscesses, Norwood and Civetta[12] found no CT to be diagnostic for abscess before the eighth postoperative day. While widely quoted in the literature, this study from the early 1980s used first-generation CT techniques and reported a sensitivity of only 48% for IAA. Recent years have seen dramatic improvements in imaging resolution and technique, such that CT is consistently reported to have greater than 90% accuracy for the detection of abscesses.[4,6,7,13] No study to date has investigated whether these improvements in imaging may translate into higher yield for early CT after abdominal or pelvic surgery.

In the current study, we demonstrated a yield of 27% when CT for suspected IAA was performed within 30 days of abdominal or pelvic surgery. When CT was negative for abscess, it demonstrated significant unexpected findings in an additional 16% of patients. There was no significant difference in diagnostic yield for abscess or other clinically important diagnostic findings when comparing CT in the first postoperative week to imaging after day 7.

The key to historical improvements in the morbidity and mortality associated with IAA has been early diagnosis and treatment.[2,7] Without treatment, IAA is reportedly associated with a greater than 80% mortality rate.[12] If an abscess is not amenable to percutaneous treatment, the ideal time for operative drainage is before the second postoperative week. As mesothelial healing is completed within 8 days of operation,[14] associated dense vascularized adhesions may make reoperation after the first week more difficult or dangerous.[15] Furthermore, the current study demonstrates that the success of percutaneous abscess drainage is not time dependent. CT for suspected postoperative IAA should therefore be performed as early as feasible.

When CT imaging was repeated in the present study after an initial CT was interpreted as negative for abscess, significant diagnostic findings were demonstrated in 50% of cases. In the majority of these positive repeat studies, the initial CT had been obtained at more than 1 week after operation. This suggests that repeat postoperative imaging should be pursued when clinically indicated, regardless of the timing or results of previous CT studies.

CONCLUSION

Contrary to historical dogma, early CT for suspected abscess after abdominal or pelvic surgery does not have a temporal limitation in diagnostic sensitivity. CT in this setting will be diagnostic in a substantial proportion of cases, the majority of which will lead to percutaneous or operative drainage. After the second postoperative day, CT for IAA should be obtained as clinically indicated, regardless of interval from surgery.

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Laparoscopic Versus Open Appendectomy for Perforated Appendicitis

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The role of laparoscopic appendectomy (LA) for perforated appendicitis is under investigation. A retrospective study was conducted to compare the outcomes of laparoscopic versus open appendectomy (OA) for perforated appendicitis. From January 2001 through December 2003, 229 patients with perforated appendicitis were treated at Far-Eastern Memorial Hospital. LA was successfully completed in 91 of 99 patients. OA was performed in 130 patients. Operation time was longer in the LA group (mean ± SD = 96.1 ± 43.1 vs. 67.8 ± 32.2 minutes, $P < 0.01$). Return of oral intake was faster in the LA group (3.2 ± 2.4 vs. 5.0 ± 7.0 days, $P < 0.01$). The intravenous antibiotic usage period was shorter in the LA group (4.4 ± 2.8 vs. 6.3 ± 7.1 days, $P < 0.01$). The postoperative wound infection rates were 15.2 % (LA group) and 30.7% (OA group). The overall infectious complication rates were 19% in the LA group and 37% in the OA group ($P < 0.01$). Hospital stay days were shorter for the LA group (6.3 ± 2.9 vs. 9.3 ± 8.6 days, $P < 0.01$). Our results indicated that laparoscopic appendectomy is a safe and effective procedure for treating patients with perforated appendicitis. (J GASTROINTEST SURG 2006;10:906–910)

KEY WORDS: Laparoscopic appendectomy, open appendectomy, perforated appendicitis

Since 1983 when Semm[1] first used laparoscopy to remove the appendix, the debate over laparoscopic appendectomy (LA) versus open appendectomy (OA) has remained active. LA has gradually gained widespread use for the treatment of acute appendicitis because meta-analyses of prospective randomized trials have concluded that LA is better than[2–6] or as good as[7] OA in terms of postoperative wound infections, analgesia requirement, hospital stay, return to work intervals, and overall recovery.

Perforated appendicitis occurs in 20% to 30% of acute appendicitis patients and is associated with much higher risks of postoperative infectious complications such as wound infection and intra-abdominal abscess.[8,9] However, only a few studies, with limited numbers of patients, have addressed the issue of whether LA is feasible for perforated appendicitis patients,[10–14] and the benefits of LA in perforated appendicitis remain uncertain. Laparoscopic appendectomy provides direct visualization during peritoneal washing and lesser wound contamination during surgery. However, concerns about an increase in infectious complications after LA for perforated appendicitis existed during the early laparoscopic era.[10,11] We conducted this retrospective study to compare the results of LA and OA treatment for patients with perforated appendicitis during the same period of time in a single hospital.

MATERIAL AND METHODS

Consecutive patients who underwent appendectomy for acute appendicitis from January 2001 through December 2003 at the Far-Eastern Memorial Hospital in Taipei, Taiwan were included in this retrospective study. All four consulting surgeons involved in the treatment of these patients were experienced in laparoscopic surgery and had performed more than 50 laparoscopic appendectomies before the initiation of the study period. As the volume of emergent service in Far-Eastern Memorial Hospital has been high, these surgeons perform at least 10 laparoscopic appendectomies per month. Therefore, LA was adopted for use in patients with acute appendicitis, even for those with perforated appendicitis. Perforated appendicitis was defined as free perforation of the appendix with intra-abdominal purulence.

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When the attending surgeons were consulted for patients diagnosed to have appendicitis, they recommended laparoscopic appendectomy as the procedure of choice. However, patients who had severe cardiopulmonary disease, sepsis, or patients who could not afford the extra fee for laparoscopic appendectomy (about 400 USD) were suggested to have open appendectomy.

Operative Procedure

Intravenous cefazolin was given 30 minutes before skin incision. Laparoscopic appendectomy was performed via three ports. A 10 mm working port was introduced below the umbilicus, one 3 mm video port was inserted through the suprapubic area, and the other 3 mm working port was inserted midway between the previous two ports. All areas of intra-abdominal purulence were aspirated and sent for cultures. The mesoappendix was dissected, and the appendiceal vessels were divided with cautery, clips, or harmonic scalpel. The base of the appendix was divided between clips or endoloops as described by Wei et al.[15] The specimen was removed in a retrieval bag that was tailored from a surgical glove. In the case of open appendectomy, a McBurney's, paramedian, or midline incision was made depending on the surgeon's preference. Both the LA and OA groups received thorough peritoneal lavage using copious amounts of warm saline before closure of the abdominal wounds. Drains were routinely placed into the Douglas pouch of the abdomen.

Postoperative Care and Follow-up

Intravenous antibiotics were given according to the results of abdominal cultures and continued until fever subsided and no leukocytosis was noted. Analgesics used included intramuscular pethidine and oral acetaminophen. The patients started their diet when their bowel movements resumed. The drains were removed when the drainage amount was less than 50 ml per day and the drainage fluid was not purulent. The patients were followed up at least once at our outpatient department after discharge.

Patients with conversion to the open procedure were included in the laparoscopy group in an analysis on an "intention-to-treat" basis. The perioperative outcomes of patients, including demographic data, operation time, return of oral intake intervals, intravenous antibiotic usage period, postoperative analgesics requirement, hospital stay days, wound infections rates, intra-abdominal infectious complication rates, and reoperation rates, were compared between the LA and OA groups. Data were expressed as means ± SD. Continuous variables were analyzed with the Student *t* test. The chi-square test was used for categorized data. A value of $P < 0.05$ was considered significant.

RESULTS

Among the 1454 patients who underwent appendectomies during the study period, there were 229 patients (15.7%) diagnosed as having perforated appendicitis. Laparoscopic appendectomy was attempted in 99 patients (43.2%), and the procedure was completed in 91. The success rate of LA in this group was 91.9%; eight patients (8.1%) had to be converted to an open procedure. Open appendectomy was performed in 130 patients (56.8%). The perioperative parameters for the two groups of patients are listed in Table 1. There was no statistical difference between the two groups in terms of sex and age. Mean ± SD operation time was 96.1 ± 43.1 minutes for the LA group and 67.8 ± 32.2 minutes for the OA group ($P < 0.01$). Return of oral intake took 3.2 ± 2.4 days for the LA patients and 5.0 ± 7.0 days for OA patients ($P < 0.01$). The duration of intravenous antibiotic usage was 4.4 ± 2.8 days for the LA group and 6.3 ± 7.1 days for the OA group ($P < 0.01$). There was no significant difference between the groups in postoperative pethidine analgesic requirement. Hospital stay was significantly shorter in the LA than OA group (6.3 ± 2.9 vs. 9.3 ± 8.6 days, $P < 0.01$).

Eight patients (8.1%) underwent conversion to the open procedure after laparoscopy. The reasons for conversion were difficulty of dissection in two patients, appendiceal masses in three patients, and necrosis at the base of the appendix in three patients.

Table 1. Demographic and perioperative parameters for patients with perforated appendicitis

	LA n = (99)	OA n = (130)	*P* value
Sex (M:F)	63:36	69:61	0.109
Age (years)	40	35	0.105
Operation time (minutes)	96.1 ± 43.1	67.8 ± 32.2	<0.0001
Return of oral intake (days)	3.2 ± 2.4	5.0 ± 7.0	0.009
Intra-venous antibiotic usage (days)	4.4 ± 2.8	6.3 ± 7.1	0.007
Pethidine use (50 mg dose)	1.67 ± 2.48	1.47 ± 1.89	0.487
Hospital stay (days)	6.3 ± 2.9	9.3 ± 8.6	0.0003

LA = laparoscopic appendectomy; OA = open appendectomy.

There were no intraoperative complications in this group.

There were no operative mortalities in this series. Sixty-seven patients (29.3%) developed postoperative infectious complications (Table 2). In the LA group, 15 patients (15.2%) developed wound infections, three patients (3.0%) developed intra-abdominal abscess, and one patient (1%) developed intra-abdominal bleeding. The latter patient needed reoperation. In the OA group, 40 patients (30.7%) developed wound infections, four patients (3.1%) developed intra-abdominal abscess, three patients (2.3%) developed enterocutaneous fistula, and one patient (0.8%) developed total wound disruption. The overall rate of infectious complications was significantly less in LA than OA patients (19.1 % vs. 36.9%, $P < 0.01$). There was no significant difference in the rate of reoperation for intra-abdominal complications between LA and OA patients (2.0% vs. 3.8%).

DISCUSSION

This study summarized our experience in treating 229 patients with perforated appendicitis over a 3-year period. Our results showed that surgeons in our hospital used laparoscopic appendectomy to treat nearly half of the patients with perforated appendicitis and that the conversion rate to the open approach was only 8.1%. The outcomes of these patients also indicated that LA is a feasible and effective approach for perforated appendicitis because it is associated with high success rates, shorter hospital stays, and fewer wound infections. Laparoscopic appendectomy has become the approach of choice at our institution for treating patients with perforated appendicitis.

Since its introduction in 1983, LA has been shown to confer advantages including shorter hospital stay, less postoperative pain, better cosmetic effects, an earlier return to work, and lower wound infection rates.[2–6] However, whether the laparoscopic approach for perforated appendicitis reduces the length of hospital stay is not yet documented.[10,14,16] The results of the Johnson and Peetz[12] study and our study showed that patients who underwent LA had a shorter hospital stay than those who had OA. We propose that the hospital stay was shortened because the reduced wound infection rate in LA patients reduced the need for intravenous antibiotics for these patients. The wound infection rates in our series were 15.2% for LA and 30.7% for OA, which is similar to the results of So et al.,[16] who found that wound infection rates were 14% for LA and 26% for OA. Wullstein et al.[17] showed that the abdominal wound infection complication rates were 6% for LA and 18.3% for OA. The wound infection rates in our series were higher than theirs but showed the same tendency.

Concerns exist about performing LA in patients with ruptured appendicitis because of the longer operation times, the increased rate of postoperative abscess, the higher conversion rates to open appendectomy, and the insecure management of the appendiceal stump. Although So et al.[16] and Ball et al.[18] showed that operation times were equivalent in both LA and OA groups, our study and those of others [12,19–22] showed that performing LA took longer operation time. Another argument about LA for perforated appendicitis was whether or not it increases the incidence of intra-abdominal infection. Frazee and Bohannon[10] treated 34 cases of gangrenous perforated appendicitis with LA and reported an incidence of 26% for intra-abdominal abscess. Bonanni et al.[11] reported 5 of 11 patients who underwent LA for perforated appendicitis required readmission, mostly due to pelvic abscess. On the other hand, Wullstein et al.[17] showed nearly the same rate of intra-abdominal abscess formation after LA (4.1%) and OA (4.9%) following treatment for complicated appendicitis patients. Similar to Wullstein et al. and the other reports,[15,17,18] the incidence of intra-abdominal infectious complications after LA for patients with perforated appendicitis in our series was not high (4.0%) and was comparable to that (6.2%) of OA. We suggest that thorough lavage under laparoscopic guide before closing the wound could help in decreasing residual fluid accumulation in patients with perforated appendicitis.

Laparoscopic appendectomy for perforated appendicitis is technically more demanding and has been associated with a higher conversion rate.[12–14,16] The conversion rate in our series seems lower (8.1%) than those of others (20.2% to 47%).[16,17]

Table 2. Infectious complications in patients with perforated appendicitis

Complications	LA	OA	*P* value
Overall (%)	19 (19.1)	48 (36.9)	0.003
Wound infection (%)	15 (15.2)	40 (30.7)	0.006
Intra-abdominal (%)	4 (4.0)	8 (6.2)	0.477
Intra-abdominal abscess	3 (3.0)	4 (3.1)	0.983
Intra-abdominal bleeding	1 (1.0)	0	0.251
Enterocutaneous fistula	0	3 (2.3)	0.128
Total wound disruption	0	1 (0.8)	0.382
Reoperation (%)	2 (2.0)	5 (3.8)	0.427

LA = laparoscopic appendectomy; OA = open appendectomy.

This, in part, might be attributed to the selection bias in this retrospective study, but the accumulated experience in laparoscopy of the four attending surgeons also played a role. Another technical detail in laparoscopic appendectomy is the management of appendiceal base. We usually divided the appendiceal base between clips. However, if the clips were not long enough, endoloops were used instead. As others series reported, there was no increased incidence of intra-abdominal abscess associated with the use of clips in closing appendiceal stumps.[15,23,24]

There is little evidence-based data to justify the role of laparoscopic management of perforated appendicitis, as few randomized trials have ever recruited a sufficient number of patients with perforated appendicitis. Several retrospective studies that recruited from 6 to 171 patients with complicated appendicitis have shown that the risks of intra-abdominal abscess and fistula formation are statistically similar between laparoscopic and open groups.[12–14,16,19,25–28] Our results showed that the laparoscopic approach produced a satisfactory outcome for 91 patients with perforated appendicitis, especially with regard to the rate of wound infection. However, as a retrospective study, our design might have the selection bias that includes the surgeons' preference, patients' disease status, and economic concerns. Although our surgeons preferred laparoscopic surgery, they carefully judged the proper use of this technique in those patients who were critically ill. Our data did not compare the inflammatory parameters such as white cell counts and C-reactive proteins between groups, as these data were not thoroughly collected in all patients. So far, Taiwan's reimbursement system does not cover laparoscopic appendectomy. Some of our patients could not afford the extra expense. These biases did have some impact on our results. For example, the open group might include patients who were delayed in diagnosis, who were poor, and who were malnourished. The infectious complications in these patients might be higher than that of the laparoscopic group. A prospective randomized study of the use of laparoscopic appendectomy versus open appendectomy for ruptured appendicitis is needed.

CONCLUSION

This retrospective study showed that laparoscopic appendectomy is a safe and effective approach for perforated appendicitis. It resulted in shorter hospital stay and reduced wound infection complications than did the open approach. Further prospective randomized study is needed to confirm the role of laparoscopic appendectomy in the management of perforated appendicitis.

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A Simple Biangulation Stapling Technique for Large Anastomoses in Gastric Surgery

Michiya Kobayashi, M.D., Ph.D., Takehiro Okabayashi, M.D., Tsutomu Namikawa, M.D., Ph.D., Ken Okamoto, M.D., Hiroyuki Kitagawa, M.D., Keijiro Araki, M.D., Ph.D.

We describe here a new technique for performing the large anastomosis between the jejunal pouch and the remnant stomach in patients undergoing proximal gastrectomy with jejunal pouch interposition. The biangulation method described in this report is a simpler technique than the existing triangulation anastomosis technique, requiring only two applications of a linear stapler. One row of staples forms the posterior wall of the anastomosis and the other forms the anterior wall. When used for jejunal pouch reconstruction after proximal gastrectomy in 12 cases of early gastric cancer, no evidence of anastomotic leakage or stenosis was apparent from barium meal studies or endoscopic examination. We find this biangulation technique to be a simple and safe procedure that is ideal for anastomoses of large diameter. (J GASTROINTEST SURG 2006;10:911–915)

KEY WORDS: Surgical stapling, proximal gastrectomy, jejunal pouch interposition, gastrointestinal anastomosis

In Japan, patients with gastric cancer are benefiting from recent advances in surgical treatment. Until recently, cancers in proximal regions of the stomach were usually managed by total gastrectomy, even when detected at an early stage. With the current interest in minimally invasive surgery, custom-made operations, and organ-preserving surgery, proximal gastrectomy is increasingly being performed. This change has been supported by improvements in surgical instrumentation. Operations have become safer and more rapid with the use of linear and circular staplers, ultrasonic cutting and coagulating devices, and vessel sealing systems.

Patients who undergo proximal gastrectomy with esophagogastrostomy tend to suffer from reflux esophagitis and from the small capacity of the remnant stomach. To solve these problems, we use a modified jejunal pouch interposition of our own design that minimizes reflux.[1] This procedure leaves an orifice for anastomosis between the jejunal pouch and the remnant stomach that is particularly large compared to the standard anastomoses involved in gastroduodenostomy, esophagojejunostomy, jejunojejunostomy, or colocolostomy. Here we describe a simple and safe technique that we have developed to perform this large anastomosis.

METHODS

After proximal gastrectomy, a jejunal pouch was made with a linear stapler. The anastomosis between the jejunal pouch and the residual stomach was then performed as follows. A series of Allis clamps were applied closely to approximate the posterior walls of the residual stomach and the jejunal pouch, along with some additional anchoring sutures. The posterior stapled line was made longer to facilitate the second series of stapling. A 100-mm-long linear stapler was used to staple the approximated walls in an inverted fashion (Fig. 1). Sutures were made to achieve hemostasis at any points of bleeding along the

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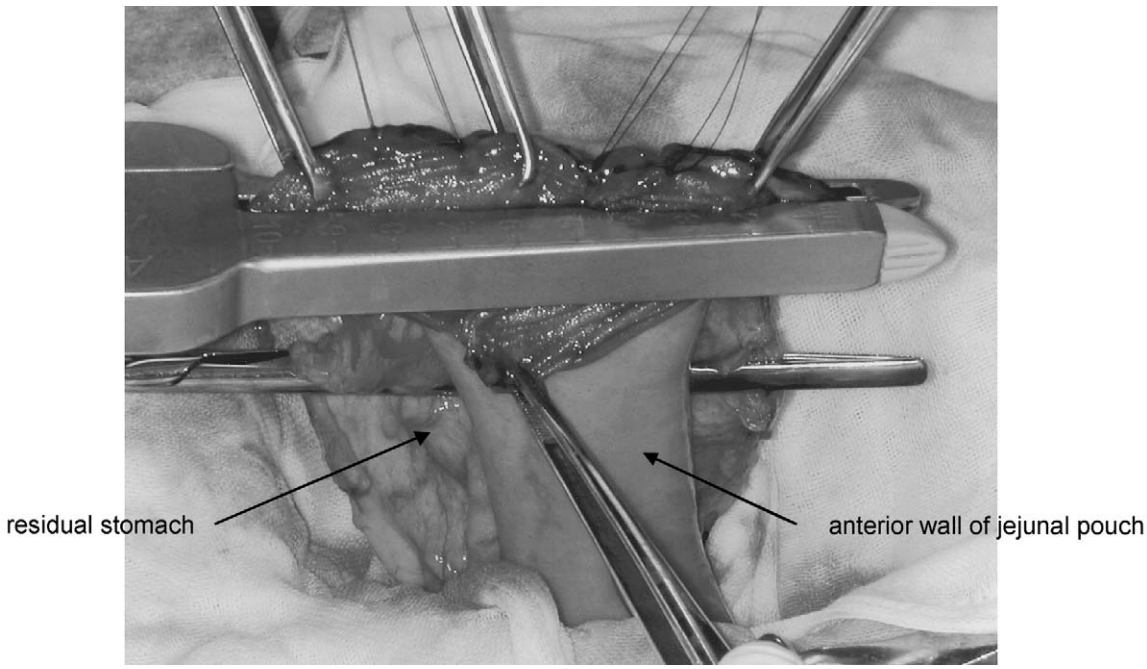

Fig. 1. Anastomosis of the posterior wall. A series of Allis clamps with additional anchoring sutures are applied closely to approximate the posterior walls of the jejunal pouch and the residual stomach.

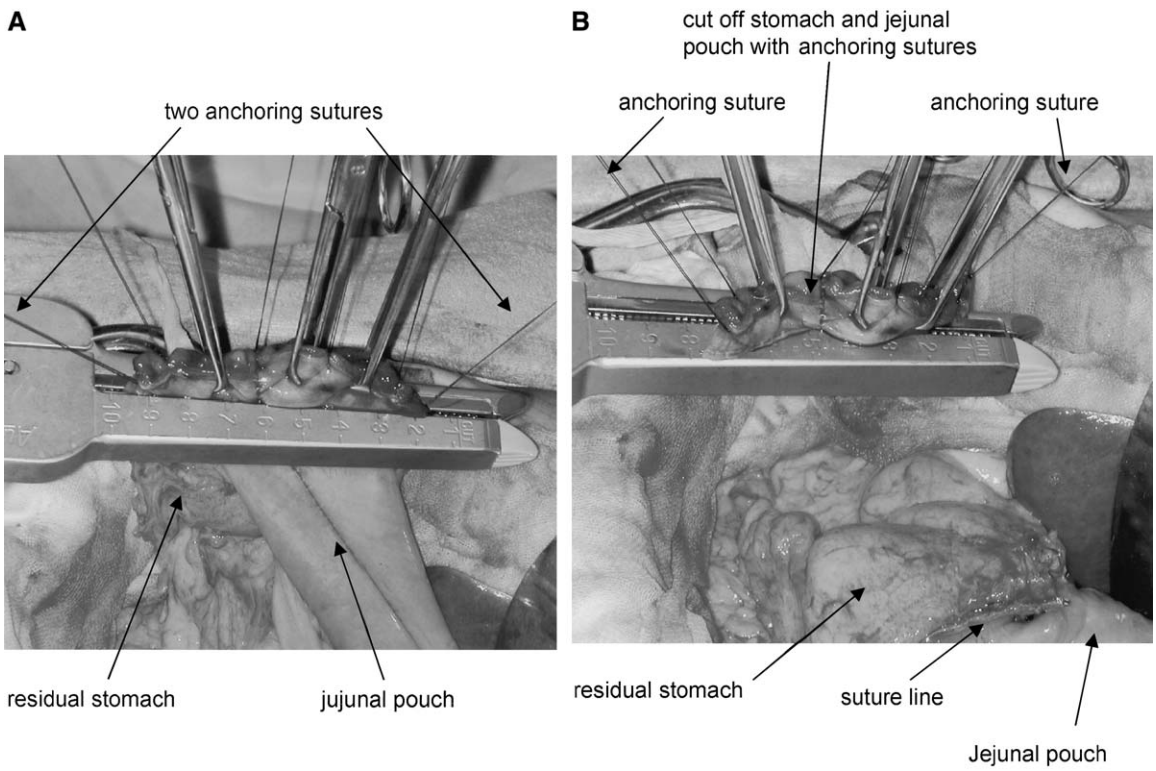

Fig. 2. Anastomosis of the anterior wall. A linear stapler is applied to cut off the two anchoring sutures at the outer edges of the anastomosis.

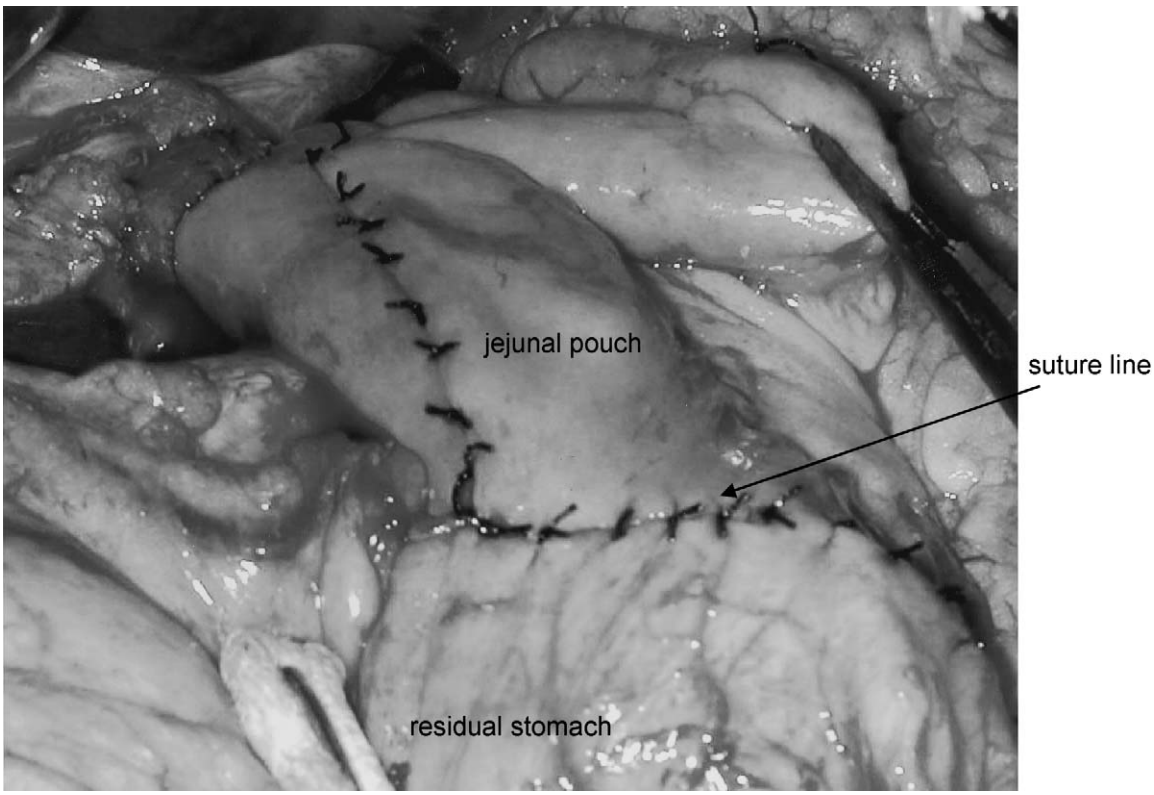

Fig. 3. After completion of the anastomosis.

stapling line. Transmural anchoring sutures were made at both ends of the linear stapling line. After anastomosis of the esophagus and jejunal pouch with a circular stapler, a series of Allis clamps was then applied closely to approximate the anterior walls of the residual stomach and the jejunal pouch, along with some additional anchoring sutures. A 100-mm-long linear stapler was used to staple the approximated walls, this time in an everted fashion. At this stage, the two anchoring sutures at the ends of the posterior stapling line were cut off in a double stapling fashion. This completed the anastomosis of the residual stomach with the jejunal pouch (Fig. 2). We added seromuscular sutures to cover the everted anastomosis line.

Figure 3 shows an operative view after a biangulation stapling anastomoses. Figure 4 shows schemata of our biangulation stapling technique. A barium meal study and endoscopic examination after the procedure showed that there was no stenosis (Fig. 5). We used this method for jejunal pouch reconstruction after proximal gastrectomy in 12 cases of early gastric cancer. No anastomotic leakages, stenoses, or other complications arose from the use of this technique.

DISCUSSION

Early gastric cancer in the upper third of the stomach rarely metastasizes to the suprapyloric or infrapyloric lymph nodes. For this reason, treatment of early gastric cancer by proximal gastrectomy with jejunal pouch interposition reconstruction is a viable option.[2,3] When proximal gastrectomy is followed by jejunal pouch interposition reconstruction, the orifice between the jejunal pouch and the residual stomach requires a particularly large anastomosis to be formed. This task is best carried out by stapling, because hand-suturing is time-consuming, even when continuous sutures are used. The triangulation stapling technique for end-to-end anastomosis was introduced by Heifetz et al.[4] and involves three applications of a linear stapler. As applied to colorectal anastomosis, subsequent large trials[5,6] found the technique to be safe, reliable, and associated with a very low incidence of anastomotic stenosis.

The triangulation stapling technique can be used to form the anastomosis between the jejunal pouch and the residual stomach. In this report, we demonstrate a new technique known as the biangulation

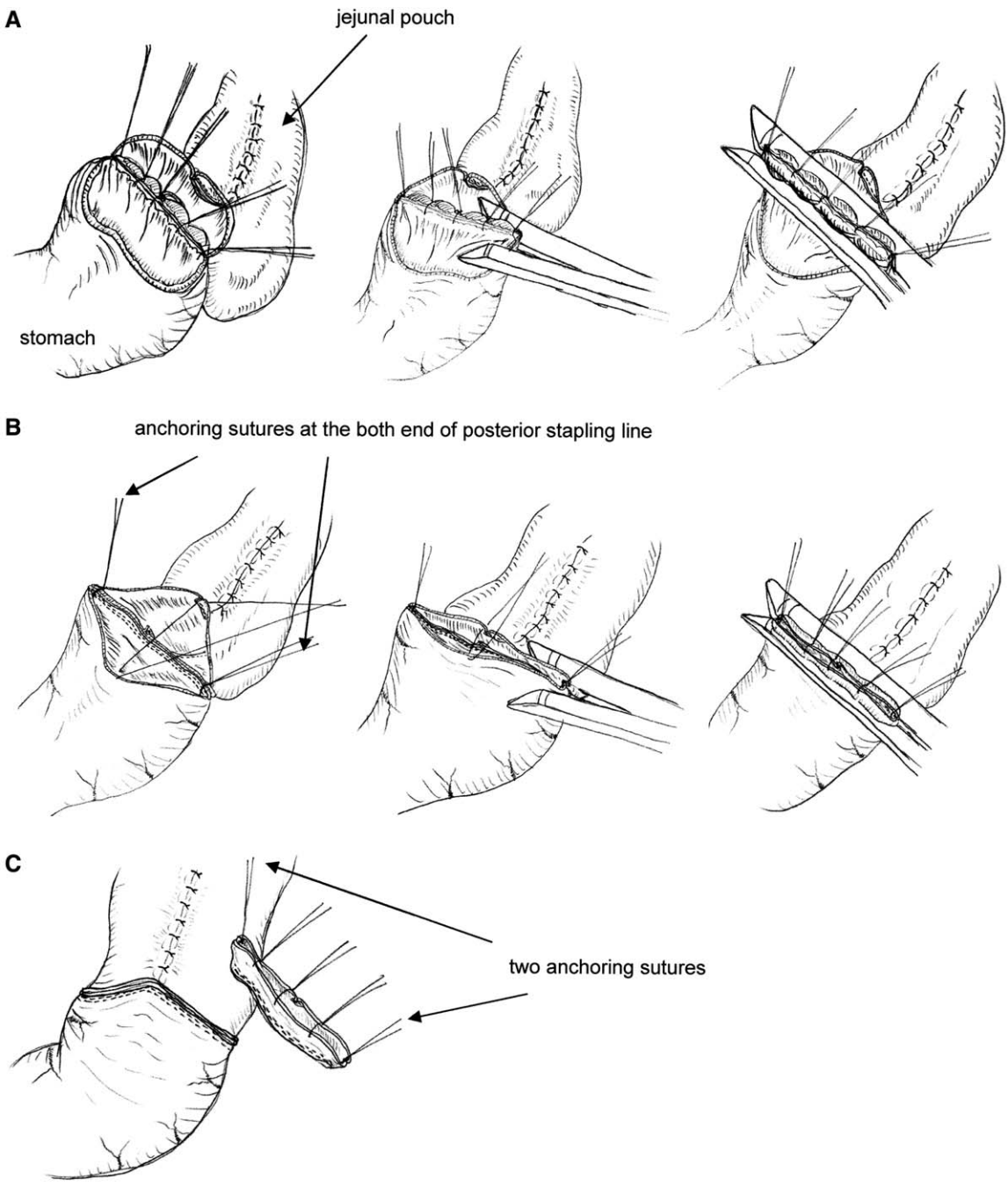

Fig. 4. Schemata of our biangulation technique. (**A**) Anastomosis of posterior wall. (**B**) After completion of anastomosis of posterior wall, two transmural anchoring sutures were made at both ends of the linear stapling line. (**C**) Anastomosis of anterior wall. Note the two anchoring sutures were cut off.

method that can successfully achieve the same procedure using only two applications of the linear stapler. Our technique works well because the orifice between the jejunal pouch and the residual stomach is particularly large, so the exact dimensions of the anastomosis are not critical. We speculated that the shape of the resulting orifice was not round but flat since the formation of stenosis did not present a problem. However, endoscopic examination has revealed that the shape of the orifice is fairly round (Fig. 3). The key steps in performing the biangulation anastomotic procedure are (1) to make anchoring sutures at both ends of the stapling line on the posterior wall, (2) to cut off the two anchoring sutures when stapling the anterior wall, and (3) to include the entire walls of both the jejunum and the stomach in the

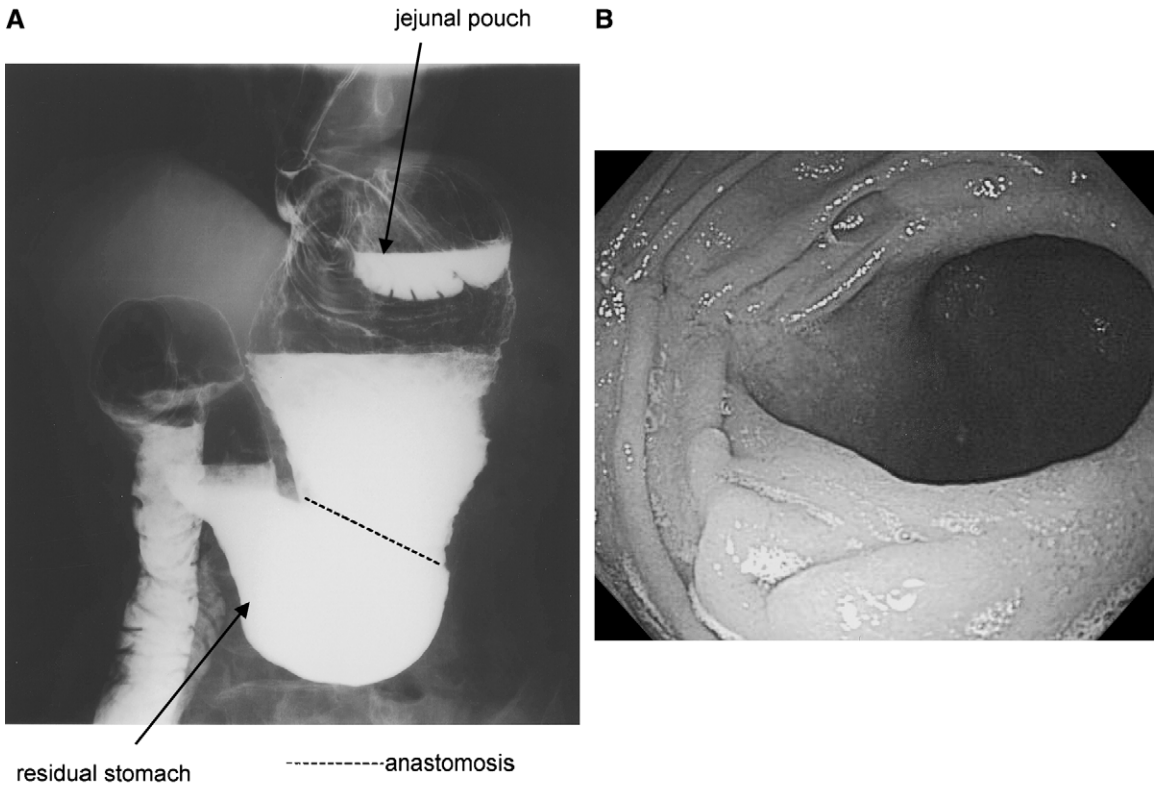

Fig. 5. Barium meal study and endoscopic examination after proximal gastrectomy with jejunal pouch interposition reconstruction, using our biangulation stapling anastomosis. (**A**) Barium meal study. (**B**) Endoscopic examination. Note the round shape of the anastomosis.

stapling lines. This new method is simple and safe and ideal for anastomoses of large diameter.

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Review Article

Adjuvant Treatment Strategies for Pancreatic Cancer

Erika A. Newman, M.D., Diane M. Simeone, M.D., Michael W. Mulholland, M.D., Ph.D.

Pancreatic cancer is a difficult and unsolved surgical problem. It remains one of the top five causes of cancer-related deaths and has the lowest 5-year survival of any cancer, largely due to late diagnosis, low resection rates, and local recurrence. Clinical trials examining the optimal timing and delivery of adjuvant therapies for pancreatic cancer have yielded controversial results. Although most experts agree that the addition of chemotherapy has survival benefit in patients with resectable pancreatic cancer, there is no consensus regarding the optimal therapeutic agents, timing (neoadjuvant versus adjuvant), and the addition of radiation therapy to the treatment regimen. Multiple phase III trials are in progress in efforts to examine these issues. Additionally, exciting progress has been made with novel chemotherapeutic combinations, and alternative treatment modalities including interferon-α, immunotherapy, and pancreatic cancer stem cells. Given the high failure pattern after surgical resection, with more than half of patients developing locoregional recurrence, all patients undergoing pancreaticoduodenectomy are candidates for adjuvant therapy. (J GASTROINTEST SURG 2006;10:916–926)

KEY WORDS: Pancreas, pancreatic cancer, adjuvant therapy, neoadjuvant therapy

In the United States, approximately 32,180 cases of pancreatic cancer are anticipated in 2005, with an expected 31,000 deaths.[1] The incidence is slightly higher in men (1.3:1) and in African Americans.[2] Most patients present with advanced disease. The 1995 National Cancer Data Base Report on Pancreatic Cancer found that of the 17,490 patients with pancreatic cancer surveyed, at least 50% of patients present with locally advanced, unresectable lesions and 35% had metastatic disease at diagnosis[3] (Table 1).

Some populations may have an increased risk for development of pancreatic cancer. Patients with hereditary pancreatitis have a cumulative risk to age 70 of 40%, and in those with a paternal pattern of inheritance, risk increases to approximately 75%.[4] Patients with chronic pancreatitis have a cumulative risk of 2% per decade, independent of the etiology.[5] Emerging evidence also suggests that some pancreatic cancer is inherited. In several studies, up to 8% of patients with pancreatic cancer have a first-degree relative with the disease.[6]

The diagnosis of pancreatic adenocarcinoma is usually made radiographically and histologically. The presence of dilated bile ducts or a mass in the head of the pancreas on ultrasound usually suggests the presence of a pancreatic tumor. Ultrasound results vary greatly depending upon the expertise of the operator, the presence or absence of bile duct obstruction, and the extent of the tumor.[7] Arterial and portal venous phase CT scan with 1.25- to 2.5-mm thin cuts is currently the diagnostic tool of choice for pancreatic cancer. Computed tomography (CT) may reveal duct dilatation, a mass lesion, or evidence of extrapancreatic spread. When combined with intravenous contrast, CT can provide useful information regarding major vessel involvement but may underestimate the degree of hepatic or lymph nodal involvement. If the ultrasound (US) or CT images do not reveal a mass, ERCP has been used, with a sensitivity and specificity of 90–95% (Fig. 1).

A number of recent reports have confirmed the accuracy of endoscopic ultrasound (EUS) in diagnosis and staging of pancreatic cancer.[8] Compared to

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Table 1. Presentation of patients with pancreatic cancer

Presentation	Percent
Resectable disease	15
Locally advanced/unresectable disease	50
Metastatic disease	35

CT, EUS detected more tumors, was more accurate in determining resectability, and was more sensitive for detecting vascular invasion.[9,10] EUS has been shown to be as accurate as angiography in detecting vascular encroachment. The accuracy of EUS depends largely upon the experience of the operator, and results may vary between endosonographers. Most authors currently recommend both EUS and helical CT as complementary staging tools, especially in cases in which the mass is not clearly visualized. EUS is accurate for local tumor (T) staging and in predicting vascular invasion and is often used as a guide for fine needle aspirate biopsy.

While routine magnetic resonance imaging (MRI) offers no significant diagnostic advantage for the staging of pancreatic cancer, magnetic resonance cholangiopancreatography (MRCP) is emerging as an attractive alternative to ERCP in detecting tumors. MRCP is as sensitive as endoscopic retrograde cholangiopancreatography (ERCP) and does not require contrast administration into the ductal system, and the morbidity of ERCP may be avoided. MRCP may be especially useful in patients who have gastric outlet obstruction or in those with altered anatomy (e.g., Billroth II). MRCP also may be useful in the setting of chronic pancreatitis or for those patients in whom ERCP provides incomplete information.[11]

Many tumor markers have been proposed for pancreatic cancer. The most widely used serum marker

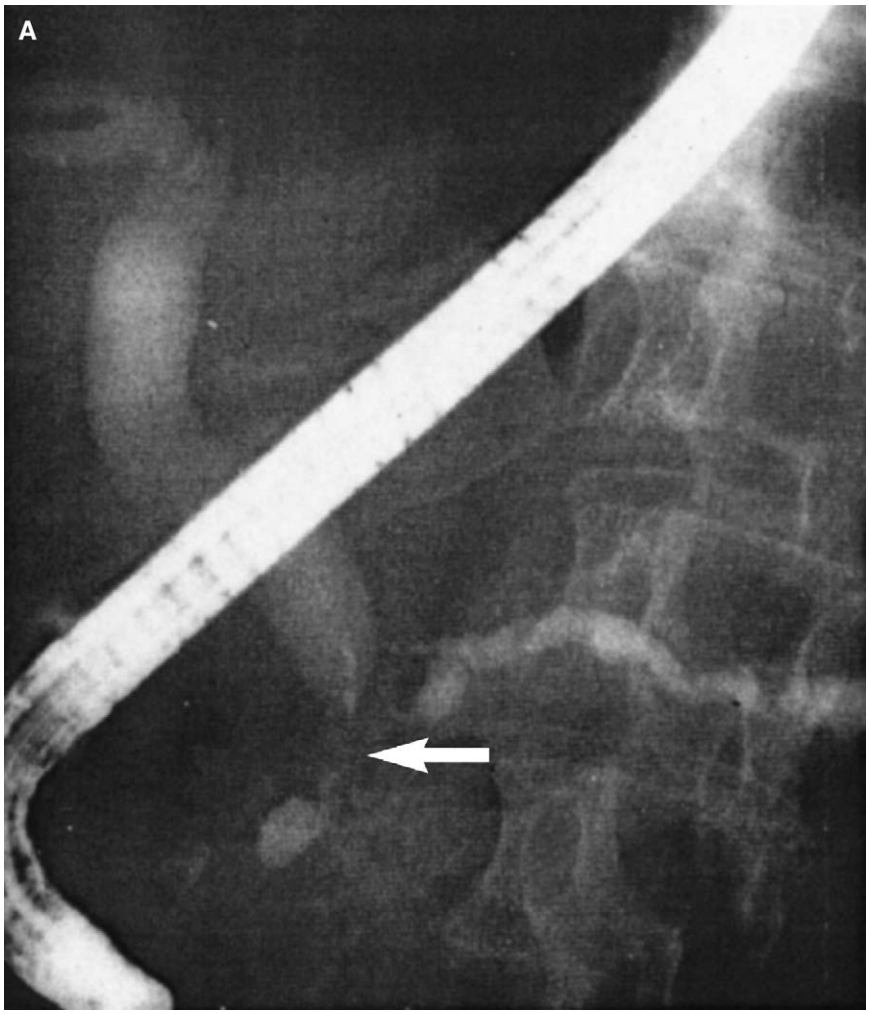

Fig. 1. Endoscopic retrograde cholangiopancreatography (ERCP) showing a doubleduct sign, characteristic of pancreatic adenocarcinoma.

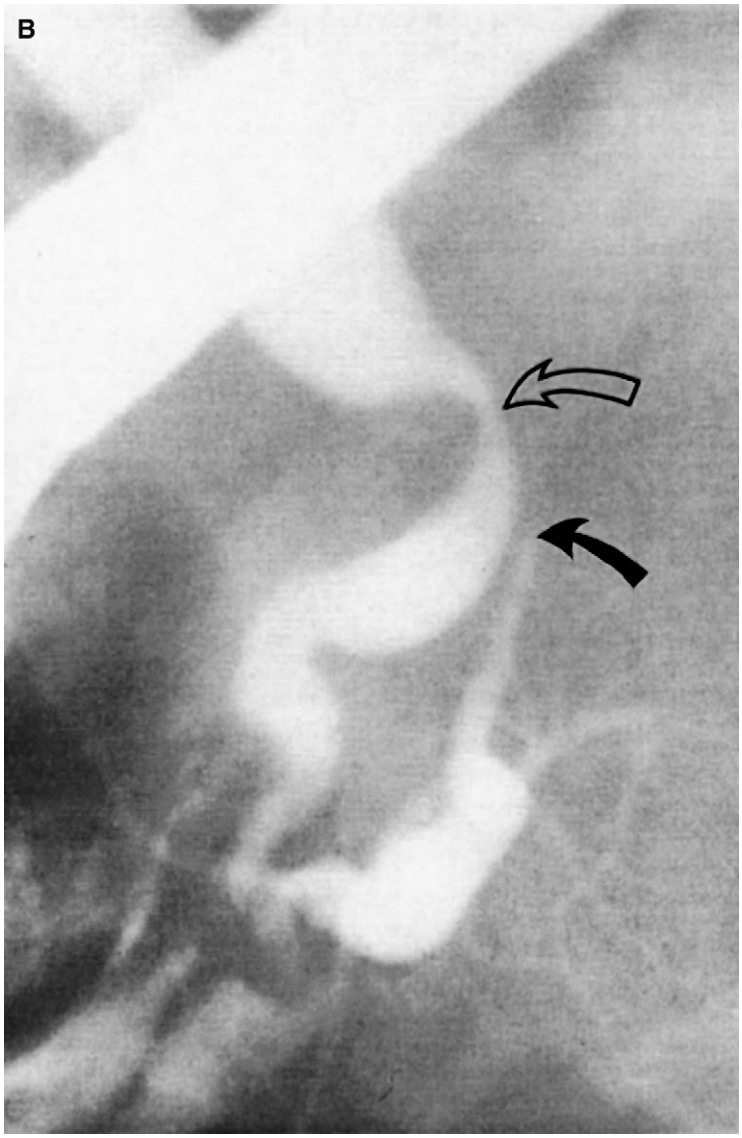

Fig. 1 (*Continued*).

for pancreatic cancer is CA 19-9. It may be useful to monitor patients for evidence of recurrent disease but is not sufficiently accurate to identify patients with small resectable tumors.[12,13] Additionally; the use of CA 19-9 is restricted by false-positive results found in patients with benign pancreaticobiliary disorders. Recently, protein- and DNA-based biomarkers have been under investigation as potential markers of invasive pancreatic cancer. Studies using gene expression profiling of resected pancreatic tumors and normal pancreatic tissue have identified multiple candidate markers of pancreatic cancer.[14,15] Several proteins, including macrophage inhibitory cytokine (MIC-1) and osteopontin, are overexpressed in primary pancreatic cancer cells and have been found elevated in the serum of pancreatic cancer patients.[16,17] MIC-1 appears to be a more sensitive marker of pancreatic cancer than CA 19-9. A recent study examined 50 patients with resectable pancreatic cancer, 50 patients with chronic pancreatitis, and 50 healthy control patients.[15] The authors found that MIC-1 performed significantly better than CA 19-9 at differentiating patients with pancreatic cancer from the control patients. Although MIC-1 was no better than CA 19-9 in distinguishing patients with chronic pancreatitis from those with cancer, the results are promising and could be helpful in the early detection of pancreatic cancer in high-risk patients.

Resection is the only potentially curative treatment for pancreatic cancer, but even patients with resectable disease have poor prognoses. Traditionally,

resectability has been determined with a contrast-enhanced helical CT scan with timed image sequences that permit the evaluation of vascular structures and metastatic disease. Partial involvement of the SMV and/or SMA on CT angiography is associated with a resectability rate of 10–50% depending on the extent of vascular encroachment, although involvement of the SMA is generally a contraindication to resection[18] (Fig. 2). Additionally, metastasis to the liver, peritoneum, and extra-abdominal sites are all contraindications to resection. Resectability also requires that the tumor does not involve other adjacent critical vascular structures such as the portal vein, inferior vena cava, aorta, celiac axis, or hepatic artery, as defined by the absence of a fat plane between the low-density tumor and the vascular structures on helical CT scan. Tseng and colleagues[19] described major vascular resection of the superior mesenteric or portal veins performed at the time of pancreaticoduodenectomy for pancreatic cancer. In their study, vein resection was performed in 141 patients in whom the tumor could not be separated from the vein. The resections included tangential resection with vein patch in 36 patients, segmental resection with primary anastamosis in 35 patients, and segmental resection with autologous interposition grafts in 55 patients. The authors compared all patients who underwent pancreaticoduodenectomy with vein resection to all patients who underwent standard resection. The need for vein resection had no impact on survival duration and the survival of those patients undergoing pancreaticoduodenectomy with vein resection had a median survival (2 years) comparable to those patients undergoing standard resection, and approximately 1 year longer than the survival of patients with locally advanced, unresectable cancer. These data support the use of vein resection as a therapeutic option in selected patients.

THERAPY FOR LOCALLY ADVANCED AND METASTATIC DISEASE

Most patients with pancreatic carcinoma are incurable at the time of diagnosis and receive primary treatment with chemotherapy and radiation (Fig. 3). The results of these treatments underlie the use of these modalities in an adjuvant setting. Therapeutic options for patients with locally advanced or metastatic disease include external beam radiotherapy alone, combined chemoradiotherapy (CRT), and single-agent or combination chemotherapy.

Radiotherapy with or without chemotherapy is associated with resolution of cancer pain in 35–65% of patients, as well as improvement in weight loss and obstructive symptoms.[20] In most cases, radiotherapy

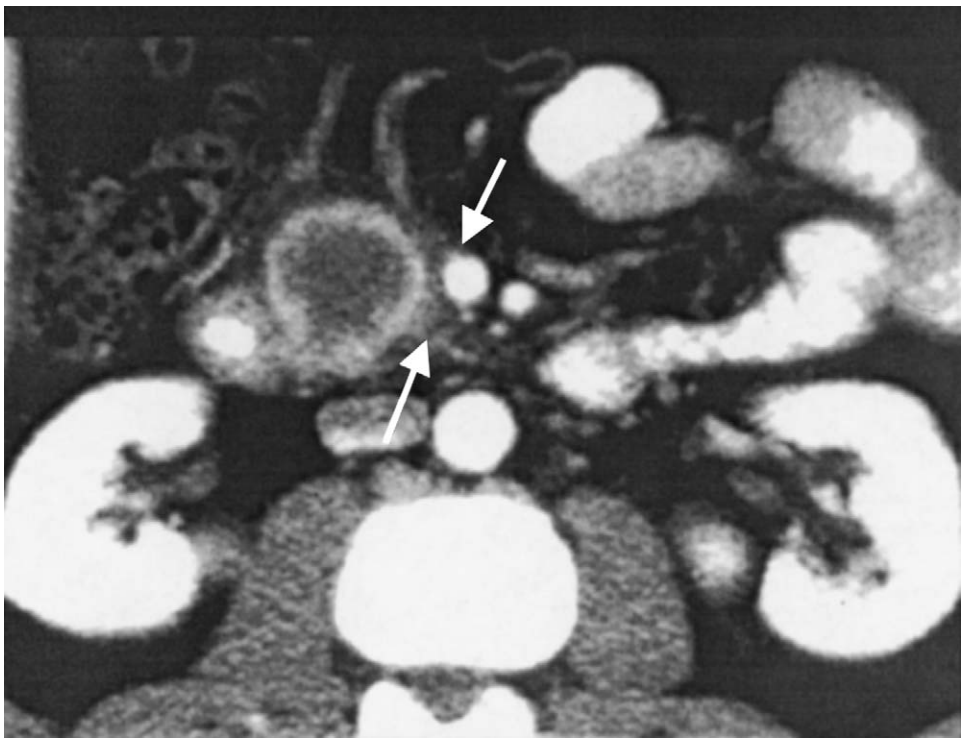

Fig. 2. CT scan showing partial encroachment of SMV by tumor. (Courtesy of Saroja Adusumilli, Department of Radiology, The University of Michigan Medical Center).

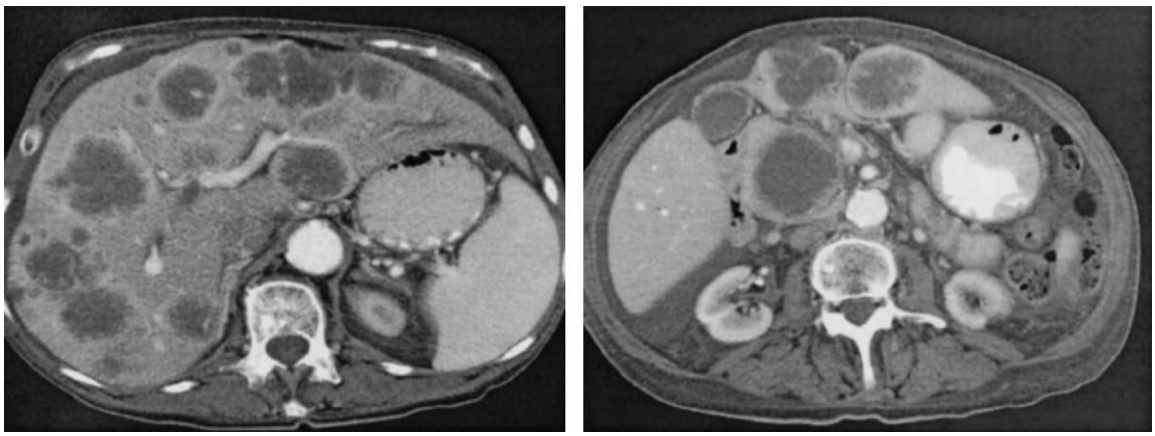

Fig. 3. CT scan of a patient with metastatic pancreatic cancer, with diffuse liver involvement. (Courtesy of Saroja Adusumilli, Department of Radiology, The University of Michigan Medical Center).

alone does not provide local control as reported by Roldan et al.[21] Even with intraoperative radiation plus external beam radiation (XRT), local progression rates are as high as 72% and survival benefit over supportive care is modest.

Multiple studies of the Gastrointestinal Tumor Study Group (GITSG) in patients with unresectable disease have shown that both survival and local control can be improved with the combination of radiotherapy and chemotherapy. Conventional radiotherapy plus 5-fluorouracil (5-FU) has been associated with a median survival of 10–11 months. Most recently, the use of gemcitabine has been explored for use in patients with metastatic pancreatic cancer. Gemcitabine has been shown to provide better symptomatic relief and has shown modest survival benefit over 5-FU.[22] A recent randomized phase II study examining constant dose-rate infusion of gemcitabine (1500 mg/m^2 over 150 minutes) revealed a significantly longer median survival (8 versus 5 months) and greater 1-year survival (29% versus 2%) relative to 5-FU and radiotherapy.[23] Additionally, new combinations are being evaluated. The combinations of gemcitabine with capecitabine and gemcitabine with oxaliplatin have both showed encouraging response rates in phase II trials for unresectable disease.[24,25]

Combination therapy remains the standard option for patients with locally advanced pancreatic cancer and increases survival in the order of a few months but rarely results in survival long term. Ongoing trials are focusing on the evaluation of new systemic agents to combine with radiotherapy and improving methods to select patients who may benefit from such therapies. A phase II trial of 13-*cis* retinoic acid and interferon-α in patients with advanced pancreatic carcinoma revealed that interferon-based therapy is tolerated and may be feasible in patients with advanced cancer.[26] The study consisted of 22 patients with histologically confirmed, unresectable pancreatic cancer. The overall median survival was 7.7 months. Toxicity associated with interferon-α was predominantly hematological (anemia and thrombocytopenia) and fully reversible after dose reduction. Combinations such as these need further investigation in phase III trials.

ADJUVANT THERAPIES FOR RESECTABLE DISEASE

Although overall survival is longer for patients who undergo pancreaticoduodenectomy compared with patients with unresectable disease, the curative resection rate is only 14%. Local recurrence is usually attributed to the difficulty of achieving microscopically disease-free surgical margins, particularly at the retroperitoneal margin. The 5-year survival rate following resection is 25–30% for node-negative disease and 10% for node-positive cancers.[27] These outcomes are improving, likely related to an increased proportion of patients undergoing operations at high-volume centers and the increased use of adjuvant therapies.[28]

Recent clinical trials have given momentum to the treatment of pancreatic cancer with adjuvant therapies. In an evaluation of 396 Medicare patients residing in one of 11 SEER (Surveillance, Epidemiology, and End Results reporting) registries who underwent resection with curative intent, the 3-year survival rate was 34% for controls and 45% among those who received adjuvant CRT.[29] The use of adjuvant CRT in patients with resected pancreatic cancer remains inconsistent. A report of treatment and survival trends for 110,313 patients, diagnosed with pancreatic cancer between 1985–1995, using the

National Cancer Database, revealed that for patients undergoing pancreatectomy, adjuvant treatment was prescribed for only 40%.[30]

The GITSG, in an early randomized study, evaluated adjuvant combination CRT (split-course 40 Gy, consisting of two courses of 20 Gy with an interval of 2 weeks, plus bolus 5-FU on the first 3 and last 3 days of radiation, followed by maintenance chemotherapy for 2 years) versus observation (OBS). This trial found an increase in median survival (20 versus 11 months), as well as an increase in 2-year survival (20 versus 10 months) in patients receiving CRT.[31] This study was criticized because of poor patient accrual, early termination, and small patient numbers, and some maintained that the XRT dose was suboptimal (some authors advocate 50 Gy as a total effective dose). However, the trial was the first prospective randomized trial suggesting survival advantage with postoperative CRT and has been generally accepted. Multiple authors have attempted to confirm its findings.

The European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 114 postoperative pancreatic cancer patients to OBS or postoperative XRT (40 Gy, split-course regimen) and 5-FU (continuous, during first week of XRT only).[32] The trial enrolled 114 pancreatic cancer patients. Sixty patients were randomized to combination therapy and 54 to OBS. In contrast to the GITSG trial, postoperative CRT was not associated with a significant improvement in median survival (19 versus 24.5 months in treatment group) or 2-year survival (26% versus 34%), with no reduction in locoregional recurrences observed. These investigators concluded that the routine use of adjuvant CRT was not warranted as standard treatment in pancreatic cancer. Much like the GITSG study, this trial was also criticized because radiation treatments were split-course and thought to be suboptimal. Additionally, the study lacked maintenance chemotherapy and there was minimal collection of information regarding surgical margins. In addition, of the 60 patients in the treatment arm of the study, 20% received no treatment due to postoperative complications or patient refusal.

Although not conclusive, these results showed a trend toward benefit of adjuvant therapy and led to the European Study Group for Pancreatic Cancer (ESPAC-1) trial, the largest reported randomized study to date investigating the role of combination chemoradiotherapy in pancreatic cancer. The investigators randomized patients into a 2 × 2 factorial design to examine the role of adjuvant chemotherapy and adjuvant chemoradiation.[33] The study enrolled 289 patients in the 2 × 2 design: 73 patients with resected cancer to chemoradiotherapy alone (21 Gy in 10 daily fractions over 2 weeks plus fluorouracil), 75 patients to chemotherapy alone (5-FU), 72 patients to both, and 69 patients to OBS. A further 68 patients were randomly assigned radiotherapy or no radiotherapy and 188 received chemotherapy or no chemotherapy. The authors reported that adjuvant combination chemoradiotherapy did not improve median or 2-year survival (15.5 months in treatment group versus 16.1 months in the control). The ESPAC-1 trial also indicated that adjuvant chemotherapy alone prolonged survival (19.7 versus 14 months). Additionally, assessment of treatment benefits within specific prognostic groups pointed to a potential role for chemoradiation only in patients with positive resection margins. This analysis has received criticism because of possible selection bias (patients and clinicians were allowed to select which trial to enter), a concern of suboptimal radiation, and for allowing the final radiation dose to be left to the judgment of the treating physicians. The treatment for patients in the chemoradiotherapy group did not include postradiotherapy adjuvant chemotherapy, making direct comparison to the GITSG trial difficult.

The varying results of these randomized trials make it difficult to establish a standard of postresection care. Additionally, there have been multiple single-institution reports evaluating adjuvant therapy. In the largest of the uncontrolled series examining combination chemoradiotherapy, Yeo et al.[34] examined 174 patients. In this study, patients were offered three options for postoperative treatment after pancreaticoduodenectomy: standard external beam radiation (EBR) consisting of 40–45 Gy with two 3-day 5-FU courses followed by weekly bolus 5-FU for 4 months or intensive therapy (EBT with 50–57 Gy followed by 5-FU plus leucovorin) or no therapy. These investigators reported that standard adjuvant combination chemoradiation therapy significantly improved survival (median survival, 19.5 months compared to 13.5 months without therapy). Intensive therapy had no additional survival advantage compared to standard therapy.

An important aspect to adjuvant chemoradiotherapy is the possibility of delaying initiation of chemotherapy by the operation and further delay by the initiation of radiation. In the EORTC trial, of 110 patients in the treatment arm, 21 (20%) received no treatment because of excessive delay due to postoperative complications. Additionally, the ESPAC-1 authors concluded that delay in the administration of chemotherapy in those patients undergoing combination chemoradiotherapy might explain the inferior outcome. The true incidence and effect of delay due to postoperative complications are unknown.

Conflicting views on the interpretation of the ESPAC-1 data has led to multiple studies now in progress in the United States and Europe. Results of the Radiation Therapy Oncology Group (RTOG 97-04) Gastrointestinal Intergroup Protocol 97-04 trial are yet to be reported. In this phase III trial examining postoperative adjuvant combination chemoradiotherapy, 538 patients were randomized after resection to receive either gemcitabine or 5-FU before and after concurrent chemoradiation (50.4 Gy total).[35] The objectives of this study are to determine whether 5-FU–based chemoradiation preceded and followed by gemcitabine improves survival compared to 5-FU–based chemoradiation preceded and followed by 5-FU treatment after resection. The study also evaluates the use of CA 19-9 as a predictor of survival after postoperative adjuvant therapy. The RTOG 97-04 trial is now closed and undergoing review. Results are anticipated soon and should provide insight into the potential survival benefit of postoperative adjuvant combination chemoradiotherapy (Table 2).

ADJUVANT CHEMOTHERAPY ALONE

The ESPAC-1 trial, as previously stated, found a potential benefit from adjuvant chemotherapy alone. These investigators reported a median survival benefit of 19.7 months in 238 patients with postoperative chemotherapy alone versus 14 months in 235 patients without treatment. A similar Norwegian trial (Bakkevold et al.[36]) of 61 patients randomized to multiagent postoperative chemotherapy (5-FU, doxorubicin, and mitomycin) versus no therapy suggested that adjuvant chemotherapy postpones the incidence of recurrence in the first 2 years but that long-term prognosis was the same between groups. Takada et al.,[37] in 2002, reported results of a randomized trial, designed to investigate the role of adjuvant chemotherapy using 5-FU–based combination chemotherapy. Of the 158 patients with pancreatic cancer enrolled in that study, there were 81 in the treatment group (mitomycin C at the time of surgery and 5-FU in 2 courses of treatment for 5 days during postoperative weeks 1 and 3, followed by 5-FU orally as maintenance until disease recurrence) and 77 patients in the control group. The authors concluded that there were no apparent differences in 5-year survival or local recurrence rates. This study was criticized for the use of oral 5-FU as maintenance therapy. There are ongoing trials investigating chemotherapy alone, including those evaluating single-agent postoperative treatment with gemcitabine.[38] Additionally, the ESPAC-3 (v2) trial, currently in progress, is addressing the question of survival benefit of single agent postoperative chemotherapy with gemcitabine versus 5-FU[39] (Table 3).

ADJUVANT RADIOTHERAPY ALONE

Bosset et al.,[40] in a prospective, nonrandomized study of 14 consecutive patients, evaluated conventional external beam radiation alone as adjuvant

Table 2. Randomized controlled trials of adjuvant chemoradiation for pancreatic cancer

Trial	Comparison	Treatment	No. of patients	Major conclusion	Major criticisms
GITSG[26]	CRT vs OBS	2 × (20 Gy in 10 fractions + bolus 5-FU, maintenance 5-FU to recurrence)	43	Increase median and 2-yr survival in CRT group	Poor patient accrural, early termination, suboptimal XRT
EORTC[27]	CRT vs OBS	2 × (20 Gy in 10 fractions + bolus 5-FU during treatment only, no maintenance 5-FU)	114	No significant improvement in median or 2-yr survival	20% of patients randomized to CRT received no treatment, suboptimal XRT, no maintenance CT
ESPAC1-2 × 2[28]	CRT vs OBS and CT vs OBS	2 × (20 Gy in 10 fractions + bolus 5-FU during treatment only for CRT group, and 5-FU + FA × 6 cycles for CT group)	289	No survival benefit for CRT, potential benefit for adjuvant CT	Possible selection bias, physicians allowed to deliver background XRT CT, no maintenance CT CRT group

GISTG = Gastrointestinal Study Group, EORTO = European Organization for Research and Treatment of Pancreatic Cancer, ESPAC = European Study Group for Pancreatic Cancer, CRT = adjuvant chemoradiation, CT = adjuvant chemotherapy, OBS = surgery alone.

Table 3. Randomized controlled trials of adjuvant chemotherapy for pancreatic cancer

Trial	Comparison	Treatment	No. of patients	Major conclusions	Major criticisms
Bakkevold et al.[30]	CT vs OBS	MMC, doxorubicin, and 5-FU	61	Postpones 2-yr recurrence, no long-term survival benefit	Small patient numbers, no maintenance CT
ESPAC[26]	CT vs OBS and CRT vs OBS	5-FU + FA	188	Potential recurrence and survival benefit for adjuvant CT	Possible selection bias, physicians allowed to deliver background XRT or CT
Takada et al.[31]	CT vs OBS	MMC and 5-FU, oral 5-FU maintenance	158	No survival or recurrence benefit	Use of oral 5-FU as maintenance CT

ESPAC = European Study Group for Pancreatic Cancer, CRT = adjuvant chemoradiation, CT = adjuvant chemotherapy, OBS = surgery alone, MMC = mitomycin C, FA = folinic acid.

treatment after curative surgery (54 Gy). The overall locoregional recurrence rate was 50%; median and 2-year disease-free survival were 12 and 23 months, respectively. These results were comparable to the results of the GITSG trial, but the study was underpowered and nonrandomized. Intraoperative radiotherapy (IORT) has been investigated for many intra-abdominal malignancies, and several authors have reported its success in resected pancreatic cancer. One such study compared 86 patients who received radiotherapy combined with resection (of those patients, 37 received postoperative radiotherapy, 14 received IORT, and 31 received both) to 64 patients who received surgery alone.[41] Adjuvant radiotherapy, including IORT, was found to provide significant survival benefit (median survival, 12.8 versus 7.9 months). Although radiotherapy alone has been used in unresectable disease for palliation of pain, it is not been accepted as the sole adjuvant treatment following curative resection and has not been shown to have superior survival benefit versus CRT or chemotherapy alone.

NEOADJUVANT THERAPY

Use of neoadjuvant chemoradiation eliminates potential treatment delays that may be associated with adjuvant therapy. Other potential benefits include increased survival, downstaging marginal lesions, and sparing patients with rapidly progressive disease unnecessary surgery. The University of Texas M. D. Anderson Cancer Center initiated studies of chemotherapy given in the preoperative setting, in efforts to minimize local tumor recurrence and maximize survival duration in patients with potentially resectable disease.[42] Data on 132 patients who received preoperative chemoradiation (either 45–50 Gy or 30 Gy with concomitant infusional chemotherapy, 5-FU, paclitaxel, or gemcitabine) followed by pancreaticoduodenectomy for cancer were retrieved from a prospective database. These investigators found an overall median survival of 21 months, and the 5-year survival was 23%. By univariate and multivariate analyses, the survival duration was superior for women and for patients without evidence of lymph node metastasis. There was no difference in survival duration for patients receiving the less toxic dose of preoperative radiation therapy or the delivery of intraoperative radiotherapy. The analysis suggested that rapid-fragmentation preoperative chemoradiotherapy, combined with pancreaticoduodenectomy, in patients with localized pancreatic cancer maximizes survival duration and may be associated with a low incidence of tumor recurrence.

There is also strong theoretical rationale for preoperative downstaging of locally advanced lesions. Mehta et al.[43] hypothesized that preoperative chemotherapy might promote tumor regression, eradicate nodal metastases and allow for definitive resection of marginally resectable lesions (as defined by portal vein, superior mesenteric vein, or superior mesenteric artery involvement). Fifteen patients with marginally resectable tumors completed neoadjuvant therapy in this study. Of the 15 patients, 9 underwent pancreaticoduodenectomy, and all had uninvolved surgical margins. Two patients had complete pathological response, and two had lymph nodal involvement. The median survival for those undergoing resection was 30 months versus 8 months in the unresected group. Six of the nine patients who underwent resection were alive at 5-year follow-up.

Studies with gemcitabine-based neoadjuvant therapy have shown promise. One author reported that a potentially curative resection was accomplished in 73% of patients after treatment with neoadjuvant

chemotherapy.[44] Ammori et al.[45] studied 67 patients with locally unresectable pancreatic cancer, treated with gemcitabine and concurrent radiation therapy. In this study, 17 of those treated (25%) underwent exploratory surgery and nine patients were able to undergo pancreaticoduodenectomy. The median survival for the resected patients was 17.6 months. Multiple phase I/II studies of gemcitabine and cisplatin as induction therapy for patients with locally advanced pancreatic cancer are currently in progress.[46] These studies have provided the framework for larger controlled trials evaluating the role of neoadjuvant therapy in the management of both resectable and marginally resectable lesions.

ALTERNATIVE THERAPEUTIC APPROACHES

Alternate adjuvant therapies have also been investigated. Recently, Picozzi et al.[47] reported results of their phase II trial examining interferon-based postoperative adjuvant chemoradiation therapy. The series consisted of 43 patients. All received XRT (45–54 Gy) and three-drug chemotherapy consisting of continuous 5-FU, weekly intravenous bolus cisplatin, and subcutaneous interferon-α. Chemoradiation was followed by continuous infusion of 5-FU (5.5 months). At mean follow-up time of 31.9 months, 67% of patients were still alive. The actuarial overall 1-, 2-, and 5-year survival rates were 95%, 64%, and 55%, respectively. This regimen has proved toxic for patients, with at least 70% reporting moderate to severe gastrointestinal toxicity. The potential survival benefit is promising, and confirmatory studies are under way.

The development of pancreatic cancer vaccines has been the recent subject of early phase trials.[48] Key signaling pathways involved in immune system regulation have been identified, and vaccines designed to target pancreatic cancer-associated antigens and regulatory signaling molecules are entering clinical trials.[49] Jaffee and colleagues performed the first phase I trial establishing the safety of a granulocyte/macrophage–colony-stimulating factor (GM-CSF)–secreting tumor in patients with resected pancreatic cancer.[50] The authors enrolled 14 patients with stage 1, 2, or 3 pancreatic adenocarcinoma, and 8 weeks after pancreaticoduodenectomy, patients received varying doses of GM-CSF–secreting tumor vaccine. Twelve of the 14 patients then went on to receive adjuvant CRT. Half of the patients also received additional vaccine doses after the completion of CRT. The treatment induced dose-dependent, systemic antitumor immunity, as measured by increased postvaccination, delayed-type hypersensitivity responses to autologous tumor cells in three patients receiving larger vaccine doses. All three patients remained disease-free and are now ⩾7-year survivors.[51] The authors were the first to document the safety of using a GM-CSF–secreting tumor vaccine in patients with pancreatic cancer. There are multiple phase II and III trials in progress evaluating immunotherapy in pancreatic cancer patients.[51]

NEW HORIZONS

There is emerging evidence that a tumor has the capacity to grow and propagate depending on a small subset of cells within a tumor, termed cancer stem cells. There has been strong evidence to support this theory in blood, brain, and breast cancers.[52] The cancer stem cell hypothesis suggests that neoplastic clones are maintained exclusively by a small subset of cells with stem cell properties within a tumor. This theory was originally based on the observation that when cancer cells of many different types were assayed for proliferative potential in various in vitro or in vivo assays, only a minority of cells were able to proliferate extensively.[50] This observation gave rise to the idea that malignant tumors are comprised of a small subset of distinct cancer stem cells, which have great proliferative potential, as well as more differentiated cancer cells, which have very limited proliferative potential. Pilot studies are currently under way to study pancreatic cancer stem cells. The information gained may lead to new avenues to identify novel tumor cell markers for diagnostic purposes and to identify new cellular targets and will provide a cell population that can be used for testing new chemotherapeutic agents, biological modifiers, and immune-based therapies.

SUMMARY

Pancreatic cancer remains a dismal disease with poor prognosis, even after curative resection without nodal involvement or metastasis. Complete surgical resection remains the only option for cure, and the rate of locoregional recurrence makes adjuvant therapy vital. There is no consensus regarding optimal therapeutic agents, method of administration, or timing (Table 4). For now, the National Comprehensive Cancer Network (NCCN) recommends that investigational options be considered in all phases of disease management. Additionally, until further data are available, the NCCN recommends postoperative RT, administered at a dose of 45–54 Gy, with concurrent 5-FU with or without additional

Table 4. Treatment options

Adjuvant regimen	Advantages	Disadvantages	Currently accepted indications
Neoadjuvant CRT	Eliminates potential treatment delays, may downstage marginally respectable lesions, identifies rapid progresses, may minimize local recurrence	May delay definitive operation	Resectable and marginally respectable lesions
Adjuvant CRT	Effective with positive surgical margins, at least 1 RTC showing survival and recurrence benefit (GITSG)	Treatment often delayed by operation, slow recovery, and disease progression	Resectable and Unresectable lesions
Adjuvant CT alone	Avoids morbidity of radiation and delays of chemoradiation, 1 RTC showing survival and recurrence benefit (ESPAC)	Less effective with positive urgical margins	Resectable lesions
Adjuvant XRT alone	Avoids toxic effects of CT, IORT shown to have survival benefit vs OBS	Not shown to have survival benefit vs CRT or CT, does not provide systemic therapy	Unresectable disease, palliation of pain

GISTC = Gastrointestinal Study Group, ESPAC = European Study Group for Pancreatic Cancer, CRT = adjuvant chemoradiation, CT = adjuvant chemotherapy, OBS = surgery alone, RTC = randomized controlled trial.

chemotherapy (gemcitabine based), or chemotherapy alone (gemcitabine based) for all patients after curative resection for pancreatic cancer, regardless of nodal status.[53] Novel chemotherapeutic approaches and improved radiotherapy techniques are becoming available as data from contemporary trials are reported.

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An Unusual Presacral Mass: Extramedullary Hematopoiesis

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Presacral masses are a rare finding in the adult patient, confronting the physician with diagnostic and therapeutic challenges. We present an unusual case of a symptomatic presacral mass caused by extramedullary hematopoietic tissue in a thalassemic patient and review the unique aspects of this entity. (J GASTROINTEST SURG 2006;10:927–929)

KEY WORDS: Extramedullary hematopoiesis, presacral mass, β-thalassemia intermedia

Presacral (retrorectal) tumors are particularly rare in the adult. They usually present with vague symptoms and are a diagnostic challenge due to difficulty in the performance of diagnostic biopsy and the need for specialized imaging required to plan surgical extirpation.[1] Traditionally, these masses are classified as cystic or solid lesions. Most cystic lesions are developmental cysts (mainly dermoid and epidermoid cysts, tailgut cysts, and cystic hamartomas),[1] and the majority of the solid lesions are neoplasms (mainly chordomas).[1,2] We, herein, present a patient with a symptomatic, solid lesion that does not fall into any of these categories.

CASE REPORT

A 48-year-old female presented to our institution complaining of painful defecation that had been bothering her for the last 3 months. There was no history of weight loss or change in bowel habits. She was diagnosed with β-thalassemia intermedia at 8 years of age, has never been in need of blood transfusions, and was lost to follow-up during the last 10 years. Her physical examination was unremarkable except for an enlarged spleen. Rectal digital examination revealed a tender posterior mass with a soft consistency and a smooth contour. Her laboratory workup was remarkable for a microcytic anemia with hemoglobin values of 9.7 g/dL, mean corpuscular volume (MCV) 63.7 fL, and platelets 90,000/mm^3. A computed tomography scan showed a 3 × 3 × 5-cm smoothly marginated, solid, presacral mass. No abnormal lymph nodes were detected.

Hepatosplenomegaly was also present. As part of the preoperative survey, magnetic resonance imaging was performed. The mass showed a high-signal intensity on T1 and T2 weight images (Fig. 1), and was uniformly enhanced after gadolinium injection. Due to the unclear nature of the mass, a diagnostic excision was performed. A posterior approach was used to reach the presacral space. The mass was encapsulated by soft, smooth fibrotic tissue and was firmly adherent to the posterior wall of the rectum, without evidence of invasion. The mass was extirpated as a whole (Fig 2). The pathologic examination of the mass showed fatty connective tissue interspaced with bone marrow trabeculae and hyperplastic hematopoietic cells (Fig 3), all consistent with a diagnosis of extramedullary hematopoiesis (EH).

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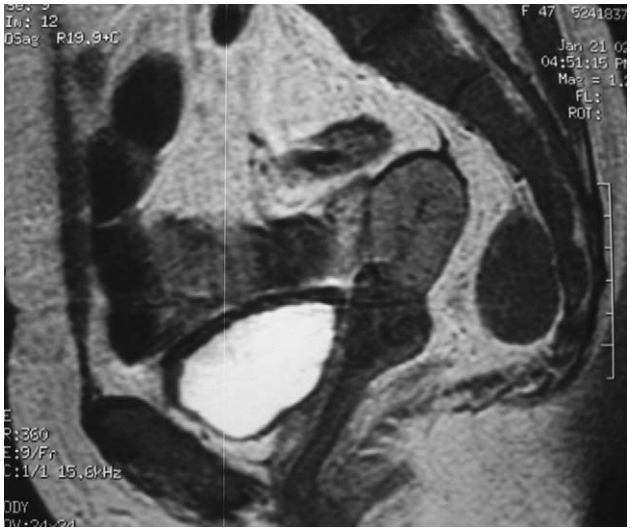

Fig. 1. Magnetic resonance imaging of the abdomen and pelvis: sagital view. A clearly demarcated presacral mass is shown.

The postoperative course was uneventful. The patient was discharged on the fourth postoperative day. On subsequent follow-up 12 months later, the patient was completely asymptomatic.

DISCUSSION

EH is the development and growth of hematopoietic tissue outside of the bone marrow. After birth, it is considered abnormal and is usually a compensatory phenomenon in diseases of reduced erythrocyte production or accelerated erythrocyte destruction.[3] The most commonly associated conditions are myelofibrosis with myeloid metaplasia, and thalassemia

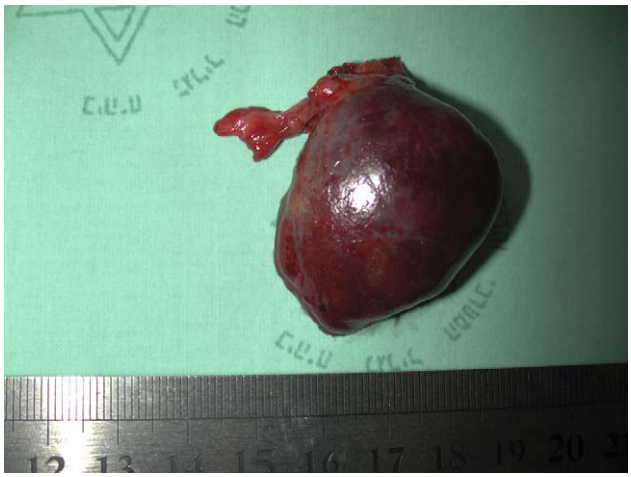

Fig. 2. Specimen after surgical extraction.

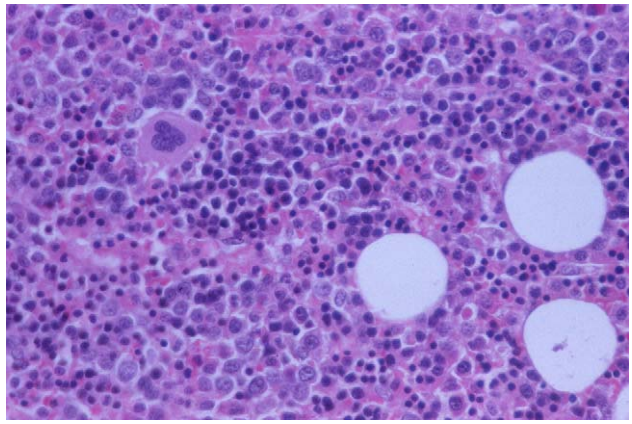

Fig. 3. Microscopic examination of the mass revealing hyperplastic hematopoietic tissue.

(mainly β-thalassemia intermedia).[3] The liver and spleen are the most common sites involved in pathologic EH. However, the process has been described in various other sites, especially the intrathoracic paravertebral location.[3,4,5] In a retrospective chart review by Cody et al.[3] of 510 cases involving EH, only 27 (5.3%) were nonhepatosplenic. Of these 27 cases, 7 (26%) were paravertebral, and the rest involved various lymph nodes (15%), retroperitoneum (15%), pleura (11%), and other less common sites. The presacral space is a particularly rare site of EH, and to date only a few other cases have been described in English literature.[3–8] Clinically, EH may present as an incidental finding or with local symptoms and signs of a mass effect. The radiographic appearance of EH has been described previously in various studies, but is generally nondiagnostic. CT scan shows a heterogeneous lobulated soft tissue density mass with a sharp demarcation.[4] Magnetic resonance imaging (MRI) usually demonstrates a high-signal intensity on T1 and T2 weighted images.[4,7] Other diagnostic modalities include ^{99m}Tc sulfur colloid bone marrow scan and angiography.[3,7] The management of these lesions is influenced by the symptoms. Asymptomatic masses can be observed safely without surgical intervention. Symptomatic masses require treatment. Ectopic hematopoietic tissue has been shown to be extremely sensitive to low doses of radiation. Koch et al. showed a 71% response rate to a radiation dose of 4.25 Gy delivered in 10 fractions.[3]

In our case the management was influenced by the symptoms and the unusual site of growth—the presacral space. Although at least half of the presacral tumors presenting in the adult are asymptomatic, and the majority are benign, it is generally recommended that these lesions be removed.[1] The role

of preoperative biopsy is controversial. Biopsy can be followed by serious and even fatal complications, including infections and bleeding from damage to the middle sacral artery.[1] Wolpert et al. recommended that preoperative biopsy be done only in solid lesions with signs of malignancy such as sacral invasion.[1] If a presacral needle biopsy is decided upon, it must be done in such a way that the needle tract can be excised en bloc with the tumor should operative excision be subsequently performed.[1,4]

In patients suffering from chronic blood dyscrasias, the possibility of EH should be taken into account during initial evaluation of space-occupying lesions. The presence of symptoms dictates the proper management, which can consist of radiographic follow-up only, radiation treatment, or surgical excision. In our case the unusual site of growth, combined with the fact that the patient was symptomatic, made us choose the surgical option.

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Consensus Statement on Surgical Journal Authorship* – 2006

In the majority of clinical and research studies submitted to surgery journals for possible publication, many individuals participate in the conception, execution, and documentation. However, recognition of work in the form of authorship has varied widely. This consensus statement is being issued to clarify and define the criteria for surgical journal authorship.

The following guidelines should be used to identify individuals whose work qualifies them as authors as distinct from those who are contributors to the work under consideration. All persons designated as authors should qualify for authorship, and all those who qualify should be so credited.

A. AUTHORSHIP CRITERIA

Individuals claiming authorship should meet all of the following 3 conditions:

1) Authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data;
2) Authors participate in drafting the article or revising it critically for important intellectual content; and
3) Authors give final approval of the version to be submitted and any revised version to be published.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Allowing one's name to appear as an author without having contributed significantly to the study or adding the name of an individual who has not contributed or who has not agreed to the work in its current form is considered a breach of appropriate authorship.

Acquisition of funding, collection of data, contributing cases, or general supervision of the research group, of itself, or just being the Chair of the department does not justify authorship if the above criteria are not fulfilled.

B. ORDER OF AUTHORS

The order of authorship on the byline should be a joint decision of the co-authors. Authors should be prepared to explain the order in which authors are listed.

C. MULTI-CENTER STUDIES

When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above, and editors will ask these individuals to complete journal-specific author and conflict of interest disclosure forms. When submitting a group-author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name.

D. CONTRIBUTORS LISTED IN ACKNOWLEDGMENTS

All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include: individuals who allowed their clinical experience (i.e. cases) to be included, a person who provided purely technical help, writing assistance, or a department Chair who provided only general support. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as "clinical investigators" or "participating investigators," and their function or contribution should be described - for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients."

Because readers may infer their endorsement of the data and conclusions, all persons listed as contributors must give written permission to be acknowledged.

E. IN CONCLUSION

This consensus statement is intended as a basic guide for authors. In the interest of promoting the highest ethics in surgical publishing and the surgical

*This Consensus statement was adapted from the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals.
For more information: http://www.icmje.org/index.html

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sciences, we ask that authors take these criteria into careful consideration when submitting a manuscript to a peer-reviewed surgical journal.

This statement is being simultaneously published in the respective journals of the members of the Surgical Journal Editors Group, as follows:

American Journal of Surgery ..... Kirby I. Bland, MD

The American Surgeon..... Talmadge A. Bowden Jr, MD

Annals of Surgery..... Layton F. Rikkers, MD

Annals of Surgical Oncology..... Charles M. Balch. MD

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British Journal of Surgery..... John Murie, MD

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