Expandable Stents for Iatrogenic Perforation of Esophageal Malignancies

Russell E. White, M.D., M.P.H., F.A.C.S., Caesar Mungatana, M.D., Mark Topazian, M.D.

The management of patients with iatrogenic perforation of esophageal cancers is controversial. We reviewed the management of perforated esophageal malignancies at a single institution with a large volume of patients with esophageal cancer. Cases of iatrogenic perforation of the esophagus occurring during a 3-year period were identified from the hospital endoscopy database. Inpatient and outpatient records were reviewed, and subjects were visited to obtain follow-up information. Perforation was suspected after 10 of 492 endoscopic dilatation procedures done in patients with obstructing esophageal malignancies. All patients were diagnosed immediately. One patient with pneumomediastinum and pneumoperitoneum died 7 days after laparotomy. Nine patients with pneumomediastinum were managed endoscopically with delayed (n = 1) or immediate (n = 8) placement of a self-expanding metal stent. Patients were treated in the hospital for an average of 5.4 days. No patients developed clinical signs of sepsis, and all were discharged tolerating a soft diet. Follow-up data were obtained for seven of nine discharged patients (range 152 to 263 days). None developed signs or symptoms of infection or recurrent dysphagia. Immediate placement of a coated self-expanding metal stent is an effective treatment for iatrogenic perforation of an obstructing esophageal malignancy. (J GASTROINTEST SURG 2003;7:715–720)

KEY WORDS: Esophageal neoplasms, esophageal perforation, stents, dilatation

Perforation of an esophageal cancer is a morbid event, and management of perforated esophageal malignancy is controversial. Although free esophageal perforation in the absence of cancer is generally managed surgically,[1–3] patients with perforated esophageal cancer are often poor surgical candidates. Our institution cares for a large number of patients with obstructing esophageal cancer, most of whom present for care with advanced disease and relative contraindications to surgery. In this report we describe our experience with placement of a self-expanding metal stent (SEMS) for the treatment of perforated esophageal cancer. This nonoperative therapy may be a useful treatment option for patients who have iatrogenic perforation of an advanced esophageal malignancy.

MATERIAL AND METHODS

We reviewed the records of all patients with dysphagia and esophageal cancer who were treated with esophageal dilatation at Tenwek Hospital between July 1998 and June 2001. Patients were identified from the hospital's endoscopy database. The outpatient and inpatient records of those suffering iatrogenic perforation were reviewed, and patients were visited to obtain follow-up information.

During the 36-month period, 492 dilatations were performed in 374 patients with dysphagia and obstructing esophageal malignancies. In the vast majority of cases, endoscopy and dilatation was carried out as an outpatient procedure using topical anesthesia with or without intravenous sedation. Prophylactic antibiotics were not routinely given. All procedures were performed without fluoroscopy, which was unavailable. Dilatation was performed with tapered dilators (Savary-Gilliard; Wilson Cook Medical, Winston-Salem, NC) passed over a guidewire. In almost all cases the endoscope would not pass through the malignant stricture, and a soft-tipped 0.035-inch guidewire (Amplatz SuperStiff or Tracer Wire; Wilson Cook Medical) was placed across the stricture under endoscopic control as previously described.[4] If difficulty or resistance was encountered

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when passing the guidewire, a chest radiograph was obtained to confirm proper placement of the guidewire prior to dilatation. Dilatation was generally performed to a diameter of between 36 and 48 F. Endoscopy was repeated immediately after dilatation to assess results. Some patients undergoing uncomplicated dilatation also had a SEMS placed, for palliation of their malignant dysphagia. Patients undergoing dilatation were observed for signs and symptoms of perforation prior to discharge.

Perforation was diagnosed in 10 cases (2% of dilatation procedures), including two cases mentioned in a previous report of our stent placement technique.[4] Mean patient age was 60 years (range 40 to 86 years). Tumors were located in the middle (7 cases) and distal (3 cases) esophagus. In five cases the perforation was seen endoscopically, immediately after dilatation, as a tear in the esophageal wall with visible mediastinal tissue. Five patients developed subcutaneous emphysema. Chest radiographs showed pneumomediastinum in all 10 cases, pneumothorax in two cases, and pneumoperitoneum in one case. Most perforations were suspected within 10 minutes, and all were diagnosed within 1 hour of dilatation.

Nine patients were managed endoscopically. The first underwent endoscopically directed placement of a nasomediastinal tube through the perforation and surgical placement of gastrostomy and jejunostomy tubes. A contrast study through the nasomediastinal tube showed an 8 cm mediastinal collection without communication to the pleura. A follow-up contrast study while on intravenous antibiotics showed a smaller collection. A noncoated SEMS was placed under endoscopic guidance on the fourteenth day. A noncoated stent was chosen to allow drainage of the residual collection back into the esophagus.

Eight patients underwent immediate placement of a coated SEMS under endoscopic control once perforation was suspected. Patients received either a coated Esophageal Wallstent II or a coated 28 mm/23 mm Ultraflex stent (Boston Scientific, Natick, MA) of sufficient length to bridge the perforation and the tumor. Coated stents were used for immediate stenting with the goal of sealing the perforation and preventing further mediastinal contamination. All stents were placed as previously described.[4] Chest radiographs were obtained after stent placement as shown in Fig. 1. All patients were treated with intravenous antibiotics followed by oral antibiotics. The two patients with pneumothorax received chest tubes. All patients were begun on liquid diets within 48 hours of stent placement and advanced to a soft diet.

The one patient with a pneumoperitoneum was taken to the operating room for exploratory laparotomy. He was found to have an unresectable gastroesophageal junction tumor, and no discrete perforation could be identified because of the bulky nature of the tumor. He was treated with omental patching of the presumed area of perforation.

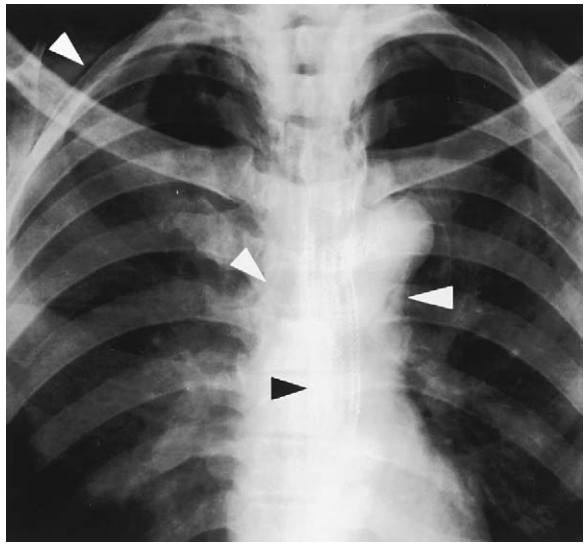

Fig. 1. Chest radiograph following immediate stent placement for iatrogenic perforation of a midesophageal carcinoma. Air is present in subcutaneous tissues and adjacent to the trachea and aorta (*white arrowheads*). An expandable stent has been placed across the perforated tumor (*black arrowhead*).

RESULTS

The nine patients managed endoscopically were treated in the hospital for an average of 5.4 days (range 1 to 17 days). Two patients had transient fever, none developed clinical signs of sepsis, and all were discharged tolerating a soft diet. After discharge, two of these patients who lived in distant parts of Kenya were lost to follow-up. Of the remaining seven patients, none developed signs or symptoms of sepsis or abscess. Five were followed to the time of their death from progressive cancer at a mean of 229 days after dilatation and suspected perforation (range 192 to 263 days), and two are alive at 152 and 216 days, respectively. At the last follow-up visit, all patients were eating a soft diet without difficulty. The one patient treated with laparotomy and omental patching developed progressive sepsis and died 7 days after operation.

DISCUSSION

Perforation of esophageal malignancy is a life-threatening complication, and the management of perforated esophageal cancer is controversial. Esophageal perforation is often managed surgically using

either primary repair, drainage with or without diversion, or resection with or without immediate reconstruction. Early recognition and prompt treatment are the most important factors influencing outcome.[1–3,5–10] Series describing surgical treatment of perforated esophageal cancer have either focused on surgical drainage and diversion alone[2] or described emergent resection of relatively early-stage cancers.[8] Patients with advanced esophageal cancer are often poor operative candidates and are best served by therapy that treats both their perforation and their dysphagia. We found that immediate placement of an esophageal SEMS was an effective treatment for iatrogenic perforation of esophageal cancer and also provided good-long-term palliation of dysphagia.

Esophageal perforation is definitively diagnosed by esophageal contrast studies, and only one of our patients had a contrast study confirming the presence and extent of perforation. Both our available resources and our management strategy precluded contrast studies prior to immediate stent placement. Occasional patients may develop pneumomediastinum after esophageal dilatation in the absence of radiographically demonstrable esophageal perforation. Nevertheless, we believe that most if not all of our patients had perforations. In half of the patients mediastinal tissue was seen during repeat esophagoscopy after dilatation, and other patients had subcutaneous air and/or pneumothorax in addition to mediastinal air on chest radiographs. We considered these findings to be indications for immediate stent placement. Contrast studies delineate the presence and extent of leakage but could further contaminate the mediastinum and would have delayed stenting considerably.

Nonoperative management of esophageal perforation is well accepted in some clinical situations. Cameron et al.[6] proposed the following criteria for the nonoperative management of intrathoracic esophageal disruption: (1) the esophageal disruption should be contained within the mediastinum or between the mediastinum and visceral lung pleura; (2) the cavity should drain back into the esophagus; (3) minimal symptoms should be present; and (4) there should be minimal evidence of clinical sepsis. These criteria have been frequently quoted and have become the standard of care for many surgeons managing patients with this potentially morbid condition. Other investigators[10–16] have added the following considerations: (1) the perforation should have occurred recently; (2) there should have been no food ingestion between injury and diagnosis; and (3) the perforation should not be in or proximal to a tumor or in the abdomen.

Some of our cases may have violated Cameron's criteria for nonoperative management. For instance, our patients with pneumothorax may have had a disruption that went beyond the mediastinum and would not have drained back into the esophagus. Nevertheless, immediate placement of a coated stent was an effective therapy, and neither sepsis nor abscess was observed during follow-up. The extent of disruption may not be a key factor guiding therapy if the perforation is immediately and successfully sealed by stent placement. A contrast study after stenting would be useful to confirm adequate occlusion of the perforation site.

This report differs from many published series of esophageal perforation because of the high prevalence of esophageal squamous cell cancer in southwestern Kenya. Our patients were a relatively homogeneous group with advanced malignant disease and severe dysphagia, most of who were not surgical candidates (because of advanced age, extreme cachexia, or metastatic disease). All patients in this report had had no oral intake for at least 8 hours prior to their dilatation and perforation; thus mediastinal contamination by food material was extremely limited. Furthermore, perforations were uniformly diagnosed quickly, with most recognized within 10 minutes. Finally, the majority of patients had bulky, large tumors. Jones and Ginsberg[7] stated that nonoperative therapy is best applied in the case of "small perforations after bougienage of peptic stricture or achalasia or after sclerosis of esophageal varices, because the presence of periesophageal fibrosis can limit contamination of the mediastinum." In our patients mediastinal contamination may have been limited by the bulk of the tumor itself and the surrounding desmoplastic response.

Treatment results after iatrogenic esophageal perforations vary tremendously with mortality rates between 0% and 84%.[14,17–20] This wide variation seems primarily the result of the very heterogeneous nature of the patient populations reported with regard to etiology of perforation, underlying condition of the esophagus, and treatment variability. Primary surgical repair of iatrogenic esophageal perforations provides excellent long-term results with low morbidity, particularly when perforations are recognized and treated early.[7,18,21] However, this form of treatment seems unreasonable in most patients with underlying esophageal malignancies. In these patients perforation typically occurs in the tumor itself, and primary surgical repair would be likely to fail. Emergency esophageal resection has been advocated for esophageal perforation, particularly when underlying esophageal disease is present.[1,3,8] However, very few patients with esophageal malignancy were included in any of these series. The few patients who did have

perforated esophageal cancers and underwent emergency resection, in general, had early-stage lesions.[8] Emergency resection in patients with advanced malignancies seems unwise. Furthermore, placement of an SEMS does not exclude a patient from the possibility of future resection. We have successfully performed resections in two patients who had undergone previous placement of an SEMS for malignant obstruction. In both cases the patients' physiologic status and cachexia improved markedly after stenting and 6 weeks of adequate oral diet, thereby prompting surgical resection.

Several other investigators have reported the use of endoluminal prostheses to treat iatrogenic perforation of esophageal malignancies. Most series provide little information on either early mortality or long-term outcome. Wesdorp et al.[9] described 34 patients in whom perforation had occurred during dilatation of esophageal tumors. In 10 cases plastic esophageal prostheses were placed immediately, and in the remaining 24 cases a prosthesis was placed within 4 to 7 days. There were two early deaths. Long-term survival and quality of swallowing were not described. Morgan et al.[22] used coated metallic endoprostheses in the management of 19 patients with perforated esophageal cancers. Mean survival was 91 days with a range of 11 to 370 days, and it is unclear how many deaths were early and caused by the perforation. Nicholson et al.[23] described the use of coated SEMS in eight patients who suffered perforation of esophageal cancers 24 hours earlier during attempted endoscopic Atkinson tube placement. There were no reported immediate complications or deaths, and survival rates were not reported. Liedman et al.[24] placed covered SEMS in four patients with perforations after dilatation procedures, most of whom subsequently underwent elective esophagectomy. Finally, Watkinson et al.[25] used covered SEMS in six patients who had perforation of esophageal malignancies during endoscopic laser treatment. One patient died 16 days after stenting, and overall survival was 49 days (range 16 to 80 days). The average hospital stay in these studies varied from 4 to 10 days.

It is unclear whether our results would extend to patients with early-stage esophageal cancer or benign esophageal strictures who suffer iatrogenic perforation. Most patients with highly symptomatic, circumferential esophageal malignancies requiring dilatation have locally advanced tumors such as those treated in this series. Our patients did not receive radiation therapy, and controversy exists regarding the role of stenting in the setting of radiation therapy.[26,27] It is unclear whether our patients would have recovered with medical management alone, without stent placement. Our patients all had severe dysphagia and would have been unable to nourish themselves without a palliative intervention such as stent placement, even if medical management of their perforation had been successful.

CONCLUSION

When perforation of an esophageal cancer is diagnosed shortly after endoscopic dilatation of a locally advanced esophageal cancer, immediate endoscopic placement of a coated, self-expanding metal stent is an effective therapy. Stent placement can treat the perforation, palliate dysphagia, and extend the life of most patients, and should be considered the treatment of choice, particularly in patients who are poor surgical candidates.

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Commentary

White et al. present provocative data concerning the effectiveness of nonoperative treatment of iatrogenic perforation of the esophagus in a unique population of patients. Ten of 492 patients undergoing palliative dilatation for bulky, advanced squamous cell carcinomas suffered iatrogenic esophageal perforation. Nine patients were effectively treated with expandable stents and antibiotics. Remarkably, two patients presented with pneumothorax, indicating that the perforation was not contained in the mediastinum. A chest tube was placed in these patients. All patients were diagnosed early (10 minutes to 1 hour after dilatation), presented with extensive tumors, and were poor surgical candidates. An additional patient with perforation of the distal esophagus and free peritoneal air was treated operatively, but died after omental patching.

Nonoperative treatment of perforated esophagus has been advocated in select patients in whom the leak is contained in the mediastinum with drainage back into the esophagus, the perforation is recent and not proximal to the tumor, and the patient has minimal symptoms and no signs of sepsis. Patients in this study did not meet all of these criteria challenging the current paradigm. Rather, nonoperative treatment was chosen because of the lack of medical resources and the poor condition of the patients. The results are therefore remarkable, considering that these patients were not optimal candidates for nonoperative therapy and had extensive disease, obstructing lesions, and, likely, poor nutrition.

However, before this practice is widely adopted, several caveats of the study must be understood. The sample size was small and two patients were lost to follow up. Outcomes would have been markedly different if one or both of the patients had septic complications after discharge. There were no comparison groups; the outcome of these patients, if they were treated with antibiotics alone or with surgery, is not known. It is also not clear whether immediate stenting is reasonable for patients who are acceptable surgical candidates. Minimal imaging studies were obtained; consequently the characteristics of the perforations before and after treatment are not known. Such data are clearly needed to define and revise the criteria for nonoperative therapy, if immediate stenting is truly more widely applicable to patients with esophageal perforation than previously thought. Therefore the results of this study are not definitive and, at best, only suggest an increased role for immediate stenting after iatrogenic perforation.

It should also be pointed out that all the patients successfully treated had large bulky tumors in the midesophagus, which the authors argue localized the perforation. If that is true, stenting may not be effective if lesions are smaller, located in the distal esophagus, or adenocarcinomas rather than squamous cell carcinomas. None of the patients in this study were treated with radiation or chemotherapy, modalities that are likely to be used throughout the world. These therapies alter the ability of the tumor to "seal" the perforation or the ability of the host to deal with the infectious complications that might ensue. Therefore the results from this report cannot be automatically extrapolated to the general treatment

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of esophageal carcinoma, which presents and is treated very differently in other health care systems. Finally, the use of immediate stenting for iatrogenic perforation in patients who have benign disease is not justified by the reasoning of these investigators because there is no bulky lesion to seal the perforation.

In summary, the data presented are quite intriguing and suggest an expanded role for immediate stenting of iatrogenic perforations of the esophagus with coated (and maybe noncoated) stents. However, the exact groups of patients who benefit from this technique, which is a prerequisite if this treatment is to be widely applied to patients with esophageal perforation, are not clearly defined. Further controlled trials are needed before the technique replaces standard approaches to this difficult problem. Such studies may now be warranted.

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Short Esophagus or Bad Dissected Esophagus? An Experimental Cadaveric Study

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Short esophagus is defined as the inability to reduce the gastroesophageal junction below the diaphragm. One of the factors responsible for this inability can be inadequate esophageal mobilization. We evaluated esophageal lengthening achieved by means of dissection in a cadaveric model. Fifty-one cadavers were dissected (27 transthoracically and 24 transhiatally). Abdominal esophageal length was assessed before and after dissection of the esophagus from the hiatus to the carina. In the transthoracic group, a mean of 1.7 ± 1.3 cm (range 0.3 to 5.0 cm) was gained with dissection. In the transhiatal group, a mean of 1.8 ± 0.8 cm (range 0 to 3.0 cm) was gained with dissection. In a comparison of results of transthoracic and transhiatal approaches, the difference was not statistically significant. We concluded that a significant increase in esophageal length was achieved after dissection; however, the access route (thorax or abdomen) did not influence the results. (J GASTROINTEST SURG 2003;7:721–725)

KEY WORDS: Esophagus, dissection, cadaver, thorax, abdomen

One of the most controversial topics in gastroesophageal reflux surgery is the short esophagus. Some experienced surgeons deny its existence, whereas others overemphasize it. It is hard to believe that so many different techniques have been created and used to treat a disease that some claim does not exist. However, it is also hard to imagine that in a series of more than 3500 patients, not a single case of short esophagus was found.[1]

Many factors can account for an inability to reduce the gastroesophageal junction below the diaphragm, but inadequate esophageal mobilization is perhaps the most significant. Belsey[2] claimed that esophageal lengthening procedures are "an excuse for not mobilizing the esophagus" and the problem is that surgeons are "too lazy to mobilize the esophagus adequately." In an experimental cadaveric study, we attempted to determine the degree of esophageal lengthening that can be achieved with dissection.

MATERIAL AND METHODS

A total of 51 fresh human cadavers were randomly divided in two groups: transhiatal and transthoracic. Autopsies had been performed on all of these cadavers in the office of the São Paulo Medical Examiner. Cadavers with hiatal hernia or evidence of thoracic or abdominal trauma were excluded from the study.

The transhiatal group consisted of 24 cadavers (19 males; mean age 43.3 years, mean height 168.3 cm). The transthoracic group consisted of 27 cadavers (19 males; mean age 45.7 years, mean height 163.1 cm). The ethics committees of the Federal University of São Paulo and the São Paulo Medical Examiner's Office approved the study.

Initial Measurements

Abdominal esophageal length was measured through a median laparotomy. The His angle (border of the serosa of the stomach with the esophagus) and the highest part of the left abdominal margin of the hiatus were used as landmarks, as previously described by Gatzinsky and Bergh.[3] The esophageal segment from the hiatus to the carina was measured through a seventh left space thoracotomy.

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Allocation

Cadavers were randomly assigned to one of two groups (transhiatal or transthoracic) after the initial measurements. Randomization was accomplished using "Random Numbers Generator" software (even numbers were allocated to the transhiatal group and uneven numbers to the transthoracic group). Randomization took place in the autopsy room, and a hand-held computer was used.

Dissection of the Esophagus

In the transhiatal group, the esophagus was dissected through the abdomen. The phrenoesophageal membrane was opened, and the esophagus was dissected using digital manipulation through the widened esophageal hiatus to the carina. In the transthoracic group, dissection was performed through a left thoracotomy. The infracarinal bronchial vagal branches were divided. In both groups the vagal nerves were preserved and kept in contact with the esophagus.

Final Measurement

After dissection, abdominal esophageal length was measured one more time through the laparotomy without any traction or tension.

Statistical Analysis

Values are expressed as mean ± standard deviation, median (range), and 95% confidence interval (CI). A value of $P < 0.05$ was considered significant. Student's *t* test, Fisher's exact test, and Pearson and Spearman correlation coefficients were used where appropriate. Ideal sample calculation (SISA; Simple Interactive Statistical Analysis Software, Hilversum, The Netherlands), considered $\alpha = 0.05$ and $\beta = 0.8$. Data from the first 10 cadavers in each group were used as parameters for calculation because of the lack of previously published data in the literature. An ideal sample consisted of 51 cases.

RESULTS

Age, sex, and height were statistically similar in the two groups. Initial measurements were also statistically similar between groups (Table 1).

In the transthoracic group, a mean increase of 1.7 ± 1.3 (median 1.2 cm [range 0.3 to 5.0 cm; 95% CI 1.2 to 2.0]) was gained after dissection (esophageal elongation). For each 1 cm of mediastinal esophagus dissected, there was a mean increase in length of 0.2 ± 0.2 (median 0.2 cm [range 0.03 to 0.7 cm; 95% CI 0.1 to 0.2]).

In the transhiatal group, a mean increase of 1.8 ± 0.8 (median 1.9 cm [range 0 to 3.0 cm; 95% CI 1.4 to 2.2]) was achieved with dissection (esophageal elongation). For each 1 cm of mediastinal esophagus dissected, there was a mean increase in length of 0.2 ± 0.08 cm (median 0.2 cm [range 0 to 0.3; 95% CI 0.1 to 0.2]). No correlation between the extent of the dissection (hiatus-carina segment) and the extent of esophageal elongation was noted (Fig. 1). A comparison of esophageal elongation between the transthoracic and transhiatal groups did not show any statistically significant difference ($P = 0.64$).

Sex did not influence abdominal esophageal length, hiatus-carina segment length, or esophageal elongation. The men were taller than the women (Table 2). Age did not influence esophageal elongation results (Table 3).

DISCUSSION

There is no universal definition of short esophagus. Large[4] defined short esophagus is an esophagus that, at operation, is not long enough to allow the esophagogastric junction to lay permanently below the diaphragm. If that definition is accepted, it becomes illogical to believe in a nonoperative diagnosis of short esophagus and to decide on a management approach without dissecting the esophagus. Several investigators (Table 4) were able to place the esophagus in an abdominal position in a significant number of patients who preoperatively were believed to have a short esophagus.

In most reports the level of dissection of the esophagus is not described. Some investigators (most of them thoracic surgeons) adopt the aortic arch[6,13] or the inferior pulmonary vein[3,14] as the limit of dissection. Laparoscopic surgeons,[12] because of the superior

Table 1. Group demographics

Group*	Sex (males/females)	Age (yr)	Height (cm)	Abdominal esophageal length (cm)	Hiatus-carina segment (cm)
Transthoracic (n = 27)	19/8	45.7	163.1	3.9	8.2
Transhiatal (n = 24)	19/5	43.3	168.3	3.0	8.6

*There were no statistical differences between the two groups.

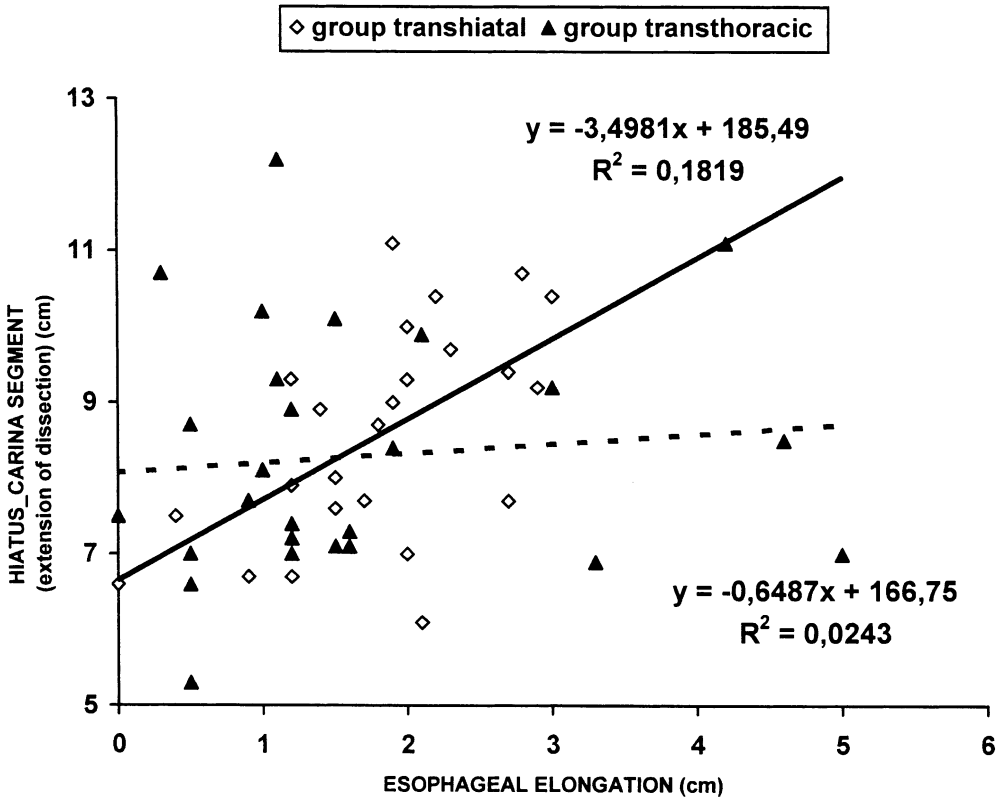

Fig. 1. Effect of extension of dissection (hiatus-carina segment length) and esophageal elongation in the transhiatal and transthoracic groups. Note that there is no correlation between the two groups.

anterior view, adopt the carina as the proximal limit of dissection. We chose the carina to be the upper limit of dissection in our study because it is a level that is easily reached from either the abdomen or the thorax.

Controversy also exists with regard to the incidence of short esophagus and differences in dissection techniques based on whether a thoracic or a transhiatal route is selected. In this era of minimally invasive surgery, the abdominal route is preferred by most surgeons because they use a laparoscopic approach.[15,16] Abdominal surgeons argue that the transthoracic route limits the ability to mobilize and adequately anchor the esophagus in the abdomen;[1] they maintain that it is easier to gauge esophageal length through the abdomen,[17] and with an abdominal approach the surgeon can use a combination of visual inspection and clinical assessment of the degree of tension on the esophagus after reduction of the gastroesophageal junction.[18] Thoracic surgeons, however, claim that esophageal mobilization is better accomplished through the thorax,[7,19] probably because it is easier to recognize tension on the esophagus from the thoracic side of the hiatus.[20]

Concerning the laparoscopic approach, some investigators believe that an unrecognized short esophagus is responsible for an increased number of anatomic failures after laparoscopic fundoplication,[21] suggesting that the presence or suspicion of a short esophagus should be a contraindication for laparoscopic fundoplication.[16] There are a number of reasons why critics of this method claim that the ability to determinate adequate esophageal length is limited

Table 2. Effect of sex on height, abdominal esophageal length, hiatus-carina segment length, and esophageal elongation

	Females (n = 13)	Males (n = 38)	*P* value
Height	154.4 ± 5.4	169.4 ± 8.2	<0.0001*
Abdominal esophageal length	3.7 ± 0.8	3.4 ± 1.5	0.46
Hiatus-carina segment length	7.9 ± 1.4	8.6 ± 1.5	0.21
Esophageal elongation	1.9 ± 1.4	1.7 ± 0.9	0.54

Values are expressed as mean ± standard deviation. (Note: only height was influenced by the sex.)
*Statistically significant.

Table 3. Effect of age on esophageal elongation

	Age <44 years (n = 24)	Age >45 years (n = 19)	*P* value
Esophageal elongation	1.5 ± 0.6	1.9 ± 1.3	0.32

Values are expressed as mean ± standard deviation. Note: There was no statistically significant difference comparing age greater than or less than the mean age in all cases [n = 5].

with laparoscopy.[22] There is increased difficulty in dissecting the esophagus posteriorly because of periesophagitis[23]; there is a tendency during laparoscopy to overestimate the intra-abdominal length of the esophagus on account of the downward tension that is placed on the esophagus by a rigid Bougie and a Penrose drain encircling the esophagus, and the anterior tension in an oblique hiatus because the pneumoperitoneum elevates the diaphragm, which is already relaxed as a result of anesthesia.[24,25]

Our results did show a significant increase in abdominal esophageal length after dissection. Although the importance of adequate esophageal mobilization cannot be denied, other factors should also be considered inasmuch as there did not seem to be a correlation between the extent of the dissection and degree of esophageal elongation, and reduction of a 5 cm hiatal hernia would require a dissection of 25 cm of the thoracic esophagus according to our results. The following putative factors may also be involved: (1) pseudoshortening of the esophagus due to an "accordion-like" folding of the esophagus in the mediastinum[21,23]; (2) compensatory elasticity of the esophagus, related to height, as proposed by Awad et al.[23,26]; and (3) spastic contraction of the longitudinal layer of the esophagus.[27]

The access route (transthoracic or transhiatal) did not influence our results. Most likely the experience gained from esophageal mobilization through the abdomen with transhiatal esophagectomy and surgical treatment of achalasia caused by Chagas disease influenced our results in favor of the transabdominal route. We also agree with Watson and DeMeester,[28] who reported that freeing of the cardia from the diaphragmatic hiatus is difficult to perform through a thoracic approach.

Table 4. Apparent short esophagus reduced at operation in different series on antireflux surgery

Reference	Apparent short esophagus reduced at operation (%)
Mittal et al. (2000)[5]	26.6
Collard et al. (1991)[6]	31.1
Gastal et al. (1999)[7]	43.1
Ritter et al. (1998)[8]	50.0
Awad et al. (2001)[9]	74.0
Johnson et al. (1998)[10]	74.0
Awad et al. (2000)[11]	79.0
Swanstrom et al. (1996)[12]	80.0

CONCLUSION

This report did answer the question of whether the condition termed short esophagus actually exists. Our experiments could be criticized because we dissected normal esophagi; that is, hiatal hernias, gastroesophageal reflux disease, and/or associated complications such as stricture were absent. Also, variables other than esophageal mobilization may be responsible for the problem of short esophagus. However, our results demonstrate that significant elongation of the esophagus is possible with full esophageal dissection.

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Boerhaave's Syndrome: Primary Repair vs. Esophageal Resection—Case Reports and Meta-Analysis of the Literature

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Boerhaave's syndrome is a life-threatening disease with a high mortality. With regard to the heterogeneity of treatment strategies, no comparative studies exist and recommendations remain controversial. Seventeen cases of Boerhaave's syndrome operated on between 1989 and 2000 at our hospital were reviewed retrospectively to compare the time period between perforation and diagnosis, and the morbidity and mortality among the different treatment options. In addition, we conducted a meta-analysis of the literature including all series containing five or more patients and compared the findings with our own data. Our patients with a perforation history of less than 12 hours showed significantly fewer signs of sepsis compared to patients with a history of more than 12 hours. In a comparison of patients with primary repair vs. patients treated with esophageal resection or an exclusion operation, no differences were found. In the literature, patients with a long period of perforation (more than 24 hours) were treated more often with an esophageal resection than patients with primary repair. In cases of Boerhaave's syndrome, primary suturing of the esophageal perforation should be reserved only for those patients presenting within 12 hours after perforation. In all other cases, depending on the extent of the tissue damage, a two-stage esophageal resection with cervical esophagostomy and gastrostomy is recommended as the safest treatment. (J GASTROINTEST SURG 2003;7:726–734)

KEY WORDS: Boerhaave's syndrome, spontaneous esophageal rupture, operative treatment, meta-analysis

Spontaneous esophageal perforation—Boerhaave's syndrome[1]—is a life-threatening injury associated with an overall mortality rate ranging from 20% to 75% depending on the onset of treatment.[2–5] Approximately 90% of ruptures occur in the left lower esophagus above the diaphragm, and only a few occur in the middle third or on the right side. Contamination of the mediastinum and pleural cavity with microorganisms, gastric acid, and digestive enzymes results in mediastinitis, sepsis, and multiple organ failure that is lethal in most cases if left untreated.[6] The "classic" triad of symptoms leading to the diagnosis of Boerhaave's syndrome includes chest pain, repeated vomiting, and subcutaneous emphysema. These "classic" symptoms may not be present in all patients, therefore delaying the diagnosis in a substantial number of patients (>50%).[4,7] To summarize, Boerhaave's syndrome requires awareness of the condition, early diagnosis, and effective immediate aggressive treatment, because a clear relationship exists between the time lapse from perforation to the onset of treatment and the rate of survival.[2] Surgical treatment should be instituted as early as possible. Because of the rare diagnosis and the small number of published series, no accepted standard treatment has been established, and recommendations in the literature remain controversial.[5] To readdress the question of staged treatment of Boerhaave's syndrome, we reviewed our cases retrospectively and performed a meta-analysis of the existing literature.

PATIENTS AND METHODS

This retrospective analysis includes 17 patients treated for Boerhaave's syndrome between October

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1989 and November 2002 at the Department of Surgery, University Hospital, Homburg/Saar, Germany. Only patients with spontaneous rupture of an otherwise normal esophagus were included in our series. Medical records were reviewed (Table 1) to identify patient characteristics, presenting symptoms, initial treatment, subsequent procedures, hospital stay, and long-term outcome. Particular attention was given to the time period between perforation and diagnosis.

In addition, a meta-analysis of all published series regarding Boerhaave's syndrome and spontaneous esophageal rupture was carried out. MEDLINE and PubMed searches as well as other registries of medical literature identified these studies. All series with at least five cases of Boerhaave's syndrome were compared with our own data (Table 2).

Statistical Analysis

Differences between our own patient data with regard to sex, age, time period, clinical signs, location of the perforation, treatment (with or without esophagectomy), and subsequent procedures (lavage, decortication, drainage, or insufficiency of the anastomosis or resection), intensive care unit stay, hospitalization, and outcome were analyzed using a Mann-Whitney U test or Fisher's exact test. Statistical analysis of the data in the literature comprised a sample size calculation to detect differences in surgical outcomes between the procedures: primary repair or T-drainage vs. esophageal resection or exclusion operation.

A value of $P < 0.05$ was considered statistically significant. Odds ratio was performed with a power of 0.9 and an α of 0.05. Ninety-five percent confidence intervals were shown along with the upper and lower limits. The SPSS computerized statistical analysis system (Chicago, IL) was used.

RESULTS

The ages of the patients (1 female and 16 males) ranged from 43 to 76 years. The presenting symptoms and signs varied widely as shown in Table 1. Twelve of the 17 patients included vomiting as one of their complaints. Chest pain at any time was noted in 10 patients and epigastric pain in nine patients. Eight patients complained of dyspnea. At the time of clinical examination, subcutaneous emphysema was seen in 11 patients. Ten patients showed signs of septic shock (fever, low blood pressure, high inflammation values) on admission to the clinic. Esophageal rupture was confirmed by standard chest x-ray examination (pneumothorax or pleural effusion in 12 patients), contrast study (14 patients), CT scan (5 patients), or endoscopy (10 patients). Six patients were treated within 12 hours of the onset of symptoms (total of 8 patients within 24 hours), whereas another nine patients had a delay in diagnosis of more than 24 hours, ranging from 2 to 10 days. Three patients with a time interval of more than 12 hours were treated conservatively with drainage of the left and/or right thorax cavity and monitoring in the intensive care unit with artificial respiration (Nos. 8, 13, and 16), mostly before transfer to our surgery center. Surgery was done immediately after admission and diagnosis of esophageal perforation. In two patients (Nos. 1 and 5) the perforation was detected in the middle portion of the esophagus. Patients with a time period of less than 24 hours and no signs of mediastinitis were treated with a primary repair, whereas patients with a time period of greater than 24 hours or signs of mediastinitis were treated with esophageal resection or drainage. No conservative treatment was used at our hospital. Seven patients (Nos. 1 to 7) underwent primary repair with a cervical esophagostomy, gastrostomy or feeding jejunostomy, and drainage of the thoracic cavity (transthoracic esophagectomy [TTE]), with the exception of patient 3 who did not undergo esophagectomy. As a subsequent procedure, esophagectomy was performed in patients 11 and 17. Staged reconstruction of the alimentary continuity was performed months later. The other patients were treated with either primary repair, with or without flap or fundoplication, or T-drainage as described in Table 1. In 12 patients a subsequent operative procedure was necessary (lavage, decortication, and drainage in seven cases), and two patients (Nos. 2 and 13) required reoperation because of insufficiency of the anastomosis or suture line. Eleven patients recovered and were discharged from the hospital. Five patients died of multiorgan failure, and one patient died of cardiac shock.

For statistical analysis, patients were divided into the following subgroups, according to the different treatments (patients with a drainage operation as the primary procedure were excluded from this analysis): (1) patients with TTE or exclusion operation as a primary procedure (Nos. 1 to 7) vs. patients with primary repair (Nos. 8 to 14); (2) primary esophagectomy (Nos. 1 to 7) vs. other treatment (Nos. 8 to 17); and (3) esophagectomy also as a subsequent procedure (Nos. 1 to 7, 11, and 17) vs. no esophagectomy (Nos. 8 to 10 and 12 to 16). When all of these subgroups were compared, no statistical significance could be seen with regard to sex, age, time period, clinical signs, location of the perforation, subsequent procedures (lavage, decortication, drainage, or insufficiency of the anastomosis or resection), stay

Table 1. Clinical signs, operation, subsequent procedures and outcome of patients with Boerhaave's syndrome

Patient	Age (yr)	Time period*	Clinical signs	Treatment	Subsequent procedures	ICU stay (days)	Hospitalization (days)	Survival
1	46	5 days	Septic shock, dyspnea, epigastric pain, vomiting, emphysema	Left and right thoracotomy, TTE, decortication, laparotomy, feeding jejunostomy	Lavage, decortication, drainage	5		No
2	67	<12 hr	Thoracic pain	Laparotomy + right thoracotomy, transthoracic esophagectomy, splenectomy, esophago gastrostomy, drainage of the right thorax cavity	2× reoperation caused by insufficiency of the anastomosis: (1) primary repair, drainage; (2) resection of the anastomosis, cervical esophagostomy, feeding jejunostomy, cholecystectomy	18	37	Yes
3	56	10 days	Septic shock, dyspnea, thoracic pain, emphysema	Laparotomy, gastrectomy, closure of the distal esophagus, cervical esophagostomy, feeding jejunostomy	Diagnostic laparotomy, tracheotomy	48	57	Yes
4	49	3 days	Dyspnea, epigastric pain, vomiting	Laparotomy, transhiatal TTE, drainage of the left and right thorax cavity	Tracheotomy	28	30	Yes
5	76	<12 hr	Septic shock, thoracic pain, vomiting, emphysema	Laparotomy, transhiatal esophagectomy, cervical esophagostomy, feeding jejunostomy, drainage of the mediastinum		2		No
6	55	9 days	Septic shock, dyspnea, thoracic pain, vomiting, emphysema	TTE, decortication, drainage of the left and right thorax cavity	Lavage, decortication, drainage	20	24	Yes

(*continued*)

Table 1. Continued

Patient	Age (yr)	Time period*	Clinical signs	Treatment	Subsequent procedures	ICU stay (days)	Hospital-ization (days)	Survival
7	43	2 days	Septic shock, dyspnea, epigastric pain, vomiting, emphysema	Right thoracotomy, transthoracic TTE, decortication	Lavage, decortication, drainage	55	65	Yes
8	68	4 days	Septic shock, dyspnea, thoracic pain, vomiting, emphysema	Left thoracotomy, primary repair (2 layer), intercostals flap, decortication, drainage of the left and right thorax cavities		7		No
9	44	<12 hr	Dyspnea, thoracic and epigastric pain, vomiting, emphysema	Laparotomy, primary repair (1 layer), decortication, drainage of the left thorax cavity		11	24	Yes
10	60	<12 hr	Thoracic pain, vomiting	Laparotomy, primary repair (1 layer), decortication, fundoplication	Wound debridement caused by infection	4	40	Yes
11	67	<12 hr	Hypodynamic shock, epigastric pain, vomiting	Laparotomy, primary repair (1 layer), decortication	Transhiatal esophagectomy, cervical esophagostomy, drainage	24	93	Yes
12	65	<24 hr	Septic shock, thoracic pain, vomiting, emphysema	Left thoracotomy, primary repair (2 layer), intercostal flap, decortication, drainage of the left thorax cavity		2		No
13	72	<24 hr	Septic shock, dyspnea, epigastric pain	Laparotomy, primary repair (1 layer), gastrostomy, splenectomy, drainage of the left thorax	2× decortication, drainage, suture feeding jejunostomy, tracheotomy, cholecystectomy	46	57	Yes
14	50	<12 hr	Thoracic and epigastric pain, emphysema	Laparotomy, primary repair (1 layer), decortication, fundoplication, drainage of the left thorax cavity	Wound debridement caused by infection	14	17	Yes

(*continued*)

Table 1. Continued

Patient	Age (yr)	Time period*	Clinical signs	Treatment	Subsequent procedures	ICU stay (days)	Hospitalization (days)	Survival
15	51	10 days	Thoracic pain, vomiting, emphysema	Left thoracotomy, T-drainage, decortication, drainage of the left thorax cavity		24	61	Yes
16	66	7 days	Septic shock, thoracic pain, emphysema	Left thoracotomy, T-drainage, decortication	Decortication, cholecystectomy, feeding jejunostomy, tracheostomy	35	42	No
17	72	2 days	Septic shock, epigastric pain, vomiting	Left thoracotomy, decortication, drainage of the right and left thorax cavities	TTE, tracheostomy	20		No

*Time period between perforation and treatment.
TTE = right thoracotomy, transthoracic esophagectomy, cervical esophagostomy, gastrostomy or feeding jejunostomy, and drainage of the thoracic cavity.

in the ICU, hospitalization, and outcome. With regard to the time period between the onset of symptoms and operation, no statistical significance could be shown when comparing patients with an early rupture (<24 hours) vs. patients with a late rupture (>24 hours). Patients with a time period of less than 12 hours (1 of 6) showed significantly fewer signs of sepsis ($P = 0.035$) than patients with a time period of more than 12 hours (9 of 11).

Meta-Analysis

Between 1970 and 2002, a total of 18 series reporting on Boerhaave's syndrome in five or more patients, which included a total of 227 patients, were published. One hundred forty-four patients were treated with primary repair (time period >24 hours: 42 of 144; mortality: 20 of 144), 46 patients with esophagectomy or an exclusion operation (time period >24 hours: 31 of 46; mortality: 9 of 46), and 37 patients with drainage alone or conservative therapy (time period >24 hours: 16 of 37; mortality: 12 of 37). With regard to the time between the onset of symptoms and subsequent treatment, patients with a long period (>24 hours) were treated more often with esophageal resection or exclusion operation (31 of 41) than patients with primary repair or T-drainage (21 of 77), with an odds ratio of 8.267 [lower limit: 3.458/upper limit: 19.762; $P \leq 0.001$]. Regarding the mortality rate, there was no difference between patients treated with esophageal resection or exclusion operation (9 of 28 patients) and those treated with primary repair (11 of 46 patients).

DISCUSSION

Since 1947, when Barrett described the first successful thoracotomy with primary closure of an esophageal perforation, approximately 1000 cases have been reported in the literature with varying treatments and outcomes.[8] Many of these published cases of Boerhaave's syndrome are included in articles on broader subjects (e.g., iatrogenic esophageal perforation, carcinoma), resulting in confusion about the therapeutic approach.[3] As shown by our cases, and in line with reports in the literature, only 50% to 70% of patients with Boerhaave's syndrome have the "classic" triad of symptoms including chest pain, repeated vomiting, and subcutaneous emphysema. Because of the lack of typical history and symptoms and early radiologic or endoscopic diagnostic evidence, nine of our patients had a delay of more than 24 hours in the diagnosis of Boerhaave's syndrome. In line with other publications, transfer of patients from other hospitals to our tertiary surgical center was frequently delayed, and patients received conservative treatment primarily. The general condition of the patient, the local condition of the esophagus, and the extent of soiling or injury to other organs determined the device or the surgical procedure. Prompt recognition and initiation of treatment

of esophageal perforations has long been recognized as being essential for a favorable outcome.[8–10] For determining a patient's prognosis, the interval between perforation and diagnosis and therapy seems to be crucial. The "golden time period" for successful therapy is within the first 24 hours. A treatment delay of more than 24 hours is associated with a higher incidence of complications and death.[9] Morbidity and mortality rates, usually the result of mediastinitis, rise dramatically after a time period of 24 hours. On the other hand, if the operation is performed within 24 hours, patients with Boerhaave's syndrome have a greater chance of complete recovery (Table 2). With regard to current treatment options in patients with Boerhaave's syndrome, a heterogeneity of management strategies has been debated in the literature,[5] in which only recommendations exist (levels of evidence 4 and 5). The esophagus has a specific anatomy with no mesentery or mesothelial cells. In cases of esophageal perforation, extreme edematous swelling of the tissue occurs, which increases progressively with time. The objective of any treatment of an esophageal rupture in patients with Boerhaave's syndrome must be the prevention of further soilage from the esophageal perforation, to eliminate subsequent infection, to restore the integrity of the gastrointestinal tract, and to maintain adequate nutrition. As reported in the literature, selected patients have been treated nonoperatively with conservative management: a nil oral regimen, nasogastric suction, pleural drainage, broad-spectrum antibiotics, and a feeding jejunostomy or total parenteral nutrition. However, treatment by drainage alone seems to be successful only in rare instances,[11] mostly cases of iatrogenic perforation.[12] These patients require careful monitoring and deterioration of their clinical condition requires crossover to operative management. Therefore we and others recommend aggressive resuscitation and immediate surgical repair in cases of Boerhaave's syndrome (see Table 2). Esophageal perforation is associated with high morbidity and mortality because the anatomic location of the organ predisposes patients to develop fatal mediastinitis and multiorgan failure.[6] Regardless of which operative technique is adopted, there is no doubt that it should be accompanied by thorough cleansing of the pleural cavity, debridement of devitalized tissue, relief of any distal obstruction, and expansion of the lungs by means of pleural drainage supplemented with elective ventilation, if necessary. Samples of pleural and mediastinal fluid for bacteriologic examination should be obtained to determine the appropriate antibiotic therapy, and adequate parenteral nutrition must be maintained.[13] Because of the initial severity of Boerhaave's syndrome and the high risk of postoperative complications, patients should always be monitored in the intensive care unit. When the diagnosis is established within 24 hours of perforation, immediate primary closure and wide drainage of the mediastinum continues to be the "gold standard" of treatment. Primary closure by a single or double layer of sutures via left or right thoracotomy,[14,15] with or without a well-vascularized pedicled tissue flap[3,10,16] or coverage by a fundoplication,[8,17] is recommended. Surgical access should be on the side of the perforation, although it is generally believed that exposure of the esophagus is better from the right side of the chest rather than from the left. The purpose of the thoracotomy is not only for surgical repair of the laceration but also for evaluation of the residual soilage in the affected pleural cavity. For successful primary treatment, the mucosal-submucosal layer must be clearly identified for an exact approximation. To prevent further leakage, testing of the suture line for tightness is recommended. Primary suturing followed by a tissue flap (pleural, muscle, diaphragmatic flaps, or Thal patch) is a technique that prevents further morbidity and possibly even death.[17] Some investigators also recommend a drainage gastrostomy,[15] whereas others prefer closure of the perforation around a T-drain.[18,19] With regard to our own patients, in the group with delayed perforation (>12 hours) a significant difference in signs of sepsis was present; we prefer a primary repair with continuous absorbable sutures followed by a tissue flap and wide drainage of the mediastinum and the contaminated pleural cavity only in patients who are seen within 12 hours of the onset of symptoms. Regarding the optimal surgical technique in cases of delayed perforation (time period >24 hours), details are debated in the literature. Some investigators suggest that primary repair of the esophagus with mediastinal drainage should be reserved for patients operated on within 24 hours of injury and recommend nonoperative management for patients with perforations who are seen late (more than 24 hours after injury),[14,20] taking into consideration that nonoperative management with simple drainage of the thoracic cavity requires a long hospital stay[14] and may result in high mortality (see Table 2). Most investigators believe that the esophagus should be preserved whenever possible (see Table 2). They recommend aggressive debridement and direct esophageal repair with a single or double layer of sutures with or without any additional operative procedure (e.g., flaps, gastrostomy) for all patients with Boerhaave's syndrome. All esophageal ruptures, irrespective of duration, should have primary suture closure in two layers reinforced with an omental flap. This procedure should

Table 2. All series with different therapeutic strategies for Boerhaave's syndrome ($n = \geq 5$ patients with Boerhaave's Syndrome in each series)

Reference	Year	No. of patients	Primary treatment	Time period <24 hr vs. >24 hr	Mortality	Recommended operation
Kollmar et al.	2003	17	3× drainage operation (1× TTE as a subsequent procedure)	0/3	2/3	
			7× primary repair (4× 1 layer, 2× 2 layer, 1× TTE subsequently)	6/1	1/7	TTE (esophagectomy), primary repair (<12 hr)
			7× TTE (1× exclusion)	2/5	3/7	
Maier et al.[9]	2001	14	5× primary repair	0/5	0/5	Primary repair, esophageal resection (critically ill patients)
			9× esophagectomy	2/7	2/9	
Lawrence et al.[15]	1999	21	2× conservative therapy	1/1	0/2	
			2× debridement, drainage	0/2	0/2	Primary repair up to 72 hr
			17× primary repair (single layer), drainage, gastrostomy	8/9	3/17	
Liu et al.[16]	1998	10	1× conservative therapy	—	0/1	
			1× partial esophagectomy	—	0/1	Primary repair, omentum pad, gastrostomy
			8× thoracotomy, primary repair, omentum pad, gastrostomy	—	2/8	
Brauer et al.[8]	1997	18	7× primary repair, fundoplication	7/0	1/18	Esophagectomy and staged reconstruction, primary repair via left thoracotomy
			11× esophagectomy	0/11		
Sabanathan et al.[10]	1994	5	5× primary repair (2 layers), omentum buttressing, drainage	1/4	0/5	Primary repair (2 layers) and omentum flap
Okitsu H et al.[20]	1993	8	2× conservative therapy	1/1	1/2	
			5× primary repair (2 layers)	2/1	2/5	Primary repair (<24 hr), drainage procedure (>24 hr)
			1× esophagectomy	1/0	0/1	
Salo et al.[21]	1992	8	8× primary repair	—	3/8	Primary repair, in severe cases esophageal exclusion or resection
Michel et al.[18]	1991	7	2× esophagectomy, gastrostomy	2/0	—	Primary repair to T-drainage
			5× primary repair or T-drainage	2/3		
Yellin et al.[14]	1989	6	3× primary repair	3/0	—	Primary repair (<24 hr), drainage alone (>24 hr)
			3× drainage alone	0/3		

(*continued*)

Table 2. Continued

Reference	Year	No. of patients	Primary treatment	Time period <24 hr vs. >24 hr	Mortality	Recommended operation
Arconada et al.[17]	1989	7	6× primary repair, fundoplication	—	—	Primary repair and fundal patch
			1× conservative therapy			
Pate et al.[3]	1989	34	4× conservative therapy, drainage	0/4	4/4	
			3× exclusion of the esophagus	1/2	10/30	Primary repair with pleural or intercostal muscle flap
			27× primary repair (20× pleural flaps)	25/2		
Hansen et al.[22]	1988	9	2× drainage alone	0/2	2/2	
			5× primary repair	3/2	4/5	Primary repair, exclusion operation in severe or >24 hr cases
			2× esophageal stapling, gastrostomy	1/1	2/2	
Graeber et al.[23]	1987	11	2× conservative therapy	2/0	0/2	
			7× primary repair	4/3	1/7	Primary repair + drainage (<24 hr)
			2× exclusion of the esophagus	1/1	0/2	
Malledant et al.[24]	1986	18	2× conservative therapy	—	—	
			4× exclusion of the esophagus			Primary repair (<12 hr)
			5× primary repair			
			7× drainage alone			
Walker et al.[13]	1985	14	2× conservative therapy	2/0	0/2	Primary repair + flap (<2 hr)
			12× primary repair (1 or 2 layers)	4/8	3/12	
Patton et al.[25]	1979	14	9× primary repair (1× + fundoplication)	5/4	1/9	
			4× gastro- and jejunostomy (exclusion)	0/4	2/4	
			1× no treatment	1/0	1/1	
Bobo et al.[26]	1970	6	3× conservative therapy	—	2/3	
			3× primary repair (2 layer)		0/3	

avoid multiple operations and a prolonged hospital stay.[3] Additionally, for perforations that go untreated for 72 hours, some investigators recommend a single-layer suture line with protective gastrostomy, combined with mediastinal drainage.[15] Even an older esophageal rupture can be treated successfully by primary suture, if the esophageal wall necrosis is not too extensive. However, the mortality rate associated with simple repair increases dramatically with increasing treatment delay. A high proportion of simple suture repairs leak. Walker et al.[13] suggested that operative debridement and initiation of adequate drainage may be the important factors in survival rather than the repair itself. In our opinion the recommendation of other investigators (see Table 2) that primary repair of the esophagus be done only within 24 hours after perforation should be reconsidered, and primary suturing should be reserved for patients with a perforation that is detected within the first 12 hours. In cases of severe destruction or necrosis of the esophageal wall, widespread mediastinitis, or hypodynamic shock, most investigators agree that an esophageal exclusion operation should be performed.[9,21] If the operation is delayed beyond 24 hours or a reperforation following direct repair cannot be sufficiently managed by drainage, exclusion

of the esophagus with suture of the perforation, wide thoracic drainage, creation of a loop or cervical esophagostomy, gastrostomy, and feeding jejunostomy are advocated.[8,22] Furthermore, transthoracic or transhiatal resection and staged reconstruction have been proposed by most investigators, with recommendations for esophageal resection in late cases.[8,21]

CONCLUSION

Without treatment, patients with esophageal rupture frequently die of mediastinitis. Because of the very small number of cases, no standard therapy has yet been developed. With the knowledge gained from recommended strategies (see Table 2) and our own experience, we believe that surgical treatment is usually required because the esophagus has a poor blood supply and the esophageal contents spill diffusely into the mediastinum. Primary suturing of the esophagus should be performed only in patients with an early perforation (within the first 12 hours). When continued mediastinitis, pleural contamination, and loss of saliva and gastric juice through the fistula has occurred, only esophageal resection can definitively eliminate the source of intrathoracic sepsis. Drainage alone fails to control sepsis.[9] Therefore, in cases of prolonged delay between rupture and diagnosis, esophageal resection with cervical esophagostomy and gastrostomy is advocated as the safest therapy.

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Infiltration of Antitumor Immunocytes Into the Sentinel Node in Gastric Cancer

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The sentinel node (SN) is regarded as the first drainage lymph node, and tumor cells are considered likely to directly affect the SN. However, few reports have identified differences between SNs and non-SNs in cancer patients. Subjects in this study included 27 patients with gastric cancer who underwent curative operation and intraoperative detection of SNs by radioisotope methods. The mean number of SNs was 3.2 (range 1 to 5). Degree of infiltration of natural killer cells, dendritic cells, MIB-1 labeling index, and CD3-ζ expression of lymphocytes in SNs and non-SNs were examined by means of immunohistochemical methods. Degree of infiltration was compared according to depth of invasion and between SNs and non-SNs. Patients with early-stage cancer displayed a greater degree of infiltration of MIB-1 labeling index and CD3-ζ expression than patients with pT2 or pT3 lesions ($P < 0.05$). The MIB-1 labeling index in SNs was significantly lower than that in non-SNs ($P < 0.05$). However, no significant difference was observed in infiltration of natural killer cells, dendritic cells, or CD3-ζ. Morphologic changes of dendritic cells in SNs were not definite. Our results suggest that SNs in gastric cancer might not be suppressed, unlike in breast cancer and melanoma. SN paralysis may depend on tumor- and organ-specific characteristics or exogenous stimulation from the gastric mucosa. Studies in progress will help to identify immunologic paralysis of the SN in various types of cancer. Attention must therefore be paid to organ specificity. (J GASTROINTEST SURG 2003;7:735–739)

KEY WORDS: Immunocytes, sentinel node, gastric cancer

The concept of sentinel lymph node mapping has already been introduced in surgery for tumors such as breast cancer and malignant melanoma.[1–3] The clinical benefit of sentinel node (SN) navigation surgery for gastrointestinal cancer has been discussed as well.[4,5] The concept of the SN is based on lymphatic flow from the primary tumor,[6] with the first regional lymph node infiltrated by migrating cancer cells considered to be the SN. Sentinel nodes and non-SNs seem to show immunologic differences.

Lymph nodes situated around the primary tumor are considered to function as an antitumor barrier, involving several types of immunocytes that exhibit an antitumor action as part of a host immunodefense.[7] We previously reported that tumor extension is negatively correlated with the infiltration of immunocytes into regional lymph nodes in node-negative gastric cancer.[8] The degree of immunocyte infiltration may reflect the antitumor function of regional lymph nodes.

Immunocyte infiltration of SNs has been reported to be distinctly different from infiltration of non-SNs in both breast cancer[9] and melanoma.[10] The study reported herein investigated differences in immunocyte infiltration between SNs and non-SNs in gastric cancer.

PATIENTS AND METHODS

A total of 27 patients with gastric cancer who underwent gastrectomy and SN exploratory surgery at Kagoshima University Hospital between 1999 and 2001 were enrolled in the study. The patients included 17 men and 10 women who ranged in age from

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31 to 86 years (mean 60 years). None of the patients had received preoperative chemotherapy. Eleven patients underwent total gastrectomy, 13 patients underwent distal partial gastrectomy, and the remaining three underwent proximal gastrectomy. All patients underwent more than D1 lymph node dissection, and dissected lymph nodes were explored for radioisotope activity using a radioisotope detector. The mean number of dissected lymph nodes was 35 (range 5 to 49). The incidence of lymph node metastasis was 29% (8 of 27 patients), and metastases were limited to compartment 1 lymph node metastasis (pN1) (Table 1). Clinicopathologic data were assessed according to methods outlined by the Japanese Gastric Cancer Association.[11]

Detection of Sentinel Nodes

The SN was detected using radioguided methods, as reported previously.[4] In short, 2 ml of Tc-labeled sulfur colloid (6 mCi total) was injected endoscopically into the peritumoral space 12 hours preoperatively. Intraoperatively, radiation levels for each lymph node were assessed using a navigational global positioning system (Tyco Electronics Japan). Lymph nodes displaying radioactivity in excess of 10 cps were considered sentinel lymph nodes. According to these radioisotope detections, 27 (93%) of 29 patients displayed SNs. Lymph nodes demonstrating uptake of less than 10 cps were regarded as non-SNs. In two lymph nodes from the same station number, immunocyte infiltration was compared between SNs and non-SNs.

Table 1. Patient information

Characteristic	No.
Age (yr)	63 ± 34 (median 60)
Sex	
Male	17
Female	10
Operation	
Total	11
Proximal	3
Distal	13
Depth of invasion	
pT1	13
pT2	9
pT3	5
Nodal involvement	
Yes	8
No	19
Histologic findings	
Differentiated	14
Undifferentiated	13
Average no. of dissected nodes	35

Evaluation of Immunocyte Infiltration in Lymph Nodes

All of the lymph nodes we examined belonged to the compartment 1 group. Antitumor lymphocytes in lymph nodes were detected by means of immunohistochemical methods. Lymph node sections 4 μm thick were cut from paraffin-embedded specimens. After deparaffinized specimens were soaked in phosphate-buffered saline solution, standard techniques for labeled avidine-biotin immunoperoxidase staining were used. CD56 (Immunotech, Roissy, France) for natural killer (NK) cells, S-100-protein (Z0311; DAKO Glostrup, Denmark) for dendritic cells, Ki-67 (M7187; DAKO, Denmark) for MIB-1 positive cells, and CD3-ζ (sc-1239; Santa Cruz Biotechnology, Inc., Santa Cruz, CA) for CD3-ζ expression were used for primary antibodies according to the formula in Table 2. Stained slides were examined and analyzed using a computer-assisted image analyzer (Olympus Japan). At ×400 magnification, a total of 10 points were selected, and immunohistochemically positive cells for NK cells and dendritic cells were counted and averaged. The MIB-1 labeling index was calculated according to the following formula:

$$\%\text{MIB-1 labeling index} = \frac{\text{Ki-67 positive cells}}{\text{Total cells}} \times 100$$

CD3-ζ expression of intranodal lymphocytes was classified into two groups: normal expression (>65% positive lymphocytes) and weak expression (≤65% positive lymphocytes) under ×100 magnification.[10] The degree of infiltration of these immunocytes was compared according to clinical stage and between SNs and non-SNs.

Statistical Analysis

Analysis of significant differences in categorical variables was performed using the *t* test. All *P* values are based on two-sided testing, and significant differences were defined at the level of $P < 0.05$.

Table 2. Immunohistochemical methods for detecting four immunocytes

Immunocyte	Antibody	Dilution	Duration	Pretreatment	
				atm	min
NK cells	CD57	50	Overnight	2	10
DC	S-100 protein	200	Overnight	—	—
MIB-1	Ki-67	50	Overnight	2	10
CD3-ζ	CD3-ζ	200	Overnight	2	10

NK = natural killer; DC = dendritic cells.

RESULTS

Positivity for NK cells, dendritic cells, and CD3-ζ were detected on cell surfaces. Conversely, MIB-1 positivity was found in nuclei. NK cells were diffusely distributed in lymph nodes. Dendritic cells and MIB-1–positive cells were predominantly distributed around the germinal center, and CD3-ζ positivity was detected in paracortical areas of lymph nodes (Fig. 1). Positive cells in the germinal center were excluded from the evaluation of effector cell infiltration because this region is involved with B cells. The mean number of positive cells was 2.4 for NK cells, 45 for dendritic cells, and 11% for MIB-1–positive cells in SNs.

Decreases in CD3-ζ expression and MIB-1–positive cells in the SNs were significantly associated with the depth of invasion (Table 3).

The number of MIB-1–positive cells in the SNs was lower than that in non-SNs ($P < 0.05$). However, no significant differences in dendritic cells, NK cells, or CD3-ζ expression existed between the two lymph node groups (Table 4). In dividing patients according to nodal involvement, significant differences were found only in the node-positive group. Morphologic changes of dendritic cells in SNs were not identified.

Table 3. Intranodal immunocyte infiltration according to depth of invasion

	pT1	pT2	pT3
DC count	46.1 ± 40	45.6 ± 30	49.9 ± 50
NK cell count	2.6 ± 3.3	2.1 ± 2.1	2.9 ± 1.6
MIB-1 labeling index	6.1 ± 7.4*	6.3 ± 9.7	2.6 ± 2.3*
CD3-ζ positivity	12 (86%)*	3 (33%)*	2 (33%)

DC = dendritic cell; NK = natural killer.
*$P < 0.05$.

DISCUSSION

MIB-1–positive cells and CD3-ζ expression in SNs decreased according to the depth of invasion. Immunocyte infiltration of lymph nodes was influenced not

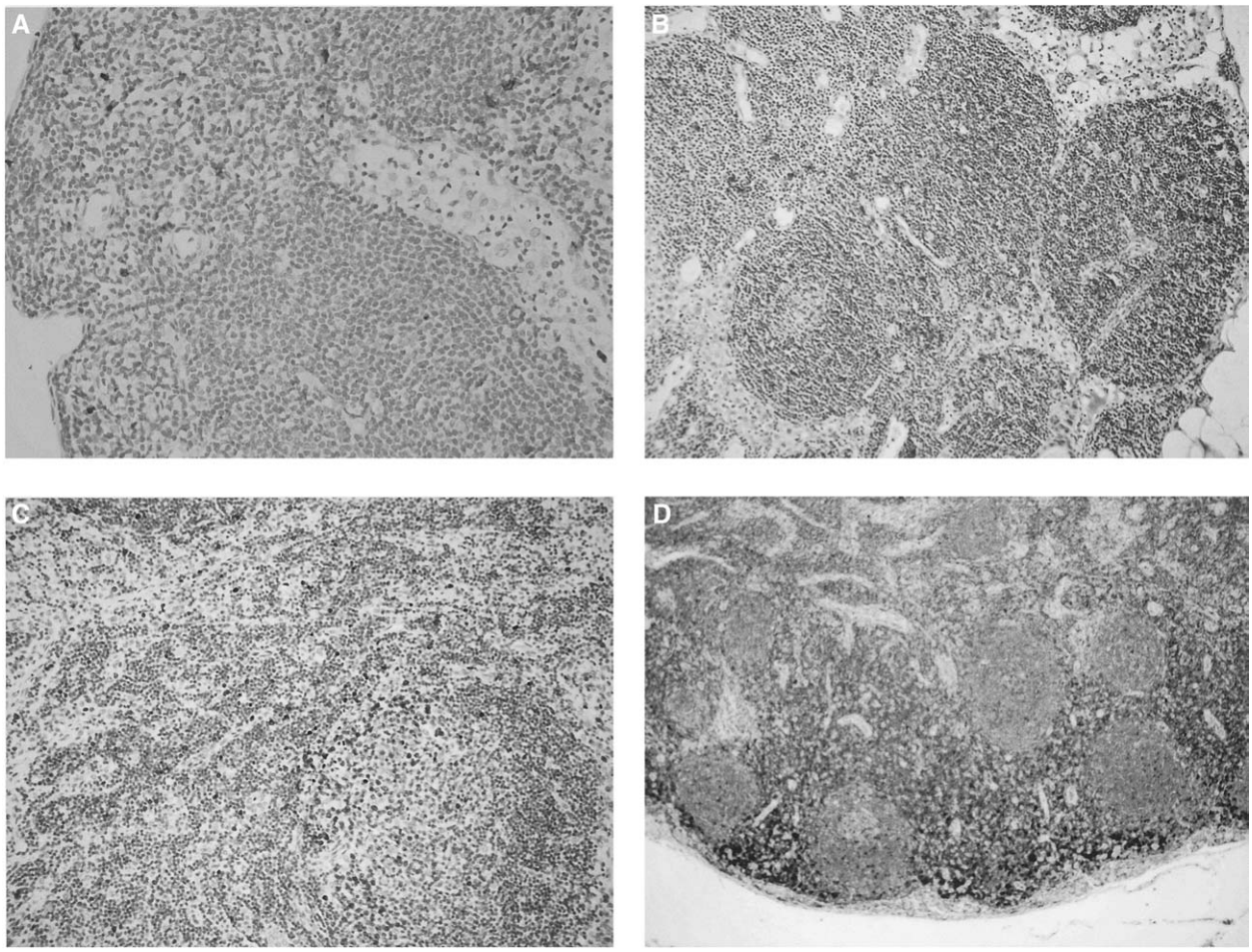

Fig. 1. Natural killer cell infiltration (**A**), dendritic cell infiltration (**B**), MIB-1–positive cells (**C**), and CD3-ζ–positive cells (**D**) in the lymph node.

Table 4. Intranodal immunocytic infiltration in sentinel or nonsentinel node

	Sentinel node	Nonsentinel node	*P* value
Total cases (n = 27)			
DC count	49.5 ± 34	44 ± 41	NS
NK cell count	3.0 ± 1.6	2.9 ± 2.0	NS
MIB-1 labeling index	3.3 ± 4.0	7.8 ± 4.3	<0.05
CD3-ζ positivity	20 (87%)	19 (85%)	NS
Node-negative cases (n = 19)			
DC count	46.1 ± 40	45.6 ± 30	NS
NK cell count	2.3 ± 3.1	1.6 ± 2.6	NS
MIB-1 labeling index	5.2 ± 7.0	8.5 ± 3.3	NS
CD3-ζ positivity	17 (90%)	18 (94%)	NS
Node-positive cases (n = 8)			
DC count	43.8 ± 40	35.4 ± 30	NS
NK cell count	2.5 ± 1.6	2.9 ± 1.6	NS
MIB-1 labeling index	3.1 ± 8.3	10.0 ± 7.3	<0.05
CD3-ζ positivity	4 (50%)	2 (25%)	NS

DC = dendritic cell; NK = natural killer; NS = not significant.

only by lymph node position (SN or non-SN) but also by extension of the primary tumor, confirming the results of a previous study.[8] The CD3-ζ expression is a crucial molecule, consisting of T-cell receptors. Tumor infiltrating lymphocytes are widely known to reduce CD3-ζ expression, which is involved in the disturbance of antigenic stimulation into cytotoxic T cells and causes immunologic paralysis.[12,13] Some intranodal lymphocytes in advanced gastric cancer may therefore be profoundly affected by T-cell paralysis.

Significantly decreased MIB-1 positivity was observed in SNs compared with non-SNs. Because the SN is considered to be the first node in the direct lymphatic drainage path from a primary tumor, SNs would naturally seem likely to reflect tumor circumstance more directly than non-SNs.[14] However, the degree of infiltration by dendritic cells and NK cells, and the CD3-ζ expression were almost identical between the two groups. These results differ from those observed in other types of cancer.[9,10] Huang et al.[9] and Cochran et al.[10] clearly demonstrated significantly less infiltration of SNs by dendritic cells and T cells as compared to non-SNs in breast cancer and melanoma. Morphologic changes to dendritic cells in SNs were also reported. Careful attention was given to this point; however, morphologic changes to dendritic cells in SNs were not apparent in the present study. Melanoma displays a unique response to cancer-specific antigens,[15] whereas gastric cancer displays poor immunoantigenicity. The lack of significant differences in the present study, with the exception of MIB-1, may therefore be related to tumor aggressiveness and antigenicity. Moreover, gastric mucosa is continually exposed to exogenous antigenic stimulation, and perigastric lymph nodes receive frequent stimulation from external sources, unlike lymph nodes draining skin or the mammary glands. Exogenous stimulation may modulate immunologic conditions between SNs and non-SNs in gastric cancer.[8]

CONCLUSION

Some differences were demonstrated between SNs and non-SNs in gastric cancer. However, these differences were not particularly clear compared to those observed in other types of cancer. Studies in progress will help in the identification of immunologic paralysis of the SN in various types of cancer. With regard to immunocyte infiltration of lymph nodes, attention must be paid to organ specificity when undertaking SN-oriented treatment.

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Functional Neuroimaging of Gastric Distention

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This study aimed to measure brain activation during gastric distention as a way to investigate short-term satiety. We estimated regional cerebral blood flow with positron emission tomography (^{15}O-water) during gastric balloon inflation and deflation in 18 healthy young women. The contrast between inflated minus deflated conditions showed activation in the following four key regions that were identified a priori: dorsal brain stem; left inferior frontal gyrus; bilateral insula; and right subgenual, anterior cingulate cortex. Extant neuroimaging literature provides context for these areas as follows: the brain stem represents vagal projection zones for visceral afferent processing; the inferior frontal gyrus serves as a convergence zone for processing food-related stimuli; and both the insula and subgenual anterior cingulate cortex respond to emotional stimulation. The identification of neural correlates of gastric distention is a key step in the discovery of new treatments for obesity. New therapies could intervene by modifying the perception of gastric distention, an important contributor to meal termination and short-term satiety. This first study of brain activation during nonpainful, proximal gastric distention provides the groundwork for future research to discover novel treatments for obesity. (J GASTROINTEST SURG 2003;7:740–749)

KEY WORDS: Obesity, gastric distention, positron emission tomography, vagus nerve, satiety, insula, claustrum

In the United States, more than 60% of the adult population is either overweight or obese.[1] Within the past 20 years, the prevalence rate has increased more than 75%. Many adverse medical conditions accompany obesity, such as adult-onset diabetes, osteoarthritis, hypertension, and heart disease. In 1999, prescription medications to treat obesity cost more than $320 million.[1] These costs do not cover indirect costs, such as lost of productivity in the work place. The search continues for effective and lasting treatments. Current surgical treatments for obesity include vertical banded gastroplasty and gastric bypass. It remains unclear whether patients maintain their weight loss long term. Critical to these approaches is the role of gastric sensation. We have only a minimal understanding of the localization and mechanisms of gastric visceral sensation in the brain. Anatomic and physiological studies in animals identify several key areas in the central nervous system that contribute to visceral processing. Central visceral projection areas include several brain stem nuclei (nucleus of the solitary tract[2,3] and the parabrachial nucleus[4]), the insula,[5,6] the anterior cingulate cortex,[7,8] and orbitofrontal regions.[9,10] Because at the present time the regions associated with gastric sensation remain unclear, we are focusing only on the neuroanatomy of these four target regions in this exploratory investigation. Although visceral sensation clearly involves more structures than just these four, a focused study is necessary to avoid the problem of multiple comparisons inherent in neuroimaging. Herein we report the results of the first study of nonpainful, proximal, gastric sensation using positron emission tomography (PET). We inserted

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a balloon into the stomach, which we alternately inflated and deflated. Changes in blood flow to the brain marked neural activation during gastric distention. We previously reported the results of PET studies identifying neural changes involved in swallowing,[11] taste,[12] and olfaction.[13]

MATERIAL AND METHODS

Subjects

The Human Subjects Committee and the Radioactive Drug Research Committee of the Minneapolis Veterans Affairs Medical Center and the Research Subject's Protection Program of the University of Minnesota approved the study protocol, which was conducted at the Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota. Subjects gave written informed consent before enrollment. We recruited 21 normal-weight women who had fasted for 12 hours (overnight). Computer-administered psychiatric screening (Diagnostic Interview Schedule)[14,15] excluded any subjects with medical, neurologic, and psychiatric disorders (including eating disorders) and drug use. Obesity and a family history of any psychiatric disorder also led to exclusion from this study. Prestudy electrocardiogram (ECG) recordings were normal as were serum sodium and potassium levels. Serum beta human chorionic gonadotrophin levels indicated absence of pregnancy. We discussed and reviewed the potential risks and discomfort involved in this study and emphasized the possibility of study termination at any time. Subjects filled out the Positive Affect and Negative Affect Schedule (PANAS)[16] to assess the trait (prestudy) and state (poststudy) level of mood.

Study Procedure

An intravenous line was inserted into the left or right antecubital vein before subjects entered the scanner. Subjects were placed in a comfortable supine position, and a three-lead ECG (MAC 12, Marquette Electronics, Inc., Milwaukee, WI) was attached. The balloon assembly consisted of a soft rubber multichannel tube component (36 F; Davol, Inc., Cranston, RI), covered distally with a rubber condom (nonlubricated Trojan; Carter-Wallace, Inc., New York, NY) tied securely with 3-0 silk. Before the balloon was inserted, the surgeon (R.L.G.) administered a light oral anesthetic (20% benzocaine spray; Beutlich L.P. Pharmaceuticals, Waukegan, IL) followed by 3 ml of 2% lidocaine viscous gel (Roxane Laboratories, Inc., Columbus, OH). The surgeon placed a small plastic mouthpiece between the teeth and inserted the tube with the deflated balloon into the subjects' mouth. The tube continued downward until a 45 cm mark opposite the incisors indicated the approximate location of the upper end of the balloon in the stomach. A test inflation of the balloon to 200 ml of water and gentle retraction for a variable length until cardia resistance gave evidence of proper placement. We decided to exclude fluoroscopic control of balloon placement from the protocol for two reasons: (1) The C-arm equipment was incompatible with the PET gantry, and (2) transportation from an x-ray facility would have prolonged the study time. Tape tied to the tube and positioned around the neck stabilized the tube position and minimized pharyngeal stimulation and oral movement.

The study aimed at three consecutive cycles of inflation and deflation (total of six scans); each scan was separated by a rest interval of approximately 10 minutes to allow for tracer decay. Prior to the inflated brain scan, we filled the balloon with water over a 2-minute period until subjects signaled a sensation, below the pain threshold, of feeling as full as after a heavy meal. We focused on individual subjective sensations of fullness rather than on a fixed volume administered to each subject. Fixed volumes could have induced quite different sensations. One of the study goals was to induce the same subjective feeling of fullness in every subject—that is, fullness similar to the feeling after consumption of a heavy meal, such as Thanksgiving dinner. The room was darkened, and subjects closed their eyes and concentrated on the stomach during the brain scan. Similarly, after stomach deflation and the rest interval, another scan was recorded using the same procedure.

Physiologic and Subjective Measures

ECGs were monitored throughout the entire procedure because of the possibility of bradycardia,[17] and tracings were recorded during the brain scans. We registered gastric volumes from the displacement of a large volumetric cylinder connected to the balloon. We measured gastric pressures from the balloon interior with a Y-connector attached to a Statham strain gauge wired to a paper polygraph (5/6 H Recorder; Gilson Medical Electronics, Inc., Middleton, WI).

Periodically, subjects self-rated their feelings of hunger, tenseness, gastric discomfort, fullness, sleepiness, and nausea on an 11 mm visual analog scale (VAS) before scan deflation and after scan inflation. (Deflated ratings were acquired before scan; inflated ratings were acquired after scan. A Wilcoxon signed-rank test for a subset of data acquired before scan deflation and after scan deflation revealed no difference between those measurements.)

Positron Emission Tomographic Imaging and Image Reconstruction

Regional cerebral blood flow (rCBF) was measured by means of PET using $H_2{}^{15}O$ to estimate brain activity during gastric distention. Because rCBF is tightly coupled to neuronal activity,[18] increased rCBF indicates dynamic activation of the brain. Brain mapping defines areas of activation during two particular tasks (e.g., inflation and deflation). Subtraction of the two activation images results in a difference image that isolates the one aspect of interest (e.g., inflation minus deflation isolates brain areas specifically active during gastric distention). To increase the signal-to-noise ratio, we averaged the subtraction images across subjects through stereotactic normalization.[19] Areas of increased rCBF were color coded in the average image. The brighter the color, the greater the difference in rCBF, which is called "activation" (e.g., relative to a control condition, here deflation).

We acquired brain activation data using an ECAT 953B camera (Siemens, Knoxville, TN) with the septae retracted (3-dimensional mode). The scanner produced 31 slices spaced 3.3 mm apart. A transmission scan was performed to correct subsequent emission images for radiation attenuation. We injected a slow bolus of $H_2{}^{15}O$ (0.25 mCi/kg) intravenously infused at a constant rate over a 30-second interval. After arrival of the radioactivity in the brain, the camera started recording for 90 seconds. Automated PET software[20] estimated rCBF from normalized tissue radioactivity (normalized to 1000 counts). Image processing for each subject included normalization for global activity, coregistration, and nonlinear warping[21] to a defined stereotactic space.[19] We smoothed images with a four-pixel (9 mm), three-dimensional, gaussian filter, resulting in images with a final resolution of 12.5 mm full-width at half-maximum.

Statistical Analysis

ECG data were analyzed by means of a one-tailed, paired-samples, Student's *t* test, and rating scores underwent Wilcoxon's signed-rank tests for comparison of inflation to deflation. Statistics from both were evaluated using SPSS for Windows 10.1 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). We corrected the results of the VAS analysis for six comparisons (six VAS subscales; Bonferroni correction). Statistical analysis for the brain activation data used the global variance of all intracerebral pixels[20] and calculated pixelwise *t* statistics.[22] We transformed the t-image into a z-map image with a chosen significance threshold of $z \geq 3.3$ ($P \leq 0.0005$).[13]

RESULTS

All but three subjects tolerated the procedure well. These three discontinued the study because of intolerance to the balloon. The remaining 18 subjects were, on average, 24 years of age and had a mean body mass index[23] of 21. For detailed demographics data, see Table 1.

Physiologic and Subjective Measurements

ECG, Volume, and Pressure. All subjects demonstrated consistent and normal ECG patterns and heart rates during the study procedure. Heart rate (HR) did not change from deflation to inflation ($HR_{deflated} = 85 \pm 13$ [mean ± standard deviation] vs. $HR_{inflated} = 83 \pm 12$, one-tailed $t_{df=10} = 1.0$, $P < 0.3$, $N = 11$). Although maximal tolerated volumes and associated pressures varied among individuals (volume range 300 to 1175 ml, pressure range 1.8 to 17.8 mm Hg), they remained consistent for each subject for the three consecutive inflations. After inflation, pressure decreases indicated the phenomenon of gastric relaxation.[24,25]

Positive Affect Negative Affect Schedule. We observed mean baseline scores of positive affect (PA) and negative affect (NA) as 36 ± 3 and 16 ± 3, respectively. State measurements after the study led to mean scores of 29 ± 8 and 12 ± 3 for PA and NA, respectively.

Visual Analog Scale. Inflation caused an immediate significant decrease in the feeling of hunger along with an immediate significant increase in the feelings of sleepiness, fullness, nausea, and gastric discomfort (hunger: Wilcoxon's $Z \leq -3.7$, $P \leq 0.006$; sleepiness: Wilcoxon's $Z \leq -2.8$, $P \leq 0.036$; fullness: Wilcoxon's $Z \leq -3.7$, $P \leq 0.006$; nausea: Wilcoxon's $Z \leq -2.8$, $P \leq 0.03$; gastric discomfort: Wilcoxon's $Z \leq -2.9$, $P \leq 0.024$; all *P* values corrected). These results will be presented elsewhere.

Brain Activation Data

Regional cerebral blood flow showed an increase in more than 20 different areas when inflated and

Table 1. Subject demographics

	N	Minimum	Maximum	Mean	±SD
Age (yr)	18	18	39	24	5
Weight (kg)	18	46	77	60	10
Height (m)	18	1.60	1.80	1.67	7
BMI (kg/m^2)	18	17	27	21	2

BMI = body mass index; N = sample size; SD = standard deviation.

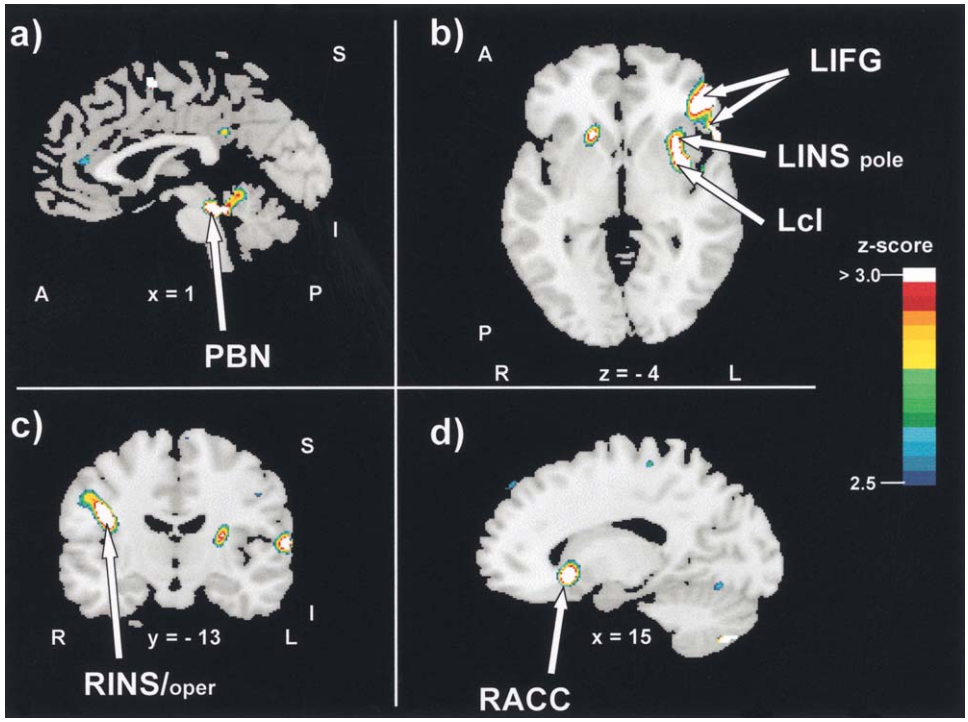

Fig. 1. Increases in regional cerebral blood flow (rCBF) during stomach distention. Brain activity was estimated with PET using ^{15}O-water in 18 healthy young women during gastric balloon inflation and deflation. Difference images (inflation minus deflation) are superimposed on a single structural magnetic resonance image (gray scale brain areas). Colored areas are coded to represent the magnitude of change in rCBF as z-scores. Letters and numbers below the slices indicate their orientation and stereotactic coordinates.[19] *Arrows* point to areas with significant changes in rCBF in four a priori defined regions of interest involved in visceral sensation: (**a**) dorsal brain stem nuclei; (**b**) left inferior frontal gyrus; (**b** and **c**) insular cortex/claustrum; (**d**) subgenual anterior cingulate cortex. A = anterior; I = inferior; L = left; Lcl = left claustrum; LIFG = left inferior frontal gyrus; LINS = left insula; LINS pole = left insular pole; P = posterior; PBN = parabrachial nucleus; R = right; RACC = right anterior cingulate cortex; RINS/oper = right insula/operculum; S = superior; x = sagittal plane; y = coronal plane; z = horizontal plane.

deflated scans were compared (threshold: $Z \geq 3.3$). Here we focus on the four well-known regions involved in visceral sensation as mentioned earlier. Fig. 1 displays activation foci in the dorsal brain stem (*panel a*); two activation peaks in the left inferior frontal cortex (LIFC; *panel b*); several activation foci in the left insula/claustrum and bilateral operculum (*panels b* and *c*); and activation in the right subgenual

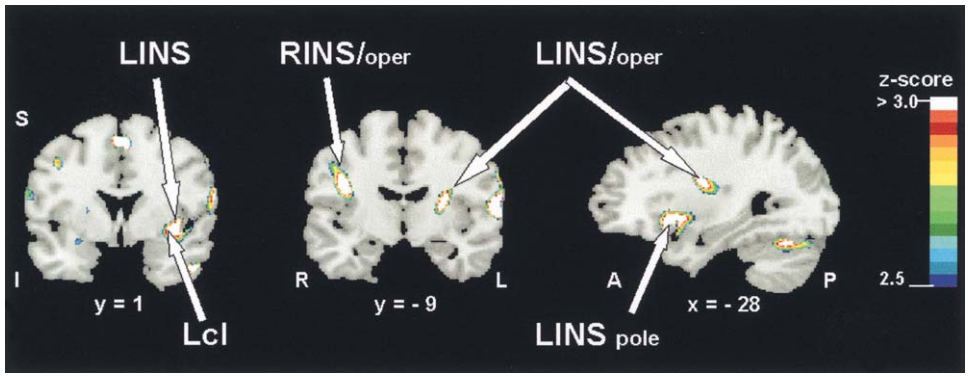

Fig. 2. Insular activation foci during stomach distention. LINS/oper = left insula/operculum. For explanation and all other abbreviations, see Fig. 1.

Table 2. Visceral projection areas showing activation during gastric distention*

Structure	x	y	z	z-score	*P* value†	N
LIFG	−55	19	−4	5.35	0.00000004	11
	−44	30	−14	4.92	0.0000004	10
Left insula pole	−28	14	−11	3.60	0.00016	18
Left insula intermediate	−39	1	0	3.38	0.00036	18
Left claustrum	−33	1	−4	3.35	0.0004	18
Left insula/parietal operculum	−30	−4	22	3.43	0.0003	18
Right insula/parietal operculum	39	−13	22	3.58	0.00017	18
RACC	15	19	−9	3.45	0.00028	18
Brain stem (PBN)	1	−33	−18	3.34	0.00042	18

LIFG = left inferior frontal gyrus; N = number of subjects contributing to activation focus; PBN = parabrachial nucleus; RACC = right anterior cingulate cortex.
*Coordinates according to Talairach and Tournoux.[19]
†Uncorrected.

anterior cingulate cortex (ACC; *panel d*). Table 2 lists the coordinates of these areas according to Talairach and Tournoux[19] with corresponding Z-Scores, uncorrected *P* values, and number of subjects contributing to each activation focus. Fig. 2 displays activation peaks in the left insula and claustrum and bilateral insula/parietal operculum in detail.

DISCUSSION

We used proximal gastric distention with a balloon to induce the feeling of satiety and fullness in normal subjects. This procedure mimicked the ingestion of a meal. Repeated stomach dilations in the same subject provided several advantages. First, averaging of scans resulted in more reliable brain activity measurements. Second, we avoided head alignment difficulties associated with different study sessions. Third, we obviated day-to-day fluctuations in mood that could affect the rating scores (e.g., anxiety). Repeated stimulation became possible because we did not give nutrients and because of the short half-life of the tracer ^{15}O (123 seconds). We simplified the study design to pure mechanical stimulation of the stomach. To our knowledge this is the first study that reports on brain activity associated with nonpainful proximal gastric distention.

Physiologic and Subjective Measurements

Volume and Pressure. We reached our study goal of mimicking a meal just with mechanical gastric distention. Observed volumes causing fullness and associated pressures at these volumes resembled the values of those reported in normal subjects after a meal.[26–28] We also found gastric relaxation after stomach distention as others have found after a meal.[24,25,29] For each subject, gastric distention volumes and pressures remained consistent for up to three subsequent inflations, showing no trend or shift of threshold to the distending stimulus. No gastric habituation occurred over this time interval. Differences in maximal tolerated volumes demonstrate the variable subjective thresholds of fullness. Geliebter and Hashim[26] also described variable thresholds and found mean differences in tolerated volumes as high as 475 ml between normal-eating and binge-eating subjects.

Positive Affect Negative Affect Schedule. Baseline ratings did not differ from the normative sample. Subjects experienced normal mood during the previous month. Scores after the study also demonstrated similarity to the normative sample. Thus we observed mood ratings in a normal range.

Visual Analog Scale. All feelings were reproducible to the same degree with the three consecutive inflations. Changes in feelings of fullness (as a sign of satiation) showed similarity with those found after the consumption of liquid meals.[30] Other researchers have employed gastric distention with an air-filled balloon to similar volumes and found similar changes in ratings for hunger and fullness.[28]

Brain Activation Data

Gastric distention altered rCBF in many areas of the central nervous system. This exploratory investigation depicts only one aspect of a much more comprehensive project, which we will elaborate on in detail elsewhere. Exploratory analyses inherit limitations regarding their interpretation. Nevertheless, given the large sample size of 18 subjects, we thought it was important to highlight some of these results separately. Increases in rCBF in the targeted visceral projection areas occurred in the dorsal brain stem, the left inferior frontal gyrus, the bilateral insular region, and the right subgenual anterior cingulate cortex.

The activation evident in the brain stem during inflation most likely corresponds to that in the parabrachial nucleus. The parabrachial nucleus receives projections from the nucleus of the solitary tract,[31] which is the primary site of subdiaphragmatic vagal afferent termination.[32] In turn, the parabrachial nucleus projects to many brain stem and forebrain regions, including the ventromedial hypothalamus, amygdaloid nuclei, and thalamic areas.[33–37] Functionally, the parabrachial nucleus is a well-recognized relay and integration site for peripheral vagal afferent information on food intake.[38–40] Activation of this brain stem area likely represents the neural processing of the sensation of fullness resulting from balloon inflation.

Lateral inferior frontal and orbitofrontal areas, which here also show increases in rCBF due to inflation, respond strongly to stimuli associated with food, such as visual, olfactory, and gustatory stimuli.[41] However, cells in this area do not respond only to taste and smell but also to affective components of food such as rewarding or aversive features.[42] The present study reveals that gastric distention by itself activated this region, thus adding the finding that neurons in this area also respond to a mechanical satiety signal. The lateral frontal cortex thus seems to represent an area of convergence for many food-related stimuli.

Insular activation during inflation reflects a visceral projection field for a variety of autonomic and visceral functions.[6,43] The insular region of the cortex constitutes the base of the Sylvian fissure and lies buried under the frontal, parietal, and temporal lobes.[44] The portions of the overlapping lobes define the frontal, parietal, or temporal operculum, respectively. We found two activation peaks in the left insula: bilateral activation in the insula/parietal operculum and one activation peak in the left claustrum. Peaks in the left insula lie ventrally and intermediately (intermediate insula) and anteriorly (insular pole). This ventral intermediate, anterior portion of the insula not only specializes in taste and smell processing,[5] but also responds especially to internally generated emotional states and potentially distressing stimuli.[45–47] Our ventral, intermediate, anterior insular results support this hypothesis. Visceral sensation represents an internal stimulus. Extreme stomach distention (below pain threshold) displays a potential danger and mainly an aversive sensation. The anterior insula seems to warn the organism of potential internal threats, which ultimately helps the organism to survive. We also found activation of the bilateral insula/parietal operculum. These peaks lie dorsally, probably extending across the peri insular sulcus into the parietal operculum. They also extend posteriorly. The dorsal insula/operculum reflects general visceral modalities such as gastric distention.[5] Activation of the different insular regions could reflect two modalities of processing the emotional aspect of visceral sensation and the sensation of gastric distention, respectively. The claustrum is considered a telencephalic nucleus bordering the insula dorsally and the amygdaloid body ventrally.[48] The dorsal claustrum, which activates during stomach distention, reciprocally connects to all regions of the cortex except the posterior temporal cortex.[49] It might transfer information among various cortical regions.[48] The claustrum participates in auditory[50] and visual[51] stimulation. Lesion studies suggest its involvement in Alzheimer's disease[52] and Parkinson's[53] disease. But the overall detailed connections and functions of the claustrum remain unknown.[53]

The activation peak in the right anterior cingulate cortex during inflation lies subgenually. This region represents a key area involved in central autonomic and visceral processing[8,54] and connects to limbic regions.[55] The anterior cingulate cortex is part of the medial network within the orbitofrontal cortex.[7,56] Via its connections to the hypothalamus and brain stem, it provides frontal cortical influence over autonomic functions. The main target region in the brain stem is the periaqueductal gray area,[56] which coordinates visceral and behavioral responses especially to inescapable stress or threatening stimuli.[57] The anterior cingulate cortex also processes sadness in healthy subjects,[58,59] and contributes to the activation pattern observed in pathologic depression.[59,60] Here we interpret subgenual anterior cingulate cortex activation as visceral processing with a negative affective component. This area could associate affect with eating.

Our results demonstrate that the stomach projects via vagal afferent pathways to visceral cortical areas that also participate in emotional and affective processing. Visceral projection areas either connect with structures of the limbic system or constitute paralimbic structures. The limbic system, in a most general way, aims at the survival of an organism, which includes initiation of feeding and drinking with the appropriate preceding behaviors including agonistic behavior (defense and attack); the latter is initiated via emotions.[61] In this respect, limbic and paralimbic areas involved in the processing of signals of satiety have a survival utility.

One has to interpret our results as representing one of the signaling pathways in food intake. We think that brain activity during proximal gastric distention in healthy subjects leads to further understanding of mechanisms of satiety and possibly the behavior of overeating. We have previously suggested

that frequent binge-vomit cycles, as observed in bulimia nervosa, could cause structural or functional changes in vagal afferent nerves.[62–65] One could speculate that such biomechanical stress could cause gastric nerve density remodeling as is seen in the heart.[66] One could further speculate that similar changes may accompany regular and frequent bouts of overeating, particularly as occurs in obese binge-eating disorder. These changes could link visceral projection areas to affective networks.

We used a temporarily inserted gastric balloon setup only as a means of studying the neural pathways of short-term satiety; this should not be mistaken for the implanted gastric balloon that is used as a treatment for obesity. Implanted gastric balloons as a sole treatment for obesity or as an adjunct to behavioral programs have only transient effects for inducing weight loss.[67–69] Gastric balloon implants only temporarily change the feelings of hunger,[70] which could indicate stomach adaptation.[70–72] Moreover, they can produce side effects such as gastric ulcers, gastric erosion, abdominal cramps, displacement, and deflation,[68,69,73–75] many of them serious. Hence the contemporary indication for gastric balloon implants is restricted to preoperative weight loss to reduce the operative risk in morbidly obese patients undergoing surgery.[76–78]

Study Limitations

One could criticize the choice of gastric distention as a stimulus of satiety on several grounds. Secondary effects could have produced the results. Responses could also differ from those resulting from normal eating experiences. For example, sensory oral stimulation from the tube could cause cephalic phase insulin responses.[79] Gastric distention likely triggered gastric hormone releases such as incretins,[80] ghrelin,[81,82] cholecystokinin, or gastrin.[83] These humoral releases could have led to the observed changes in subjective feelings. Yet we did not find elevated plasma cholecystokinin levels after balloon distention and only a 30-minute delayed gastric acid release (unpublished data). Humoral releases are either slow-acting mechanisms (cholecystokin, gastrin)[83] or fast-acting mechanisms (ghrelin,[81,82] incretins[80]) and therefore could have affected the repeated ratings. The rapid and temporary changes in VAS ratings argue against such humoral effects. Also, ratings remained consistent across the three consecutive cycles of inflation and deflation; no accumulated effects occurred. We did not study neuropeptides, such as melanin-concentrating hormone or orexin/hypocretin, whose target nuclei remain unknown.[84] Nor did we study hormones released in different sites (other than gastrointestinal), for example, the adipocyte hormones resistin[85] and leptin,[86] which represent important regulators in eating. They may be more important than mechanical gastric signaling.

Another secondary effect on the VAS rating scores could have resulted from the confining, lengthy nature of the study, which could have blunted subjects' sensations. But we reproduced all feelings to the same degree with the three consecutive inflations. Also, the target sensations, namely, fullness and lack of hunger, showed greater changes than the other sensations throughout the study procedure.

One could object that sensations and stomach relaxation to gastric inflation might differ from the values observed after nutrient meals. Subjective rating scales after gastric distention alone show very similar values as reported by others after meals.[30,87] A study that compared both postballoon and postprandial physiologic stomach relaxation in the same subject found similar responses.[88] Thus the mechanical stimulus evoked the same subjective feelings and physiologic gastric relaxation response as a meal.

One could argue that rCBF increases in our study resulted from esophageal but not gastric sensation.[89–91] However, in our study the tube stimulated the esophagus during both conditions. Thus subtraction of deflated from inflated activation should have eliminated esophageal activation.

Another issue is image averaging across subjects. Between-subject averaging is the standard analysis paradigm for PET studies. Our subjects could not tolerate a more prolonged study session that would allow enough cycles of distention and relaxation for within-subject averaging. Although the average is the best group estimate, we included in our results the number of subjects contributing to each activation focus to highlight the prevalence of responses across the group. Therefore averaging across the group of subjects was appropriate.

CONCLUSION

This is the first study to identify brain areas activated by proximal gastric distention below the pain threshold. These results may provide useful comparisons with future data from patients suffering from eating disorders and/or obesity, and may ultimately lead to alternative treatments.

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Gastrointestinal Symptomatic Outcome After Laparoscopic Roux-en-Y Gastric Bypass

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Laparoscopic Roux-en-Y (RY) gastric bypass is an effective treatment for morbid obesity. However, little information is available regarding the gastrointestinal symptomatic outcome after laparoscopic RY gastric bypass for morbid obesity. The purpose of this study is to identify changes occurring in gastrointestinal symptoms after laparoscopic RY gastric bypass. A previously validated, 19-point gastrointestinal symptom questionnaire was administered prospectively to each patient seen for surgical consultation to treat morbid obesity. Patients rated the degree to which each symptom affected their lives on a 0 to 100 mm Liekert scale with 0 indicating absence of a symptom, 33 indicating the symptom was present occasionally, 67 indicating the symptom occurred frequently, and 100 indicating the symptom was continuous. The same survey was readministered 6 months postoperatively. The mean of each symptom (preoperative vs. postoperative value) was compared using Student's t test with significance at $P < 0.05$. Forty-three preoperative patients (age 37.3 ± 8.6 years; body mass index 47.8 ± 4.9) and thirty-five, 6 months' postoperative patients (81% follow-up; body mass index 31.6 ± 5.3) completed the questionnaire. The result for each symptom is expressed as mean ± standard deviation of preoperative vs. postoperative scores. Significantly different symptoms include the following: abdominal pain 23.3 ± 26.4 vs. 8.6 ± 13.5, $P = 0.003$; heartburn 34.0 ± 26.6 vs. 8.0 ± 14.0, $P = 0.0001$; acid regurgitation 28.1 ± 24.0 vs. 10.7 ± 21.0, $P = 0.001$; gnawing in epigastrium 19.3 ± 22.7 vs. 7.5 ± 16.0, $P = 0.01$; abdominal distention 38.2 ± 31.5 vs. 11.1 ± 19.2, $P = 0.0001$; eructation 27.7 ± 24.4 vs. 15.5 ± 16.9, $P = 0.01$; increased flatus 40.2 ± 25.7 vs. 25.2 ± 25.3, $P = 0.005$; decreased stools 5.4 ± 16.8 vs. 17.4 ± 20.0, $P = 0.0005$; increased stools 23.9 ± 26.7 vs. 6.5 ± 11.7, $P = 0.0005$; loose stools 29.7 ± 26.5 vs. 17.5 ± 20.0, $P = 0.03$; urgent defecation 34.3 ± 26.5 vs. 14.3 ± 19.3, $P = 0.0009$; difficulty falling asleep 44.1 ± 38.4 vs. 27.5 ± 32.9, $P = 0.05$; insomnia 42.4 ± 36.2 vs. 21.6 ± 30.5, $P = 0.008$; and rested on awakening 65.1 ± 33.8 vs. 30.5 ± 28.8, $P = 0.0001$. Symptoms that did not significantly change included the following: nausea/vomiting 17.2 ± 22.7 vs. 22.1 ± 19.9, $P = 0.33$; borborygmus 28.8 ± 25.2 vs. 26.8 ± 29.7, $P = 0.75$; hard stools 10.3 ± 22.9 vs. 7.1 ± 18.6, $P = 0.56$; incomplete evacuation of stool 17.2 ± 22.8 vs. 13.4 ± 21.7, $P = 0.45$; and dysphagia 10.9 ± 15.6 vs. 17.7 ± 28.4, $P = 0.18$. Laparoscopic RY gastric bypass significantly improves many gastrointestinal symptoms experienced by morbidly obese patients without adversely affecting any of the measured parameters. This information is useful in preoperative counseling to assure patients of overall symptomatic improvement after this operation in addition to significant weight loss and improvement of comorbid conditions. (J GASTROINTEST SURG 2003;7:750–753)

KEY WORDS: Gastrointestinal, symptoms, outcomes, laparoscopic, gastric bypass

Recently, laparoscopic Roux-en-Y (RY) gastric bypass has gained popularity in the surgical treatment of morbid obesity and has been shown to provide similar weight loss with fewer complications than open Roux-en-Y gastric bypass.[1,2] Surgical treatment of morbid obesity has been shown to be superior to dieting and behavior modification for long-term weight loss and improvement of associated comorbidities.[3]

It is estimated that world wide more than 500 million adults are overweight, and more than 250 million are obese.[4] Obesity is an epidemic in the United States, and its prevalence continues to rise,[4,5] making it the second leading cause of preventable death in

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the United States. Increasing at its current alarming rate, obesity will likely surpass smoking as the number 1 cause of preventable death in the near future. Many studies have examined several different outcomes after laparoscopic RY gastric bypass, but none specifically addressing the gastrointestinal symptomatic outcome. This study compares preoperative gastrointestinal symptoms in morbidly obese patients to those of postoperative patients following laparoscopic RY gastric bypass.

MATERIAL AND METHODS

From April 2000 to February 2001, a total of 43 patients evaluated for surgical treatment of morbid obesity were prospectively administered a previously validated 19-part gastrointestinal symptom questionnaire.[6,7] The 19 symptoms were abdominal pain, gnawing sensation in the epigastrium, nausea and vomiting, borborygmus, abdominal distention, increased flatus, decreased passage of stools, increased passage of stools, loose stools, hard stools, urgent need for defecation, feelings of incomplete evacuation, dysphagia, heartburn, acid regurgitation, eructation, difficulty falling asleep, insomnia, and feeling rested when awakening. The patients rated the severity of each symptom by placing an "X" on a 100 mm Liekert scale. A numerical score of 0 represented no symptoms, a score of 33 indicated that symptoms occurred occasionally, a score of 67 indicated symptoms occurred frequently, and a score of 100 indicated that the symptoms were severe, continuous, and interfered with daily activities. The symptom score was designated as the distance in millimeters of the "X" from the left end of the scale. The questionnaire was readministered to patients 6 months postoperatively after laparoscopic RY gastric bypass. The preoperative and postoperative symptom scores are expressed as mean ± standard deviation and are compared using Student's t test with significance at $P < 0.05$.

RESULTS

Forty-three preoperative patients (age 37.3 ± 8.6, body mass index [BMI] 47.8 ± 4.9) and thirty-five 6 months' postoperative patients (81% follow-up, BMI 31.6 ± 5.3) completed the questionnaire. Patients had statistically significant weight loss with a 34% reduction in BMI. Significantly different symptom scores for preoperative vs. postoperative values are expressed in Tables 1 and 2. Abdominal pain, gnawing sensation in the epigastrium, abdominal distention, increased flatus, decreased passage of stools, increased passage of stools, loose stools, urgent need for defecation, heartburn, acid regurgitation, eructation, difficulty falling asleep, insomnia, and feeling rested when awakening were all significantly improved after laparoscopic RY gastric bypass. Nausea and vomiting, borborygmus, hard stools, feelings of incomplete evacuation, and dysphagia were not significantly altered following laparoscopic RY gastric bypass. These results are presented in Table 3.

DISCUSSION

Although many of the comorbidities of morbid obesity are well documented and well understood, gastrointestinal symptoms have been less well documented and their etiology remains somewhat unclear. The proposed etiology of many of the existing preoperative symptoms in morbidly obese patients has been related to increased intra-abdominal pressure. The increased intra-abdominal pressure in obese patients results in a chronic abdominal compartment syndrome, which can produce marked irritable bowel type–symptoms.[8] Irritable bowel–type symptoms (abdominal distention, increased flatus, urgent need for defecation, decreased passage of stools, and increased passage of stools) were significantly improved 6 months after laparoscopic RY gastric bypass (see Tables 1 and 2). If, indeed, increased intra-abdominal pressure is the source of the symptoms of irritable bowel syndrome in morbidly obese individuals, then patients can be informed of the expected improvement as weight loss occurs and pressure decreases.

The higher pressure also aggravates or causes hiatal hernia making gastroesophageal reflux symptoms common among morbidly obese persons. These

Table 1. Symptoms with significant improvement

Symptom	Preoperative	Postoperative	*P* value*
Abdominal distention	38.2 ± 31.5	11.1 ± 19.2	0.0001
Decreased passage of stools	5.4 ± 16.8	17.4 ± 20.0	0.0005
Increased passage of stools	23.9 ± 26.7	6.5 ± 11.7	0.0005
Urgent need for defecation	34.3 ± 26.5	14.3 ± 19.3	0.0009
Heartburn	34.0 ± 26.6	8.0 ± 14.0	0.0001
Acid regurgitation	28.1 ± 24.0	10.7 ± 21.0	0.001
Insomnia	42.4 ± 36.2	21.6 ± 30.5	0.008
Feeling rested when awakening	65.1 ± 33.8	30.5 ± 28.8	0.0001

*Significant *P* value <0.05.

Table 2. Symptoms with significant improvement

Symptom	Preoperative	Postoperative	*P* value*
Abdominal pain	23.3 ± 26.4	8.6 ± 13.5	0.003
Gnawing sensation in the epigastrium	19.3 ± 22.7	7.5 ± 16.0	0.01
Increased flatus	40.2 ± 25.7	25.2 ± 25.3	0.005
Loose stools	29.7 ± 26.5	17.5 ± 20.0	0.03
Eructation	27.7 ± 24.4	15.5 ± 16.9	0.01
Difficulty falling asleep	44.1 ± 38.4	27.5 ± 32.9	0.05

*Significant *P* value <0.05.

symptoms (i.e., gnawing in the epigastrium, heartburn, acid regurgitation, and eructation) all showed significant improvement after laparoscopic RY gastric bypass (Tables 1 and 2). Frezza et al.[9]reported symptomatic improvement in gastroesophageal reflux disease in 238 patients who underwent laparoscopic RY gastric bypass with follow-up as late as 3 years. Many morbidly obese patients demonstrate evidence of sleep apnea on polysomnography. Obstructive sleep apnea is much more common in morbidly obese patients with some studies reporting a 12- to 30-fold increase in symptoms in this population.[10] The pathophysiology of obstructive sleep apnea in morbidly obese persons is excessive soft tissue in the neck leading to airway narrowing and obstruction.[11,12] This study demonstrates a significant improvement in symptoms of insomnia, difficulty falling asleep, and feeling rested when awakening. These findings are consistent with results of previous studies showing that even minimal weight loss improves the symptoms of obstructive sleep apnea.[12]

Approximately one third of morbidly obese patients exhibit habits of overeating that can cause gastric distention and abdominal pain.[13] In addition to many physical comorbid conditions, there are significant psychopathologic factors affecting the morbidly obese.[14] Depression, low self-esteem, and poor body image are common among obese persons. This altered self-image may cause morbidly obese patients to over-report gastrointestinal symptoms. Self-esteem and depression are both improved in the majority of morbidly obese patients who accomplish significant weight reduction.[13] The significant reduction in the severity of abdominal pain may be a result of decreased oral intake with less gastric distention or, perhaps, the improved self-image and self-esteem that often occur after significant weight loss.

Table 3. Symptoms with no significant difference

Symptom	Preoperative	Postoperative	*P* value*
Nausea and vomiting	17.2 ± 22.7	22.1 ± 19.9	0.33
Borborygmus	28.8 ± 25.2	26.8 ± 29.7	0.75
Hard stools	10.3 ± 22.9	7.1 ± 18.6	0.56
Feelings of incomplete evacuation	17.2 ± 22.8	13.4 ± 21.7	0.45
Dysphagia	10.9 ± 15.6	17.7 ± 28.4	0.18

*Significant *P* value <0.05.

It is of particular importance that nausea and vomiting and dysphagia did not change significantly compared to the preoperative population (Table 3). Postoperative nausea, vomiting, and dysphagia are symptoms of known complications of the operation (bowel obstruction, anastomotic stricture, Roux limb herniation, etc.) and should alert the surgeon to a potential problem. These symptoms should not be dismissed as "normal" postoperative sequelae because they are improved based on these data.

CONCLUSION

Laparoscopic RY gastric bypass significantly improves many of the gastrointestinal symptoms experienced by morbidly obese patients without adversely affecting any of the measured parameters. This information is useful in preoperative counseling to ensure patients of overall symptomatic improvement after this operation. Surgeons should be aware that adverse symptoms are usually indicative of a problem that warrants investigation.

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Choledochal Cyst or Pancreatic (Retention) Cyst: A Case Report

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Right upper quadrant cystic lesions can be difficult to differentiate using noninvasive imaging modalities. The following case report dicuss the common cystic lesions of the hepatoduodenal ligament and right sided pancreas. (J GASTROINTEST SURG 2003;7:754–757)

KEY WORDS: Choledochal cyst, pancreatic cyst

A 64-year-old woman was seen at a local hospital with a 1-month history of epigastric pressure associated with meals and certain body positions. She denied any weight loss and her appetite was normal. She had one episode of nausea but no emesis. Her medical history included hypercholesterolemia and hypertension. She had no history of pancreatitis, biliary disease, or ethanol abuse. Physical examination findings included mild midepigastric tenderness and right upper quadrant abdominal fullness. There was no jaundice. On laboratory evaluation the white blood cell count and the serum electrolyte, bilirubin, and alkaline phosphatase levels were all normal. Serum amylase, lipase, and hepatic transaminase levels were moderately elevated. Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were normal. Radiologic studies included contrast-enhanced computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP), both of which were officially reported to show a fusiform dilatation of the extrahepatic biliary tree (Figs. 1 and 2). A presumptive diagnosis of choledochal cyst (type I) was made. The patient was referred to The Johns Hopkins Hospital, where an operative resection was planned.

Operative exploration of the abdomen showed a uniformly dilated extrahepatic biliary tree and an 8 cm benign-appearing cystic mass in the posterior aspect of the head of the pancreas and uncinate process, which compressed the common bile duct laterally against the duodenal wall. A pylorus-preserving pancreaticoduodenectomy was necessary to completely excise the lesion. The patient had an uncomplicated recovery.

Gross pathologic evaluation revealed an 8×6 cm cystic mass containing serosanguinous fluid in the head of the pancreas. The body and tail of the pancreas were grossly normal. The cut margin of the common bile duct was 1.5 cm in diameter. The duodenum was grossly normal. Microscopic evaluation revealed normal pancreatic parenchyma, multiple foci of pancreatic intraepithelial neoplasia (PanIN), including PanIN-2, and patchy chronic pancreatitis. Mucinous epithelium was completely absent from the cyst, and no foci of any other kind of epithelium were present. There were no inflammatory changes surrounding the cyst to suggest rapid cyst enlargement and subsequent epithelial loss. There was no communication between the cyst and the main pancreatic duct. Foci of PanIN-1a were present at the pancreatic margin. The common bile duct showed no dysplasia. The resection margins and all of the included lymph nodes were negative for invasive neoplasia. These pathologic findings were most consistent with a diagnosis of pancreatic retention cyst. Nine months after her operation, the patient had fully resumed normal activities and was asymptomatic.

DISCUSSION

Cystic lesions of the pancreas are a diverse group of disorders that range from benign to frankly malignant

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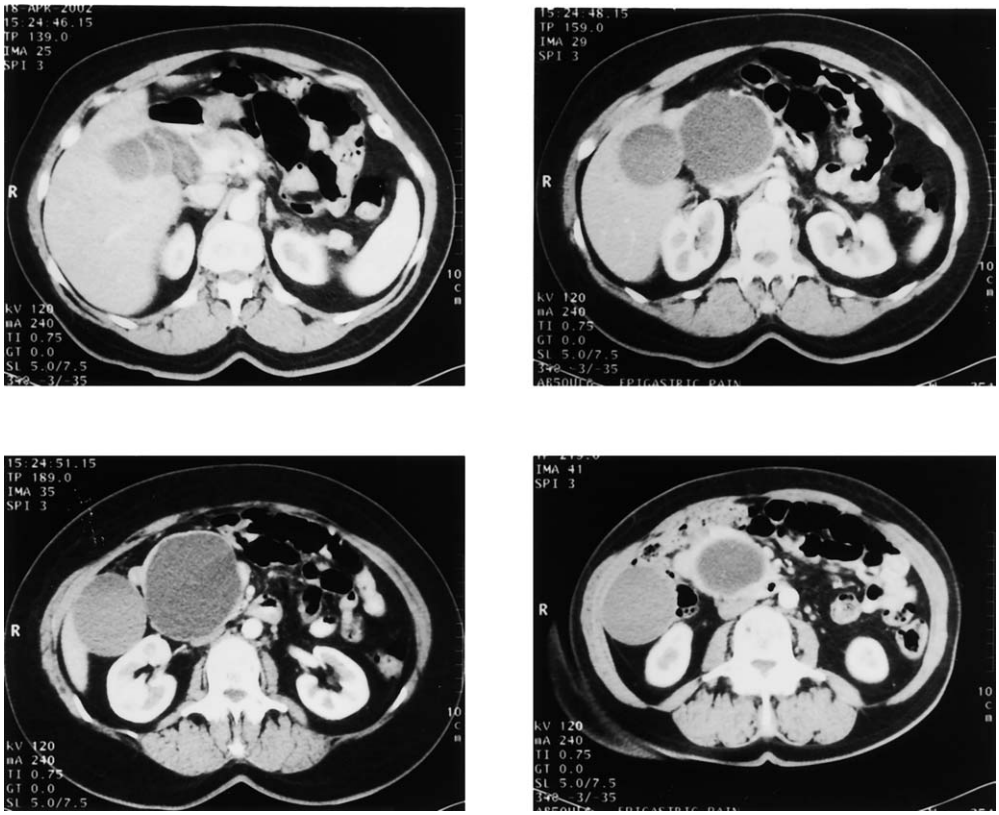

Fig. 1. Series of abdominal CT images with both oral and intravenous contrast revealing a large gallbladder and an 8 cm cystic lesion. The lesion extends from the hepatic hilum (*top left*) inferiorly to the point where it is surrounded by pancreatic parenchyma (*bottom right*).

lesions, and include those with varying degrees of malignant potential. Although the widespread use of CT and MRI has led to an increase in detection of these lesions, it remains difficult to accurately determine the specific type of lesion that is present on the basis of imaging studies alone. In a report by Procacci et al.,[1] when pseudocysts were excluded, CT imaging led to the correct diagnosis of cyst pathology in only 60% of patients. Although MRCP is particularly useful in the evaluation of suspected intraductal papillary mucinous neoplasms,[2] conventional MRI has not yet offered a measurable advantage over CT in determining the pathology of other cystic lesions of the pancreas. Endoscopic ultrasound imaging can provide detailed diagnostic information about cystic lesions of the pancreas and biliary tree. On endoscopic ultrasound images, benign cystic lesions of the pancreas, including pseudocyst, congenital cyst, and retention cyst, appear as thin-walled, nonseptated, simple cysts.[3,4] Endoscopic retrograde cholangiopancreatography or percutaneous cholangiography should reliably distinguish cystic lesions of the biliary tree from a cystic lesion of the pancreas. However, because of the increased risk of complications associated with these invasive procedures, each should be reserved for those cases in which less invasive studies are nondiagnostic.[5]

Aspiration of fluid from pancreatic cysts may also provide useful information about these cysts and should be considered in those cases in which diagnostic or therapeutic uncertainty remains despite thorough radiographic investigation.[6] Cyst fluid can be obtained by transabdominal ultrasound, endoscopic ultrasound, or CT-guided fine-needle aspiration. Analysis of cyst fluid includes measurement of amylase and lipase, mucin content, fluid viscosity, tumor markers (e.g., CEA, CA19-9, and CA 72-4), and cytologic examination.[7–9] In patients with a benign-appearing cystic lesion of the pancreas and a history of pancreatitis, elevated levels of amylase and lipase in the cyst fluid are suggestive of pseudocyst.[8,9] Sperti et al.[7] found the combination of elevated levels of pancreatic cyst fluid CA 72-4 and serum CA 19-9 were highly suggestive of either mucinous cystic neoplasm or pancreatic adenocarcinoma.[7] Alternatively, high levels of serum CA 19-9 in a patient with a

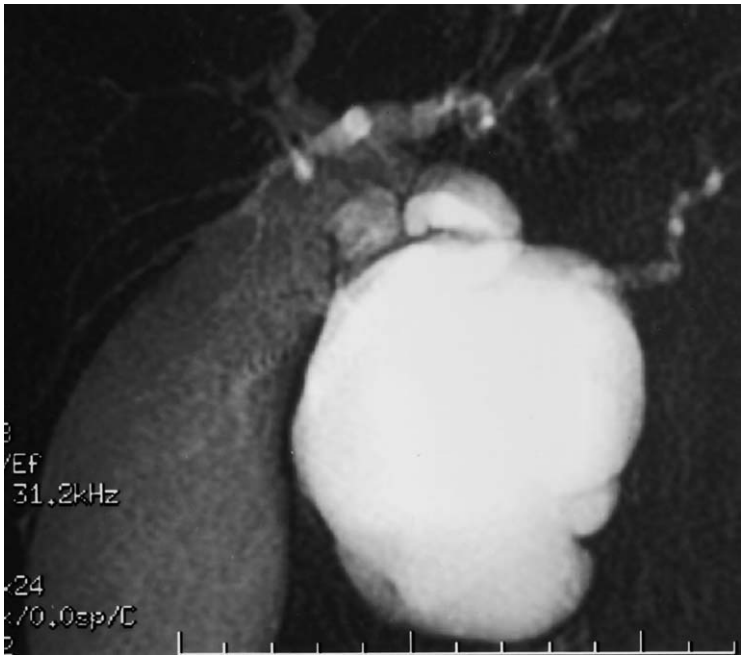

Fig. 2. MRCP image showing nondilated intrahepatic ducts, a large gallbladder, and a large, nearly spherical cystic lesion residing in the lower hepatoduodenal ligament and head of the pancreas.

pancreatic cyst should raise suspicion for a retention cyst, with or without synchronous pancreatic adenocarcinoma.[10] The preceding diagnostic studies notwithstanding, a diagnosis made prior to pathologic evaluation of the resected cyst can be incorrect, and may result in inappropriate treatment of patients with cystic lesions of the pancreas.[11] Moreover, for patients with symptomatic cystic lesions of the pancreas that are not pseudocysts, there is no need for cyst aspiration to analyze fluid because surgical resection is the appropriate treatment.

A pancreatic retention cyst is a distinct type of cystic lesion that may be congenital or may result from pancreatic ductal obstruction in the setting of pancreatic carcinoma.[12] Although they are uncommon, retention cysts have been reported in up to 15% of patients with pancreatic carcinoma.[13] In the case reported here, a retention cyst was present in the setting of low-grade pancreatic intraepithelial neoplasia (PanIN), a precursor to infiltrating pancreatic ductal adenocarcinoma.[14] However, low-grade PanIN lesions are not uncommonly seen incidentally at the time of histologic evaluation of pancreatic resection specimens, when the natural history of low-grade PanINs is unknown.

Choledochal cysts, which are seen in both adults and children, typically are associated with biliary-type symptoms (discomfort, fever, jaundice) and findings on CT and MRI that mimic those that are associated with a pancreatic cyst.[15] When choledochal cyst is suspected, but cannot be confirmed by noninvasive imaging studies, endoscopic cholangiography or percutaneous cholangiography should lead to the correct diagnosis.[16] Choledochal cysts have the potential to be associated with either infectious complications or biliary epithelial malignancy, and are therefore usually treated by complete excision of the cyst followed by biliary reconstruction.[15,16]

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Delayed Gastric Emptying After Pylorus-Preserving Pancreatoduodenectomy Is Strongly Related to Other Postoperative Complications

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Patients undergoing pylorus-preserving pancreatoduodenenectomy (PPPD) have a risk of up to 50% for developing delayed gastric emptying (DGE) in the early postoperative course. From 1994 to August 2002, a total of 204 patients underwent PPPD for pancreatic or periampullary cancer (50%), chronic pancreatitis (42%), and other indications (8%). Retrocolic end-to-side duodenojejunostomy was performed below the mesocolon. DGE was defined by the inability to tolerate a regular diet after day 10 (DGE10) or day 14 (DGE14) postoperatively, as well as the need for a nasogastric tube at or beyond day 10 (DGE10GT). Postoperative morbidity was 38%, 30-day mortality was 2.9%, and median postoperative length of stay was 15 days. DGE occurred in 14.7% (DGE10), 5.9% (DGE14), and 6.4% (DGE10GT), respectively. After further exclusion of 21 patients (10.3%) with major complications and no possible oral intake (because of death, reoperation, or mechanical ventilation), the frequencies of DGE10, DGE14, and DGE10GT in the remaining group of 183 patients were 9%, 2%, and 2%, respectively. Multivariate analysis revealed postoperative complications ($P < 0.001$), the presence of portalvenous hypertension ($P < 0.01$), and tumors as indications for surgery ($P < 0.01$) as independent risk factors for DGE10. The overall incidence of DGE was low after PPPD. In those patients experiencing DGE, however, other postoperative complications were the most important factor associated with its occurrence. (J GASTROINTEST SURG 2003;7:758–765)

KEY WORDS: Delayed gastric emptying, pylorus-preserving duodenopancreatectomy, pancreatic cancer, chronic pancreatitis

Pylorus-preserving pancreatoduodenectomy (PPPD) was reintroduced by Traverso and Longmire[1] in 1978 as an alternative to the classic Whipple operation. Compared to the Whipple procedure, PPPD is associated with shorter operation times, less blood loss, and fewer complications.[2] Therefore PPPD has become the standard procedure in oncologic pancreatic surgery in many centers. It also plays an important role in patients undergoing surgery for chronic pancreatitis.[3]

Despite an in-hospital mortality rate of less than 5% in many experienced centers, morbidity is still relatively high after pancreatoduodenectomy.[4–6] Delayed gastric emptying (DGE) is one of the most relevant and frequent postoperative complications published and has been reported in the range of 19% to 57%.[4,7,8] Although DGE has also been reported after gastric surgery alone or other types of abdominal surgery,[9] it has been identified as a frequent and specific complication after pancreatic head resection, especially after PPPD. A high rate of DGE after PPPD has even led to a switch back to the Whipple operation in at least one leading pancreatic surgery center.[3,5]

The origin of DGE after pancreatoduodenectomy is not clear. DGE has been discussed in relation to the surgical approach such as pylorus preservation,[10] preservation of the right gastric artery,[11] or enteral nutrition in the postoperative course.[7,12] The physiologic impact of the duodenum on gastrointestinal

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function has been examined, as low blood levels of motilin (which originates from the duodenum) are associated with reduced gastric motility.[13] As a consequence, gastric emptying has been improved by the application of erythromycin, which is an agonist to motilin.[14]

In contrast to these specific reasons for DGE, other investigators reported that postoperative complications, postoperative sepsis, and the need for reoperation are the principal causes of DGE.[8,15]

Definition of DGE after pancreatoduodenectomy is not used consistently. Reviewing the published data, it is not possible to find a general criterion for DGE. Delayed gastric emptying has been defined, for example, by the need for a gastric decompression tube[8] as well as the inability to consume a regular diet.[10] The point in time from when DGE has been defined varies from 7 to 14 days after surgery.

In this article we report our experience with DGE in more than 200 patients undergoing PPPD during an 8-year period. For a better understanding of DGE and for comparison of our results with previously published data, we applied three different definitions of DGE. We further used univariate and multivariate analyses to assess possible risk factors for DGE in our patients.

MATERIAL AND METHODS

From 1994 to August 2002, a total of 204 patients whose median age was 58 years (range 30 to 77 years) underwent PPPD. Demographic and disease-related data are presented in Table 1. Indications for surgery were pancreatic, periampullary, or another type of cancer (n = 103; 50.5%), chronic pancreatitis (n = 86; 42.2%), and other (n = 15; 7.4%). Sixteen of the 86 patients with chronic pancreatitis had generalized (n = 4) or regional (n = 12) portal hypertension due to occlusion or compression of (parts of) the portalvenous system.

Surgical Technique and Postoperative Care

The surgical procedure was standardized throughout the study period. The duodenum was resected 0.5 to 2 cm distal to the pylorus. The right gastric artery was always transected. After removal of the specimen, the jejunum was brought up to the subhepatic space through a slot in the right portion of the transverse mesocolon. An end-to-side pancreatojejunostomy and an end-to-side hepaticojejunostomy were performed. These anastomoses were generally created by means of a full-thickness technique using interrupted polydioxanone sutures. Afterward the distal portion of the stomach/duodenum was pulled through another slot in the left half of the transverse mesocolon. An end-to-side retrocolic duodenojejunostomy was thus created approximately 50 cm distal to the biliary anastomosis below the mesocolon (Fig. 1). The duodenojejunostomy was also created using interrupted stitch techniques.

If the operations were performed for malignant tumors, a lymphadenectomy was carried out along the hepatoduodenal ligament, common hepatic artery, vena cava, superior mesenteric vein, and along the right side of the superior mesenteric artery. No lymphadenectomy was performed in patients with proved benign disease. The pancreatic and biliary anastomoses were always drained using flat silicone drains, which were taken out through the right abdominal wall.

Table 1. Demographic and disease-related characteristics of 204 patients treated by pylorus-preserving pancreatoduodenectomy

Median age (years)	58 (30–77)
Sex	
(male:female)	129:75
Indications for surgery	
Chronic pancreatitis	88 (42.2%)
Malignancies	103 (50.5%)
Cancer pancreatic head	63
Carcinoma of the ampulla	23
Distal bile duct cancer	14
Duodenal cancer	1
Other malignancies	2
Other	15 (7.4%)
Jaundice	111 (54.4%)
Preoperative biliary drainage	105 (51.5%)
Diabetes	53 (26.0%)

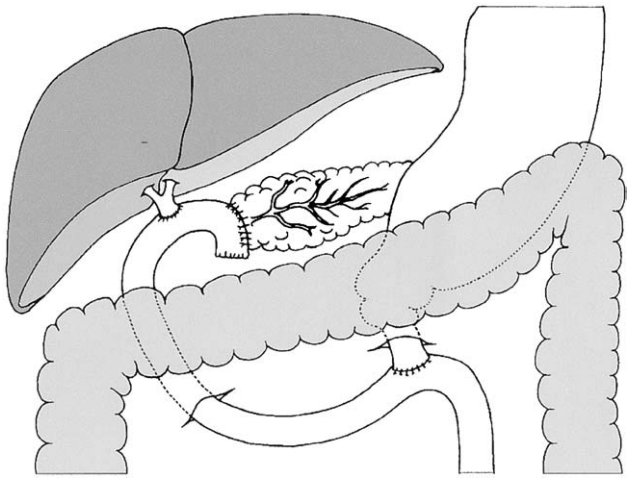

Fig. 1. Schematic illustration demonstrating the reconstruction technique used in pylorus-preserving pancreatoduodenectomy.

Since 1997 a nasojejunal feeding tube with an accessory gastric draining channel (Freka Trelumina; Fresenius Kabi GmbH, Germany) has been placed in 146 patients (72%) at the end of the operation. In these patients enteral feeding was generally started on day 1 after surgery with 500 ml of tea via this feeding tube. This was increased to 1000 to 1500 ml of a standardized elemental diet on day 2 or 3. In the absence of relevant gastroparesis, oral fluid intake was also started within 48 hours after surgery. When patients did not develop DGE, the nasojejunal tube was withdrawn on day 4 or 5, with subsequent return to a regular diet.

Perioperative care was standardized throughout the study period. Postoperatively the patients remained in the surgical intensive care unit for at least one night. All patients received octreotide three times, 100 μg for 5 to 7 days. Prokinetic drugs (e.g., erythromycin) were not used routinely but were prescribed in a few patients with DGE.

Data Acquisition

Since the beginning of the study period, the most relevant patient- and surgery-related data were entered prospectively into a computerized database. For the purpose of this study, additional data were obtained retrospectively from the hospital charts.

Definition of Delayed Gastric Emptying

For the purpose of our study, DGE was defined as the inability to consume a regular diet by day 10 (DGE10) or day 14 (DGE14) postoperatively as well as the need for a nasogastric drainage tube on or beyond day 10 (DGE10GT). The three different definitions could be applied well since nutrition, type and duration of gastric tubes, vomiting, and gastrointestinal function were completely documented in the hospital charts.

Statistical Analysis

By means of univariate and multivariate analysis, we examined a total of 16 perioperative parameters to assess their influence on the occurrence of DGE. The impact of potential risk factors on the development of DGE was univariately analyzed using the chi-square statistic. For multivariate analysis of risk factors for DGE, variables associated with postoperative complications in univariate analysis (with $P < 0.2$) were entered into a binary logistic regression model with stepwise forward selection strategy using the likelihood ratio statistic.

This model requires at least one event (patient) per cell in the 2×2 univariate tables. However, none of the patients without other postoperative complications showed DGE at postoperative day 14. To allow calculation of the likelihood ratio in the binary logistic regression model, a value of 1 was added to this group.

Statistical analysis was performed using SPSS for Windows (release 10; SPSS Inc., Chicago, IL).

RESULTS

The median duration of surgery was 470 minutes (range 270 to 870 minutes) in the 204 patients undergoing PPPD. The median volume of transfused packed red cells was 1200 ml (range 0 to 9600 ml). The median postoperative length of stay in the surviving patients was 15 days (range 9 to 59). The 30-day mortality rate was 2.9% with an overall morbidity of 38%. DGE as defined at day 10 after surgery was the most frequent sole postoperative complication in our study group (Table 2). However, only three patients (1.6%) had DGE10 as the sole complication (without other postoperative complications).

Delayed Gastric Emptying

One week after PPPD, half of the patients were already on a regular diet without vomiting, and 94% of all patients were consuming a regular diet within 14 days after surgery. In the complete study group of all 204 patients, the frequency of postoperative DGE was 14.7% after 10 days (DGE10), 5.6% after 14 days (DGE14), and 6.4% in those needing gastric decompression at or beyond day 10 (DGE 10GT), respectively (Table 3). By regarding the occurrences of DGE10 and DGE14, it was evident that two

Table 2. Most relevant postoperative complications after 204 pylorus-preserving pancreatoduodenectomies*

Type of complication	No.	%
DGE10	30	14.7
Wound infection	17	8.3
Pancreatic leakage	21	10.3
Intra-abdominal abscess	16	7.8
Pneumonia	13	6.4
DGE14	12	5.9
DGE10GT	13	6.4
Postoperative abdominal bleeding	6	2.9
Pancreatitis	4	2.0
Biliary leakage	2	1.0
Gastrointestinal bleeding	4	2.0
Cholangitis	4	2.0
Vascular	4	2.0
Cardiac	3	1.1

*Multiple complications per patient possible.

Table 3. Incidence of delayed gastric emptying in all patients (n = 204): Further analysis of a subgroup (n = 183) of patients without inability to eat due to death, reoperation, and/or mechanical ventilation

	All patients (n = 204)		Potentially able to eat (n = 183)	
	No.	%	No.	%
DGE10	30	14.7%	17	9.3%
DGE14	12	5.9	4	2.2%
DGE10GT	13	6.4%	4	2.2%

thirds of the patients who experienced DGE at day 10 postoperatively returned to normal gastric emptying within the following 4 days.

Univariate analysis of 16 perioperative parameters showed that the occurrence of postoperative complications, the simultaneous resection of other organs, a preoperatively increased creatinine level, more than 1000 ml of packed red cells transfused, the presence of portalvenous hypertension, and surgery performed within the first half of the study period (before January 1, 1999) were associated with a higher frequency of DGE10 (Table 4). Portalvenous hypertension was present exclusively in patients with chronic pancreatitis. Despite the significantly higher rate of DGE10 in the presence of portalvenous hypertension, however, DGE was not more frequently in the complete subgroup of all patients with chronic pancreatitis. DGE10 was strongly related to the presence of other postoperative complications. As already noted, only 3 of 128 patients (2%) without other complications experienced DGE, whereas among the remaining 78 patients with other postoperative complications 27 (35%) had DGE10 ($P < 0.001$).

When analyzing risk factors for DGE14, univariate analyses revealed other postoperative complications ($P < 0.001$), concomitant resection of other organs ($P < 0.01$), patient age greater than 65 years ($P < 0.01$), and absence of early enteral nutrition ($P < 0.03$) as risk factors for DGE14. It is of note that none of the patients without other postoperative complications had DGE 14 days after surgery.

Furthermore, the presence of other postoperative complications ($P < 0.001$), patient age over 65 years ($P < 0.01$), resection of other organs ($P < 0.04$), and presence of tumors as an indication for surgery (compared to chronic pancreatitis; $P < 0.05$) were significantly associated with DGE10GT by univariate analysis.

In multivariate analysis of factors influencing the occurrence of DGE10 (Table 5), the presence of other postoperative complications ($P < 0.001$), tumors as an indication for surgery (compared with chronic

Table 4. Univariate analysis of the influence of 16 perioperative parameters on the occurrence of delayed gastric emptying at 10 days

Parameter	No.	DGE10	*P* value
Sex			
Male	129	15	1.0
Female	75	15	
Other organs resected*			
Yes	16	50	<0.001
No	188	12	
Postoperative complications			
Yes	78	35	<0.001
No	128	2	
Age (yr)			
>65	49	22	0.1
<66	155	12	
Preoperative albumin			
<35 g/dl	52	12	0.65
Normal	152	16	
Preoperative hemoglobin			
<7.4 mmol/L	44	21	0.23
Normal	160	13	
Preoperative creatinine			
>88 μmol/L	29	31	<0.02
Normal	175	12	
Preoperative bilirubin			
>22 μmol/L	67	16	0.63
Normal	137	14	
Preoperative leukocytes			
Elevated	47	15	1.0
Not elevated	157	15	
Blood transfused			
>1000 ml	104	21	0.01
Up to 1000 ml	100	8	
Preoperative diabetes			
No	151	13	0.82
Yes	53	15	
Underlying disease			
Chronic pancreatitis	86	11	0.14
Other	118	18	
Preoperative biliary drainage			
Yes	105	12	0.33
No	99	17	
Early enteral feeding			
Yes	159	12	0.06
No	45	24	
Study period			
First half	100	21	<0.02
Second half	104	9	
Portalvenous hypertension			
No	188	12	<0.005
Yes	16	44	

*Resection of other organs in the 18 patients: splenectomy (10), colonic resection (4), partial liver resection (2), and nephrectomy (2).

Table 5. Results of multivariate analysis of risk factors for delayed gastric emptying in all patients and after exclusion of 21 patients unable to eat for other reasons

Definition of DGE	Independent risk factors	*P*	Relative risk	95% confidence interval
All 204 patients				
DGE10	Portalvenous hypertension	<0.01	16	2.3–111
	Tumors	<0.01	9	1.8–44
	Other complications	<0.001	21	5.8–78
DGE14	Other complications	<0.01	18	2.3–143
DGE10GT	Other complications	<0.01	22	2.8–123
	age >65 yr	<0.01	7.6	2.1–28
183 patients potentially able to eat				
DGE10	Other complications	<0.001	11.7	3–45

pancreatitis; $P < 0.01$), and the presence of portalvenous hypertension ($P < 0.01$) were independently associated with DGE10. Multivariate analysis further demonstrated that the presence of other postoperative complications (DGE14 and DGE10GT) and patient age greater than 65 years were independent risk factors for the other definitions of DGE (see Table 5).

DGE After Exclusion of Patients Unable to Eat for Other Reasons

According to its definition, DGE may also be found in patients who are not able to eat for reasons other than impaired gastric function itself. To clarify this and, therefore, to assess gastric emptying in patients who are potentially able to eat, we reassessed DGE after the exclusion of 21 patients who could not eat because of major complications. These 21 patients had had a reoperation and/or were on mechanical ventilation. All five patients who died postoperatively were in this group and thus were also excluded.

Among the remaining 183 patients potentially able to eat, the frequencies of DGE were 9.2% (DGE10), 2.2% (DGE14), and 2.2% (DGE10GT). Again, multivariate analysis revealed other postoperative complications as risk factor for DGE. It is of note that in this analysis, after previous exclusion of patients with reoperation and/or mechanical ventilation, 14 of 17 patients with DGE10 had other postoperative complications. Because of the low frequency of DGE14 and DG10GT in this subanalysis of 183 patients potentially able to eat, risk factors could not be identified for these two definitions of DGE.

The occurrence of other postoperative complications was the strongest predictive factor for the development of further or concomitant DGE. To analyze which preoperative or intraoperative factors may predict DGE, we repeated all multivariate calculations without considering other postoperative complications as a potential risk factor. In these analyses the resection of other organs, tumors as an indication for surgery (as compared to chronic pancreatitis), a preoperatively elevated creatinine level, the presence of portalvenous hypertension, and patient age over 65 years were associated with the different definitions of DGE.

To evaluate which factors lead to other postoperative complications and therefore predispose to patients to DGE, we performed independent factor analyses of the remaining 15 parameters to find out which factors independently may increase the rate of postoperative complications. Multivariate analysis showed that a preoperatively elevated creatinine level ($P < 0.03$) and the concomitant resection of other organs ($P < 0.03$) were significantly associated with the occurrence of other postoperative complications.

DISCUSSION

DGE is a frequent complication after PPPD. Its occurrence has been published in the past in up to 57%.[16] Recent studies still report an overall incidence of DGE of 12% to 35%.[7,8,10,17] In a large study, Yeo et al.[4] observed DGE as the most frequent sole postoperative complication (19%) after pancreatoduodenectomy.

The wide range of DGE in the different studies can be explained partially by differences in the definition of this complication. For a better comparison of our data with published reports, and to assess the relevance of DGE in our patients, we simultaneously applied three different established definitions of this complication.

In our study DGE10, defined as inability to eat normally 10 days after surgery, also was the most frequent complication after PPPD. However, we could demonstrate that DGE played only a minor overall role after PPPD because two thirds of those patients who experienced DGE 10 days after surgery were able to eat regularly 4 days later.

We found that DGE was strongly related to other postoperative complications. Approximately one third of the patients with other postoperative complications had DGE10, whereas only 2% of the patients without other complications developed DGE10. Regarding DGE 14 days after surgery, it was of note that none of the patients without other postoperative complications had symptoms of DGE.

By multivariate analysis we were able to demonstrate that patients with tumors (as compared with chronic pancreatitis) and patients with portalvenous hypertension (all with concomitant chronic pancreatitis) were at risk for the development of DGE. Surgery in patients with malignant tumors differs from surgery in patients with chronic pancreatitis by lymphadenectomy. By removing lymphatic tissue and disturbing local innervation, lymphadenectomy may be associated with DGE after PPPD.

In our study, patients with portalvenous hypertension had more postoperative complications and greater amounts of blood loss. Despite these facts, multivariate analysis revealed an independent risk for DGE10 in these patients. DGE in these patients, therefore, is probably not related alone to the increased complication rate. It is possible that gastric venous stasis contributed to disturbances of gastric emptying in those patients.

The exclusion of patients who were unable to eat for other reasons such as reoperation and/or mechanical ventilation enabled us to further assess the "true" relevance of DGE. In this subanalysis only 2% of the patients showed relevant disturbances of gastric emptying 14 days after surgery.

The reasons why DGE develops after PPPD are poorly understood. There are several factors that may contribute to the development of DGE such as the correlation of DGE with other postoperative complications, the anatomic location of the stomach and the duodenojejunostomy, innervation of the stomach and the duodenum,[16,18,19] blood supply[2,16,20] to the distal stomach, and postoperative changes in gastrointestinal hormones.[13,14,21–23]

Delayed Gastric Emptying and Postoperative Complications

The influence of complications on the appearance of DGE has already been reported in several studies.[6,8,10,15,24,25] In a small study by Kimura et al.,[15] all 10 patients with septic postoperative complications also had DGE. In a large number of patients, the group from Amsterdam were able to demostrate that the presence of intra-abdominal complications was the most significant factor for DGE, which occurred in 65% of the patients with those complications.[6] In another study of 51 patients undergoing PPPD, Horstmann et al.[10] found that DGE almost never occurred after uncomplicated surgery (3% DGE), whereas the rate of DGE increased significantly to one third in patients with other postoperative complications.

The reasons why other postoperative complications may lead to DGE are not fully understood. Although postoperative complications may prevent patients from eating (because of reoperation and/or mechanical ventilation), we still found the presence of postoperative complications to be an independent risk factor for DGE 10 days after surgery in the subgroup of patients potentially able to eat. It has been suggested that gastroparesis as a consequence of local inflammation may be the main cause of DGE in these cases.[6] Despite those suggestions for a major role of other complications in the pathogenesis of DGE, this fact was not supported by the study by Jimenez et al.[3] from Boston where only 1 of 17 patients with DGE had an abdominal complication.

Delayed Gastric Emptying and Location of the Duodenojejunostomy

It has been suggested that the location of the duodenojejunostomy and the type of reconstruction may influence postoperative gastric emptying in different ways.[10,17,26] A mechanical etiology for DGE was proposed by at least two groups.[10,26] They suspected that the so-called "antecolic reconstruction," in which the relatively fixed stomach is anastomosed above the transverse mesocolon to the draining jejunal loop, may lead to an angulation or torsion of the stomach, resulting in an outflow obstruction. In both studies DGE was observed significantly less frequently when the anastomoses were performed below the transverse mesocolon ("retrocolic reconstruction").

In addition to this mechanical theory, it has also been suggested that the anatomic location of the duodenojejunostomy in the neighborhood of the field of pancreatic head resection and the biliary and pancreatic anastomoses (position above the mesocolon) may promote DGE by local inflammation. This inflammation can be induced in this location by residual hematomas, lymphatic fistulas after resection, or leakage from the pancreatic or biliary anastomoses. After the technique was changed to a reconstruction below the mesocolon, rates of DGE decreased in two series.[10,27] In line with these results, our data also suggest that the type of reconstruction may be the key to avoiding DGE after PPPD.

We also perform the duodenojejunostomy below the mesocolon. In contrast to both groups, however, the distal stomach in our patients is taken down to the

inframesocolic region through a separate incision in the transverse mesocolon.

Enteral Nutrition and Delayed Gastric Emptying

The value of early enteral nutrition after major abdominal surgery is still controversial. Enteral nutrition was suggested to prevent gut mucosal atrophy and therefore breakdown of the mucosal barrier with subsequent bacterial translocation. Although several advantages such as reduction of septic complications, improved wound healing,[28,29] and reduced weight loss[30,31] have been demonstrated, an overall benefit of early enteral nutrition with regard to morbidity and mortality after pancreatoduodenectomy has not been shown in recent studies.[32,33] Other publications showed rather an opposite influence of early enteral feeding. It correlated with an impaired postoperative course such as DGE or impaired respiratory mechanics.[7,32] Following a classic Whipple resection, early enteral feeding via nasogastric tube was associated with a significantly higher frequency of DGE.[7] Because of the previously published advantages, we also started early enteral nutrition via a nasojejunal feeding tube in 1997. According to our data, early enteral feeding via the jejunal route does not promote DGE.

CONCLUSION

Our results demonstrate that DGE alone is not necessarily a relevant complication after PPPD by means of our operative technique. DGE is almost absent in patients without other postoperative complications. Our data suggest that a variety of intraabdominal complications might be responsible for DGE. Risk factors for those complications such as impaired renal function, extended resection (lymphadenectomy, resection of other organs), or portalvenous hypertension (in patients with chronic pancreatitis) may therefore predict DGE after PPPD.

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Surgical Resection Following Radiation Therapy With Concurrent Gemcitabine in Patients With Previously Unresectable Adenocarcinoma of the Pancreas

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The combination of gemcitabine with concurrent radiation therapy (Gem/RT) is a promising new approach that is being investigated in patients with unresectable pancreatic cancer. However, substantial toxicity with this combination has also been observed. This review was conducted to determine whether Gem/RT could be safely delivered in the neoadjuvant setting, based on our experience with this combined therapy in a cohort of patients with previously unresectable pancreatic cancer, who subsequently underwent surgical resection. Between July 1996 and June 2001, a total of 67 patients with locally unresectable pancreatic cancer, without distant metastatic disease, received Gem/RT at our institution. Seventeen patients (25%) underwent exploratory surgery following Gem/RT, and nine underwent standard Whipple resection. Thus 9 (52%) of 17 patients who had exploratory operations or 9 (13%) of 67 patients, underwent surgical resection. Thirty-day mortality after resection was 0%, and there were no major surgical complications. Median length of hospital stay was 14 days (range 11 to 19 days). With a median follow-up of 32 months, median survival for the resected patients was 17.6 months (95% confidence interval 12.6 to 37.3 months). Median survival for the remaining 58 patients was 11.9 months (95% confidence interval 9.6 to 14.7 months, $P = 0.013$). We conclude that surgical resection may be safely performed after Gem/RT in a select group of patients initially considered to have unresectable pancreatic cancer. The use of Gem/RT in a neoadjuvant setting is currently being investigated in a multi-institutional phase II trial. (J GASTROINTEST SURG 2003;7:766–772)

KEY WORDS: Pancreatic cancer, gemcitabine, chemoradiotherapy, Whipple resection

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the United States, with an estimated 29,700 deaths in 2002.[1] Overall survival at 5 years is less than 5%. Among those who undergo surgery with curative intent and receive adjuvant chemoradiotherapy, the 5-year survival rate rises to approximately 20% to 30%.[2,3] Unfortunately the vast majority of patients who are first seen with pancreatic cancer are not candidates for resection because they have locally advanced disease or distant metastases.

Patients who have unresectable disease are often treated with concurrent fluorouracil (5-FU)–based chemoradiotherapy, based on early trials by the Gastrointestinal Tumor Study Group, which demonstrated a modest survival benefit with chemoradiotherapy when compared to radiation therapy or chemotherapy alone.[4,5] Occasionally chemoradiation will downstage unresectable pancreatic tumors to allow for surgical resection.[6–11] Several investigators have specifically studied neoadjuvant chemoradiotherapy to improve outcome among patients initially judged to have resectable lesions.[3,12] A practical issue which supports this approach is that prolonged recovery after surgery may prevent delivery of postoperative adjuvant therapy. In addition, a preoperative

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course of treatment provides an interval window to identify patients with progressive metastatic disease, sparing these patients an operation that would contribute little to overall management. Neoadjuvant therapy may also increase the likelihood of a potentially curative resection. Theoretical considerations supporting a preoperative approach include increased effectiveness of radiation on well-oxygenated cells that have not been rendered hypoxic as a result of surgery, and reduction of the number of viable tumor cells shed into the peritoneum or bloodstream.

The use of gemcitabine with concurrent radiotherapy (Gem/RT) represents an alternative approach to improve outcomes in patients with pancreatic cancer. Gemcitabine has been shown to provide a survival advantage over 5-FU in patients with locally advanced (unresectable) or metastatic pancreatic cancer, as well as symptomatic relief in patients with metastatic pancreatic cancer in whom prior treatment with 5-FU has failed.[13,14] Thus integration of gemcitabine with radiation in a combined-modality regimen warrants investigation. This investigation is prompted further by laboratory studies that have demonstrated potent radiosensitization with gemcitabine in human cancer cell lines including pancreatic cancer cell lines.[15] Since 1996 our institution has conducted sequential phase I trials investigating the use of gemcitabine with concurrent radiation therapy in patients with pancreatic cancer. The initial trial attempted to determine the maximum tolerable dose of gemcitabine when delivered once weekly, concurrent with a relatively conventional course of radiation therapy (50.4 Gy in 1.8 Gy fractions).[16] The second, an alternative strategy, used a standard dose of gemcitabine (1000 mg/m^2/wk), considering the clinical benefit associated with its use as a systemic agent, and investigated the tolerable radiation dose that could be delivered to the primary tumor (without inclusion of regional lymph nodes basins).[17] The goal of this approach was to maximize the systemic drug effect while providing local control through sensitization of a modest radiation dose. Escalation of the radiation dose was achieved by increasing the fraction size, thus keeping the duration of radiation at 3 weeks. In the third trial, cisplatin was added to the combination of standard-dose gemcitabine and concurrent radiation therapy in an attempt to further improve the control of local and systemic disease.[18] Each trial required documentation of locally advanced, unresectable disease. Our experience indicates that Gem/RT resulted in sufficient tumor regression in some patients to allow surgical resection. This study examines a group of patients at a single academic center who were initially diagnosed as having locally unresectable pancreatic adenocarcinoma, yet underwent surgical resection after Gem/RT. The review was conducted to determine whether surgical resection could be performed without undue morbidity or mortality such that Gem/RT could be further investigated in the neoadjuvant setting.

PATIENTS AND METHODS

Eligibility

Patients eligible for this review included those with locally advanced pancreatic cancer who received Gem/RT during one of the phase I clinical trials noted earlier, or "off protocol" based on the trial investigating radiation dose escalation with full-dose gemcitabine. These latter patients were treated at a radiation dose level previously judged to be tolerable during periods when the protocol itself was closed to patient accrual. The radiation dose escalation trial and the cisplatin dose escalation trial allowed for entry of patients with proved or suspected metastatic disease. These patients were excluded from this review because they never would have been considered candidates for surgical resection. The determination of unresectability was made after surgical consultation, based on evaluation including CT, endoscopic ultrasound imaging, magnetic resonance imaging, or surgical exploration. Each of the phase I trials was approved by the institutional review board of the University of Michigan Medical School. Institutional review board approval was also obtained for retrospective review of the "off study" patients.

Treatment

Patients treated in the trial of gemcitabine dose escalation were a subgroup of the entire population of a multi-institutional phase I study. Gemcitabine was delivered once weekly, with conventional radiation therapy directed at the tumor and regional lymphatics. A margin of 3 cm around the gross target volume was required for the initial field (39.6 Gy). This margin was reduced to 2 cm for the final boost (10.8 Gy). The starting dose of gemcitabine was 300 mg/m^2, and this dose was escalated in subsequent patient cohorts to 700 mg/m^2 based on the presence or absence of dose-limiting toxicity in cohorts of three to six patients at each dosage level. Approximately 4 weeks after completion of chemoradiotherapy, a CT scan was obtained to assess response. Four additional treatments with gemcitabine alone were then prescribed by the protocol. Patients treated in the trial of radiation dose escalation received gemcitabine at a dosage of 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Radiation therapy (15 fractions)

was initiated on day 1 and was planned with three-dimensional radiation treatment planning to cover only the gross tumor volume (i.e., no elective nodal irradiation). Doses of 24 to 42 Gy (1.6 to 2.8 Gy fractions) were investigated. Dose escalation was based on the presence or absence of dose-limiting toxicity in cohorts of three to six patients at each dosage level. A second cycle of gemcitabine alone was intended following a 1-week rest. A repeat CT scan was obtained 2 weeks after this second cycle of gemcitabine, approximately 6 weeks after completion of radiation therapy. Patients treated on the cisplatin dose escalation trial received gemcitabine as in the preceding trial, concurrent with 36 Gy in 2.4 Gy fractions. Cisplatin was given on days 1 and 15 of each cycle. Patients were assigned doses ranging from 30 to 50 mg/m^2 based on a phase I trial design that used the time-to-event continual reassessment method.[19] Evaluation for response occurred as it did with the radiation dose escalation trial. In both trials, additional gemcitabine-based chemotherapy could be delivered at the discretion of the treating physician. Patients were evaluated clinically, immediately after post-therapy CT. Clinical and radiographic findings for those patients who remained without evidence of local or distant progression were then presented to a multidisciplinary gastrointestinal tumor board where decisions regarding surgical intervention versus continued chemotherapy were made. Patients who received additional chemotherapy alone and remained without evidence of local or distant disease progression were presented again, generally after two to four cycles of chemotherapy. The acute toxicity, late toxicity, response rates, patterns of failure, and survival data from each of the phase I trials have been reported in separate publications.[16–18]

Retrospective Evaluation of Unresectability and Surgical Experience

For the purpose of this review, helical CT scans (which had been obtained from all patients within 2 weeks of initiation of treatment) were reviewed, and patients were classified into two categories using the criteria defined in the national comprehensive cancer network (NCCN) guidelines for pancreatic cancer.[20] Borderline resectable lesions are those with severe unilateral superior mesenteric vein/portal impingement, tumor abutment on superior mesenteric artery, or colon invasion. Locally unresectable lesions are those with superior mesenteric artery/celiac/hepatic artery encasement, aortic/inferior vena cava invasion or encasement, or superior mesenteric vein/portal occlusion. Patient records were then reviewed to identify those patients who underwent surgical exploration, with or without resection. Data were available for all patients who underwent a surgical procedure. Major surgical complications were defined as the occurrence of anastomotic leakage, postoperative intra-abdominal or gastrointestinal hemorrhage or fistula, intra-abdominal abscess, pneumonia, catheter-related sepsis, thromboembolic events, reoperation, or death, in keeping with the definition employed by prior investigators.[3]

Assessment of Pathologic Response

All histologic slides were reviewed by a single pathologist (J.G.), and assessment of responses was characterized and graded using a system previously described by Evans et al.[21] (Table 1). The degree of fibrosis was characterized simply as minimal, moderate, or extensive.

Statistical Considerations

Survival was calculated from the date that treatment was initiated to the date of death or last follow-up. Survival curves were calculated by the product-limit (Kaplan-Meier) method. The statistical significance of differences between survival curves was established by the log-rank test. Confidence intervals (CI) for binomial probabilities were calculated by the likelihood ratio method. STATA 7.0 (College Station, TX) was used for all statistical analyses.

RESULTS

Sixty-seven patients with locally advanced, unrespectable pancreatic cancer without evidence of distant metastases were treated with Gem/RT between

Table 1. Grading system for evaluating the effects of chemoradiation treatment

Grade	Histologic appearance
I	Characteristic cytologic changes of malignancy are present, but very little (<10%) or no tumor cell destruction is evident
II	In addition to characteristic cytologic changes of malignancy, 10%–90% of tumor cells are destroyed
IIa	Destruction of 10%–50% of tumor cells
IIb	Destruction of 51%–90% of tumor cells
III	Few (<10%) viable-appearing tumor cells are present
IIIM	Sizable pools of mucin are present
IV	No viable tumor cells are present
IVM	Acellular pools of mucin are present

July 1996 and June 2001. Most (n = 44) were treated with one of three phase I protocols, as described previously. The remaining patients (n = 23) received treatment as per the radiation dose escalation trial, off protocol, with a radiation dose previously judged to be tolerable (all ≤36 Gy). These patients were treated during periods in which the protocol itself was closed to accrual. Patient and tumor characteristics are shown in Table 2. The median age for the three groups combined was 63 years (range 41 to 85 years). Fifty-eight patients had adenocarcinoma of the pancreatic head, whereas nine patients had lesions in the body or tail of the pancreas. The average tumor size by CT scan was 4.0 cm, with a range of 2 to 7 cm. At the time of treatment, designation as unresectable was based on helical CT alone in 28 patients, endoscopic ultrasound imaging alone in eight, both modalities in 14, magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) in two, and exploratory laparotomy in 15 (including nine who initially underwent surgical exploration at the University of Michigan). On retrospective review of CT scans alone, 18 patients were considered to have borderline resectable lesions based on NCCN criteria, whereas 49 patients were considered to have tumors that were locally unresectable.

Evaluation for disease status by helical CT 4 to 6 weeks after completion of Gem/RT showed evidence of local progression in 12 patients, four of whom also developed distant metastases. Eleven of these patients were initially considered to have unresectable tumors. Two additional patients were shown to have distant metastases without local progression. Ten patients underwent surgical exploration after this initial evaluation, and five underwent standard Whipple resection 8 to 12 weeks after completion of Gem/RT. The radiologic response noted in one of these patients is shown in Fig. 1. Seven patients underwent surgical exploration after additional gemcitabine-based chemotherapy and subsequent reevaluation. Four underwent standard Whipple resection 17 to 25 weeks after completion of Gem/RT. Of those patients who underwent surgical exploration but not resection, three had metastatic disease and five had local tumors that were not amenable to resection.

Table 2. Patient characteristics

	Gem dose escalation	RT dose escalation	Cisplatin dose escalation	All
Age (yr)				
Median	63	65	61.5	63
Range	54–79	41–85	45–77	41–85
Sex (M:F)	4:8	24:15	10:6	38:29
Location				
Head	10	35	13	58
Body	2	3	1	6
Tail	0	1	2	3
Borderline	2	13	3	18
Unresectable	10	26	13	49
Size (cm)				
Median	4.0	4.0	4.5	4.0
Range	2.5–5	2–7	3–6.1	2–7

Overall, 17 patients underwent surgical exploration, 11 from the borderline group and six from the unresectable group. Six of 11 patients in the borderline group underwent resection. This represents 33% (6 of 18) of those patients initially considered borderline. Four of these six patients were considered borderline resectable based on the results of both CT and endoscopic ultrasound evaluation. Three of the six patients in the unresectable group who underwent surgical exploration had a resection. This represents 6% (3 of 49) of those patients initially considered unresectable. Each of these three patients was initially judged to be unresectable based on results of prior exploratory laparotomy (including two who underwent prior surgical exploration at the University of Michigan by the same surgeon, who subsequently performed the resection).

Thus 9 (52%) of 17 patients undergoing surgical exploration or 9 (13%) of 67 in the entire cohort underwent surgical resection. Resections were performed in 2 (16.6%) of 12, 5 (12.8%) of 39, and 2 (12.5%) of 16 patients treated in the gemcitabine dose escalation trial, radiation dose escalation trial (or off protocol), and cisplatin dose escalation trial, respectively. All resected patients had lesions of the pancreatic head. Initial tumor size ranged from 2.5 to 4.4 cm. The median operative time for Whipple resection was 7.7 hours (range 6.4 to 8.2 hours). Median estimated blood loss during resection was 515 ml (range 150 to 1000 ml). Three patients required blood transfusions in the operative or perioperative period. Length of hospital stay ranged from 11 to 19 days, with a median of 14 days. There were no major surgical complications, no patients required readmission, and the 30-day mortality rate following resection was 0%. Only one patient had a complicated postoperative course; this patient subsequently had a peritoneal recurrence and died 5 months postoperatively.

Pathologic evaluation revealed no evidence of malignancy in the surgical margins and regional lymph nodes in six of the nine patients who underwent resection. Two patients were noted to have less than 10% viable-appearing tumor cells present (grade III response; Fig. 2), whereas one patient had a grade IIb response. The remainder had a response less than

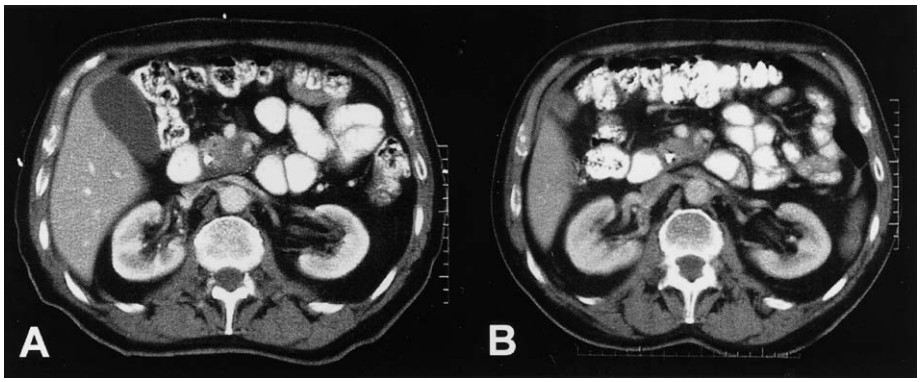

Fig. 1. CT scan of a patient initially considered unresectable based on endoscopic ultrasound images and helical CT scans. On retrospective review of the CT scan, the lesion was considered borderline resectable (**A**). Interval reduction in size was noted after Gem/RT (**B**), and surgical resection was performed.

or equal to Grade IIa. The degree of fibrosis was considered to be extensive in six patients.

With a median follow-up of 32 months, median survival for the resected patients (n = 9) was 17.6 months (95% CI 12.6 to 37.3 months). Among these nine patients, two were noted to have evidence of local recurrence, one was noted to have both local and distant recurrences, two developed distant metastases, and one died without a documented site of failure. Three of nine resected patients are alive and without evidence of progression or metastases at 16 to 45 months. Median survival for the remaining 58 patients was 11.9 months (95% CI 9.6 to 14.7 months), which is significantly less than survival among resected patients ($P = 0.013$) (Fig. 3).

DISCUSSION

The primary objective of this review was to determine whether surgical resection of pancreatic cancer after gemcitabine-based chemoradiotherapy was associated with any apparent increase in the morbidity or mortality associated with surgery. The concern for potentially increased morbidity is based on observation of late toxicity in a small fraction of patients who received Gem/RT in the trials described previously, and the recognition that gemcitabine increases radiosensitivity of both normal and malignant tissue.[16,17,22] The concern was also based on the observation of major surgical complications in 10% to 30% of patients receiving neoadjuvant chemoradiotherapy in recent investigational trials.[12,23–25] Although the data are limited to an experience in nine patients, there is no apparent increase in morbidity or mortality considering that no patient in our study experienced major operative complications or died during the perioperative period. However, it is important to note that a detailed comparison of other factors such as operative time, estimated blood loss, or length of hospital stay between our experience and experience from the investigational neoadjuvant chemoradiotherapy trials referenced earlier is not entirely appropriate in as much as many patients in those trials underwent major vascular resection and reconstruction, whereas none of the patients in this study underwent more than standard Whipple resection. Nonetheless, the lack of surgical complications in our patient population suggests that the use of Gem/RT in a neoadjuvant setting for patients with resectable pancreatic cancer could be considered a feasible approach.

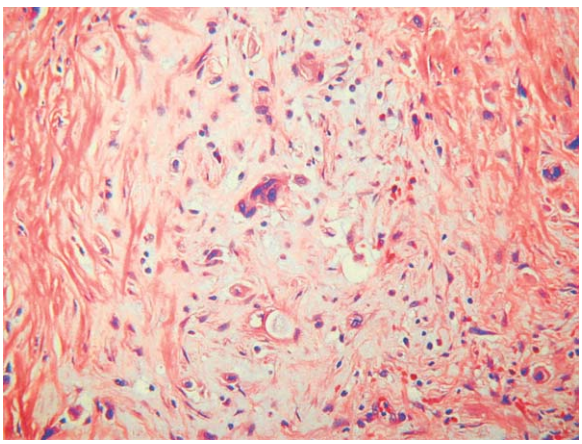

Fig. 2. Medium-power photomicrograph showing clusters of carcinoma cells in a myxoid stroma surrounded by dense fibrosis. This represented a small area of residual tumor in a patient (shown in Fig. 1) with a grade III response.

Equally encouraging is the observation that three patients with pancreatic cancer judged unresectable at the time of exploratory laparotomy subsequently underwent successful resection after Gem/RT with both nodes and margins negative. Other investigators have reported similar experiences following the delivery of preoperative chemoradiotherapy, particularly

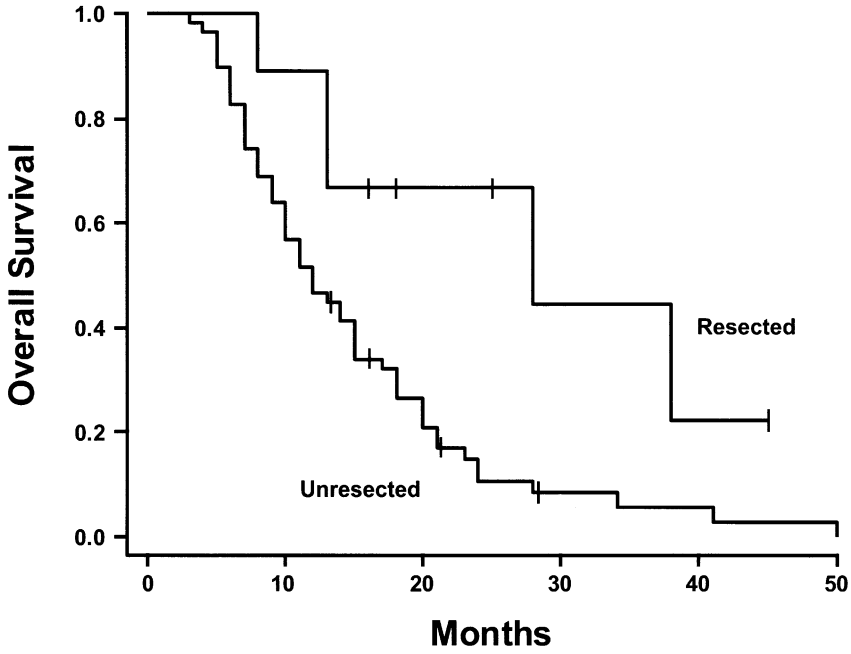

Fig. 3. Actuarial overall survival with a median potential follow-up of 32 months.

when the prior surgical exploration occurred at an outside institution.[6] The observation of grade IIb and III treatment effects in three patients compares favorably with the experience reported by Pisters et al.[24,25] following neoadjuvant regimens consisting of rapid fractionation with 5-FU or paclitaxel. Yet again, these comparisons are limited by the number of patients in each study, among other factors.

A variety of gemcitabine-based chemoradiotherapy remains have been investigated, primarily in patients with unresectable disease. The regimens investigated to date include gemcitabine dose escalation with conventional radiation therapy (as in the initial trial described earlier), gemcitabine dose escalation (once weekly) with rapid fractionation,[26] twice-weekly gemcitabine with conventional radiation therapy,[27] the addition of gemcitabine to 5-FU and radiation therapy,[28] the combination of gemcitabine and paclitaxel with conventional radiation therapy,[29] and full-dose gemcitabine with radiation therapy directed to the primary tumor alone (as in the second trial described earlier). Few have been investigated in phase II trials. Gemcitabine dose escalation with conventional radiation therapy has been investigated in the neoadjuvant setting, but has not been fully reported.[30]

We have elected to further investigate the use of full-dose gemcitabine with radiation therapy in a multi-institutional phase II trial, which allows for entry of patients with potentially resectable pancreatic cancer. Our selection of this regimen was based on experience gained in the phase I trials and the recognition that a regimen emphasizing systemic treatment may provide an advantage over more conventional combined-modality approaches, considering the systemic nature of the disease. The inclusion of patients with potentially resectable disease was based on our experience with patients undergoing surgical resection after Gem/RT, the potential advantages associated with the use of neoadjuvant therapy, and the desire to proceed with an approach providing full-dose systemic therapy to early-stage (resectable) patients. These patients, who are likely to have the lowest systemic disease burden, may ultimately experience the greatest benefit from further development of neoadjuvant combined-modality regimens that emphasize systemic therapy.

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Ampullary Carcinoid Tumors: Rationale for an Aggressive Surgical Approach

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Two cases of ampullary carcinoid tumor are reported. These tumors are among the most rare of GI tract carcinoids and appear to have a distinct presentation and biological behavior from carcinoids arising in the duodenum. The existing literature is reviewed with attention to the implications for surgical management of this rare disease. (J GASTROINTEST SURG 2003;7:773–776)

KEY WORDS: Ampullary carcinoid, duodenal carcinoid, pancreaticoduodenectomy

Carcinoid tumors are rare neuroendocrine neoplasms that may secrete vasoactive substances such as serotonin and tachykinins responsible for the well-described carcinoid syndrome. Carcinoids occur most commonly in the gastrointestinal tract with the appendix (45–60%), small bowel, and rectum accounting for the majority of cases. Carcinoids of the duodenum are rare, accounting for <5% of all gastrointestinal tract carcinoids. Rarer still are carcinoids that arise adjacent to or directly from the Ampulla of Vater. While both duodenal and ampullary carcinoids are sometimes referred to under the broad term "ampullary carcinoid," there is evidence to suggest that duodenal and ampullary carcinoids have distinct origins and biological behaviors. In a recent report on duodenal carcinoid the authors observed that the prognosis of duodenal carcinoids, like those arising in the appendix, most often correlates closely with their size at presentation.[1] Tumors <2 cm have a low risk of lymph node metastasis, and may be managed by local excision with an excellent prognosis. In contrast, those tumors >2 cm have a high propensity for locoregional and distant metastasis. We have recently treated two patients with ampullary carcinoid, one with a tumor arising from the minor papilla and another with a carcinoid arising in the ampulla with extension to the pancreatic duct. In this article, we discuss these two patients in the broader context of ampullary carcinoid tumors and their clinical presentation, management, and prognosis.

CASE PRESENTATIONS

Case 1

A 43-year-old Caucasian male presented with an 8-year history of persistent epigastric and right-side abdominal pain that was not associated with nausea or vomiting. He reported no weight loss and specifically denied diarrhea, flushing, or any respiratory difficulties. His past medical history was significant only for hypertension. The patient underwent a laparoscopic cholecystectomy with worsening of his abdominal pain in the months following the procedure. Nineteen months following the cholecystectomy, due to persistent symptoms, he underwent an ERCP. Findings at that time included an enlarged and ulcerated minor papilla (Fig. 1). Biopsies revealed carcinoid tumor.

Following the ERCP, the patient underwent an abdominal CT scan that was negative for lymphadenopathy or visceral metastases. A chest x-ray was also negative. He then underwent a pancreaticoduodenectomy at which time a small mass was palpable in the second portion of the duodenum. No enlarged regional nodes were noted and there was no evidence of visceral metastases. Pathologic analysis revealed a 1.5 cm carcinoid tumor of the minor papilla invading through the duodenal wall into the peripancreatic soft tissues. All margins of resection were negative for tumor. One of 16 lymph nodes contained metastatic carcinoid tumor. Thus, this tumor was pathologic Stage III (T3N1M0) according to American Joint

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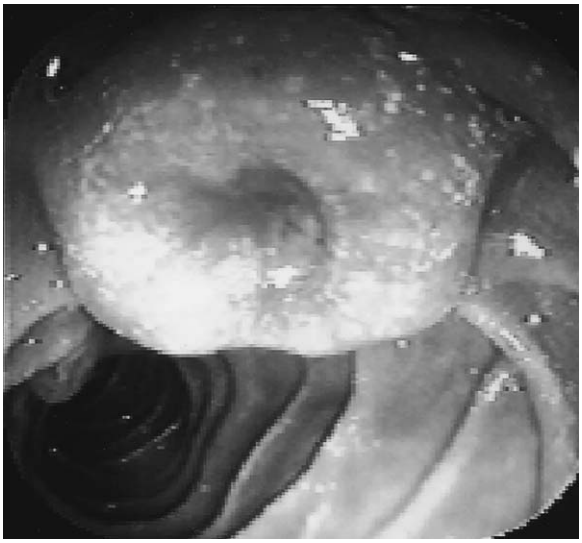

Fig. 1. Endoscopic view of periampullary carcinoid arising at the minor papillae.

Committee on Cancer criteria. Immunohistochemical staining of the tumor was positive for synaptophysin and negative for gastrin. The patient had an unremarkable hospital course and was discharged on postoperative day 8. He remains disease-free 39 months following resection.

Case 2

A 46-year-old Caucasian woman presented with a 2-year history of constant mid-epigastric pain. Over the course of 12 months her abdominal pain worsened and she developed chronic diarrhea prompting her to seek medical attention. The patient's past surgical history was significant for a cholecystectomy 15 years prior to referral, three Cesarean sections, lysis of adhesions, total abdominal hysterectomy, and a bilateral tubal ligation. Her past medical history was significant for major depression that developed after her abdominal pain began. This was most notable for a suicide attempt due to despair over her physical condition. Her social history was significant only for cigarette smoking with no history of alcohol use.

On two separate occasions, laboratory evaluation revealed mildly elevated amylase and lipase levels. Due to the presumed diagnosis of recurrent acute pancreatitis, the patient was initially evaluated with an ERCP. This revealed a mildly dilated main pancreatic duct with a normal common and intrahepatic bile ducts. On a subsequent evaluation, the patient was again noted to have a mildly elevated lipase level and was started on pancreatic enzyme replacement for presumed recurrent acute and chronic pancreatitis. She continued to have abdominal pain and an endoscopic ultrasound was performed. This revealed a 3–4 mm main pancreatic duct and changes consistent with chronic pancreatitis mainly confined to the pancreatic head. Repeat ERCP with sphincterotomy revealed an 11-mm common bile duct. The pancreatic duct was extremely difficult to cannulate due to ampullary stenosis. Once injected, the main pancreatic duct was found to be mildly dilated to 4 mm. Given the presence of ampullary stenosis of unclear etiology, recurrent episodes of pain and pancreatic enzyme elevation, and changes of chronic pancreatitis within the pancreatic head by endoscopic ultrasound, following her second ERCP the patient was referred for surgical evaluation. Due to uncertainty in diagnosis, our generally unfavorable experience with pancreatic duct sphincteroplasty and the fact that the pancreatic duct dilation was not great enough for pancreaticojejunostomy, pancreaticoduodenectomy was recommended. The patient underwent pancreaticoduodenectomy without complication and pathologic analysis revealed a carcinoid tumor arising at the ampulla and extending to the main pancreatic duct with mild focal chronic pancreatitis with fibrosis (Fig. 2). No evidence of nodal metastasis was present and the surgical margins were free of tumor. Immunohistochemical staining of the tumor was positive for synaptophysin and negative for gastrin. The patient had an unremarkable postoperative course and was discharged on postoperative day 9. She remains free of disease 33 months following surgery.

DISCUSSION

Demographics and Presentation

Our review of four studies found a total of 90 reported cases of ampullary carcinoid including our two patients.[2–5] The mean patient age was 52 years (range 23–86). Of the 87 patients in whom gender was reported, the M:F ratio was roughly 2:1 with 60 men and 27 women. The only apparent risk factor for ampullary carcinoid appears to be the presence of neurofibromatosis type I (von Recklinghausen's disease).[6] Of the 90 patients reported in the literature, 21 (23%) had neurofibromatosis. Thus, it is likely, though unproven, that mutation of the NF-1 tumor suppressor gene may predispose to the development of ampullary carcinoids.

The most common presenting symptom of ampullary carcinoid is jaundice, present in 59% of patients. In this regard, ampullary carcinoid differs from duodenal carcinoid in which the most common presenting symptom is abdominal pain (Table 1).[7] For ampullary carcinoid, abdominal pain is the second

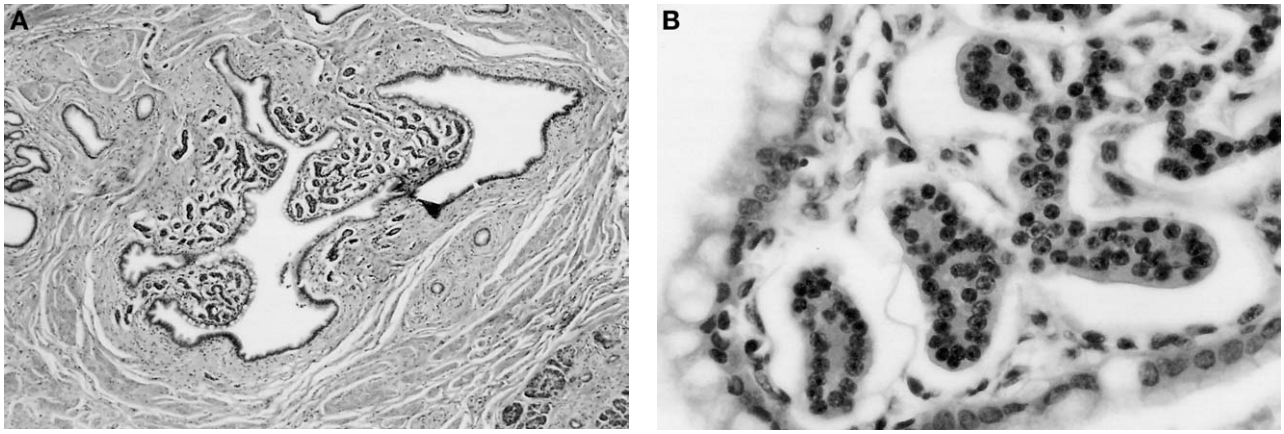

Fig. 2. A, Carcinoid tumor arising at the periampullary pancreatic duct. **B**, High-power view demonstrates small monotonous appearing cells with uniform, deeply chromatic nuclei characteristic of carcinoid tumor.

most common presenting symptom, present in 37% of patients. Weight loss has been reported in 10% of patients. There have been three patients who presented with documented acute pancreatitis, and three others who presented with upper gastrointestinal bleeding. One of the remarkable findings of this group of patients is the near absence of clinical findings of carcinoid syndrome. In only two of the 90 patients was there a reported history of flushing, diarrhea, and asthma, and both of these patients had extensive liver metastases.

Diagnosis

From the available data, it is striking that in only 15% (12 of 78) of patients with ampullary carcinoid was the diagnosis of carcinoid tumor established preoperatively.[2–5] Both of our patients had a delay in diagnosis that was greater than one year. This long latency from the onset of symptoms to diagnosis is likely due to the technical difficulty of discerning small masses present around the ampulla. Upper endoscopy and ERCP are the most effective diagnostic tools. As for other periampullary malignancies, helical CT scan is the test of choice to stage the disease if a diagnosis can be established preoperatively. Because of the rarity of ampullary carcinoid there are no prior reports describing use of endoscopic ultrasound in its diagnosis or staging. In the second case, endoscopic ultrasound was utilized and revealed changes consistent with chronic pancreatitis, but did not reveal the tumor, likely due to its extremely small size. Even with this, it is certainly reasonable to extrapolate from the existing literature on pancreatic carcinoma that suggests endoscopic ultrasound (EUS) is highly accurate in detecting tumors as small as 1 cm. EUS can accurately assess the presence of local lymph node enlargement and the relationship of periampullary tumors to the mesenteric and celiac artery branch vessels. The ability to perform needle biopsy is another advantage to EUS. Thus, EUS will likely serve as another useful diagnostic modality in the diagnosis and staging of ampullary carcinoid.

Table 1. Presenting symptoms of ampullary versus duodenal carcinoids

Symptom	Ampullary carcinoid (%)	Duodenal carcinoid
Jaundice	59	7
Abdominal pain	37	34
Weight loss	10	0
Upper gastrointestinal bleeding	3	11
Acute pancreatitis	3	5
Lower gastrointestinal bleeding	0	4

Tumor Characteristics

Of the 73 cases with available information, the mean tumor diameter was 2.2 cm (range 0.1–6). Thirty-one tumors were >2 cm in diameter and 15 (48%) of these tumors had metastasized. In comparison, 17 of 42 (40%) patients with tumors ≤2 cm had metastatic disease.[2–5] Of the total group of 90 patients, 31 had metastases to regional lymph nodes, four to the liver only, two had metastases to liver and lymph nodes, and two had metastases to the pancreas. One patient had bone metastases and a single patient had peritoneal metastases involving small bowel mesentery.

Immunohistochemistry

Two studies have examined the expression of vasoactive substances by ampullary carcinoid tumors. A

study by Hatzitheoklitos et al. reported immunohistochemical staining of 24 ampullary carcinoid tumors and found that 58% stained for somatostatin.[2] Staining for neurotensin, serotonin, pancreatic polypeptide, calcitonin, and vasoactive intestinal peptide (VIP) was present in one patient each. Two patients had tumors that stained for gastrin, however, neither patient demonstrated signs of Zollinger-Ellison syndrome.

A second study by Makhlouf et al. analyzed immunohistochemical staining in 12 cases of ampullary carcinoid (AC) and 53 cases of duodenal carcinoid (DC).[4] This study revealed the presence of somatostatin in 67% AC versus 30% DC; serotonin in 17% of AC versus 38% of DC and the complete absence of gastrin staining in AC compared with 56% of DC. All 12 AC stained positive for synaptophysin. This study confirmed that AC's frequently express somatostatin. They also noted that no AC patients had symptoms of somatostatin syndrome (diabetes mellitus, diarrhea, and cholelithiasis). Interestingly, 9% of the DC patients had Zollinger-Ellison syndrome while greater than half of those patients had positive gastrin staining by immunohistochemistry. These studies support the hypothesis that ampullary carcinoid tumors are a distinct subset of carcinoid tumors occurring in the duodenum and have unique biochemical and biological characteristics.

Treatment and Prognosis

Our review of 90 patients with ampullary carcinoid found that 52 were treated with pancreaticoduodenectomy and that 22 were treated with local excision of the tumor.[2–9] Three patients were treated with palliative or bypass operations and in 13 cases there was no available data concerning therapy. Local excision was generally performed on patients with tumors $\leq$2 cm in diameter while pancreaticoduodenectomy was performed in patients with tumors $>$2 cm.

There have been 11 deaths reported in the literature with follow-up ranging from 3 months to 10 years. Three patients died of liver metastases at 5 and 6 months and 5 years after resection by pancreaticoduodenectomy. Three patients died of postoperative complications and one died preoperatively of cardiac failure. One patient died of local recurrence 20 months following local excision. There were three other deaths due to metastatic disease at presentation.

Summary and Therapeutic Strategy

Ampullary carcinoids are among the rarest of gastrointestinal tract carcinoid tumors. Affected patients are more often males in their fifth and sixth decade of life. Patients with neurofibromatosis type 1 appear to be at increased risk for the development of ampullary carcinoid. Patients most often present with jaundice or nonspecific upper abdominal pain, and only rarely present with carcinoid syndrome. Ampullary carcinoids frequently express somatostatin. Unlike carcinoid tumors of the duodenum and appendix, for ampullary carcinoid, there appears to be no correlation between tumor size and the presence of metastases at the time of operation. Duodenal carcinoid tumors $<$2 cm have a 4% incidence of metastases and those $>$2 cm or invading the muscularis propria have a 40% incidence of metastases. In contrast, while the majority of ampullary carcinoid tumors are indolent in nature, tumor size is not a reliable predictor of aggressiveness and some patients will recur and die of their disease. Therefore, for appropriate risk patients, our recommendation is to perform a pancreaticoduodenectomy with the hope to achieve complete extirpation of the tumor and to provide the best chance for cure.

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Laparoscopic Stapled Left Lateral Segment Liver Resection—Technique and Results

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Because of the favorable anatomy of the left lateral segment of the liver, a totally laparoscopic approach to resection is feasible. Herein we describe a technique for laparoscopic stapled resection of the left lateral segment of the liver, including the necessary anatomic criteria for a safe operation and data on clinical outcome. Five patients at our center underwent laparoscopic exploration, ultrasound examination, and resection of segments II and III. After complete mobilization of the left lateral segment and minimal portal dissection, the totally laparoscopic resections were performed with two endoscopic staple loads (4.5 mm × 60 mm) applied sequentially across the portal pedicle and the left hepatic vein. The mean operative time was 182 minutes (range 130 to 240 minutes), blood loss was 41 ml (range 25 to 50 ml), and length of hospital stay was 2.2 days (range 1 to 3 days). All three patients with malignancy had negative surgical margins. All five patients returned to normal activity or work by 1 week postoperatively. There were no complications. Patients with isolated malignant and benign diseases of the left lateral segment of the liver are candidates for totally laparoscopic resection, if evaluation demonstrates a normal liver character and hepatic parenchymal thickness less than 3 cm overlying the ligamentum venosum groove. Such patients benefit from the minimally invasive approach, with no compromise in the surgical result as compared to the open approach. (J GASTROINTEST SURG 2003;7:777–782)

KEY WORDS: Liver resection, laparoscopy, surgical staples, ultrasound

Liver resection has not been readily adopted into the field of laparoscopy, in general because of a lack of appropriate instrumentation to allow an operation that would parallel the open procedure. The ideal laparoscopic liver resection would achieve the same end as the open procedure, but without the added morbidity of a traditional incision.

The anatomy of the left lateral segment of the liver[1] lends itself to minimally invasive resection, given recent advances in endoscopic stapling devices. Many liver surgeons now perform open left lateral segment resections with standard TA staplers (U.S. Surgical, Norwalk, CT). Such resections take advantage of the thinness of the liver overlying the ligamentum venosum groove, the absence of potential risks of hilar biliary dissection, and the ease with which staples can control the left hepatic vein in the liver. As long as no dissection is done medial to the round and falciform ligaments, the ascending branch of the left portal vein and the recurrent portal structures related to segment IV will remain undisturbed. A number of reports have described various laparoscopic approaches to liver resection,[2–6] but herein we describe a totally laparoscopic technique for resection of the left lateral segment of the liver. Our technique is applicable for patients with benign or malignant lesions of this part of the liver.

MATERIAL AND METHODS

Between March 1, 2002 and November 30, 2002, a total of five patients with diseases confined to the left lateral segment of the liver were evaluated for laparoscopic resection. Disease-specific preoperative

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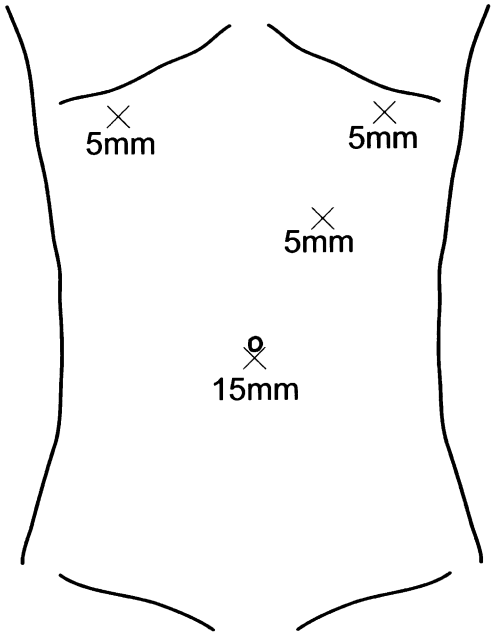

Fig. 1. Diagram of the abdomen showing port site placement.

evaluations were carried out to confirm the appropriateness of resection (e.g., chest roentgenography, abdominal computed tomography (CT), and positron emission tomography (PET) to rule out metastatic disease in patients with colorectal cancer).[7] For all five patients, a laparoscopic approach was deemed feasible because of the absence of any clinical risk of hepatic fibrosis, the thinness of the liver at the planned resection line, and an expectation of adequate margins in the three cancer patients.

Preoperative Feasibility Evaluation

We used CT scanning or magnetic resonance imaging to evaluate the left hemiliver and the thickness of the liver overlying the ligamentum venosum groove. Based on our previous experience with open staple application in left lateral segment resections, we thought that a normal liver, less than 3 cm thick, would allow reliable seating and deployment of current laparoscopic staplers. The liver thickness at the cephalad aspect of the groove is difficult to evaluate; in axial imaging the curve of the liver is parallel to the transverse slice. This issue required evaluation by intraoperative ultrasound imaging.

Operation

The patient was positioned supine and secured to allow maximal lateral rotation of the table as well as steep reverse Trendelenburg positioning. Ports were placed as shown in Fig. 1. The two 5 mm lateral ports in both upper quadrants were placed to allow access to the falciform ligament, the suprahepatic vena cava, and the left triangular ligament. The two left-sided ports were used for portal dissection. The 5 to 15 mm port at the umbilicus was placed to allow access for the ultrasound probe and stapler. We used both a 5 mm and 10 mm laparoscope.

After initial placement of the ports, adhesions were lysed as necessary. The falciform and left triangular ligaments were sharply mobilized to the level of the left hepatic vein and vena cava. The tissue overlying the vena cava and the left hepatic vein were dissected, but the vena cava and left hepatic vein were not exposed.

Laparoscopic ultrasound examination was performed through the umbilical port, to rule out the presence of other lesions in the liver and to determine the feasibility of stapled resection for that patient. The thickness of the liver parenchyma—between the insertion of the falciform ligament anteriorly and the ligamentum venosum groove posteriorly—was measured by placing a blunt grasper from the right upper quadrant port along the groove, up to the level of the diaphragm near the left hepatic vein. The thickness was then measured from the ultrasound probe to the echogenic grasper shaft (Fig. 2). The cephalad extent of the portal structures was also identified, as was the location of the left hepatic vein. At that point the table was rotated well to the right; the liver was flipped to the right, allowing dissection of the portal structures (Figs. 3 and 4).

The bridge of tissue that overlies the round ligament is variable but, when present, must be divided in order to fully expose the pedicles to segments II and III. We avoided complete dissection of the portal pedicles because it would compromise secure staple fixation by excessively thinning the tissues. Although variability in hepatic artery anatomy can be expected, the branch(es) to segments II and III are superficial to the portal vein in this orientation and can be readily dissected. The artery was controlled proximally and divided with the harmonic scalpel distally. Division of the artery will expose the segment III portal vein branch, but dissection and division of this portal vein branch are optional. The surgeon may choose to divide this structure prior to stapler application if the laparoscopic hepatic ultrasound image indicates that both the segment III and segment II portal vein branches will not be completely divided by the first stapler application. In our five patients leaving the round ligament intact assisted with liver fixation during the medial rotation; it also retained the landmark so that no dissection was done medially (thereby avoiding the risk of devascularizing segment IV or of injuring the left hepatic duct). Dissection of the bile

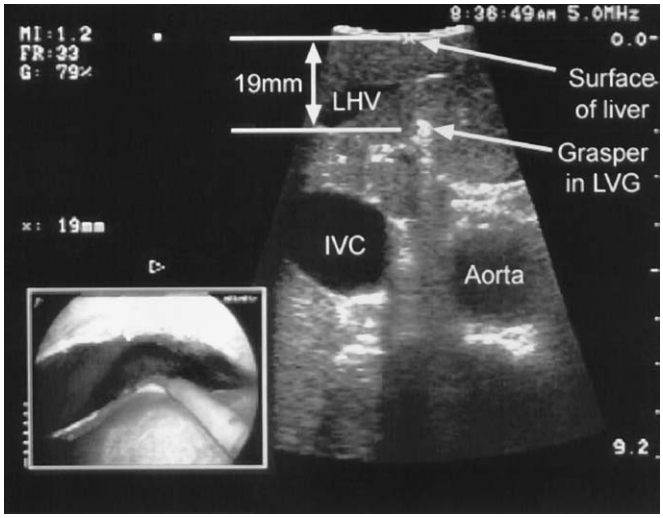

Fig. 2. Laparoscopic ultrasound view. The hepatic parenchymal thickness is measured at the ligamentum venosum groove, and its relationship to the left hepatic vein is assessed. LHV = left hepatic vein; LVG = ligamentum venosum groove; IVC = inferior vena cava.

ducts deep to the portal vein is unnecessary; the fibrous tissues are retained and staple purchase on these critical structures is promoted by retention of the connective tissue bulk.

The 60 mm long Universal Endo GIA II stapler (U.S. Surgical, Norwalk, CT) was loaded with 4.5 mm staples and placed through the umbilical port. It is important to note that at least two staple applications must be planned (Fig. 3): the first to control the remaining portal pedicle structures to segments II and III (Fig. 5) and the second to control the left hepatic vein (Fig. 6). In all five of our patients, we positioned the tip of the first stapler just distal to the end of the portal structures as identified with ultrasound. The second stapler was then placed, dividing the remaining portion of the liver including the left hepatic vein. We achieved excellent coaptation of the portal and hepatic vein staple applications. However, in a patient with a 3 cm thick liver and recurrent pyogenic cholangitis, we saw some

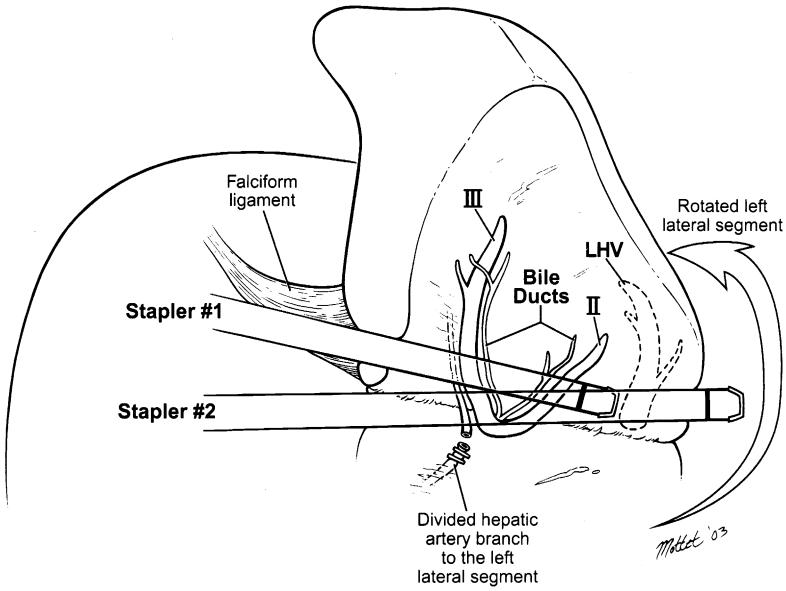

Fig. 3. Illustration of left lateral segment anatomy and stapler placement. This depicts a representative view of the liver from the left upper quadrants 5 mm port camera. The left lateral segment has been elevated and rotated to the patient's right. The stapler applications are depicted. LHV = left hepatic vein.

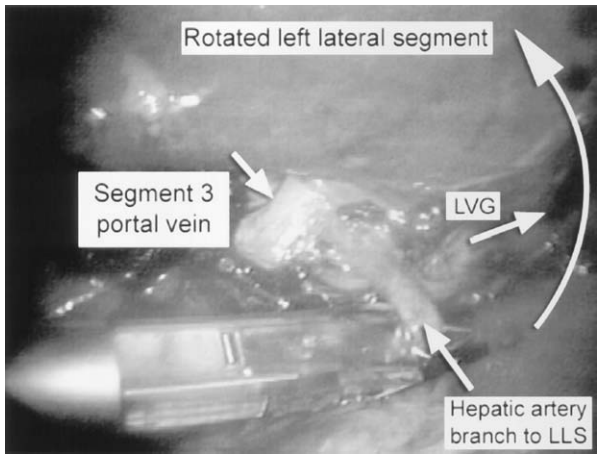

Fig. 4. Left lateral segment vascular dissection. The hepatic artery is being clipped; the segment III portal vein branch is noted. LLS = left lateral segment; LVG = ligamentum venosum groove.

nonbleeding cracking of the liver parenchyma near the most caudal aspect of segment III.

In all five patients, we either applied 5 ml of fibrin glue (Baxter Medical, Deerfield, IL) to the staple lines or oversewed the staple lines with a fine absorbable monofilament suture. Drains were selectively placed through one of the 5 mm ports. The specimen was placed in a specimen bag (Cook Surgical, Bloomington, IN) and removed intact through an extension of the umbilical port (along any previous incision if present, or through a Pfannenstiel incision).

RESULTS

Characteristics of our five patients and their resections are summarized in Table 1. The mean operative time was 182 minutes (range 130 to 240 minutes). The first operation took the longest; operative time has declined with increased experience. No patients required blood product transfusion, and the estimated blood loss ranged from 25 to 50 ml. There were no bile leaks and no other complications. All five patients were started on a normal diet on the day after surgery and discharged home when they tolerated oral pain medication and were passing flatus. The median length of stay was 2.2 days. All patients resumed their normal activity or work within 1 week. None of the three cancer patients had positive surgical margins; all three remain alive, without local tumor recurrence (follow-up time, so far, is short).

DISCUSSION

Laparoscopic approaches to liver resection are attracting increased attention, especially in centers with specific interests in open liver surgery. Most published reports have involved resection of peripheral lesions or treatment of cysts.[2–6] The trend toward minimally invasive treatment of liver tumors has led to an increase in the use of tumor ablation. But even in experienced hands the local failure rate is approximately 10%.[8,9] Our technique retains the benefits of both laparoscopy and resection, obviating the debate for patients with isolated lesions of the left lateral segment.

Staplers have been popular in liver surgery for vascular control. Endoscopic vascular staplers are routinely used to divide hepatic veins and portal pedicles. Stapling techniques are widely applied in liver surgery for those purposes, as described in standard texts.[10–12] But little is written about other uses of staplers for liver resection because their general application in the division of parenchyma is limited. Laparoscopic stapling does pose some unique challenges, and the adverse consequences of ill-advised or ineffective staple application could be significant. Our criteria for stapler application were derived from our experience with open resection and have proved to be reproducible in this particular laparoscopic operation. The general thickness of the liver is easily assessed by current axial imaging technologies, but in the region of the left hepatic vein, the thickness is more accurately determined in the operating room. There, as outlined previously, we placed the blunt probe in the ligamentum venosum groove with interrogation by laparoscopic ultrasound examination (Fig. 2). In the future, dissection of the liver parenchyma in patients with thick livers may expand the application of the laparoscopic stapled technique; studies are underway. In our technique of stapled left lateral segment resection, we found that coaptation of Glisson's capsule on the anterior and posterior surfaces of the ligamentum venosum promotes bile

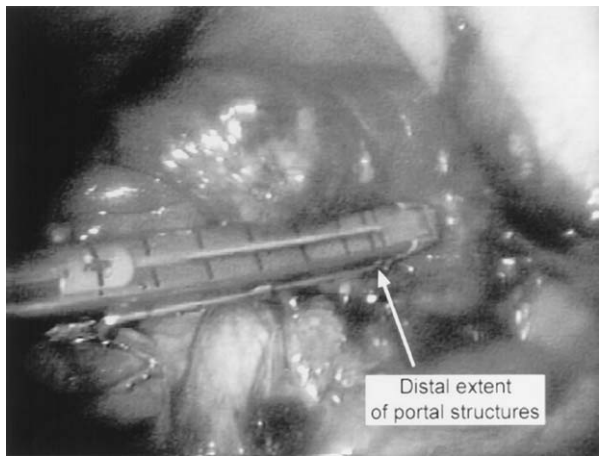

Fig. 5. The first stapler application controls the portal pedicle.

Table 1. Patient characteristics

Patient age (yr)	Sex	Diagnosis	EBL (ml)	Operative time (min)	Tumor size (cm)	Margin (cm)	Length of stay (days)
81	M	Metastatic nasopharyngeal carcinoma	25	240	4.5	>1	2
29	F	Focal nodular hyperplasia	50	130	7	Neg	3
56	F	Metastatic colorectal cancer	50	210	8	0.9	3
54	M	Recurrent pyogenic cholangitis	30	180	NA	NA	1
47	M	Metastatic colorectal cancer	50	150	4.5	>1	2

NA = not applicable; Neg = negative; EBL = estimated blood loss.

stasis. We also found that liver thickness <3 cm allowed secure placement and deployment of the current Endo GIA II stapler.

In the sagittal plane, the 60 mm long stapler was able to encompass the entire left lateral segment portal pedicle. But care must be taken to identify and mark the structure—visually (on the undersurface of the liver) as well as with ultrasound imaging (to avoid partial division). The presence and location of any scissural branch[13] of the left hepatic vein must be confirmed; awareness of its relationship to the staple line is important.

In this operation the left hepatic vein is the most dangerous structure dealt with. Failure to secure it during laparoscopy would risk air embolus or catastrophic bleeding. Dissection of the falciform and left triangular ligaments, up to the level of the vena cava, is sufficient. The stapler can then be easily placed *past* the edge of the liver, ensuring complete security and division of the left hepatic vein. Those two critical areas, the left lateral segment portal pedicle and hepatic vein, should be marked and divided with two stapler applications.

The need for any portal dissection lateral to the round ligament can be questioned. We thought that the ease with which the hepatic artery branch and the segment III portal vein branch could be controlled, remote from the line of transection, warranted the additional time involved. This limited portal dissection also decreased the chance of failed hemostasis, a potential problem with 4.5 mm staples. Although we used fibrin glue (Baxter Health Care, Deerfield, IL) to support the staple lines, the surgeon must be prepared to suture the staple line closed if any bleeding or bile leakage occurs. In the report by Cherqui et al.[14] of a laparoscopic donor left lateral segment liver resection, they showed the feasibility of complete dissection of all critical structures, including the bile duct; however, in the nontransplant setting, such complete dissection is not necessary. A recently published report of laparoscopic left lateral segmentectomy described conventional portal dissection and parenchymal transection with individual ligation and division of vascular structures.[15] We believe that when the criteria outlined in our report are confirmed, extensive portal pedicle dissection plus intraparenchymal hepatic vein isolation would prolong the procedure and increase the risk of hemorrhage.

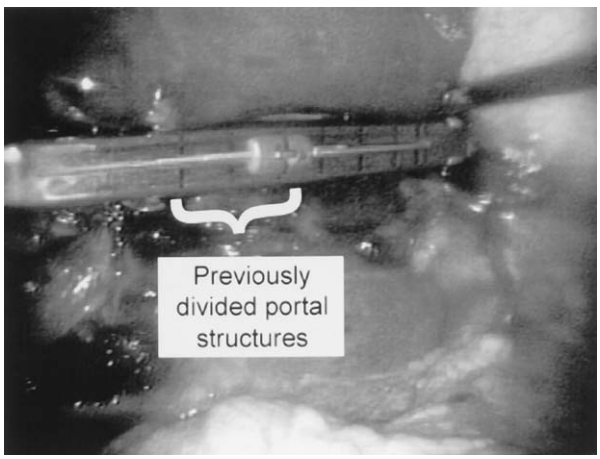

Fig. 6. The second stapler application controls the left hepatic vein.

In summary, our series demonstrated the applicability of a staple technique for totally laparoscopic left lateral segment liver resection. The technique is reproducible when these steps are followed:

1. Confirm that the liver parenchyma is normal and soft
2. Verify that the thickness of the liver at the ligamentum venosum groove is <3 cm
3. Perform minimal dissection of the portal and left hepatic vein, in order to promote secure staple purchase
4. Plan for two applications of the 60 mm long Endo GIA II stapler (4.5 mm staples)—the first for the portal structures and the second for the left hepatic vein.

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Influence of Postoperative Acute-Phase Response on Angiogenesis and Tumor Growth: Open vs. Laparoscopic-Assisted Surgery in Mice

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Inflammatory responses and tumor growth are increased after laparotomy compared with laparoscopy in some animal models. Proinflammatory cytokines interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) upregulate the expression of vascular endothelial growth factor (VEGF). Our aim was to investigate the influence of postoperative inflammatory responses on angiogenesis and tumor growth. 5×10^6 B51LiM cells were injected into the cecal wall of Balb/c mice. After 2 weeks, the animals were randomized into the following three groups: open cecectomy (OC), CO_2–laparoscopic-assisted cecectomy (LC), and helium–laparoscopic-assisted cecectomy (LH). On postoperative day 12, the mice were killed. Tumor load scores and weight were significantly greater after laparotomy than after laparoscopy. Serum IL-6 levels 6 hours after surgery (OC: 4157 ± 1297 pg/ml vs. LC: 2514 ± 1417 pg/ml vs. LH: 2255 ± 1714 pg/ml) and VEGF levels on postoperative day 12 (OC: 231 ± 125 pg/ml vs. LC: 45 ± 9 pg/ml vs. LH: 49 ± 8 pg/ml), measured by enzyme-linked immunosorbent assay, were significantly higher in the laparotomy group. Microvessel density was also significantly higher in the OC group (OC: 34.3 ± 11.5 vs. LC: 15.5 ± 12.5 vs. LH: 18.5 ± 11.9). There was a positive correlation between IL-6 and VEGF postoperative serum levels (rho = 0.67; $P < 0.001$). We concluded that increased systemic levels of proinflammatory cytokines and VEGF are associated with increased angiogenesis and tumor growth after laparotomy compared to laparoscopy in mice. (J GASTROINTEST SURG 2003;7:783–790)

KEY WORDS: Laparoscopy, angiogenesis, colon cancer, IL-6, IL-1β, VEGF

Tumor growth and development of metastases are accelerated after laparotomy compared with laparoscopy in some animal models.[1–5] Furthermore, a subset analysis within a recent randomized clinical trial has shown a lower recurrence rate and better survival in patients with stage III colon cancer who undergo laparoscopic-assisted resection compared with laparotomy.[6] However, the mechanisms responsible for these differences are not known.

One essential component for tumor recurrence and formation of metastases is angiogenesis, the development of new vessels by sprouting of new capillaries from existing vessels. In the absence of angiogenesis, tumors cannot grow beyond a diameter of 1 to 2 mm.[7] Vascular endothelial growth factor (VEGF) is the most potent angiogenic cytokine; it not only is a mitogen for endothelial cells, but it also enhances microvascular permeability, thereby facilitating tumor cell extravasation at the surgical site.[8] Increased angiogenesis and elevated serum VEGF levels are associated with decreased disease-free[9] and overall survival[10] in patients with colorectal cancer.

Interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) are proinflammatory cytokines produced by a variety of activated cell types.[11] Serum IL-6 and IL1-β levels are early and sensitive markers of tissue damage because they rise in proportion to the surgical

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trauma.[11,12] Because injury is less intensive after laparoscopic surgery than after open surgery, the inflammatory response and cytokine activation have been shown to be less significant.[13–16] Interestingly, recent studies have shown that IL-6 and IL-1β stimulate VEGF messenger RNA expression in different carcinoma cell lines.[17–19]

The type of gas used in laparoscopic surgery may also influence the rate of tumor growth. In vitro, tumor cell growth is significantly lower after incubation in a helium-rich environment compared to CO_2.[20,21] In vivo, tumor growth and metastases are promoted by CO_2 compared with helium.[22,23] It has recently been shown that transient exposure to acidosis inhibits endothelial cell apoptosis and induces an increased level of VEGF messenger RNA expression.[24]

The main purpose of this study was to test the hypothesis that the differential tumor growth after open and laparoscopic surgery is due to differences in the magnitude of the inflammatory response and angiogenesis during the postoperative period. We also hypothesized that peritoneal acidosis during CO_2 laparoscopy may enhance VEGF expression and new vessel formation compared to laparoscopic surgery with helium.

MATERIAL AND METHODS

Animals

Sixty-eight Balb/c mice (Charles River Laboratories, Wilmington, MA), 6 to 8 weeks of age, weighing 19 to 21 grams, were used for the experiments. The animals were allowed free access to a standard laboratory diet and water, according to the Institutional Animal Care and Use Guidelines. All procedures described were reviewed and approved by the Mayo Animal Care and Use Committee in accordance with National Institutes of Health Guidelines.

Tumor Cell Line

A colonic adenocarcinoma cell line (51BliM), obtained from Dr. Bresalier of the Henry Ford Health Sciences Center, Detroit, MI, was used in this study. The 51BliM line is syngeneic to the Balb/c mouse strain.[25] Cell cultures were kept in RPMI 1640 medium supplemented with 10% fetal bovine serum, penicillin, and streptomycin at 37° C in an atmosphere of 5% carbon dioxide.[26] Viability of cells, determined by the trypan blue exclusion test, always exceeded 95%.

Induction of a Colonic Solid Tumor

A solid tumor was induced in the cecum, according to the description by Bresalier et al.[27] Mice were anesthetized by intraperitoneal injection of ketamine/xylazine (100/10 mg/kg). A 5 mm midline incision was made, and 5×10^6 viable tumor cells in 0.1 ml cell culture medium were injected into the cecal wall from the serosal side. The serosal surface at the injection site was painted with betadine to kill free tumor cells before the cecum was placed back into the abdominal cavity. The abdominal wall was closed with interrupted 3-0 vicryl sutures.

Operative Groups and Surgical Procedures

Two weeks after the cecal injection, the animals were randomly assigned by computer-generated numbers to one of the following three groups: resection of the cecum through a laparotomy (OC); CO_2-laparoscopic cecectomy (LC); or helium-laparoscopic cecectomy (LH). A pilot study with 15 mice showed that at this time cecal tumors of approximately 5 mm were present without macroscopic peritoneal or liver spread in approximately 85% of the animals. A single surgeon performed all procedures.

In the OC group, a 35 mm midline incision was made, adhesions were dissected, and the cecum was brought out, ligated with 3-0 silk just beyond the ileocecal junction, and resected. A small cecal stump remained at the ileocolic junction. Bowel continuity was not interrupted. The small bowel but not the tumor was manipulated. The wound was protected during the procedure with sterile gauze dampened with betadine. After 40 minutes, the laparotomy was closed with a running 3-0 vicryl suture.

In the laparoscopic groups, a 5 mm transverse incision was performed in the left flank and a 5 mm trocar (Ethicon Endo-Surgery, Inc. Cincinnati, OH) was placed. A pneumoperitoneum was created through that port with CO_2 or helium to a maximum pressure of 4 mm Hg. Two additional ports were placed in the subxiphoid area (16-gauge angiocatheter) and in the right flank (14-gauge angiocatheter), respectively. A 5 mm laparoscopic camera (Stryker Corp., Postage, MI) was inserted via the left flank trocar, and the abdomen was inspected to rule out the presence of metastases. Animals were maintained under pneumoperitoneum for a total of 30 minutes. The small bowel but not the tumor was manipulated during the operative time. After desufflation, the cecum was exteriorized through the left flank incision, which was protected as in the open cecectomy group and extended as necessary. The cecum was resected as described previously. This wound and the other

ports were then closed using interrupted 3-0 vicryl sutures. The total operative time was 40 minutes.

All resected cecums were inspected carefully to confirm the presence or absence of tumor. Those without grossly evident tumors were dropped from the study. The maximum diameter of the tumor was measured and the cecal wall was weighed. Animals with metastatic disease at the time of the cecectomy were also dropped from the study.

The intraperitoneal pH was recorded at baseline, at 10, 20, and 30 minutes during insufflation, and 10 minutes after desufflation.[28] An 18-gauge needle microelectrode (Microelectrodes Inc., Lebanon, NH) was placed through the right flank port in contact with the peritoneal surface and connected to a Corning 220 pH meter. Because helium laparoscopy causes no changes in peritoneal pH[28] we decided to use the LH group as our control group.

Blood Sampling and Cytokine Assays

Venous blood (0.3 ml) was taken from the retroorbital sinus under methoxyflurane anesthesia before the cecal injection and 6 hours, 24 hours, 48 hours, and 5 days after the cecectomy, and at the time the animals were killed.[5,29] Serum collected was stored at −80° C for cytokine assays. IL-6, IL-1β, and VEGF were measured by enzyme-linked immunosorbent assay (ELISA) with commercially available kits (Opteia mouse IL-6 kit; BD Pharmingen, San Diego, CA and Quantikine mouse IL-1β and VEGF kits; R&D Systems, Minneapolis, MN).

Macroscopic Evaluation and Tissue Handling

All animals were killed 12 days after cecal resection. Tumor growth was evaluated in the abdominal wall, cecal stump, parietal peritoneum, mesentery, omentum, retroperitoneum, liver, and kidney by an observer who was blinded as to which group the mice belonged. A modified cancer index was used to score tumor growth at each site as follows: 0 = no tumor; 1 = diameter less than 0.5 cm; 2 = diameter between 0.5 and 1 cm; 3 = diameter between 1 and 1.5 cm; 4 = diameter between 1.5 and 2 cm; and 5 = diameter exceeding 2 cm.[2] A total tumor load score was calculated by adding the scores calculated at each site. In addition, the total tumor load was weighed. Samples were obtained from the cecal stump and parietal peritoneum, fixed with zinc, and processed for histologic examination. Paraffin-embedded sections were cut at 4 μm and stained with hematoxylin and eosin.

Immunohistochemical Study for CD31

Angiogenesis was assessed using standard immunohistochemical methods to identify tumor microvessels. Tissue sections were incubated overnight at 4° C with rat antimouse CD31 (Pharmingen) at a dilution of 1:30. Visualization of the antigen-antibody reaction was carried out using the Vectastain Elite ABC kit (Vector Laboratories, Burlingame, CA). Diaminobenzidine tetrahydrochloride was used as a chromogen and counterstaining was done with a light hematoxylin stain. Negative control specimens consisted of omission of the primary antisera.

Angiogenesis Grading and Microvessel Density Estimates

All estimates were conducted in a blinded manner. Methods used in our laboratory have been previously published and are similar to standard methods used by other investigators.[30] For simple grading, slides were scanned at 100×, 200×, and 400× magnification, and based on the extent of microvessel staining; each slide was then assigned an angiogenesis grade of low, intermediate, or high. The entire sample was considered when assigning the angiogenesis grade. For estimates of microvessel density (MVD), each slide was first scanned at 100× magnification to determine three hot spots defined as areas containing the maximum number of microvessels. The microvessels were then counted in each of the three spots at 400 × magnification. Areas of staining with no discrete breaks were counted as a single vessel. MVD was estimated by determining the average number of vessels in each of the three hot spots.

Statistical Analysis

With 10 animals in each of the three treatment groups, there should be at least an 80% chance (statistical power) of detecting a difference in the mean response that is greater than or equal to 1.4 standard deviations of the individual measurements. For example, if the standard deviation of VEGF is 10 pg/ml,[29] then there should be 80% power to detect a difference in mean VEGF that is greater than or equal to (1.4 × 10) 14 pg/ml.

Based on the results of our pilot study, we estimated that approximately 20% of the animals would be excluded at the time of cecectomy because of the absence of macroscopically visible tumor or the presence of distant metastases. In addition, we anticipated a perioperative mortality rate close to 20% based on previous studies of laparoscopic-assisted resection of solid tumors.[31] The sample size was increased accordingly to have a minimum of 10 mice in each group available for analysis.

Nominal variables were compared among the three groups using the chi-square test. Continuous variables were compared among the three groups using the Kruskal-Wallis test because of the non-normal

distribution of those variables in this study. Comparisons between two groups were made by means of the Mann-Whitney test. A two-tailed value of $P < 0.05$ was considered statistically significant. To assess the degree of association between the variables, the Spearman rank correlation coefficient was calculated. Significance was taken at the 5% level. All calculations were done with JMP, SAS Institute (version 4.0.4).

RESULTS

Operative Findings and Postoperative Mortality

Four of the 68 mice that were used in this study died within 48 hours of cecal ischemia after the cecal injection. Thus 64 mice were randomized into the following three study groups: 23 mice were assigned to the OC group; 20 mice to the LC group; and 21 mice to the LH group. A total of 11 animals (17%) were excluded from the study after randomization. In nine cases, three mice in each group, there was no tumor in the cecum at the time of resection, and in two animals, one in the OC group and one in the LC group, there were peritoneal implants, probably because of the spillage of cells during the cecal injection. The remaining 53 mice underwent surgical procedures as described in Material and Methods.

The length of the midline incision in all of the animals in the OC group was 35 mm compared with 6.9 ± 1.8 mm and 7.5 ± 2.2 mm in the LC and LH groups, respectively. The mean size of the tumors (OC: 4.5 ± 2 mm vs. LC: 4.4 ± 1.5 mm vs. LH: 5.4 ± 1.9 mm) and the weight of the cecal wall (OC: 43.4 ± 33.3 mg vs. LC: 47.2 ± 20.9 mg vs. LH: 54.6 ± 25.5 mg) did not differ among the three groups. The neoplasms formed a mass in the serosal soft tissues with extension into the muscularis propria and, in some cases, focal invasion of the mucosa. The neoplastic cells were ovoid to mildly spindled, and formed nests and sheets. There was a high nucleus-to-cytoplasmic ratio with nuclei showing moderate pleomorphism and nucleolus formation. Cytoplasmic mucin was not identified.

There were no significant differences in the postoperative mortality rates among the three groups (OC: 21% vs. LC: 25% vs. LH: 27.7%). The most common cause of death was respiratory failure during the operation, followed by peritonitis secondary to intestinal perforation. In two animals the cause of death was unknown. Thus 40 animals remained to be killed after 12 days: 15 mice in the OC group, 12 mice in the LC group, and 13 mice in the LH group.

Intraoperative monitoring showed a consistent drop in the pH to below 6.5 in the LC group (Fig. 1). The mean pH decreased immediately after insufflation with CO_2 and returned to normal 10 minutes after the end of the procedure. No significant change in pH was observed in the LH group.

Tumor Recurrence

The weight of the animals at the time of death was significantly lower in the OC group compared with both laparoscopic groups (OC: 19.9 ± 1.1 grams vs. LC: 21.2 ± 1 grams vs. LH: 21.3 ± 0.7 grams; $P < 0.01$). There was no significant difference in the incidence of tumor recurrence among the three groups (OC: 80% vs. LC: 77% vs. LH: 75%). However, the tumor load score and total tumor weight were significantly greater in the OC group compared with the two laparoscopic groups (Fig. 2). The most frequent site of recurrence in all groups was the cecal stump, followed by the midline laparotomy wound and the peritoneum. Only one animal out of 12 in the LC group developed a tumor node in one of the trocar sites. No other port-site metastases were observed. Three mice in the OC group (20%) had liver metastases, but this was not observed in any of the animals in the LC and LH groups ($P < 0.05$).

Intratumoral Microvessel Density

Angiogenesis was significantly increased in the OC group. The mean ± standard deviation tumor MVD was 34.3 ± 11.5 vessels per high-power field in the OC group, 15.5 ± 12.5 in the LC group, and 18.5 ± 11.9 in the LH group ($P < 0.01$). There was no significant difference in MVD between the LC and LH groups. Results were similar when angiogenesis grading was used instead of MVD. By grading, high angiogenesis was present in 80% of tumors in the OC group, 37% in the LC group, and 33% in the LH

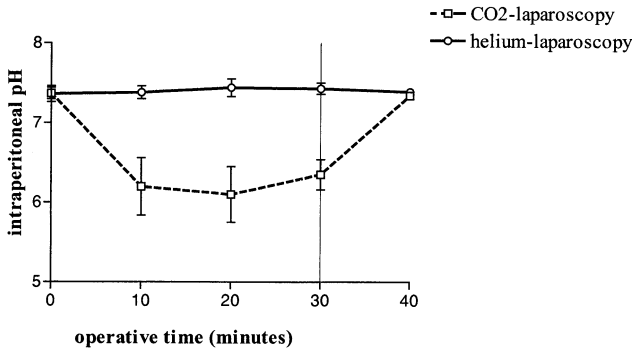

Fig. 1. pH changes during laparoscopy with CO_2 and helium. Monitoring was begun before insufflation and continued every 10 minutes until the end of the surgical procedure.

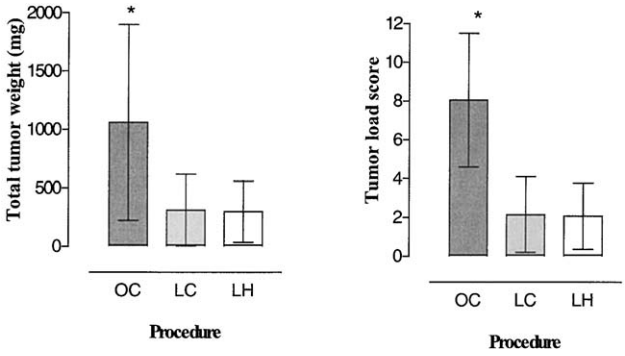

Fig. 2. Mean (standard deviation) total tumor weight and tumor load scores of the three operative groups. *$P < 0.05$ compared to the other two groups.

group ($P < 0.05$). MVD correlated positively with the tumor load score (rho = 0.7; $P < 0.001$) and with the total tumor weight (rho = 0.63; $P < 0.001$).

Serum levels of Interleukin-6, Interleukin-1β and Vascular Endothelial Growth Factor

The serum level of IL-6 was highest 6 hours after the procedure in each group (Fig. 3). The IL-6 serum level was significantly greater at 6 hours in the OC group compared to both laparoscopic groups. This significant difference persisted for 24 hours after the surgical procedure. There was no difference in the postoperative serum IL-6 levels between the two laparoscopic groups. Serum IL-1β levels 24 hours after surgery were significantly greater in the OC group. Again there was no difference between the two laparoscopic groups (Fig. 4). Serum VEGF levels 12 days after surgery and immediately before the mice were killed were also significantly greater in the OC group (Fig. 5).

There was a significant positive correlation between serum IL-6 levels at 6 hours and peak serum VEGF levels (rho = 0.67; $P < 0.001$). Correlation between IL-1β peak levels at 24 hours and VEGF

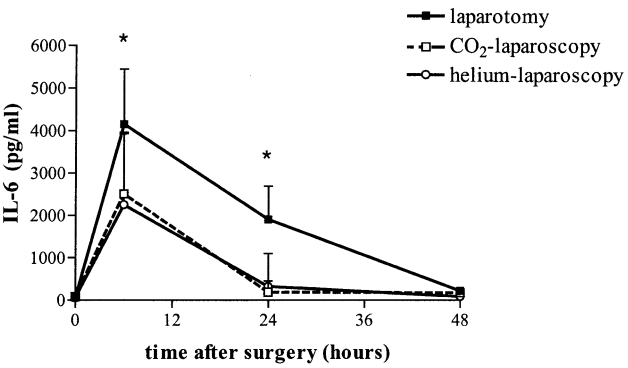

Fig. 3. Serum IL-6 levels after surgery in the three operative groups. *$P < 0.01$ compared to the other two groups.

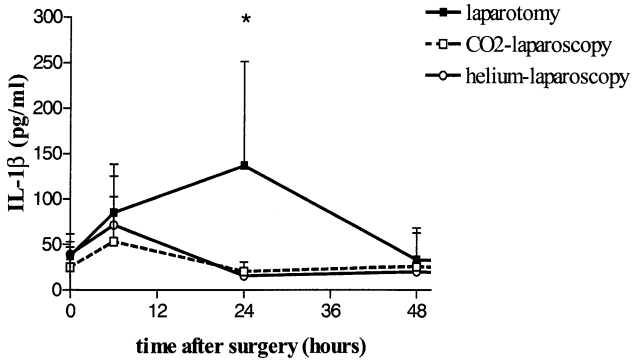

Fig. 4. Serum IL-1β levels in the three operative groups. Significant differences were found at 24 hours after surgery. *$P < 0.05$ compared to the other two groups.

serum levels at the time the mice were killed was poor (rho = 0.15; $P = 0.7$). There was a significant positive correlation between peak VEGF serum levels and total tumor weight and tumor load scores (rho = 0.6; $P < 0.001$). VEGF serum levels also correlated with MVD (rho = 0.55; $P < 0.01$).

DISCUSSION

The results of ongoing multicenter randomized trials will ultimately determine the influence of the surgical approach on port-site metastases, recurrence, and long-term survival in patients with colon cancer.[32,33] In the meantime, a number of experimental studies have been performed comparing the effects of pneumoperitoneum on tumor growth and metastasis with laparotomy. In agreement with other rodent models, our study showed that tumor growth and development of metastases are accelerated after laparotomy compared with laparoscopy.[1–5] Other studies, however, have failed to show any difference between the two surgical procedures[26,34] or have

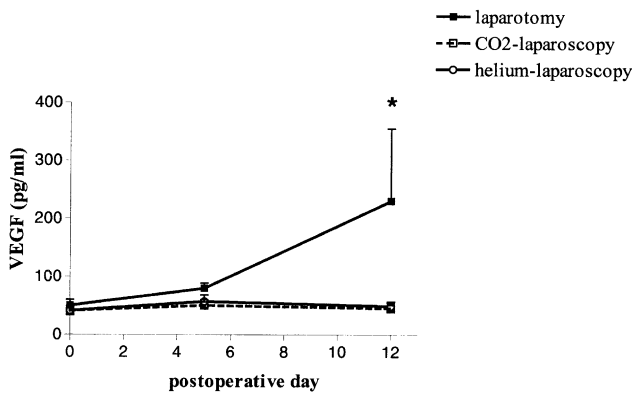

Fig. 5. Serum VEGF levels after the surgical procedure in the three study groups. *$P < 0.01$ compared to the other two groups.

found an even greater rate of tumor growth associated with the use of laparoscopy.[35,36] There may be several explanations for these contradictory results. First, the use of cell suspension models produces an extremely high number of free intraperitoneal malignant cells that may eliminate or reduce differences between procedures. Second, complete laparoscopic resection of solid tumors in small animals is technically difficult and may be more traumatic than open resection, resulting in spillage of more tumor cells into the peritoneal cavity.[31] Despite the lack of consistency in these results, we believe that animal models of solid colon cancer are still a good tool for understanding the mechanisms underlying tumor growth after surgery.

Perioperative mortality in the present study was higher than expected, although there were no differences among the treatment groups. Most deaths occurred during the operation as a result of respiratory failure, particularly in the two laparoscopic groups. The fact that mice were not intubated but were breathing spontaneously during surgery may have been responsible, at least in part, for the deaths resulting from respiratory problems. In other cases, death was due to peritonitis secondary to inadvertent intestinal perforation. We found that resection of the cecum 12 days after cecal injection was difficult because of intraperitoneal adhesions. Earlier resection after the initial orthotopic implantation of tumor cells might facilitate the procedure.

In agreement with findings in other clinical and experimental studies, we found that serum levels of IL-6 and IL-1β were not only higher but also remained elevated for a longer period of time after open surgery than after laparoscopic surgery.[5,13–16] These proinflammatory cytokines are the major mediators of the acute-phase response, and they have been accepted as markers of tissue trauma after surgery.[11,12] Therefore our results support the hypothesis that postoperative inflammatory response is greater after laparotomy compared with laparoscopy. Whether the diminished cytokine responses in laparoscopic tumor surgery are correlated with reduced postoperative tumor growth has not been previously investigated.

Some experimental studies have indicated that systemic immunity is better preserved after laparoscopic surgery than after open surgery.[37,38] Theoretically, the greater immunosuppression after open surgery might facilitate postoperative tumor growth and would explain the differences observed in some animal models. However, the beneficial effects of laparoscopy on the immune system have not been consistently demonstrated, particularly when local intraperitoneal immunity has been considered,[28,39] and other factors involved in tumor growth should be investigated. Toward this end, the results of the present study show that angiogenesis, assessed by VEGF serum levels and tumor MVD is increased after open surgery compared with laparoscopy.

Angiogenesis is regulated both by inducers and inhibitors of endothelial cell proliferation and migration produced by the tumor cells and other cells within the microenvironment surrounding the tumor. Changes in the relative balance of inducers and inhibitors can activate the so-called angiogenic switch enhancing the formation of new vessels that are essential for expansion of a tumor mass.[7] One of the most potent proangiogenic factors is VEGF. In both proliferation and chemotaxis assays, VEGF can elicit a positive response from capillary endothelial cells.[7] In patients with colorectal cancer, elevated serum VEGF levels and increased tumor MVD have a significant correlation with decreased disease-free[9,40] and overall survival.[10]

Many different factors may alter the balance of proangiogenic and antiangiogenic cytokines.[29,41,42] Recently it has been shown that IL-6 and IL-1β stimulate VEGF mRNA expression in different carcinoma cells lines.[17–19] Other evidence supports the role of IL-6 in angiogenesis and tumor growth. In patients with advanced breast, ovarian, and colorectal cancer, serum IL-6 levels correlate with serum VEGF levels.[43] In one study conducted in 208 patients with colorectal cancer, a high preoperative serum concentration of IL-6 was associated with advanced tumor stage and poor outcome.[44]

Our results show a significant positive correlation between postoperative serum IL-6 and VEGF levels and also between VEGF levels, MVD, and tumor growth, suggesting that an increased and persistent expression of proinflammatory cytokines may activate the normal quiescent vasculature to sprout new capillaries.[7] Interestingly, it has been shown that the presence of an acute-phase response 3 months after curative surgery for colorectal cancer is associated with a higher rate of tumor recurrence.[45] By stimulating angiogenic pathways, an increased inflammatory response may provide an environment in which residual viable cancer cells present within the bowel lumen,[46] in the surgical field,[8] and in the venous blood[47] are more likely to survive and progress to a local or distant recurrence.

It can be argued that the timing between the increases in IL-6 serum levels in the open cecectomy group and the increases in VEGF levels make it difficult to explain a causal relationship, despite the positive correlation between both cytokine serum levels. However, this timing could be explained by the participation of other mediators of VEGF-enhanced expression by IL-6. In this sense recent in vitro studies

have shown that IL-6 increases cyclooxygenase-2 (COX-2) expression in human cancer cells, and it is well known that COX-2 stimulates VEGF expression and new vessel formation.[48]

We have not confirmed the results of previous reports showing greater tumor growth after CO_2 laparoscopy compared with helium laparoscopy. The observation of those differences suggested a negative role for CO_2 in that it alters the pH in the peritoneum and impairs local defense and immune competence. As expected, we found a drop in the intraperitoneal pH in the LC group but not in the LH group. Based on the finding in some in vitro studies,[24,49] we hypothesized that peritoneal acidosis might enhance VEGF expression and new vessel formation, but there was no difference in VEGF serum levels or in MVD between the two laparoscopic groups. Although we did not measure local tissue VEGF levels, our results suggest that the type of gas used in laparoscopic surgery has no influence on tumor angiogenesis.

CONCLUSION

The results of the present study show that increased systemic levels of proinflammatory cytokines and VEGF are associated with increased angiogenesis after laparotomy compared with laparoscopy in mice. This may, in part, be responsible for the increased tumor growth after laparotomy compared to laparoscopy observed in some animal models.

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Treatment of Hepatocellular Carcinoma Using Percutaneous Radiofrequency Thermoablation: Results and Outcomes in 56 Patients

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The aim of this study was to evaluate the efficacy of and tolerance for radiofrequency thermoablation (RFTA) in patients with hepatocellular carcinoma (HCC). From March 1999 to September 2001, a total of 56 patients (46 men and 10 women) whose mean age was 67.8 years (range 51 to 76 years) underwent RFTA for 71 HCCs at our institution. RFTA was carried out in 45 patients with one lesion less than 6 cm in diameter, in seven patients with two lesions less than 4 cm in diameter each, and in four patients with three lesions less than 3 cm in diameter each. The mean diameter of the lesions was 4.1 cm (range 0.8 to 6.0 cm). The etiology of the cirrhosis was alcoholism in 31 patients, post–hepatitis C in 19 patients, post–hepatitis B in four patients, and hemochromatosis in two patients. Forty-five patients were classified as Child stage A and 11 were Child stage B. No ascites, prothrombin time >60%, and platelet count <60,000/mm^3 were needed. Two types of cooled needles were used depending on the size of the lesion (a needle 15 cm in length was used for 2 or 3 cm tumors, and a cluster of needles was used for tumors larger than 4 cm). Helical computed tomography was performed 8 weeks after treatment. The main criterion for a complete response was the presence of a hypodense lesion without contrast enhancement. Mean follow-up was 14 months. Complete tumor destruction was achieved in 50 (89.2%) of 56 patients after one session and in 52 (92.8%) of 56 after two sessions. Twelve months later, a complete response was confirmed in 45 patients (80.3%), four patients had a local recurrence and new liver nodules, and three patients had died (one of bone metastasis, one of acute alcoholic hepatitis, and one of bronchial carcinoma). Thirty-nine patients (69.6%) were still in complete remission 36 months later, and a new HCC had developed in six patients. At 36 months 49 of 56 patients were alive and 39 of 56 were free of disease. Patients with HCCs that developed following viral cirrhosis had a worse prognosis than those with HCCs that occurred after alcoholic cirrhosis (2-year survival, 57.7% vs. 77.7%; $P = 0.0241$). It was concluded that radiofrequency ablation is an effective treatment for HCC, although the prognosis is better in patients who develop HCC after alcoholic cirrhosis compared to those in whom HCC occurs after viral cirrhosis. (J GASTROINTEST SURG 2003;7:791–796)

KEY WORDS: Hepatocellular carcinoma, percutaneous treatment, radiofrequency thermoablation

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Surgical resection can be a curative treatment for HCC.[1,2] However, this cancer is usually associated with liver cirrhosis or chronic hepatitis so most patients with HCC are not candidates for surgical resection because of poor hepatic reserve. Several minimally invasive techniques, such as percutaneous ethanol injection,[3–6] radiofrequency thermoablation (RFTA),[7–17] percutaneous microwave coagulation,[18,19] interstitial laser photocoagulation,[20] and percutaneous acetic acid injection,[21,22] have been used to treat HCC and metastatic liver tumors.

Percutaneous ethanol injection is the most widely performed local treatment for small HCCs. The prognosis for patients with HCCs ≤3 cm in diameter who are treated with percutaneous ethanol injection is comparable to the prognosis for patients who are

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treated with surgical resection.[23] Recent reports have indicated that RFTA is very effective for local control of small HCCs. It appears that in the future RFTA might be an alternative to percutaneous ethanol injection,[24] and to surgery as well. The purpose of our study was to evaluate the effectiveness of RFTA in treating patients with HCC and also the patients' ability to tolerate this treatment.

MATERIAL AND METHODS

Patients

Between March 1999 and September 2001, a total of 56 consecutive patients (46 men and 10 women) whose mean age was 67.8 years (range 51 to 76 years) underwent RFTA for 71 HCCs at our institution. The diagnosis of HCC was confirmed in all patients by ultrasound-guided biopsy. Biopsy specimens were obtained from solitary nodules or, in patients with two or three nodules, from the largest nodule. Pretreatment imaging studies included abdominal ultrasonography, dynamic computed tomography (CT), and alpha-fetoprotein serum levels.

RFTA was carried out in 45 patients with one lesion less than 6 cm in diameter, in seven patients with two lesions less than 4 cm in diameter each, and in four patients with three lesions less than 3 cm in diameter each. The mean diameter of the lesions was 4.07 cm (range 8 to 60 mm) (Table 1). Cirrhosis was confirmed by histologic examination in 26 of 56 patients and by radiologic findings (ultrasound images and CT scans) in the other patients. The etiology of the cirrhosis was alcoholism in 31 cases, hepatitis C in 19 cases, and hepatitis B in four cases; in two cases cirrhosis was attributed to hemochromatosis (Table 2). Forty five patients were Child stage A and 11 patients were Child stage B. No ascites, prothrombin time >60%, and platelet counts >60,000/mm^3 were needed. Informed consent was obtained from all patients before the RFTA treatment was begun.

Radiofrequency Thermal Ablation

Principle of Radiofrequency Ablation. Thermal injury to living tissue is known to begin at 42C. Lethal exposure times at this temperature range from 3 to 50 hours depending on the tissue involved. At temperatures above 43C, lethal exposure times decrease exponentially; at 46C, 8 minutes of exposure is sufficient to cause cell death, and at temperatures above 60C, denaturing of tissue collagen begins and cell death is inevitable. Therefore, when treating cases where injury to normal tissue is not a concern, temperatures of this magnitude are desirable. In clinical practice the tissues around the tip of a needle electrode are heated to 100C, the temperature required to induce the desirable degree of injury. It is known, however, that rapid heating to too high a temperature (>100C) dramatically increases tissue impedance, and the deposition of radiofrequency energy, heat diffusion, and further coagulation necrosis are limited. Using ultrasound or CT guidance, a radiofrequency needle electrode is percutaneously introduced directly into a tumor. When the electrode is connected to a generator producing alternating electric current, radiofrequency is emitted from its tip and current within the radiofrequency range (460 kHz) passes into surrounding tissue. The current agitates ions of tumor tissue around the needle electrode, and the frictional heat produced by ionic agitation induces cellular death via coagulation necrosis. By changing the intensity and duration of the alternating current and the size of the electrode, the size of the thermal lesion can be controlled.

The device used in this study was manufactured by Radionics–Tyco Healthcare (Burlington, MA); it includes a needle electrode with a tip that is internally cooled with chilled saline solution, a process thought to increase the size of the thermal lesion. The device is equipped with a 200-watt generator and uses either a single 17-gauge straight electrode or clustered electrodes in a triangular shape. With this device thermal lesions up to 5 cm in diameter can be treated. The needle is introduced into the liver tumor under ultrasound guidance; it is then connected to a radiofrequency generator and a pump carrying cold saline solution to the needle to avoid puncture burns. RFTA was performed for a period of 900 to 1200 seconds per tumor to maintain an intratumoral temperature

Table 1. Diameter of the HCC treated

	Lesion size (diameter)				
	<2 cm	2–3 cm	3–4	4–5 cm	>5
No. of HCCs	9	11	27	13	11

HCC = hepatocellular carcinoma.

Table 2. Child stage of HCC treated by RFTA

	Etiology of cirrhosis			
	Alcoholism	Post–hepatitis C	Post–hepatitis B	Hemochromatosis
Child class A	24	17	2	2
Child class B	7	2	2	0

HCC = hepatocellular carcinoma; RFTA = radiofrequency thermoablation.

above 65C (Fig. 1). Patients were completely sedated with propofol during the entire RFTA procedure.

Effectiveness of Radiofrequency Thermoablation

All treatment sessions were completed within 1 month after therapy was begun. Dynamic CT was performed 1 month after the initial treatment and then every 4 months for the first 3 years. When a nonenhancing area with a diameter equal to or greater than that of the treated nodule was detected, tumor necrosis was considered to be complete (Fig. 2). When nodule enhancement was seen on CT scans obtained 1 month after the initial treatment, the therapeutic effect was considered to be incomplete. The follow-up period ranged from 6 to 36 months (mean 20 months).

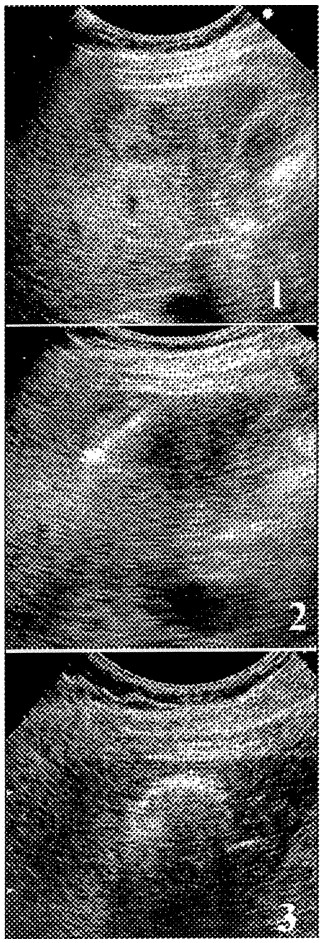

Fig. 1. Steps involved in RFTA. *1*, Small HCC in segment IV. *2*, Placement of the "cooled needle." The needle must cross the lesion. *3*, After RFTA. RFTA = radiofrequency thermoablation; HCC = hepatocellular carcinoma.

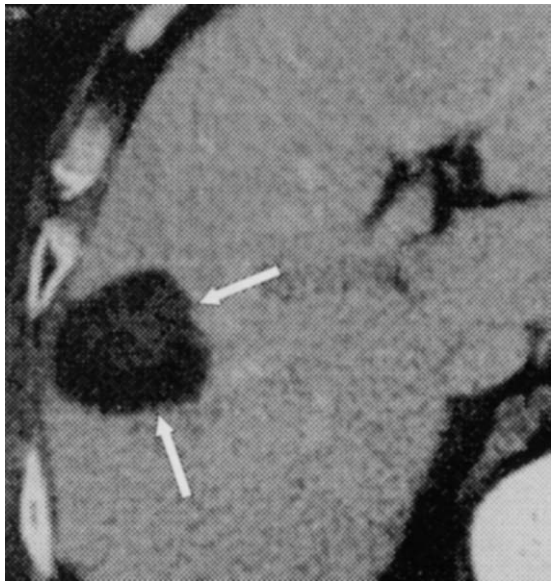

Fig. 2. Computed tomographic scan after radiofrequency thermoablation. *Arrows* indicate areas of necrosis.

RESULTS

Ninety sessions of RFTA were performed (mean 1.6 per patient). The complication rate was very low. One patient had a skin burn. Peritoneal bleeding occurred in another patient but no surgery was necessary, and the patient left the hospital 1 week later.

The mean time required for RFTA (including general anesthesia and RFTA) was 54 ± 18 minutes per session. Intravenous administration of an analgesic was needed immediately after treatment in 27 patients. Complete tumor destruction (evaluated by CT 1 month after the initial procedure) was achieved in 50 (89.2%) of 56 patients and in 64 (90.1%) of 71 nodules after one session and in 52 (92.8%) of 56 patients and 66 (92.9%) of 71 nodules after two sessions. The four nodules with an incomplete therapeutic effect, the diameters of which were 3.6, 4.4, 5.0, and 5.2 cm, were near the hepatic vein. During follow-up, residual foci of untreated disease were seen in these four nodules. These four patients were treated by percutaneous ethanol injection (3 cases) and by surgery (1 case).

Four patients had a local recurrence and new liver nodules 4, 6, 10, and 12 months after the initial RFTA session, and three patients died of bone metastasis (1 patient), acute alcoholic hepatitis (1 patient), and bronchial carcinoma (1 patient). Two of the four patients who had a local recurrence and new lesions were treated by chemoembolization using lipidol and doxorubicin. The other two were included in a protocol evaluating the antitumoral effect of long-acting somatostatin.

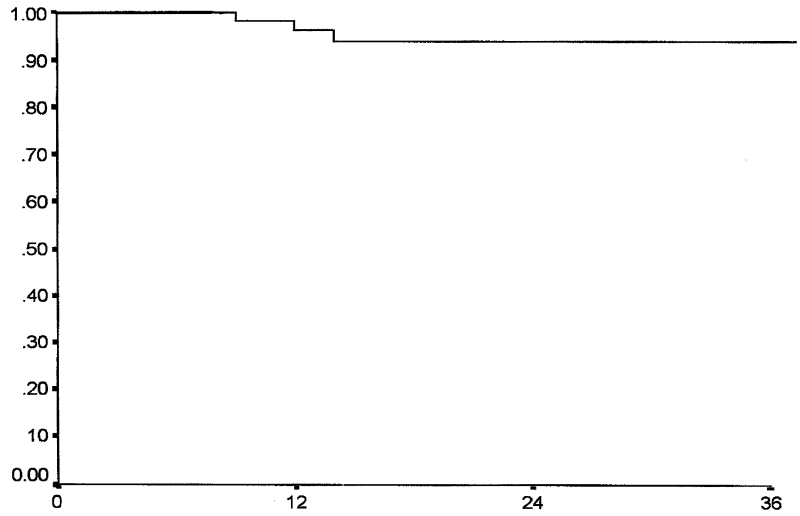

Fig. 3. Overall survival (percent of patients $\times 10^{-2}$ [vertical axis] against time [months, horizontal axis] in 56 patients).

A new HCC appeared in six patients. At the end of the study 49 of 56 patients were alive and 39 (69.6%) of 56 in the complete remission group were free of disease. To summarize, four patients had a local recurrence with new liver lesions (7.1%), bone metastasis was diagnosed in one patient (1.7%), and a new HCC was discovered at follow-up in six patients (10.7%). Cumulative survival rates were 96.2%, 94.2%, and 94.2% at 1, 2, and 3 years, respectively (Fig. 3). Mean survival time was 36 months (confidence interval 35 to 38 months). Disease-free survival was 82.1%, 73.8%, and 70.3% at 1, 2, and 3 years, respectively (Fig. 4). Concerning the disease-free survival, there was no significant difference between HCCs that developed in patients with alcoholic cirrhosis compared to those with post–hepatitis C cirrhosis. The 2-year disease-free survival rates were 77.7% for alcoholic cirrhosis and 57.7% for post–hepatitis C cirrhosis ($P = 0.0241$) (Fig. 5). During follow-up the two patients with post–hepatitis C cirrhosis underwent liver transplantation. Pathologic examination of the resected liver did not show any residual tumor at 6 and 12 months after the initial RFTA. The HCCs treated were 22 and 36 mm in diameter, respectively.

DISCUSSION

Percutaneous ethanol injection has gained fairly wide acceptance as a safe, inexpensive, and effective method for treating HCCs.[3–6] However, percutaneous ethanol injection is occasionally ineffective

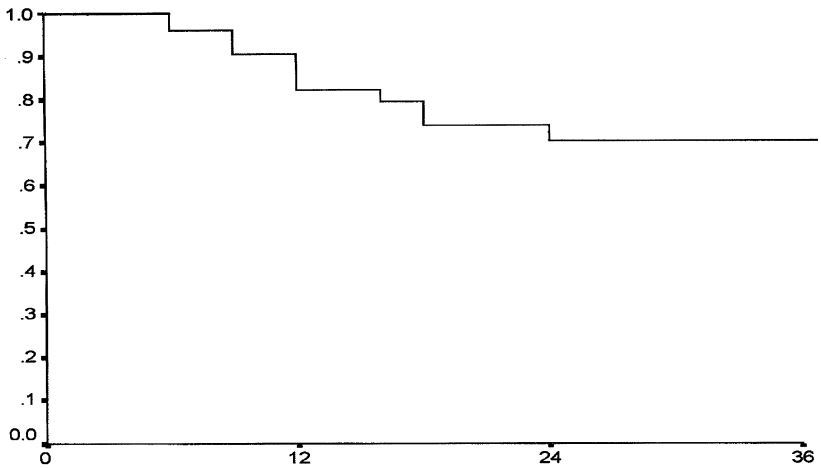

Fig. 4. Disease-free survival in 56 patients (percent of patients $\times 10^{-2}$ [vertical axis] against time [months, horizontal axis] in 56 patients).

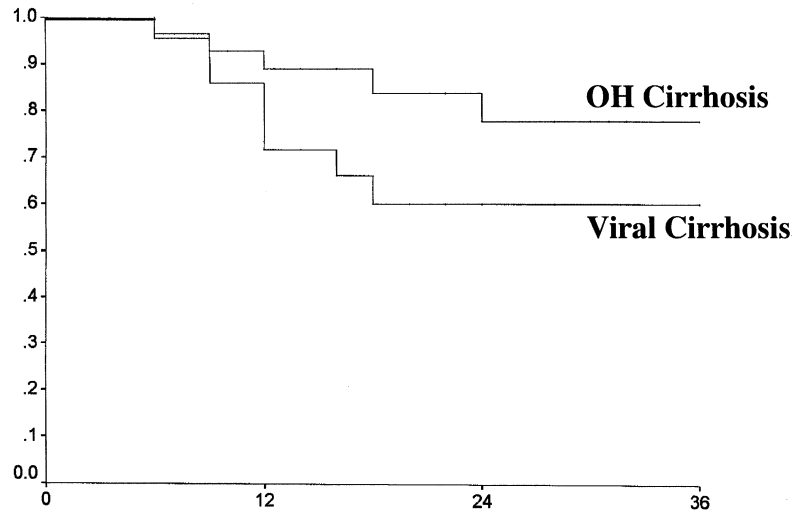

Fig. 5. Survival of patients (percent of patients $\times 10^{-2}$, vertical axis) with alcohol-induced (OH) cirrhosis (n = 31 patients) vs. viral cirrhosis (n = 23 patients) against time (months, horizontal axis). $P = 0.0241$.

when there is intra- or extracapsular invasion, because ethanol diffusion is blocked by fibrous tissue.[25] The rates of residual foci of untreated disease with percutaneous ethanol injection are not low (10.5% to 26.0%). Tumor regrowth usually occurs from the margin of the tumor because of the nonhomogeneous distribution of the ethanol in the tumor.[5] RFTA may help those treating these tumors to overcome the limitation of pharmacologic therapeutic diffusion. In a study published by Livraghi et al.,[24] the rates of complete necrosis with RFTA and percutaneous ethanol injection were 90% and 80%, respectively. Horigome et al.[18] observed percutaneous microwave coagulation to be superior to percutaneous ethanol injection for treating patients with HCCs ≤15 mm in diameter.

In our study a complete therapeutic effect (evaluated by CT) was achieved in 64 of 71 HCCs treated with one or two sessions of RFTA. Thus RFTA may produce sufficient ablation of the tumor and the surrounding parenchyma, and could become the treatment of choice for HCCs ≤5 cm in diameter and the main alternative to percutaneous ethanol injection and surgery.

Three types of RFTA electrodes are currently available commercially: two brands of retractable needle electrodes (model 70 and model 90 StarBurst XL needles; RITA Medical Systems Inc., Mountain View, CA, and the LeVeen Electrode System; RadioTherapeutics Corp., Sunnyvale, CA) and an internally cooled electrode (Cool-Tip RF System; Radionics–Tyco Healthcare, Burlington, MA). De Baere et al.[26] showed that the internally cooled electrode produced substantially larger lesion than the expandable needle in animal livers.

The rate of complete necrosis in HCCs treated by RFTA has been reported to be in the range of 90% to 96%, and the rate of residual foci of untreated disease ranges from 4% to 10%.[27,28] Our study showed similar results—that is, more than 90% of complete necrosis and 9.8% of residual malignant tissue. On the other hand, during follow-up in our study, two patients underwent liver transplantation. Pathologic examination of the resected liver did not show any residual tumor.

The first problem with RFTA is mainly the reduced area of coagulation or ablation produced by the cooling effect of hepatic blood flow. Thus ablation therapy performed during interrupted hepatic blood flow carried out with balloon occlusion of the hepatic artery and hepatic vein is another treatment option. This technique is more invasive, however, because the ablation must be performed during angiography. In such cases RFTA followed by percutaneous ethanol injection should be effective because the size of the area ablated with ethanol is not affected by the cooling effect.

The second problem is the new hepatic or extrahepatic metastatic disease. Curley et al.[11] published the findings in a large series of more than 100 patients. The HCCs were treated either percutaneously or during laparotomy. The lesions ranged in size from 0.5 to 12 cm. The recurrence rate in that series was 2.4%, and 28% of the patients developed a new hepatic or extrahepatic disease.

In our study four patients developed a local recurrence with new liver lesions (7.1%), distant visceral metastasis occurred in one patient (1.7%), and a new HCC was diagnosed during follow-up in six patients (10.7%). The question remains, "Is adjuvant therapy

needed after RFTA for HCC?" There are no answers in the literature. Preliminary studies showed that combining RFTA with chemoembolization did not produce any increase in complete necrosis.[29]

CONCLUSION

Percutaneous RFTA was found to be a simple and safe technique. In 90% of cases complete destruction of HCCs less than 5 cm in diameter was achieved with this technique. Thus RFTA appears to be an effective treatment for HCC, but new hepatic or extrahepatic metastatic disease remains a problem.

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Radiofrequency-Assisted Liver Resection

Mattia Stella, M.D., Andrea Percivale, M.D., Massimo Pasqualini, M.D., Alberto Profeti, M.D., Nicola Gandolfo, M.D., Giovanni Serafini, M.D., Riccardo Pellicci, Ch.M.

Radiofrequency (RF)-assisted thermal ablation has been used with increasing frequency for unresectable hepatic tumors. This new approach employs RF energy to coagulate the liver at the hepatic resection line after which hepatic resection is performed with the use of a common scalpel. This procedure was used in three patients with hepatocellular carcinoma and in five patients with colorectal metastasis to the liver. These eight patients underwent a total of two left bisegmentectomies, three segmentectomies, and seven wedge resections. Mean operative time was 220 minutes. A mean of 78 sessions of RF-assisted ablation were required for these resections. Mean blood loss was 46 ml; no device other than RF ablation was required to obtain hemostasis. None of the patients needed a blood transfusion. Preoperative hemoglobin was 12.8 gm/dl and postoperative hemoglobin was 11.3 gm/dl. There were no perioperative deaths. Postoperative complications occurred in two patients: a liver abscess in one and heart failure in the other. The mean hospital stay was 9.4 days. This new approach, integrated with other techniques, reduces blood loss and coagulates the margins of resection during liver surgery. This new technique has two limitations: (1) it cannot be applied near main portal pedicles, and (2) it requires a long operative time. The best indication for this technique is when segmentectomy is required in patients with cirrhosis. Its role in major hepatic resections has yet to be determined. Further progress in the development of thermal ablation techniques and experience gained during the learning curve should help reduce the operative time, thereby improving the safety and efficacy of this procedure. (J GASTROINTEST SURG 2003;7:797–801)

KEY WORDS: Liver resection, liver tumors, radiofrequency ablation

Hepatic resection remains the best treatment for liver tumors.[1-3] Unfortunately, resection of hepatic malignancies is possible in only 20% of patients at the time they are first seen.[4] Radiofrequency (RF)-assisted thermal ablation has been increasingly used for unresectable hepatic tumors.[2,5,6] This new procedure employs the heat produced by an RF needle electrode to coagulate the liver tissue before cutting it, thus permitting liver resection with reduced blood loss.[7,8] This report describes the technical aspects of this new approach and presents the results in a series of patients in whom the technique was used.

MATERIAL AND METHODS

From June to November 2002, eight patients (4 men and 4 women) underwent RF-assisted liver resection. Mean age was 64.8 years (range 55 to 72 years). Three patients had hepatocellular carcinoma, and the other five had colorectal liver metastasis. All patients underwent physical examination, preoperative computed tomography (CT) of the abdomen and chest, and blood tests for the presence of tumor markers (carcinoembryonic antigen, alpha-fetoprotein, and CA 19-9). A total of 12 tumors were treated. The mean diameter of the tumors was 20.7 mm (range 8 to 60 mm.). Two left bisegmentectomies, three segmentectomies, and seven wedge resections were performed (Table 1). One patient underwent associated intraoperative RF ablation of one liver nodule, which could not be resected. In one case a right colectomy was performed. The surgical technique (hepatic coagulating technique) used was the one described by the investigators who first developed it.[7,8] Once the type of hepatectomy is planned, based on the results of visual and manual exploration and ultrasound examination

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Table 1. Results of liver resection using radiofrequency ablation

Patient	Segments resected*	Blood loss (ml)	Operative time (min)
1	II, III	40	210
2	I, II, III, WR IV	70	420
3	VII, WR II, WR VIII	5	170
4	WR II/IV	10	180
5	VI	40	180
6	WR IV/VIII	5	180
7	WR V	150	240
8	WR VI	50	180

WR = wedge resection.
*Tumor was between segments II and IV.

of the liver, the line of resection is marked by diathermy on the liver surface; the next step is the application of RF energy by a 3-cm exposed end probe (total length 20 cm), which is cooled with saline solution at 0C (Cool Tip RF; Radionics, Burlington, MA) (Fig. 1). A 480 kHz RF generator (CC1 Cosman Coagulator System, Radionics) was used; during the procedure, tissue impedance, generator power output, and electrode tip temperature were controlled. The needle was placed in the parenchyma under ultrasound guidance. RF should last 60 seconds to obtain a zone of tissue necrosis with a radius of at least 1 cm and a depth of 3 cm. The procedure starts from the deepest to the most superficial point of the tissue at the resection line, and the number of sessions of RF ablation depends on the thickness of the parenchyma that needs to be coagulated. After complete coagulation of the tissue is achieved, the probe is placed 2 cm away from the point of previous application. Then a new application is initiated. Once RF thermal ablation has been completed along the resection line, the liver resection can be performed with the use of a common scalpel (Fig. 2). In the case of an incomplete coagulation, additional applications of RF can be performed during resection of the parenchyma to obtain a bloodless hepatic resection margin (Fig. 3). In the case of V segmentectomy, because RF sessions were performed close to the main right biliary duct, a prophylactic transcystic drainage tube (Pedinielli; Porges S.A., Le Plessis Robinson, France) was left in place for 15 days. An infrahepatic drainage tube also remained in place.

RESULTS

There were no operative deaths. Mean operative time was 220 minutes (range 170 to 420 minutes). The resections required a mean of 78 sessions (range 20 to 200 sessions) of RF ablation. The mean blood loss was 46 ml (range 5 to 150 ml), and nothing (e.g., stitches, clips, tissue glue, argon beam coagulation) besides the RF energy was required to obtain adequate hemostasis. None of the patients received blood transfusions, and the Pringle maneuver was never required. One patient had significant intraoperative

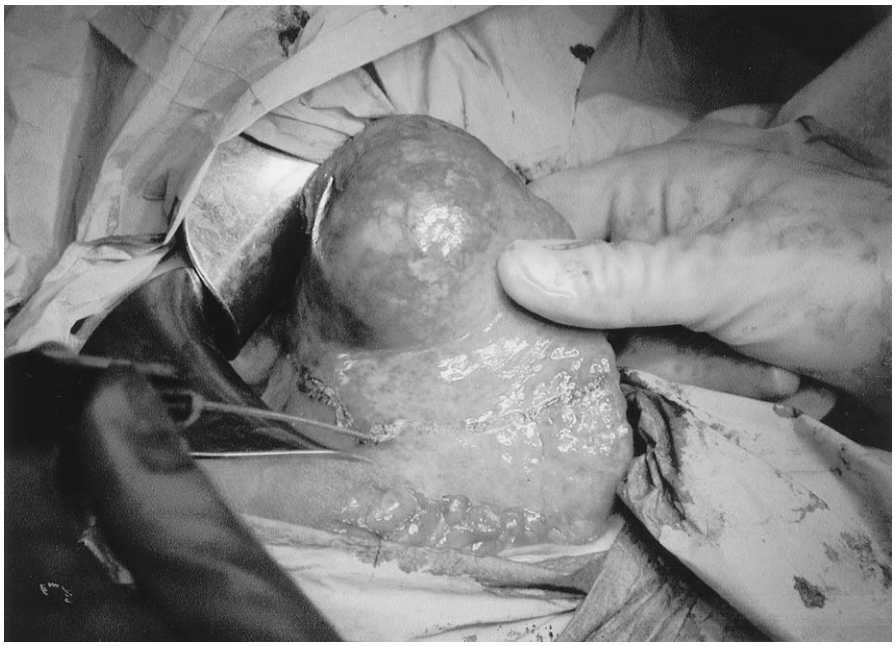

Fig. 1. Radiofrequency-assisted coagulation is employed along the marked line of resection.

Fig. 2. Liver resection is performed by cutting the coagulated tissue with a common scalpel.

bleeding (total blood loss 150 ml) due to incomplete coagulation of a blood vessel. The bleeding was managed with manual compression and further sessions of RF-assisted therapy. Mean preoperative hemoglobin was 12.8 g/dl (range 10.1 to 15.9 gm/dl), and postoperative hemoglobin was 11.3 g/dl (range 8.5 to 13.4 g/dl). All patients had a postoperative increase in transaminase and bilirubin levels, which normalized within 10 days (Table 2). Severe complications occurred in two patients (25%). One month after operation, one patient developed an abscess at the site of resection. The abscess required percutaneous ultrasound-guided drainage. The second patient, a 72-year-old person who had prior cardiac failure, had worsening of the disease postoperatively; this patient was treated with drugs and a

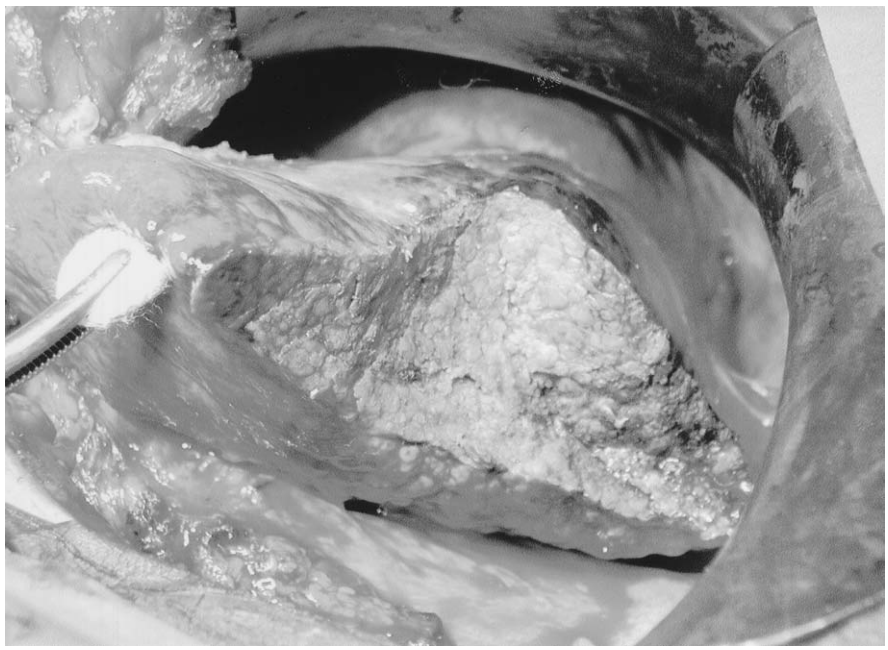

Fig. 3. Resection has been completed. Margins of resection after hepatectomy are shown.

Table 2. Blood tests before and after liver resection using radiofrequency-assisted coagulation

Substance	Preoperative	Postoperative day 1	Postoperative day 10
Mean AST (U/l)	Normal	718.2 (range 344–1157)	Normal
Mean ALT (U/l)	Normal	643 (range 345–1200)	Normal
Total bilirubin (mg/dl)	Normal	1.8 (range 1.4–2.9)	Normal
Hemoglobin (g/dl)	12.8 (range 10.1–15.9)	11.3 (range 8.5–13.4)	NA

AST = serum asparate aminotransferase; ALT = serum alanine-aminotransferase; NA = not available.

short stay in the intensive care unit. A second-degree burn under the dispersive pad occurred in one patient and was managed with daily dressing. The mean postoperative hospital stay was 9.4 days (range 5 to 20 days).

DISCUSSION

At present, liver resection is the best treatment for liver tumors.[1,2,8] RF-assisted thermal ablation is currently used to destroy unresectable liver nodules.[6,9] RF energy through frictional heating induces coagulation and necrosis of neighboring tissues as the temperature is increased above 45° C.[1,2,5] A different use for RF thermal energy has recently been proposed; this involves using RF to obtain a line of coagulation at the resection line before dividing the line with a scalpel, thereby permitting a bloodless liver resection.[7,8] A similar concept has also been applied during laparoscopic partial nephrectomy.[10]

Improved techniques for liver resection, better monitoring during anesthesia, and the introduction of a number of technical devices (e.g., ultrasound scalpel, bypolar forceps, and argon beam coagulator) have resulted in reduction in perioperative morbidity and mortality, even though liver surgery still remains a challenging procedure.[7,11,12,13] Moreover, intraoperative blood loss and the subsequent need for blood transfusion are considered significant risk factors for increased mortality and morbidity, poor postoperative outcome, and a shorter duration of disease-free survival.[12-18] RF-assisted liver resection has been developed to minimize blood loss. Hemostasis is obtained only by RF thermal energy; no additional devices (e.g., stitches, knots, clips, or glue) are needed.[7,8] The Pringle maneuver is not usually required during RF-assisted liver resection, thus avoiding liver ischemia and its attendant morbidity and mortality in patients with liver cirrhosis.[19] On the one hand, the resection line to which RF is applied consists of a coating of approximately 1 cm of coagulated tissue, a further assurance of a complete resection of neoplastic disease with negative gross margins. On the other hand, it may also result in a major sacrifice of normal parenchyma in comparison to standard techniques.[7,8] The operative time is usually shorter,[7] although we did not experience a shorter operative time in our series. The main reasons for the lengthy operative times in our series were the large number of RF sessions we performed and our gradual ascent up the steep learning curve. We tried using two RF needles at the same time in an attempt to shorten the operative time. However, we believe that new technical devices are needed to reduce the operative time.[7,8] Even if a right hepatectomy with hepatic coagulating techniques is used,[8] the best indication for the RF-assisted technique remains segmental resection, particularly of the cirrhotic liver. The main problem with major resection concerns the area close to the hilum and the major liver structures (inferior cava vein and main hepatic veins), but in this case structural ligation of the main portal pedicles could be performed.[7] Complications relating to the biliary tree following RF-assisted thermal ablation are well known and are described in the literature.[6] For these reasons tumors close to the main portal bifurcation (1.5 to 2 cm) are excluded from RF treatment[5,9,20] or if RF ablation is performed, a prophylactic biliary stent is placed.[2] A cooling system for the biliary tree that is used during RF-assisted thermal ablation and employs a pump containing saline solution chilled to 4C has also been described.[21]

CONCLUSION

RF-assisted thermal ablation techniques offer additional improvements in outcome after hepatic surgery. Its main feature is a decrease in blood loss at the line of liver transection with consequent benefits in the areas of perioperative mortality, morbidity, and postoperative outcome.[7,8] The technique is best used for segmental resections in patients with liver cirrhosis, whereas its role during major lobar hepatectomies has yet to be defined.[7] Further improvements in technology and progress along the learning curve are likely to shorten the operative time and increase the efficacy of this procedure.[7,8]

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Subdiaphragmatic Bronchogenic Cyst Masquerading as an "Adrenal Incidentaloma"

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A subdiaphragmatic, retroperitoneal bronchogenic cyst arising from the stomach is reported in a patient who was referred for evaluation of what was thought to be an adrenal tumor. To our knowledge, less than 20 cases of retroperitoneal bronchogenic cyst have been reported in the English literature. A bronchogenic cyst may be indistinguishable from an adrenal tumor and, although rare, should be considered in the differential diagnosis of a retroperitoneal mass. (J GASTROINTEST SURG 2003;7:802–804)

KEY WORDS: Subdiaphragmatic, retroperitoneal bronchogenic cyst

A bronchogenic cyst is a congenital abnormality of the tracheobronchial analge arising from the primitive foregut. It is present in the mediastinum in 90% of cases, most commonly in the posterior aspect of the superior mediastinum. Rarely, bronchogenic cysts are found in an extrathoracic location. We present a patient who had a large, incidentally discovered retroperitoneal mass that was thought to be a left adrenal tumor which, after resection, was determined to be a bronchogenic cyst arising from the posterior wall of the stomach.

CASE REPORT

A 59-year-old Caucasian woman was referred to our institution for evaluation of a left adrenal mass that was incidentally discovered during a workup for jaundice. A CT scan of the abdomen demonstrated a 7.0×5.0 cm homogeneous mass thought to be arising from the left adrenal gland (Fig. 1). The mass was described as uniformly echogenic and arising from the left adrenal gland on abdominal ultrasound examination. The patient had no history of hypertension or prior malignancy. She denied having any of the following: headaches, palpitations, diaphoresis, abdominal pain, anxiety disorder, easy bruising, or glucose intolerance. Her medical history was notable only for hypothyroidism. There was no family history of endocrinopathies. She had a history of heavy alcohol use. A liver biopsy was consistent with alcoholic liver disease. On examination, her blood pressure was 209/90 mm Hg, heart rate 102 beats/min, and weight 68 kg. She had no thyromegaly or dominant thyroid nodule. There was no evidence of moon facies or prominence of the supraclavicular fat pads. Results of an abdominal examination were unremarkable.

She underwent a workup to exclude a functioning adrenal tumor, which included a 24-hour urine test for vanillylmandelic acid, normetanephrine, metanephrine, catecholamines, cortisol, and aldosterone, all of which were normal. Her serum potassium level was 3.7 mmol/L and her international normalized ratio was 1.5. The hyerprothrombinemia was corrected with vitamin K, and a left adrenalectomy was recommended because of concern about adrenocortical carcinoma given the large size of the mass.

Laparoscopic evaluation revealed that the mass involved the posterior wall of the stomach, and the decision was made to convert to an open laparotomy. This revealed a submucosal mass of the posterior wall of the stomach, which was excised. The left adrenal gland was normal in appearance and was uninvolved by the tumor mass. The patient recovered from surgery without incident.

Pathologic evaluation revealed a cystic mass that was filled with thick mucin. Microscopically the cyst was partially lined by ciliated pseudostratified

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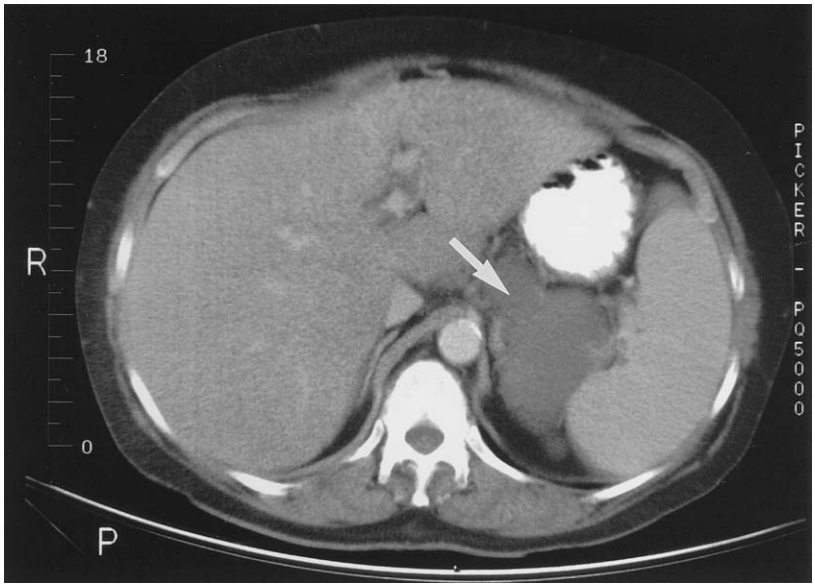

Fig. 1. A 7.0 × 5.0 cm homogeneous mass (*arrow*) medial to the hilum of the spleen and posterior to the fundus and body of the contrast-filled stomach.

epithelium with goblet cells (Fig. 2). It also contained abundant smooth muscle, with mixed serous glands and a small focus of cartilage (see Fig. 2). The denuded portions of the cyst wall revealed chronic inflammation with abundant macrophages. The adjacent gastric mucosa appeared normal.

DISCUSSION

Bronchogenic cysts originate from an accessory lung bud of the primitive foregut after the third week of embryonic life. Most commonly, bronchogenic cysts migrate caudally with the esophagus and are eventually found in the posterior mediastinum near the carina attached to the tracheobronchial tree or the esophagus. In rare instances the cyst may separate completely from its origin and, as a result, may be found in unusual sites, such as the skin, pericardium, or intraspinal locations.[1,2] A subdiaphragmatic, retroperitoneal bronchogenic cyst is extremely rare, with less than 20 cases reported in the English literature.[1–6] It is postulated that the abnormal bud of the tracheobronchial tree migrates to the abdomen prior to the fusion of the pleuroperitoneal membrane.[1,4] Retroperitoneal bronchogenic cysts occur with equal frequency in men and women,[4] in contrast to cutaneous bronchogenic cysts, which are four times more common in men.[2] The cyst is lined with pseudostratified columnar or ciliated cuboidal epithelium. The wall of the cyst contains smooth muscle bundles with occasional hyaline cartilage and mixed serous and mucinous glands.[1]

Most retroperitoneal bronchogenic cysts are found in the region of the left adrenal gland, superior to the tail of the pancreas. Our patient's bronchogenic cyst was unilocular. It arose from the stomach but did not communicate with the gastric lumen. It was filled with thick mucin, and this was the likely explanation for why the mass did not appear cystic on abdominal ultrasound images or CT scans.

Most bronchogenic cysts are small, and they are usually discovered incidentally. Patients are usually asymptomatic, however, they may present with epigastric or left upper quadrant abdominal pain. CT of the abdomen usually demonstrates a unilocular mass with smooth borders. When there is communication between the cyst and the stomach, an upper gastrointestinal series may demonstrate an irregularly lobulated fluid collection with an air-fluid level posterior to the gastric fundus.[3] Endoscopic ultrasound imaging is of value for demonstrating the submucosal location of the cyst. It is also of value in helping to delineate masses involving the posterior stomach from masses involving the tail of the pancreas or the left adrenal gland. Malignant transformation is rare. A case of a retroperitoneal bronchogenic cyst attached to the ascending colon with associated adenocarcinoma has been reported.[6]

The differential diagnosis of a retroperitoneal cyst with ciliated pseudostratified, columnar epithelium also includes the following: bronchopulmonary sequestration, teratoma, and cysts of urethelial and mullerian origin. The key component in differentiating a bronchogenic cyst from bronchopulmonary sequestration is the absence of lung parenchyma and

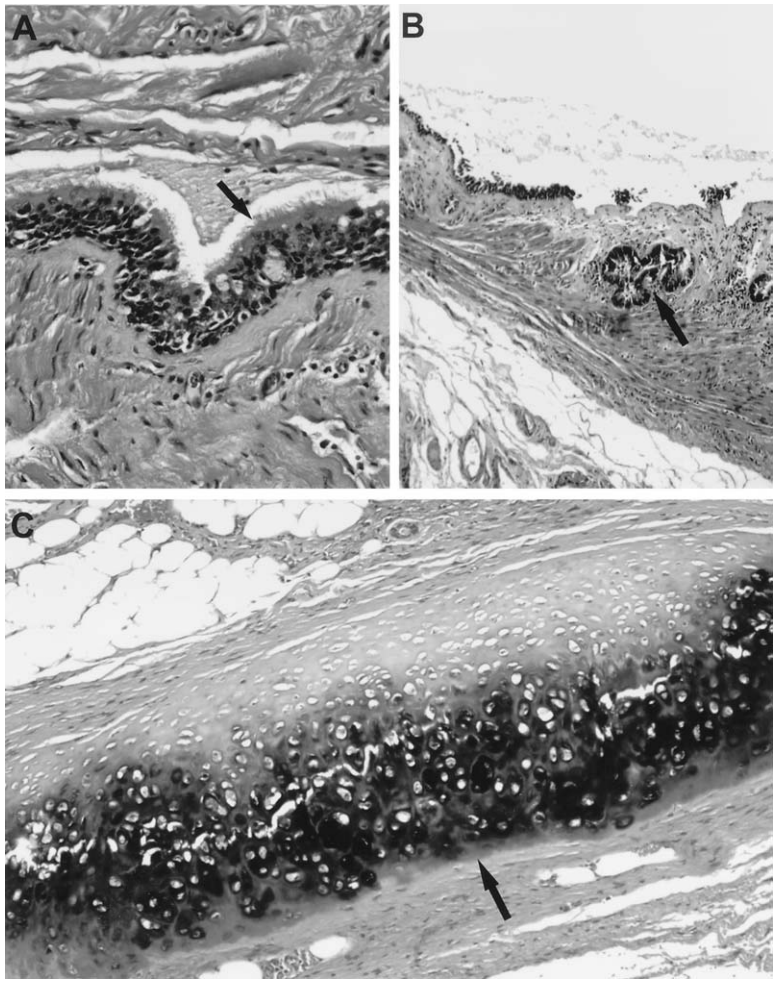

Fig. 2. Microscopic sections of the bronchogenic cyst demonstrating the ciliated pseudostratified epithelium (*arrow*) (**A**), mucous glands (*arrow*) (**B**), and cartilage (*arrow*) (**C**).

pleural investments in a bronchogenic cyst. Submucosal mixed serous and mucous glands are not present in retroperitoneal cysts of urogenital origin, and teratomas contain all three germinal layers, which distinguishes them from bronchogenic cysts.

In summary, a bronchogenic cyst, although rare, should be considered in the differential diagnosis of a retroperitoneal mass. When a bronchogenic cyst arises from the posterior wall of the stomach superior to the tail of the pancreas without communication with the gastric lumen, it may be indistinguishable from an adrenal tumor. A definitive diagnosis of a bronchogenic cyst is made by histologic examination. Characteristic features such as a ciliated pseudostratified epithelial lined cyst with smooth muscle, goblet cells, and occasional cartilage are essential for diagnosis of a bronchogenic cyst.

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Idiopathic Segmental Infarction of the Greater Omentum: A Rare Cause of Acute Abdomen

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Idiopathic segmental infarction of the greater omentum is a rare cause of acute abdomen. Patients, typically children or obese males in their fifties, present with abdominal pain located in the right upper or lower quadrant, mimicking cholecystitis and appendicitis. CT scanning and ultrasound imaging both may show a well-circumscribed soft tissue mass. Retrospective review of all patients treated for idiopathic segmental infarction of the greater omentum occurred from January 1993 to December 2001. Nine patients were treated successfully, six surgically and three medically. Conservative management of segmental infarction of the greater omentum can be proposed when correctly diagnosed by ultrasound imaging or CT scanning and the patient's condition is stable. If not, laparoscopic removal of the involved segment of the greater omentum is the treatment of choice. (J GASTROINTEST SURG 2003;7:805–808)

KEY WORDS: Acute abdomen, greater omentum, necrosis, laparoscopy

Idiopathic segmental infarction of the greater omentum (ISIGO) is a rare cause of acute abdomen mimicking acute appendicitis and cholecystitis. Less than 350 cases have been published[1] since its first description by Bush[2] in 1896. ISIGO is mainly observed in children[3] and in 40- to 50-year-old obese men.[4] Patients present with acute abdominal pain and localized signs of peritonitis. Blood parameters usually show a mild inflammation with elevated white blood cell count and C-reactive protein.[5] The radiological appearance of omental infarction is characteristic when present, and diagnosis can be made by ultrasound or CT-scanner.[1,6–10] We report nine cases of ISIGO with emphasis on diagnostic and treatment modalities.

MATERIAL, METHODS, AND RESULTS

From January 1993 to December 2001, nine patients, seven males and two females with a mean age of 40 years (range 27–78 years) were admitted because of acute abdominal pain localized to the right lower quadrant (6/9, 66%), left upper quadrant (2/9, 22%) and right upper quadrant (1/9, 12%) (Table 1). Guarding and low-grade fever were present in 8 patients (89%) and 5 patients (56%), respectively. Laboratory findings included elevated C-reactive protein (8/9, 89%) and white blood cell count (4/9, 44%). Abdominal ultrasound showed no abnormality in two patients. CT-scanner was conclusive for segmental infarction of the greater omentum in 4 out of 5 patients. Three patients with typical clinical and radiological findings were treated conservatively with success. Six patients were operated on (laparoscopy 5/6, laparotomy 1/6) because of unclear diagnosis or steadily worsening pain. Laparotomy was performed in one patient because of multiple previous abdominal surgeries. The diagnosis was confirmed in all patients (6/6), and the infarcted omentum was removed. Microscopic examination of the omentum showed ischemic infarction. The postoperative course was uneventful, and the mean hospital stay was 4.7 days (range: 3–7).

DISCUSSION

Primary idiopathic segmental infarction of the greater omentum is a rare cause of acute abdominal

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Table 1. Clinical features of nine patients with idiopathic segmental infarction of the greater omentum

Patient Sex Age	Pain (yr)	Guarding	Fever (° C)	WBC (/mm^3)	CRP (mg/L)	Surgical history	Clinical diagnosis	Treatment
M 38	RLQ	+	37.7	16,800	88	No	Appendicitis	Laparoscopy
M 32	RLQ	+	37.8	11,400	36	Appendectomy	ISIGO	Laparoscopy
M 27	RLQ	+	37.2	9,500	20	No	Appendicitis	Laparoscopy
M 27	RUQ	+	37.2	12,300	<5	No	ISIGO	Laparoscopy
F 78	LUQ + epigastric	+	36.0	9,100	56	Appendectomy gastric ulcer	Peritonitis	Laparoscopy
M 59	RLQ + right flank	+	37.1	9,400	132	No	ISIGO	Medical
M 33	RLQ	+	36.9	13,500	NA	No	Appendicitis	Laparotomy
F 34	RLQ	−	36.3	9,800	10	No	ISIGO	Medical
M 34	LUQ	+	37.5	9,100	34	Appendectomy	ISIGO	Medical

CRP = C-reactive protein (normal value <10 mg/L); M = male; F = female; RLQ = right lower quadrant; RUQ = right upper quadrant; LUQ = left upper quadrant; NA = not available; WBC = white blood cell count (normal value <10,000/mm^3); ISIGO = idiopathic segmental infarction of the greater omentum.

pain mimicking conditions such as appendicitis, cholecystitis, and colitis. The disease has first been described by Bush in 1896.[2] Less than 350 cases have been published in the current literature.[1] Most of the patients are children (15%)[3] and 40- to 50 year-old males with a sex ratio male:female of 2:1.[4] Most patients present with abdominal pain localized mainly in the right lower or upper quadrant (90%) based on the involved part of the omentum.[11–13] Local guarding and rebound tenderness are common findings.[14] Laboratory tests usually show elevated white blood cell count and C-reactive protein.[5] Preoperative diagnosis can be made by radiological imaging. Computed tomography and ultrasound both may show a well-circumscribed, ovoid or cake-like soft tissue mass characteristically located in the superficial paraumbilical region (Fig. 1 A and 1 B).[1,6–10,15–17] The clinical presentation of ISIGO often leads to false diagnosis of acute appendicitis in 66%, and acute cholecystitis in 22%.[18–19] Differential diagnosis includes acute appendicitis, acute cholecystitis, pancreatitis, duodenal ulcer, colon diverticulitis, strangulated hernia, ovarian torsion, mesenteric thrombosis, aortic aneurysm, omental metastases, and primary liposarcoma of the omentum.[10,17,21]

The pathogenesis of ISIGO is unknown. Most authors agree with the hypothesis of anomalous arterial

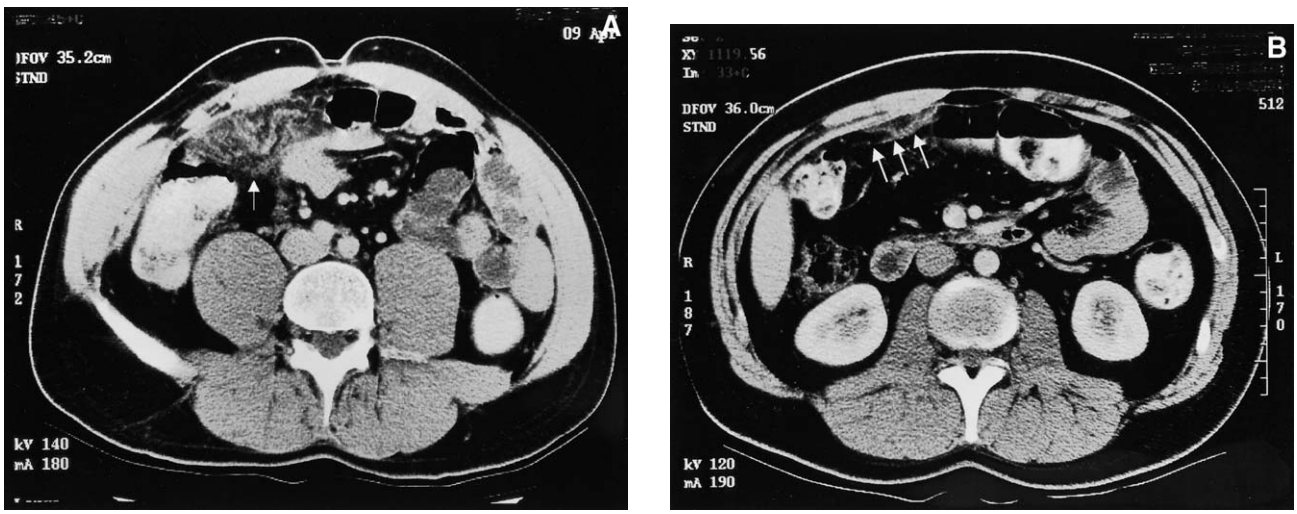

Fig. 1. Abdominal CT scan: A) fat interspersed with hyperattenuating streaks (arrow), and B) ovoid tissue mass in the paraumbilical region (arrows), two typical findings of idiopathic segmental infarction of the greater omentum.

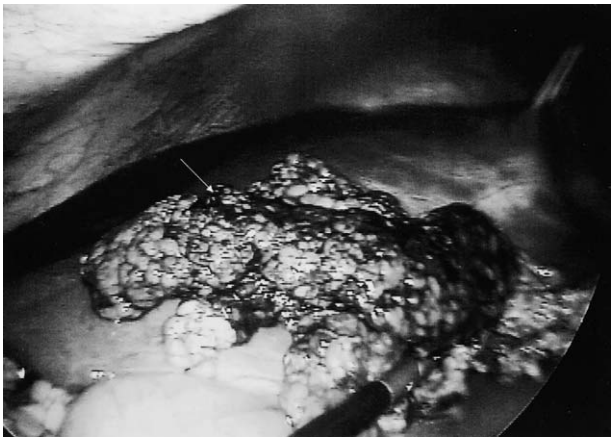

Fig. 2. Laparoscopic view of idiopathic segmental infarction of the greater omentum (*arrow*).

blood supply to the omentum,[18–20] mainly its right lower side, associated with mechanical factors. Those include venous kinking secondary to abdominal pressure increase, compression of the greater omentum between the liver and the abdominal wall,[22] vascular congestion after large meals or during cough, especially in obese patients,[6,21] and congestion of mesenteric veins caused by right-sided heart failure with secondary dilatation and hemorrhagic ischemia of the omentum.[14]

Patients presenting typical imaging findings of ISIGO may be treated conservatively.[1,6,7,9,10,23,24] Rare complications of medical treatment such as septic shock,[12,25] peritoneal adhesion,[14] and peritoneal abscess[1] have been reported. Patients with unclear radiological findings or deteriorating conditions mandate surgical exploration of the abdomen. Bloody ascites with normal appendix and segmental necrosis of the omentum are usually found (Fig. 2). The laparoscopic approach for suspected ISIGO is efficient and safe with a low morbidity and no mortality.[4,8,19,26–28]

Preoperative diagnosis was made in five out of our nine patients (55%) based on computed tomography. Three patients with image-based diagnosis were treated medically. Surgery was the treatment because of suspected acute appendicitis or peritonitis of unknown origin in four patients, and ISIGO with deteriorating conditions in two patients. Uneventful recovery was the rule for all nine patients.

CONCLUSION

Idiopathic segmental infarction of the greater omentum is a rare cause of acute abdomen of unknown etiology. The right side of the omentum is affected in the majority of patients (90%) leading to initial false diagnosis of acute appendicitis and cholecystitis. Clinical and laboratory findings are nonspecific. When ultrasound or computed tomography establishes the diagnosis, patients can be managed conservatively providing the patient's condition is stable. Unclear findings or deterioration in the patient's condition mandate surgical exploration, preferably by laparoscopy.

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Stapled Hemorrhoidectomy: Initial Experience of a Latin American Group

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The purpose of the present study was to determine the value of circular hemorrhoidectomy (procedure for prolapse and hemorrhoids [PPH]) on the basis of data collected prospectively during the initial experience of a group of Latin American surgeons. Between 2000 and 2001, PPH was performed using a circular stapler in 177 patients who had third- and fourth-degree hemorrhoidal disease. The average age of the patients was 47.7 years (range 26 to 85 years). Anal bleeding was the most common preoperative complaint (93.2%) followed by anal pain (60.2%), anal itching (43%), and constipation (41%). Hemorrhoids were classified as third degree in 132 patients (74%) and fourth degree in 45 patients (25.4%). Skin tags were detected in 86 patients (48.8%) and rectocele in 14 patients (7.9%). Data collected included patient demographics, type of anesthesia, and specific details of the surgery such as duration of the operation, distance from the staple line to the dentate line, need for complementary hemostasis, and any unexpected occurrences. Postoperative data collected included the degree of pain, which was evaluated on the basis of the type and dosage of analgesics required, laxative consumption, and the presence of bleeding, fever, urinary retention, or hematomas. Each patient completed a written questionnaire addressing these events. Patients returned for follow-up visits on days 7, 15, 30, and 90. Responses to pain, bleeding, fever, anal continence, recurrence of hemorrhoids, and level of satisfaction were compiled. The duration of the procedure ranged from 6 minutes to 2 hours (average 23 minutes), and most operations lasted no more than 20 minutes, with the exception of one that lasted 2 hours because of intraoperative bleeding. Intraoperative problems were minor. An additional one or a few sutures were required in 58.7% of patients to achieve perfect hemostasis. In 128 patients (72.3%) the hospital stay was less than 24 hours. Same-day surgery was chosen for 37 patients (20.9%). Pain was controlled with analgesia only using one to six doses of oral dipirona in 126 patients. Five patients were readmitted to the hospital: four for control of bleeding and one for conventional hemorrhoidectomy due to an acute episode of external hemorrhoidal thrombosis. At day 30, patients rated the efficacy of the procedure in alleviating preoperative symptoms as follows: 77.5% excellent; 16% good; 5.3% average, and 1.2% poor. At 3 months postoperatively no patient had had a recurrence of hemorrhoidal prolapse, and there were no instances of stenosis or anal incontinence. Surgeons also rated the efficacy of the procedure as excellent in 75%, good in 19.8%, average in 4.7%, and poor in 0.6%. With proper selection of patients and adequate stapling technique, stapled hemorrhoidectomy may be considered safe; it is easily learned, has a satisfactory degree of pain, and is well accepted by both patients and surgeons. (J GASTROINTEST SURG 2003;7:809–813)

KEY WORDS: Hemorrhoids, PPH circular stapler

Treatment of hemorrhoidal disease depends largely on the severity of the disease. Conservative treatments such as dietary changes, rubber band ligation, and infrared photocoagulation are preferred for first- and second-degree hemorrhoids. Third- and fourth-degree hemorrhoids are generally surgically excised. The operations described by Milligan and Morgan[1] and Ferguson et al.[2] are the procedures

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performed the most around the world with satisfactory results in terms of relief of symptoms, but both are prone to complications and are notoriously painful.[3–6] Modifications including the addition of anal dilation and internal sphincterotomy, relaxants, and new techniques are constantly being sought to decrease postoperative pain but without significant improvement.[5] In 1993 Longo[7] described a hemorrhoidectomy technique called the procedure for prolapse and hemorrhoids (PPH), which used a specially designed stapling device to treat prolapse and hemorrhoids. The rationale for stapled hemorrhoidectomy as suggested by Longo is associated with important changes in the theory behind the pathogenesis of hemorrhoids and their surgical treatment. Internal hemorrhoids develop when cushions of vascular tissue in the anus undergo pathologic changes. These cushions are considered to have an important role in maintaining anal continence because they act in conjunction with the internal anal sphincter to allow complete closure of the anal canal.[8–10] Stapled resection of a complete circular strip of mucosa above the dentate line, in addition to reducing the size of the hemorrhoidal cushions by interrupting their blood supply, is supposed to lift them into the anal canal. Whereas conventional surgical hemorrhoidectomy involves excision of the hemorrhoidal plexus, anoderm, and perianal skin, stapled hemorrhoidectomy simply excises a ring of rectal mucosa above the hemorrhoids. By avoiding multiple excisions and suture lines on the sensitive anal mucosa below the dentate line, there appears to be far less pain with PPH compared to conventional techniques.[5,7,11–20] The purpose of the present study was to determine the value of circular hemorrhoidectomy (PPH) on the basis of prospective data collected during the initial experience of a group of Latin American surgeons.

METHODS

A group of colorectal surgeons from Latin America participated in a scientific meeting organized by Ethicon Endo-Surgery, a division of Johnson & Johnson, Brazil, to obtain detailed information on PPH. The study was approved by the ethics committee of the University Hospital of the Medical School of São Paulo, and three patients from the Coloproctology Unit were operated on by Dr. Antonio Longo.[7]

A protocol was designed that could be applied prospectively by surgeons attending the meeting. The ethics committees of each of their institutions reviewed this protocol before the study was begun. Patients with internal third- and fourth-degree hemorrhoidal disease were enrolled in the protocol. Patients with hemorrhoidal thrombosis, fissures, fistulas, or other anorectal abnormalities and those with suppressed immune systems were excluded. All patients were prepared for surgery with a phosphate enema, and all were given one prophylactic dose of intravenous cefoxitin or metronidazole. A regional (epidural or intradural) anesthetic block or general anesthesia was administeed, and patients were placed in a lithotomy or a jackknife position.

The technique used in all procedures was the one reported by Longo, in which an anal rectractor and the Proximate HCS33 circular stapler (Ethicon Endo-Surgery, Cincinnati, OH) were used. Only one 2-0 polypropylene endoanal purse-string suture was placed circumferentially 4 cm cranial to the anal verge encompassing the mucosa and submucosa, avoiding gaps in the suture line. The stapler was introduced through the anus, and the purse-string suture was tied down onto the shaft of the instrument. Retraction of the suture pulled the attached rectal mucosa into the stapler. The instrument was closed and fired, thus incorporating the mucosal tissue into the purse-string suture within the head of the gun. A circular knife excised the excess tissue within the purse-string suture and the anastomosis was performed using a double row of titanium staples. The instrument was withdrawn and the staple line was inspected for hemostasis. Any detectable area of bleeding was sutured with monocryl sutures. When prominent skin tags were present, they were resected. The excised tissue was sent for histopathologic examination.

Data collected included demographic information as well as symptoms of hemorrhoidal disease, bowel habits, anal continence, results of proctologic examination, type of anesthesia, patient positioning, and surgical details such as the duration of the operation (beginning with the intraoperative examination and cleansing of the anal canal until the end of the procedure), distance from the stapled area to the dentate line, the need for complementary hemostasis, and any unexpected occurrences. Postoperative data collected included the degree of pain as well as the following: defecation (spontaneous or associated with the operation), laxative consumption, bleeding, fever, urinary retention, and hematoma. Pain was evaluated according to the type and dosage of analgesics required. Each patient completed a written questionnaire concerning all of these events.

Patients returned for follow-up visits on days 7, 15, 30, and 90. Responses regarding pain, bleeding, fever, anal continence, symptoms, hemorrhoidal recurrence, and level of satisfaction were compiled. A rectal examination and sigmoidoscopy on days 15 and 30 were performed to assess the height and integrity

of the suture line and the presence of anal stenosis, abscess, or anal fissure. Follow-up visits continued for a minimum of 3 months after surgery.

RESULTS

Between 2000 and 2001 a total of 177 patients were operated on and completed the study. There were 101 males. The average age was 47.7 years (range 26 to 85 years). Anal bleeding was the most common preoperative complaint (93.2%) followed by anal pain (60.2%), anal itching (43%), and constipation (41%). Two patients (1.1%) complained of diarrhea, two (1.1%) were incontinent for feces, and five (2.8%) for flatus. Hemorrhoids were considered third degree in 132 patients (74.6%) and fourth degree in 45 patients (25.4%). Skin tags were detected in 86 patients (48.8%) and rectoceles in 14 patients (7.9%).

The duration of the PPH ranged from 6 minutes to 2 hours (average 23 minutes). The suture line was, on average, 3.8 cm above the dentate line. No stapler failure was detected. An additional one or a few sutures were required for hemostasis in 104 patients (58.7%). Resection of skin tags during PPH was performed in 86 cases (48.5%). One hundred forty patients were hospitalized; the duration of hospitalization was less than 24 hours in 128 (72.3%), 2 days in 11 (6.2%), and 3 days in three (1.6%). Same-day surgery was chosen for 37 patients (20.9%).

One to six doses of oral dipirona was sufficient for pain control in 126 patients (71.7%). Eighty-two patients (46.3%) required additional pain control and were given nonsteroidal anti-inflammatory drugs (diclofenac or equivalent). No patient needed opiates for pain control. Analgesic usage decreased over time, usually by day 4. By day 7 most patients no longed required analgesics.

Laxatives to ease defecation were given to 71.7% of the patients. The first defecation occurred after an average of 31 hours (range 12 to 72 hours). First defecation requiring analgesia with oral dipirona alone was reported by 46.9% of all patients. Sixty-eight patients (38.4%) did not have any bleeding related to the first defecation. Non–defecation-related bleeding occurred in 23 patients (13.2%). Bleeding was more frequent during the first three postoperative days. Five patients (2.9%) required readmission to the hospital and surgical intervention to control bleeding, and one patient received a blood transfusion.

Five patients (2.9%) had one episode of fever (> 37.5° C), which resolved without additional therapy. In one patient a localized suppuration above the staple line was detected at follow-up examination on day 7. Antibiotics were prescribed and the infection subsided.

Rectal examination on day 15 was not painful in 42.3% of patients, and sigmoidoscopy demonstrated that a complete line of staples was still present in 6.6% of patients. Rectal examation and sigmoidoscopy on day 30 showed complete healing of the rectal mucosa in 33.6% of patients, and 40% showed evidence of hemorrhoid reduction. Eighty-two patients (46.3%) were reexamined 6 months after operation.

One patient was incontinent for flatus and another had liquid feces. Although "soiling" was not recorded preoperatively, 13 patients at day 7 and three patients at day 30 reported at least one incident of soiling. After 3 months, none of the patients had hemorrhoidal prolapse or anastomotic stricture on rectal examination, and none had fecal incontinence.

By day 30 the efficacy of the procedure in alleviating the preoperative symptoms was rated as follows: excellent in 77.5% of patients, good in 16%, average in 5.3%, and poor in 1.2%. At 3 months preoperatively none of the patients had a recurrence of hemorrhoidal prolapse or stenosis or anal incontinence. Surgeons also rated the efficacy of the procedure as follows: excellent in 75%, good in 19.8%, average in 4.7%, and poor in 0.6%.

DISCUSSION

Although PPH is a relatively new technique, many of the published studies consider the procedure to be an improvement in the treatment of hemorrhoidal disease.[7,14,16,18,21] Cheetham et al.[22] estimated that 50,000 stapled hemorrhoidectomies had already been performed in Europe by 2000. The rationale for this procedure is associated with important changes in the theory behind surgical treatment of hemorrhoids. A complete circular strip of rectal mucosa above the dentate line is supposed to lift the hemorrhoidal cushions into the anal canal. Excision of excess hemorrhoidal tissue reduces the obstruction of the canal and interrupts the blood flow to distal hemorrhoids, thereby inhibiting symptomatic recurrence.

The experience with circular stapled hemorrhoidectomy in Latin America began in 2000, and its use is becoming increasingly more widespread. As of July 2002 a total of 1180 of the procedures had been performed by a group of 30 surgeons. The present study represents the experience with the first 177 patients. The technique was considered easy to learn and quick to perform by the surgeons who participated. Most operations lasted no more than 20 minutes, with a mean duration of 23 minutes, with the exception of one that lasted 2 hours; this delay

was a consequence of intraoperative hemorrhaging and difficulties in achieving hemostasis. The operative time decreased with experience, and when there was no bleeding the procedure took no more than 10 minutes. Intraoperative problems with the exception of bleeding were minor. Bleeding at the staple line requiring additional sutures was identified in 58.7% of patients. This was not considered a complication but rather a routine part of the operation because careful revision of hemostasis is mandatory until a completely dry suture line is achieved. Postoperative bleeding requiring readmission to the hospital occurred in five patients; four of them underwent surgical revision and one required blood transfusion. In the series presented by Ho et al.,[14] bleeding during hospitalization with the staple technique was comparable to that observed with conventional treatment.

The correct placement of the purse-string suture is critical to the success of the operation. When this suture is placed very high, it may decrease the probability of complete reduction of hemorrhoidal prolapse; if the suture is low, 2 cm or less above the dentate line, postoperative pain is often increased, possibly because a portion of the hemorrhoids may have been included and squamous epithelium may be found in the surgical specimen. In the present study the average length of the suture line was 3.8 cm, and no anoderm was found on histopathologic examination. It is also essential that it not be deeper than the submucosa. This precaution also helps to avoid the inclusion of neighboring structures into the anastomosis, particularly the posterior wall of the vagina. In patients with rectocele, traumatic injury of the vagina may occur, inducing the formation of a rectovaginal fistula.[23] In our study PPH was performed in 14 patients with rectocele, and this complication was avoided by palpating the vaginal wall before firing the stapler.

The principal advantage of stapled hemorrhoidectomy is the reduction of postoperative pain with an earlier return to normal activities when compared with conventional procedure.[14,17,19,23–25] Absence of trauma to the sensitive mucosa and skin incision and suturing in less sensitive areas might be responsible for this reduction in postoperative pain. Because of pain, conventional techniques often require a 2- to 3-day hospital stay followed by an additional 15- to 30-day period of convalescence.[22] Most of the surgeons who participated in the present study usually keep their patients in the hospital for 24 to 72 hours after a conventional hemorrhoidectomy in contrast to the PPH technique, whereas more than 92% of our patients were hospitalized for less than 24 hours, and some were not hospitalized at all because pain was not an issue. In 71% of the patients, spontaneous pain was controlled with oral dipirona only, which was usually only necessary until day 4. After the first bowel movement, almost half of the patients did not require any additional doses or changes in dipirona only or in other nonsteroidal anti-inflammatory drugs. It is important to note that prior to surgery most patients were anxious and fearful of postoperative pain and the first defecation. Some studies have also reported a statistically significant decrease in pain compared to conventional techniques.[14,17,19,23–25] Only one report to date has shown persistent pain following surgery.[22]

During the immediate postoperative period, one patient developed thrombosis of the external hemorrhoidal plexus and had to undergo a conventional excision on postoperative day 5. Proper selection of patients is critical to the success of this type of operation. Patients with thrombosed external hemorrhoids or associated infection should be excluded. Patients with second- or third-degree hemorrhoids that do not respond to nonoperative treatment are the best candidates for stapled hemorrhoidectomy. Fourth-degree hemorrhoids may be also treated in this manner but the patient should be informed that more pain is to be expected and the cosmetic result might not be ideal.

Sigmoidoscopy on days 15 and 30 showed that the staple line and the anal canal had quickly healed. These results correlate well with the lack of pain and lack of symptoms reported by patients during this period.

Anal incontinence is a possible side effect of any hemorrhoidal procedure because dilation or retraction of the anal sphincter may cause injury to the sphincter. With PPH, injuries to the anal sphincter can also be caused by the introduction of the stapler head.[14] At 4 years after the Milligan-Morgan conventional hemorrhoidectomy, Bennett et al.[26] reported minor incontinence in 26% of patients. In the present study only one patient reported anal incontinence, and soiling was reported by 13; however, these problems were completely resolved in all patients after 3 months. Infection associated with hemorrhoidectomy is also a potential risk, even with the concomitant use of antibiotic prophylaxis. Because PPH involves simultaneous stapled closure of the wound and excision of the excess tissue without any dissection, the potential for contamination of the wound is eliminated thereby decreasing the risk of infection. However, this complication may occur as a consequence of hematoma formation. In our study all patients received preoperative intravenous antibiotics and only one patient had a fever, which quickly subsided after the administration of oral antibiotics.

Because of complete alleviation of the symptoms of hemorrhoidal disease, 93.5% of patients reported satisfaction with the procedure by day 30. Surgeons rated the results as good to excellent in 94.8% of patients because of quick healing and few complications.

CONCLUSION

With proper selection of patients and adequate surgical technique, stapled hemorrhoidectomy may be considered a safe procedure; it is easily learned, is associated with a manageable degree of pain as evidenced by the use of analgesics, and is well accepted by patients and surgeons. However, prospective, randomized, comprehensive studies focusing on potential problems such as achieving optimal hemostasis, equipment costs, and long-term results will clarify the additional potential benefits of PPH for both patients and physicians.

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Does an Ileoanal Pouch Offer a Better Quality of Life Than a Permanent Ileostomy for Patients With Ulcerative Colitis?

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Although an ileoanal pouch is frequently offered to patients with ulcerative colitis, it is still not clear to what extent this operation offers advantages over a permanent ileostomy. The aim of this study was to determine whether patients with a pouch have less morbidity and a better quality of life than a matched group of patients with a Brooke ileostomy. Nineteen patients (12 males and 7 females, median age 41 years) who had undergone total colectomy and ileoanal pouch formation for ulcerative colitis were individually matched with patients who had had a panproctocolectomy and ileostomy; patients were matched for disease process, sex, age, socioeconomic status, and time since surgery. Quality of life was assessed using the Short-Form 36 version 2 questionnaire, the inflammatory bowel disease questionnaire, and a few additional questions on perception of body image. The scores were compared using the nonparametric Wilcoxon signed-rank test for paired samples. The number and type of postoperative complications, as well as the number of operative stages, were recorded prospectively. Restorative proctocolectomy was associated with a significantly better perception of body image than a permanent stoma, although quality of life in general was similar in both groups. Patients with a pouch had more long-term complications than patients with an ileostomy within the same period of time (52.6% vs. 26.3%). The median number of stages for pouch construction was two, compared to a median of one stage for an ileostomy ($P < 0.0001$). Because of the high long-term complication rate and the relatively small quality-of-life advantage associated with restorative proctocolectomy, patients need to be counseled thoroughly before agreeing to this operation. (J GASTROINTEST SURG 2003;7:814–819)

KEY WORDS: Ulcerative colitis, quality of life, morbidity, ileoanal pouch, ileostomy

Since the first restorative proctocolectomy with ileoanal pouch formation was performed in humans by Nils Kock in 1968,[1] followed by the classic description by Parks and Nicholls[2] in 1978, this operation has come to be considered the "first-choice" operation for ulcerative colitis.[3] However, panproctocolectomy plus permanent ileostomy has been referred to as "the yardstick" operation for this disease.[1] Thus the operation of choice for ulcerative colitis remains a subject of some debate.

The concept of a restorative proctocolectomy with a pouch is attractive, but it is a technically demanding operation with high morbidity, irrespective of whether or not a temporary ileostomy is used.[4–12] What is ultimately important to the patient is whether this operation offers a better quality of life and fewer side effects than a standard panproctocolectomy and conventional (Brooke) ileostomy.

The quality of life of patients who have had surgery for ulcerative colitis has been reported in a number of studies. Prospective studies have shown that quality of life improves after both restorative and nonrestorative surgery.[13–16] Studies comparing quality of life between patients who have a pouch and those who have an ileostomy provide conflicting conclusions. Pemberton et al.[17] concluded that patients with an

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ileoanal pouch had a better performance status in some areas than those with a Brooke ileostomy. Using the same cohort of patients, this group also concluded that quality of life was better in patients with a pouch.[18] On the other hand, McLeod et al.,[14] with the use of generic questionnaires, and Jimmo and Hyman,[19] with the use of only a disease-specific questionnaire, did not find any differences in quality of life between patients with a pouch and those with an ileostomy. However, the use of unvalidated questionnaires,[17,18] as well as differences in the characteristics of the groups of patients being compared (e.g., sample size, age, sex, and time since surgery),[14,17–19] limits the value of the findings from these studies.

The present study was a matched-pair comparative study using well-validated and reliable generic and disease-specific questionnaires. The aim of this study was to determine whether, in patients suffering from ulcerative colitis, a restorative resection with ileoanal pouch formation (RP + P) offers less morbidity and a better quality of life than a permanent (Brooke) ileostomy (PPC + I).

PATIENTS AND METHODS

All patients with ulcerative colitis requiring surgery, who were referred to two Teaching Hospitals (Ninewells Hospital, Dundee; and Raigmore Hospital, Inverness, Scotland) were well informed about the surgical options available. The decision of whether to perform (RP + P or PPC + I) was made jointly by the patient and the surgeon.[20]

Twenty-five patients who had undergone a completed RP + P for ulcerative colitis between 1988 and 1997 at Raigmore Hospital and between 1995 and 1997 at Ninewells Hospital were identified from hospital records as still living within the catchment areas of their respective hospitals. These patients had had their operations completed at least 1 year prior to the study. They were contacted by mail and by telephone and invited to participate in the study.

Nineteen patients who had undergone RP + P participated. They were individually matched with 19 other patients who had undergone PPC + I for time since surgery (within 4 months of each other), sex, age (within 4 years of each other), and socioeconomic status, because these are variables that have been shown to affect quality of life.[21] Socioeconomic status (deprivation category or "Depcat") was determined using the Carstairs index, an index of deprivation based on the postal code.[22]

All patients gave their full informed consent and completed the two questionnaires—the Short-Form 36 version 2 (SF-36 II) and the inflammatory bowel disease questionnaire (IBDQ)—and answered additional questions concerning body image. The SF-36[23] measures subjective health status or health-related quality of life and is designed to be self-administered. It consists of 36 items, measuring eight dimensions of health on multi-item scales. The eight dimensions measure physical functioning, social functioning, role limitations due to physical and emotional problems, mental health, energy and vitality, body pain, and general health perception. The scoring scale ranges from 0 to 100, with lower scores indicating worse health. For this study we used the SF-36 version 2 (SF-36 II),[24] which has an improved layout, wording, and scaling, as well as improved reliability over the original version of the SF-36.[24–26]

The Inflammatory Bowel Disease Questionnaire (IBDQ)[27] consists of 32 items that are grouped into the following four dimensions: bowel symptoms, systemic symptoms, emotional function, and social function. The answers are rated on a seven-point Likert scale. The score for each dimension is summated to give a dimension score. Linear transformation of each of these scores provides a standardized score ranging from 0 (minimum) to 100 (maximum).

Surgery for ulcerative colitis leads to an alteration in physical appearance as a result of abdominal wall and perineal scarring and the presence of a temporary or permanent ileostomy. Perception of body image is therefore an important aspect of the quality of life of these patients, although this has only been demonstrated in patients with stomas.[28] Because an appropriate questionnaire measuring this dimension in this group of patients was not available for our study, we designed a few questions for this purpose. The answers to the questions on body image were rated on a four-point Likert scale, and the scores were summated and transformed linearly, to yield a standardized score ranging from 0 (very poor body image) to 100 (excellent perception of body image). The number and type of postoperative complications, as well as the number of operative stages, were recorded prospectively.

The study was given full approval by the Tayside Committee on Medical Research Ethics and the Highland Health Board Ethics Committee.

Statistical Analysis

Nonparametric tests were used because the scores were not normally distributed. The differences in the median number of complications and the median number of operative stages between the two groups were compared using a Wilcoxon signed-rank test for paired data. The quality-of-life scores were expressed as standardized median scores and interquartile ranges. Differences in quality-of-life scores

between groups were evaluated using the Wilcoxon test. A 5% level of statistical significance was used for clinical variables ($P < 0.05$). A 2% level of significance was chosen for quality-of-life variables ($P < 0.02$) to reduce the risk of type I errors arising from multiple testing. All analyses were carried out using the SPSS version 8.0 statistical package (SPSS, Chicago, IL).

RESULTS

There were 12 males and seven females in each group. The median ages of the pouch and ileostomy groups were similar (41 years vs. 40 years). The median times since surgery were also similar (41 vs. 43 months). Patients' socioeconomic status was similar in both groups.

Operation Stages

Twelve patients had a pouch constructed in two stages (total colectomy, ileoanal pouch formation, and temporary ileostomy followed by closure of ileostomy), whereas seven needed three stages to achieve the same result (subtotal colectomy and terminal ileostomy, then proctectomy, ileoanal pouch construction, and defunctioning of the ileostomy, and closure of the ileostomy as the last stage). Four patients had an S-pouch, one had a W-pouch, and 14 had a J-pouch. The S-pouch–anal and W-pouch–anal anastomoses were hand sutured, whereas the J-pouch–anal anastomoses were stapled. Fifteen patients had a PPC + I done in one stage, whereas four had the same operation done in two stages (subtotal colectomy and ileostomy followed by anoproctectomy). The median number of stages for pouch construction was two (range 2 to 3), compared to a median of one stage for an ileostomy (Wilcoxon signed-rank test, $z = 3.9$, $P < 0.0001$).

Postoperative Complications

The short- and long-term complications associated with both pouch and stoma surgery are shown in Tables 1 and 2. The short-term complications are those that were recorded in the hospital following all of the stages of each operation (excluding closure of the ileostomy in pouch patients). There were more short-term complications associated with a PPC + I, and these were mainly related to the perineal wound. On the other hand, the patients with a pouch had more long-term complications than those who had a stoma. This, however, was restricted to the development of recurrent attacks of pouchitis, with 9 of the 19 pouch patients (47%) affected a year or more after the final stage of the operation. Pouchitis was characterized by recurrent episodes of frequent watery diarrhea with bleeding and macroscopic inflammatory changes in the pouch at sigmoidoscopy.[20] Patients suffering from pouchitis were frequently treated with metronidazole and with immunosuppressants in severe cases. Some required in-hospital treatment.

Table 1. Short-term complications following surgery (excluding those associated with closure of temporary ileostomy)

	Pouch	Ileostomy
Abdominal wound infection	2	1
Perineal wound infection	0	6
Small bowel obstruction	1	1
Deep venous thrombosis	1	0
Total complications*	4	8
No. of patients	4	8
% of patients with complications	21.1	42.1

*Wilcoxon signed-rank test, $z = -2.0$, $P = 0.046$.

Table 2. Long-term complications following surgery (1 year or more after the final stage of each operation)

	Pouch	Ileostomy
Small bowel obstruction	1	1
Incisional hernia	1	1
Perineal fistula	0	1
Stomal prolapse	0	2
Pouchitis	9	0
Total complications*	11	5
No. of patients	10	5
% of patients with complications	52.6	26.3

*Wilcoxon signed-rank test, $z = 2.5$, $P = 0.014$.

Quality-of-Life Scores

The IBDQ and the SF-36 II scores are shown in Tables 3 and 4, respectively. There were no significant differences between the scores of the ileoanal pouch patients and those of the ileostomy patients. However, the responses to the body image questions revealed that restorative proctocolectomy was associated with a better perception of body image than a permanent ileostomy (median scores and interquartile ranges: 88.9 (77.8 to 100) vs. 77.8 (44.4 to 88.9), $z = 2.4$, $P = 0.015$).

DISCUSSION

In this study 19 patients with a pouch were individually matched with 19 patients with a permanent ileostomy for disease process, time since surgery, sex, age, and socioeconomic status. The outcome after both operations was measured in terms of short-term and long-term complications, operative stages, and quality of life. Although operative complications were

Table 3. Median standardized IBDQ scores for patients with an ileoanal pouch and ileostomy (interquartile range)*

	Pouch	Ileostomy	z	*P* value
Bowel symptoms	81.7 (75.0–93.3)	80.0 (71.7–85.0)	0.99	0.32
Systemic symptoms	80.0 (63.3–90.0)	83.3 (63.3–90.0)	−0.59	0.56
Emotional function	84.7 (77.8–91.7)	80.6 (61.1–88.9)	1.16	0.25
Social function	95.8 (87.5–100)	91.7 (83.3–100)	0.31	0.76
Global score	85.4 (79.7–88.5)	80.7 (65.6–84.9)	0.58	0.56

*Wilcoxon signed-rank test.

recorded prospectively, quality of life was assessed once, 1 year or more after the final operative stage.

In the short term, we found that the number of complications was higher in those who had an ileostomy, and these complications were mainly related to the perineal wound. In contrast, in the series of Jimmo and Hyman,[19] patients with a pouch suffered from more short-term side-effects than patients with a stoma.[19] In the long term, patients with a pouch participating in our study had more problems than patients with an ileostomy. This is in agreement with findings in other studies,[19] but in our cohort this was due mainly to pouchitis, a well-recognized complication that does not affect patients with an ileostomy.[10,11,20,29–31] Other complications associated with a pouch, such as anastomotic leaks, anastomotic strictures, and fistulas, have been described and reviewed[1,4–12,19,20,29–31] but were not experienced by the participants in this study.

Another disadvantage faced by patients with a pouch was the number of staged operations. In this series restorative proctocolectomy was carried out in at least two stages. However, in most cases PPC + I can be completed in one stage. Performing RP + P in stages has been the subject of some debate. A number of centers perform single-stage procedures, even in patients with acute or toxic colitis,[4,5,12] but many surgeons prefer the safe practice of defunctioning the pouch–anal anastomosis and then closing the loop ileostomy at a later stage.[1,6,10,11,20] Although closure of the defunctioning (or temporary) ileostomy is associated with complications such as leaks and small bowel obstruction, Pemberton in Sugerman et al.,[12] argues that "most surgeons… continue to believe they would rather deal with the mostly tiresome complications associated with an ileostomy than the potentially catastrophic pelvic sepsis and pouch failure that can occur in patients without a diverting stoma" (see expert comment).[12] At our institutions all ileoanal pouches, both for ulcerative colitis and familial polyposis coli, are protected by an ileostomy that is usually closed after a pouchogram at approximately 3 months.

Quality of life is now recognized as an important measure of the outcome of surgery.[32] It is a multidimensional concept, and as such it has been recommended that both generic and condition-specific questionnaires be used concurrently in quality-of-life studies.[32–34] In this study two standardized quality-of-life questionnaires were used, a generic (SF-36 II) and a condition-specific (IBDQ) instrument. In addition, a few questions were designed to measure perception of body image. Our results show that, in general, the quality of life in those patients with a pouch was similar to the quality of life in those with an ileostomy. Therefore, in terms of physical, social, and emotional function, as well as disease/treatment-related symptoms, there is no measurable difference in the type of surgery for the cure of ulcerative colitis. This is broadly in agreement with the findings in two previous studies that used generic questionnaires[14]

Table 4. Median SF-36 II scores for patients with an ileoanal pouch and ileostomy (interquartile range)*

	Pouch	Ileostomy	z	*P* value
Physical function	95.0 (85.0–100)	90.0 (75.0–100)	1.18	0.24
Role-physical	93.8 (68.8–100)	100.0 (75.0–100)	−0.53	0.60
Role-emotional	100.0 (83.3–100)	100.0 (83.3–100)	0.57	0.57
Social function	100.0 (75.0–100)	100.0 (75–100)	−0.25	0.81
Mental health	85.0 (75.0–90.0)	75.0 (70.0–85.0)	1.50	0.14
Energy-vitality	62.5 (50.0–81.3)	75.0 (50.0–81.3)	−0.69	0.49
Pain	88.9 (66.7–100)	88.9 (77.8–100)	−1.27	0.21
General health profile	62.0 (50.0–77.0)	77.0 (57.0–82.0)	−0.38	0.70

*Wilcoxon signed-rank test.

and a disease-specific questionnaire.[19] The results of our study have also shown that perception of body image was measured as being better in those with a pouch. Perception of body image has been shown to be generally low in some patients with stomas, both colostomies and ileostomies,[28] but a matched comparison of body image between patients with ileostomas and those with ileoanal pouches for ulcerative colitis has not been previously reported. It is of interest to note that an improvement in body image among patients with a pouch does not translate into a better quality of life as measured by the SF-36 II and the IBDQ. This suggests that the degree of body image impairment experienced by patients with an ileostomy is unlikely to have a major impact.

This study therefore shows that a high quality of life is possible for those patients who are suitably selected for either a pouch or an ileostomy, although it is not appropriate to conclude that both operations would be equally good for every patient. We concur with the conclusions of both Weinryb et al.[13] and McLeod et al.[14] that it is most likely the elimination of the disease, rather than the type of procedure performed, that has the main impact on quality of life. In addition, the results suggest that most patients have adapted themselves well to their new postoperative status, be it with a pouch or a stoma. This would not have been possible without medical, nursing, and community support. Certainly at our institutions there are dedicated pouch and stoma nurses, with further support being provided by local branches of the National Association for Colitis and Crohn's Disease. A prospective longitudinal study that measures quality of life at various intervals postoperatively will help to determine the length of time over which this adaptation occurs.

The study has its limitations because of the small sample size. However, the formulation of matched patient groups prevents the results from being distorted by confounding variables and therefore ensures a high psychometric quality. A larger sample size would permit further statistical analyses using multiple regression techniques, in order to determine the relationships between a number of variables such as pouch and ileostomy function and operative complications and quality of life. This study, in accordance with previous studies on quality of life after surgery for ulcerative colitis, also has an inherent selection bias. In most instances, patients chose the operation to which they did not have an aversion, a factor that could have a bearing on the results. Although a randomized prospective trial eliminates selection bias, this type of study is impossible to carry out in this regard. Another limitation of the study is that the questions on body image perception have not been validated. The results, however, highlight the importance of measuring body image perception in patients who have had surgery for ulcerative colitis, and emphasize that further study and analysis of this dimension in these patients is warranted.

CONCLUSION

The findings in this study have implications for obtaining informed consent when discussing surgery for ulcerative colitis. If a permanent ileostomy can be avoided, most patients will wish to explore this option. They must, however, be carefully counseled and informed that restorative proctocolectomy is associated both with a higher rate of long-term complications (mainly recurrent pouchitis) and more operative stages than proctocolectomy with ileostomy, and that there is little to choose from between the two options in terms of quality of life.

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Book Review

History of the Pancreas: Mysteries of a Hidden Organ
John M. Howard and Walter Hess. New York, NY: Kluwer Academic/Plenum Publishers, 2003. Pages: 729. Price: $150.

John Howard and Walter Hess have authored a history of the pancreas that is a well-written, comprehensive, masterful, and compelling chronicle. This book contains more than 2000 references, 3 maps, 111 drawings, portraits, and illustrations, 105 photographs, 32 documents reproduced in full or in part, and 11 tables as well as a complete name and subject index. In addition, there are many quotes from original documents and a first-time translation into English of important operative reports. The authors cite with accuracy the discoveries that have incrementally increased our understanding of the pancreas from ancient Egypt to modern times. More than that they provide sketches of the lives of those men and women responsible for those advances. The stories of these men and women and their patients who often sacrificed their lives, knowingly or unknowingly, in contributing to our knowledge of the pancreas are sometimes inspiring, often poignant, sometimes tragic, but as related by the authors always instructive and entertaining. This history is stirring and grips the reader's attention. Thanks to the authors' exhaustive research rather than a sterile listing of discoveries and dates, we are provided insight into the motivations, hardships, and sometimes triumphs of those whose efforts made them.

It is doubtful that this wonderful history of the pancreas could have been constructed without the collaboration of an American and a European author. The monumental task of searching out and assembling the original documents, illustrations, photographs, reproductions, translations, and journal articles that constitute the sources of *History of the Pancreas: A Hidden Organ* from numerous archives, journals, and museums on both continents must have taken years of work including innumerable phone calls and correspondence. That only two men could produce such a comprehensive and well-written and well-illustrated history of the pancreas is astonishing in itself. The authors' effort, diligence, and dedication cannot be overstated. The research necessary to identify and give appropriate weight and priority to the many persons responsible for so many different discoveries, innovations, and new operations and techniques makes one cringe at the thought of how much time this must have taken. How exciting it is to have several reports not previously available in English translated for us in full, such as the operative reports of Kausch, Hirschel, and Tenani.

Let's be clear. Comprehensive as it is, this is a history of the pancreas in the context of Western Civilization. The history of pancreatic knowledge as developed in Asia has not been included in this history except as it applies to Japan. There is nothing from China or India. Perhaps, if the authors want to update this history in the future or add to it, they should involve authors from China, Japan, and India.

Organization

History of the Pancreas: Mysteries of a Hidden Organ is organized for easy reference into chapters that cover the history of acute and chronic pancreatitis, exocrine and endocrine function, benign and malignant tumors of the pancreas, and pancreatic function among topics. Specifically, the first chapter on the early anatomists (114 references) is followed by a chapter on the exocrine pancreas (101 references) and one on the endocrine pancreas (218 references). Then there are, in succession, chapters on acute pancreatitis (376 references), chronic pancreatitis (219 references), pseudocyst and cystic tumors (157 references), trauma (112 references), congenital anomalies (118 references), tumors of the ampulla of Vater and pancreas (197 references), and treatment of these tumors (202 references). These chapters are followed by one on progress in the diagnosis of pancreatic disease (190 references) and transplantation of the pancreas and islet cells (94 references). There is a brief chapter on the lessons of history and application to the future as viewed by the authors. An important additional feature of the book is an appendix, which includes a brief summary of the major pancreatic societies in the Western world and Japan as well as important international meetings whose major themes have been devoted to the pancreas. The name and subject indexes are quite adequate and make it simple to locate subjects and individuals of interest to the reader.

Content

After the chapter on the early anatomists, the succeeding chapters follow a similar pattern in which we are sequentially and chronologically taken by the

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authors from the earliest observations concerning the subject of the chapter to our present-day understanding. For example, in the chapter on acute pancreatitis we are taken from the observations of Ambrose Pare, reported in 1579, step by step through literally hundreds of observations and discoveries that have brought us to our present-day state of knowledge about the pathogenesis, diagnosis, treatment, and outcomes of acute pancreatitis and its complications.

Authors' Frame of Reference and Point of View as Historians

John Howard and Walter Hess have led very productive professional lives, and both have made significant contributions to our understanding of pancreatic disease. Both have received recognition for these contributions in the form of honors from their peers, membership in prestigious societies, and visiting professorships around the world, all of which they richly deserve. They have applied these professional skills to this magnificent work on the history of the pancreas. They function as historians during two very contrasting periods. The first is the historical past, prior to their coming of age as pancreatologists, and the transition to the second phase, which occurred in the 1950s, when their professional careers blossomed and they began to make contributions themselves to our knowledge of pancreatic disease. With regard to the first period, the authors objectively and dispassionately sort out with diligent scholarship the conflicting claims of priority for significant discoveries as seen from the present. Their objective treatment of their subject and their dispassionate perspective are made possible and enhanced by the fact that they are not contemporaries, nor did they personally know the persons responsible for these discoveries. The passage of time also has allowed the authors to sort out the "wheat from the chaff" in terms of the significance of many of the discoveries and the persons responsible for them. Their decision making and judgments regarding priority and significance are thus free from contamination by their own political considerations, passion, personal bias, ego, reputation, ambition, desire for recognition, and vested interests. Once the authors themselves become participants and are involved in unraveling the mysteries of the pancreas and laying claim to priority for making some of these discoveries, they lose some of their objectivity as historians and become advocates and promoters of their own interests and friends. One of the authors has cited his own contributions 20 times. This number exceeds that of any other living pancreatologist included in the book and is one more than the combined number of citations attributed to John Cameron, William Go, Andrew Warshaw, John Ranson, and Edward Bradley. Among many others not mentioned or cited are such well-known pancreatologists as Dana Andersen, Gerard Aranha, E.J. Balthazer, V. Balakrishnan, Peter Banks, Claudio Bassi, Richard Bell, Murray Brennan, William Chey, Kevin Conlon, Doug Evans, Aaron Fink, Joe Fischer, Thomas Foitzik, Christopher Forsmark, Patrick Freeny, P.J. Geevarghese, Frederick Gorelick, Lucius Gullo, Jacob Izbicki, Raymond Joehl, Andrew Kingsnorth, Ernst Klar, Richard Kozarek, Michael Larvin, Stephen Leach, Marcus Lerch, Albert Lowenfels, Michael McMahon, Joachim Moosner, Michael Mullholland, Isto Norback, Kjell Ohlsson, A. Papp, Paolo Pederzoli, Sergio Pedrazzoli, C.S. Pitchumoni, Howard Reber, R. Roscher, R.C.G. Russell, Ashok Saluja, Michael Steer, William Steinberg, Makota Sunamura, James Toouli, Phillip Toskes, David Whitcomb, J.A. Williams, and Michael Zinner. All have made contributions to our understanding of the pancreas and its diseases. Whether the contributions of some of these individuals and others not mentioned are more significant than some of those cited in the book can be left to future historians. In fairness to the authors, the explosion of knowledge in recent years has complicated their task of identifying significant discoveries and assigning priority to the persons responsible. When I looked at the PubMed website, I made the following observations: under acute pancreatitis, 9683 references were cited; under chronic pancreatitis, 6558 references; under cancer of the pancreas, 19,081 references; and under pancreas transplantation, 4795 references. Most of these reports have been published within the last 6 years.

Omissions

Decisions regarding what should or should not have been included in *History of the Pancreas: Mysteries of a Hidden Organ* are subjective. In my opinion, inclusion of a number of topics and discoveries by its authors would have strengthened this book. The absence of any discussion on current management of pancreatic fistulas, ascites, or pseudoaneurysms of the pancreatic and peripancreatic vessels with and without active bleeding surprises me. In addition, it is not made clear that pseudoaneursyms of the pancreatic and peripancreatic vessels are usually associated with pseudocysts and when they are present what their management ought to entail. (There is a three-sentence paragraph on hemoductal pancreatitis [p. 218] but no mention of how the problem should be managed.)

The management of sterile necrosis is obliquely addressed from the perspective of one of the author's

personal experience, but generally accepted principles of management as to when and under what conditions operative intervention is indicated are not spelled out. The technique for assessing the presence or absence of infection in necrotic pancreatic or pancreatic tissues by percutaneous CT scan or ultrasound-guided aspiration for Gram stain and culture are not mentioned by the authors.

There is no mention of the plague of "stent" pancreatitis, which is caused by aggressive endoscopists leaving stents in for months at a time in patients with often questionable indications (e.g., abdominal pain of unknown origin) turning what appears to be initially a normal pancreatic duct system into something compatible with advanced chronic pancreatitis.

The section on Hereditary Pancreatitis includes nothing about the identification of a specific gene abnormality associated with hereditary pancreatitis, which was first reported in 1996, and the subsequent explosion of information about genes associated with acute and chronic pancreatitis, as well as genetic mutations associated with "Tropical Pancreatitis," a type of pancreatitis common to India and Bangladesh and not included in the authors' list of causes of pancreatitis.[1–3]

The assessment of the effectiveness of operations purported to relieve pain in patients with chronic pancreatitis has been markedly improved over the last decade. The authors do not mention these improvements, which include the use of visual analogue scales to assess pain and quality-of-life measures. The usefulness of multicenter trials and randomized control trials performed by the same surgeons comparing the outcomes of two different operations in the same patient population and the need for long-term follow-up are significant developments not commented on by the authors. In this same chapter, I was surprised to learn that I had been "working predominantly in the Veterans Adminstration Hospital at Sacramento, California." (p. 299) My only contact with the Veterans Adminstration was at the Martinez Veterans Hospital in Martinez, CA, a Dean's Hospital for the University of California Davis between the years 1976 and 1980.

The brief section on International Congresses does not include the 1983 Cambridge Meeting on the classification of acute and chronic pancreatitis. At this international multidisciplinary meeting, the first attempt was made to develop a clinically useful definition of acute and chronic pancreatitis based on knowledge of ductal and parenchymal changes detected by the newly developed technologies of ultrasound, CT scanning, angiography, and endoscopic retrograde cholangiopancreatography. The 1963 Marseille conference cited by the authors developed only a histopathologic definition of acute and chronic pancreatitis, which was of limited usefulness to clinicians. The Cambridge group also cited as complications of acute pancreatitis necrosis, hemorrhage, pseudocyst, and abscess.[4] Neither the 1984 Marseille meeting[5] nor the 1988 Marseille–Rome International conference[6] to update the classification of acute and chronic pancreatitis and their complications is mentioned by the authors. Most surprising to me is the absence of any discussion of the International Symposium, which was held in Atlanta, GA, September 11–13, 1992. A 40-member multidisciplinary group (anatomy, gastroenterology, internal medicine, pathology, radiology, and surgery) from 15 countries developed a series of definitions and a clinically based classification system for acute pancreatitis, which was universally accepted and continues to be used to this day.[7] The multidisciplinary international Zurich workshop on alcoholic chronic pancreatitis, which was held in March 1996 with 38 participants, is also not included.[8]

Errors

History of the Pancreas: Mysteries of a Hidden Organ took years of research to compile, and I make no pretense of having independently verified the authenticity of this impressive work. This is a very important book that will be read for years to come, and the authors have done such a fine job in their meticulous research for most of it that I am doubly disappointed that one area in which I have intimate knowledge, having been co-chairman of The Pancreas Club, Inc. for 20 years, is written in a well-intentioned but casual and sloppy manner without proper verification of the facts. It is painful to think that misinformation about The Pancreas Club will be read and believed by many who, as I do, place great credence on the authors' scholarship. This section starts out with the incorrect name of the club referring to it as the Pancreas Club (American). Its name as incorporated is The Pancreas Club, Inc., and it has been since 1975. The report is unbalanced; approximately one fifth of the content is devoted to the second meeting when there were 35 other meetings of equal or greater significance, such as the reconstitution of the club in 1975 after the prior leadership lost interest in the club and neglected to organize a meeting in 1974. The authors omitted other important steps in the evolution of the club and its operation. There are several statements on page 670 that are incorrect. "The program committee constitutes its working hierarchy, although to permit incorporation three directors were recently chosen and the club still has no constitution or bylaws." John Ranson,

William Schiller, and I in fact incorporated The Pancreas Club, Inc. in Lansing, MI, in 1975. We drove together from Ann Arbor to take this essential step. Shortly afterward, in 1976, it received 403b(c) tax-exempt status from the IRS as an educational organization partly because of the pro bono work of the Conlin law firm in Ann Arbor acting on our behalf. The Pancreas Club, Inc., of course, has had a constitution and bylaws since its incorporation in 1975; these are on file with the Department of Corporations in Michigan and with the IRS because neither incorporation nor a tax-exempt organization status can be obtained without them. The list of those who were participants at the first meeting is not correct. The leadership of the club has held the title of Chairman or Co-Chairman rather than Secretary ever since the incorporation in 1975. The listing of the chairmen who succeeded William Schiller and me who took office in 1996 were not stated correctly by the authors. Richard Bell, Bill Nealon, and Michael Sarr served as chairmen in 1996. Since then Richard Bell and Michael Sarr have been succeeded by William Traverso and Douglas Evans. An accurate and complete history of The Pancreas Club, Inc. from 1966 to 2000 can be found at the club's website (www.pancreasclub.com).

Audience

Most pancreatologists and surgical historians will want to purchase this book. It seems unlikely, because of the cost, that many medical students or residents will avail themselves of this book. However, I am confident that medical students and residents will use it widely as a library reference regarding pancreatic history. Readers will find that this book is not a "state of the art" understanding of the pancreas and its diseases in the year 2003, nor is it the definitive history of the last 50 years of pancreatic discoveries. This perspective will have to wait until the principals of the present have disappeared from the scene. It is, however, the finest history of the pancreas yet available.

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Erratum

The articles in the "2002 Consensus Conference on Management of Obesity," by Aaron S. Fink, M.D., June Stevens, M.S., Ph.D., Kimberly P. Truesdale, Ph.D., Lee M. Kaplan, M.D., Ph.D., Thomas A. Wadden, Ph.D., Brian G. McGuckin, M.Ed., Rebecca A. Rothman, B.A., Stephanie L. Sargent, B.S., Samuel Klein, M.D., Philip R. Schauer, M.D., and Harvey J. Sugerman, M.D., published in the May/June 2003 issue of the JOURNAL OF GASTROINTESTINAL SURGERY (2003;7:433–437), should have had the following section title: "Management of Obesity: The 2002 SSAT/ASBS Workshop Report."

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