Surgical Therapy for Esophageal Adenocarcinoma

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The incidence of esophageal adenocarcinoma has risen substantially over the past few years, and now surpasses the incidence of esophageal squamous cell carcinoma in Western countries. This rise is unparalleled and can only be explained by the rising incidence of Barrett's esophagus—a direct consequence of abnormal gastroesophageal reflux—in Western countries. Dr. Prateek Sharma, in this symposium, addresses the epidemiology and pathogenesis of cancer of the esophagogastric junction and emphasizes this rapid increase that we have observed. Dr. Jeffrey Peters characterizes the uniqueness of esophageal adenocarcinoma and the changes observed in the presentation and management of this tumor. Dr. Lee Swanstrom addresses the use of minimally invasive therapies to treat esophageal adenocarcinoma. Finally, Dr. Kenneth Wang discusses the multiple elements that we have today to treat esophageal adenocarcinoma.

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Cancer of the Esophagogastric Junction: Epidemiology and Pathogenesis

Prateek Sharma, M.D.

There has been a recent increase in the incidence of adenocarcinoma of the distal esophagus and the esophagogastric junction (EGJ).[1] The incidence of and mortality rates for non-cardia gastric cancer have steadily declined in the Western world, whereas those for cardia and esophageal cancer have increased. However, a great deal of controversy remains regarding the classification, epidemiology, and pathogenesis of tumors of the EGJ.[2] Whereas some investigators consider these tumors to be very similar to esophageal adenocarcinomas, others regard them as gastric cancers. Moreover, a variety of definitions have been used to describe EGJ cancers; one example describes them as "tumors of the distal third of the esophagus plus the proximal stomach—i.e., the cardia." To further confuse the situation, the ICD codes "cardia" as EGJ cancers and, of course, there is no consensus on the definition of cardia. Moreover, until the 1980s there was no distinction between cardia and distal gastric cancers, and these were all lumped together as gastric cancers. At a recent consensus conference of the International Gastric Cancer Association and the International Society for Diseases of the Esophagus. EGJ cancers were defined as tumors that have their center within 5 cm proximal and distal of the anatomic cardia and have the following subdivisions:[3]

1. Type I - The distal esophagus, "more than 1 cm above the EGJ"
2. Type II - True cardia, "1 cm above to 2 cm below the EGJ"
3. Type III - Subcardia "more than 2 cm below the EGJ"

Alternative classifications have been suggested by Clark et al.,[4] who defined an EGJ cancer as one in which the epicenter of the tumor is at the anatomic junction, and investigators from Mayo Clinic, who stated if the junction included more than 50% of the tumor, it would be classified as an EGJ cancer.[5] Again, all this attention to EGJ cancers would not have occurred except for the rapidly rising incidence of cancer in this location, specifically in white men.

Most patients with EGJ cancers are white men who have a mean age of approximately 60 years; Barrett's esophagus as a precursor lesion has been reported in 11% to 42% of these patients.[6–8] However, other investigators have reported these tumors to be related to cardia intestinal metaplasia rather than Barrett's esophagus.[9] Thus, the precise origin of these tumors—that is, from intestinal metaplasia within the esophagus (Barrett's esophagus) or within the cardia (cardia intestinal metaplasia)—remains controversial. Patients with Barrett's esophagus and cardia intestinal metaplasia have been shown, in recent studies, to differ in terms of demographics, symptoms of gastroesophageal reflux disease (GERD), *H. pylori* status, and cytokeratin immunoreactivity; patients with Barrett's esophagus are mainly white men with symptoms of GERD, and they are less likely to have *H. pylori* infection as opposed to patients with cardia intestinal metaplasia.[10–12] Moreover, factors associated with EGJ cancers are similar to those related to distal esophageal adenocarcinomas. Risk factors for EGJ cancers include long-standing symptoms of gastroesophageal reflux, obesity, and smoking.[13–15] On the other hand, EGJ cancers probably have no association with *Helicobacter pylori*, as opposed to distal gastric cancers, which are strongly linked to *H. pylori* infection. There is also some evidence that cagA+ strains of *H. pylori* may have an inverse relationship to distal esophageal and EGJ cancers.[16]

But in terms of patient management and approaches to different therapeutic options for EGJ cancers, do the classification, epidemiology and pathogenesis re-

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ally matter? Probably not; however, if we are to develop any meaningful preventive strategies, tailor therapy, or develop surveillance programs, the pathogenesis and epidemiology of EGJ cancers become very important. Having an agreement on the classification of these tumors, identification of specific biomarkers/risk factors, and a better understanding of the etiology and pathogenesis of EGJ cancers are some of the issues that need to be defined in the future.

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Surgical Treatment of Esophageal Adenocarcinoma: Concepts in Evolution

Jeffrey H. Peters, M.D.

The diagnosis of esophageal cancer is a devastating event for a person. The American Cancer Society estimates that 12,300 new cases of esophageal cancer and 11,900 deaths from the disease will occur in 1998.[1] Clearly, cure is a challenge. Clinicians have two options available to them; the first is to assume that most, if not all, esophageal tumors extending beyond the mucosa are systemic at the time of diagnosis, and thus palliation is the mainstay of therapy. The second is to select treatment with curative intent, recognizing that long-term survival will occur in the minority of patients. Increasing evidence suggests that cure is possible and that the second approach will benefit the largest number of patients.

CONCEPTUAL BASIS FOR TREATMENT DECISIONS

The shift in the epidemiology of esophageal cancer from predominantly squamous carcinoma, which is seen in association with smoking and alcohol, to adenocarcinoma in the setting of Barrett's esophagus is one of the most dramatic changes that has occurred in the history of human neoplasia. Although esophageal carcinoma is a relatively uncommon malignancy, its prevalence is exploding, largely as a result of the well-established association between gastroesophageal reflux, Barrett's esophagus, and esophageal adenocarcinoma.[2] Once a nearly uniformly lethal disease, survival is improving as advances in the understanding of its molecular biology surveillance and improvements in staging, surgical techniques, and neoadjuvant therapy are translated into clinically relevant improvements in the everyday care of patients.

The clinical picture of esophageal adenocarcinoma is changing. It now occurs (1) with considerably greater frequency, (2) in younger patients, and (3) is often detected at an earlier stage.

These facts support rethinking the traditional approach of assuming palliation in all patients. It is one thing to contemplate palliation of dysphagia in an 80-year-old man with a 5cm distal esophageal cancer and yet another to treat a 47-year-old father of three with a barely visible lesion detected on surveillance endoscopy. Treatment approaches can be divided into those patients with localized, regional, or systemic disease (Fig. 1).

PATIENTS WITH A HIGH PROBABILITY OF DISEASE CONFINED TO THE MUCOSA (LOCALIZED)

The detection of esophageal cancer at a stage when the disease may be confined to the mucosa, once a decidedly rare clinical occurrence, has recently become commonplace. The clear link between Barrett's esophagus and esophageal adenocarcinoma, the liberal use of flexible endoscopy, and the widespread adoption of surveillance programs have all contributed to this fact. Thirty percent of patients with esophageal adenocarcinoma recently undergoing esophageal resection at the University of Southern California had tumors confined to the mucosa or submucosa.[3] Other institutions have also documented this important trend.[4] These changing demographics markedly increase the population of patients with curable esophageal cancer, underscoring the importance of a curative resection.

Techniques of curative resection range from endoscopic mucosal ablation to radical en bloc esophagectomy. There has been considerable enthusiasm for mucosal ablation, particularly photodynamic therapy[5,6] and endoscopic mucosal resection.[7] To date, the risk-benefit ratio has not been adequately evaluated. Options for curative esophageal resection include transhiatal or transthoracic simple esophagectomy, en bloc esophagectomy, and more recently,

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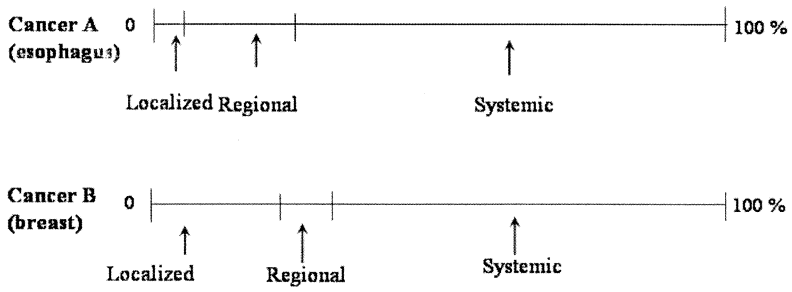

Fig. 1. Conceptual representation of the proportions of local, regional, and systemic disease in esophageal and breast cancer. The relative proportions change from one type of tumor to another and may also change significantly with changing tumor biology and methods of detection.

vagal-sparing esophagectomy. Selection among these options, without compromising the chance of curative resection, is critically dependent on accurate identification of the location and depth of the tumor (intramucosal vs. submucosal) and/or the presence of regional lymph node metastases. The accuracy of endoscopic ultrasound imaging in determining the depth of tumors confined to the esophageal wall is questionable. In most hands, the resolution of the present-day endoscopic ultrasonographic systems is not sufficient to predictably distinguish small tumors, which may or may not have invaded beyond the muscularis mucosa.

We have recently used the presence or absence of an endoscopically visible lesion in patients with biopsy-proved high-grade dysplasia or intramucosal carcinoma as a predictor of tumor depth and nodal metastases. The data indicate that a positive biopsy result in the absence of an endoscopically visible lesion almost always corresponds to an intramucosal tumor without nodal metastases.[3] Among patients with high-grade dysplasia, 43% proved to harbor occult adenocarcinoma at resection. It is important to note that when there was no visible lesion on endoscopy, 88% of the tumors were intramucosal and 12% were submucosal. Only 1 of 10 patients with no visible lesion had lymph node involvement either histologically or immunohistochemically (Fig. 2). In contrast, patients with endoscopically visible tumors had a high prevalence of tumors that penetrated beyond the mucosa (75%) and 56% had positive nodes.

Patients with high-grade dysplasia and intramucosal carcinoma are best treated by a total esophagectomy in which all Barrett's tissue is removed along with any potential associated adenocarcinoma. Options include transhiatal esophagectomy or more recently, vagal-sparing esophagectomy. The vagal-sparing approach is suitable only when there is reasonable certainty of the absence of regional nodal disease. Reconstruction is accomplished by means of either the stomach (transhiatal) or colon (vagal-sparing) with the anastomosis in the neck. The mortality associated with this procedure should be less than 5%, particularly in centers experienced in esophageal surgery.[8] Functional recovery is excellent, particularly in the group undergoing vagal-sparing esophagectomy.

PATIENTS WITH A HIGH PROBABILITY OF REGIONAL DISEASE

In the presence of a small (<1 to 2 cm) endoscopically visible lesion, the possibility of a submucosal tumor is high, but the probability of cure is also significant (Fig. 3). Because tumors that invade the muscularis mucosa into the submucosa have a 60% or more incidence of lymph node metastasis, it seems prudent to perform a lymphadenectomy in association with esophagectomy in the treatment of visible lesions, regardless of the histologic findings on biopsy (i.e., high-grade dysplasia or intramucosal carcinoma). Splenectomy and extended gastric resection need not be part of the resection, however. Recent data indicate that given an early adenocarcinoma in Barrett's esophagus, nodal metastases are limited to the periesophageal location and do not involve the splenic artery, splenic hilum, or greater or lesser curvature of the stomach.[9] These findings further question the increasing trend of using endoscopic ablative techniques in the treatment of high-grade dysplasia and early adenocarcinoma. They suggest that cure may be compromised in the presence of a visible lesion. In the absence of a visible lesion, directing these endoscopic therapies becomes difficult. Hagen et al.[10] recently reviewed 100 consecutive patients who underwent en bloc esophagectomy for esophageal adenocarcinoma. None of these patients received pre- or postoperative chemotherapy or radiation therapy. The aim of the study was to relate the extent of disease to prognostic features, timing and mode of recurrence, and survival

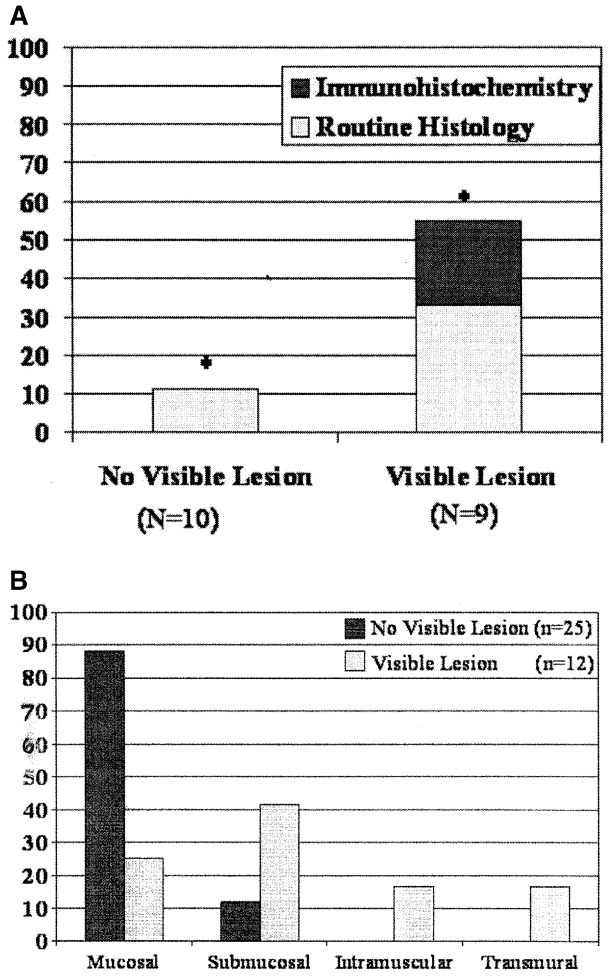

Fig. 2. A, Relationship between the presence of an endoscopically visible lesion and the presence of lymph node metastases. Vertical axis shows the percentage of tumors with associated lymph node metastases. **B,** Comparison of depth of tumor penetration in patients with occult adenocarcinoma based on the presence of an endoscopically visible lesion. Vertical axis shows the percentage of tumors. Horizontal legend is depth of penetration. (From Nigro JJ, Hagen JA, DeMeester TR, et al. Occult esophageal adenocarcinoma: Extent of disease and implications for effective therapy. Ann Surg 1999;230:433–440.)

after en bloc resection. The median follow-up in surviving patients was 40 months with 23 patients surviving 5 years or more. Overall actuarial survival at 5 years was 52% (Fig. 4). Fifty-five of the tumors were transmural and 63 patients had lymph node involvement. Metastases to celiac (n = 16) or other distant node sites (n = 26) were not associated with decreased survival. Remarkably, local recurrence was seen in only one patient. Latent nodal recurrence outside the surgical field occurred in nine patients, and systemic metastases in 31. It was concluded that long-term survival from adenocarcinoma of the esophagus can be achieved in more than half of the patients who

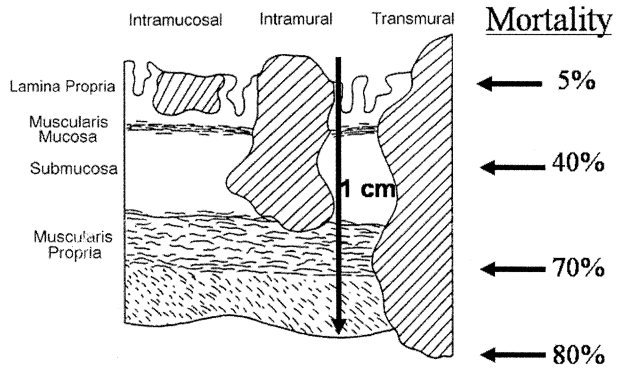

Fig. 3. Schematic representation of various stages of tumor depth (*oblique lines*) and their associated 5-year mortality rates.

undergo en bloc resection. One third of patients with lymph node involvement survived for 5 years and local control is excellent after en bloc resection.

PATIENTS WITH A HIGH PROBABILITY OF SYSTEMIC DISEASE

In patients presenting with dysphagia and large (>3 to 4 cm) endoscopic tumors, cure is unlikely. It is this population, presently 50% to 70% of patients referred for surgical resection, that is best suited for transhiatal esophagectomy. Surgical resection has been shown to provide superior palliation of dysphagia compared to radiotherapy alone,[11] and given a population with extensive disease, this is likely true of multimodal therapy as well. Orringer et al.[12] has reported[12] their 22-year experience with more than 1000 transhiatal esophagectomies at the University of Michigan. Seventy-five percent of the patients had malignant disease and 96% underwent reconstruction using the stomach. Mortality was 4% and declined significantly over the years; 13% had clinically evident anastomotic leaks. Median hospital stay was 7 days, and 70% of the patients had an excellent or good functional outcome. The primary downside to transhiatal esophagectomy and gastric pull-up is that many, if not most, patients will require one or two postoperative dilations of the anastomosis. Refractory strictures are uncommon.

ADJUVANT THERAPY

Pre- and postoperative adjuvant therapy for esophageal cancer has been studied for nearly 50 years. To date, no definitive benefit has been shown, although there are hints of progress. Adjuvant radiation therapy alone has been well studied and does

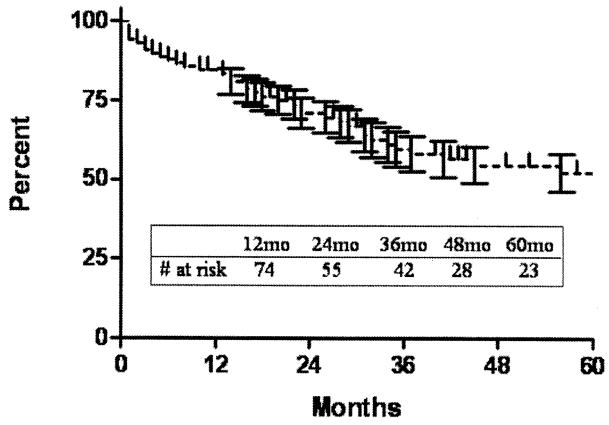

Fig. 4. Actuarial survival including operative mortality for 100 patients undergoing en bloc esophagectomy for cure of esophageal carcinoma. (From Hagen JA, DeMeester TR, Peters JH, et al. Curative resection for esophageal adenocarcinoma: Vertical axis indicates the percentage of patients surviving. Analysis of 100 en bloc esophagectomies. Ann Surg Oct 2001;234:520–530.)

not prolong survival.[13–15] Most prospective studies of neoadjuvant chemotherapy have shown no benefit, including the recent United States trial reported by Kelson et al.[16] The possibility that preoperative neoadjuvant 5-fluorouracil/platinum–based chemotherapy may indeed provide a small benefit was recently raised by a medical research council trial in the United Kingdom.[17] This trial is one of the few, if not the only one, to include enough patients (n = 800) to detect small differences. Two thirds of them had adenocarcinoma and tumors of the distal third of the esophagus. The trial, reported to date in abstract form only, showed a 10% absolute survival benefit at 2 years for the group receiving neoadjuvant chemotherapy.

Preoperative combination chemoradiation therapy has also been reported in a single study to be beneficial.[18] Four other prospective randomized studies have not shown a benefit. Complete response rates for adenocarcinoma range from 17% to 24%.[19–21] Most studies have shown a survival benefit only in the subset of patients with no residual tumor at the time of resection (i.e., complete response). The question remains whether this justifies treatment of all patients, particularly in light of the substantial morbidity and mortality that has been associated with multimodal therapy.

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Minimally Invasive Surgical Approaches to Esophageal Cancer

Lee L. Swanstrom, M.D.

The principal reason to consider a less invasive approach to esophageal cancer is to minimize the operative morbidity in order to maximize the patient's quality of life after diagnosis of this highly lethal disease. Most patients who are diagnosed with esophageal cancer in North America will die of the disease (Fig. 1). Traditionally, surgery has offered the only hope of a cure. Unfortunately, substantial cure rates apply only to early-stage disease, which is seldom encountered (Table 1). Radical treatment, the patient's only hope, traditionally involved major access—either a thoracotomy, laparotomy, both, or a thoracoabdominal incision. These access choices were often made only to find that the patient had unresectable disease, and typically involved a long hospital stay, wound complications, frequent chronic pain, and a convalescence that often occupied the remainder of the patient's limited life span.[1] It is small wonder that a concerted effort is underway to find less morbid treatment options. Unfortunately, options such as endoscopic stents or photodynamic ablation (PDA), not to mention primary chemoradiation therapy (which further subjects the patient to the prolonged ill effects of systemic chemotherapy), have poor cure rates even for early cancers—although they are relatively effective means of palliation. Surgically curative resections have recently been shown to have a 52% 5-year cure rate in selected patients.[2] The optimal solution for patients with potentially curable disease would therefore be a minimally invasive replication of standard open techniques such as the Ivor Lewis or transhiatal esophagectomy.

The advent of laparoscopic antireflux surgery and the subsequent development of paraesophageal hiatal hernia repair, Heller myotomy, thorascopic Collis gastroplasty, and other advanced esophageal surgical procedures provided the tools and access for endoscopic esophagectomy. The first efforts involved thoracoscopic mobilization of the esophagus with subsequent laparotomy for the gastric mobilization and tube creation. First described by Cuschieri et al.,[3] and later refined by Collard et al.,[4] this approach allowed a minimally invasive staging procedure, as well as a complete and thorough mediastinal dissection, while avoiding the major morbidity of a thoracotomy. Early results, however, showed only a small decrease in the length of hospital stay and in postoperative pain. Other partially endoscopic techniques have been described including laparoscopic gastric mobilization with subsequent thoracotomy for the esophagectomy[5] and the use of hand-assisted techniques to replicate Orringer's transhiatal approach.[6]

Totally endoscopic techniques were first described by DePaula et al. in 1995. These investigators described a laparoscopic equivalent of Orringer's transhiatal esophagectomy with a cervical anastomosis in addition to the five laparoscopic ports needed for the gastric mobilization. Subsequently we described the value of laparoscopically performing a mediastinal node dissection and placement of enteral feeding access.[8] Other groups have performed thoracoscopic dissection of the esophagus with a subsequent separate laparoscopic gastric mobilization and tailoring along with selective adjunct procedures such as pyloroplasty or feeding jejunostomy.[9,10]

PATIENT SELECTION

Candidates for minimally invasive esophageal resections include patients who have stage 4 disease but who require resection for palliation (dysphagia, bleeding, pain, etc.). These patients have a limited life expectancy because of their advanced disease and can benefit from the least morbid palliation available. The well-documented benefits of laparoscopic or thoracoscopic access (shorter hospital stay, less pain, rapid recovery) are especially beneficial for these patients.

Endoscopic resections may also be the optimal treatment for patients with early-stage cancer—T1

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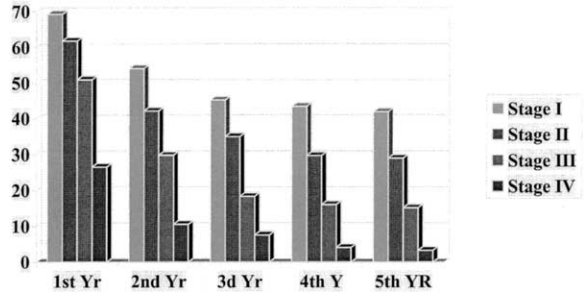

Fig. 1. Five-year survival rates for esophageal carcinoma by stage at presentation according to the American Cancer Society: National Cancer Data Base Annual Review of Cancer Patient Care, 1996. Vertical axis = percentage of patients alive.

lesions or even high-grade Barrett's dysplasia. Although detection of early esophageal cancers remains an elusive public health goal, when they are found, these lesions are curable by means of simple surgical resection, and en bloc resection seems to be unnecessary. Concern that laparoscopic approaches could compromise the adequacy of resections, either by an inadequate node clearance or by insufficient margins, are therefore less compelling.

Perhaps the most controversial indication for minimally invasive resections is moderate-stage disease (T2 or T3 lesions, evidence of confined local spread, or limited node involvement). Treatment of this group of patients engenders debate aside from the issues of laparoscopic approaches. In our opinion, however, this group would benefit from endoscopic approaches whether one is a believer in the "aggressive approach" (neoadjuvant chemoradiation and/or radical en bloc resection) or the minimalist approach (transhiatal esophagectomy or even no treatment at all). Depending on each surgeon's philosophical approach to esophageal cancer, an endoscopic resection offers some distinct advantages. Certainly laparoscopy and thoracoscopy have a well-established benefit as a staging tool to eliminate major interventions in widespread disease. For those favoring an aggressive "wide margin" approach, laparoscopy offers the ability to replicate the standard Ivor Lewis procedure, including mediastinal and celiac node dissection under the uniform lighting and magnification offered by the scope. There may also be potential survival advantages conferred by the documented decrease in immunosupression with endoscopic approaches. Likewise, advocates of transhiatal resections, who believe that the added morbidity of a major en bloc resection is not justified by the miniscule increase in survival, should be strong supporters of laparoscopic transhiatal esophagectomy as the least morbid alternative of them all. Obviously, concerns such as the possibility of port-site tumor dissemination, as well as the difficulty of these approaches, are relevant and need to be addressed by well-constructed outcomes studies.

Table 1. Stage of diagnosis at first presentation of esophageal cancer[11]

Esophageal cancer presenting stage	I	II	III	IV
Stage at first presentation (% of patients)	13.6	25.7	26.5	31.7

SURGICAL TECHNIQUES

Laparoscopic transhiatal esophagectomy is an extension of the techniques used for laparoscopic antireflux surgery and for the most part requires the same patient preparation, anesthesia techniques, and instrumentation. Patients should undergo a complete colon preparation including oral antibiotics in case the gastric pull-up fails and an alternative, a colon interposition, is needed. Our surgical approach is a modification of one described by DePaula et al.;[7] we use a five-port technique, with the patient positioned on a split-leg table with monitors at the head of the table (Fig. 2). Extra-long laparoscopic instruments (45 cm), including an angled laparoscope, atraumatic graspers, and long bipolar scissors, are very useful. A flexible upper endoscope is frequently very useful in these procedures, both to determine the margins of resection (replacing the ability to palpate in open surgery) and to evaluate the integrity of the several anastomoses at the conclusion of the operation. The procedure begins with a thorough exploration, including laparoscopic ultrasonography, of the hemithorax (cancers of the middle and upper third) or abdomen (cancers of the lower third). If non-nodal extraesophageal disease is detected and the patient does not meet the criteria for a palliative resection, the procedure can be terminated at this point and the patient discharged home for hospice care or systemic chemotherapy. If there is no evidence of widespread disease, the procedure begins with gastric mobilization. A limited "Kocherization" of the duodenum is performed and the gastrohepatic ligament is divided, allowing access to the celiac node bundle, which we remove at this point for staging purposes. The greater curvature of the stomach is mobilized using the ultrasonic coagulating shears, taking great care to avoid injury to the gastroepiploic vessels. Retrogastric attachments are likewise divided, which will eventually expose the left gastric artery and vein,

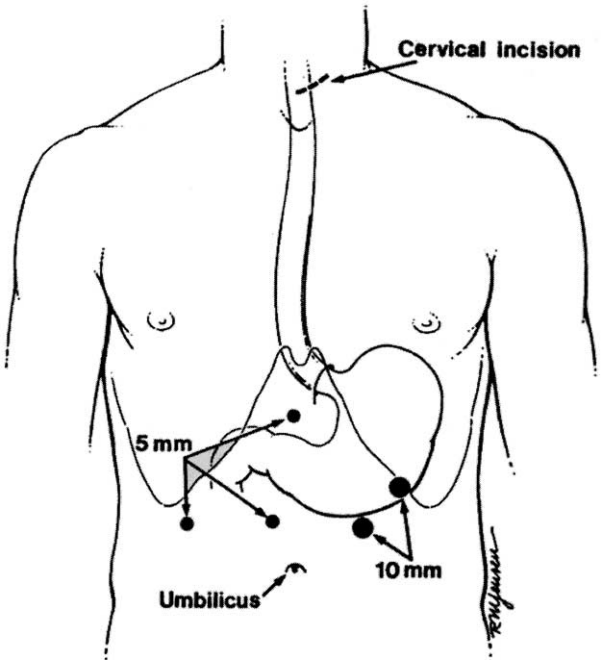

Fig. 2. Site of port and incision placement for totally laparoscopic esophagectomy. (From Swanstrom LL, Hansen PD. Laparoscopic total esophagectomy. Arch Surg 1997;132:943–949.)

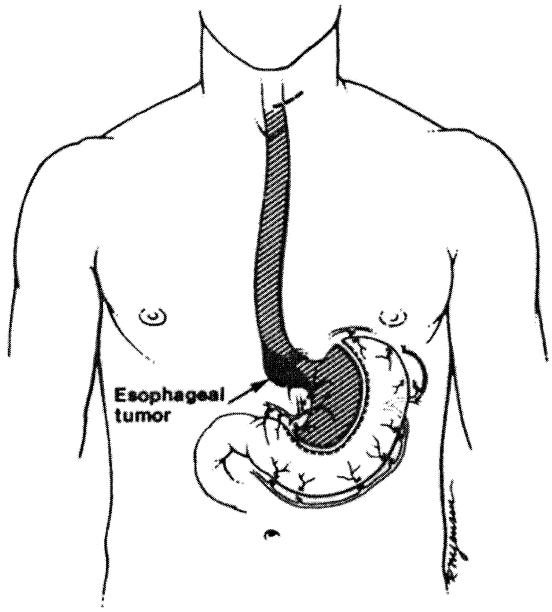

Fig. 3. Extent of esophageal and gastric resection (*hatched lines*) and mobilization with resection lines for the laparoscopic total esophagectomy. (From Swanstrom LL, Hansen PD. Laparoscopic total esophagectomy. Arch Surg 1997; 132:943–949.)

which we divide with an endoscopic vascular stapler cartridge. Narrow gastric tubes as the pull-up have been shown to have optimal physiologic function (shorter transit times, less stasis and reflux) and are therefore our preference. Use of a 2 to 2.5 cm. gastric tube has also been shown to obviate the need for a pyloroplasty or pyloromyotomy to ensure gastric emptying. Creation of the gastric tube is accomplished by means of multiple firings of an articulating endoscopic linear stapler (Fig. 3). We often insert a 45 bougie along the greater curvature of the stomach as a guide for creation of the tube. Next the hiatus is opened widely and the esophagus is dissected using the ultrasonic coagulating shears, bipolar scissors, and some blunt dissection. By widening the hiatus so this transhiatal dissection can be carried up to the tracheal bifurcation in most instances. A second team can begin an antegrade dissection of the esophagus via a small left cervical collar incision. Once the two dissection planes are completed, the stomach is divided; an endoscopic camera bag is inserted into the abdomen and placed around the esophagus, which is then withdrawn from the cervical incision. The tailored gastric tube is pulled up to the neck under laparoscopic visualization to avoid twisting. A hand-sewn esophagogastric anastomosis is created while the laparoscopic team fixes the rim of the hiatus to the gastric remnant. Finally, a feeding jejunostomy is placed in the small intestine laparoscopically.

Thoracoscopic/Laparoscopic Esophagectomy

An alternative to the laparoscopic transhiatal approach is a three-stage procedure, as described by Fernando et al.[9] This approach involves a standard right chest thoracoscopy, where after an exploratory staging procedure the mediastinal pleura is opened and the azygos vein is divided with the endoscopic vascular stapler. The esophagus is surrounded by a Penrose drain for retraction and mobilized using the ultrasonic coagulating shears. After the esophagus has been completely freed from the thoracic inlet to the hiatus and all sampled lymph nodes have been placed in a specimen bag and removed, the thoracoscopy is terminated and the patient is positioned for laparoscopy as detailed earlier. Once again, a Kocher maneuver is used for the duodenum, and the stomach is mobilized, divided, and tailored into a narrow tube with endoscopic staplers. The proximal gastric tube is sewn to the end of the esophagus. A cervical incision is made in the left side of the neck, and the esophagus is located, surrounded and dissected into

the abdomen. The specimen is withdrawn through the neck incision and sent for confirmation of adequate margins of resection. An esophagogastrostomy is created either with a stapler or by standard suturing techniques. Once again, pyloroplasty, feeding jejunostomy, and other procedures are performed as indicated.

After surgery, patients who have had an endoscopic esophagectomy experience many of the same benefits that any laparoscopic patient is known to have—less pain, rapid recovery of gastrointestinal function, a shorter hospital stay, and rapid recovery. We typically check the integrity of the gastrointestinal tract by obtaining an upper gastrointestinal study on postoperative day 2 and start the patient on a pureed diet if the results are normal. Patients are discharged home when they are eating, tolerating supplemental tube feedings, and have adequate pain control.

Table 2. Minimally invasive esophagectomy results, Legacy Health System, 1995–2000

Patients
26 patients–mean age 58 yr (range 36–84 yr)
12 adenocarcinoma, 2 squamous cell carcinoma (6 Barrett's esophagus with high-grade dysplasia)
2 refractory strictures
3 end-stage achalasia
1 esophageal "failure" sp long myotomy
Technique
20 laparoscopic transhiatal
4 laparoscopic/thoracoscopic
2 adherent middle third tumor
1 failed gastric tube
1 end-stage achalasia
1 laparoscopic-assisted transhiatal hernia
1 conversion to open procedure
For hemodynamic instability
Results
Average operative time (hr) 6.25 (range 4.5–9)
Mean blood loss (ml) 500 (range 150–1200)
Intraoperative complications in 3 (11%)
Partial gastric tube loss
Gastroduodenal artery injury
Stay in intensive care unit (days) 15 (48% of patients)
Hospital stay (days) 5.5 (range 4–12)
Postoperative complications
2 anastomotic leaks (7%)
7 dysphonia (transient in 6) (28%)
1 pneumonia
1 subclavian vein thrombosis
5 severe reflux (1 stricture) (19%)
At follow-up (mean 39 mo)
1 patient with benign disease died of congestive heart failure
6 patients with cancer died of disease

RESULTS

There are relatively few published outcomes of totally laparoscopic or thoracoscopic esophagectomy. Table 2 lists the acute outcomes from the experience at Legacy Health System with minimally invasive resections performed between 1995 and 2000 for a variety of benign and malignant indications. There has been only one comparative study that directly measured the advantages of minimally invasive approaches over standard open techniques. This retrospective analysis by Nguyen et al.[10] compared 18 thoracoscopic/laparoscopic resections (for a variety of indications) with 16 Ivor Lewis resections and 20 open transhiatal resections. Results showed an equal incidence of short-term complication rates among the three, but clear superiority for the minimally invasive approach with regard to time in the operating room, blood loss, stays in the intensive care unit, and overall length of stay in the hospital.

CONCLUSION

Endoscopic resections, either laparoscopic or combined thoracoscopic and laparoscopic, are possible and seem to offer decreased patient morbidity; this is an important consideration for most patients needing an esophagectomy. Their effectiveness as a curative procedure for cancer and the degree of recovery benefit over open resection remains to be documented. These procedures represent some of the technically most challenging cases for the laparoscopic surgeon and require both advanced skills in laparoscopy as well as a thorough knowledge of esophageal surgery.

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Multimodality Therapy for Gastroesophageal Cancers

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Multimodality therapy has undergone significant advances in recent years. Physicians have begun to recognize that cancer of the gastroesophageal junction is not a localized disease and often has spread systemically. In addition, recent studies have shown that better cancer control is achieved with a combination of treatments in comparison to single-modality therapies. In the case of chemotherapy and radiation therapy, chemotherapeutic drugs often have a radiosensitizing effect. Patients who respond to chemoradiation appear to be good candidates for curative esophagectomy. A similar situation is found in the treatment of early localized cancers. It has been found that more extensive therapy is needed for the residual noncancerous but premalignant mucosa because of the high risk that new cancer will develop. All of these events have led to the combination of various treatments with encouraging results.

Cancers of the gastroesophageal junction are among the most rapidly increasing cancers in white men. The most common form of therapy for these cancers involves multimodality therapy because there is often evidence of metastasis at the time of detection. These cancers are thought to be due to the increase in intestinal metaplasia of the esophagus and may be related to intestinal metaplasia of the gastric cardia although this has not been proved.[1] The metaplasia in the esophagus is thought to be due to chronic gastroesophageal reflux disease.[2] It is this metaplasia that predisposes patients to the development of adenocarcinoma. The metaplasia appears to progress from nondysplastic mucosa, to low-grade dysplasia, to high-grade dysplasia, and eventually to cancer. This sequence has been established for the distal esophagus, but intestinal metalasia of the gastric cardia may have a difference history. Intestinal metaplasia of the stomach does not appear to have the degree of cancer risk as in the esophagus.[3] Cancers of this region are difficult to assess in terms of their origin because the larger a cancer becomes, the less evidence there is of the intestinal metaplasia that may have been present. However, it seems that overall they should be treated similarly as distal esophageal cancers surgically in terms of lymph node dissections. These cancers do, however, seem to respond to chemoprevention strategies such as selenium more than noncardia gastric cancers.[4] The multimodality approaches to these cancers are dependent on cancer staging and focus on chemotherapy, ionizing radiation, and endoscopic therapy.

CANCER STAGING

The traditional approaches for cancer staging include computerized tomography of the chest and upper abdomen to determine if the lesion has spread beyond the regional lymph nodes. Distant metastases are best assessed with this modality, although positron emission tomography (PET) appears to have promise in assessing distant metastasis.[5] This technology measures the release of a radiolabeled glucose (18-fluoro-deoxy-D-glucose) derivative to assess the degree of metabolic activity in a tissue. Because cancers are generally hypermetabolic, the PET scan offers a total body assessment for metastatic disease. In comparison trials with computerized tomography, PET scans seem less sensitive to local-regional spread of disease, although they may be more sensitive for recurrent disease in which anatomic structures are distorted.[6,7] Determination of locally advanced disease and regional lymph nodes may be best assessed by endosonography.[8] This technique has the capability of performing fine-needle aspiration of suspicious lymph nodes. Staging by means of laparoscopy and video-assisted thoracoscopy may be more accurate for assessment of locally advanced disease, although it is more invasive.[9]

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Proposals have been made to classify lymph nodes in the celiac area and gastrohepatic ligament as N2 nodes rather than the current American Joint Committee on Cancer system of M1 nodes.[10] This appears to be sensible because these nodes do represent more extensive nodal metastasis rather than the visceral metastasis that the M1 designation usually indicates.

CHEMOTHERAPY, RADIATION, AND SURGERY

The rationale for the use of combined-modality therapy has traditionally been based on the radiosensitizing effects of chemotherapy. Studies have shown that combined modality therapy appears to be more effective in the treatment of esophageal cancers and cancers of the gastroesophageal junction.[11,12] Traditionally, 5-fluorouracil (5-FU) is the predominant radiosensitizer in cancers of the gastroesophageal junction. When administered concomitantly with radiation therapy, 5-FU is a nonspecific radiosensitizer that does produce increased damage to mucosal surfaces and normal tissues. Newer radiation sensitizers such as paclitaxel (Taxol) are also being investigated and show some promise in combination with 5-FU and cisplatinum. Paclitaxel may increase the cell population, those in the G2M phase of the cell cycle, that is most sensitive to radiation damage.[13] In addition to using these chemotherapeutic agents as radiosensitizers, there is also evidence that cancers of the gastroesophageal junction are actually systemic diseases rather than a focal process. These chemotherapeutic drugs may be indicated to treat more widespread disease as well as to enhance the effects of localized radiation. These cancers normally present as stage III disease with evidence of nodal involvement in both the esophageal and celiac or left gastric region. In addition, a recent study suggests that the occurrence of bone metastasis may have been underestimated because prior specimens were inadequate. The use of rib resection compared to iliac crest biopsy increased the yield of positive tissue from 0% to 48%.[14] The combination of chemotherapy plus ionizing radiation may be justified not only from the standpoint of enhancing the effects of radiation therapy but also from a standpoint of eliminating systemic disease.

Chemotherapy for these junctional cancers also reflects that they represent adenocarcinoma of the esophagus. These regimens usually include 5-FU and cisplatin, which have been proved to have activity against both adenocarcinoma and squamous cell cancers of the esophagus. Other agents that have been tried in the past have included bleomycin and mitomycin C, but these agents are not currently being investigated. Chemotherapy and radiation have been shown to be effective as a preoperative or neoadjuvant strategy.[15] Approximately 46 nonrandomized studies and six randomized trials have been performed, the results of which suggest that this regimen of 5-FU, cisplatin, and radiation can produce complete remission in up to 60% of patients at 5 years, which is an advantage over previous therapy. The results of six randomized studies are actually split with three favoring neoadjuvant therapy and the other three showing no difference after follow-up periods extending to 3 years. The results of theses randomized studies are summarized in Table 1.

The use of neoadjuvant therapy for cancers of the gastroesophageal junction remains indeterminate. One group that seems to benefit from neoadjuvant therapy is patients who have a complete response to the chemotherapy and radiation. If surgery is performed, these patients appear to have a much better prognosis, which may be partially due to the treatment of disease away from the field of resection.[22–24]

The method of surgical resection has been debated with a recent randomized trial comparing transhiatal to transthoracic esophagectomy demonstrating no statistical difference in outcome with either procedure, although the investigators believed that the transthoracic approach allowed for a more controlled procedure.[25] More debatable has been the need to perform a more complete lymph node dissection. The three-field lymph node dissection that includes the cervical lymph nodes has been championed by surgeons who have found high rates of cervical lymph node metastasis (16.6%) with cancers of the gastroesophageal junction.[26] In addition, multiple series from Japan have been published, which detail that this operation should be the standard for esophageal squamous cell cancer, because 5-year survival rates as high as 59% have been reported.[27] On the other hand, the morbidity and mortality of this procedure appear to be increased, and failures of two-field lymph node resection are often not in the cervical region.[28] It is currently believed that two-field dissection in combination with multimodal therapy with chemoradiation may be the best approach for tumors of the gastroesophageal junction.

ENDOSCOPIC THERAPY

Endoscopic therapy for junctional cancers can be divided into early-stage disease and late-stage disease. The most recent advances in endoscopic therapy for junctional cancers have been in early-staged cancers. Techniques have been developed that permit endoscopic treatment of these cancers. Endoscopic

Table 1. Prospective randomized trials of neoadjuvant therapy for esophageal cancer

Reference	No. of patients	Radiation dose (Gy)	Chemotherapy	Median survival (mo)	*P* value
Nygaard et al.[16] (1992)					
CRT + Surgery	47	35	Cisplatinum Bleomycin	7	0.3
Surgery	41			6	
Le Prise et al.[17] (1994)					
CRT + Surgery	41	20	5-FU, cisplatin	10	0.6
Surgery	45			11	
Apinop et al.[18] (1994)					
CRT + Surgery	35	40	5-FU, cisplatin	10	0.4
Surgery	34			7	
Walsh et al.[19] (1996)					
CRT + Surgery	58	40	5-FU, cisplatin	16	0.01
Surgery	55			11	
Bosset et al.[10] (1997)					
CRT + Surgery	143	37	Cisplatin	19	0.8*
Surgery	139			18	
Urba[21] (1997)					
CRT + Surgery	50	45	5-FU, cisplatin, Vinblastine	17	0.04†
Surgery	50			18	

CR = complete remission; CRT = chemoradiation therapy.
*At 3 years, the survival difference was 40% with neoadjuvant therapy vs. 28% with surgery alone, which was significant at $P = 0.003$.
†At 3 years the survival difference was 32% with neoadjuvant therapy compared to 15% for surgery alone accounting for the difference in the groups.

mucosal resection was first developed for treatment of gastric and squamous esophageal cancers in Japan.[29,30] In this technique the mucosa of the esophagus is elevated using injection of saline, hypertonic glucose, or other substances capable of creating a cushion under the mucosa. The mucosa is then elevated further using either mechanical means such as biopsy forceps, a variceal ligation band, or a vacuum from the endoscope's suction channel to create a pseudopolyp, which can be removed with a snare. Commercially available "caps" can be obtained that are fitted onto the end of an endoscope and allow a specialized snare to be fitted around the "lip" of the cap. The tissue can then be suctioned into the cap and the snare tightened, which allows removal of the suctioned tissue. These methods are capable of removing very large pieces of tissue. Using an endoscopic dissection technique in which a needle-knife device was used for cutting around a gastric cancer, a lesion 6 cm in diameter was successfully removed.[31] This technique has also been applied to Barrett's esophagus where superficial cancers have been treated with a combination of endoscopic mucosal resection and photodynamic therapy. Although endoscopic mucosal resection can often remove a reasonably sized lesion, there is often residual premalignant or even malignant tissue that remains after resection, which needs to be treated.[32] Photodynamic therapy can treat these other areas since it does not require tissue targeting. With the use of this combined therapy of mucosal resection followed by photodynamic therapy, our group has been able to achieve a complete remission rate of 94% in 17 patients after a median follow-up of 13 months. Photodynamic therapy alone has been used to treat these small cancers with success rates of roughly 74% to 100% in small series (Table 2).[33–35]

One of the important advantages of combined-modality therapy with endoscopic mucosal resection is the ability to accurately stage the cancer. In the earlier study by Sibille et al.,[36] staging was primarily by the diameter of the lesion, whereas later studies relied on endoscopic ultrasound imaging. The use of mucosal resection allows the depth of penetration to be determined by histologic examination, which is presumed to be the most accurate method of analysis.

Multimodality palliation of advanced esophageal cancers has been reported. Initially, thermal methods of tumor destruction had been used to improve dysphagia in patients with esophageal cancer.[37] This predominantly was accomplished with Nd:YAG lasers, which produced deep thermal injury and could

Table 2. Photodynamic therapy of superficial esophageal cancers

Reference	No. of patients	Photodynamic agent	Complete remission
Sibille et al.[36] (1995)	123	HpD	74%*
Gossner et al.[34] (1999)	58	ALA, mTHPC	62%
Panjehpour et al.[35] (2000)	17	Photofrin II	100%
Etienne et al.[33] (2000)	10	Temoporfin	100%
Buttar et al.[32] (2001)	17	Photofrin II	94%†

*Disease-specific 5-year survival; overall 5-year survival was 25%.
†Combination therapy with endoscopic mucosal resection.

quickly reestablish an esophageal lumen. The use of expandable metal stents has revolutionized the care of these patients because insertion of expandable stents is much simpler than insertion of the earlier plastic stents, although complications still persist.[38] Interestingly, a recent randomized study comparing expandable stents to repeated thermal therapy found that thermal therapy resulted in enhanced quality of life and longer median survival compared to stents.[39] Some investigators have combined thermal palliation with external radiation therapy in an attempt to enhance palliation. However, a recent comparative trial did not find any advantage to using laser therapy in combination with radiation therapy over expandable stents in palliation of dysphagia or survival.[40] This study did not assess the quality of life of these patients. The use of combined-modality therapy in palliation of cancer-related dysphagia may be of benefit, but few studies have been conducted and more research is needed.

SUMMARY

Multimodality therapy is the key to the treatment of carcinomas of the gastroesophageal junction. Chemoradiation followed by esophagectomy appears to be the standard therapy at the present time. Selected patients who respond completely to the chemotherapy and radiation are probably the best candidates for esophagectomy. Although extended lymph node dissection is advocated, there are not sufficient data to determine whether the increased morbidity of the procedure is justified by the improvement in outcome for junctional cancers. Early cancers in nonsurgical patients could potentially be treated by endoscopic methods including endoscopic mucosal resection, which permits accurate staging, and photodynamic therapy, which permits treatment of residual premalignant tissue. Palliation of patients with advanced cancers of the gastroesophageal junction is probably best managed with expandable metal stents, although there is some evidence to suggest that thermal methods of palliation may enhance the quality of life in these patients.

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Clinical and Histologic Follow-Up After Antireflux Surgery for Barrett's Esophagus

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There are few prospective studies that document the histologic follow-up after antireflux surgery in patients with Barrett's esophagus, as defined by the recently standardized criteria. We report the clinical, endoscopic, and histologic results of patients with Barrett's esophagus followed postoperatively for at least 2 years. Diagnosis of Barrett's esophagus required preoperative endoscopic evidence of columnar-lined epithelium in the esophagus and a biopsy demonstrating specialized intestinal metaplasia, which stains positively with Alcian blue stain. Between April 1993 and November 1998, a total of 104 patients meeting these criteria underwent fundoplication (laparoscopic [n = 84] or open [n = 6] nissen, laparoscopic Toupet [n = 11], laparoscopic Collis-Nissen [n = 1], Collins-Toupet [n = 1] or open Dor [n = 1]). Short-segment Barrett's esophagus (length of intestinal metaplasia <3 cm) was found preoperatively in 34% and low-grade dysplasia in 4% of patients. All patients were contacted yearly by mail, phone, or clinic visit. At a mean follow-up of 4.6 years (range 2 to 7.5 years), 81% of patients had stopped taking antisecretory medications and 97% were satisfied with the results of their operations. Eight patients have undergone reoperation for recurrence of symptoms. Two patients have died and two were excluded from endoscopic biopsy because of portal hypertension. Sixty-six patients complied with the surveillance protocol, and their histologic results were returned to our center. Symptomatic follow-up of the 34 patients who refused surveillance esophagogastro and duodenoscopy revealed two patients who were taking medication for reflux symptoms. None of the patients have developed high-grade dysplasia or esophageal carcinoma during surveillance endoscopy (337 total patient-years of follow-up). The incidence of regression of intestinal metaplasia to cardiac-fundic–type metaplasia after successful antireflux surgery is greater than previously reported. We suspect that this is a result of longer follow-up and the inclusion of patients with short-segment Barrett's esophagus. A substantial number of patients with Barrett's esophagus who are asymptomatic after antireflux surgery refuse surveillance endoscopy. (J GASTROINTEST SURG 2002;6:532–539) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Barrett's esophagus, antireflux surgery, outcome regression

Barrett's esophagus, a consequence of chronic gastroesophageal reflux disease (GERD), is defined as the presence of specialized intestinal metaplasia in the tubular esophagus. This definition has been standardized to include any length of columnar-lined esophagus that contains specialized intestinal epithelium on histologic section, as demonstrated by the presence of acid-mucin–containing goblet cells.[1,2] It has been estimated that one out of every eight persons with weekly heartburn symptoms has Barrett's esophagus.[3,4]

The goals of treating Barrett's esophagus are threefold: (1) to eliminate GERD symptoms, thereby restoring a normal quality of life; (2) to prevent the complications of GERD; and (3) to provide surveillance endoscopy to detect esophageal adenocarcinoma or premalignant (high-grade) dysplasia at a stage that can be treated effectively with esophagectomy.

Advances in laparoscopic surgery have resulted in a dramatic increase in the number of patients with GERD who are treated surgically. Reports of higher failure rates in laparoscopically treated patients with Barrett's esophagus have raised concerns about the use of laparoscopic access for treatment of Barrett's esophagus.[5] Other surgeons believe it is not the access but the operation (i.e., fundoplication) that leads

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to recurrent symptoms, and that patients with Barrett's esophagus manifest fundoplication failure sooner and more frequently than those without Barrett's esophagus.[6]

Not all agree with this conclusion. We have previously reported that symptomatic outcome of fundoplication in a small group of patients with Barrett's esophagus was identical to that in patients without Barrett's esophagus.[7] We have not previously looked at histologic outcomes of fundoplication in patients with Barrett's esophagus. It was our aim in this study to reexamine the symptomatic outcome of an enlarging cohort of patients and to determine whether antireflux surgery affected the natural progression of Barrett's esophagus from metaplasia to dysplasia to adenocarcinoma in patients undergoing fundoplication at our institution.

PATIENTS AND METHODS

Study Design

Prospectively acquired data from a large cohort of patients undergoing laparoscopic fundoplication between April 1993 and November 1998 were sorted to identify all patients with histologically confirmed Barrett's esophagus. Additional data were collected by review of patient charts, retrieval of endoscopy and histology reports from outside institutions, patient questionnaires, and by direct patient interviews.

Patient Population

A total of 130 consecutive patients were identified in the database who had a preoperative diagnosis of Barrett's esophagus. All medical records were reviewed to confirm that preoperative endoscopy reports documented a length of visible columnar-lined epithelium in the esophagus and that histologic examination confirmed the presence of intestinal metaplasia. This was determined by the presence of acid-mucin–containing goblet cells, which stained positively with Alcian blue stain.

Of the 130 patients initially identified from the database as having Barrett's esophagus, 26 were excluded either because intestinal metaplasia was not documented (n = 20) or because an endoscopically visible length of columnar-lined epithelium was not documented (n = 6). Thus our study population comprised 104 surgically treated patients who met the standardized criteria for Barrett's esophagus. This represents 10% of 1006 patients who underwent antireflux operations at our center during the same time period. Patient demographics and preoperative clinical features are presented in Table 1. Six patients had undergone seven previous antireflux procedures consisting of Nissen fundoplication in four, Belsey Mark IV procedures in two, and Toupet fundoplication in one.

Table 1. Preoperative clinical features of patients with Barrett's esophagus

Mean age (yr)	50.8 ± 11.5 (range 25–79)
Male (%)	62 (60%)
Median duration of symptoms (yr)	8 (IQR 4.5, 15)
Median duration of medical treatment (yr)	3 (IQR 1, 8)
Current alcohol abuse (>8 drinks/wk)	6 (6%)
Smoker (>10 pack-year history)	16 (15%)
Esophageal symptoms (moderate, severe)	66 (63%)
Extraesophageal symptoms (moderate, severe)	32 (31%)

IQR = interquartile range.

Preoperative Evaluation

All patients were evaluated by means of esophagogastroduodenoscopy (EGD), esophageal motility studies, and contrast esophagram (Table 2). Ambulatory 24-hour pH and gastric emptying studies were used selectively according to criteria previously described.[8] All patients completed a standardized preoperative symptom questionnaire. This questionnaire, which was based on a four-point scale ranging from 0 (no symptoms) to 3 (severe symptoms) queried for the presence of esophageal reflux symptoms (heartburn, regurgitation, chest pain, dysphagia) and/or extraesophageal reflux symptoms (asthma, cough, hoarseness).

Uncomplicated, quiescent Barrett's esophagus was found in 61 patients (27 women and 34 men), and complicated or active Barrett's esophagus was found

Table 2. Preoperative testing of patients with Barrett's esophagus

Mean endoscopic length of columnar-lined epithelium (cm)	4.4 ± 3.3
Low-grade dysplasia	4 (4%)
Short-segment Barrett's esophagus (columnar-lined epithelium <3 cm)	35 (34%)
Complicated Barrett's esophagus	43 (41%)
Erosive esophagitis	23 (23%)
Esophageal ulcer	14 (13%)
Peptic esophageal stricture	17 (16%)
Hiatal hernia >5 cm	8 (8%)
Median lower esophageal high-pressure zone pressure (mm Hg)	9.5 (IQR 6, 15.7)
Ineffective esophageal motility	12 (12%)
Ambulatory pH study (mean % total time pH < 4.0; n = 40)	17.6 ± 12

IQR = interquartile range.

in 43 patients (15 women and 28 men). Preoperative disease control was achieved in all patients by means of intensive medical therapy and dilatation of strictures to at least 45 F with Maloney or Savary dilators.

Surgical Procedure

The surgical procedure was tailored to patient physiology based on preoperative testing according to criteria previously described.[9] Nissen fundoplication was performed in 91 patients, Toupet fundoplication in 12 patients, and Dor fundoplication in one patient. Collis gastroplasty was performed in two patients in conjunction with fundoplication. Ninety-seven patients (93%) had their initial operations performed at our center using laparoscopic techniques.

Endoscopic Surveillance

All endoscopic procedures at our institution were performed under conscious sedation using a video endoscope. The length of Barrett's esophagus was measured as the distance from the proximal margin of columnar epithelium to the gastroesophageal junction, as determined by the proximal margins of the gastric mucosal folds. Biopsies were performed using the jumbo biopsy forceps, following an established protocol of four-quadrant biopsy every 2 cm of visible columnar epithelium.[10] All patients with Barrett's esophagus were required to undergo EGD with directed mucosal biopsy every 2 years unless this was needed earlier to confirm healing of esophagitis, to evaluate the presence of symptoms, or to follow a segment of dysplastic Barrett's esophagus. Because 80% of the patients lived more than 50 miles from our center, all patients had the option of having their surveillance endoscopies performed by a local physician.

Symptomatic and Quality-of-Life Assessment

A symptom assessment questionnaire was mailed to all patients yearly with instructions to return the most recent endoscopy and biopsy results to our center along with the questionnaire. Patients who did not return the questionnaire were then contacted and interviewed over the telephone. All 104 patients were located. Ninety-nine patients (95%) completed postoperative clinical questionnaires and, of these, 66 (66%) have complied with the recommended surveillance endoscopy protocol and have undergone at least one postoperative endoscopic examination. Two patients had died (one died in the perioperative period and one died of pancreatic cancer). Three patients declined to participate in any follow-up activities. Quality-of-life assessment was performed postoperatively in 45 patients using the Medical Outcomes Study Short Form 36 (SF-36).

All surveillance endoscopy reports (including results of endoscopic and histologic studies) were entered into a database and analyzed using Microsoft Excel (Microsoft Corp., Redmond, Washington) and SAS programs (SAS Inc., Cary, North Carolina). Nonparametric data were analyzed by means of Fisher's exact test and chi-square test where appropriate. Normally distributed continuous data were analyzed using Student's *t* test.

RESULTS

At a mean follow-up of 4.6 years (range 2 to 7.5 years), 97% of patients reported satisfaction with their operations. In the 45 patients who returned the SF-36 questionnaire, seven of eight quality-of-life fields had improved statistically from preoperative measures and were statistically identical to those of age-matched control subjects in the general population (Fig. 1). Twenty patients were taking antisecretory medications for symptoms of GERD or dyspepsia, and 27 patients reported moderate-to-severe symptoms; however, six patients had only extraesophageal GERD symptoms. Only five patients required postoperative dilatation, and none of the patients showed signs of severe erosive esophagitis or esophageal ulcers on their most recent EGDs.

At a mean time of 15.2 months after the first operation (range 8 to 23 months), eight patients underwent 10 reoperations for recurrent GERD symptoms associated with anatomic fundoplication failure. One additional patient underwent reoperation in the immediate postoperative period for herniation of the fundoplication that was associated with retching. Reoperation consisted of Nissen fundoplication in all patients, with concomitant Collis gastroplasty in three patients. The most recent EGD (which was performed at a facility near the patient's home in most patients) revealed possible disruption, slip, or herniation of the fundoplication in 17 patients; however, four of these patients were asymptomatic, three patients had a normal-appearing fundoplication on contrast esophagram, five additional patients had normal ambulatory pH studies, and the remaining five patients had their symptoms controlled with medication. None of these patients have scheduled a reoperation.

There was no progression of intestinal metaplasia to adenocarcinoma or high-grade dysplasia in any of the patients surveyed, for a total of 337 patient-years of follow-up. Of the 66 patients who remain on a surveillance protocol (Table 3), 32 (48%) had persistent intestinal metaplasia on the most recent

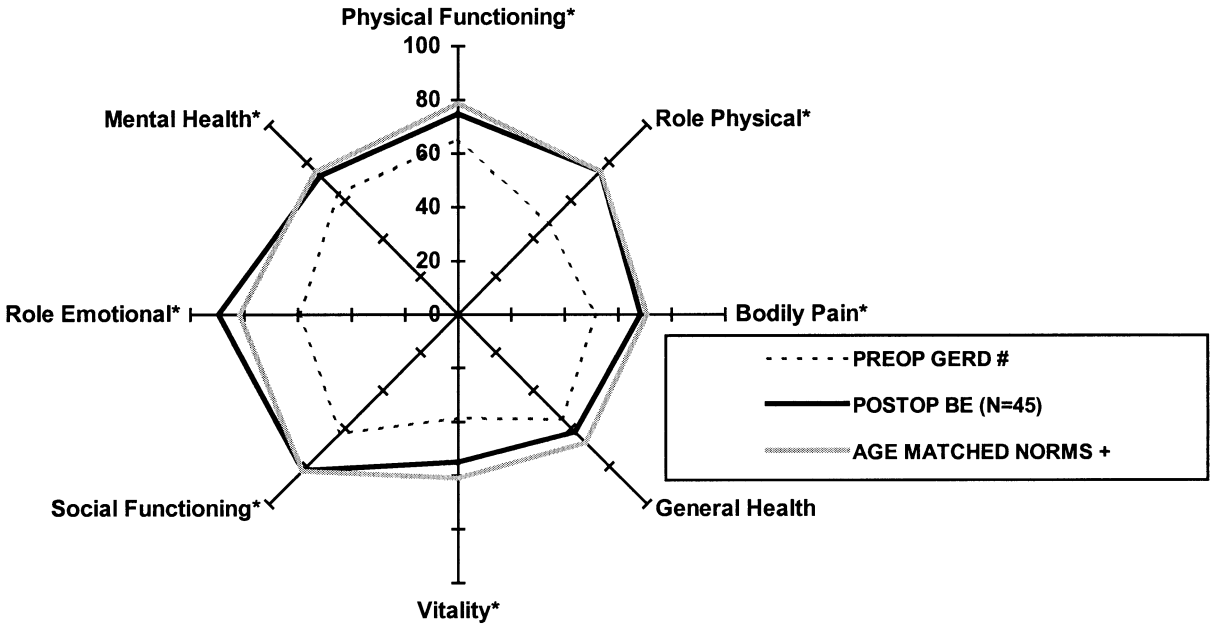

Fig. 1. Health-related quality of life assessed by SF-36. No difference was found in mean scores between postoperative patients with Barrett's esophagus and age-matched normal subjects. *Significant difference ($P < 0.05$) between established preoperative scores in patients with GERD and postoperative scores in patients with Barrett's esophagus.[11,12] # = Data derived from reference 11; + = data derived from reference 12.

endoscopic biopsy. One patient had progression of intestinal metaplasia to low-grade dysplasia during follow-up. There were 21 patients (32%) who had visible lengths of columnar-lined esophagus but loss of intestinal metaplasia on the most recent biopsy. The mucosa seen was cardiac- or cardiac/fundic-type in all patients who displayed loss of intestinal metaplasia. There were an additional 10 patients (15%) who had no visible length of columnar-lined epithelium in the esophagus. Of these patients, biopsy showed intestinal metaplasia localized to the gastroesophageal junction in three patients (cardiac intestinal metaplasia). Patients with loss of intestinal metaplasia had shorter mean lengths of preoperative visible columnar-lined epithelium and longer follow-up than patients with persistent intestinal metaplasia. No other clinical variable predicted the loss of intestinal metaplasia after antireflux surgery (Table 4). Of the 31 patients who had regression of intestinal metaplasia on the most recent biopsy, 13 patients (42%) had

Table 3. Histologic results in patients undergoing surveillance endoscopy ($N = 66$)

Progression to adenocarcinoma/high-grade dysplasia	0
Low-grade dysplasia	1 (2%)
Persistence of intestinal metaplasia in columnar-lined esophagus	32 (48%)
Visible columnar-lined epithelium not biopsied	2 (3%)
Loss of intestinal metaplasia in tubular esophagus	31 (47%)
No visible columnar-lined epithelium in esophagus	10 (15%)
Cardiac or cardiac/fundic–type mucosa only	21 (32%)

Table 4. Comparison of patients with regression and persistence of intestinal metaplasia

	Persistent IM (N = 33)	Loss of IM (N = 31)	*P* value
Age at operation (yr)	51.3 ± 11.4	49.9 ± 10.7	NS
Length of IM (cm)	5.5 ± 3.7	2.8 ± 2.4	<0.01
Duration of follow-up (yr)	4.7 ± 1.3	5.6 ± 1.7	<0.05
Complicated Barrett's preoperatively	12	13	NS
Need for reoperation	3	4	NS

IM = intestinal metaplasia; NS = not significant.
The patient with low-grade dysplasia is included in the persistent IM group.

had similar histologic findings on a previous surveillance endoscopy.

Nine patients underwent endoscopic mucosal thermal ablation of Barrett's esophagus using a KTP laser. The long-term results in this subgroup of patients revealed loss of intestinal metaplasia in eight of them.[13] Table 5 shows the long-term results in the non–laser-treated population. When analyzed by preoperative length of the Barrett's segment, patients with short-segment Barrett's esophagus were more likely to display regression (59%) than patients with traditional (long-segment) Barrett's esophagus (30%) ($P = 0.05$).

Thirty-four patients have not undergone surveillance endoscopy, despite recommendations. Clinical assessment of the nonsurveyed population reveals that these patients are more likely to be asymptomatic and to be off all antisecretory medications (Table 6). These patients have also been followed for a shorter median time period than the surveyed population.

DISCUSSION

In this study we have demonstrated that patients with Barrett's esophagus are unlikely to suffer histologic progression during intermediate- to long-term follow-up after successful antireflux surgery. In fact, 47% of patients had regression of Barrett's esophagus postoperatively. In 32%, only cardiac-fundic–type mucosa was found in the biopsies, and in 15% there was complete regression of all columnar-lined epithelium.

Regression is best defined by a total loss of intestinal metaplasia in the esophagus, because it is intestinal metaplasia that is directly responsible for the progression to adenocarcinoma.[14] Cardiac and cardiac-fundic–type mucosa in the distal esophagus are not premalignant lesions, and intestinal metaplasia isolated to the gastric cardia has not been shown to increase the risk of esophageal adenocarcinoma in recent studies.[15,16] Although the risk of progression to cancer does not directly correlate with the length of the Barrett's esophagus segment,[17] the prevalence of dysplasia is greater with longer segments of Barrett's esophagus.[18,19] This finding may be related to the quantity of intestinal metaplasia that is at risk for histologic progression. In a recent study, when intestinal metaplasia was confined to the gastric cardia, regression could be demonstrated in 73% of patients after successful antireflux surgery, compared to a 4% regression rate for longer segments of Barrett's esophagus.[20] In another study, intestinal metaplasia was lost in 50% of surveillance biopsies in patients treated medically with segments of Barrett's esophagus less than 2 cm.[19] In yet another study, short-segment columnar-lined esophagus (<3 cm) contained intestinal metaplasia in only 27% of biopsies, compared to a finding of intestinal metaplasia in 93% of biopsies in long-segment columnar-lined esophagus (≥3 cm).[21] Although patients with short-segment Barrett's esophagus may develop cancer, extra vigilance is due those with longer segment disease.

In this study, when the histologic results were stratified by the length of Barrett's esophagus found preoperatively, those patients with short-segment

Table 5. Histologic results excluding nine laser-treated patients and two patients who underwent endoscopy without biopsy (n = 55)

	Short-segment BE (CLE length <3 cm) (N = 22)	Long-segment BE (CLE length ≥3 cm) (N = 33)
Loss of IM	8 (38%)	6 (18%)
Squamous esophagus	5 (24%)	4 (12%)
Regression of BE	13 (59%)*	10 (30%)
Persistent IM/ LGD	9 (41%)	23 (70%)

BE = Barrett's esophagus; CLE = columnar-lined esophagus; IM = intestinal metaplasia; LGD = low-grade dysplasia.
*$P = 0.05$ compared to patients with long-segment BE (Fisher's exact test).

Table 6. Comparison of clinical outcomes in the endoscopically surveyed and nonsurveyed groups

	Total (n = 104)	Surveyed (n = 66)	Not surveyed (n = 34)	*P* value
Moderate, severe GERD symptoms	28 (27%)	23	5	<0.05
Antisecretory medications	20 (19%)	18	2	<0.05
Reoperation	9 (9%)	7	2	NS
Mean postoperative interval (yr)	4.7 ± 1.7	5.0 ± 1.6	4.1 ± 1.6	<0.05

NS = not significant.
Patients who have died or were not eligible for surveillance endoscopy are excluded from analysis.

Barrett's esophagus were more likely to have regression of intestinal metaplasia after antireflux surgery than those with long-segment disease. The regression rate we observed may reflect the large proportion of patients with short-segment Barrett's esophagus in this surgical series. The other factor contributing to the high rate of regression that we report may be the duration of follow-up, because it appears that regression increases with time after a successful antireflux operation. Some investigators have advocated documenting regression only when histologic findings are similar on two biopsies separated by at least 6 months.[18,20] Because most of our patients undergo surveillance endoscopy by their local physicians, this was not always feasible; however, 42% of the patients who demonstrated regression had at least two endoscopic biopsies, separated by at least 1 month, demonstrating this finding. It may be that further histologic follow-up of this cohort of patients may diminish the frequency of postoperative histologic regression somewhat.

In this study, we included only those patients who were at least 2 years out from their operation, because all had an immediate preoperative biopsy, and the recommended interval for surveillance endoscopy is 2 years for nondysplastic Barrett's esophagus.[10,22] By excluding all patients within 2 years of operation, before postoperative surveillance biopsy is indicated, we had the unique opportunity to identify a cohort of patients who have not complied with surveillance recommendations. In this study, 34 patients (33%) declined or delayed surveillance endoscopy. Most of these patients have not seen their referring physicians since their antireflux operations. Patients who declined or delayed surveillance endoscopy were more likely to be asymptomatic and more likely to be free of all GERD medications. The mean postoperative interval of these nonsurveyed patients was less than that of the surveyed population, yet we continue to urge our patients to undergo surveillance endoscopy every 2 years, and more frequently if dysplasia is suspected or identified. This also applies to asymptomatic patients because symptomatic response may not reflect complete reflux control,[23] and the molecular event triggering the neoplastic cascade may be independent of the surgical intervention.

Despite the histologic response to surgery presented with this series, 27% of patients reported moderate-to-severe reflux symptoms postoperatively and 9% required surgical revision. Similarly, 80% of medically treated patients with Barrett's esophagus continue to have reflux after the initiation of proton pump inhibitors.[23] Barrett's esophagus represents the worst form of GERD and is more resistant to standard surgical and medical therapy than milder forms of GERD. It is not enough to initiate medical or surgical therapy in patients with Barrett's esophagus, and then cease active follow-up except for interval endoscopy. Although still unsubstantiated, it is beginning to appear that the best histologic outcomes in Barrett's esophagus result from aggressive management of the symptomatic or anatomic failures.

Of the reported cases of progression of Barrett's esophagus to adenocarcinoma that develop after antireflux surgery, most have occurred early in the postoperative period or in patients with evidence of fundoplication failure.[6] We attribute our success at the histologic control of Barrett's esophagus to the aggressive management of the 10% to 20% of patients who have failed primary therapy. We maintain a low threshold for performing postoperative physiologic and anatomic studies in patients with recurrent GERD symptoms, and then offer reoperation for those with anatomic damage of their fundoplication.[24]

Most failures in this series were caused by herniation of the fundoplication. To minimize this complication, adequate esophageal mobilization, effective crural closure, and accurate assessment of esophageal length are essential components of a successful antireflux operation. Esophageal lengthening (Collis gastroplasty) should be considered when 2 cm of intra-abdominal esophagus cannot be maintained without traction, and in all patients who have experienced recurrent herniation of their fundoplication.[25,26] In this series we also report that 17 antireflux valves were abnormal, as judged by follow-up EGD. In the absence of complete photographic documentation, we find that these assessments are frequently inaccurate if performed by a person who is not familiar with the endoscopic appearance of an intact fundoplication. To reassure the asymptomatic patients of this finding, we perform a barium esophagram, and/or EGD. In symptomatic patients we will add a 24-hour pH study if the anatomic assessment is normal.

This study has several limitations. Patients underwent surveillance endoscopy predominantly by their referring gastroenterologists, and therefore we are dependent on the expertise of the referring physician. However, we identified only two patients who did not have an appropriate biopsy with this strategy. Emerging series of medically treated patients with nondysplastic Barrett's esophagus report a progression rate to adenocarcinoma of approximately one cancer per 200 patient-years of follow-up, so it would take a much larger series with longer follow-up to determine if antireflux surgery actually reduced the incidence of progression to adenocarcinoma.

We have previously reported excellent symptomatic outcome after laparoscopic fundoplication in pa-

tients with Barrett's esophagus.[7] This study provides longer follow-up of our Barrett's esophagus population and confirms that, although the rate of fundoplication failure is high, clinical outcomes in most patients are excellent, especially when a liberal stance toward reintervention is maintained. In addition, there is a higher rate of loss of intestinal metaplasia than we anticipated, and longer histologic follow-up of this population is required to determine whether this is a durable regression. Although it is still too early in our follow-up to determine whether this aggressive surgical approach to the management of nondysplastic Barrett's esophagus has affected the rate of progression to adenocarcinoma, our initial success at preventing progression and initiating regression in this cohort of patients is encouraging.

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Discussion

Dr. D.W. Rattner (Boston, MA): Congratulations on a very nice study. I wonder, in light of this study, whether you would compare your conflicting results with those published in *JAMA* by Spechler et al. (Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of a randomized controlled trial. JAMA 285:2331–2378, 2001.) within the past month regarding prevention of adenocarcinoma and regression to Barrett's esophagus?

Dr. S. Bowers: To prevent cancer, it is very important to identify those patients who fail primary therapy, and that is what I think we have been very effective in doing. We clearly have had fundoplication failures; however, by physiologically studying patients who have recurrent symptoms or progression of dysplastic Barrett's esophagus and identifying fundoplication failure and correcting it either surgically or with medication, we believe that is what has enabled us to prevent progression of Barrett's esophagus in our population. We do not have enough patient-years or follow-up data to declare victory over adenocarcinoma, certainly.

Dr. R.W. Aye (Seattle, WA): The University of Washington has identified patients who develop squamous reepithelization over the top of glandular mucosa. I am not sure if that is what you were referring to when you noted ". . .visible regression but still metaplasia present . . ." or did you see any of those patients?

Dr. Bowers: We had three patients with intestinal metaplasia localized to the gastric cardia who had had a previous segment of visible columnar epithelium, but on repeat endoscopy the visible columnar epithelium in the esophagus was gone, but on biopsy the gastric cardia still had intestinal metaplasia, and we do not know what that means. We do not think that this represents a precancerous lesion as intestinal metaplasia of the esophagus does.

Dr. M.B. Zaman (Dublin, Ireland): In the columnar-lined epithelium, your biopsies showed disappearance of the intestinal metaplasia. You gave your patients the option of going to their local centers for biopsy. How happy are you with this biopsy system? You are not sampling the gastric mucosa and is this the true representation at the end of the esophagus?

Dr. Bowers: We found that 42% of the patients who had regression, that is, loss of intestinal metaplasia, had loss of intestinal metaplasia on more than one biopsy 6 months apart, and that would be an obvious criticism—that we were not performing thorough biopsies. But we believe a large number of our patients, who we are calling "regression of Barrett's," did fulfill the criteria in that they had multiple biopsies. Again, we have to rely on our gastroenterology colleagues as does everyone in the "real" world, and that is how I would answer that. We did not have the ability to bring everyone back and perform biopsies on them ourselves.

Long-Term Efficacy of Total (Nissen-Rossetti) and Posterior Partial (Toupet) Fundoplication: Results of a Randomized Clinical Trial

Cecilia Hagedorn, M.D., Hans Lönroth, M.D., Ph.D., Lars Rydberg, M.D., Ph.D., Magnus Ruth, M.D., Ph.D., Lars Lundell, M.D., Ph.D.

The efficacy of fundoplication operations in the long-term management of gastroesophageal reflux disease (GERD) has been documented. However, only a few prospective controlled series support the long-term (>10 years) efficacy of these procedures, and further data are required to also determine whether the type of fundoplication affects the frequency of postfundoplication complaints. The aim of this study was to conduct a randomized, controlled clinical trial to assess the long-term symptomatic outcome of a partial posterior fundoplication as compared to a total fundic wrap. During the years 1983 to 1991, a total of 137 patients with chronic gastroesophageal reflux disease were enrolled in the study; 72 were randomized to semifundoplication (Toupet) and 65 to total fundoplication (Nissen-Rossetti). A standardized symptom questionnaire was used for follow-up of these patients. A total of 110 patients completed a median follow-up of 11.5 years; 54 had a total wrap and 56 underwent a partial posterior fundoplication. During this period, seven patients required reoperation (Nissen-Rossetti in 5 and Toupet in 2), 11 patients died, and nine patients were lost to follow-up or did not comply with the follow-up program. Control of heartburn (no symptoms or mild, intermittent symptoms) was achieved in 88% and 92% in the total and partial fundoplication groups, respectively, and the corresponding figures for control of acid regurgitation were 90% and 94%. We observed no difference in dysphagia scoring between the two groups, although odynophagia was somewhat more frequently reported in those undergoing a total fundoplication. On the other hand, a significant difference was observed in the prevalence of rectal flatus and postprandial fullness, which were recorded significantly more often in those undergoing a total fundoplication ($P < 0.001$ and $P < 0.03$, respectively). Posterior partial fundoplication seems to maintain the same high level of reflux control as total fundoplication. Earlier observations demonstrating the advantages of a partial fundoplication, which included fewer complaints associated with gas-bloat, continue to be valid after more than 10 years of follow-up. (J GASTROINTEST SURG 2002;6:540–545) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Gastroesophageal reflux disease, total fundoplication, partial fundoplication, postfundoplication symptoms, gas-bloat symptoms, Barrett's esophagus

Although the role of the minimally invasive approach to antireflux surgery is rapidly expanding,[1,2] we still must rely on open surgery when the long-term efficacy of similar procedures remains in doubt. Numerous reports present outcome data extending to more than 5 years after the operation. In similar studies, a consistent message emerges—that is, despite excellent reflux control, some problems remain after total fundoplication. As a possible consequence of that experience, a number of modifications of the original Nissen fundoplication procedure have been introduced.[3–15] With growing insight into the mechanical consequences of total fundoplication, the adverse effects associated with a supracompetent high-pressure zone in the lower esophageal sphincter area have become apparent.[13,16–18] In similar situations the sphincter relaxes incompletely on swallowing, which is accompanied by the abolition of gas reflux and an inability to belch. Partial fundoplication procedures seem to be associated with a lower incidence of mechanical complications,[19,20] but results have been presented to suggest that reflux con-

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trol may be suboptimal and less durable than what can be achieved after a total fundoplication.[21,22] We have previously reported the 3-year follow-up results from a randomized, controlled clinical trial comparing total and posterior partial fundoplication; these results showed similar levels of reflux control for these two procedures, although the posterior partial fundoplication offered the advantage of resulting in fewer complaints associated with gas-bloat.[20] This report presents the results of the ongoing long-term follow-up of these patients.

PATIENTS AND METHODS

Originally, 137 patients with a long clinical history of gastroesophageal reflux disease (GERD) were enrolled and randomized into the trial. Relevant clinical details from this patient cohort have been presented previously.[20] Sixty-five patients were randomized to Nissen-Rossetti total fundoplication and 72 to posterior partial fundoplication as described by Toupet.[23] The study protocol was approved by the local ethics committee, and informed consent was obtained from all participants.

All operations were performed using a laparotomy incision, and a posterior crural repair was done only if results of preoperative barium radiography and endoscopy revealed an obvious hiatal hernia and if the surgeon considered the hiatus to be markedly wide. In total, 45% of the patients underwent a crural repair using nonabsorbable sutures. In both groups, the fundus of the stomach was generously mobilized by dividing the short gastric vessels. The distal esophagus was exposed through the hiatus by opening the phrenicoesophageal membrane and making an opening 3 to 4 cm wide above the hepatic branch of the anterior vagus nerve. The partial fundoplication encircled 180 to 200 degrees of the esophageal circumference. Further details regarding the operative procedure can be found in the report by Lundell et al.[20]

Endoscopic examinations were carried out before patients were enrolled in the study and at 1, 3, and 5 years after operation. A conservative definition of Barrett's esophagus was applied at the time of enrollment.[24] Each patient was interviewed at 3, 6, and 12 months and then yearly for the first 5 years after the operation. The same interview was conducted at the time of long-term follow-up. The interview included questions pertaining to symptoms of gastroesophageal reflux, as well as those specifically related to the fundoplication procedure. At each assessment, patients were evaluated by an independent observer. Unless otherwise stated, each symptom was scored on a scale of 0 to 3 (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms). Mild symptoms were those that were easily controlled by dietary measures, occasional use of antacids, and so forth. Severe symptoms included those that required continuous medical treatment or other therapeutic interventions, or those that caused the patient considerable discomfort.

Of the original 137 patients, 11 died of unrelated causes during the follow-up period. A careful review of these patients' files contained no information to suggest incomplete reflux control or antisecretory drug consumption. Five patients (all of whom had a total wrap) underwent reoperation, mainly for paraesophageal herniation of the stomach (four had not had a crural repair), and two patients who had a partial wrap required reop-

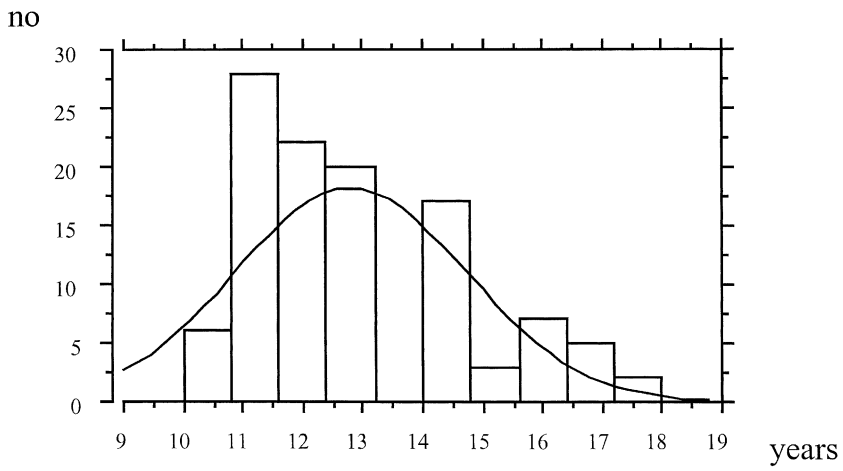

Fig. 1. Number of patients followed after a Nissen-Rossetti or Toupet fundoplication and the length of follow-up (years).

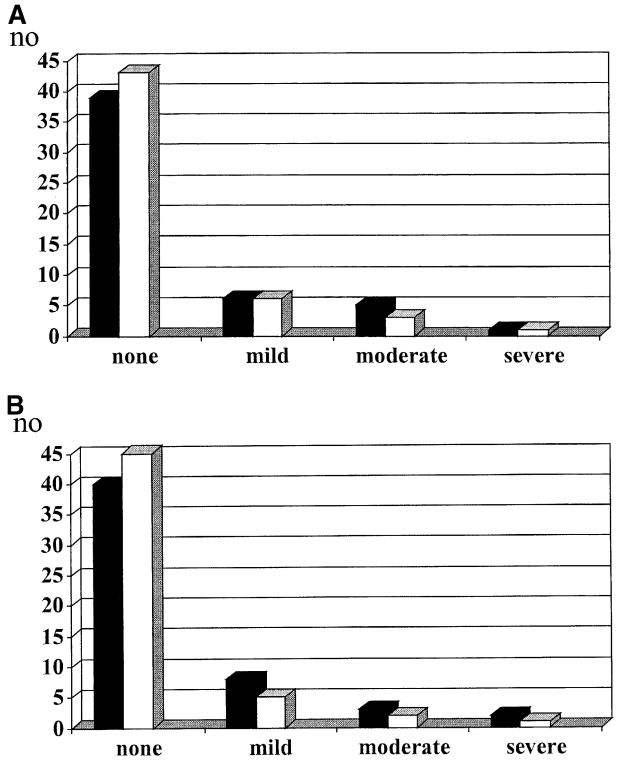

Fig. 2. Symptom control obtained after either a total or partial posterior fundoplication. **A,** Heartburn. **B,** Acid regurgitation. ■ = Nissen-Rossetti; □ = Toupet.

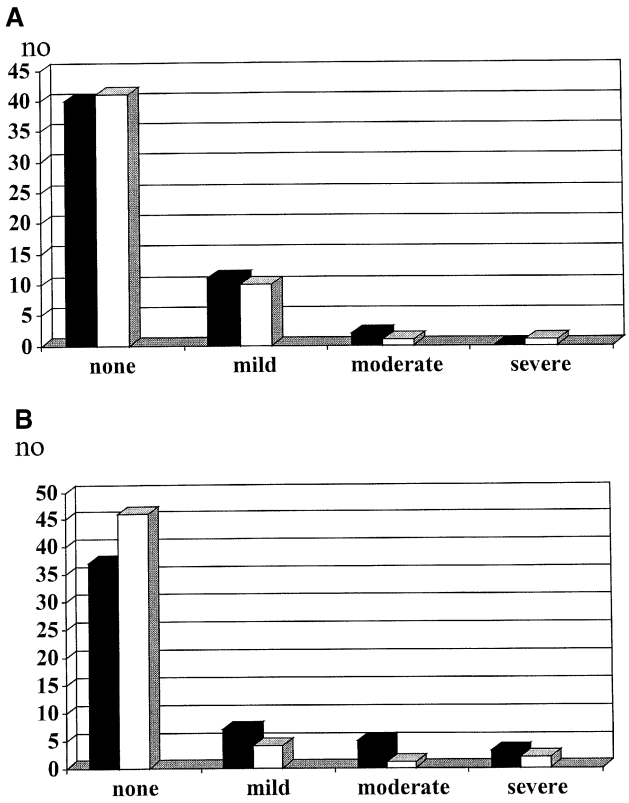

Fig. 3. Obstructive complaints after either a total or partial posterior fundoplication. **A,** Dysphagia. **B,** Odynophagia. ■ = Nissen-Rossetti; □ = Toupet.

eration, one of which had a recurrence of reflux. Nine patients were lost to follow-up or refused to answer the questionnaire and/or undertake any other follow-up measures. We were able to retrieve clinical data from general practitioner files, and so forth, in seven of these patients, again without any indications of reflux recurrence. In total, 110 patients were reinvestigated, 73 of which were men. Their mean age at the time of operation was 53 years. Fifty-four patients had a Nissen-Rossetti total fundoplication and the median follow-up was 11.5 years (range 9 to 17 years) (Fig. 1).

Eighteen patients were classified as having Barrett's esophagus at the time they were enrolled in the study.[24] At the time of follow-up, 15 of these patients remained in the trial; two were lost to follow-up and one had undergone reoperation. Among these 15 patients, 11 had a Nissen-Rossetti total fundoplication and only four had a posterior fundoplication. During the follow-up period, no patients in this group developed dysplasia in the columnar-lined esophagus and/or adenocarcinoma.

Statistical Analysis

Statistical analysis was carried out after cross-tabulation of the data and subsequent use of the Mantel-Haenzel, chi-square, and Fisher's exact tests. All data are presented as mean and standard error.

RESULTS

No symptoms or mild symptoms of reflux were recorded in 90% of the patients regardless of whether they had initially had a Nissen-Rossetti total fundoplication or a Toupet posterior partial fundoplication, respectively (Fig. 2). Several more patients (although not a significant number) who had a Nissen-Rossetti fundoplication complained of odynophagia, but no differences in dysphagia scores were observed between the two study groups (Fig. 3).

In terms of postfundoplication complaints, we recorded a significant difference in favor of those undergoing a partial fundoplication, with lower scores for flatulence and postprandial fullness in the latter group (Fig. 4) ($P \leq 0.03$). When questioned specifically, 71% of our patients reported an ability to belch irrespective of group affiliation (Fig. 5). Somewhat unexpectedly, we recorded an ability to vomit in 38% of patients undergoing a posterior partial

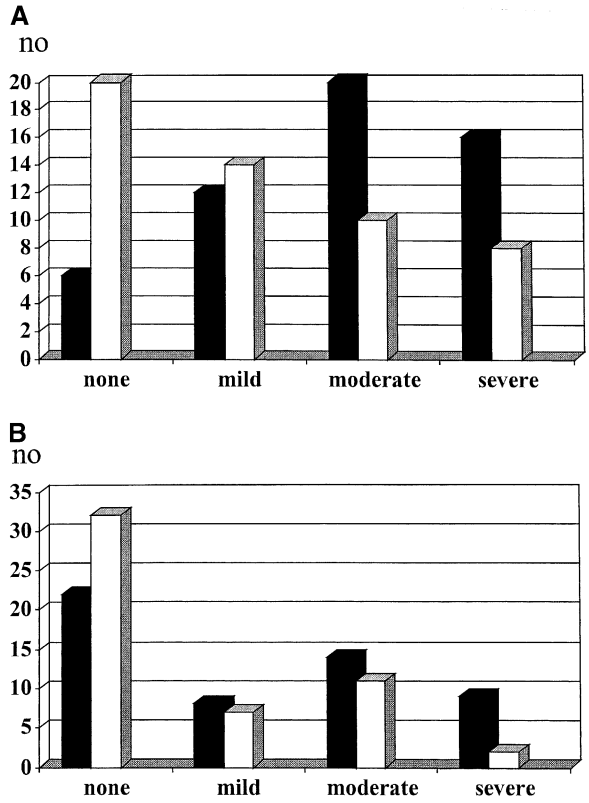

Fig. 4. Postfundoplication complaints after either a total or partial posterior fundoplication. **A,** Flatulence. **B,** Fullness. ■ = Nissen-Rossetti; □ = Toupet.

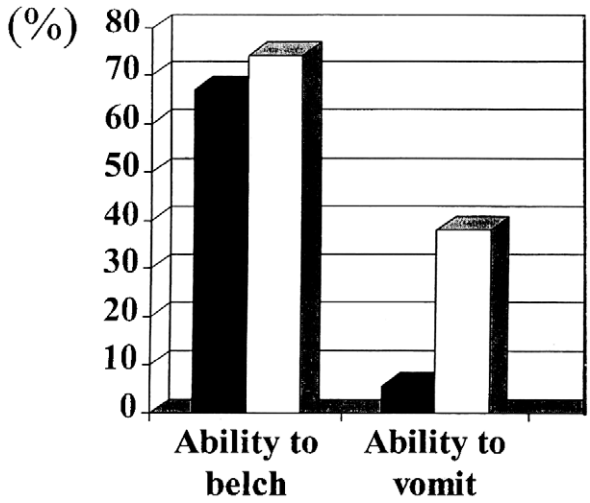

Fig. 5. Ability to belch or vomit after either a total or partial fundoplication. ■ = Nissen-Rossetti; □ = Toupet; $P < 0.0001$.

fundoplication, as compared to only a few among those who had a total fundoplication ($P < 0.0001$).

When the 15 patients with Barrett's esophagus were compared to those without Barrett's esophagus, we found the level of reflux control to be almost identical, demonstrating the same high level (score of 0 to 1) of heartburn control (90% vs. 92%, respectively). The corresponding figures regarding control of acid regurgitation were 91% and 100%, respectively. The comparatively few cases of Barrett's esophagus and the skewed distribution did not allow a comparison between the two operative approaches.

DISCUSSION

An ideal antireflux procedure should be safe, effective, durable, and relatively easy to teach, learn, and perform; it should also be free of troublesome mechanical complications. The total fundoplication in the form of a Nissen procedure is the most widely used antireflux operation worldwide. Although its efficacy is well documented, the clinical success rate in terms of gastroesophageal reflux control is frequently compromised by troublesome mechanical side effects. These side effects seem to be related to the construction of a supracompetent antireflux barrier at the gastroesophageal junction, the consequence of which is the inability to adequately vent air from the stomach. Furthermore, in patients prospectively studied after a total fundoplication, it has been suggested that compensatory mechanisms are operational within the esophageal wall to overcome an outflow obstruction in the gastroesophageal junction; these mechanisms are expressed in terms of increased esophageal peristaltic wave amplitude to facilitate bolus transfer.[25–27] It has been suggested that these mechanical adverse consequences may be counteracted by making the wrap shorter and looser, and by adding an intraoperative bougie.[28] In this context, it is interesting to note that we did not record any difference in obstructive complaints between our patients randomized to either a total or a posterior partial fundoplication, even when these patients were investigated more than 10 years after the operation. The fact that we observed a few more complaints of odynophagia in those who had a total wrap may be a subtle sign of an esophageal outflow obstruction.

The ultimate goal, when performing antireflux surgery, is to restore the physiology of the complex antireflux mechanics that reside within the gastroesophageal junction and to normalize the anatomy without producing additional adverse effects. We have previously presented data demonstrating that a posterior partial fundoplication achieves the same level of reflux control as a total fundoplication. We have now extended these observations to beyond 10 years of follow-up. These findings are also supported by others who have conducted long-term follow-up in a consecutive series of

patients undergoing other types of posterior partial fundoplications.[29,30] Based on the reassuring long-term follow-up data, it is difficult to understand why some investigators have found the Toupet partial fundoplication not to be as successful, in severe cases of reflux disease, as total fundoplication when performed by means of a laparoscopic approach.[22] It cannot be denied, of course, that some procedures are more difficult to perform when modern minimally invasive techniques are applied. In a search for factors that may have affected the outcome after the respective procedures, we have been unable to demonstrate that the severity and duration of disease, or hiatal closure by crural repair, or body mass index (BMI) had any impact on the level of long-term reflux control.[31]

We have previously shown that a partial fundoplication is accompanied by a lower frequency of mechanical complications, which also allows patients to more effectively vent air from the stomach.[32] It may therefore appear contradictory that we found no differences between the two fundoplication groups when we specifically asked our patients about their ability to belch. On the other hand, studies have shown that the characteristics of the common cavity during manometry, after instillation of air into the stomach,[26] are the only reliable indicators of a postoperative patient's capacity to vent air from the stomach. Furthermore, our observation of higher rates for the ability to vomit in patients undergoing a Toupet fundoplication may simply reflect a retrograde voluntary esophageal emptying.

The key mechanisms behind side effects after fundoplication procedures seem to reside in the postoperative function of the lower esophageal sphincter (LES) and its capacity to relax on appropriate stimulation. Results from our laboratory suggest that a partial posterior fundoplication normalizes the LES tone, does not impair the ability of the LES to relax on proper stimulation, and counteracts the triggering of transient LES relaxation.[26] In fact, the LES tone approaches the level seen in healthy subjects and, more important, only occasionally were LES pressure levels recorded to be $\leq$2 mm Hg, which is the level considered to allow free reflux to occur over the barrier. We can therefore conclude that these early postoperative observations seem to coincide well with both the durability of reflux control and the decrease in postfundoplication complaints after a posterior partial fundoplication.

During the "short-term" follow-up of this patient cohort ($\leq$5 years),[19,20] we were able to also objectively evaluate the level of reflux control with the use of endoscopy and ambulatory 24-hour pH monitoring. In these studies, as well as in others,[33] a close correlation does exist between symptom relief (objectively assessed) and healing of esophagitis, as well as control of acid reflux. The scientific validity of our observations with regard to long-term outcome after the respective operations had definitely been strengthened by the addition of 24-hour pH monitoring data in each individual case. However, we had to prioritize the number of invasive studies that our patients could be exposed to, and according to the present protocol these investigations are carried out in those patients who have passed the 15-year follow-up time point.

Finally, we obtained some important information regarding the management of patients with Barrett's esophagus (columnar-lined epithelium), who represent the severe end of the spectrum of complications associated with chronic GERD. Previous data have indicated that antireflux surgery is associated with less favorable outcomes in patients with Barrett's esophagus compared to non-Barrett's patients[29,34] These investigators found that the clinical scoring closely paralleled the results obtained by 24-hour pH monitoring in each individual case. In our cohort of patients with long-segment columnar-lined epithelium, we observed no differences at all in the long-term symptomatic outcome compared to patients without Barrett's esophagus. These results confirm those obtained by others,[35] including a recently reported trial with a 5-year follow-up comparing antireflux surgery with modern proton pump inhibitor therapy.[36] Again, it should be emphasized that these observations must be substantiated by endoscopy and acid reflux parameters.

In conclusion, our previous observations on the efficacy and advantages of a posterior partial fundoplication, in terms of reflux control and postfundoplication complaints, can now be extended to more than 10 years, emphasizing the durability of a similar operative reconstruction.

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Ligand Activation of Alternatively Spliced Fibroblast Growth Factor Receptor-1 Modulates Pancreatic Adenocarcinoma Cell Malignancy

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Pancreatic adenocarcinoma continues to be a devastating tumor (28,000 new cases per year in the United States; 10% 2-year survival). Pancreatic adenocarcinoma frequently (90% of the time) overexpresses fibroblast growth factor ligands (FGF-1 and FGF-2) and alternatively spliced high-affinity receptors (FGFR-1β) (FGFR-1α was previously found in normal pancreatic tissue). To study the significance of this observation in vitro, PANC-1 cells were stably transfected via the pMEXneo vector containing FGFR-1α (PANC-1α) or FGFR-1β (PANC-1β) isoforms. Cells were treated with 1 mg/ml of 5-fluorouracil. Cells were evaluated for growth inhibition, apoptosis (propidium iodide staining and flow cytometry, caspase 3 activation) and for Bcl-x_L/BAX expression (by Western blot analysis). In vivo, 7×10^6 cells of each isoform were injected into nude Balb/c mice for xenograft formation (N = 10). Compared to PANC-1β (9%) in vitro, 5-fluorouracil–induced death was significantly ($P < 0.05$) increased in PANC-1α (20%) at 24 hours. Increased cell death in PANC-1α was mediated by activated caspase 3 and was correlated with decreased expression of Bcl-x_L/BAX. In vivo, PANC-1β readily demonstrated formation of tumor xenograft at 2 weeks, whereas PANC-1α did not form tumors. Alternative splicing of FGFR-1 to the β isoform appears to correlate with pancreatic adenocarcinoma cell growth in vivo and resistance to chemotherapy. Inhibition of FGFR-1 splicing or overexpression of FGFR-1α inhibits pancreatic adenocarcinoma cell growth in vivo and restores cytotoxic responses to chemotherapy, thereby suggesting the basis of rational interventional strategies for this devastating tumor. (J GASTROINTEST SURG 2002;6:546–553) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Pancreatic cancer, chemotherapy, FGF receptor, apoptosis

Pancreatic adenocarcinoma continues to be an aggressive malignant disease with few long-term survivors. The 2-year survival rate is less than 10%.[1] Numerous studies have correlated the survival rate of pancreatic adenocarcinoma with the overexpression of fibroblast growth factor(s) (FGF).[2,3] In pancreatic adenocarcinoma FGF-1 (acidic FGF) and FGF-2 (basic FGF) were found to be overexpressed and localized to the malignant ductal cells.[4–7] Overexpressed FGF-1 and FGF-2 in pancreatic adenocarcinoma have also been accompanied by the overexpression of FGF receptor (FGFR).[8,9] Five FGFRs and their isotype variants were identified.[3,10] Many of these variations occur in the genes of FGFR-1. Two variations, FGFR-1 α and β isoforms, have been found to be post-translational splicing products of FGFR-1. FGFR-1α has an extracellular domain consisting of three immunoglobulin-like loops and a putative nuclear localization peptide. Truncation of the N-terminal first immunoglobulin-like loop gives rise to the FGFR-β isoform.[3] Studies with polymerase chain reaction (PCR) revealed a dominant expression of FGFR-1β in pancreatic adenocarcinoma, breast cancer, and astrocytomas, whereas FGFR-1α appears to be the predominant isoform in normal pancreatic tissue.[11,12] Although one study showed the ratio of expressed β and α isoform to be correlated with prognosis clinically in patients with breast cancer,[12] the relationship between the overexpressed FGFR-β isoform and the pathobiology of pancreatic

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adenocarcinoma has not been well defined. To further study the roles of the overexpressed FGFR-1 isoform in pancreatic adenocarcinoma, we transfected cDNA of both FGFR-1 α and β isoform into the PANC-1 cell line. The sensitivities of these transfected cells to chemotherapy, the potential to form tumors in nude mice, and the possible mechanisms were studied.

MATERIAL AND METHODS

Gene Transfection and Cell Culture

Complementary DNA from human FGFR-1 α and β isoforms was inserted into the eukaryotic expression vector (pMEXneo plasmid) as previously described[13] (Fig. 1). Primary human pancreatic adenocarcinoma line (PANC-1) was purchased from American Type Culture Collection. Primary cells were transfected with vectors containing FGFR-1α and FGFR-1β cDNA using calcium phosphate–mediated precipitation.[14] Cells transfected with vector containing neomycin-resistant gene only were used as control specimens. Transfected cells were selected in Dulbecco's modified Eagle medium (DMEM) containing 10% fetal calf serum; penicillin/streptomycin, 10 units/100 μg/ml; and geneticin (Invitrogen, San Diego; CA), 800 μg/ml, for 14 days. Selected clones from each isoform were cultured in culture medium without Geneticin and were evaluated for their sensitivity to 5-fluorouracil (5-FU). To maintain the transfected clones, geneticin, 800 μg/ml, was added to the culture medium for 7 days after cells were passaged three to four times.

RNA Extraction and Reverse Transcription–Polymerase Chain Reaction

Total RNA was extracted from transfected cells using the guanidinium thiocyanate method as previously described.[15] Purified RNA was reverse transcribed in the reverse transcriptase buffer containing 0.5 mmol/L each dNTP Stratagene, La Jolla, CA), 0.8 units/μl Rnasin (Promega, Madison, WI), 0.0165 μg/μl oligo(dT), and 8 units/ml Moloney murine leukemia virus reverse transcriptase (Life Technologies, Inc.). The reaction was initiated at 42° C for 10 minutes, then continued at 37° C for 45 minutes, and was stopped at 95° C for 5 minutes. Complementary DNA of FGFR-1 isoforms was amplified from cDNA preparations with 0.05 μg/μl Taq polymerase (Molecular Biology Resources, Milwaukee, WI), 15 pmol primers, and 0.2 mmol/L each dNTP. After the samples were preheated at 95° C for 5 minutes, the amplification was performed for 35 cycles with cycling times of 94° C for 15 seconds, 56° C for 15 seconds, and 72° C for 2 minutes 11 seconds. The reaction was stopped at 72° C for 7 minutes. The sequence of the primer used for FGFR-1α was 5′-CTCTAT GCTTGCGTAACCAGCAGC-3′ and 5′-GGGTA

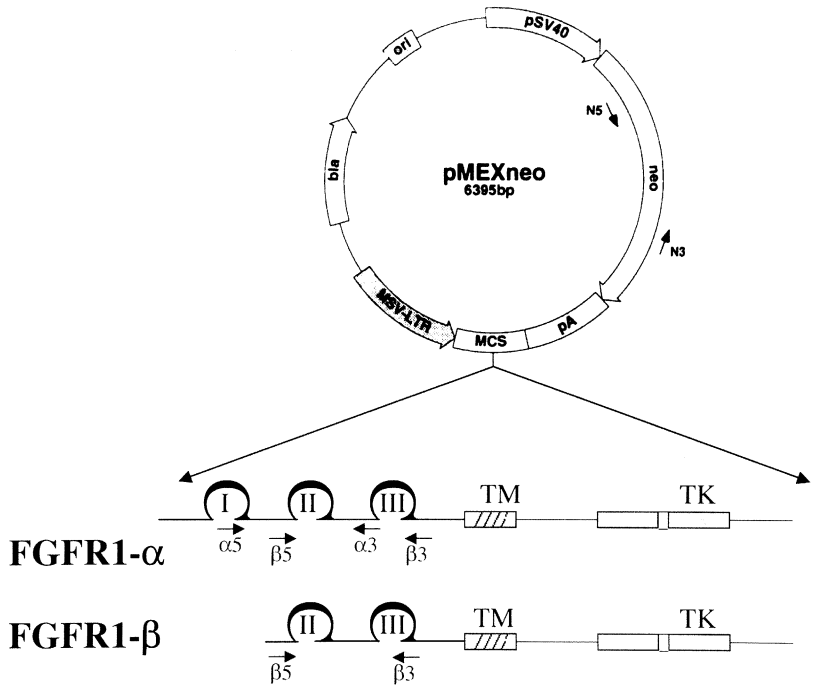

Fig. 1. Vector organization and FGFR-1 isoforms structure. TM = transmembrane; TK = tyrosine kinase; α5 and α3 = 5′ and 3′ primers for FGFR-1α isoform; β5 and β3 = 5′ and 3′ primers for FGFR-1β isoform.

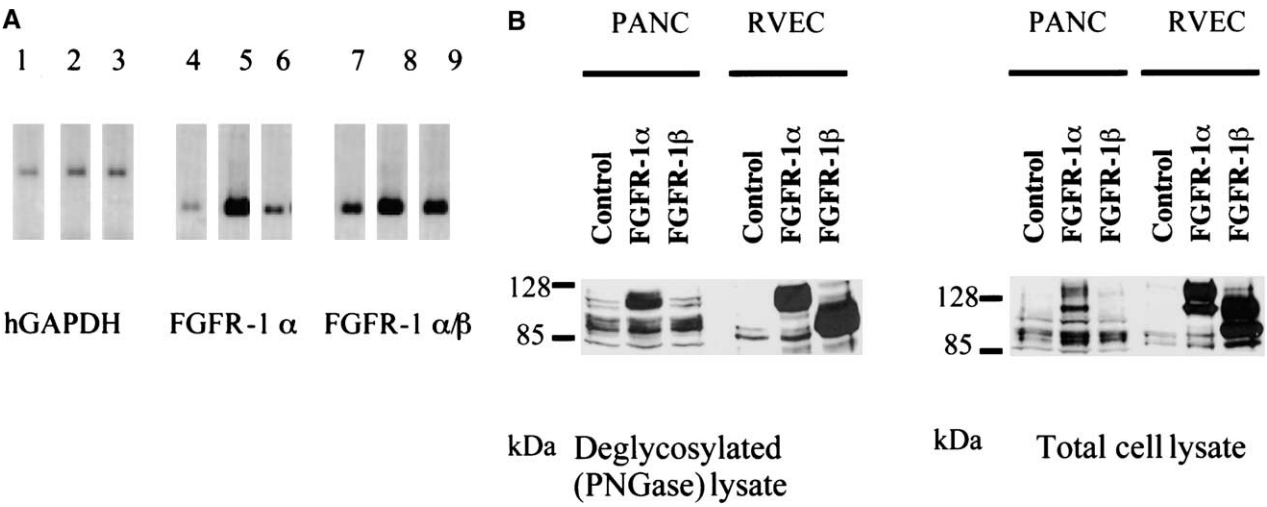

Fig. 2. Results of RT-PCR. **A**, Cells transfected with control vector had dominant expression of FGFR-1β isoform. Cells transfected with FGFR-1β isoform showed a low expression of FGFR-1α isoform. **B**, The molecular weights of expressed FGFR-1 isoforms were similar to the proteins expressed on RVEC cells. It appeared that expressed FGFR-1α isoform on PANC cells was glycosylated, and the molecular weight decreased to ~106 kDa after deglycosylation. No obvious glycosylation was detected on the expressed FGFR-1β isoform in PANC cells. Primers: pmn = 1, 4, 7; PANC-1α = 2, 5, 8; PANC-1β = 3, 6, 9.

GCAACGTGGAGTTCAT-3′. The fragment amplified included the first immunoglobulin-like loop. The sequence of the primer used to amplify FGFR-1α/β was 5′-GACAGTGAAGTTCAAATGCCC-3′ and 5′-GCTTGGCGGGTAACTCTATC-3′. Samples were analyzed with 1% agarose gel (Fig. 2, A).

FGF Stimulation and 5-FU Treatment

Transfected cells were plated and cultured in 100 mm petri dishes, 3×10^5 cells per dish. FGF-1/heparin, 50 ng/50 units/ml, was added to the culture medium daily. Two days after FGF-1/heparin stimulation, 5-FU (1 mg/ml) was added to the culture medium. Cells were maintained in the culture medium containing FGF-1/heparin for another 24 hours.

To observe the regulatory effects of FGF-1 on Bcl-x_L and BAX, transfected cells were cultured for 8 and 24 hours in the presence of FGF-1/heparin (50 ng/50 units/ml). Cells were then lysed and subjected to sodium dodecyl, sulfate–polyacrylamide gel electrophoresis (SDS-PAGE).

SDS-PAGE and Western Blotting

Cultured cells were washed with 5 ml of phosphate-buffered saline (PBS) twice and scraped with cell scraper. Cells were centrifuged and resuspended in radio immunoprecipitation assay (RIPA) lysis buffer (1% triton X-100, 0.1% SDS, 1% sodium deoxycholate, 50 mmol/L Tris/HCl, pH 7.5, and 1 mmol/L EDTA, 50 μl/1 × 10^6 cells) or triton lysis buffer (for FGFR-1 detection; Biosource, Camarillo, CA) with 1 mmol/L phenylmethylsulfonyl fluoride, 10 μg/ml leupeptine, and 10 μg/ml aprotinin. The mixture was incubated at 4° C for 30 minutes and centrifuged at 700*g* for 10 minutes. Supernatant fluid was harvested and the protein concentration was measured with a bicinchoninic acid (BCA) kit (Pierce, Rockford, IL).[16] Proteins of cell lysates were separated with 10% or 15% SDS-PAGE and transferred electronically to polyvinylidene difluoride membrane (PVDF; Millipore, Bedford, MA). After blocking with 5% nonfat dry milk in Tris-buffered saline solution with 0.05% Tween 20, membranes were probed with monoclonal antibodies against human Bcl-x_L, BAX (Southern Biotechnology Associates, Inc., Birmingham, AL), or polyclonal antibody against FGFR-1 (Santa Cruz Biotechnology, Santa Cruz, CA), followed by horseradish peroxidase–conjugated rabbit antimouse IgG antibody, or horseradish peroxidase–conjugated goat antirabbit IgG antibody. To show that expressed FGFR-1 is the product of glycosylation, cell lysate was deglycosylated using a deglycosylation kit according to the manufacturer's instruction (New England Biolab, Beverly, MA). Briefly, cell lysate, 100 μg, was denatured by heating at 100° C for 10 minutes. Cell lysate was then mixed with 4 μl of N-glycosidase (PNGase) in the buffer supplied from the kit and incubated for 1 hour at 37° C. In

this experiment, rat vascular endothelial cell line (RVEC) transfected with FGFR-1 isoforms was used as positive control specimens. The reaction was stopped by adding sample loading buffer. The results were detected using an ECL kit (Kirkegaard & Perry Laboratories, Gaithersburg, MD) and analyzed with Image J Software (National Institutes of Health).

Cell Death Detection and Caspase 3 Inhibition Test

To observe the effects of transfection of FGFR isoforms on the sensitivity of chemotherapy, we tested the cell death rate using flow cytometry after adding 5-FU to culture medium. Twenty-four hours after treatment with 5-FU, cells were washed twice with phosphate-buffered saline solution. Because of the possible apoptosis induced by cell detachment, cells were incubated with propidium iodide (PrI) (Molecular Probe, Eugene, OR), 1.25 μg/ml, in phosphate-buffered saline for 10 minutes at room temperature in the dark. Cells were washed again after incubation and were detached from dishes with cell dissociation solution (Mediatech Inc., Herndon, VA). Cells were centrifuged and resuspended in 500 μl of phosphate-buffered saline. Stained cells were analyzed using flow cytometry to detect PrI-positive cells. The experiments were performed in triplicate, and each experiment was repeated three times. Data were expressed as mean ± standard deviation.

The death of cells after treatment with 5-FU may be due to apoptosis or necrosis. Most apoptosis is induced by the activation of caspase cascade, especially caspase 3. To determine whether the cell death was mediated through an activated caspase 3 pathway, caspase 3 inhibitor (DEVD-CHO; Calbiochem, San Diego, CA), 2 μmol/L, was added to the culture medium 1 hour before 5-FU was added. Cells were then treated with 5-FU for 24 hours and the death rate was measured as described earlier. Similarly, data were collected in triplicate from three different experiments.

Tumor Inoculation

Primary PANC-1 cells transfected with FGFR-1α and FGFR-1β isoforms were maintained in DMEM medium containing 10% fetal bovine serum and FGF-1/heparin, 50 ng/50 units/ml, for 3 days. Cells were trypsinized, washed with phosphate-buffered saline, and resuspended in DMEM culture medium (7×10^6/500 μl). Cells were injected subcutaneously into Balb/C nude mice on their backs. Each mouse received 7×10^6 cells in one injection at two separate sites. Five mice were injected with each cell type. Visible masses were seen 2 weeks after the inoculation. The sizes of the tumors were then measured weekly for another 4 weeks. Mice were then killed and tumor samples were harvested for examination.

RESULTS

FGFR-1 Isoform Gene Transfection and Protein Expression

The results of RT-PCR showed that the dominant form of FGFR-1 expressed on PANC-1 cells is the β isoform (see Fig. 2, *A*). The results also showed the transfection of FGFR-1 isoforms cDNA and expression of FGFR-1 RNA and proteins were successful (see Fig. 2, *A* and *B*).

FGFR-1α Isoform Gene Transfection Increased the Sensitivity of PANC Cells to 5-FU

Twenty-four hours after treatment with 5-FU, more cell death was detected in cells transfected with FGFR-1α isoform cDNA (Fig. 3). The death rate of control cells, which predominantly expressed FGFR-1β isoform, was similar to that of the cells transfected with FGFR-1β isoform. The death rate of control cells was 9.6% ± 1%; the death rate of β isoform was 9.2% ± 1% and of α isoform was 19.6% ± 0.9% ($P = 0.0195$).

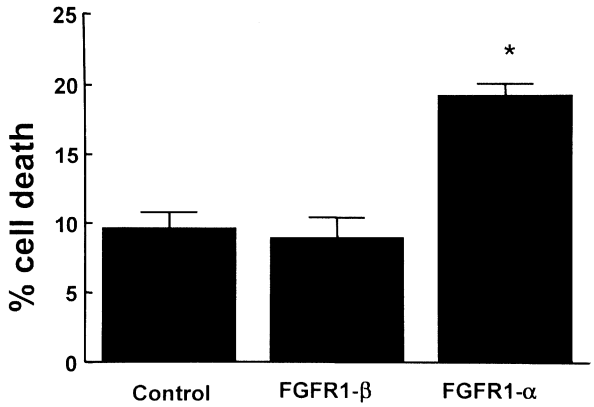

Fig. 3. Cell death detection (positive PrI-staining cells) using flow cytometry. Transfected cells were plated on 100 mm Petri dishes and treated with 5-FU after exposure to FGF/heparin for 2 days. Cells were stained with propodium iodide and examined using flow cytometry. More cell death was seen on the cells transfected with FGFR-1α isoform compared to the cells transfected with control vector or FGFR-1β isoform ($P < 0.05$).

Death of Cells Transfected With FGFR-1α Isoform Was Mediated by Activated Caspase 3

Caspase 3 inhibitor decreased the killing of 5-FU to cells transfected with FGFR-1α isoform by nearly 40% ($P < 0.05$). Caspase 3 inhibitor did not show significant changes for the killing of cells transfected with FGFR-1β isoform and vector control (Fig. 4).

Expression of BAX and Bcl-X_L Were Modulated by Transfection of FGFR-1 Isoforms

Expression of BAX was found to be slightly higher at protein level in cells transfected with FGFR-1α isoform cDNA. Treatment with FGF-1/heparin increased the expression of BAX in cells transfected with FGFR-1α. The change in Bcl-x_L was subtle and was found to be slightly higher in cells transfected with FGFR-1β isoform 16 hours after treatment with FGF-1/heparin. Cells transfected with FGFR-1α isoform showed a lower ratio of Bcl-x_L and BAX (Fig. 5). Treatment with FGF-1/heparin further decreased this ratio in cells transfected with FGFR-1α isoform cDNA (Fig. 6).

Tumor Inoculation

Transfection of FGFR-1β isoform cDNA into PANC cells induced aggressive growth of these cells in nude mice. Within a period of 6 weeks, these cells formed solid tumors in four of five mice inoculated (Fig. 7), whereas cells transfected with FGFR-1α isoform did not grow after inoculation.

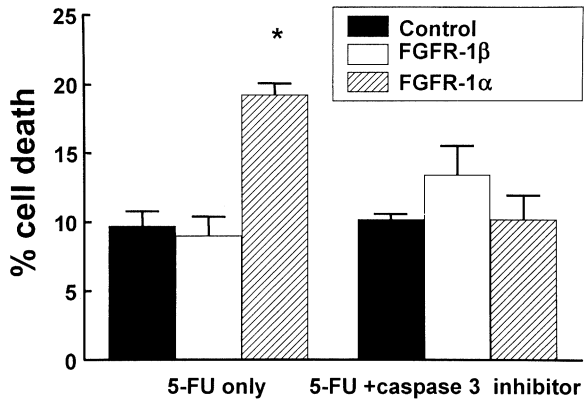

Fig. 4. Effect of caspase 3 inhibitor on cell death induced by 5-FU. Caspase 3 inhibitor (DEVD-CHO), 2 μmol/L, was added to the culture medium of transfected cells 1 hour before 5-FU was administered. Cells were then stained with propidium iodide and examined using flow cytometry. Caspase 3 inhibitor decreased the death rate induced by 5-FU on the cells transfected with FGFR-1α isoform ($P < 0.05$). There was no significant change in the cell death rate in the cells transfected with control vector or FGFR-1β isoform.

DISCUSSION

Our study showed a distinct difference in sensitivity of the FGFR-1 isoform–transfected cells to the chemotherapy agent 5-FU. Cells transfected with the FGFR-1β isoform were more resistant to 5-FU compared to cells transfected with the FGFR-1α isoform. The results also showed a more aggressive growth potential for the cells transfected with FGFR-β isoform in nude mice. Numerous reports have revealed augmented signals induced by FGF and FGFR in a variety of cancers. These augmented signals may be due to the overexpressed FGF on the tumor.[2] It may also be related to the altered isoform of FGFR expressed on these cancer cells causing increased affinity for FGF. Normally, signal transduction of the FGF family is ubiquitous, and it is essential for the development and maintenance of organ homeostasis. Previous studies have shown that the dominant FGFR-1 isoform in normal tissues is FGFR-1α and that FGFR-1β is the dominant isoform in cancer. Wang et al.[17] have proved that the binding affinity of FGF to β isoform is higher than that to α isoform. Differential binding of FGF to FGFR may greatly change the biological consequences of the interactions between FGF and FGFR. Binding of FGF induces dimerization of FGFR and subsequent phosphorylation of tyrosine kinases. Further phosphorylation of downstream kinases such as c-Src, FRS2, and FAK may produce signal propagation and may induce a variety of cellular responses.[18–21] Our laboratory has demonstrated increased c-Src activity in pancreatic adenocarcinoma and other tumors.[22–24] The overexpression of FGFR β isoforms in pancreatic adenocarcinoma may produce an alternative signaling pathway, thus allowing for increased tumor resistance. Likewise, our attempts to overexpress FGFR-1α have shown its ability to alter the cancer cell phenotype, which may indicate divergent signaling pathways between the isoforms.[25] Therefore alterations in the expressed FGFR isoform in pancreatic adenocarcinoma may play a critical role in the responses to treatment and growth behavior. The differences in phosphorylation of downstream kinases and subsequent signal transduction induced by different alternative splicing products of FGFR-1 are unknown and are the ongoing project in this laboratory.

The phenomenon that normal pancreatic tissue and pancreatic adenocarcinoma express different FGFR-1 isoforms indicates that this is a pathologic

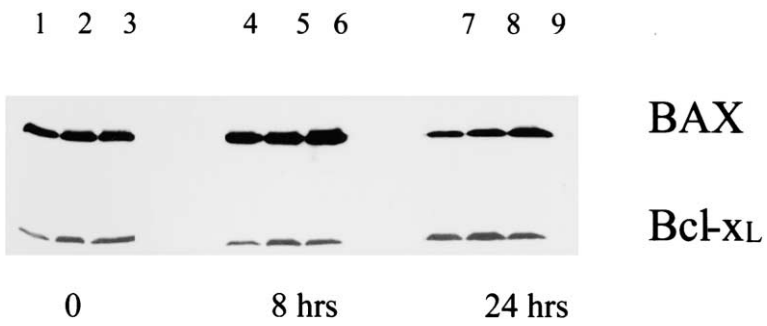

Fig. 5. Western blot of BAX and Bcl-x_L on transfected PANC cells. Transfected cells were cultured in the presence of FGF/heparin. Cell lysate was harvested at designated times. Equal amounts of proteins were loaded and separated using SDS-PAGE, and transferred electronically to the PVDF membrane. Antiapoptotic protein, Bcl-x_L, was probed using monoclonal antibody against human Bcl-x_L followed by horseradish peroxidase–conjugated goat antimouse IgG. Membranes were then incubated with stripping buffer (62 mmol/L Tris, pH 6.8, 2% SDS, 0.66% β-mercaptoethanol) for 30 minutes at 55° C. Membranes were probed with mouse antihuman BAX antibody to detect BAX after adequate washes. BAX had a higher expression on cells transfected with FGFR-1α isoform, whereas the change in Bcl-x_L was subtle and had a slightly increased expression on cells transfected with FGFR-1β isoform 24 hours after FGF/heparin treatment. FGF-1 treatment increased the expression of BAX on these cells. Control = lanes 1, 4, 7; FGFR-1β = lanes 2, 5, 8; FGFR-1α = lanes 3, 6, 9.

change that occurs during tumorigenesis. It is caused by alternative splicing of the FGFR-1 gene during RNA processing.[26] Alternative splicing of genes is a common phenomenon in many cancers.[27] It involves many different genes and is related to a variety of specific tumor characters.[26,27] The alternative splicing of FGFR-1 to produce FGFR-1β isoform in pancreatic adenocarcinoma is caused by exclusion of α-exon during RNA transcription.[26] It was postulated that the default pathway during RNA transcription is to exclude α-exon, and α-exon inclusion is highly regulated by the status of cell differentiation.[28–30] The inclusion of α-exon produces FGFR-α isoform with lower affinity for FGF and is important in well-differentiated cells.[29,30] In cancer cells with high differentiating potential, the recognition of α-exon is repressed.[28] Two repressors have been located on the FGFR-1 gene. One is a 62 bp intron sequence located 97 bp downstream from the α-exon, and another is 250 bp upstream from the α-exon.[28,31] In α-exon, a 69 bp sequence is required for α-exon inclusion and serves as α-exon inclusion enhancer.[32] It is hypothesized that the loss of regulation of these repressors and enhancers in cancer causes dominant expression of FGFR-1β isoform.[28] Modification of alternative splicing pathways may be an approach to enhance the effect of chemotherapy in cancers.[27] 5-FU is an antimetabolite drug with a false pyrimidine base. Resistance to 5-FU is related to several mechanisms such as transport, metabolism, molecular mechanism, protection from apoptosis, and resistance via cell cycle kinetics.[33] The effect of 5-FU is a combined result of these factors. In this study we focus on the apoptosis mechanism induced by 5-FU. 5-FU has been reported to cause apoptosis in the treatment of a variety of tumors.[33–35] Our results also suggest that apoptosis is involved in the death of transfected PANC cells after the use of 5-FU. PANC cells transfected with control vector and FGFR-1β isoform all present minor killing 24 hours after exposure to 5-FU. Cell death in these transfected cells cannot be inhibited by caspase 3 inhibitor, indicating that the death of these cells is caused either by necrosis or apoptosis that is unrelated to activation of caspase 3. Transfection of FGFR-1α isoform ap-

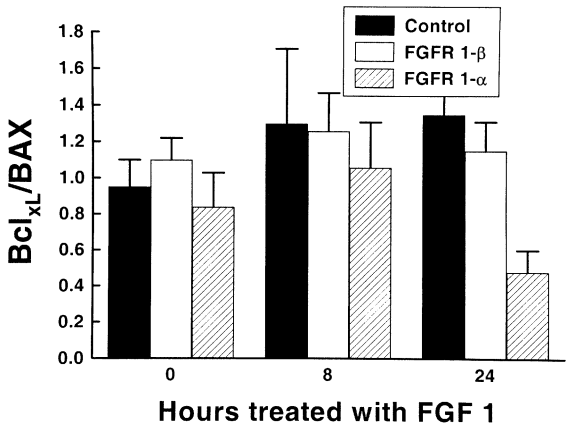

Fig. 6. Ratio of Bcl-x_L/BAX. Results from Fig. 5 were analyzed with Image J software. The area ratios of Bcl-x_L and BAX bands were plotted and showed a decreased ratio of Bcl-x_L/BAX on cells transfected with FGFR-1α isoform. FGF-1 treatment further decreased this ratio.

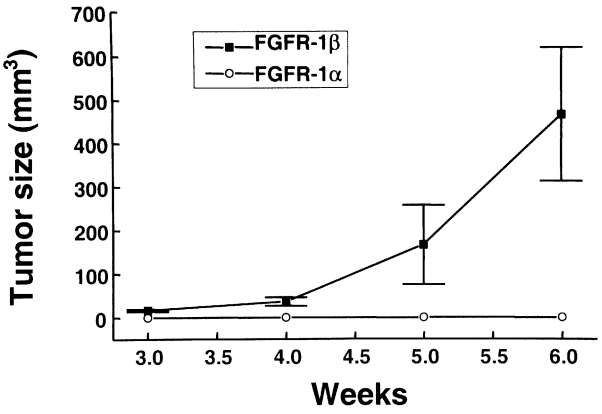

Fig. 7. Sizes of tumors inoculated with cells transfected with FGFR-1β isoform.

pears to increase the sensitivity to 5-FU by activating caspase cascade and subsequently inducing apoptosis. Caspases are a group of cysteine enzymes involved in apoptosis. Caspase precursors are constitutively expressed in living cells. During apoptosis, mitochondria release cytochrome C, and some caspase-activating proteins such as Apaf-1, via several different mechanisms.[36,37] Caspase cascade is then activated to execute cell death by proteolysis.[38] One group of proteins, the Bcl-2 family, has been studied extensively and is considered a key regulator of apoptosis. Among them, BAX is proapoptosis, whereas Bcl-x_L is antiapoptosis.[39] Bcl-x_L has been found to be expressed in many malignant tumor and has been implicated in promoting resistance to chemotherapy.[39–41] In PANC cells transfected with FGFR-1β isoform, Bcl-x_L was upregulated, whereas cells transfected with FGFR-1α isoform had lower expression. In contrast, the expression of BAX was low in the cells transfected with FGFR-1β isoform, and higher in the cells with FGFR-1α isoform. The mechanisms of these proteins in the regulation of apoptosis are not fully understood. It was postulated that the pro- and antiapoptotic proteins might form heterodimers and titrate each other's function and their relative concentrations might decide the cell fate in response to the apoptotic signals.[39] In isolated mitochondria, BAX could trigger the release of cytochrome C.[42,43] Both BAX and Bcl-x_L can form ion channels in synthetic lipid membrane.[44,45] The pore-forming activity of BAX can be antagonized by Bcl-2, another antiapoptotic protein.[45] These two proteins have distinct characteristics including ion selectivity, conductance of voltage dependence, and rectification and possess different pore activity at selected membrane sites.[44] Because the tendency of well-differentiated cells is to express the α isoform of FGFR-1,[29,30] the high expressed level of BAX in these cells may be important in controlling cell life span by promoting apoptosis. Maintaining the proper ratio of BAX and Bcl-x_L in cells may be a potential approach for increasing the sensitivity of cells to chemotherapy or even immunosurveillance. The mechanisms of the regulatory effects of FGFR-1 isoforms to Bcl-2 family proteins are unknown. Differential expressions of FGFR isoforms may induce different signal transduction pathways, affecting proapoptotic or antiapoptotic signaling in this tumor, leading to either increased tumor resistance or sensitivity to current treatment strategies. Hence altering the expression of growth factor receptors or blocking their signal with small molecules may lead to novel treatment regimens for this disease.

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An Integrated Approach to Intestinal Failure: Results of a New Program With Total Parenteral Nutrition, Bowel Rehabilitation, and Transplantation

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Intestinal failure can be treated with bowel rehabilitation, total parenteral nutrition, or intestinal transplantation. Little has been done to integrate these therapies for patients with intestinal insufficiency or failure and to develop an algorithm for appropriate use and timing. We established a multidisciplinary program using bowel rehabilitation, total parenteral nutrition, or intestinal transplantation as appropriate in a large population. Evaluation included clinical, pathlogic, and psychosocial assessments and assignment to therapy based on the results of this evaluation. Of 59 patients evaluated for life-threatening complications of intestinal failure, 68% were considered appropriate candidates for transplantation, 10% were managed with rehabilitation, and 17% were maintained on optimized long-term parenteral nutrition. Nineteen transplants were performed, with 78% patient survival and 66% graft survival. Patient survival among isolated intestine recipients was 90%. All patients managed with rehabilitation were weaned from parenteral nutrition within 6 months. Long-term management with parenteral nutrition resulted in a significant number of deaths both among patients waiting for a transplant and those who were poor candidates for transplant. Intestinal rehabilitation, when successful, is optimal. For patients with irreversible intestinal failure, isolated intestinal transplantation holds particular promise. Parenteral nutrition is plagued by high failure rates among this population of debilitated patients compared with the general parenteral nutrition population. Integration of these therapies, with individualization of care based on a multidisciplinary approach and perhaps with earlier isolated intestinal transplantation for patients with irreversible intestinal failure, should optimize survival. (J GASTROINTEST SURG 2002;6:554–562)
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KEY WORDS: Intestinal transplantation, intestinal failure, total parenteral nutrition, bowel rehabilitation

Intestinal failure can be defined as the inability to maintain fluid and electrolyte balance and/or nutritional balance without special support.[1] This diagnosis has become applicable to an increasing number of patients, as developments in medical practice have allowed individuals with short-bowel syndrome and other functional intestinal disorders to survive for extended periods. The term intestinal failure is meant to refer to an irreversible state, and the condition has been considered an indication for intestinal transplantation.

With improvements in intestinal rehabilitation, however, some patients thought to suffer from intestinal failure my actually improve; these patients are better described as having a reversible state referred to as intestinal insufficiency. Furthermore, improvements in total parenteral nutrition (TPN), remedial intestinal surgery, and intestinal transplantation have also provided new treatment options for patients once thought to have irreversible intestinal failure.[2–5] The appropriate order and timing of application of these new options is often unclear, however.

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Whereas good-risk patients may do well with either remedial surgery, intestinal rehabilitation, or intestinal transplantation, predicting failure among patients who may be poor candidates for a given therapy has been more difficult. The ability to identify factors that predict failure of a given therapy in certain patients would allow us to offer appropriate alternatives to individuals in whom the chances of success are optimal.

Several variables predicting failure of patients on different therapies have recently been recognized. These include the presence of a high jejunostomy or high parenteral lipid content (>1 g/kg/day) in adult patients on long-term parenteral nutrition.[6,7] Ultrashort-bowel syndrome (<50 cm of jejunoileum in adults), low jejunoileal–to–body weight ratio, and absence of the ileocelcal valve, to a lesser extent, have been associated with failure in patients undergoing attempts at rehabilitation.[8–10] Remedial surgery to improve transit time and transplantation in highly sensitized patients[2,11] have both been fraught with high failure rates. Although transplantation has appropriately been reserved for patients in whom more conservative therapies have failed, guidelines for timing of referral of patients—and particularly, for identification of patients who might benefit from earlier transplantation—are lacking.

In 1997 we established a program in intestinal transplantation as part of a multidisciplinary approach to the management of adults and children with intestinal failure. Our aim was to integrate all existing therapies for patients with intestinal insufficiency or failure and to develop an algorithm for clinical management. We thought that a timely move from types of therapy on which patients were faring poorly despite optimal clinical care would allow us to optimize the results of transplantation. Here we present our algorithm and preliminary results with an initial series of patients.

MATERIAL AND METHODS

Evaluation

Patients referred for consideration for intestinal transplantation underwent extensive medical, pathologic, and nutritional evaluations directed by their histories (see Tables 1 and 2), as well as psychosocial and psychiatric evaluations. Patients with short-gut syndrome were evaluated additionally by means of D-xylose measurements, stool fecal fat, and anatomic studies, as well as review of any history of infection. Patients with motility disorders underwent antroduodenal motility and anorectal manometric studies, as well as a pathology review to confirm the diagnosis. Patients with signs or symptoms of liver dysfunction underwent biopsy and standard hepatologic assessment. Patients were additionally assessed for transplant candidacy by measurement of panel-reactive antibody (PRA; sensitization to human leukocyte antigens), cytomegalovirus, and Epstein-Barr virus status. Children also underwent serologic studies for other common viral infections. Details of the criteria for candidacy for various treatments as applied to patients with short-gut syndrome or motility disorders are summarized in Figs. 1 and 2.

Candidacy for Rehabilitation. Rehabilitation was considered for any patient who demonstrated a tolerance for enteral feeding. Adult patients who were tolerating at least some enteral feeding, with more than 50 cm of healthy jejunoileum (no intrinsic mucosal disease), who were or could be put into continuity, were considered candidates for rehabilitation. Pediatric patients who tolerated continuous tube feeding and who had more than 20 cm of jejunoileum were considered for rehabilitation. Patients were considered rehabilitated only when they were free of any intravenous therapy for 3 months, with stable weight and a stable serum albumin level. Patients with motility disorders were not considered for intestinal rehabilitation, nor were patients who had failed prior aggressive attempts at feeding. Enteral nutrition was encouraged in all patients, regardless of their ability to undergo weaning from TPN. It should be noted that two adult patients (Nos. 4 and 25) were not on TPN at the time of referral, despite having less than 50 cm of jejunoileum. These patients were maintained off TPN.

Candidacy for Long-Term Parenteral Nutrition. Patients with no chance of intestinal rehabilitation who were or could be put into anatomic continuity were considered candidates for long-term parenteral nutrition. Patients with high levels of sensitization to human leukocyte antigens (PRA > 70%) and who were not candidates for transplantation were kept on parenteral nutrition. Patients with poor hygiene, psy-

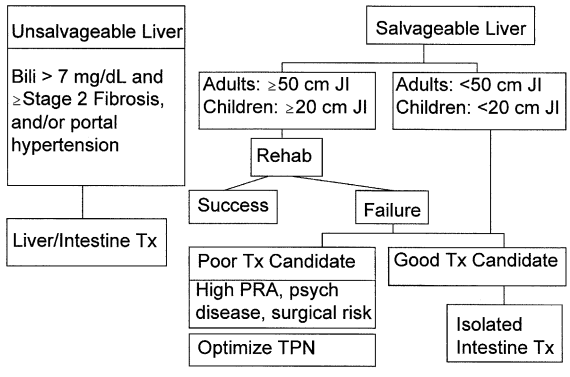

Fig. 1. Algorithm for management of patients with short-gut syndrome.

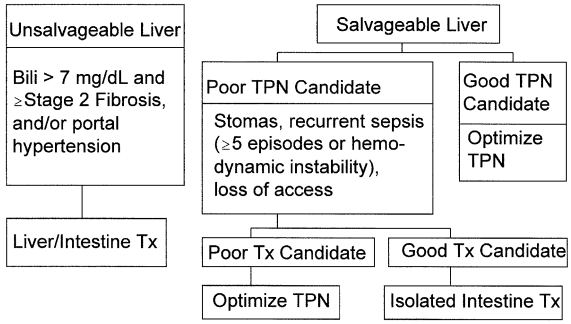

Fig. 2. Algorithm for management of patients with dysmotility or hypersecretory states.

chiatric disease, or social supports were considered poor candidates for long-term parenteral nutrition.

Candidacy for Transplantation. Patients with no chance of intestinal rehabilitation were considered for early transplantation, even in lieu of recurrent or life-threatening complications of parenteral nutrition. This generally included patients with type 1 anatomy, or what we term a "nonreconstructible gastrointestinal tract"[12]—that is, patients with no small bowel, gastrostomy, and/or duodenostomy tubes, and difficult electrolyte management. Such patients are usually hospital bound with no appreciable quality of life. Patients with line sepsis as their primary complication of parenteral nutrition were considered for transplantation if they had had more than five episodes of sepsis or had a history of hemodynamic instability with any such episodes. Most such patients referred had already had more than 10 such episodes. Patients with no prior sepsis but with thrombosis of two or more major vessels were considered for transplantation. Patients with stage 2 fibrosis or worse and patients with cholestasis resistant to alterations in parenteral nutrition (bilirubin >7 mg/dl) or signs of portal hypertension were considered for transplantation or composite organ allografts. Patients with locally unresectable central abdominal tumors causing obstruction were also considered candidates for transplantation. Those with disabling psychiatric disorders were not candidates for transplantation.

Treatment

Intestinal Rehabilitation. A slow weaning from parenteral nutrition was initiated over 6 months in accordance with improvements in gastrointestinal function. Glutamine was used as the sole tropic supplement, starting with 6 g/day orally and increasing daily over 2 weeks up to 30 g/day in divided doses as previously described by others.[3] Antidiarrheal medications (including imodium, lomotil, and tincture of opium) were used liberally in accordance with volume and type of malabsorptive symptoms. One adult patient (Table 2, patient 7), who was 3 years post resection, was additionally treated with a somatostatin analogue for a high-output jejunal fistula and rapid transit. Patients were weaned from antidiarrheal medications as tolerated, once parenteral nutrition had been discontinued for 3 months, if serum albumin and protein levels and body weight were stable.

Table 1. Characteristics of pediatric patients with short-gut syndrome at referral

				Residual intestine					
Patient	Age (mo)	Diagnosis	Liver disease*	Jejunum (cm)	Ileum	Ileocecal valve	Colon	Continuity	Therapy
1	11	NEC	Yes	15	—	—	L	Yes	Transplant
2	18	NEC	No	44		—	L	Yes	Rehab
3	8	Omphalocele	Yes	10	0	—	L	Yes	Transplant
4	3	Volvulus	No	10	0	—	L	Yes	Transplant
5	7	NEC	Yes	7	0	—	L	No	Transplant
6	7	NEC	Yes	13	0	—	L	No	Transplant
7	6	Omphalocele	Yes	10	0	—	L	Yes	Transplant
8	6	NEC	Yes	35	0	—	L	Yes	Transplant
9	24	Intestinal atresia	Yes	20	0	—	L	Yes	Transplant
10	9	Omphalocele	Yes	20	0	—	L	No	Transplant
11	18	NEC	Yes	15	0	—	L	Yes	Transplant
12	4	NEC	Yes	22	0	—	L	Yes	Transplant
13	10	Gastroschisis	Yes	12	0	—	L	Yes	Transplant
14	3	Volvulus	Yes	0	0	—	L	No	Transplant
15	12	NEC	Yes	32	0	—	L	Yes	Transplant
16	15	NEC	Yes	90	0	—	L	Yes	Transplant

NEC = necrotizing enteric colitis.
*Liver disease (bilirubin > 7 mg/dl, or clinical portal hypertension), when present, was due to TPN.

Table 2. Characteristics of adult patients with short-gut syndrome at referral

Patient	Age (yr)	Diagnosis	Liver disease	Residual intestine				Continuity	Therapy
				Jejunum (cm)	Ileum (cm)	Ileocecal valve	Colon		
1	60	Crohn's disease	*PSC	15	0	—	L	Yes	Transplant
2	41	Trauma	No	10	0	—	L	Yes	Transplant
3	56	SMV thrombosis	No	60	5	+	All	Yes	Rehab
4	34	Crohn's disease	No	30	0	—	None	No	Rehab
5	44	SMA thrombosis	No	15	0	—	L	No	TPN
6	49	Crohn's disease	Yes/HCV	90	0	—	L	No	Rehab
7	58	SMA thrombosis	No	15	0	—	None	No	TPN
8	53	SMV thrombosis	Yes/TPN	5	0	—	L	No	TPN
9	43	SMV thrombosis	No	0	0	—	L	No	Transplant
10	42	SMV thrombosis	Yes/TPN	15	0	—	L	Yes	TPN
11	32	Trauma	No	25	0	—	L	No	Transplant
12	53	PAN	Yes/TPN	15	0	—	L	No	TPN
13	24	Desmoid tumor	Yes/TPN	0	0	—	—	No	Transplant
14	32	SMV thrombosis	No	0	0	—	L	No	Transplant
15	38	Encapsulating peritonitis	No	0	0	—	L	No	TPN
16	56	SMA thrombosis	No	15	0	—	L	No	Transplant
17	39	Adhesions	Yes/TPN	15	0	—	L	Yes	Transplant
18	54	SMA thrombosis	Yes/TPN	5	0	—	L	Yes	Transplant
19	51	Crohn's disease	No	25	0	—	L	Yes	Transplant
20	65	SMA thrombosis	Yes/TPN	5	0	—	L	No	Transplant
21	42	Encapsulating peritonitis	No	5	0	—	L	Yes	Transplant
22	61	Crohn's disease	Yes/TPN/HCV	50	0	—	L	Yes	Transplant
23	49	Radiation	No	40	0	—	L	No	Transplant
24	49	Volvulus	No	15	0	—	L	Yes	Transplant
25	44	Volvulus	No	30	0	—	L	Yes	Rehab

HCV = hepatitis C virus; PAN = polyarteritis nodosum; PSC = primary sclerosing cholangitis; SMA = superior mesenteric artery; SMV = superior mesenteric vein; TPN = total parenteral nutrition.

All patients who used narcotic analgesics were evaluated by a multidisciplinary pain service and slow-weaning protocols were initiated.

Parenteral Nutrition. A standard parenteral nutrition formula was used, providing between 1 and 2 L/day for 25 to 30 kcal/kg body weight. A standard fat emulsion of either 10% or 20% was given to provide between 20% and 30% of total calories for adult patients. Amino acids of 1.0 to 1.5 g/kg body weight/day were added. This regimen was begun as a 24-hour infusion and then cycled at night to 12 to 14 hours as tolerated. Oral intake was encouraged even in patients who were not considered candidates for rehabilitation.

Transplantation. In most patients, either an isolated intestinal allograft or a composite liver–intestine allograft was transplanted; in one patient, a stomach–pancreas–small bowel graft was used. All operations were performed with the use of whole organs from cadaveric donors. Human leukocyte antigen matching was random. Isolated intestinal allografts were placed in the abdominal cavity with infrarenal aortic–to–graft mesenteric arterial inflow and systemic drainage in most cases. Proximal continuity was restored end to end, and a distal ileocolostomy with venting chimney was constructed when recipient left colon was present and functional. In combined liver–small bowel transplants, a native portocaval shunt was performed for venous drainage of the native upper abdominal viscera and composite liver–bowel grafts were used as previously described.[13] In children the infrarenal aorta was used for inflow to the graft; in adults the supraceliac aorta was used. The intact duodenum and biliary tract were transplanted with a rim of pancreas in this operation.[14] In the single patient who received a modified multivisceral graft without the liver, a large central tumor encasing mesenteric, splenic, and portal veins was resected, requiring exenteration of the stomach, pancreas, spleen, left kidney, small bowel, and right colon. A composite stomach, pancreas, and small bowel graft was placed with infrarenal aortic

inflow via a bifurcation graft of donor subclavian artery and drainage into the portal vein of the native liver, in a manner similar to that described in two previous cases.[13]

Lymphocytotoxic crossmatches were performed in all patients before transplant. Our protocol required a negative T-cell lymphocytotoxic crossmatch for isolated intestinal allografts. For composite liver–small bowel grafts, we did not require a negative crossmatch because of the resistance of the liver to antibody-mediated rejection and the purported protective effect of the liver graft over concomitantly transplanted organs.

Immunosuppression was accomplished with steroid induction (1 g methylprednisolone for adults or 20 mg/kg for children intraoperatively, then tapered in a standard manner), tacrolimus enterally from postoperative day 1, and daclizumab, 1 mg/kg intravenously every 2 weeks for 10 weeks. An aggressive prophylactic antibiotic regimen was also used (Table 3). Mild-to-moderate rejection was treated with intravenous methylprednisolone for two consecutive days. Severe rejection was treated with a 7- to 14-day course of OKT3. Post-transplant alimentation was begun early, with a preliminary tube-feeding regimen of isosmotic semielemental formula with supplemental glutamine, transitioned over 3 weeks to a modified diet with low-fat and low-nondigested cellulose. Diet was then liberalized as tolerated over time.

RESULTS

Evaluation

During the first two years of the program, 59 patients (39 adults and 20 children) were evaluated for possible intestinal transplantation. Distribution of diagnoses in adults and children is shown in Fig. 3.

Table 3. Immunosuppression and prophylaxis regimens

Immunosuppression
Tacrolimus
Daclizumab
Steroids
Mycophenolate mofetil
Negative cytotoxic crossmatch before transplant
Prophylaxis
Ganciclovir intravenously for 2 weeks, followed by CMV polymerase chain reaction
Cytogam for 12 weeks
CMV matching for seronegative patients
CMV-negative blood
Standard antibiotics

CMV = cytomegalovirus.

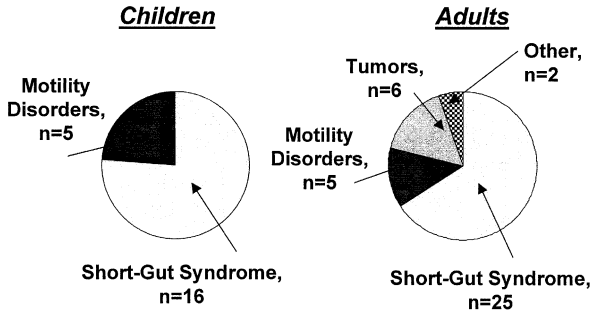

Fig. 3. Distribution of diagnoses among adult and pediatric referrals.

Disorders were categorized as short-gut syndrome (n = 41; 69%), motility (n = 10; 17%), and low-grade tumors (n = 6; 10%). Two other patients were referred for unusual indications that did not meet the criteria for intestinal failure; one had recurrent bleeding from an unknown source in the small bowel, and one had Crohn's disease but did not yet have short-gut syndrome or require parenteral nutrition.

Characteristics of pediatric (n = 16) and adult (n = 25) patients referred with short-gut syndrome are detailed in Tables 1 and 2. In pediatric patients with short-gut syndrome, the mean residual jejunal length was 22 cm. No pediatric patient with short-gut syndrome had any residual ileum or ileocecal valve, although all maintained residual left colon. Additionally, in four children, the upper gastrointestinal tract was not in continuity with the colon; these four all had end-stage liver failure at the time of referral. Overall, 14 of the 16 children with short-gut syndrome had end-stage liver disease at referral.

In adults with short-gut syndrome, the average residual jejunal length was 19.6 cm. Only one patient had residual ileum (5 cm) and an intact ileocecal valve. Fourteen (56%) of 25 adults with short-gut syndrome

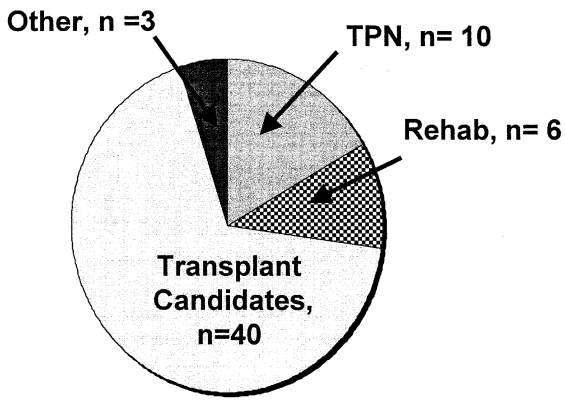

Fig. 4. Therapy recommended at completion of multidisciplinary evaluation (n = 59).

had the upper gastrointestinal tract out of continuity with the colon; seven of these patients had less than or equal to 5 cm of jejunum. Only two adults with short-gut syndrome had at least 50 cm of residual jejunum. Forty percent of adults with short-gut syndrome were referred with end-stage liver disease.

Forty patients (68%) were accepted and listed for transplantation. Six (10%) were good candidates for intestinal rehabilitation. Ten (17%) were accepted as candidates for long-term parenteral nutrition (Fig. 4). In all cases, these patients had contraindications to transplantation and were therefore placed in the parenteral nutrition arm of the study. The contraindications to transplantation were psychiatric disorder in four, high sensitization with normal liver function in two, chronic abdominal sepsis in two, and concomitant systemic disease in two (Guillain-Barré syndrome and intestinal polyarteritis nodosum). Three patients were not candidates for any therapy; two did not have intestinal failure and were not on parenteral nutrition, and one was moribund and died during preliminary transplant evaluation.

Rehabilitation Group

Five adults and one child with short-gut syndrome underwent rehabilitation, as described earlier. All but one had the gastrointestinal tract in continuity with the jejunoileum greater than 50 cm, but none had an intact ileocecal valve. One child had 42 cm of jejunoileum. One adult had hepatitis C with stage 2 fibrosis, but no signs of portal hypertension, Crohn's disease, and a midabdominal fistula through a mesh. This fistula was closed when intestinal continuity was restored, and the mesh was removed with primary reconstruction of the abdominal wall. (This was the sole remedial operation performed in our series.) The patient was then weaned from parenteral nutrition. All six patients (100%) were weaned from parenteral nutrition between 3 and 6 months from the beginning of medical therapy. All have remained free of any parenteral alimentation to current follow-up with a mean of 429 days since therapy was initiated. There were no deaths.

Parenteral Nutrition Group

Ten patients were continued on long-term parenteral nutrition. Five remain alive on chronic cycled parenteral nutrition, including one who was referred with cholestasis and fibrosis, which resolved after alterations in the parenteral nutrition formulation. Four patients died, all of sepsis. In each case, the patient received extensive line-care counseling and had experienced recurrent episodes of line-related sepsis before and after our evaluation. All patients were evaluated by hydrogen breath testing for bacterial overgrowth and empirically treated with intestinal decontamination without success. None of these deaths occurred in patients with liver disease. One patient had concurrent Guillain-Barré syndrome and was bedridden, and one patient had concurrent polyarteritis nodosum with chronic abdominal sepsis from ischemic enteritis despite prior massive intestinal resection. One patient with psychiatric disease and liver dysfunction is currently awaiting transplantation at another center.

Transplant Group

Forty patients were accepted into the transplantation program. Every pediatric patient recommended for transplantation had end-stage liver disease at the time of referral. Additionally, all adult patients recommended for transplantation had ultrashort-gut syndrome (<50 cm), and the majority (73%) also had either concomitant end-stage liver disease or a gastrointestinal tract out of continuity.

Twenty patients (50%) underwent transplantation: 18 at our center and two at other centers after double listing. Eleven patients are presently awaiting transplantation (1 for retransplantation after primary graft enterectomy). Ten (25%) died awaiting transplantation. One patient with a massive desmoid tumor and polyposis, for whom transplantation was recommended, refused the procedure and is currently alive.

Nine adults and nine children received 19 allografts at our center. Ten patients received isolated intestinal transplants, eight received composite liver–small bowel transplants, and one received a stomach–pancreas–small bowel graft with portal drainage into the native liver. In one case, an isolated intestine was transplanted into a patient with no jejunoileum who had suffered mesenteric vein thrombosis; the disease recurred after cessation of anticoagulation for minor gastrointestinal bleeding, and the patient underwent allograft enterectomy and successful retransplantation. Two other recipients of isolated intestinal allografts are alive after allograft enterectomy for severe exfoliative rejection, one of whom is awaiting retransplantation.

There have been four deaths (22%) related to transplantation. One recipient of a liver-bowel transplant died with poor early graft function; another died with primary nonfunction of the liver portion of the graft. One of our patients developed severe isolated intestinal allograft rejection and died of sepsis. The multivisceral transplant recipient died 6 months after transplantation as a result of sepsis of unclear

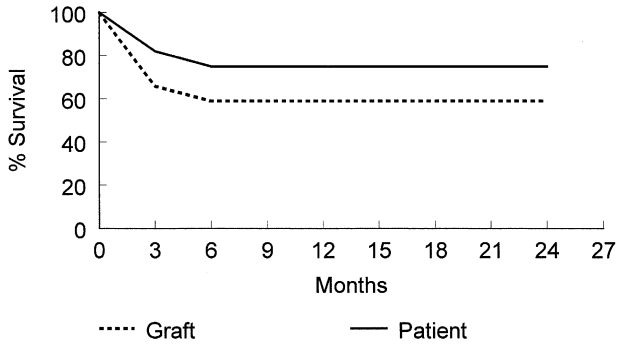

Fig. 5. Actuarial patient and graft survival for all recipients.

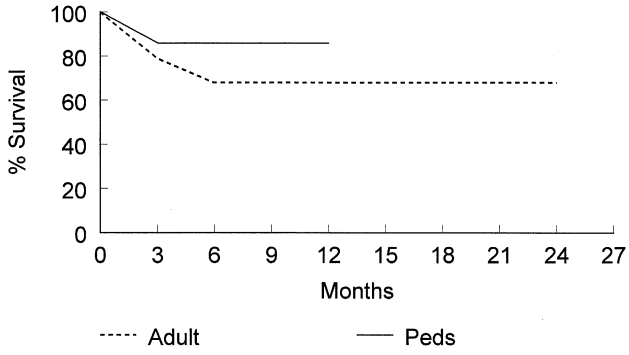

Fig. 7. Effect of candidate age on success of transplantation.

etiology after a protracted course from severe reperfusion syndrome in the native liver at transplant.

All other transplanted patients (78%) are alive and well with functioning grafts, with a median follow-up of 281 days and median allograft follow-up of 253 days (1 retransplant) (Fig. 5). No patient with a surviving graft requires any intravenous alimentation or medications, although most patients require some oral antidiarrheal medication. All children but one still receive nighttime tube feedings and daily oral intake, as they learn to eat.

Of the 40 patients accepted as transplant candidates, 10 (5 adults and 5 children) died while awaiting transplantation. Six died of line-related sepsis without liver failure, three died of line-related sepsis with severe cholestatic liver disease or cirrhosis, and one died of tumor progression after being removed from the waiting list. No patient died of liver failure without concomitant sepsis.

Overall, among the transplant recipients, children fared better than adults, and patients who received isolated intestinal allografts fared better than those who received multiorgan grafts. The high rate of death among candidates who did not receive transplants confirmed their advanced disease and inability to survive on parenteral nutrition. Kaplan-Meier survival rates for all groups are shown in Figs. 6 to 8.

DISCUSSION

Until recently, the problem of infection coupled with the need for intensive immunosuppression to maintain the lymphoid-rich intestine has made intestinal transplantation impractical. Results today, although they are improving, are suboptimal. It is clear, however, that when the small bowel is replaced successfully, near-normal gastrointestinal function is restored.[15,16] The dramatic benefit achievable with successful intestinal transplantation is the reason why interest in this treatment has persisted despite more conservative alternatives.

Until now, intestinal transplantation has been reserved for patients at the end of life who are suffering the ravages of protracted malnutrition and end-organ failure. For these patients, transplantation has been heroic salvage therapy. This point is confirmed by our finding that patients who were poor candidates for intestinal transplantation also fared poorly

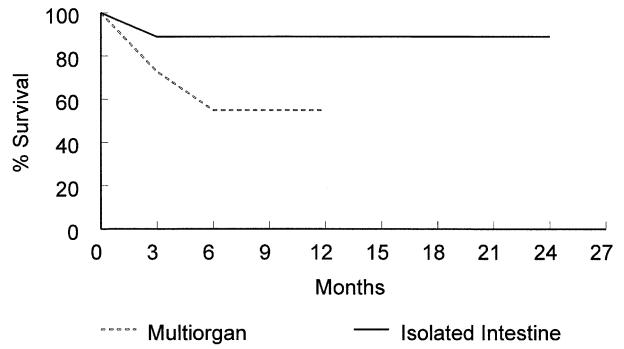

Fig. 6. Survival of patients who received either isolated intestinal allografts or multiorgan allografts.

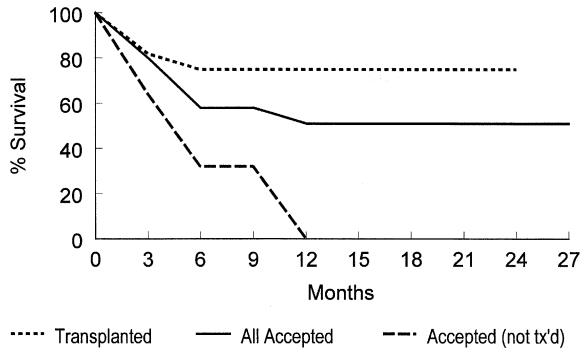

Fig. 8. Comparison of survival between patients undergoing transplantation and those accepted as candidates for transplant who did not receive an organ during follow-up (n = 40).

on parenteral nutrition. Half of these patients died during the 2 years of our program, most of line-related sepsis, despite excellent line-care teaching and home care. Additionally, 25% of patients listed for transplantation died while waiting. These patients were not fortunate enough to receive organs in a timely fashion; instead, available organs were given to patients who had greater medical urgency. Clearly, our patients who died while waiting had advanced disease and were much sicker than the standard pool of patients on parenteral nutrition with benign disease. Stable patients who are thriving on parenteral nutrition are not referred to our program. Comparisons of survival between the intestinal transplant patient population and large series that include all patients treated with parenteral nutrition are misguided, as these are two nonequivalent groups of patients.[17]

Early in our program we were reluctant to perform transplantation in patients on parenteral nutrition on the basis of recurrent line-related sepsis alone, without liver disease. Yet the majority of deaths in patients who died on parenteral nutrition or awaiting transplantation were related to this complication, even some patients with normal liver synthetic function and lack of significant cholestasis. Furthermore, recurrent line-related sepsis was not necessarily associated with poor hygiene or nonsterile technique. It appears that some patients are simply more prone to line sepsis than others. Bacterial overgrowth has been described as one such contributing factor,[18] although we were unable to confirm this as causative in our patients. Finally, the underlying diagnosis has been reported to predict the likelihood of long-term survival on parenteral nutrition, with current candidates for intestinal transplantation (patients with motility disorders, radiation enteritis, and mesenteric ischemic disorders) faring poorly on parenteral nutrition.[19]

Based on our experience, we believe that "good-risk" candidates for isolated intestinal transplantation should be offered grafts early in the course of their intestinal disease. With isolated intestinal transplants, we have achieved a high patient survival rate (near 90%), and patients can be salvaged with parenteral nutrition if they are among the one third of transplant recipients who fail. In this way, frequent death among patients on the waiting list, experienced by all intestinal transplant programs, might be avoided. With intestinal transplantation provided only as late salvage therapy, results in the overall candidate pool are poor because a high percentage die without receiving a transplant. Survival among patients who will die without a transplant might improve to an acceptable level if appropriate candidates could be identified and transplanted earlier.

Recent reports on patients with intestinal failure confirm our suspicion that those with gastrointestinal tracts out of continuity or with an ultrashort gut have poorer long-term survival on parenteral nutrition and that cholestatic liver disease associated with parenteral nutrition is more common than was previously thought.[7,10] In our algorithm, all patients with short-gut syndrome recommended for transplantation had an ultrashort gut and many were out of intestinal continuity. Current literature[6–8,10,19] demonstrates that such patients would probably remain dependent on TPN for life. Given the poor long-term survival of such patients and the high likelihood of eventual development of liver disease, we recommended isolated intestinal transplantation for these patients. It should be noted that an attempt at further intestinal rehabilitation may result in weaning from parenteral nutrition in occasional patients with ultrashort-gut syndrome (<50 cm of jejunoileum). However, this possibility must be weighed against the very real risk of death from sepsis during this process, something proven to occur frequently in our series. Additionally, glutamine should be used with caution in this population at high risk for the development of occult liver disease.

As the severe shortage of cadaveric livers worsens, transplantation of composite allografts will become increasingly difficult to justify.[20] Further, it is notable that three of our four deaths after transplantation were directly related to poor liver function in multiorgan recipients. The sole death in an isolated intestinal recipient probably could have been prevented by earlier graft enterectomy, a lesson we learned from this experience and have applied successfully since. Early graft enterectomy and cessation of immunosuppression allows rescue therapy with either parenteral nutrition or retransplantation.[21]

This series is our first attempt at developing clinical criteria to identify patients at high risk of death on other types of therapy and to improve overall survival with timely transplantation. This strategy has been applied for other conditions such as cholestatic liver diseases unrelated to parenteral nutrition.[22] An instrument such as the Mayo rating scales for primary biliary cirrhosis and primary sclerosing cholangitis[23,24] is much needed for patients with intestinal failure. We hope to decrease our rate of death from sepsis among patients on the waiting list with earlier transplantation and, in the future, with living donor transplantation for selected patients.

The ultimate indications for intestinal transplantation may be short-gut syndrome or functional disorders of the intestine before the development of severe liver disease. Notably, although our series thus far is small, patient survival after isolated intestinal transplantation

is nearly 90%, which is higher than that in patients receiving composite grafts. This finding is in contrast to reports of an immunologic advantage of multiorgan allografts. Although the liver may confer some immunologic privilege, the ability to remove a graft and use parenteral nutrition as interval salvage therapy may permit higher overall patient survival, as recently reported by Sudan et al.[25] as well. Parenteral nutrition could thus be used in a manner similar to the way dialysis is used for end-stage renal disease. Nevertheless, more timely transplantation has not led us to a higher graft survival than previously reported.[11,16]

In summary, the combination of early transplantation in good-risk candidates and rescue parenteral nutrition for failure may allow two thirds of patients to return to good functional status and the majority of the other third to be maintained on parenteral nutrition. In our algorithm, transplantation is offered to good-risk candidates who would otherwise be doomed to lifelong TPN. As intestinal transplantation continues to improve, with innovations in viral infection control and immunosuppression, we believe that a transition to this algorithm is indicated. By offering early transplantation predominantly to patients with no jejunoileum, many of whom were warehoused in chronic care facilities with no hope of any functional quality of life, we avoided underuse of intestinal rehabilitation, which carries the best prognosis of all for this debilitated population.

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Reduction of Intestinal Neoplasia With Adenomatous Polyposis Coli Gene Replacement and COX-2 Inhibition Is Additive

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Mutations of the adenomatous polyposis coli (APC) gene are implicated early in colorectal tumorigenesis. Restoration of normal APC expression through gene therapy may prevent or reduce intestinal neoplasia. Furthermore, the relationship between colorectal tumors and increased cyclooxygenase-2 (COX-2) activity provides a rationale for the use of selective COX-2 inhibitors such as rofecoxib (Vioxx) to prevent the formation of polyps. This study was performed to determine the effects of liposome-mediated APC gene therapy and a selective COX-2 inhibitor on intestinal neoplasia in vivo. Five-week-old Min mice weaned on a 30% high-fat diet were randomized to receive no treatment (control), APC only, Vioxx only, and APC/Vioxx. APC-treated mice received a plasmid containing the human APC cDNA (pCMV-APC) mixed with a liposome preparation that was administered biweekly. Vioxx was administered at 200 ppm in the high-fat rodent chow. The control mice were treated similarly with a plasmid construct lacking the APC gene. Confirmation of exogenous APC gene expression was determined by Western blot analysis. After 2 months, there was a 54% and 70% reduction in the total number of intestinal polyps after APC and Vioxx treatment, respectively. Combined APC/Vioxx therapy reduced polyp formation by 87%. The reduction of intestinal neoplasia by APC gene replacement and COX-2 inhibition suggests their separate roles in intestinal tumorigenesis. Each modality, both individually and together, may prove therapeutic and therefore contribute to new strategies in the prevention and treatment of colorectal cancer. (J GASTROINTEST SURG 2002;6:563–568.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Colorectal polyps, adenomatous polyposis coligene, gene therapy, cyclooxygenase-2 inhibition

Colorectal tumorigenesis is mediated in part by the mutation of tumor suppressor genes that maintain the normal function of gastrointestinal epithelium. The adenomatous polyposis coli (APC) gene is implicated early in the development of both familial and sporadic colorectal cancer.[1–3] Germline mutations of the APC tumor suppressor gene are found in patients with familial adenomatous polyposis coli, an autosomal dominant disorder characterized by the formation of numerous polyps throughout the gastrointestinal tract capable of malignant transformation. Furthermore, similar APC gene mutations that lead to the translation of truncated proteins are found in the majority of sporadic colorectal tumors.[4]

Whereas the inactivation of tumor suppressor genes and the overexpression of oncogenes play an important role in tumor initiation, other biochemical pathways may also be critical in promoting tumorigenesis once it has been genetically established. Prostaglandin synthesis mediated through increased cyclooxygenase-2 (COX-2) activity may be associated with decreased apoptosis and the promotion of angiogenesis in neoplastic tumors.[5–7] The relation-

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ship of colon cancer cells to increased levels of prostaglandins provides the rationale for the early use of nonsteroidal anti-inflammatory drugs (NSAIDs) as possible agents for chemoprevention. Numerous studies in animals and humans suggest that regular use of NSAIDs may prevent adenomatous polyp formation through the inhibition of COX-2 activity.[7–9]

The Multiple Intestinal Neoplasia (Min) mouse possesses a mutation of the APC gene responsible for tumor suppression, and consequently develops neoplastic intestinal polyps with elevated COX-2 levels similar to patients with familial adenomatous polyposis and sporadic colorectal cancer.[10,11] Linkage analysis and direct sequencing of this gene in the Min mouse have determined approximately a 90% homology to the human APC gene.[12] Such an animal model offers the unique opportunity to study not only familial adenomatous polyposis, but also the development of colorectal tumorigenesis from polyp formation to carcinoma in vivo.

Our laboratory has developed a method to repetitively introduce and express exogenous genes in the gastrointestinal tract using liposome-mediated gene transfection or liposomal "gene therapy."[13,14] This strategy of gene replacement has been developed to study the biologic function of normal and mutated APC genes in intestinal tumorigenesis within the Min mouse. Any loss of APC gene expression may lead to tumor formation and, therefore, restoration of APC expression early in tumorigenesis may prevent malignancy. Because higher levels of exogenous APC gene expression is not toxic to normal murine gastrointestinal epithelium, its enhanced or restored expression may lead to the cessation of polyp growth and, ultimately, the prevention of colorectal cancer.[14]

Despite observation of elevated COX-2 expression in APC mutated tumors, and the effectiveness of NSAIDs in reducing polyp formation in Min mice, there is little evidence to suggest a direct interaction of APC gene expression with prostaglandin-mediated pathways. Determining an association between the APC gene and COX-2 has important clinical implications inasmuch as it justifies the use of COX-2 inhibitors for the chemoprevention of colorectal cancer, especially in hereditary colorectal cancer syndromes. In such genetically predisposed patients, COX-2 inhibition may prevent further genetic events toward colorectal tumorigenesis. Furthermore, the method of liposomal gene therapy described here may lead to future clinical trials for the treatment of colorectal cancer, possibly in combination with COX-2 inhibitors. This report describes the cumulative reduction of polyp formation by the reintroduction of normal APC gene expression and selective COX-2 inhibition within the intestinal epithelium of the Min mouse.

MATERIAL AND METHODS

Animals

Adult male Min (C57BL/6J-*Min*/+) mice (Jackson Laboratory, Bar Harbor, Maine) were mated with normal (C57BL/6J-+/+) female mice to maintain an inbred breeding colony from which to generate animals for all experiments. Because the Min mouse is heterozygous for the Apc^{Min} mutation, offspring were screened for the Min/+ genotype at 5 weeks of age using a previously described polymerase chain reaction.[15] Mice were systematically assigned to treatment and control groups to normalize the distribution of males and females and to avoid the clustering of individual mice from single litters. The animals were housed in forced-air Thoren microisolator cages at a density of three animals per cage in 12-hour light/dark rooms within a facility accredited by the American Association for Accreditation of Laboratory Animal Care at the University of Chicago.

Diet and Drug Administration

Study mice were fed a modified 30% high-fat (lard) diet (Purina Test Diets, Richmond, Indiana) or a 30% high-fat diet plus 200 pip of the COX-2 inhibitor Vioxx (Merck & Co., Inc., West Point, Pennsylvania). The 30% high-fat diet was selected on the basis of previous studies from our laboratory that have shown a two- to threefold increase in polyp formation in Min mice fed this diet (data not shown). Food and water were freely available at all times. Mice were monitored for health every 3 days and were weighed weekly. All drug/food admixtures were prepared immediately before use, and all unused rodent diet was stored at 4° C for no longer than 3 months. Fresh diet with and without Vioxx was provided every 3 days.

Plasmid Constructs

An APC gene construct (pCMV-APC) containing a full length of human APC cDNA inserted into the *Bam*HI site of a cytomegalovirus (CMV) promoter-driven construct has been previously described.[16] The control experiments used the same plasmid backbone without the APC cDNA insert (pCMV-neo). Produced in large quantities from transformed competent *E. coli* (Stratagene, La Jolla, California), the plasmid constructs were purified

through standard anion exchange columns (Qiagen, Valencia, California).

Liposome and DNA Plasmid Transfection of Min Mice

The plasmid constructs were mixed with liposome (Lipofectin, Gibco BRL, Gaithersburg, Maryland) maintaining a plasmid DNA (20 μg):liposome (5 μl) ratio of 4:1. Before mixing, liposome was stabilized in small volumes of OPTI-MEM I medium with reduced serum (Gibco BRL) for 30 to 45 minutes at room temperature. After the addition of the plasmid, the resulting admixture was inverted several times and incubated for an additional 15 minutes at room temperature before administration. Each mouse was then gavaged transorally with the liposome-plasmid admixture using a 24 g × 1 inch feeding needle with a 1.25 mm ball tip (Popper and Sons, Inc., New Hyde Park, New York) inserted gently into the esophagus. The final volume of transfectant ranged from 0.3 to 0.5 ml per treated mouse. The mice were observed for several minutes after treatment to ensure that the transfectant was retained.

Animal Experiments

There were four experimental groups (n = 10 for each group): control, APC only, Vioxx only, and combined APC/Vioxx. Mice assigned to the control group were administered pCMV-neo biweekly for 2 months and maintained on the 30% high-fat diet. Mice assigned to the APC-only treatment arm were similarly administered pCMV-APC. For the Vioxx-only group, mice were fed the 30% high-fat diet with Vioxx for 2 months. Animals assigned to the APC/Vioxx study arm were given pCMV-APC biweekly for 2 months and maintained on the high-fat diet containing Vioxx.

Determination of Intestinal Neoplasia

After a 2-month period, the mice were killed in accordance with current National Institutes of Health guidelines. Autopsies were performed and the entire gastrointestinal tract of each mouse was removed for dissection. The stomach was omitted from the analysis because of its low tumor incidence. The small intestine was divided into two segments (proximal and distal) of equal length. The colon and small bowel segments were opened longitudinally using iris scissors and then washed extensively with 1 × phosphate-buffered saline solution. The tissues were additionally rinsed with 1 × phosphate-buffered saline and immediately examined under a Nikon stereo dissecting microscope with dark field transillumination. The number of polyps was counted on a calibrated stage micrometer.

Confirmation of Exogenous APC Expression

Tissue specimens were lysed in Trizol buffer (Gibco BRL) for protein analysis. Protein separation was performed by vertical 2% agarose gel. After overnight capillary transfer onto polyvinylidene difluoride (PVDF) membrane (Bio-Rad Laboratories, Hercules, California), hybridization using a monoclonal anti-APC (Ab-1) antibody (Oncogene Research Products, Cambridge, Massachusetts) was performed according to the manufacturer's instructions. After incubation with horseradish peroxidase–conjugated goat antimouse antibody (Bio-Rad Laboratories), visualization of the blot using the Enhanced Chemiluminescence Detection System (Amersham, Arlington Heights, Illinois) demonstrated two bands in the Min mouse: normal (full-length) APC protein at 300 kDa and mutated (truncated) APC protein at 100 kDa. Quantified by densitometry, expression of exogenous APC was determined by the increase in the full-length (300kDa) band relative to the truncated (100 kDa) band.

Statistical Methods

Results are expressed as mean ± SEM. Statistical comparisons between the different treatment groups for polyp count and Western blot quantitative values were performed by analysis of variance. A P value ≤ 0.05 was considered significant.

RESULTS

Introduction of Normal Human APC Gene Into Min Mice

The Min mouse is heterozygous for a nonsense germline *Apc* mutation, thereby expressing both full-length (300 kDa) and truncated (100 kDa) protein. Mice within the APC treatment groups after a 2-month period showed increased expression of normal human APC protein. Significantly higher levels of normal APC expression were shown by an increased ratio of full-length protein relative to the truncated protein (Fig. 1). As expected, the mice treated only with Vioxx showed no increase in normal APC gene expression as compared to pCMV-neo (control) mice. There was no apparent toxicity related to the liposomal APC gene transfections over the 2-month period. There were no deaths associated with the gavage technique.

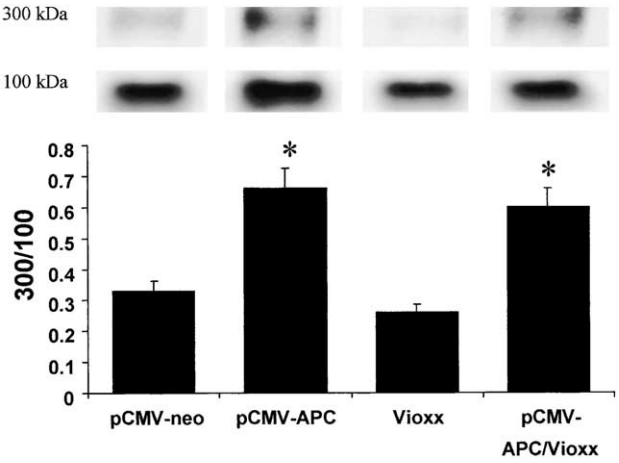

Fig. 1. Exogenous APC protein expression in the small bowel of the Min mouse. After 2 months, protein lysates from the distal small bowel of animals within each treatment arm were analyzed for APC protein expression by Western blot analysis. All mice expressed normal (full-length) and mutated (truncated) APC proteins. The presence of exogenous human APC protein was determined by an increase in the intensity of the full-length (300 kDa) band relative to the truncated (100 kDa) band through densitometry. Columns = ratio of the 300 kDa band to the 100 kDa band; bars = SEM. The increase in normal APC protein within the pCMV-APC and pCMV-APC/Vioxx groups reached statistical significance. * $P < 0.05$ vs. pCMV-neo (control) group.

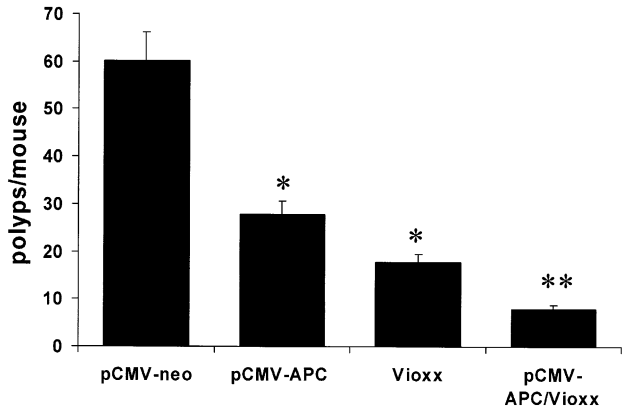

Fig. 2. Effect of APC gene replacement therapy and selective COX-2 inhibition on polyp formation in the Min mouse. The total number of polyps from all intestinal segments is represented as the mean number of polyps per mouse where n = 10 for each treatment group. After 2 months, mice were killed and the polyps were counted under a 10× dissecting stereo microscope. Columns = mean number of polyps per mouse; bars = SEM. The reduction of polyps within each treatment arm was statistically significant by analysis of variance. (* $P \leq 0.05$ vs. pCMV-neo (control) group. ** $P \leq 0.005$ vs. pCMV-neo (control) group.)

Effects of APC Gene Replacement and COX-2 Inhibition on Intestinal Neoplasia

After 2 months, small and large intestine from the Min mice were examined for intestinal polyps. Min mice treated with pCMV-APC demonstrated a 54% reduction in the total number of intestinal polyps (APC, 27.8 ± 3.4 vs. control, 60.2 ± 7.1). There was a similar reduction (70%) in polyps in the Vioxx-treated mice (Vioxx, 17.8 ± 4.2 vs. control). The combined APC/Vioxx treatment group (APC/Vioxx, 7.9 ± 1.0 vs. control) demonstrated the greatest reduction (87%) in polyps after 2 months (Fig. 2). This cumulative reduction in intestinal polyps was apparent throughout the intestine, especially in the distal small bowel (Table 1). Analysis of variances between treatment groups revealed that the sequential reduction in polyps by APC gene replacement and COX-2 inhibition was significant within all segments of the intestinal tract including the colon.

DISCUSSION

Inactivation or mutation of the APC gene occurs early in the development of colorectal cancer.[3] Several studies suggest that APC expression is closely associated with cytoskeletal protein β-catenin. APC gene mutations cause the aberrant accumulation of β-catenin, which then binds T-cell factor-4 (Tcf-4), thereby promoting overexpression of *c-myc* leading to neoplastic growth[17,18] Furthermore, when restored in APC-deficient cancer cell lines of the colon, APC gene expression will inhibit cell growth through the induction of apoptosis.[19] These results suggest that APC expression is essential for the maintenance of normal intestinal epithelium. Because any loss of normal APC function may lead to tumor formation, restoration of APC early in tumorigenesis may prevent neoplasia, in part, presumably through apoptosis. Nevertheless, like many other

Table 1. Distribution of intestinal polyps

Treatment group	Proximal small bowel	Distal small bowel	Colon
pCMV-neo	15.1 ± 1.8	43.3 ± 5.8	1.8 ± 0.4
pCMV-APC	9.7 ± 1.3*	17.1 ± 2.5†	0.7 ± 0.2*
Vioxx	6.2 ± 1.3†	10.9 ± 2.8†	0.7 ± 0.3*
pCMV-APC/ Vioxx	3.1 ± 0.7†	4.5 ± 1.1†	0.3 ± 0.2*

Values for polyp distribution indicate mean number of polyps per mouse per intestinal segment ± SEM where n = 10 for each group.
*$P \leq 0.05$ vs. pCMV-neo (control).
†$P \leq 0.005$ vs. pCMV-neo (control) by analysis of variance.

important regulators of cell growth, APC probably exerts its effects through several pathways.

Other biochemical pathways may also be critical in promoting tumor growth once tumorigenesis has been genetically established. Numerous studies in humans with familial adenomatous polyposis and in Min mice suggest that regular use of NSAIDs may prevent the formation of adenomatous polyps through prostaglandin-dependent pathways by the direct inhibition of COX-2 and/or the induction of apoptosis.[7–9] Cell-cultured enterocytes that overexpress COX-2 demonstrate decreases in cell cycle arrest and a resistance to apoptosis.[20] Conversely, increased apoptosis in colon cancer cell lines and in Min mice has been shown consistently with COX-2 inhibition through sulindac administration.[7,21] COX-2 expression has not been consistently shown to alter intestinal cell proliferation, which suggests that the primary effect of COX-2 on cell growth is related to apoptosis. Finally, intestinal cells overexpressing COX-2 show alterations in cell-to-cell adhesion and stimulate endothelial migration suggesting enhanced angiogenesis.[5]

The results presented in this study demonstrate that exogenous APC gene replacement and COX-2 inhibition can individually reduce intestinal polyps in the Min mouse. The combination of both APC gene therapy and Vioxx has a greater inhibitory effect when compared to either single-treatment arm. A comparison of the APC-treated mice with the untreated (control) group demonstrates a 54% reduction in polyp formation. Additionally, comparison between the group treated with combined APC/Vioxx and the group treated with Vioxx only shows a strikingly similar inhibitory effect (56%), which is presumably reflective of the impact of the APC gene therapy. A similar analysis comparing the Vioxx-treated group with the control group and the combined APC/Vioxx treatment group with the APC-treated group, respectively, suggests that Vioxx is responsible for approximately a 70% reduction in polyp formation. More important, this consistent inhibitory effect of either APC gene therapy or COX-2 inhibitors on polyp formation, regardless of the influence of the other treatment modality, suggests that colorectal tumorigenesis is mediated by APC and COX-2 expression through independent pathways. Furthermore, the reduction of intestinal neoplasia seen in the combined-treatment group is additive because the two treatments together produce an enhanced effect less than or equal to the sum of their separately measured individual effects.

Despite the observations of COX-2 overexpression in APC-mediated tumorigenesis and the effectiveness of NSAIDs in reducing polyp formation, there is still little evidence to support a direct interaction of prostaglandin-mediated pathways with specific genetic alterations involving the APC gene.[6,7,9] There has been indirect evidence of a potential interaction of the APC gene with COX-2 as shown by cross-breeding experiments with COX-2 knockout mice and APC-mutated strains similar to the Min mouse.[21] A successive reduction in polyp size and number was demonstrated in crossbred mice heterozygous and homozygous for loss of COX-2 expression. Furthermore, recent studies in vitro demonstrate that APC gene expression and sulindac inhibit PPARδ, a mutual target gene, thereby revealing an association between genetic alterations underlying tumorigenesis and cancer chemoprevention.[22] The effectiveness of some NSAIDs in preventing tumorigenesis could therefore be linked to genetic defects that underlie tumor initiation, and to the ability of these chemopreventive agents to counterbalance the consequences of these genetic defects. In this study the effect of Vioxx used to attenuate the phenotype of a specific APC genetic event serves as important evidence that COX-2 activity plays an important role in genetically mediated colorectal tumorigenesis.

When the results of this study are considered together, the study suggests that there may be different pathways for tumorigenesis to develop. Our results show that exogenous APC gene restoration and COX-2 inhibition can prevent tumor formation. Other studies, both in vitro and in vivo, suggest alternative pathways in which selective COX-2 inhibitors such as Vioxx are believed to prevent colorectal cancer.[6] The presence of these alternative pathways potentially enhances the role of selective COX-2 inhibitors for chemoprevention against colorectal cancer, especially in hereditary syndromes. In such genetically predisposed patients, even in the absence of COX-2 overexpression, selective COX-2 inhibitors could alter cell cycle events and thereby prevent further genetic mutations toward the development of colorectal cancer.

Continued development of effective gene replacement therapy and chemoprevention offers promising new strategies in the treatment of colorectal cancer. The most desirable genetic and chemopreventive therapies are those modalities that selectively target tumor formation and progression with minimal long-term toxicity. Reversing or correcting those alterations that occur early in tumorigenesis are of most interest in devising effective therapeutic strategies in preventing colorectal cancer. This study provides evidence that exogenous APC gene replacement and selective COX-2 inhibition can equally reduce polyp formation in the Min mouse. Furthermore, either modality in itself may lead to clinical trials in the prevention and treatment of colorectal cancer.

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Use of a Bipolar Vessel-Sealing Device for Parenchymal Transection During Liver Surgery

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Most blood loss during liver resection occurs during parenchymal transection, and multiple approaches have been developed to limit blood loss. The purpose of this study was to evaluate a new bipolar vessel-sealing device in hepatic surgery, particularly whether the device would permit safe transection without routine inflow occlusion. Twenty-seven hepatic procedures were performed using the device after preliminary studies to adapt its use to the liver. Inflow occlusion was used when necessary to control blood loss but not as a routine. The device worked well for transection through normal liver during common liver operations such as right hepatectomy. It worked less well for enucleations. Inflow occlusion was used in approximately 10% of resections, exclusive of enucleations, and about 25% of these patients were transfused during surgery or in the postoperative period. We conclude that the device is a useful tool in standard liver resections. (J GASTROINTEST SURG 2002;6:569–574) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Liver resection, bipolar cautery, liver tumor

Most blood loss during liver resection occurs during parenchymal transection. As a result, multiple approaches have evolved to reduce hemorrhage during this phase of the procedure. These may be grouped into three types of strategies—(1) those that limit blood flow through the liver during transection by prophylactic occlusion of vessels, (2) those that reduce pressure in the hepatic veins, and (3) those that prevent blood loss from blood vessels along the plane of transection during division of the parenchyma.

Techniques that limit blood flow by occlusion may limit antegrade flow through hepatic arteries and the portal veins only, or also limit retrograde flow through the hepatic veins. The most commonly used technique for limiting blood flow through the liver is inflow occlusion (Pringle maneuver). Total vascular exclusion and inflow occlusion with vascular preconditioning are variations of this method.[1] Pressure in the hepatic veins may be kept at low levels by placing the patient in the Trendelenburg position during transection and maintaining the central venous pressure at low levels, the latter by limiting the volume of intravenous infusion.[2] The original method for controlling blood loss along the line of transection was the "finger fracture" technique, in which the hand of the surgeon is inserted into the parenchyma to fracture and disperse the parenchyma and to isolate, ligate, and then divide palpable vessels. This finger fracture technique was refined over time to one in which small sections of parenchyma are sequentially isolated with a surgical instrument such as a right-angled clamp. The isolated sections of parenchyma are then ligated or clipped, usually after some clearing of the parenchyma from the vessels by an instrument. A variation of this approach is to clear the parenchyma with an ultrasonic dissector and then ligate or clip exposed vessels. Unipolar cautery and standard bipolar cautery have been used to occlude smaller vessels when using this technique; the harmonic scalpel has also been used. Manual compression of the parenchyma adjacent to the line of resection or the use of a liver clamp may aid these techniques. Another related approach is to place deep sutures along the line of resection before initiating the transection. With these techniques, resection has become quite safe and major blood loss is uncommon. Nonetheless, there is still room for improvement, and it would be desirable to have a quick and reliable means of transecting the parenchyma without using clips or ligatures, especially one that avoided routine use of inflow occlusion.

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The purpose of this report was to present our experience with a computer-controlled bipolar vessel-sealing device (LigaSure, Valleylab Inc., Boulder, Colorado). In experimental studies, the instrument has been shown to permanently occlude blood vessels as large as 7 mm in diameter by fusing the collagen matrix in the vessel wall. We have used the bipolar vessel-sealing device (BVSD) in 27 consecutive patients undergoing liver resection, without planned inflow occlusion.

METHODS

All procedures performed at a time when the BVSD (Fig. 1) was available are included in this study. The study was begun in January 2000 and completed in April 2001, but the duration of the study was approximately 10 months because the BVSD was not available to us for a 6-month interval during this time period. The terminology for liver anatomy and resections used in this report is the Brisbane 2000 terminology of the International Hepato-Pancreato-Biliary Association.[3]

The initial parts of the procedures were performed in a standard fashion, depending on the type of resection. Patients undergoing right hemihepatectomy (segments 5 to 8) or right trisectionectomy (segments 4 to 8) were prepared for parenchymal transection by isolation, occlusion, and transection of the right portal pedicle, either by dissection of individual components of the pedicle or by total pedicle division with a stapler, as described by Launois and Jamieson.[4] The liver was also dissected off the inferior vena cava, isolating and dividing caudate veins and the right hepatic vein. For lesser resections such as bisegmentectomies (two Couinaud segments) or segmentectomy (one Couinaud segment) or for enucleations, no preliminary dissection of blood vessels was used.

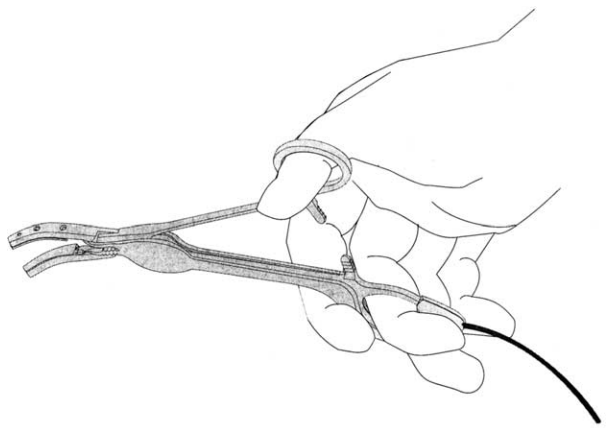

Fig. 1. Bipolar vessel-sealing device used in this study.

Inflow occlusion was not routinely used. It was instituted in the course of transection when, in the judgment of the surgeon and anesthesiologist, the degree of blood loss that was occurring was likely to result in the need for a blood transfusion. Inflow occlusion was considered once blood loss exceeded 500 ml. However, the decision to perform a transfusion was also based on other clinical factors such as the patient's preoperative hematocrit value, age, cardiac status, and hemodynamic state. For instance, larger amounts of blood loss (up to 1 liter or more) were permitted before inflow occlusion was initiated in young healthy individuals with normal preoperative hemoglobin levels than in other individuals. In the postoperative period, blood transfusions were given on the basis of the patient's age, cardiac status, and hemodynamic condition. For instance, patients with a known cardiac condition were transfused when the hematocrit value was less than 30%. On the other hand, young, healthy, hemodynamically stable patients were not transfused until the hematocrit fell below 22%.

Before the present study was initiated, a preliminary study was performed to refine the application of the BVSD to hepatic transection. Two problems were encountered when its use was first attempted in the liver. The end of each blade of the BVSD used in this study was blunt and had a cross-sectional area of 4×3 mm. Thus it was not possible to insert a blade of the clamp directly into the liver. It was also difficult to place the clamp around pieces of tissue that were isolated in the conventional way using a right-angled clamp. Attempts to do so often led to bleeding caused by mechanical trauma to small vessels. Second, after coagulation, the clamp frequently became adherent to liver tissue, and consequently, additional trauma and bleeding occurred during freeing of the clamp. Also, after the clamp was freed, it was frequently coated with coagulated liver tissue, which had to be removed from the clamp between applications, slowing the progress of the procedure.

The technique was modified as shown in Fig. 2. The first modification was to develop a technique to create a tunnel in the liver in an atraumatic fashion, into which one blade of the clamp could be inserted. This was achieved by using a "Berlisher," a clamp whose characteristics are that it has a mildly pointed tip and a shaft that broadens out rapidly to a size that is slightly larger than one blade of the BVSD. The pointed tip of the closed instrument is carefully inserted into the liver and moved forward in a gentle manner, testing by feel to find a passageway along which there is no resistance due to vessels. Its tip readily enters the liver substance and the shaft, which follows, creates a tunnel in the liver that is

wide enough to accept one blade of the BVSD. Once such a tunnel is created, the BVSD is inserted. The second modification is to crush the enclosed tissue with the BVSD several times before applying power. This has the effect of dispersing hepatic soft tissue from between the blades of the clamp, leaving the intact vessels behind. Once this is achieved, power is applied until the audible signal indicating completion of coagulation is heard. Often a second application of power is used. The BVSD is then released and the vessels, which now resemble parchment paper, are cut with a scissors. When cysts were enucleated, there was no actual parenchymal transection, but the BVSD was used to coagulate vessels entering the cyst after these vessels had been isolated using right-angled clamps. In the patient with polycystic disease, the clamp was applied to the septa between cysts, along the line of demarcation of the planned resection.

At the conclusion of the resection, the cut surface of the liver or the cyst bed was examined for bile leaks, which were sutured when identified. Drains were used only for nonanatomic resections such as cyst enucleations.

RESULTS

The BVSD was used in 27 procedures in 14 women and 13 men (median age 65 years [range 26 to 77 years]). The most common indications for surgery were metastatic colorectal cancer isolated to the liver in 13 patients and hepatocellular cancer in five patients. Two patients had metastatic neuroendocrine cancer and two had a mesenchymal hamartoma. The following diagnoses were present in one patient each: gallbladder cancer, intrahepatic gall-

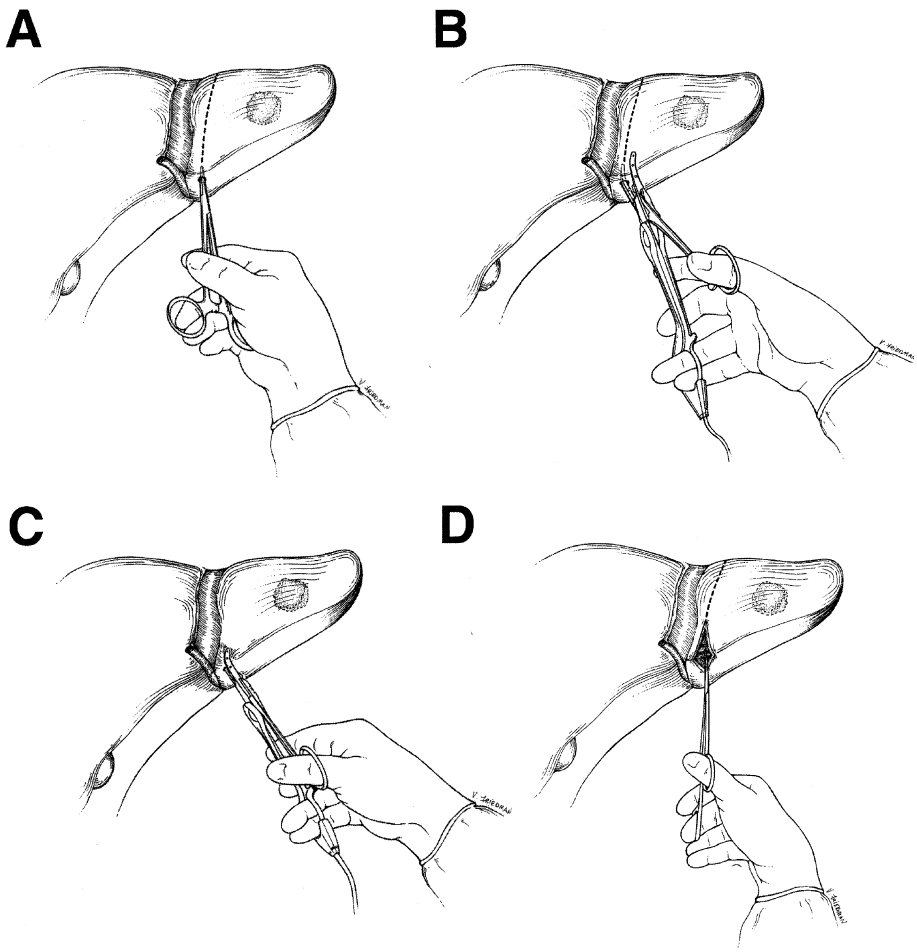

Fig. 2. Technique for use of a bipolar vessel-sealing device in hepatic surgery. **A**, A tunnel is created in the liver with a clamp. **B**, One blade of the bipolar vessel-sealing device is inserted into the tunnel. **C**, The liver parenchyma is crushed and then power is applied. **D**, After the clamp is removed, the cauterized vessels are cut with scissors.

stones, thrombosed hemangioma, polycystic liver disease, and biliary cystadenoma.

The operations performed were right hepatectomy (Couinaud segments 5 to 8) in eight patients, right trisectionectomy (Couinaud segments 4–8) in two patients, bisegmentectomy 2,3 (left lateral sectionectomy) in seven patients, and two other bisegmentectomies. Three patients had resection of one segment or less. Three patients had enucleation of hamartomas or cystadenomas, and one patient with polycystic disease had bisegmentectomy 2,3, as well as a nonanatomic resection of the dome of the right liver.

The BVSD worked effectively in the 23 procedures that required transection through normal or relatively normal hepatic parenchyma. This group included the following procedures: two trisectionectomies, eight hepatectomies, 10 bisegmentectomies, and three resections of one segment or less.

Inflow occlusion was used in 2 (9%) of 23 of these procedures. Intraoperative blood loss varied from 100 to 2500 ml with a median blood loss of 500 ml. Blood loss exceeding 1 liter occurred in 5 of 23 patients. Blood was given intraoperatively to 4 (17%) of 23 patients: 2 units of packed red blood cells in three patients and 3 units in another patient. The latter patient had had prior hepatic surgery and underwent a right hemihepatectomy for a large right hepatic tumor invading the diaphragm, part of which was also resected. Most of the blood loss in this procedure occurred before transection of the liver. Four patients were transfused within the first 48 hours after surgery. One patient who received 2 units of packed red blood cells intraoperatively received another 2 units, whereas the patient who received 3 units intraoperatively required an additional transfusion of 3 units of packed red blood cells within the first 48 hours after surgery. Two other patients who were not transfused intraoperatively received 1 and 2 units of packed red blood cells, respectively, during the 48-hour period after surgery, one within the first 24 hours after surgery. In the 10 resections of a hemiliver or more, inflow occlusion was used once and blood transfusions were given during three of these procedures. Transection of liver tissue using the BVSD was quite rapid. Although this was not a comparative study, it was quite obvious that the method was much faster than the usual techniques that employ ultrasonic dissection, or even the clamp and tie method.

The BVSD was much less effective for enucleations and in the patient with polycystic disease of the liver. Inflow occlusion was required in three of four of these patients. Recorded blood loss in these patients was 200 ml, 1800 ml, 3500 ml, and 4000 ml, respectively. Three of four patients were transfused intraoperatively with 2, 7, and 10 units of packed red blood cells, respectively. Additional blood transfusions, consisting of 1 and 2 units of packed red blood cells, were given during the postoperative period to two of these patients. The patient who received 7 units of blood had a giant cystadenoma of the right hemiliver and caudate lobe that abutted the right and middle hepatic veins intrahepatically. When inflow occlusion was instituted, it was relatively ineffective in controlling bleeding from tributaries of these veins.

In contrast to standard parenchymal transections, the tunnel technique described in the Methods section (see Fig. 2) cannot be used in enucleations. Instead, vessels entering the cyst or hamartoma must be isolated by dissection and then coagulated. These vessels are often thin walled and short, and it is difficult to position the instrument, as it is currently configured, under these vessels without injuring the vessel.

The patient who had polycystic disease received 10 units packed red blood cells. This patient had intrahepatic portal hypertension, presumably because of pressure of the cysts on the hepatic veins. After a few attempts to employ the BVSD, its use was abandoned because of failure to control bleeding from thin-walled veins in the thick fibrous septa between cysts. The procedure was continued by serial clamping and oversewing along the planned line of resection. Even with this technique, there was considerable blood loss.

Considering the group as a whole, blood transfusions were given to a total of 8 (29%) of 27 patients, 6 (22%) of 27 intraoperatively, 7 (26%) of 27 intraoperatively or within the first 24 hours after surgery, and 8 of 27 intraoperatively or within the first 48 hours postoperatively. The median number of units transfused was zero.

The 30-day mortality rate was zero. There was one postoperative death 91 days after a right hepatectomy for metastatic colorectal cancer. The patient, a 68-year-old man, had two comorbid conditions, obesity and chronic obstructive lung disease. He required ventilation for a protracted period after surgery and eventually died of pulmonary problems. There were postoperative complications in eight other patients. Mild transient postoperative confusion occurred in two elderly patients. Other complications that occurred in individual patients were atrial fibrillation and a pulmonary embolus in one patient and a urinary tract infection, prolonged ileus, and an ascites leak at a drain site, which was resolved by suture closure. The patient with polycystic liver disease developed a bile leak that resolved spontaneously. None of the other patients

developed bile leaks or evidence of postoperative blood loss.

DISCUSSION

This prospectively collected series of hepatic procedures demonstrates that the BVSD is a safe and effective instrument for transection of liver parenchyma during standard liver resections. The instrument efficiently and permanently coapts hepatic veins and arteries up to several millimeters in diameter. Although it appeared to be effective in occluding segmental portal pedicles and hepatic veins as large as the middle vein tributaries from segments 5 and 8, we did not rely on it to occlude these larger structures permanently. Instead it was our routine to oversew these larger vessels after coagulation and division. Intrahepatic biliary radicals smaller than segmental branches were not oversewn and seemed to be well sealed by the BVSD. This conclusion is made on the basis of the fact that bile leaks were recognized infrequently at the end of the transections and no postoperative bile leaks occurred in any patient who had an operation that required transection through normal or nearly normal liver tissue. The instrument appears to cause little lateral damage. The area of coagulation outside the clamp seems to extend approximately 1 ml on either side. However, we have not studied this systematically.

This study has also shown that major anatomic liver resections can usually be performed without inflow occlusion and with infrequent need for blood transfusion when the BVSD is used. Our results compare favorably with reports in which inflow occlusion was used routinely. For instance, Dematteo et al.[5] recently reported that 38% of patients in a large series of liver resections received intraoperative transfusion or transfusion within the first 24 hours after surgery. The comparative value in this study is 27%. Nuzzo et al.[6] reported on 61 patients who had liver resections under inflow occlusion or total vascular exclusion, half of which were major resections. Of these, 25 (41%) of 61 patients were transfused intraoperatively. The comparative value in this study was 22%. In a randomized controlled trial comparing inflow occlusion with and without preconditioning, 3 (25%) of 12 patients without preconditioning received intraoperative blood transfusions as opposed to none of 12 who were preconditioned.[1] Such comparisons among studies can act only as a rough guide, but the figures indicate that blood loss was no worse when this BVSD was used without routine inflow occlusion than when standard techniques for hepatic resection are used with routine inflow occlusion.

Routine use of inflow occlusion is a common practice in liver surgery.[5] It is usually safe and effective in reducing blood loss. There are circumstances where inflow occlusion may be particularly undesirable, such as when only a small volume of liver will remain or when hepatic reserve is compromised by preoperative jaundice, or in the presence of underlying liver disease, advanced age, or perhaps prolonged preoperative chemotherapy. The insult of intraoperative ischemia due to inflow occlusion adds another risk factor for poor postoperative liver function. A combination of advanced age, prolonged treatment with chemotherapeutic agents, and the need for a resection of four or more hepatic segments is not unusual in patients with metastatic colorectal cancer. Ischemic preconditioning[1] and use of short intermittent periods of inflow occlusion[5] are strategies used to limit ischemic injury during inflow occlusion. We are not recommending abandonment of inflow occlusion in hepatic surgery, but we believe it is worthwhile to work toward a technique that does not require routine use of this method but is still relatively rapid and bloodless. The BVSD seems to contribute to this goal. Most of the blood loss that occurred during the hepatic transections came as a result of oozing from the cut surface rather than from visible vessels. This type of blood loss seemed to be most prominent when patients had had prolonged periods of chemotherapy and was associated with a softening of the liver. More effective means of controlling this type of bleeding during transection are needed.

We did not find the BVSD to be effective in dealing with the short, often wide, and thin-walled veins that are found when enucleating cystadenomas and mesenchymal hamartomas. We did not enucleate any hemangiomas, but presumably the same problems would be encountered. These veins are not normal anatomic structures but dilated veins that have very little collagen in their walls. Vessel occlusion by the BVSD occurs by means of denaturation and fusion of collagen, and as a result the BVSD is relatively ineffective for very thin–walled veins. Another problem is that these veins are very easily traumatized both during their dissection and when the clamp is applied. These problems may be eliminated as new configurations of the BVSD are introduced, but the problem of lack of collagen may still be limiting. The BVSD worked particularly poorly in the patient with polycystic liver disease. It was unable to attain hemostasis of the high-pressure veins within thick fibrous septa between some of the cysts. Cirrhosis is another condition in which inflow occlusion may be undesirable, but our experience in the patient with intrahepatic portal hypertension due to poly-

cystic disease suggests that it will not be useful if intrahepatic portal hypertension is present in a patient with cirrhosis.

Some practice is required for the use of the BVSD, but the learning period is short. When the tissue in the clamp is very thin, the current may short circuit across the tips and the error signal will sound. This can usually be overcome by relaxing the pressure on the tissue. The coagulated tissue line is approximately 2 to 3 mm in diameter and slightly curved like the clamp. Once the clamp is removed, care must be taken to cut within the edges of the coagulated tissue.

A preliminary report on use of the BVSD in six patients undergoing liver surgery appeared in the literature as we were completing our study.[7] The technique used was quite different from ours in that the ultrasonic dissector was used to clear liver tissue from vessels prior to coagulation with the BVSD. We had also attempted this approach but found it very much slower than simply crushing the tissue as described in our report.

In summary, the BVSD allows safe transection of hepatic parenchyma during standard liver operations. Inflow occlusion and blood transfusions are needed infrequently when this method is used. Postoperative bleeding or bile leaks were not encountered. The BVSD was much less effective for controlling vessels when enucleating cysts, and was ineffective in a patient with polycystic disease and portal hypertension.

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Effect of Intraoperative Cholangiography During Cholecystectomy on Outcome After Gallstone Pancreatitis

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Acute gallstone pancreatitis has traditionally been managed by early cholecystectomy with intraoperative cholangiography (IOC). To evaluate the effect of IOC on patient outcome, we analyzed all patients operated on for acute gallstone pancreatitis at our institution over a 3-year period. A total of 200 patients (37 open, 163 laparoscopic) were evaluated. Nineteen of 34 patients who underwent preoperative endoscopic retrograde cholangiopancreatography (ERCP) were found to have common bile duct (CBD) stones. The 59 patients who underwent cholecystectomy with IOC had significantly longer operative times compared to the 141 patients who underwent cholecystectomy alone (167 vs. 105 minutes for open [$P = 0.008$] and 89 vs. 68 minutes for laparoscopic [$P < 0.0001$] operations). Of the 59 patients who underwent IOC, only nine (15%) had abnormal cholangiograms, and CBD exploration in seven revealed stones in four patients, edematous ampullae in two, and no abnormality in one. Six of eight patients (5 IOC, 3 no IOC) who required immediate postoperative ERCP were noted to have CBD stones. Patients who underwent IOC had significantly longer postoperative hospital stays (3.8 vs. 2.0 days [$P = 0.007$]). The incidence of retained CBD stones following surgery was similar (5.1% IOC, 2.8% no IOC). Although 7 of 122 patients who underwent laparoscopic cholecystectomy without IOC were readmitted, only one was found on ERCP to have a retained CBD stone. Age, sex, preoperative days, procedure type, and biliary-pancreatic complications after discharge did not differ significantly between patients with and without IOC. We conclude that IOC in patients operated on for acute gallstone pancreatitis results in a longer operative time and a prolonged postoperative course, but has no effect on the incidence of retained CBD stones. (J GASTROINTEST SURG 2002;6:575–581.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Cholecystectomy, cholangiography, gallstone pancreatitis

It is generally agreed that biliary or gallstone pancreatitis is caused by either a transient or persistent obstruction of the ampulla of Vater by biliary calculi. Although the clinical course of the pancreatitis is usually self-limited and benign, significant adverse outcomes with mortality rates approaching 9% have been reported.[1] Because of this, treatment of acute gallstone pancreatitis usually includes timely surgical removal of the gallbladder in hopes of preventing further attacks and removal of any residual calculi from the extrahepatic biliary tract. As surgical and endoscopic technology and experience have evolved over the past decade, recommendations for preoperative endoscopic evaluation and treatment of common bile duct (CBD) stones have ranged from mandatory and urgent endoscopic retrograde cholangiopancreatography (ERCP) in all cases[2] to, more recently, selective preoperative ERCP for stone removal based on clinical presentation and laboratory values.[3–5]

The surgical treatment of acute gallstone pancreatitis has also evolved, especially in this era of minimally invasive techniques. Studies have demonstrated that with increasing reliance on laparoscopic techniques, coupled with preoperative or postoperative ERCP, hospital stays and CBD explorations have significantly decreased in the past few years.[6] Because of the perceived risk of retained CBD calculi, traditional teaching has been that patients who did not meet the criteria for preoperative ERCP should undergo mandatory intraoperative cholangiography (IOC) at the time of surgical removal of the gallbladder.[4,6] However, over the past several years

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we have become increasingly impressed with the infrequency with which routine IOC demonstrates CBD stones at the time of surgery in patients with acute gallstone pancreatitis. It has been well demonstrated that routine IOC in patients with acute cholecystitis or cholelithiasis, especially those undergoing laparoscopic cholecystectomy, should probably be abandoned because of its low yield and significant rate of false positive cholangiograms.[7] Because of this, in our practice, we have become extremely selective in the performance of IOC in patients with acute gallstone pancreatitis to the point where it is now performed very uncommonly. The purpose of this study was to document the outcome of a management regimen in patients with acute gallstone pancreatitis that does not include IOC.

PATIENTS AND METHODS

We retrospectively analyzed the medical records of all patients operated on for acute gallstone pancreatitis at the Olive View–UCLA Medical Center, a Los Angeles County public hospital, from January 1, 1996 through December 31, 1998. The diagnosis of acute gallstone pancreatitis was based on the following criteria: (1) upper abdominal pain and tenderness; (2) elevation more than threefold in either the serum amylase level (>285 U/L), the serum lipase level (>790 U/L), or both; and (3) documentation of gallstones on ultrasonography. Specifically excluded were patients with acute pancreatitis from other etiologies, acute or chronic cholecystitis, cholangitis, or cholelithiasis without acute gallstone pancreatitis. The records were reviewed for age, sex, presenting symptoms and time course, laboratory findings (both on admission and within 24 hours of surgical removal of the gallbladder), preoperative, intraoperative, and postoperative findings and/or procedures, length of hospital stay, and complications. The information extracted was analyzed and comparisons were made using Fisher's exact, Student's *t*, Pearson's correlation, and logistic regression tests. Differences were considered significant at $P < 0.05$.

RESULTS

For this 36-month period, 200 patients were diagnosed and treated for acute gallstone pancreatitis at our facility. This represents 13.7% of all patients operated on for gallstone disease during this time. The 29 men and 171 women had a mean age of 36.9 years (range 14 to 72 years). All patients complained of abdominal pain, with two thirds of them reporting epigastric pain (radiating to the back in 35%), 22% reporting right upper quadrant pain (6 of whom that stated the pain radiated to the back), and the remaining 11% reporting more generalized abdominal pain. Seventy-five percent of the patients also reported nausea with vomiting, whereas another 9% stated that they had nausea alone. These symptoms were present for a mean of 1.8 ± 1.3 days (range 0.5 to 7 days). The mean length of hospitalization from admission to cholecystectomy was 5.3 ± 3.0 days (range 1 to 26 days), whereas the mean time from surgery to discharge was 2.5 ± 3.3 days (range 1 to 26 days). The admission and immediate preoperative laboratory values for all patients are shown in Table 1. There was a very significant decrease in all of the laboratory values between hospital admission and surgery.

All 200 patients underwent cholecystectomy with no deaths. Thirty-seven patients (18.5%) had open cholecystectomy (either primarily or after conversion from laparoscopic cholecystectomy), whereas the remainder underwent laparoscopic cholecystectomy. Fifty-nine patients (29.5%) underwent IOC, whereas 141 (70.5%) did not. Of these 141 patients, 30 had had a previous ERCP and no IOC was deemed necessary. The remaining 111 patients therefore had neither preoperative nor intraoperative ductal imaging. Table 2 summarizes the demographic and oper-

Table 1. Admission and immediate preoperative laboratory values for all patients

Test	Mean admission value ± SD (range)	Mean immediate preoperative value ± SD (range)	*P* value
Amylase (U/L)	1222 ± 1391 (57-9087)	124.7 ± 119 (11-850)	<0.0001
Lipase (U/L)	13,708 ± 15,680 (92-88,385)	644 ± 846 (28-5728)	<0.0001
Alkaline phosphatase (U/L)	182.6 ± 119.6 (33-787)	140.2 ± 84.7 (39-555)	<0.01
AST (U/L)	246.2 ± 244.8 (11-1632)	82.1 ± 67.8 (14-473)	<0.001
ALT (U/L)	323.5 ± 262.2 (17-1204)	154.8 ± 127.8 (15-822)	<0.001
Total bilirubin (mg/dl)	2.2 ± 1.6 (0.3-9.2)	1.3 ± 1.0 (0.4-7.2)	<0.001
White blood cells ($\times 10^3/mm^3$)	12.3 ± 5.0 (4.3-34.2)	9.0 ± 3.7 (2.0-28.8)	<0.001

ALT = alanine aminotransferase; AST = aspartate amino transferase; SD = standard deviation.

Table 2. Comparison of demographic information of patients based on whether or not IOC was performed

	IOC (N = 59)	No IOC (N = 141)	*P* value
Age (yr)	38.2 ± 16.3	36.3 ± 12.6	0.41
Sex (M/F)	10/49	19/122	0.52
Prehospital symptoms (days)	1.7 ± 1.3	1.8 ± 1.3	0.72
No. of OCs/length of operation (min)	18/167.2 ± 85.9	19/104.7 ± 27.2	0.008
No. of LCs/length of operation (min)	41/88.5 ± 27.2	122/68.2 ± 23.6	<0.0001
Preoperative hospitalization (days)	5.4 ± 3.6	5.2 ± 2.7	0.67
OC/LC	6.2 ± 5.7/5.2 ± 2.2	4.4 ± 1.9/5.4 ± 2.8	0.72/0.22
Postoperative hospitalization (days)	3.8 ± 4.6	2.0 ± 2.4	0.007
OC/LC	7.5 ± 6.5/2.2 ± 2.3	5.0 ± 4.8/1.5 ± 1.3	0.22/0.06

IOC = intraoperative cholangiography; LC = laparoscopic cholecystectomy; OC = open cholecystectomy.

ative information on these groups of patients. In both groups IOC significantly increased the operative time, but it should be noted that the operative times reflect the entire operation including six open and one laparoscopic CBD explorations. Interestingly, although there was a significant difference in the postoperative hospital stay between the IOC and no IOC groups, when the patients were stratified according to type of operation, the significance of the difference vanished. There was no significant difference between the IOC and no IOC groups with respect to the remaining demographic information.

Very early in the study time frame, four patients in the IOC group had undergone preoperative ERCP with clearance of stones, but the surgeon decided to perform IOC anyway to make certain all stones had been removed. An abnormality was noted in only 9 (15.2%) of the 59 patients who underwent IOC. No flow into the duodenum was observed in two patients and seven were noted to have filling defects consistent with CBD stones. CBD exploration performed in seven of these patients (6 open common duct explorations and 1 transcystic laparoscopic procedure) demonstrated only ampullary edema in both patients with no flow into the duodenum and no abnormality in one of the patients with a filling defect, whereas the other four patients with filling defects had stones successfully removed. The remaining two patients with filling defects found during laparoscopic cholecystectomy with IOC had stones successfully removed by immediate postoperative ERCP. Thus IOC was falsely positive in only one patient inasmuch as six patients had stones and two patients had edematous obstruction of the ampulla. Six of the nine patients with an abnormal IOC had undergone open cholecystectomy and all six had also had open CBD explorations, which revealed CBD stones in three of them (Table 3). Two of the patients who had open CBD explorations also required postoperative ERCP to correct problems noted on postoperative T-tube cholangiography (1 tube dislodgement with bile leakage requiring a stent and 1 complete CBD obstruction from a kinked tube, which was removed and replaced with a stent.

In the immediate postoperative period, defined as the time between cholecystectomy and hospital discharge, a total of eight patients underwent ERCP. As noted earlier, two of these ERCP procedures were because of concern about problems with the operatively placed common bile duct T-tubes, whereas two more were for removal of known CBD stones demonstrated on IOC. Four patients (1 IOC, 3 no IOC) underwent ERCP because of persistence of preoperative symptoms. In all four patients the stones were successfully removed. Following discharge from the hospital, an additional eight patients (1 IOC, 7 no IOC) underwent ERCP for recurrent upper abdominal pain. Only one patient from the no IOC group demonstrated retained stones, which were successfully removed. The remainder of the studies were normal (see Table 3). In summary, in

Table 3. Circumstances surrounding documentation of CBD stones

	IOC (N = 59)	No IOC (N = 141)
CBD stones documented	9 (15.3%)	21 (14.9%)
Preoperative ERCP	4 (6.8%)	30 (21.3%)
CBD stones found	2 (3.4%)	17 (12%)
Operative CBD exploration	7 (11.9%)	0
CBD stones found	4 (6.8%)	0
Postoperative ERCP	5 (8.5%)	3 (2.1%)
CBD stones found (known)	2 (3.4%)	0
CBD stones found (retained)	1 (1.7%)	3 (2.1%)
Postdischarge ERCP	1 (1.7%)	7 (5.0%)
CBD stones found (retained)	0	1 (0.7%)

CBD = common bile duct; ERCP = endoscopic retrograde cholangiopancreatography; IOC = intraoperative cholangiography.

Table 4. Comparison of laboratory and demographic data in patients based on documented presence of CBD stones

	CBD stones (N = 30)	No CBD stones (N = 170)	*P* value
Age (yr)	31.8 ± 11.7	37.9 ± 13.9	0.03
Sex (M/F)	3/27	26/144	0.44
Prehospital symptoms (days)	2.2 ± 1.8	1.7 ± 1.2	0.13
Admission laboratory values			
Amylase (U/L)	985.5 ± 934.6	1264.3 ± 1455.3	0.18
Lipase (U/L)	13,206.9 ± 18,055.9	13,797.2 ± 15,275.7	0.85
Alkaline phosphatase (U/L)	221.7 ± 133.0	175.7 ± 116.1	0.06
AST (U/L)	327.3 ± 311.9	231.7 ± 228.9	0.12
ALT (U/L)	416.4 ± 273.5	306.9 ± 257.5	0.04
Total bilirubin (mg/dl)	2.9 ± 1.6	2.0 ± 1.5	0.005
White blood cells ($\times 10^3$ mm^3)	10.7 ± 4.6	12.1 ± 5.0	0.09
Preoperative hospitalization (days)	5.1 ± 2.0	5.3 ± 3.1	0.68
Postoperative hospitalization (days)	3.1 ± 2.7	2.4 ± 3.4	0.30
Operation type (OC/LC)	8/22	29/141	0.22

Abbreviations as in Tables 1, 2, and 3.

the no IOC group, only four patients (2.8%) who had retained CBD stones could be identified in the postoperative period.

A total of 30 (15%) of the 200 patients were proven to have CBD stones either by CBD exploration or ERCP stone extraction. Table 4 compares demographic and laboratory information for these patients and those in whom no CBD stones could be demonstrated. As is shown, patients proven to have CBD stones were, as a group, younger and had higher total bilirubin and alanine aminotransferase values on admission. The remaining differences were not significant.

Thirteen in-hospital complications occurred in 11 patients. These were quite varied and included problems such as preoperative development of acute respiratory distress syndrome, postoperative multisystem organ failure, and retained CBD stones following surgery. These are listed in Table 5. In addition, 10 other patients were readmitted to the hospital from 2 days to 10 months postoperatively for wound infection and development of pancreatic pseudocyst (n = 1) and recurrent upper abdominal pain similar to their initial presentation (n = 9), eight of whom required ERCP to rule out retained CBD stones as noted earlier. These patients are also included in Table 6.

Our evolving clinical practice with regard to IOC is shown in Table 7. As can be seen, the frequency with which we performed IOC decreased from over 55% in 1996 to 9% in 1998. In addition, open cholecystectomy decreased from 25% to 9% of cases within the same time frame. The frequency with which preoperative ERCP was performed varied little during the 3 years, but the frequency of postoperative ERCP definitely trailed downward.

Table 5. In-hospital complications in patients operated on for gallstone pancreatitis

Complications	No. of patients
Preoperative	
Slow resolution of large peripancreatic phlegmon	1
Development of acute respiratory distress syndrome	2
Development of delirium tremens	1
Septic shock	1
Intraoperative	
Injury to cystic duct—common duct junction during laparoscopic cholecystectomy requiring conversion to open cholecystectomy and placement of T-tube	1
Postoperative	
Tracheostomy for ventilator support	1
Multisystem organ failure	1
Recurrent or continued preoperative symptoms necessitating ERCP	4
Bile leakage requiring ERCP stent placement	1

DISCUSSION

Pancreatitis due to gallstones accounts for approximately 40% of all cases of pancreatitis and currently accounts for up to 90% of cases of acute pancreatitis occurring in the United States.[8] Because eradication of the gallbladder and any stones in the CBD prevents further attacks of pancreatitis, the treatment of acute gallstone pancreatitis has traditionally included

Table 6. Reasons for hospital readmission and findings

Reason for readmission	LC/OC	IOC	Time from surgery	ERCP	Stones
Wound infection; pancreatic pseudocyst	OC	Yes	10 days	No	No
Recurrent abdominal pain	LC	No	10 mo	Yes	Yes
Recurrent abdominal pain	LC	No	6 wk	Yes	No
Recurrent abdominal pain	LC	No	7 wk	Yes	No
Recurrent abdominal pain; nausea; ↑ lipase	OC	Yes	4 mo	Yes	No
Recurrent abdominal pain	LC	No	4 mo	Yes	No
CBD obstruction from T-tube with cholangitis, recurrent abdominal pain	OC	Yes	3 wk	Yes	No
Recurrent abdominal pain; nausea; vomiting	LC	No	2 days	No	No
Recurrent abdominal pain; ↑ lipase; ↑ liver function tests	LC	No	5 mo	Yes	No
Recurrent abdominal pain; nausea	LC	No	1 wk	Yes	No

Abbreviations as in Tables 2 and 3.

surgical removal of the gallbladder once the pancreatitis has resolved. This is coupled with the performance of some type of procedure to ensure that the CBD is free of gallstones that could trigger a recurrence of the pancreatitis.[8] Because of this risk of recurrence of pancreatitis or other biliary-pancreatic complications, which was reported to be as high as 87% in one recent study,[9] early performance of the cholecystectomy (defined as within 1 week of admission to the hospital) has become the accepted standard.[6,10,11] Paradoxically, although the likelihood of biliary and/or pancreatic complications directly increases with increases in the preoperative time interval, the frequency with which stones can be expected to be found in the CBD decreases with increasing preoperative time. The magnitude of this decrease has been reported to range from 70% at the time of admission to less than 20% by hospital day 4.[12] Our own experience demonstrated that after an average of 5.3 days in the hospital, only 11 (6.6%) of the 166 patients who did not meet the criteria to undergo preoperative ERCP were ultimately found to have CBD stones.

One of the areas of significant change over the past decade has been the method of CBD visualization in patients with acute gallstone pancreatitis. In the era of open cholecystectomy, performance of IOC was mandatory. As the era of minimally invasive surgery has progressed, mechanisms other than IOC for duct visualization have been proposed. Urgent mandatory preoperative ERCP was initially not only touted as the optimal method of ensuring that the CBD was free of stones, but was also thought to offer the best opportunity for successful removal of the gallbladder laparoscopically.[13] However, more recent studies have suggested the definite superiority of a more selective approach to the use of preoperative ERCP.[14,15] This has been predicated on the fact that the frequency with which CBD stones are actually found on mandatory ERCP is low, and the small but real complication rate of ERCP. Even employing a selective approach to the performance of preoperative ERCP, nearly 45% of the patients in our own series who underwent preoperative ERCP were noted to have no stones in the CBD.

Table 7. Practice evolution in treatment of patients with gallstone pancreatitis

Procedure	1996 (N = 48)	1997 (N = 74)	1998 (N = 78)
OC + IOC	10 (20.8%)	8 (10.8%)	0
OC no IOC	2 (4.2%)	10 (13.5%)	7 (9.0%)
LC + IOC	17 (35.4%)	18 (24.3%)	7 (9.0%)
LC no IOC	19 (39.6%)	38 (51.4%)	64 (82.1%)
Preoperative ERCP	7 (14.6%)	10 (13.5%)	17 (13.0%)
Postoperative ERCP	3 (6.3%)	4 (5.4%)	2 (2.6%)

Abbreviations as in Tables 2 and 3.

Over the past several years, even the selective approach to preoperative ERCP in patients with acute gallstone pancreatitis has continued to evolve. Currently the absolute indication for performing preoperative ERCP is typically a specific admission value. Based on our experience, we believe that the absolute indications recently proposed by Soetikno and Carr-Locke[5] of a serum bilirubin level greater than 5.0 mg/dl on admission and/or severe cholangitis are the most appropriate. Recognizing that patients without these findings can still have CBD stones, especially in light of our finding of a significant elevation in the admission serum bilirubin level in patients with proven CBD stones, we would also propose a relative indication for the performance of preoperative ERCP. This would be an admission serum total bilirubin level of 3.0 to 5.0 mg/dl *and* ultrasonographic evidence of CBD dilatation (which others have defined as an internal diameter >8 mm). The coupling of both these absolute and relative indications for preoperative ERCP should be able to identify, and treat

via papillotomy, the vast majority of patients with persistent CBD stones during the preoperative period. An additional benefit would be that such an expectedly low likelihood of persistent CBD stones should obviate the need for IOC at the time of cholecystectomy.

Our finding of a true positive rate of just over 8% in these patients with acute gallstone pancreatitis who underwent IOC does not differ significantly from the frequency with which asymptomatic unsuspected CBD stones were historically noted on IOC.[16,17] Because the consequences of these stones in these patients have been minimal, both in the open and laparoscopic cholecystectomy eras, mandatory IOC is being increasingly discouraged, and the performance of either an operative or endoscopic procedure to remove these stones has been shown to have little specific benefit.[7,17] These studies of patients with acute gallstone pancreatitis confirm our findings that despite IOC, the frequency of retained CBD stones postoperatively (either in the immediate postoperative period or following hospital discharge) is not significantly different from that in patients who did not undergo IOC. Similar to our results, the performance of IOC did not significantly alter the likelihood of a retained stone. Therefore, the logical conclusion is that it is not necessary to perform IOC at the time of cholecystectomy. Endoscopic and laparoscopic ultrasonographic evaluation of the extrahepatic biliary tree has been recently touted for its ability to identify CBD stones. Although we have no experience with this technique, reports of greater than 90% sensitivity and specificity have been recently published.[18]

Our practice of performing ERCP in the immediate postoperative period in those patients who did undergo IOC and have continued or recurrent symptomatology is supported by others.[9,11] It is interesting to note that the results of these studies echo our own in that whether or not a patient undergoes open or laparoscopic cholecystectomy (each with or without IOC), there was no significant difference in the frequency with which retained stones were found. It can be argued that performing IOC would allow easy recognition of those patients who definitely have CBD stones who would benefit from elective postoperative ERCP and would also theoretically rule out retained stones as a cause of recurrent symptoms in the postoperative period in those patients with a normal IOC. However, these suppositions do not agree with our experience, because one can never completely exclude a retained stone as a cause of recurrent symptomatology, even in a patient with a normal IOC. Thus postoperative ERCP would be required whether or not IOC was performed. This argument is particularly cogent in patients who have a recurrence of upper abdominal pain following discharge. Regardless of the type of surgical procedure performed, whether or not IOC was performed, or even whether ERCP with papillotomy was performed, endoscopic investigation of the CBD will be necessary because the possibility of a retained stone always exists. Therefore whether or not IOC is performed has altered neither the postoperative nor the postdischarge management of patients with acute gallstone pancreatitis with recurrent symptoms.

CONCLUSION

We believe the most appropriate management of patients with acute gallstone pancreatitis is early laparoscopic cholecystectomy with no IOC when their symptoms have subsided, coupled with preoperative ERCP in specifically selected patients. We recommend as an absolute indication for preoperative ERCP the presence of severe cholangitis and/or an admission serum bilirubin level greater than 5.0 mg/dl, and as relative indications for preoperative ERCP an admission serum bilirubin value between 3.0 mg/dl and 5.0 mg/dl with underlying ultrasonographic evidence of CBD dilatation. From our data it is expected that the conversion rate to open cholecystectomy from laparoscopic cholecystectomy should be less than 10%. Since no IOC would be performed, there will be a significant decrease in both operative time and postoperative hospitalization. Patients with either a continuation of preoperative symptoms or recurrent symptoms following discharge from the hospital should undergo investigation of the CBD by ERCP (with concomitant papillotomy if necessary).

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Systemic Response in Patients Undergoing Laparoscopic Cholecystectomy Using Gasless or Carbon Dioxide Pneumoperitoneum: A Randomized Study

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In general, laparoscopic cholecystectomy produces a surgical stress response very similar to which occurs after open cholecystectomy. The question is whether the pneumoperitoneum constitutes a significant pathophysiologic trauma, which might be followed by profound changes in the stress response. We conducted a prospective, randomized trial involving 50 consecutive patients scheduled for laparoscopic cholecystectomy, who had a body mass index equal to or less than 30 kg/m^2 with no acute cholecystitis, pancreatitis, or liver or renal disease. These patients were randomized to undergo either the gasless (GLC, n = 24) or the carbon dioxide pneumoperitoneum (CLC, n = 26) procedure. Perioperative assessment of cortisol, insulin, glucose, and C-reactive protein levels was the main determinant of outcome. During the operative procedure, significantly higher levels of serum cortisol and insulin were found in the CLC group than in the GLC group ($P < 0.05$). No difference in glucose levels was observed between the two groups. The inflammatory response was moderate in both groups. However, on postoperative day 1 the median C-reactive protein level was significantly higher in the GLC group than that in the CLC group ($P < 0.05$). Carbon dioxide and the positive intra-abdominal pressure during conventional laparoscopy may contribute to the activation of the surgical stress response. (J GASTROINTEST SURG 2002;6:582–586.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Pneumoperitoneum, gasless, laparoscopy, stress response, cholecystectomy

Surgical injury is followed by changes in the immune, endocrine, and inflammatory responses; together these constitute the stress response.[1] Within open surgery the responses apparent are proportional to the degree of injury[2] and are supposed to be correlated with the subsequent clinical development of complications.[3,4] Laparoscopic cholecystectomy causes less deterioration of postoperative pulmonary function and less postoperative pain in comparison to open cholecystectomy, and the recovery time is shorter after laparoscopic cholecystectomy.[5] However, in general, laparoscopic cholecystectomy produces a stress response very similar to that which occurs after open cholecystectomy.[5,6] The question is whether the pneumoperitoneum constitutes a significant pathophysiologic trauma, which might be followed by profound changes in the stress response. It is documented that carbon dioxide (CO_2) pneumoperitoneum induces complex hemodynamic changes that consist of substantial increases in mean arterial pressure, cardiac index, and systemic and pulmonary vascular resistance.[7] It may be hypothesized that the soluble CO_2 and the enhanced sympathetic outflow, mediated by afferent impulses resulting from the distention of the peritoneum, may stimulate the stress response.

Recently a number of mechanical elevators of the anterior abdominal wall have been developed to perform gasless laparoscopy[8] in an attempt to profit from the minimally invasive approach without inducing the pathophysiologic changes associated with CO_2 pneumoperitoneum.[9] This new mechanical method makes it possible to compare the pathophysiologic effects of laparoscopic surgery, performed with and without CO_2.

This study compares the pattern and magnitude of the intraoperative and postoperative systemic responses in patients randomly assigned to undergo either conventional laparoscopic cholecystectomy (CLC) or gasless laparoscopic cholecystectomy (GLC).

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MATERIAL AND METHODS

Patients

Fifty consecutive patients with symptomatic cholecystolithiasis who fulfilled the inclusion criteria were randomly allocated to either the CLC or the GLC group. The allocation sequence was generated by random numbers using Documenta Geigy software (Copenhagen, Denmark) . Patients were randomly allocated by opening sealed envelopes on the day of the operation. The intervention assignments were unknown to the patients and the nursing staff of the ward. The data were collected from December 1, 1998, to October 1, 1999. Informed written consent was obtained from all elective patients over the age of 18 years with a body mass index equal to or less than 30 kg/m^2. Patients with acute pancreatitis, cholecystitis, cholangitis, blood diseases, rheumatic diseases, acute infectious diseases, and renal or liver diseases were excluded from the study. The study was approved by the local ethics committee.

Anesthesia

To avoid interference with pulmonary or circulatory function, patients were not premedicated. Local anesthetic (bupivacaine 0.25%) was injected before the insertion of the ports (total 10 ml) and subdiaphragmatically (20 ml) after the gallbladder had been removed. Anesthesia was induced with 2.5 mg midazolam and a bolus injection of 2.5 mg/kg propofol intravenously. Patients were given a 5 μg dose of fentanyl during the first hour of anesthesia and another 2.5 μg/kg in the ensuing hours; both doses were administered intravenously. Patients were ventilated by means of a Servo 900 C respirator (Siemens, Solna, Sweden) with a tidal volume of 7 ml/kg, frequency of 12/min, and FIO_2 of 0.30. An antiemetic dose of Ondansetron (4 mg intravenously) and ketoprophen (100 mg) was given 30 minutes before the expected time of extubation. Patients were given a combination of 2.5 mg neostigmine and 0.4 mg glycopyrron at the end of the anesthesia to prevent postanesthetic relaxation. Postoperatively, ketoprophen (100 mg bid) and paracetamol (1 g qid) were given as a standard dose. Morphine injections were given when requested by the patient and recorded in the patient's chart.

Operations

Three surgeons experienced with CLC and GLC performed all operations. In the CLC group, the laparoscopic cholecystectomy was performed using conventional CO_2 pneumoperitoneum at a pressure of 12 mm Hg; two 10 mm ports and two 5 mm ports were used as well. In the GLC group, two curved steel needles were inserted into the subcutaneous space and attached to a mechanical arm affixed to the operating table (Laparotensor, L&T, E. Lucini, Milano, Italy). A minilaparotomy (15 mm) was performed through the umbilicus. An unvalved 10 mm port was inserted along with one 10 mm and two 5 mm unvalved ports. By elevating the abdominal wall, a working chamber was created and cholecystectomy was performed using identical techniques and instrumentation. Cholangiography was not routinely performed. However, in two patients (one from the CLC group and one from the GLC group) cholangiography was performed to determine the presence of bile duct stones. Perioperative complications such as bleeding and perforation of the gallbladder were recorded. Gentamicin, 240 mg, was given to all patients 1 hour before the procedure.

Postoperative Course

Pain and activity levels were scored daily by the patients. Nausea, dizziness, fatigue, pneumonia, wound complications, and fever were recorded daily for 14 days.

Blood Collection and Processing

Blood samples were obtained from a forearm vein by fresh venipuncture on admission (phase 1), after induction of anesthesia (phase 2), after CO_2 insufflation/traction and introduction of the laparoscope (phase 3), 30 minutes after introduction of the laparoscope (phase 4), 10 minutes after exsufflation of CO_2/traction (phase 5), four hours after extubation (phase 6), and 24 hours postoperatively (phase 7). A 21 G butterfly cannula was inserted, and Monovette plastic vacuum tubes (Sarstedt, Numbrecht, Germany) containing 1+9 0.106 mol/L sodium citrate and Stabilyte (Sarsted, Numbrecht, Germany) tubes with 1+9 0.5 citrate buffer, pH 4.3, were filled. Brief stasis was applied to optimize venipuncture but released before the tubes were filled, and the first tube was discarded. Samples were cooled in melting crushed ice without being handled. Blood was centrifuged within 30 minutes at 4° C and 2000×*g* for 20 minutes, and serum was kept at −80° C until analysis.

Assays

The effects on the intraoperative and postoperative endocrine metabolic responses were assessed by measuring serum insulin (s-insulin), serum glucose (s-glucose), and serum cortisol (s-cortisol) levels. The inflammatory response was assessed by measuring serum C-reactive protein. Serum insulin was measured by a commercially available kit, Dako Insulin (Dako Diagnostics Ltd., Cambridgeshire, U.K.). The measuring

Table 1. Patient data

	Conventional laparoscopic cholecystectomy (n = 26)	Gasless laparoscopic cholecystectomy (n = 24)
Median age (yr)	52 (range 29–75)	49.5 (range 29–71)
Male/female ratio	8/18	7/17
Median body mass index (kg m^{-2})	26 (range 20–30)	27 (range 23–30)
Median duration of operation (min)	78 (range 45–170)	102 (range 40–210)
Median hospital stay (days)	1 (range 1–31)	1 (range 1–3)

range was 22 to 396 pmol/L. Intra- and interassay coefficients of variation were 3.0% and 8.0%, respectively. Cortisol was measured by Orion Diagnostica Cortisol (Orion Diagnostica, Espoo, Finland), a commercially available kit. The measuring range 10 to 2000 nmol/L. Intra- and interassay (coefficients of variation were 3.4% and 7.6%, respectively. s-Glucose was measured automatically by a routine glucose oxidase method (Vitros 950, Johnson & Johnson, Rochester, New York). C-reactive protein levels were measured by turbidimetric immunoassay.

Statistics

The unpaired Mann-Whitney U test was used to compare the data in the two study groups (CLC and GLC). Friedman's analysis was used to detect changes with time within each group. Data are expressed as median and upper and lower quartiles. P values of < 0.05 were considered significant. Patient data were included in the analysis until the time of conversion to open cholecystectomy. Data from patients in the GLC group who were converted to CLC were analyzed in accordance with intention to treat.

RESULTS

Clinical Data and Perioperative Course

The two groups were comparable with regard to age, sex, body mass index, duration of the operation, and length of hospital stay (Table 1). The trial profile is outlined in Fig. 1. Three patients in the GLC group were converted to open cholecystectomy because of a poor overview resulting from empyema and chronic inflammation of the gallbladder. One patient in the CLC group was converted to open surgery because of chronic cholecystitis and Mirizzi's syndrome. No statistically significant difference was found in conversion rates ($P = 0.136$).

In the GLC group, one patient with empyema of the gallbladder was converted to CLC because of difficulties in exposing the triangle of Calot. The patient was discharged on postoperative day 3 and had an uneventful course.

In the CLC group, one patient developed bile leakage from an accessory duct, which was complicated by intra-abdominal abscess formation. The patient was treated by endoscopic stenting and drainage of the abscess. The patient was discharged after 31 days. No major intraoperative or postoperative complications occurred in either group.

Convalescence

The period until complete relief of pain was achieved was 5 days (range 1 to 15 days) in the GLC group and 8 days (1 to 15 days) in the CLC group ($P > 0.05$). The period until return to full activity was significantly shorter in the GLC group (6 days [range 1 to 15 days])

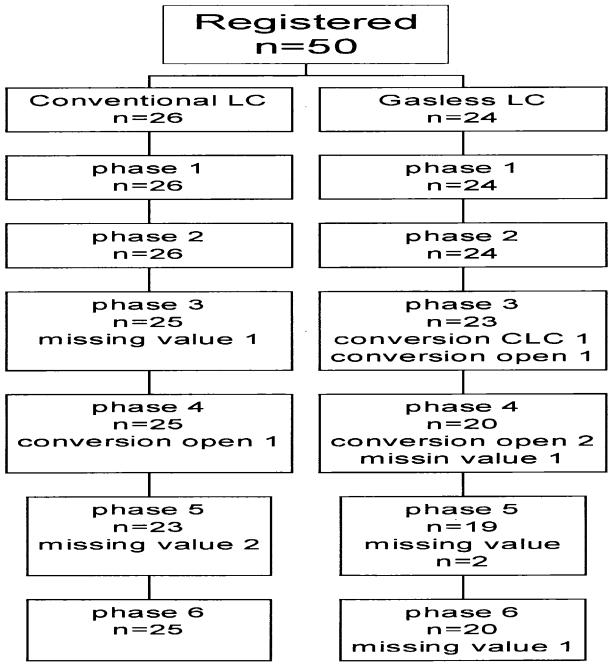

Fig. 1. Trial profile. CLC = conventional laparoscopic cholecystectomy; LC = laparoscopic cholecystectomy.

than in the CLC group (6 days [range 1 to 15 days] vs. 8.5 days [range 2 to 15 days]; $P < 0.05$). No difference was found between the groups with regard to fatigue, dizziness, nausea, and overall satisfaction with the outcome of the operation.

Stress Response

Changes in s-cortisol are shown in Fig. 2, *A*. In the CLC group there was a significant increase during the operation. In the GLC group the s-cortisol decreased significantly during the first phase of the operation, followed by a steady increase ($P < 0.05$). A significant difference was found between the two groups in phases 3 and 4. Immediately after operation, the s-cortisol level decreased significantly in both groups. No significant difference was found between the two groups on postoperative day 1. Comparing preoperative values with postoperative values, no difference was found in either group.

Changes in s-insulin are shown in Fig. 2, *B*. During the operation the s-insulin level increased significantly and then decreased immediately after surgery. In both groups the s-insulin levels were significantly increased on postoperative day 1 as compared to the preoperative levels in both groups. During the operation, a significant difference between the two groups was observed only in phase 4.

Changes in s-glucose are shown in Fig. 2 *C*. The pattern followed that of s-insulin, with a significant increase during the operation and a significant decrease postoperatively. No difference between the two groups was found. Changes in C-reactive protein levels are shown in Fig. 2 *D*. Preoperatively and during the operation, the median values were less than 10 in both groups. Postoperatively, the C-reactive protein levels increased significantly in both groups. On postoperative day 1, the C-reactive protein level in the GLC group was significantly higher group than that in the CLC group.

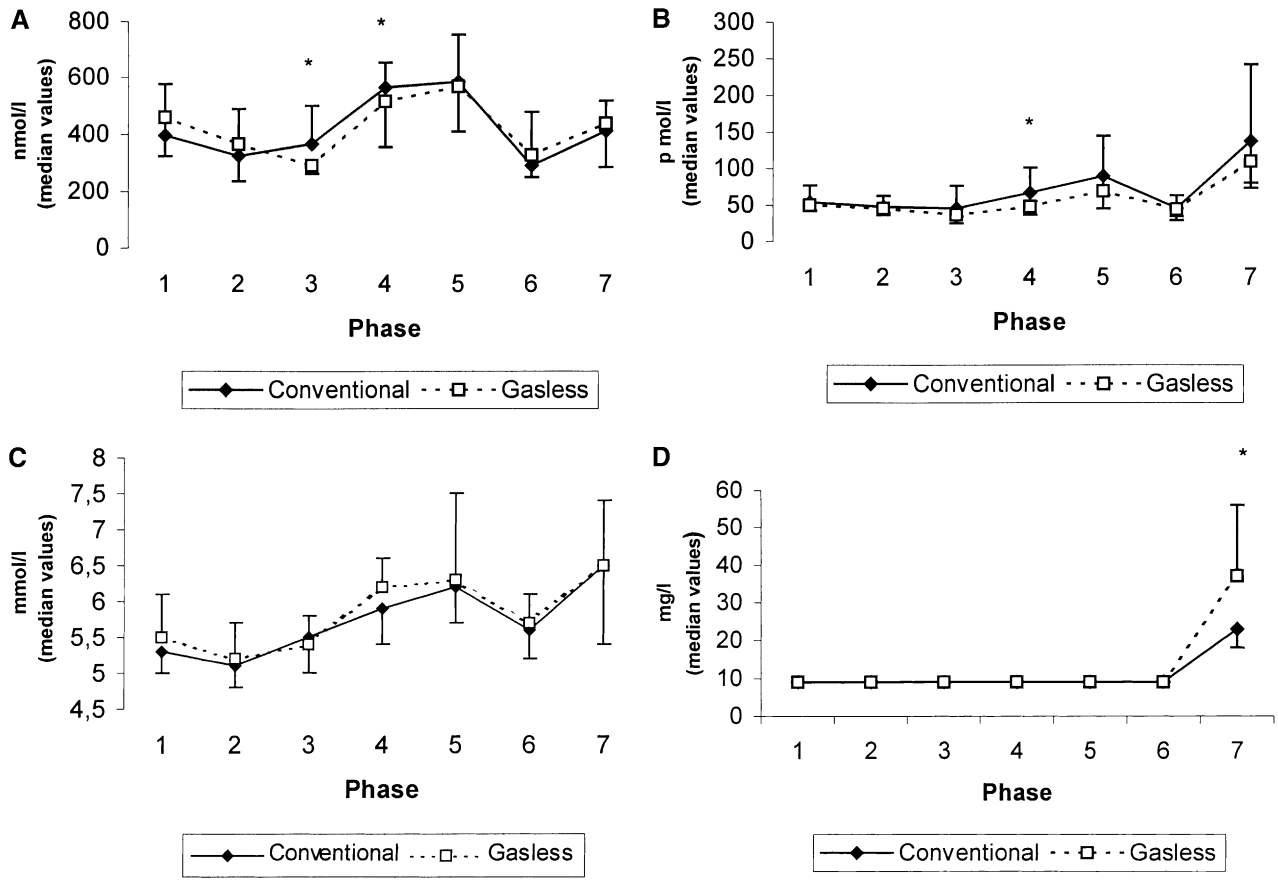

Fig. 2. Changes in serum cortisol (**A**), serum insulin (**B**), serum glucose (**C**), and C-reactive protein (**D**) levels. Phase 1 = preoperatively; phase 2 = after induction of anesthesia; phase 3 = after CO_2 insufflation/traction and introduction of the laparoscope; phase 4 = 30 minutes after introduction of the laparoscope; phase 5 = 10 minutes after exsufflation of CO_2/release of traction; phase 6 = four hours after extubation; phase 7 = 24 hours postoperatively. Median values; *$P < 0.05$.

DISCUSSION

During the operation, reduced endocrine and metabolic responses were observed in the GLC group compared to the CLC group. Postoperatively, however, the inflammatory response was more pronounced in the GLC group.

The stress response has been investigated in several studies comparing laparoscopic and open surgery in an effort to explore possible physiologic differences that might be of clinical importance.[6,10] To date, no major differences in the endocrine, metabolic, or immune response have been observed in favor of the laparoscopic procedure.[6] In a randomized study comparing laparoscopic and open cholecystectomy, Ortega et al.[10] did not demonstrate any difference in levels of cortisol or adrenocorticotropic hormone between the two groups. On the contrary, the serum levels of epinephrine, antidiuretic hormone, and glucose were higher intraoperatively in the laparoscopic group. One explanation for these results might be that the stress response is stimulated by the CO_2 pneumoperitoneum. Other studies have observed increasing concentrations of vasopressin and catecholamines during laparoscopy using CO_2 pneumoperitoneum.[11,12] The effects of abdominal distention with CO_2 are complex and may combine endocrine, metabolic, and inflammatory responses, direct mechanical compression effects, and changes induced by absorbed CO_2.

In a randomized study comparing conventional CO_2 with a combined abdominal wall lift and CO_2 insufflation for laparoscopic cholecystectomy, Koivusalo et al.[13] showed a significant increase in the plasma noradrenaline concentration in both groups, although the increase was slightly higher in the CO_2 group.[14]

Comparing GLC with CLC, Koivusalo et al.[9] found an increasing concentration of noradrenaline and epinephrine during the operation in both groups, with no differences between the two groups. However, the hemodynamic response of the GLC group was more stable with reduced blood pressure and heart rate as compared to that of the CLC group. The release of catecholamines can be inhibited by the use of clonidine, thereby improving the hemodynamic response during laparoscopy.[12] Clonidine has no effect, however, on the release of cortisol and vasopressin.[12] Thus the increasing concentration of cortisol is not secondary to the catecholamine and blood pressure responses observed during CO_2 pneumoperitoneum.

The fact that in our study the s-cortisol and s-insulin levels in the CLC group increased intraoperatively suggests that the intraoperative endocrine and metabolic stress responses may be influenced by the pneumoperitoneum.

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Detecting Blunt Pancreatic Injuries

Robert L. Cirillo, Jr., M.D., Leonidas G. Koniaris, M.D.

Pancreatic injury after blunt abdominal trauma is exceedingly uncommon, occurring in less than 5% of major abdominal injuries. When blunt pancreatic injury does occur, however, it is notoriously difficult to identify. The use of serum amylase has been advocated in the diagnosis of such injury, yet it is neither sensitive nor specific. Computed tomography has become widely accepted in the evaluation of hemodynamically stable patients after blunt abdominal trauma, although it is clearly not a sensitive modality for the detection of pancreatic injury. In fact, numerous examples of normal CT scans with missed pancreatic injury have been documented. However, careful attention to CT technique and awareness of the CT manifestations of pancreatic injury may facilitate the diagnosis of pancreatic injury. Additionally, important information about the pancreatic duct can be obtained with the use of MRI-pancreatography or endoscopic retrograde pancreatography. Accurate, timely identification of major pancreatic ductal injury is imperative because delay in diagnosis and associated vascular injuries are largely responsible for the high morbidity and mortality associated with blunt pancreatic trauma. Blunt pancreatic trauma can be managed successfully by means of both operative and selective approaches. (J GASTROINTEST SURG 2002; 6:587–598.) © 2002 The Society For Surgery of the Alimentary Tract, Inc.

KEY WORDS: Pancreatic trauma, pancreas surgery, pancreas radiography

Pancreatic injury from blunt trauma is infrequent, although its incidence has risen dramatically due to an increased number of motor vehicle accidents over the past 40 years.[1–3] Pancreatic injuries caused by blunt trauma have been reported to occur in 0.2% to 12% of all major abdominal injuries.[3–21] Larger series, however, report an incidence of less than 5%.[3–21] Because of failure to consider the diagnosis and the fact that the clinical, laboratory, and radiographic findings of blunt pancreatic injury are nonspecific, a lapse of time between injury and the diagnosis often occurs. This is unfortunate because the greatest determinant of morbidity from blunt pancreatic injury, if associated acute vascular injuries are excluded,[4,7,9,21–26] is a delay in diagnosis and the development of subsequent sepsis.[3,6,10,11,22] Thus early diagnosis is important in reducing the overall morbidity and mortality associated with pancreatic injury. The trauma team therefore needs to maintain a high index of suspicion for the possibility of a pancreatic injury and pursue selective studies such as repeat CT, MRI-pancreatography (MRP), or endoscopic retrograde pancreatography (ERP) to make such a diagnosis.

CT is an integral part of the evaluation of all hemodynamically stable patients with blunt abdominal trauma because of the high overall sensitivity and specificity of CT scanning in detecting traumatic injuries. CT detection of pancreatic injuries, however, is challenging and requires close attention to technique and awareness of the subtle changes produced by pancreatic injury.[4,5] Although FAST (focused abdominal sonography for trauma) ultrasound is being used increasingly in the evaluation of traumatized patients, in the detection of blunt pancreatic trauma it is limited. Additionally, MRP and ERP are two useful imaging modalities for the detection of post-traumatic pancreatic injury and hyperamylasemia.

MECHANISM

Blunt pancreatic injury occurs when a blow to the epigastric area results in compression of the pancreas between the vertebral column and the anterior ab-

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dominal wall. This usually transpires on compression against the steering wheel in a motor vehicle accident in adults, from bicycle handlebar injuries in children, and from child abuse in infants.[3,21] Pancreatic injury is more common in children and young adults because they have a thinner or absent mantle of protective fat that surrounds the pancreas in older adults.

Anterior compression of the pancreas against the spine is the classic description of injury to the pancreas with blunt abdominal trauma, and this usually occurs just to the left of the superior mesenteric vessels. Anterior vector forces are also frequently associated with injuries to the liver, gallbladder, major vessels, stomach, and transverse colon. Blows to the left side of midline may injure the distal body or tail of the pancreas and may be associated with injuries to the spleen, stomach, descending colon, and left kidney. In contrast, blows from the right side may injure the pancreatic head or uncinate process along with the bile duct, duodenum, liver, right kidney, and ascending colon.

INCIDENCE

Although the incidence of pancreatic injury is low, the associated morbidity and mortality of such injuries are high, thus making accurate early diagnosis and treatment imperative.[22–24] Morbidity rates in patients with blunt pancreatic trauma range from 30% to 50%, whereas reported mortality rates have ranged from 10% to 30%.* Both the morbidity and mortality of blunt pancreatic trauma increase substantially with the degree of pancreatic injury and in those patients with combined injuries. Isolated trauma to the pancreas is seen in only 30% of cases[6,7,26] and is associated with a 3% to 10% mortality rate.[37] Most patients with pancreatic injuries will have at least one associated injury, with an average of 3 to 4.1 associated intra-abdominal injuries per patient.[3,21] The most commonly associated solid organ injuries include injuries to the liver, spleen, duodenum, stomach, and kidneys.[4,26,33] In those patients with blunt pancreatic injuries who have associated organ injuries, a 20% or greater mortality rate has been reported.[15,21,26,28] Most of the early deaths attributed to pancreatic trauma are the result of exsanguinating hemorrhage from associated vascular injuries. Infection, which is usually caused by a pancreatic fistula, remains the primary cause of late death both in patients with isolated pancreatic injuries and those with pancreatic and associated injuries.[21]

*References 1, 3, 4, 6, 7, 10–13, 15, 21, and 25–36.

Classification

Various classification schemes have been developed to grade pancreatic injury. The most commonly used is the American Association for the Surgery of Trauma (AAST),[38] although a system devised by Lucas[22] is also widely used. The AAST classification grades injuries on a scale of I to V (Table 1). Grade I injuries are minor contusions (hematoma) or lacerations of the pancreas without ductal injury; grade II injuries represent a major contusion or parenchymal laceration without dutal disruption; grade III injuries involve distal transection or parenchymal injury with a ductal injury; grade IV injuries consist of proximal transection or parenchymal injury; and grade V injuries involve massive disruption to the pancreatic head. This classification is often used because it focuses on both the anatomic location and the extent of the pancreatic injury, as well as the condition of the pancreatic duct. Accurate grading by the AAST scheme helps to define practical treatment guidelines (Table 2).

PRESENTATION AND DIAGNOSIS

The retroperitoneal location of the pancreas protects it from most instances of blunt abdominal trauma. However, the retroperitoneal location also minimizes signs or symptoms of such injuries, which are often vague and nonspecific. The degree of abdominal pain or tenderness cannot be used as a discriminator between mild and major pancreatic injury.[19,21,26,28] Moreover, major pancreatic injury with minimal epigastric discomfort may be further masked by other associated injuries including long bone fractures. The diagnosis of blunt pancreatic injury should be suspected in patients with epigastric or diffuse abdominal tenderness, leukocytosis, or epigastric abdominal wall ecchymoses.[10,26] In patients with a history of a steering wheel compression of the epigastrium during a motor vehicle or handlebar accident, the clinical suspicion of pancreatic injury should be aroused and careful additional investigative studies pursued regardless of the degree of abdominal pain.

Serum amylase is a mainstay in the diagnosis of pancreatitis. For blunt pancreatic injury, however, initial serum amylase levels are neither sensitive nor specific.* The initial serum amylase value may be normal in as many as 40% of cases of blunt pancreatic trauma.[3,21,44] Nonetheless, hyperamylasemia, along with the mechanism of injury, should serve to heighten one's suspicion regarding the possibility of blunt pancreatic

*References 3, 4, 6, 7, 10, 22, 24, 25, 28, 30, 33, 37, and 39–43.

Table 1. American Association for the Surgery of Trauma pancreatic injury grading scale

Grade	Injury description	
I	Hematoma	Minor contusion without ductal injury
	Laceration	Superficial laceration without ductal injury
II	Hematoma	Major contusion without ductal injury or tissue loss
	Laceration	Major laceration without ductal injury or tissue loss
III	Laceration	Distal transection or pancreatic parenchymal injury with ductal injury
IV	Laceration	Proximal transection or pancreatic parenchymal injury involving the ampulla
V	Laceration	Massive disruption of the pancreatic head

From Moore EE, Cogbill TH, Malangoni MA, Jurkovich GJ, Champion HR, Gennarelli TA, McAninch JW, Pachter HL, Schackford SR, Trafton PG. Organ injury scaling. II: Pancreas, duodenum, small bowel, colon, and rectum. J Trauma 1990;30:1427–1428.

trauma. Hyperamylasemia has been reported to ultimately develop in up to 90% of patients with pancreatic trauma.[6,10] Repeat serum amylase measurements should therefore be obtained to increase the sensitivity and specificity for detecting blunt pancreatic trauma.[25,45] Although an elevated serum amylase level may indicate the possibility of pancreatic injury, the absolute value cannot be used as a marker for the degree of injury. Amylase levels can be variably elevated in patients with pancreatic contusions or ductal disruptions.[10] Moreover, numerous cases of total disruption of the main pancreatic duct with normal serum amylase levels for 24 to 48 hours after the initial injury have been reported.[3,15,21,26,28] In all cases, development of hyperamylasemia should initiate further evaluation with additional diagnostic studies, including repeat CT scans, and either ERP[46] or MRP.[22,26,47,48]

Hyperamylasemia is not pathognomonic for pancreatic injury since both salivary gland trauma and small bowel injuries may also cause hyperamylasemia.[3,15,21,26,28] Certain centers may distinguish amylase derived from the pancreas or salivary glands, as they are different isoenzymes: pancreatic (p-amylase) and salivary (s-amylase).[49] Such assays are of limited practical utility and are not readily available at most clinical centers.[44] Moreover, the major concern raised by an elevated amylase level is the differentiation between pancreatic trauma and small bowel injury, which the amylase isoenzyme measurement will not determine. No additional information appears to be added with lipase determination.[40–44] Based on its nonspecific and delayed elevation after blunt pancreatic injury, amylase may only be used as a marker for potential injury and elevation of serum amylase should a minimum initiate immediate abdominal imaging.

Trypsinogen-activating peptide is another pancreatic enzyme that may be used in evaluation for possible blunt pancreatic injury, although its use has not been thoroughly evaluated in clinical trials to date.

Diagnostic peritoneal lavage is both a sensitive and specific modality for identifying patients with hyperamylasemia resulting from an occult small bowel injury; however, it has proved to be insensitive in the detection of pancreatic injury.[23] Moreover, duodenal injuries may be missed when this modality is used. Therefore it should be reserved for select patients

Table 2. Management options based on American Association for the Surgery of Trauma guidelines

Grade	Treatment options
I	Fix associated injuries
	Observation, drainage if needed (operative or percutaneous)
II	Fix associated injuries, ERP or MRP
	Observation, drainage if needed (operative or percutaneous)
III	Fix associated injuries
	Consider middle-segment pancreatectomy, spleen-preserving distal pancreatectomy, distal pancreatectomy
	Drainage suggested, consider pancreatic sphincterotomy
IV	Fix associated injuries
	Consider middle-segment pancreatectomy, Roux-en-Y to disrupted region,
	Pyloric exclusion, duodenal diverticulization
	Extensive drainage suggested, consider pancreatic sphincterotomy
V	Fix associated injuries
	Consider middle-segment pancreatectomy, Roux-en-Y to disrupted region,
	Pyloric exclusion, duodenal diverticulization, rarely pancreaticoduodenectomy
	Extensive drainage suggested, consider pancreatic sphincterotomy

when there is a question of small bowel injury, or as an adjunct to CT or in certain patients who are being considered for urgent laparotomy.

ULTRASOUND

Ultrasound imaging, particularly as part of the initial assessment of trauma patients, has proved to be a highly effective and reliable imaging technique for the examination of free abdominal fluid. FAST ultrasound is increasingly being used at a number of centers as the initial imaging modality to assess trauma patients,[50–52] although a steep learning curve does exist.[53–56] Ultrasound images are easily obtained and are highly sensitive and specific in determining the presence of intra-abdominal hemorrhage; however, such is not the case when ultrasound is used to detect acute blunt pancreatic trauma.[50] Ultrasound evaluation of blunt pancreatic trauma is also sometimes difficult in that certain confounding factors may mask the diagnosis. These include overlying bowel gas from the gastric bubble or duodenum, obesity, and overlying subcutaneous emphysema. The use of ultrasound may lead the trauma team to operate because of the discovery of free abdominal blood in the setting of a hemodynamically unstable patient. In patients who remain hemodynamically stable, additional imaging, specifically CT, should be performed.

Endoscopic ultrasound, which uses higher frequency signals and thus provides higher resolution images, may prove in the future to be an accurate means of imaging pancreatic injury. To date, however, reports of its use in the setting of trauma evaluations have been limited.

COMPUTED TOMOGRAPHY

Technique

Meticulous attention to the scanning technique is important to avoid a missed pancreatic injury. This requires adequate bowel opacification with contrast material, gastric decompression, sedation of the patient if required, and repeat scans if the initial images are not satisfactory. The faster scanning time of newer scanners greatly reduces bowel artifacts and resolves many previous technical problems. Proper bolus administration during helical CT scanning is critical to minimize missed ductal disruption. However, the timing of CT in pancreatic trauma is also important, as patients who undergo scanning immediately after trauma may demonstrate little evidence of post-traumatic injury or pancreatitis.

The bowel should be opacified with approximately 500 ml of contrast medium given either orally or through a nasogastric tube approximately 30 to 60 minutes before CT with an additional 250 ml administered just before scanning. The oral contrast medium layers over the posterior gastric wall when the patient is lying supine and thus outlines the posterior gastric anatomy, highlighting the region between the gastric wall and the pancreas. For intravenous contrast, approximately 100 to 150 ml of 60% nonionic intravenous contrast material can be administered by power injector at 3 to 5 ml/sec. A dynamic scanning technique with the acquisition of both hepatic arterial and portal venous phase imaging should be obtained. For children, the dosage of intravenous contrast medium should be altered for body weight. Helical scanning should begin approximately 28 seconds after the start of the injection. Scans are usually obtained at 7.5 mm intervals with a pitch of 3:1 from the dome of the diaphragm through the abdomen. A pitch of 6:1 can be used for agitated patients to minimize scanning time. Although restraints or sedation are sometimes required, motion artifacts are usually minimal in modern scanners. The images should be reviewed on the console immediately after the injection to appreciate subtleties. Soft tissue, lung, and bone window settings should also be used to evaluate the images on the CT console while the patient is still on the scanning table. With multislice technology, image thickness can be retrospectively changed to 3.5 mm increments or smaller if needed.

CT Imaging Features

There are many CT findings that are suggestive of pancreatic injury (Table 3). Specific signs of pancreatic injury include pancreatic laceration or fractures (Figs. 1, 2, 3, 4, 5, and 6), fluid separating the

Table 3. CT findings suggestive of pancreatic injury

Focal or diffuse pancreatic enlargement/edema
Pancreatic hematoma
Pancreatic laceration
Inflammatory changes in the peripancreatic fat and mesentery
Fluid separating the splenic vein from the posterior aspect of the pancreas
Thickening of the left anterior renal fascia
Fluid in the anterior and posterior pararenal spaces, transverse mesocolon, and lesser sac
Hemorrhage into the peripancreatic fat, mesocolon, and mesentery
Pseudocyst formation
Fluid surrounding the superior mesenteric artery
Extraperitoneal and intraperitoneal fluid
Pancreatic ductal dilatation

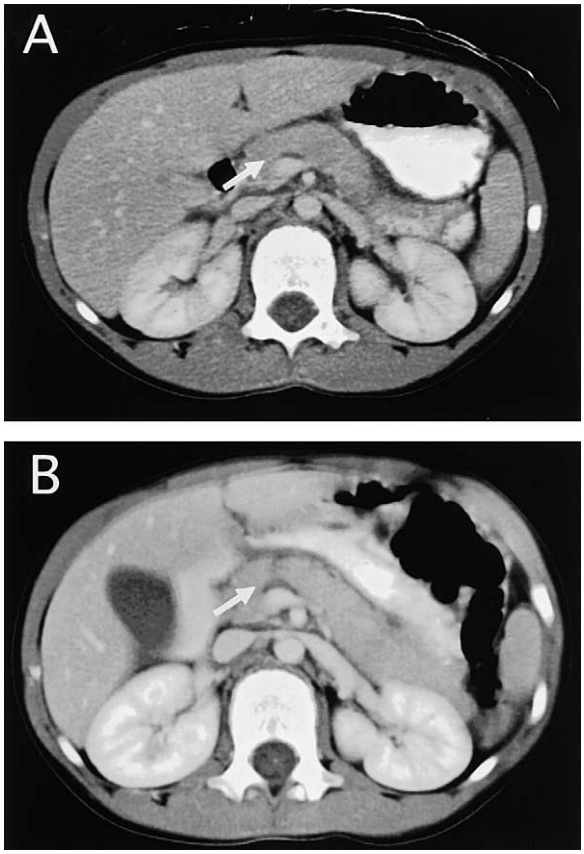

Fig. 1. A, A 14-year-old adolescent boy involved in a motor vehicle accident shows subtle fluid anterior to the splenic vein confluence (*arrow*). **B**, CT scan 48 hours after initial CT shows an evolving subtle laceration (*arrow*) perpendicular to the long axis of the pancreas.

splenic vein and pancreas, and pancreatic hematoma (see Fig. 5). Highly suggestive signs in the proper clinical context include pancreatic ductal dilatation and pancreatic enlargement. Although these findings are specific for or highly suggestive of pancreatic trauma, they may be absent[57] because signs of pancreatic injury are often initially subtle (see Figs. 1 and 2). The delay in CT findings of pancreatic injury are especially pronounced in pediatric patients who often lack the contrast provided by surrounding adipose tissue to appreciate pancreatic injuries. Over time, pancreatic injuries in adults and children tend to become more radiographically apparent with the development of post-traumatic pancreatitis, edema, leakage of pancreatic enzymes, and subsequent autodigestion of the surrounding parenchyma (see Figs. 1, 2, and 3).

On CT scans, pancreatic contusions appear as focal or diffuse areas of low attenuation within the normally enhancing parenchyma. Lacerations of the pancreas are demonstrated by a low-attenuation line oriented perpendicular to the long axis of the pancreas (see Figs. 1 and 2). This occurs most commonly in the neck of the pancreas and results from anterior pancreatic compression.[16,58] In some patients a pancreatic cleft can be identified, usually between the neck and body of the pancreas (Fig. 7). This cleft is a normal variant and should not be construed as an injury. Pancreatic lacerations may involve only a portion of the pancreatic surface or they may extend through the entire pancreas, resulting in a transection. The depth of the laceration has been correlated with the probability of pancreatic ductal injury.[59] If the laceration is less than 50% of the thickness of the pancreas, pancreatic ductal injury is usually not observed; nonetheless, such patients should undergo additional imaging studies, ERP or MRP, to evaluate the relationship of the pancreatic duct to the laceration. Injuries involving more than 50% of the thickness usually have ductal injury and may warrant surgical exploration or therapeutic ERP (see Table 2).

In many patients the only finding of pancreatic injury is post-traumatic pancreatitis, which appears as focal or diffuse pancreatic enlargement that may progress on serial CT examination. However, this may take up to 24 to 48 hours to develop and therefore may not be apparent on scans obtained immediately after injury.[13,37]

Acute fluid collections (pseudo-pseudocysts) and pseudocyst formation are commonly found in patients who have sustained undetected pancreatic trauma (Figs. 7 and 8). These peripancreatic fluid collections look similar to those caused by other types of pancreatitis and appear as low-attenuation fluid collections with associated mass effect and minimal peripancreatic edema and inflammatory change.[60] A patient with a post-traumatic pseudocyst should be considered to have a ductal leak until proven otherwise, and ERP or MRP is warranted in these cases (see Table 2).

Fluid separating the splenic vein and the pancreas (see Fig. 9) has been suggested as a means of determining a pancreatic injury and was found in 90% of cases of pancreatic injury in the study by Lane et al.[61] Normally the splenic vein is closely apposed to the posterior aspect of the pancreas or is separated from the pancreas by a thin layer of fat. In a patient with insinuating fluid between the splenic vein and the pancreas and a history of abdominal trauma, a pancreatic injury should be suspected. However, a study by Sivit et al.[60] noted that 60% of patients with pancreatic injury and 48% of patients with fluid in the anterior pararenal space without pancreatic injury also had this finding. The finding of fluid separating the splenic vein and the pancreas was associated with at least one or more additional CT findings in the diagnosis of pancreatic injury. These additional findings included fluid in the anterior pararenal space,

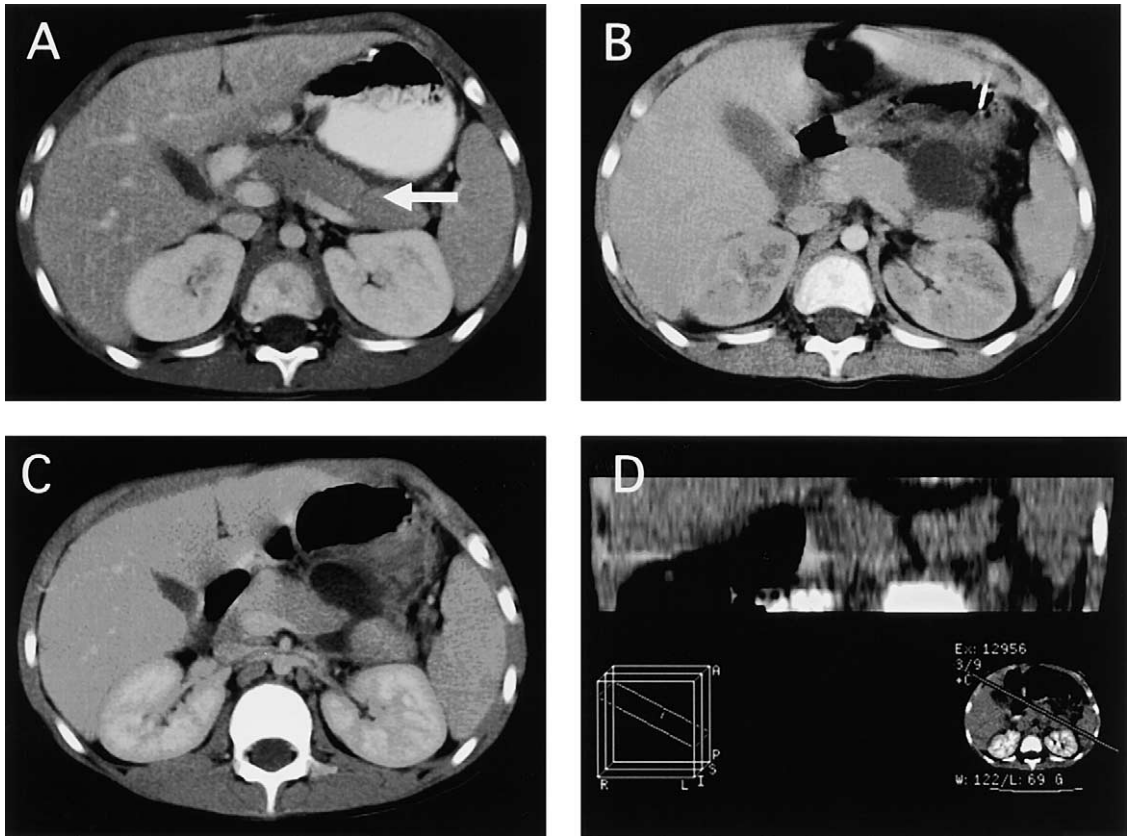

Fig. 2. A, A 17-year-old male patient after a motor vehicle accident with elevated amylase shows a subtle linear density in the tail of the pancreas (*arrow).* **B**, Forty-eight hours after the initial CT scan, an acute peripancreatic fluid collection is forming. **C**, The pseudo-pseudocyst becomes partially encapsulated at 10 days. **D**, Coronal reformatted images at 10 days show well-defined transection. ERP performed after initial CT scan (3A) shows extravasation in the tail of the pancreas (*large arrow*).

thickening of the anterior renal fascia, fluid in the lesser sac, and parenchymal laceration or transection. Therefore, although fluid separating the splenic vein from the pancreas is often seen with pancreatic injury, this alone is not a sensitive sign of injury and is rarely the only abnormal CT finding in patients with pancreatic injury.

ACCURACY OF COMPUTED TOMOGRAPHY

CT is the diagnostic modality of choice for evaluating stable patients after blunt abdominal trauma.[13,18,36,61–64] CT is both more sensitive and specific than ultrasonography. However, CT has certain limitations in the detection of pancreatic injury and is the least sensitive in detecting injury to the pancreas among all solid abdominal organs.[65] CT, nonetheless, is useful not only for detecting pancreatic injuries but also for differentiating minor injuries from those that require surgical exploration.

Historically, pancreatic injury has reportedly been diagnosed by means of CT in 67% to 85% of all cases,[13,57] but many of these studies involved older technology and today the sensitivity should exceed 80%.[13,18,21,37,65,66]

The ability of CT scanning to facilitate accurate diagnosis of pancreatic injury depends on the quality of the CT scanner, the imaging technique, the experience of the observer, and the timing of the examination.[21] In the study by Arkovitz et al.[66] CT had an 85% sensitivity within the first 24 hours after the acute pancreatic injury and a 90% sensitivity overall. Within the first 12 hours after the initial injury, CT scans may appear normal in a significant fraction of injuries.[13,37,67] This is due to the obscuration of the fracture plane, hemorrhage, and close apposition of the pancreatic fragments.[5,13] It is not until repeat scanning at 12 to 24 hours that an abnormality which was initially ambiguous or subtle becomes evident. Overall, the trauma team must remain cognizant of the fact that CT scans may initially appear normal in the first 12 hours after blunt pancreatic injury in

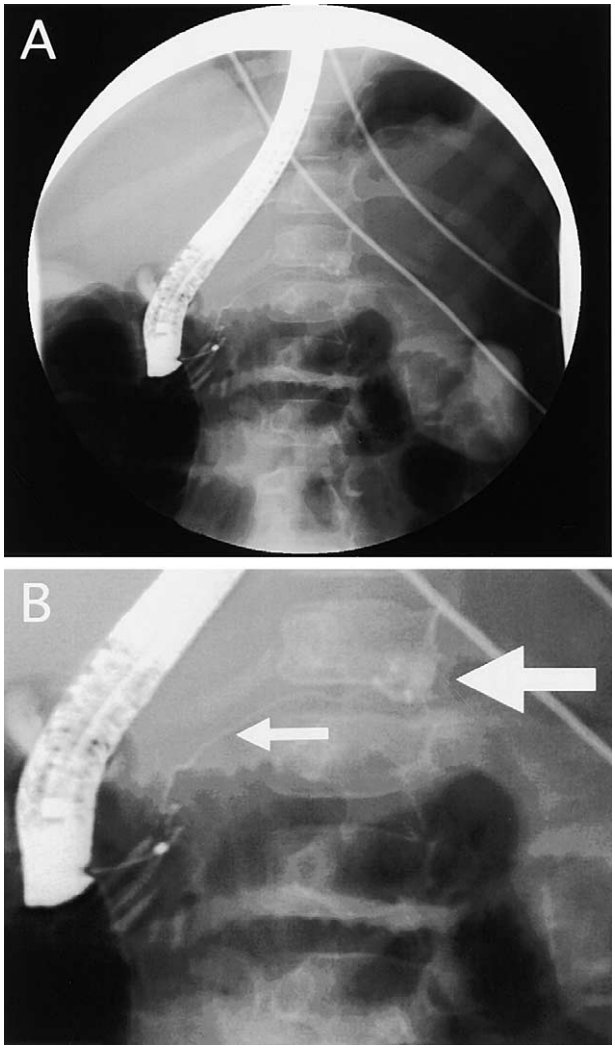

Fig. 3. A, ERP of patient in Fig. 2 after initial CT scan (see Fig. 2, *A*) shows extravasation in the tail of the pancreas. **B**, Close-up of pancreatic duct and communicating peripancreatic collection (*large arrow*).

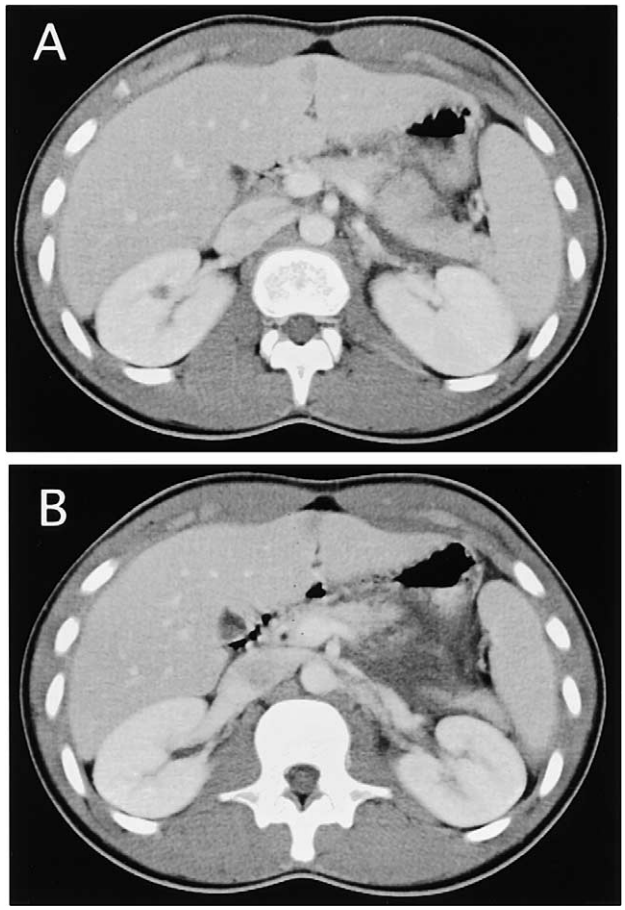

Fig. 4. A, A 29-year-old man involved in a high-speed motor vehicle accident shows a grade III injury with distal transection, peripancreatic edema, and fluid anterior to the left renal vein. **B**, CT scan 96 hours later shows degradation and necrosis of the surrounding pancreatic tissue by enzymatic release.

20% to 40% of patients, and continued vigilance for the presence of such injuries must be maintained.

Overall, the sensitivity in detecting all grades of pancreatic injury is approximately 80%, but the accuracy of detecting a major ductal injury by CT has been reported to be as low as 43% even with modern imaging techniques.[13,18,26,37,67] Further analysis of missed injuries has also suggested that when CT is inaccurate in grading the degree of pancreatic injury, usually a lower grade of injury is diagnosed than that actually found at laparotomy.[4,16,68] The problem of under-recognized and missed blunt pancreatic injuries is even more apparent in patients with minimal retroperitoneal fat (see Fig. 1).

The trauma team must therefore remember that the diagnosis of pancreatic injury by means of CT is challenging (see Fig. 1), and it is not uniformly accurate in detecting all types of blunt pancreatic injuries.[18,37] Careful attention to technique, careful examination of the CT images, possibly with multiple experienced readers, and attention to the possibility of missed injuries, especially those involving the pancreatic duct, must be kept in mind and constantly reevaluated. The failure of admission CT to diagnose pancreatic injuries may not be a reflection of diagnostic inaccuracies, as some have expressed,[20,26,65] but rather the evolution of these injuries. For these reasons, repeat CT should be considered in stable patients when there is a strong suspicion of pancreatic injury. Moreover, continued additional investigative studies may be warranted if any uncertainty about the condition of the pancreas exists, especially in patients who have questionable findings on CT, elevated serum amylase levels, or unexplained abdominal pain.

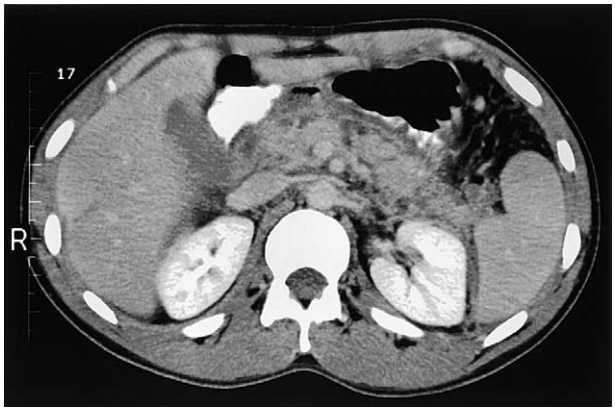

Fig. 5. A 28-year-old male patient after a motor vehicle accident with elevated amylase shows maceration of the pancreas with numerous low-density lines throughout the parenchyma.

ERP AND MRP

ERP is the "gold standard" in the preoperative identification of pancreatic ductal injury, but it may be difficult to perform on an emergency basis and is an extremely invasive procedure. Additionally, ERP should be used with caution in the traumatized patient who has a potentially normal pancreas because ERP-induced pancreatitis can be severe and lethal. The study of Bilbao et al.[69] reported a 15% complication rate for experienced endoscopists and up to a 62% complication rate for those with less experience among patients in whom an adequate study was obtained. Failure to cannulate the pancreatic duct or otherwise inadequate pancreatography occurs in up to 30% of cases.[46–48] The most clinically evident and common complication following ERP is the development of severe pancreatitis within the first 24 hours after the procedure. ERP-induced pancreatitis usually results from excessive injection pressure into the pancreatic duct. Other complications of ERP include cholangitis, pancreatic sepsis, drug reactions, and instrument-induced injury to the gastrointestinal tract including perforation and bleeding.[69,70] The usefulness of ERP is maximized when the procedure is performed within 12 to 24 hours of injury because early diagnosis prevents late complications.[70,71]

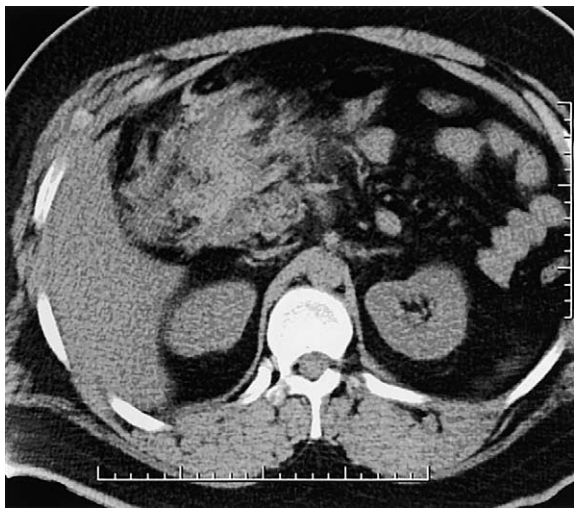

Fig. 6. An unrestrained 65-year-old man involved in a high-speed motor vehicle accident shows a combined pancreaticoduodenal injury with enlargement, edema, and a hematoma surrounding the pancreatic head and duodenum (grade V).

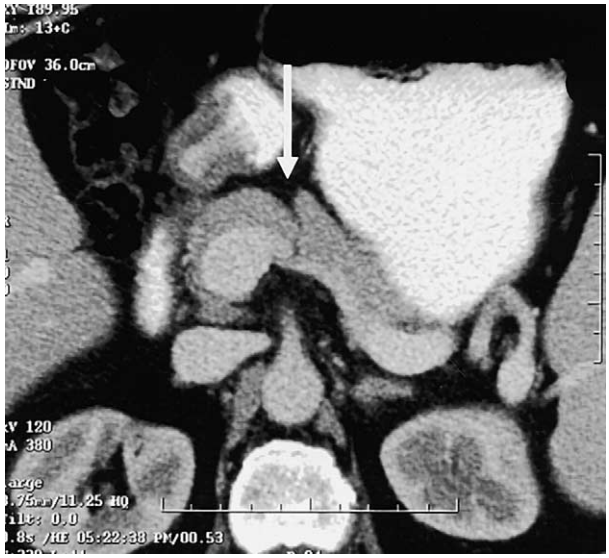

Fig. 7. A 57-year-old woman who had fallen off a ladder and complained of persistent abdominal pain shows a pancreatic cleft (*arrow*), a normal variant, in the pancreatic neck. No other CT evidence of abdominal trauma was found and the serum amylase level was normal.

ERP may also be used as a therapeutic modality. Numerous examples of successful endoscopic stenting of pancreatic duct disruptions have been reported. ERP has been used both in the semiacute setting and after the development of a pancreatic fistula to successfully place a stent across the injury and allow subsequent closure of the ductal disruption.[72,73]

Increased experience with MRP has suggested that MRP may prove to be the imaging test of the future in the detection of pancreatic ductal injury.[71] MRP is noninvasive and is not associated with the complications of ERP.[71] Contrast material is not needed because MRP uses stationary water in the pancreatic secretions to contrast against the organ on heavily T_2-weighted images. The historic downside of MRP has been an inability to perform therapeutic interventions in the management of biliary stone disease, but such limitations are not applicable to the majority of pancreatic trauma evaluations. Moreover, should it be used as a screening test for subse-

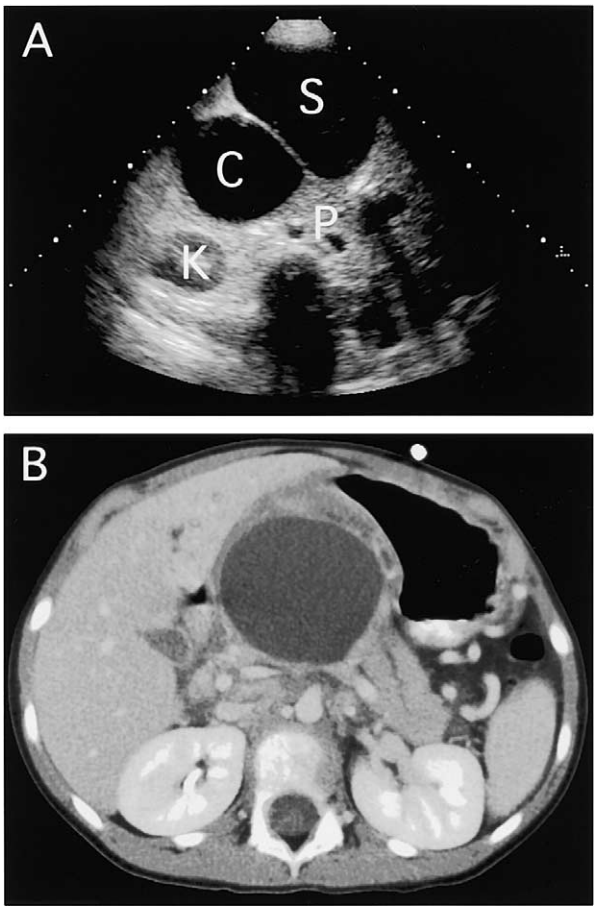

Fig. 8. A, A 10-year-old girl who underwent imaging for an increasing abdominal mass 15 days after a fall onto bicycle handlebars shows a large pancreatic pseudocyst with dilatation of the distal pancreatic duct. **B**, CT scan demonstrating pseudocyst. K = kidney.

quent ERP, patient risk of ERP-associated morbidity and mortality may be reduced. Although the validity of MRP in evaluating pancreatic trauma has not been prospectively evaluated, preliminary results in the evaluation of blunt pancreatic trauma are promising, suggesting that MRP may be a sensitive and specific tool for this purpose.[74]

Both CT and either MRP or ERP are sometimes essential for the proper diagnosis of pancreatic injury. CT is better at providing a panoramic view of both the pancreas and the abdomen, whereas MRP or ERP is better at delineating ductal involvement. Emergency ERP or MRP may be required to investigate pancreatic injuries when CT findings are equivocal or when the scans are technically inadequate. Centers that cannot provide these modalities in the setting of potential blunt pancreatic trauma should consider transferring patients to alternate centers where these studies may be available.

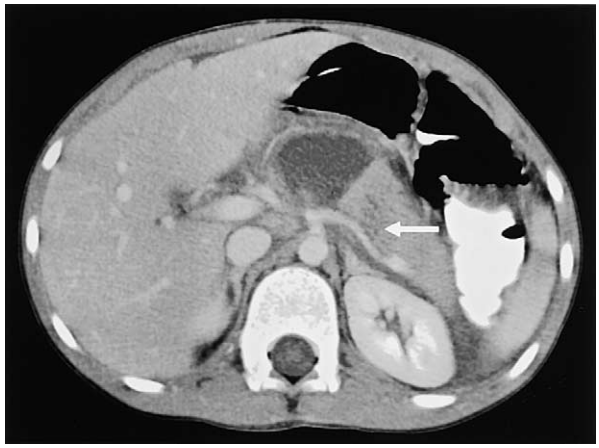

Fig. 9. A 16-year-old boy with persistent abdominal pain after a bicycle accident 1 week earlier shows a pancreatic pseudocyst and fluid posterior to the splenic vein (*arrow*).

MANAGEMENT

The management of blunt pancreatic injuries has relied heavily on determining the severity of the injury, the location of the injury, and the presence or absence of associated intra-abdominal injuries (Fig. 10). Generally, in the absence of associated injuries, most authors would support conservative management in dealing with blunt pancreatic injuries without ductal disruption.[15,23,25,27,37] If patients are selected for nonoperative management of isolated blunt pancreatic injury, ductal integrity should be verified by ERP or MRP because injury to the main pancreatic duct occurs in approximately 15% of cases.[75,76] Successful management of isolated ductal disruptions with endoscopically placed stents may be considered if local endoscopic expertise is available.[72,73,77] If surgical exploration is undertaken, most pancreatic injuries not involving the pancreatic duct can be managed by simple closed drainage. In patients with multiple injuries, initial surgical management should be directed at control of hemorrhaging, treatment of other life-threatening injuries, wide external drainage, and debridement of devitalized tissue. Definitive surgical control of the pancreas can always be deferred.[1,78]

Surgical management of pancreatic injury emphasizes damage control, adequate drainage of the pancreatic bed, and debridement of devitalized tissue. This topic has been well reviewed by a number of investigators.[3,26,32,79] Briefly, there are several surgical issues to consider, which are outlined in Table 2. Pancreaticoenteric anastomosis is extremely challenging in patients with blunt injury to a previously normal gland and is associated with a high risk of fistula.[3,26,37] In addition, preservation of pancreatic and splenic tissue should be considered because of the

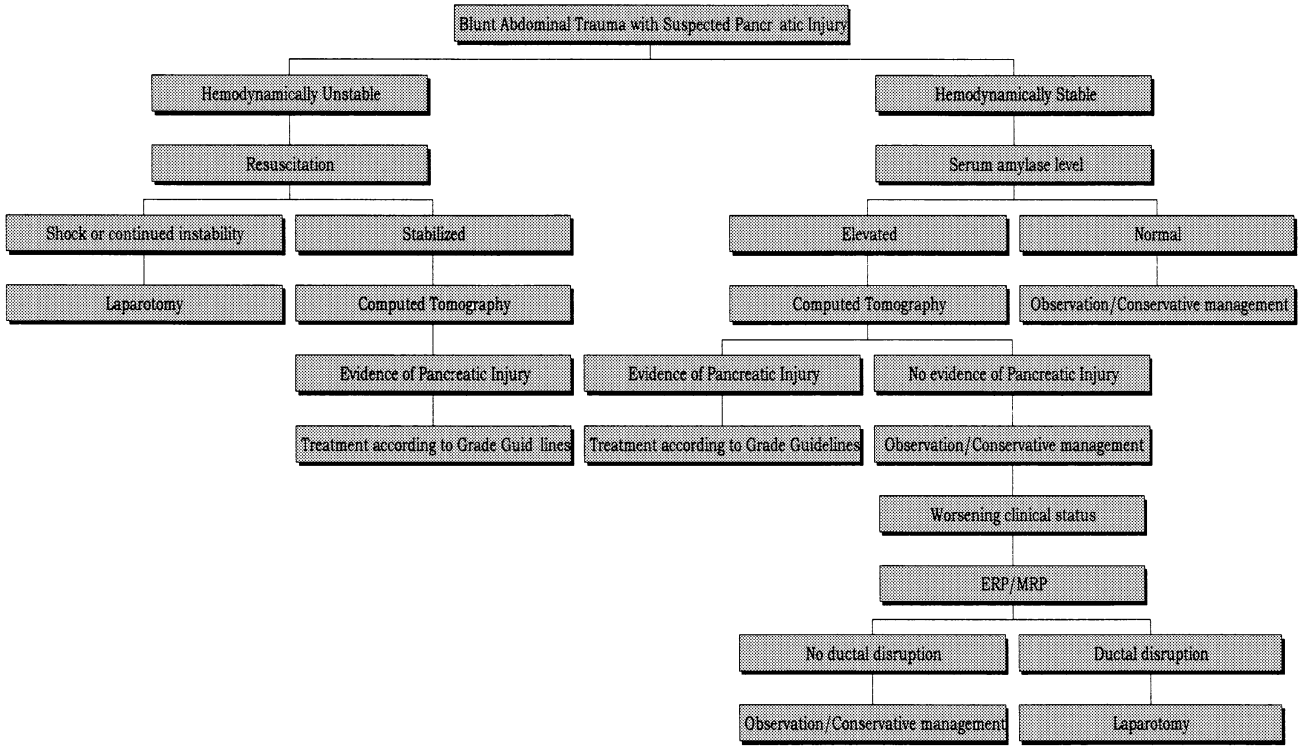

Fig. 10. Diagnostic algorithm for management of suspected pancreatic trauma.

complications of long-term diabetes and asplenism, especially in younger trauma patients. A variation of the middle-segment pancreatectomy may be considered for transections of the pancreatic neck not amenable to pancreatic stenting.[80] Also, distal pancreatectomy with splenic preservation should be considered if the patient is stable. If a "second-look" laparotomy is planned, the pancreatic anastomosis may best be performed at the second procedure.[1,78] Stapling off of the pancreas without reanastomosis should be avoided if possible, but the surgeon should recognize this option in extreme circumstances.[81]

CONCLUSION

Pancreatic trauma is an uncommon sequela of major blunt abdominal trauma and is often overlooked in the evaluation of these patients. One must be aware of the potential for this injury since pancreatic trauma after blunt abdominal trauma is a difficult diagnosis to make. The findings may be subtle initially and become more pronounced as post-traumatic pancreatitis develops. One must be aware of the characteristics and clinical and surgical implications of pancreatic injury as a prerequisite for the triage and optimal management of these patients. Expedient identification and treatment are required to prevent secondary life-threatening complications.

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Inducible Nitric Oxide Synthase Knockout Mice Are Resistant to Diet-Induced Loss of Gut Barrier Function and Intestinal Injury

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Loss of gut barrier function has been documented to occur in animals receiving total parenteral nutrition (TPN) and certain liquid diets. However, the mechanisms responsible for diet-induced gut barrier dysfunction remain to be fully determined. Thus we tested the hypothesis that increased intestinal nitric oxide production contributes to this phenomenon. To test this hypothesis, iNOS-deficient (iNOS −/−) mice and their wild-type littermates (iNOS +/+) were fed either chow or TPN solution for 14 days. Subsequently they were killed and gut barrier function was assessed by measuring bacterial translocation to the mesenteric lymph node (MLN) complex. Additionally, intestinal bacterial population levels, gut morphology, plasma and intestinal nitric oxide levels, as well as intestinal levels of the nitric oxide synthase (NOS) enzymes cNOS and iNOS, were measured. Bacterial translocation occurred in the iNOS +/+ but not the iNOS −/− mice receiving oral TPN solution. Oral TPN-induced bacterial translocation was associated with increased intestinal bacterial population levels as well as morphologic evidence of intestinal injury. Plasma and intestinal levels of the nitric oxide products, nitrite/nitrate, were increased in the iNOS +/+ mice fed the TPN solution but not in the chow-fed groups or the iNOS −/− mice receiving TPN solution. Last, intestinal iNOS, but not cNOS, activity was increased in the iNOS +/+ oral TPN-fed mice. These results implicate a role for increased intestinal nitric oxide production, through iNOS, in the pathogenesis of oral TPN-induced gut barrier dysfunction and injury. (J GASTROINTEST SURG 2002; 6:599–605.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: iNOS knockout mice, elemental diet, gut barrier function

The loss of gut mucosal barrier function and the subsequent translocation of bacteria from the gut have been implicated in the development of sepsis, postinjury hypermetabolism, and distant organ injury.[1] Consequently a large number of studies have been carried out investigating potential mechanisms by which various clinically related factors, such as the route and composition of the diet, could impair intestinal mucosal barrier function and promote bacterial translocation.[2] Total parenteral nutrition (TPN) solution given enterally or parenterally, as well as certain liquid enteral diets, have been documented to lead to loss of gut barrier function and bacterial translocation.[3–6] However, the exact mechanisms responsible for diet-induced loss of gut barrier function remain to be determined. Determination of the mechanisms of diet-induced loss of intestinal barrier function is likely to be of clinical importance, based on experimental studies and prospective randomized clinical trials documenting that specialized enteral diets reduce the incidence of major infectious complications as compared to patients fed with non–immune-augmented enteral diets or patients fed parenterally.[7–10] Because studies indicate that nitric oxide plays a role in decreasing mucosal integrity and promoting gut barrier failure,[11,12] we tested the hypothesis that increased nitric oxide production is involved in diet-induced gut barrier failure and bacterial translocation.

MATERIAL AND METHODS

Animals

The iNOS-deficient mice (iNOS −/−) used in these experiments were originally provided by Merck Research Laboratories through Dr. S. J. Leibovich,

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Professor of Anatomy, New Jersey Medical School. Male iNOS −/− or their wild-type littermates (iNOS +/+), weighing 26 to 35 grams, were used in this study. The animals were housed under barrier-sustained conditions and received acidified water. The mice were maintained according to the recommendations of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The experiments were approved by the University of Medicine and Dentistry of New Jersey Animal Care Committee.

Experimental Design

To determine the relationship between diet-induced bacterial translocation, mucosal injury, and iNOS activity, wild-type and iNOS-deficient mice were randomized to receive either normal laboratory chow or TPN solution for 14 days. A 14-day period was chosen because our previous studies had documented that oral TPN-induced bacterial translocation was fully established at this time point.[13] The TPN solution contained 4.25% amino acids, 28% glucose, electrolytes, and multivitamins and has been described previously.[13] The TPN solution contained 1333 total kcal and had a nonprotein:nitrogen ratio of 151:1. Based on previous studies, the TPN-fed mice received 307 kcal/kg body weight/day.[3] The TPN solution was prepared asceptically and administered in sterile feeding bottles. The TPN solution and feeding bottles were changed every 2 days. The chow-fed mice received the same caloric amount of nutritional support as the oral TPN-fed mice.

At the end of the 14-day period, the mice were killed with an overdose of sodium pentobarbital. At the time of death, ileal segments were harvested for nitrite/nitrate, cNOS, and iNOS measurements, as well as for histologic examination and measurements of bacterial population levels. Systemic blood samples were also collected to assay for the plasma levels of the nitric oxide products nitrite/nitrate. In addition, bacterial translocation to the mesenteric lymph node (MLN) complex and cecal bacterial population levels were determined.

Bacterial Translocation and Intestinal Population Levels of Bacteria

Using pentobarbital anesthesia, the MLN complex was harvested and the level of translocating bacteria quantified as previously described.[14] Briefly, using sterile technique, the MLN complex was harvested, weighed, and homogenized in 0.5 ml of broth. Aliquots (0.2 ml) were plated onto blood and MacConkey agar plates. The plates were examined after 24 and 48 hours of aerobic incubation at 37° C. After the MLNs had been harvested, the cecum and a segment of the distal ileum were removed. They were divided in two and each piece was weighed. To determine total intestinal bacterial population levels, one piece of the ileum and one piece of the cecum were homogenized. Serial dilutions of the homogenate of the cecum and ileum were plated onto blood and MacConkey agar plates to estimate total cecal and ileal bacterial population levels. Growth on blood agar plates estimates total aerobic bacteria, both gram-positive and gram-negative, whereas only gram-negative enteric bacilli grow on the MacConkey agar plates. To determine mucosal-associated bacterial population levels, the second piece of ileal and cecum was vortexed in saline solution three times for 5 minutes each time. This vortexing procedure removes intestinal bacteria that are not adherent to the mucosa.[15] Subsequently the vortexed intestinal samples were quantitatively cultured as described above.

Nitrite and Nitrate (NO_2^-/NO_3^-) Assay and NOS Activity Assays

Small portions of the terminal ileum were removed, weighed, homogenized, and centrifuged at 3000 rpm for 10 minutes. Systemic (cardiac) blood samples were collected in syringes containing 100 units of heparin and centrifuged to remove the cellular components. The tissue and plasma samples were stored at −20° C until the assays were performed. NO_2^-/NO_3^- levels of each sample were measured with the nitrate reductase and Greiss reagent as previously described.[12]

Both the calcium-dependent (cNOS) and calcium-independent (iNOS) NOS activities were determined using a minor modification of the method of Brown et al.[16], as previously described. Briefly, a segment of the ileum was removed and stored at −70° C. On the day of assay the tissues were homogenized in 20 mmol/L HEPES containing 0.2 mmol/L phenylmethylsulfonyl fluoride, 0.1 mmol/L ethylenediaminetetra-acetic acid (EDTA), 1 mmol/L dithiothreitol, and 10 μmol/L tetrahydrobiopterin at pH 7.4. Conversion of radiolabeled arginine to the nitric oxide coproduct citrulline in the homogenate was then determined in an assay system containing 0.05 mol/L HEPES, 1 mmol/L $MgCl_2$, 0.1 μmol/L FAD, 0.1 mmol/L NADPH, 1 mmol/L $CaCl_2$, and 10 μmol/L [^{14}C]L-arginine in a total volume of 200 μl. The NOS activity was expressed as activity per milligram of protein weight of the sample (pmol/min/mg protein). The protein concentration was assayed spectrophotometrically by the Coomassie blue

method (Bio-Rad Laboratories, Hercules, Calif.). Bovine serum albumin was used as a protein standard. The level of iNOS activity was detected in the presence of 1 mmol/L ethylene glycol tetra-acetic acid (EGTA). Product formation that was inhibited by in vitro incubation with 1 mmol/L L-NMMA was used for background NOS activity.

Ileal Histology

The mucosal structure of the terminal ileum was analyzed by light microscopy in a blinded fashion. After immersion in 10% buffered formalin overnight at room temperature, the ileal samples were dehydrated and embedded in paraffin. Five random fields (100 × magnification) were evaluated per animal. The incidence of ileal villus damage was determined by dividing the number of injured villi by the total number of villi examined.

Statistical Analysis. Results were expressed as mean ± standard deviation (SD). Translocation incidence (discontinuous data) was evaluated by chi-square analysis with the Yates correction. Continuous data were analyzed by one-way analysis of variance using the post hoc Neuman-Keuls test or by the Student's *t* test. Probabilities less than 0.05 were considered significant.

RESULTS

During the 14-day feeding period, the mice from each of the groups gained weight. Although the iNOS +/+ mice fed chow gained the greatest amount of weight (6.9% of their body weight) and the iNOS −/− mice fed the TPN solution gained the smallest amount of weight (2.8% of their body weight), there were no statistical differences in weight gain among the four dietary groups.

Bacterial translocation to the MLN complex did not occur in the iNOS −/− or their wild-type iNOS +/+ littermates fed chow. However, after 14 days on the oral TPN diet, bacterial translocation to the MLN complex occurred in 75% of the iNOS +/+ but only 12.5% of the iNOS −/− mice ($P < 0.05$) (Table 1). This increase in bacterial translocation in the TPN-fed iNOS +/+ mice was associated with a greater than 1 log increase in cecal and ileal bacterial population levels (Table 2). When bacterial population levels of enteroadherent, mucosal-associated bacteria were measured, a similar result was observed (Table 3). Only in the iNOS +/+ mice fed the TPN solution was there an increase in ileal and cecal enteroadherent bacterial population levels ($P < 0.01$).

Because the iNOS −/− mice fed TPN solution were relatively resistant to TPN-induced bacterial translocation and intestinal bacterial overgrowth, we measured nitrite/nitrate levels in the plasma and ileal mucosa of the iNOS +/+ and iNOS −/− mice fed chow or TPN solution (Fig. 1). The levels of both plasma and ileal mucosal nitrite/nitrate were higher in the iNOS +/+ mice fed TPN solution than any of the other groups ($P < 0.01$). When ileal mucosal cNOS and iNOS levels were compared between the iNOS +/+ mice fed chow or TPN solution, it was apparent that the iNOS levels were higher in the TPN-fed mice than in the chow-fed mice ($P < 0.01$) (Fig. 2).

Last, we assessed whether the degree of mucosal injury was less in the TPN-fed iNOS −/− than in the TPN-fed iNOS +/+ mice by examining the histology of the ileum (Table 4). In the iNOS +/+ TPN-fed mice, there was a 9.5% incidence of villus injury. In contrast, the incidence of villus injury was similar between the iNOS −/− TPN-fed, and the chow-fed groups indicating that iNOS −/− mice were resistant to TPN-induced mucosal injury.

DISCUSSION

We and others have previously reported that TPN solution administered either enterally or

Table 1. Effects of TPN adminstration on bacterial translocation and mucosal injury in iNOS knockout mice

		Incidence and magnitude of bacterial translocation to MLN		
			Magnitude of BT (log_{10} CFU/g tissue)*	
Group	N	BT to MLN (%)	Total aerobes	Gram-negative enterics
iNOS +/+ chow	8	0		
iNOS +/+ TPN	8	75†	3.2 ± 0.29	2.9 ± 0.34
iNOS −/− chow	8	0		
iNOS −/− TPN	8	12.5	2.4	3.3

BT = bacterial translocation; CFU = colony-forming units.
†Magnitude of BT computed on only those MLNs that contained viable bacteria.
*$P < 0.05$ vs. all other groups; data expressed as mean ± SD.

Table 2. Effects of TPN on bacterial population levels of ileum and cecum

Group	N	Bacterial population levels of ileum (log_{10} CFU/g)		Bacterial population levels of cecum (log_{10} CFU/g)	
		Total aerobes	Gram-negative enterics	Total aerobes	Gram-negative enterics
iNOS +/+ chow	8	5.76 ± 0.2	5.54 ± 0.3	7.81 ± 0.2	7.59 ± 0.2
iNOS +/+ TPN	8	7.04 ± 0.5*	6.95 ± 0.5*	9.22 ± 0.3*	8.87 ± 0.2*
iNOS −/− chow	8	5.71 ± 0.4	5.50 ± 0.4	7.97 ± 0.2	7.84 ± 0.3
iNOS −/− TPN	8	6.11 ± 0.7	5.86 ± 0.8	7.98 ± 0.5	7.69 ± 0.6

*P <0.01 vs. all other groups; data expressed as mean ± SD.

parenterally, as well as certain liquid enteral diets, are associated with loss of gut barrier function, bacterial translocation, and disruption of the normal ecology of the intestinal microflora.[3–6] A number of therapeutic maneuvers have been successfully used to protect the intestine against diet-induced loss of barrier function. These include the administration of bulk fiber,[5,13] glutamine,[17,18] and certain trophic gut hormones.[6,19] However, the mechanisms responsible for diet-induced loss of gut barrier function and bacterial translocation remain to be fully determined.

Recent studies have shown a correlation between gut inflammatory states, ischemia-reperfusion–mediated gut injury, and increased nitric oxide production.[11,20,21] In these studies increased nitric oxide levels appear to be primarily related to increased nitric oxide production by the inducible form of nitric oxide synthase (iNOS). Thus we tested whether iNOS knockout mice (iNOS −/−) were more resistant to diet-induced loss of gut barrier function than their wild-type littermates (iNOS +/+). We chose to use iNOS −/− mice rather than using pharmacologic inhibitors of iNOS, because the use of iNOS knockout animals avoids the potential confounding effects of pharmacologic inhibition of NOS. The observation that oral TPN solution promotes gut injury, loss of barrier function, and bacterial translocation in the wild-type mice is consistent with our previous studies in both rats and mice[3,5,22] and indicates that the resistance of the iNOS −/− mice to TPN-induced gut injury and bacterial translocation is not related to the strain of the mice tested. Our results showing that oral TPN-induced bacterial translocation did not occur in the iNOS −/− mice extends the work of Hsu et al.,[23] who recently reported that diet-induced bacterial translocation and increased gut permeability could be reduced by the oral administration of NOS inhibitors. The fact that both plasma nitrite/nitrate levels, as well as intestinal nitrite/nitrate levels, and iNOS activity were increased in the iNOS +/+ mice receiving oral TPN solution as compared to the iNOS −/− TPN-fed group and the chow-fed groups further supports a role for increased intestinal nitric oxide production in the pathophysiology of oral TPN-induced bacterial translocation and gut injury.

That increased nitric oxide levels can lead to impaired intestinal barrier function both in vitro and in vivo has been documented in a large number of studies. Prolonged exposure of cells to large amounts of nitric oxide has been documented to cause cellular damage,[11] inhibit cellular respiration,[24] and lead to the production of the oxidant peroxynitrite.[25] In addition to causing cellular injury and dysfunction, high levels of nitric oxide can lead to the maldistribution of regional blood flow.[26] In fact, cell culture and ex vivo intestinal studies have documented that nitric oxide as well as nitric oxide donors directly increase intestinal permeability,[27] increase enterocyte monolayer permeability,[29,30] deplete adenosine triphosphate, and decrease tight junction integrity.[28] These effects of nitric oxide on enterocyte barrier function have also been

Table 3. Effects of TPN on enteroadherent bacterial population levels of ileal and cecal mucosa

Group	N	Adherent bacteria to ileal mucosa (log_{10} CFU/g)		Adherent bacteria to cecal mucosa (log_{10} CFU/g)	
		Total aerobes	Gram-negative enterics	Total aerobes	Gram-negative enterics
iNOS +/+ chow	8	4.01 ± 0.4	3.80 ± 0.5	5.92 ± 0.3	5.78 ± 0.3
iNOS +/+ TPN	8	5.13 ± 0.5*	5.05 ± 0.5*	7.17 ± 0.4*	7.07 ± 0.4*
iNOS −/− chow	8	3.80 ± 0.2	3.65 ± 0.3	5.75 ± 0.2	5.56 ± 0.2
iNOS −/− TPN	8	4.17 ± 0.8	4.08 ± 0.8	6.28 ± 0.7	6.06 ± 0.7

*P < 0.01 vs. all other groups; data expressed as mean ± SD.

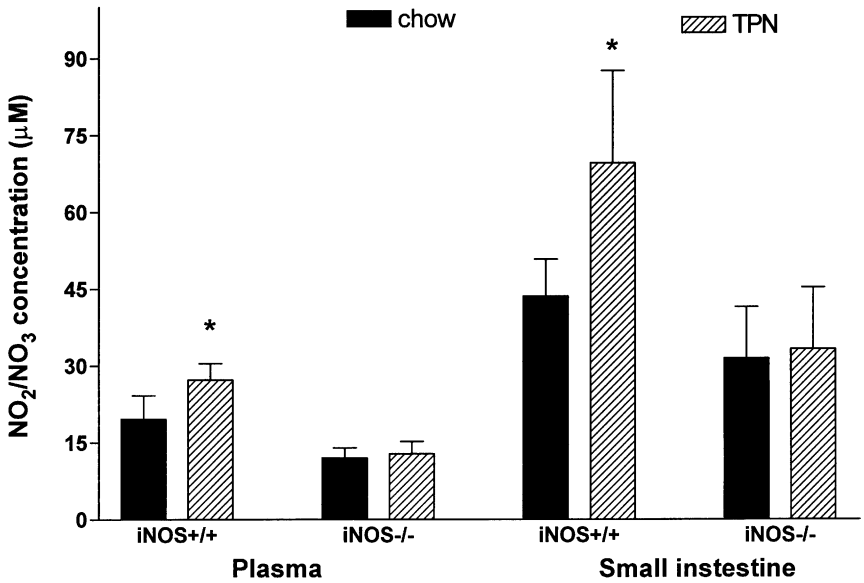

Fig. 1. Plasma and intestinal nitrite/nitrate levels are highest in the iNOS +/+ mice fed TPN solution. Data are expressed as mean ± SD with n = 8 mice per group. *P <0.01 vs. all other groups.

documented to be exacerbated at acidic pH levels.[29] Thus our finding that oral TPN-induced increases in intestinal nitric oxide levels and iNOS activity are associated with bacterial translocation and histologic injury in the iNOS +/+ mice is not surprising. Although oral TPN feeding for 14 days was associated with increased intestinal iNOS activity and plasma nitric oxide levels in the iNOS +/+ mice, these increases were two- to threefold lower than those observed in our previous experiments where these mice were challenged with endotoxin[12] or subjected to superior mesenteric artery occlusion.[30] These differences in intestinal iNOS activity and nitric oxide production may account for the fact that the histologic extent of gut injury in the oral TPN-fed iNOS +/+ mice was also approximately half of what was observed after endotoxin challenge or superior mesenteric artery occlusion in our previous studies.[12,30]

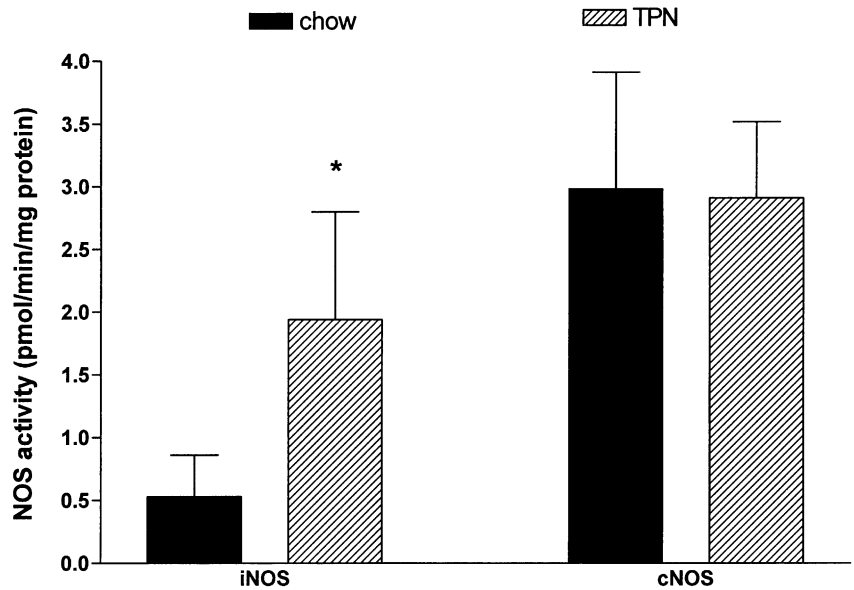

Fig. 2. Ileal mucosal iNOS but not cNOS activity was increased in iNOS +/+ mice fed TPN solution. Data are expressed as mean ± SD with n = 8 mice per group. *P <0.01 vs. chow-fed mice.

Table 4. Magnitude of ileal mucosal damage in iNOS +/+ and iNOS −/− mice with or without TPN

Group	N	No. of villi examined	Percentage of villi injured
iNOS +/+ chow	4	463	1.6 ± 1.1
iNOS +/+ TPN	4	484	9.5 ± 2.5*
iNOS −/− chow	4	424	1.0 ± 0.7
iNOS −/− TPN	4	493	2.4 ± 1.1

*$P < 0.01$ vs. all other groups; data expressed as mean ± SD.

To begin to determine the mechanism by which oral-TPN increased intestinal iNOS activity and nitric oxide production in the gut of the iNOS +/+ mice, we quantitated both total ileal and cecal bacterial population levels as well as the number of intestinal enteroadherent bacteria. The oral TPN-fed iNOS +/+ mice had a greater than 1 log higher level of enteroadherent intestinal bacteria than the oral TPN-fed iNOS −/− mice or the chow-fed control mice. Since incubation of enterocytes with bacteria as well as endotoxin has been documented to increase enterocyte production of nitric oxide as well as cytokines,[27,31] it is possible that oral TPN-induced bacterial overgrowth contributed directly and/or indirectly to the observed increase in intestinal nitric oxide production in the oral TPN-fed iNOS +/+ mice. Although diet-induced intestinal bacterial overgrowth is likely to have contributed to oral TPN-induced bacterial translocation and increased intestinal nitric oxide production, other factors appear to be involved. For example, the reason why intestinal bacterial overgrowth occurs in the oral TPN-fed iNOS +/+ but not in the iNOS −/− mice is unclear.

In summary, the current study implicates a role for diet-induced intestinal nitric oxide production in the pathogenesis of oral TPN-induced bacterial translocation, loss of gut barrier function, and gut injury. Although the mechanisms of how oral TPN solution promotes increased intestinal iNOS activity and nitric oxide production remains to be fully clarified, it appears that diet-induced intestinal bacterial overgrowth is involved.

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Factors Affecting Surgical Risk in Elderly Patients With Inflammatory Bowel Disease

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The operative treatment of elderly patients with inflammatory bowel disease (IBD) has often been avoided in favor of medical management because of a perceived increase in surgical risk. This study sought to define the following in the elderly IBD patient population: (1) the risk of surgical management and (2) those factors affecting risk. Thirty patients with IBD, aged 60 years or more, who were surgically managed by a single surgeon over a 10-year period, were retrospectively matched to 75 patients with IBD who were less than 60 years of age; patients were matched according to sex, date of surgery, and type of surgery performed. Regression analysis using generalized estimating equation methodology to account for the matched clusters of patients was performed to evaluate the effect of age group on the complication rate, operating room time, and length of hospital stay. Presence of comorbid conditions, surgical indications, prior surgery for IBD, and the use of immunosuppressive medications were studied in multivariate models, adjusting for age group. By means of univariate analysis, the odds of complications in elderly IBD patients were shown to be statistically higher than the odds seen in younger patients (47% vs. 20%, $P = 0.01$). Also observed in the elderly group were a longer length of hospital stay (11.5 days vs. 7.1 days, $P = 0.001$) and longer operating room time (249 minutes vs. 212 minutes, $P = 0.02$). Multivariate analysis revealed that the effect of age remained statistically significant, even when adjusted for potential confounding variables such as comorbidity, medications, date of diagnosis of IBD, and indications for surgery. The complication outcome was significantly associated with the surgical indication, with obstruction, fistula, and bleeding having increased odds of complications as compared with other indications (odds ratio = 1.7 vs. 4.2 vs. 7.2, respectively, $P = 0.02$). The length of hospital stay similarly was significantly associated with the surgical indication (fistula, 10.5 days vs. bleeding, 9.8 days vs. obstruction, 7.4 days vs. other, 9.3 days; $P = 0.04$) and a history of prior surgery. A significant interaction for length of hospital stay was present between age group and prior surgery status (with prior surgery: old, 18 days vs. young, 6.4 days, $P = 0.0001$; without prior surgery: old, 9.5 days vs. young 7.3 days, $P = 0.10$). Elderly patients with IBD have an increased rate of postoperative complications along with an increased length of hospital stay and increased operating room time. This effect of age persists when adjusted for comorbidity and immunosuppressive therapy. Complications are most dependent on surgical indications, with obstruction being the least and bleeding the worst predictive factors. The longest hospital stay is associated with patients who require surgery for fistulous disease and patients who have undergone previous surgery. The fact that the higher complication rate seen in older patients with IBD is associated with disease-defined surgical indications suggests that IBD in elderly patients may be more aggressive than what is observed in younger individuals. (J GASTROINTEST SURG 2002;6:606–613.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Crohn's disease, ulcerative colitis, inflammatory bowel disease

Inflammatory bowel disease (IBD) (Crohn's disease and ulcerative colitis) is typically regarded as a disease of the young. Age-specific epidemiologic data suggest, however, that incidence rates are bimodal with the greater incidence occurring at the beginning of the third decade of life, with a second mode between the ages of 55 and 70 years.[1] Studies have also suggested that IBD in elderly patients is different from the IBD seen in young patients, arguing for two variant disease phenotypes. IBD in older patients may involve different segments of the alimentary tract, with a poorer response to therapy, a higher rate

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of complications, and increased mortality.[2–5] More recent studies have refuted this concept arguing that age-dependent differences are related to misdiagnosis and referral bias.[4,6,7]

Although the primary treatment of patients with IBD is usually medical, a significant proportion of patients undergo surgical treatment of their disease. A reported increase in surgical complication rates has been attributed to the presence of comorbid conditions in this elderly group.[8] In fact, there are no studies objectively assessing the results of surgical management of elderly patients with IBD as compared to younger patients. The present study, therefore, sought to define the complication rate associated with the surgical care of elderly patients with IBD relative to younger patients and attempted to define the factors possibly affecting this risk.

METHODS

All patients undergoing laparotomy for IBD from 1989 to 1999 by a single colorectal surgeon at The Milton S. Hershey Medical Center of Pennsylvania State University were identified by means of the operating room registry. Thirty patients aged 60 years and above were identified and arbitrarily defined as the elderly IBD group. A total of 227 IBD patients under the age of 60 years were identified from this time period and were defined as the young group.

Each of the 30 elderly patients was randomly matched with one to three patients in the young group who were the same sex, had the same type of operation (ileal pull-through, ileocolectomy, proctocolectomy, small bowel resection, or total abdominal colectomy), and whose date of surgery was within 2 years of the elderly patient's surgery. Secondary matching variables included case type (urgent vs. elective) and disease (Crohn's disease vs. ulcerative colitis). Although the primary set of matching conditions was required, the secondary set was applied in efforts to identify the "best" matches available without making the criteria so strict as to preclude finding any matches for a given elderly patient. Patients who were matched were not constrained to have the same case type and disease; however, most resulting clusters of grouped individuals did match on these variables (only 5 of 30 clusters had mixed case types, and a separate six clusters had mixed diseases). Matching was employed in this study to economize on data abstraction, given the small number of elderly patients relative to young patients and, more important, to control for the matching variables, which were believed to be potential confounding factors. Matching was performed using an SAS statistical software package (SAS Institute Inc., Cary, North Carolina) macro written and documented at the Mayo Clinic.[9] This process identified 75 young patients who were individually matched to one of the 30 elderly patients. Sizes of matched clusters ranged from two (consisting of one elderly and one young patient) to four (consisting of one elderly and three young patients). Every elderly patient was matched and retained in the analysis (i.e., matching was complete) for a total of 30 matched clusters.

After the matched clusters of patients were defined, additional information was abstracted from their medical records for purposes of analysis. Variables that were documented at this time included the following: medications used on admission and at the time of discharge; date of diagnosis of IBD; previous surgeries for IBD; comorbid condition(s) (see Results); and indication for surgery (bleeding, fistula, obstruction, other). Outcome variables that were abstracted from medical records and the operating room registry included length of time in the operating room, postoperative complications, and length of hospital stay. Postoperative complications were defined as any unanticipated event that required either a therapeutic intervention or lengthened hospital stay.

Statistical Methods

For the postoperative complication outcome, logistic regression models were employed to characterize the effect of age group (elderly vs. young) on the odds of experiencing a complication. For the operating room time outcome, standard regression models were used to examine the effect of age group on operative time measured in minutes. For the length of stay outcome, which typically has a very skewed distribution, a log link and Poisson distribution were used to fit generalized linear regression models. Results from the length of stay models are summarized as ratios. For all regression analyses, generalized estimating equation[10] methodology was implemented to fit models that accounted for the correlation within clusters of patients as defined through the matching process. An exchangeable correlation structure was specified. Univariate models examining the effect of age group alone on the various response variables were fit and summarized. In addition, multivariate models were fit to evaluate the effects of the following potential confounding variables: presence of comorbid condition(s), surgical indications, prior abdominal surgery for IBD, and use of immunosuppressive medications (steroids, Imuran), as well as 5-ASA derivatives. In each multivariate model, the age group effect was included, by design, along with one of the additional variables. Interaction terms were assessed for

differential age effects within levels of the potential confounding variable. All analyses were performed using the SAS statistical software package, release 8.1 for Unix. All reported *P* values are two sided.

RESULTS

A total of 105 patients with IBD were studied (30 elderly and 75 young). Patient demographics and characteristics are reported in Table 1. All patients had biopsy-defined disease prior to surgery. Cardiovascular comorbid conditions (n = 17) included history of myocardial infarction, congestive heart failure, and hypertension. Pulmonary comorbid conditions (n = 2) were both asthma related and required inhalation therapy but no steroids. The metabolic comorbid conditions (n = 7) included three patients with insulin-dependent diabetes (elderly group), three patients with thyroid disorders, and one patient with short-bowel syndrome (all in the young group). Other comorbid conditions (n = 16) included history of cancer treated for cure (n = 5), seizures (n = 1), primary sclerosing cholangitis (n = 2), obesity as defined by a body mass index greater than 30 (n = 4), history of cerebrovascular accident (n = 2), history of liver transplantation (n = 1), and multiple sclerosis (n = 1).

There was a significant increase in the complication rate, length of hospital stay, and time in the operating room in the elderly group as compared to the young group (Table 2). For both young and elderly patients with IBD, the complication rate was much higher in those requiring an urgent vs. an elective procedure (elderly, 80% vs. 40%, younger, 56% vs. 15%). A descriptive analysis of study groups is seen in Table 3 and the type and number of complications seen in the two groups are presented in Table 4. The two cardiac complications were both non–life-threatening arrhythmias that responded to medical management. The high ileostomy output in the two patients in the elderly group resulted in dehydration that required intravenous rehydration and institution of antimotility/bile acid–binding agents. Of the five patients who developed a wound infection, four were treated with local wound care and one patient (young group) required reoperation for fascial dehiscence. Three patients in each group devel-

Table 1. Patient characteristics

	Age <60 yr (N = 75)	Age ⩾60 yr (N = 30)
Age at surgery (mean ± SD)	37 ± 11 yr (range 16 to 57 yr)	66 ± 6 yr (range 60 to 81 yr)
Sex		
Male	26 (35%)	10 (33%)
Female	49 (65%)	20 (67%)
Type of surgery		
Ileal pull-through	8 (11%)	3 (10%)
Ileocolectomy	35 (47%)	12 (40%)
Proctectomy	15 (20%)	9 (30%)
Small bowel resection	2 (3%)	1 (3%)
Total abdominal colectomy	15 (20%)	5 (17%)
Disease		
Crohn's disease	52 (69%)	18 (60%)
Ulcerative colitis	23 (31%)	12 (40%)
Comorbidity (at least one)	20 (27%)	15 (50%)
Cardiovascular	8	9
Pulmonary	1	1
Metabolic	4	3
Other	9	7
Type of surgery		
Elective	66 (88%)	25 (83%)
Urgent	9 (12%)	5 (17%)
Primary reason for surgery		
Bleeding	19 (25%)	9 (30%)
Fistula	11 (15%)	3 (10%)
Obstruction	24 (32%)	5 (17%)
Other	21 (28%)	13 (43%)
Prior surgery		
Yes	24 (32%)	7 (23%)
No	51 (68%)	23 (77%)

Table 2. Results of univariate regression analysis for each outcome

Outcome	Model-estimated means (95% CI)		Effect Old vs. young (95% CI)*	*P* value
	Young (<60 yr)	Old (≥60 yr)		
Complication rate (%)	20.0 (11.8, 31.7)	46.7 (29.9, 64.2)	3.5 (1.4, 9.1)	0.0092
LOS (days)	7.1 (6.3, 8.0)	11.5 (8.6, 15.4)	1.6 (1.2, 2.1)	0.0005
OR time (min)	212 (190, 235)	249 (215, 283)	36.9 (6.5, 67.3)	0.0172

CI = confidence interval.
*For complication rate, the odds ratio is represented. For length of hospital stay (LOS), the ratio of the LOS for the older group vs. the younger group is represented. For operating room (OR) time, the difference in means is given.

oped postoperative ileus that was managed conservatively with nasogastric decompression and intravenous fluids. Two patients in each group required reoperation for signs of peritonitis, with one patient in the young group developing a small bowel perforation secondary to cytomegalovirus enteritis. In the one patient in the elderly group who was operated on for small bowel perforation, this was secondary to an unrecognized enterotomy at the time of the initial surgery. No deaths occurred in either group.

To elucidate the possible cause of these differences, the data underwent multivariate analysis to examine the effect of age in the presence of potential confounding variables that had not been taken into account during the matching process. The multivariate analysis also allowed us to determine whether any of these other variables were associated with the study end points. For the complication rate, the age effect remained significant ($P \leq 0.02$) in the presence of each of the variables. In addition, none of the variables showed a significant interaction with age group.

Table 5 presents the effect of studied variables on the complication rate. As shown, the reason for surgical intervention was the only factor that significantly affected the complication rate ($P = 0.02$). Bleeding, fistula, obstruction, and other indications for surgery were shown to have progressively decreasing odds of complications. Because of this significant effect, pairwise comparisons were performed to determine which categories had significantly dif-

Table 3. Descriptive analyses of studied groups

Variables	Complications		LOS (days)		OR time (min)	
	<60 yr	≥60 yr	<60 yr	≥60 yr	<60 yr	≥60 yr
Case type of surgery						
Elective (n = 20)	10/66 (15%)	10/25 (40%)	6	8	207	248
Urgent (n = 9)	5/9 (56%)	4/5 (80%)	9	14	192	256
Disease						
Crohn's disease (n = 17)	8/52 (15%)	9/18 (50%)	6	11	196	230
Ulcerative colitis (n = 12)	7/23 (30%)	5/12 (42%)	7	8	225	277
Sex						
Male (n = 11)	7/26 (27%)	4/10 (40%)	7	8	248	261
Female (n = 18)	8/49 (16%)	10/20 (50%)	6	9	182	243
Comorbidity						
Yes	6/20 (30%)	8/15 (53%)	6	8	212	257
No	12/55 (22%)	6/15 (40%)	6	8	203	241
Medication						
Imuran						
Yes	3/20 (15%)	7/13 (54%)	7	8	228	248
No	12/55 (22%)	7/17 (41%)	6	8	197	250
Prednisone						
Yes	13/62 (21%)	11/26 (42%)	7	8	208	245
No	2/13 (15%)	3/4 (75%)	5	9	189	274
ASA						
Yes	9/40 (22%)	10/19 (53%)	6	8	193	244
No	6/35 (17%)	4/11 (36%)	6	8	218	258

Summary table of the descriptive analysis of each group representing comparisons between age groups based on differing matching variables.

Table 4. Complication rates and type

Complications	Ages <60 yr (N = 75)	Age ⩾60 yr (N = 30)
Overall	15 (20%) patients had 16 complications	14 (47%) patients had 16 complications
Transfusion	1 (1%)	3 (10%)
High ileostomy output	0	2 (7%)
MI/CHF/arrhythmia	1 (1%)	1 (3%)
DVT	2 (3%)	1 (3%)
Wound infection	1 (1%)	4 (13%)
Postoperative ileus	3 (4%)	3 (10%)
Reoperation	2 (3%)	2 (7%)
Small bowel perforation	1	1
Anastomotic leak	1	0
Adhesiolysis	0	1
Other	6 (8%)	0
Mortality	0	0

CHF = congestive heart failure; DVT = deep venous thrombosis; MI = myocardial infarction.

Table 5. Complication rate: Results of multivariate analysis adjusting for age group

Variable	Odds ratio (95% CI)	*P* value
Comorbidity		
Any vs. none	1.98 (0.87, 4.47)	0.1014
Primary reason for surgery		
Bleeding vs. fistula vs. obstruction vs. other		0.0226
Pairwise comparisons		
Bleeding vs. fistula	1.74 (0.33, 9.22)	0.5158
Bleeding vs. obstruction	4.18 (1.28, 13.65)	0.0180
Bleding vs. other	7.22 (1.92, 27.10)	0.0034
Fistula vs. obstruction	2.40 (0.54, 10.63)	0.2484
Fistula vs. other	4.15 (0.57, 30.48)	0.1616
Obstruction vs. other	1.73 (0.51, 5.88)	0.3810
Prior surgery		
Any vs. none	1.25 (0.47, 3.38)	0.6540
Prednisone use		
Yes vs. no	0.50 (0.10, 2.59)	0.4068
Imuran use		
Yes vs. no	1.01 (0.38, 2.65)	0.9880
ASA use		
Yes vs. no	1.69 (0.63, 4.50)	0.2957

Multivariate analysis examining the effects of specific variables on complication rates; all models adjusted for the age effect, which remained significant in the presence of the other variables. The primary reason for surgery is significantly associated with the complication rate, and the presence of comorbidity is marginally associated with the complication rate (Other = cancer surveillance, unresponsive to medication, pouchitis, perforation, and pain).

ferent complication rates. The complication rate for those with bleeding as the primary indication differed significantly from the rates for those with obstruction and "other" as the primary indications (odds ratio = 4.2, $P = 0.02$ and odds ratio = 7.2, $P = 0.003$, respectively). Also notable is the marginally significant effect of comorbidity on complication rates. Those with at least one comorbid condition were almost twice as likely to experience a complication as those with no comorbidity (odds ratio = 1.98, $P = 0.10$); however, this difference was not significant at the 0.05 level.

Using multivariate analysis, in a similar fashion, the same studied variables were considered for their effect on time in the operating room. (Table 6) and length of hospital stay (Table 7). Again, the effect of age remained significant in the presence of each of the possible confounding variables (for operating room time, age effect $P \leqslant 0.055$ in all models and for length of stay, age effect $P \leqslant 0.0014$ in all models). A significant interaction between age group and prior surgery status was identified for the length of stay outcome (interaction $P = 0.0091$), as discussed below. Results of the multivariate analysis for operating room time are shown in Table 6. None of the variables studied showed a significant association with operating room time. However, when these analyses were applied to length of hospital stay (Table 7), there was a significant association with primary reason for surgery ($P = 0.04$). In this regard, patients with fistulas had the longest length of stay at 10.5 days followed by bleeding (9.8 days), other (9.3 days), and obstruction (7.4 days). All patients with fistulas underwent surgery without delay, implying that this greater length of stay was not due to an additional period of preoperative medical management. Pairwise comparisons revealed that length of stay for patients with obstruction was significantly lower than length of stay for those with other reasons for surgery ($P = 0.04$); no other comparisons achieved statistical significance.

Because of the highly significant interaction between prior surgery status and age group for the length of stay outcome, the effects of age were examined within each prior surgery category. When comparing young and old patients who had had prior surgery, the length of stay for the older patients was 2.8 times higher than the length of stay for the younger patients (95% CI (1.8, 4.4); P=0.0001); whereas older patients who had not had prior surgery had a length of stay that was only 1.3 times higher than that of younger patients who had not had prior surgery (95% confidence interval 0.95 to 1.8; $P = 0.10$). The significant interaction between prior surgery status and age group for the length of stay outcome showed that the effect of age is greater

Table 6. Operating room time: Results of multivariate analysis adjusting for age group

Variable	Mean OR time (min)	Difference (95% CI)	*P* value
Any comorbidity			
Yes	231.8	2.5 (−26.9, 32.0)	0.8671
No	229.3		
Primary reason for surgery			
Bleeding/toxic megacolon	230.6	NA	0.1358
Fistula	275.6		
Obstruction	201.3		
Other	234.7		
Prior surgery			
Any	255.7	33.5 (−24.1, 91.0)	0.2547
None	222.2		
Prednisone use			
Yes	229.1	−11.2 (−63.1, 40.7)	0.6723
No	240.3		
Imuran use			
Yes	231.4	0.8 (−28.2, 29.9)	0.9547
No	230.5		
ASA use			
Yes	226.7	−10.3 (−47.4, 26.8)	0.5871
No	236.9		

Multivariate analysis examining the effects of specific variables on operating room (OR) time; all models adjusted for the age effect, which remained significant in the presence of the other variables. None of these variables was significantly associated with OR time. CI = confidence interval; NA = pairwise comparisons nonapplicable because of a nonsignificant main effect.

for those who have had prior surgery. There was no obvious explanation for this effect.

DISCUSSION

The surgical management of IBD in the elderly patient has often been approached more hesitantly than that of the younger patient. This bias is based on a perception of greater operative risk because of the presence of comorbidity. The present study statistically confirms this anecdotal impression of increased operative risk but refutes the contention that increased comorbidity status is entirely responsible for this effect. Our data suggest that other factors are more important. The older patients in the present study had a higher incidence of comorbid conditions (50% vs. 27%) and a much higher incidence of perioperative complications (46% vs. 20%); however, the higher rate of complications could not be entirely statistically explained by the presence of co-

Table 7. Length of stay: Results of multivariate analysis adjusting for age group

Variable	Mean LOS (days)	Ratio (95% CI)	*P* value
Any comorbidity			
Yes	8.3	0.85 (0.64, 1.15)	0.2943
No	9.7		
Primary reason for surgery			
Bleeding/toxic megacolon	9.8		0.0357
Fistula	10.5		
Obstruction	7.4		
Other	9.3		
Pairwise comparison			
Bleeding vs. fistula		0.93 (0.54, 1.61)	0.7996
Bleeding vs. obstruction		1.33 (0.92, 1.92)	0.1302
Bleeding vs. other		1.05 (0.71, 1.54)	0.8141
Fistula vs. obstruction		1.43 (0.95, 2.13)	0.0836
Fistula vs. other		1.12 (0.70, 1.79)	0.6247
Obstruction vs. other		0.78 (0.63, 0.99)	0.0400
Prior surgery*			
Age <60 + prior surgery	6.4	0.87 (0.70, 1.09)	0.2246
Age <60 without prior surgery	7.3		
Age ⩾60 + prior surgery	18.0	1.89 (1.08, 3.29)	0.0254
Age ⩾60 without prior surgery	9.5		
Prednisone			
Yes	8.9	0.90 (0.58, 1.39)	0.6336
No	9.9		
Imuran			
Yes	8.2	0.86 (0.66, 1.14)	0.2950
No	9.5		
ASA			
Yes	8.7	0.90 (0.68, 1.20)	0.4788
No	9.6		

Multivariate analysis examining the effects of specific variables on length of stay (LOS); all models adjusted for the age effect, which remained significant in the presence of the other variables. Primary reason for surgery is significantly associated with LOS.

*A significant interaction existed between prior surgery status and age group ($P = 0.0091$); therefore, results are presented within each age group for this variable. Prior surgery status is significantly associated with LOS for older patients but not for younger patients.

morbid conditions ($P = 0.101$). There was no significant interaction between age group and comorbidity status, indicating that the effect of a comorbid condition on the complication rate was similar for young and old patients. Also, when adjusting for the presence of comorbidity, the age effect remained significant for all three outcome variables (complication rate, $P = 0.0171$ operating room time, $P = 0.0261$; length of hospital stay, $P = 0.0014$). The presence of comorbidity, therefore, did not fully explain the worse outcomes in the older group.

Interestingly, the primary reason for surgery was the main explanatory variable (aside from age group) that was associated with any of the outcomes mentioned. The specific reason for surgery was associated with both the increased rate of complications and the increased length of stay, after adjusting for the age effect. Those with bleeding as the primary reason for surgery had the highest level of complications, followed by fistula, obstruction, and other indications. Patients with fistulas had the longest length of stay, followed by bleeding, other indications, and obstruction. The other interesting determination involving length of stay was prior surgery status, with a mean length of stay of 18 days in the elderly group who had had prior surgery as compared to 6.4 days in the younger group who also had undergone previous surgery for IBD. When analyzing the groups individually, those older patients with prior surgery had a length of stay that was 1.9 times longer than that of older patients with no history of prior surgery. Among younger patients, those with prior surgery had a length of stay 0.9 times as long as that in younger patients with no history of prior surgery. The effect was significant ($P = 0.03$) in the elderly group, but not in the young group, suggesting that prior surgery somehow puts only older patients at risk for longer length of stay. The fact that a diagnosis-defined (i.e., IBD-defined) surgical indication was statistically responsible for the increased complication rate, length of stay, and operating room time measures suggests that IBD is different and possibly more aggressive in elderly patients.

No studies have been performed to date that explore the possible differences in IBD between young and old patients relating to surgical outcomes. Most reported studies discuss the clinicopathologic features of these diseases with emphasis on the diagnosis and management of IBD in different age groups and do not focus on surgical outcomes. Despite the lack of surgical treatment–based studies, many past clinical reports suggest that there is a difference between old and young IBD patients with respect to disease characteristics. Brandt et al.[5] reported in 1982 that "the prognosis for colitis in elderly patients, regardless of type, is worse than in young patients." Their study included ulcerative disease, Crohn's disease, and ischemic colitis. Additionally, Wagtams et al.[7] compared Crohn's disease in both a young and an old cohort and determined that "Crohn's disease in the elderly appears to be characterized by a more rapid development," although they compared the clinicopathologic features of the diseases as opposed to surgical outcomes. Nonetheless these studies suggest that IBD in elderly patients is of a different phenotype. Although these studies provide evidence for differences in IBD between young and old patients, many retrospective reviews suggest that these early reports may have been erroneous because of difficulties in differentiating between IBD and other intestinal disorders such as diverticulitis or ischemic colitis. Gupta et al.,[11] in 1985, could not substantiate the more serious clinical course observed in elderly IBD patients, and Grimm and Friedman[6] and Softley et al.[12] reported that the "recent epidemiologic and clinical reports indicate that the outlook for older patients with inflammatory bowel disease is more favorable than previously suspected." These studies, however, were limited to the comparison of specific and general disease symptoms and failed to address age-defined surgical outcomes that were the focus of this report. Nonetheless, it appears that most clinicians agree that there is an age-related difference between elderly and young patients with IBD concerning the characteristics and course of IBD. Our current report also suggests that there is, indeed, a difference in IBD phenotype between young and old patients when comparing surgical outcomes. Intuitively, it is not unreasonable to hypothesize that patients who have been asymptomatic yet genetically predisposed to IBD for their entire lives only become diseased when a more virulent form of IBD manifests later in life.

In summary, old and young patients with IBD differed significantly with regard to complication rates, time in the operating room, and length of hospital stay when similarly treated for their disease. These differences were not explained when adjusted for possible confounding variables such as comorbidity and use of immunosuppressive agents. Some other factor(s) appear to be responsible for these differences, with specific disease-related surgical indications being most directly responsible for the identified increases in complication rates, operating room time, and length of hospital stay.

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Breast Cancer Masquerading as a Primary Gastric Carcinoma

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The differentiation between primary gastric cancer and a metastatic breast tumor to the stomach is important for planning of treatment and to spare the patient unnecessary surgery. We report a rare case of breast cancer with metastasis to the stomach. The diagnosis was established by histologic and immunohistochemical analyses of biopsies of the stomach lesion using gross cystic disease fluid protein-15, cytokeratin, carcinoembryonic antigen, and epithelial membrane antigen. Positivity for gross cystic disease fluid protein-15 with negative staining for carcinoembryonic antigen supported the diagnosis of a breast cancer metastasis. The patient was treated with systemic chemotherapy without surgery and is still alive 2 years after initial referral for a gastric neoplasm. (J GASTROINTEST SURG 2002;6:614–616.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Breast cancer, metastases, stomach, immunohistochemistry

The most frequent sites of metastases of breast cancer are nodes, skin and soft tissues of the chest wall, bones, lungs, liver, and brain. In rarer cases, metastases have been described in other sites including the gastrointestinal tract. In such cases, the clinical presentation mimics a primary gastrointestinal tumor with symptoms that can be similar, albeit nonspecific, with the most common presentation being jaundice or biliary obstruction. The radiologic and endoscopic findings can also be compatible with those of a primary gastrointestinal tumor. However, when faced with a patient who has a history of breast cancer, the clinician must have a high level of suspicion and review with the pathologist the histopathology of the primary breast tumor and the gastrointestinal biopsies. We describe a case of breast carcinoma metastatic to the stomach that was detected with immunohistochemical analysis.

CASE REPORT

Clinical History and Surgical Treatment

Ten years before presentation with dysphagia, the patient had a T2N1M0 breast cancer treated by a modified radical mastectomy. Estrogen receptors were positive and progesterone receptors were negative. The lesion's histologic type was lobular. The patient did not receive any adjuvant therapy and a systemic workup at this time including a bone scan and abdominal ultrasound imaging was negative. In 1991 a bone scan demonstrated the presence of multiple foci of metastases and, as a result, tamoxifen, 20 mg daily, was started. In 1997 the bone metastases progressed and a 10 mm nodule on the chest wall was noted. Tamoxifen was discontinued and alendronate started. The patient did not take the alendronate because of gastric discomfort. A few months later bone metastases were still in progression and a second nodule appeared on the thoracic wall. The patient was then referred to a medical oncologist in February 1998. Anastrozole (an aromatose inhibitor), 1 mg orally, and pamidronate (an osteoclast inhibitor), 60 mg intravenously every 4 weeks, were started. One month later the patient was complaining of progressive dysphagia with a weight loss of 20 pounds. A barium upper gastrointestinal examination demonstrated encasement of the entire body of the stomach (Fig. 1). The esophagus, gastric fundus, and antrum all appeared normal. This appearance was quite consistent with a linitis plastica–type lesion. Abdominal ultrasonography demonstrated prominent gastric walls without any evidence of intra-abdominal metastases. Gastroscopy showed thick and rigid folds in the body of the stomach suspicious for linitis plastica. Multiple endoscopic biopsies were done.

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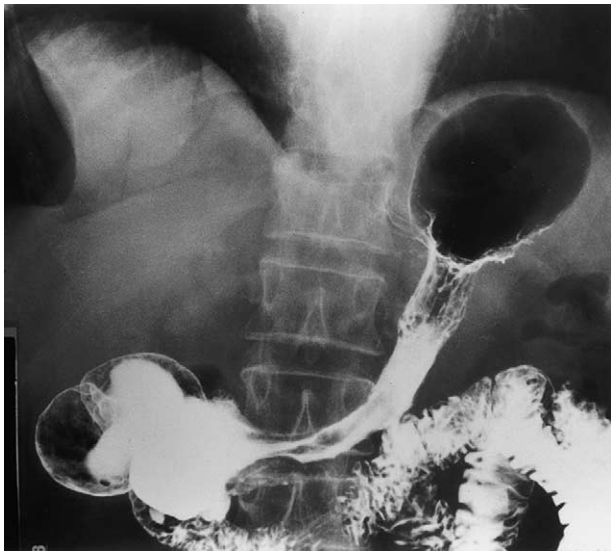

Fig. 1. Upper gastrointestinal barium examination showing encasement of the entire body of the stomach consistent with linitus plastica. This persisted under fluoroscopy and did not represent spasm.

Pathology and Follow-Up

The biopsies showed minute implants of carcinoma with signet ring morphology in a gastric-type mucosa with nonspecific mild active chronic gastritis (Fig. 2). Immunohistochemical analysis was carried out on formalin-fixed paraffin sections using the avidin-biotin-peroxidase complex method. The following antibodies were used: gross cystic disease fluid protein (GCDFP-15), cytokeratin, carcinoembryonic antigen (CEA), and epithelial membrane antigen. The positivity of GCDFP-15 monoclonal antibody with concurrent negativity for CEA in the infiltrating cells of signet ring morphology argues strongly for a mammary origin as opposed to a primary lesion of the stomach.

In view of these findings it was decided to treat the patient for metastatic breast cancer and not perform surgery. Two years after the initial referral for a so-called gastric cancer, the patient was still taking arimidex, eating normally with a stable weight, and had no gastrointestinal symptoms.

DISCUSSION

Metastatic involvement of the gastrointestinal tract is rare. Breast cancer is one of the more frequent tumors implicated. Breast cancers can spread to the liver, peritoneum, colon adnexa, retroperitoneum, and small bowel.[1] The reported incidence of gastric metastasis from a breast cancer varies from 2% to 18%.[2-6] Other tumors that are known to metastasize frequently to the stomach are melanoma and renal cell carcinoma.[7] The discovery of a gastric tumor in a patient with a history of breast cancer is more likely to be a primary gastric lesion, but a metastasis from the breast tumor is possible and must be ruled out. Many cases of metastatic breast tumors have been reported to occur several years after the diagnosis of the primary breast lesion. The differentiation between the two tumors is important in order to establish the correct treatment and avoid needless surgery.

The clinical presentation being the same for both types of tumors, it is not possible to clinically differentiate a primary gastric tumor from a breast metastasis. Radiologic and endoscopic evaluations, although nonspecific, may show features that can point toward the diagnosis of metastasis. These include an extrinsic lesion of the gastric wall not reaching the mucosa, multiple lesions, and signs of linitis plastica. Radiologic evidence of linitis plastica has been reported, particularly with metastatic involvement of the stomach by a lobular type breast carcinoma as seen here. Because the lesion is often limited to the submucosal and seromuscular layers of the stomach, the endoscopic evaluation may show only discrete mucosal abnormalities. Deep biopsies are hence necessary to obtain representative material, although this was not specifically done in this case.

Immunohistochemical analysis may be the only reliable modality for differentiation of the two tumors. The comparison of the metastatic lesion with the primary breast lesion may show a similar histologic picture. The most frequent histologic type of breast cancer associated with gastric metastasis is the lobular type, which frequently shows a signet ring morphology giving rise to potential confusion with a primary signet ring or diffuse-type gastric adenocarcinoma. Immunohistochemical analysis is a necessary adjunct for differential diagnosis. Estrogen and progesterone receptors can be present occasionally in a primary gastric tumor, but a high level favors a breast cancer metastasis. Positivity for GCDFP-15 monoclonal antibody in a stomach lesion is very suggestive of a breast metastasis. GCDFP-15 has not been widely studied, but has been found to be negative in primary stomach cancer and positive in breast cancer.[8]

The treatment recommendation for gastrointestinal metastasis from breast cancer is systemic treatment of the metastatic disease. The response rate in one series was approximately 30%[5] and survival exceeding 1 year has been reported.[1] Surgical treatment must be reserved for patients who develop a complication such as obstruction or hemorrhage from the tumor.[2,4,5]

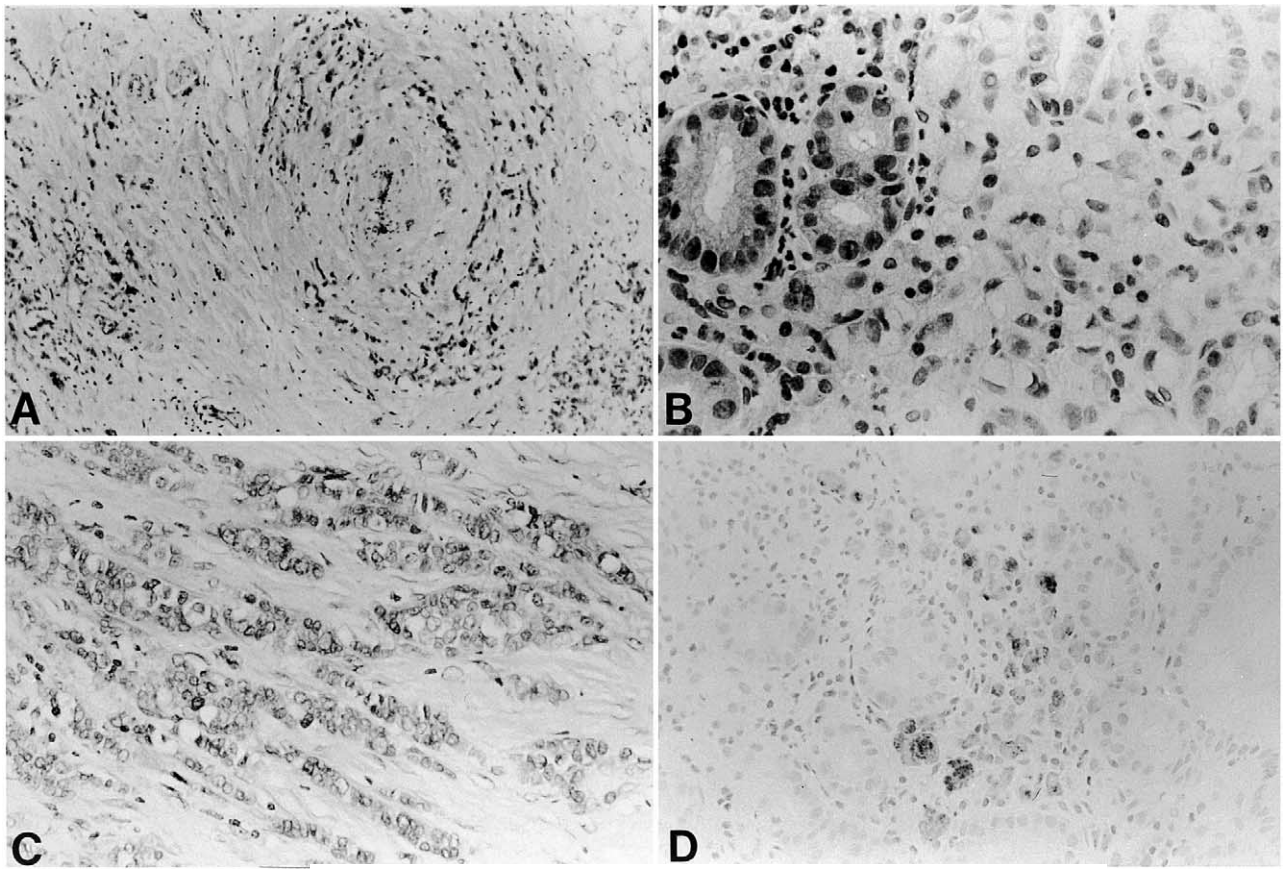

Fig. 2. **A**, Targetoid infiltration. **B**, Focus of signet ring cells in the gastric wall. **C**, Single-file invasion characteristic of infiltrating lobular carcinoma. **D**, Signet ring cells strongly positive for BRST-2.

CONCLUSION

Primary gastric cancer can be distinguished from metastases from a breast cancer by means of immunohistochemical analysis. In the current case, immunohistochemical markers helped support the diagnosis of a metastatic lesion to the stomach that grossly presented as linitus plastica. An attempt at primary resection was avoided and palliative surgery was and should be reserved for hemorrhage or obstruction that might not have been controllable by endoscopic therapy.

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Surgical Treatment of Hilar Bile Duct Carcinoma: Experience With 25 Consecutive Hepatectomies

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To evaluate our recent surgical policy regarding hilar bile duct carcinoma, we evaluated 62 cases treated between 1976 and 1993, and 25 cases treated between 1994 and 2000. In the late period we used percutaneous transhepatic portal vein embolization (PTPE) before extended right hepatectomy; S4a + S5 + S1 hepatectomy for elderly patients and those with poor liver function; and routine total caudate lobectomy including the paracaval portion and resection of the inferior portion of the medial segment (S4a). Sixty-five (74.7%) of the 87 patients underwent hepatectomy: 40 in the early period and 25 in the late period. Bile duct resection alone was performed in 22 patients, all in the early period. Resection was curative in 54.8% in the early period and 88.0% in the late period. The 3- and 5-year survival rates in the early period were 27.1% and 20.2%, respectively, as compared to 59.9% and 49.9% in the late period. Analysis of the 25 hepatectomies in the late period revealed improved survival times compared to patients treated by PTPE with extended right hepatectomy. No complications occurred after extended left hepatectomy or S4a + S5 + S1 hepatectomy, but four patients (16%) who underwent extended right hepatectomy plus PTPE died postoperatively. Our policy has resulted in improved outcome in patients with hilar bile duct carcinoma. (J GASTROINTEST SURG 2002;6:617–624.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Surgical treatment, hilar bile duct carcinoma, curative resection, survival rate

Curative resection is essential to achieving long-term survival in hilar bile duct carcinoma.[1–4] Because hilar bile duct tumors are in close proximity to vital structures in the hepatic hilum, such as the hepatic artery and portal vein, and they tend to spread to the proximal biliary tract and the perineural and perilymphatic spaces, margin-negative resection is often technically impossible. Nevertheless, surgeons have been striving to obtain margin-negative resections by applying a variety of operative procedures, ranging from local resection to aggressive resection, with or without vascular surgery. Local resection procedures have been shown not to be curative,[5–7] and although aggressive resection provides a means of curative resection, the high perioperative morbidity and mortality do not improve the overall survival benefit.[8–10] This has convinced us that the optimal approach is to perform the minimal parenchymal resection required for curative resection.

Over the past 24 years (1976 to 2000), resection of hilar carcinoma has been performed at our institution by different surgical teams using a variety of surgical strategies. In 1994, with all previous experience in mind, the surgical protocol for hilar carcinoma was changed to application of percutaneous transhepatic portal vein embolization (PTPE) before extended right hepatectomy; parenchyma-preserving limited hepatectomy for elderly and poor-risk patients; and routine total caudate lobectomy, resection of the inferior portion of the medical segment (S4a), and intraoperative confirmation of negative margins at the cut end of the intrahepatic ducts. This strategy had not been consistently applied before 1994. This report compares surgical outcomes during two periods—the early period from 1976 to 1993 and the late period from 1994 to 2000—and summarizes our experience with 25 consecutive liver resections for hilar carcinoma during the 7 years of the late period.

PATIENTS AND METHODS

Between 1976 and 2000, a total of 113 patients with hilar bile duct carcinoma were treated in the

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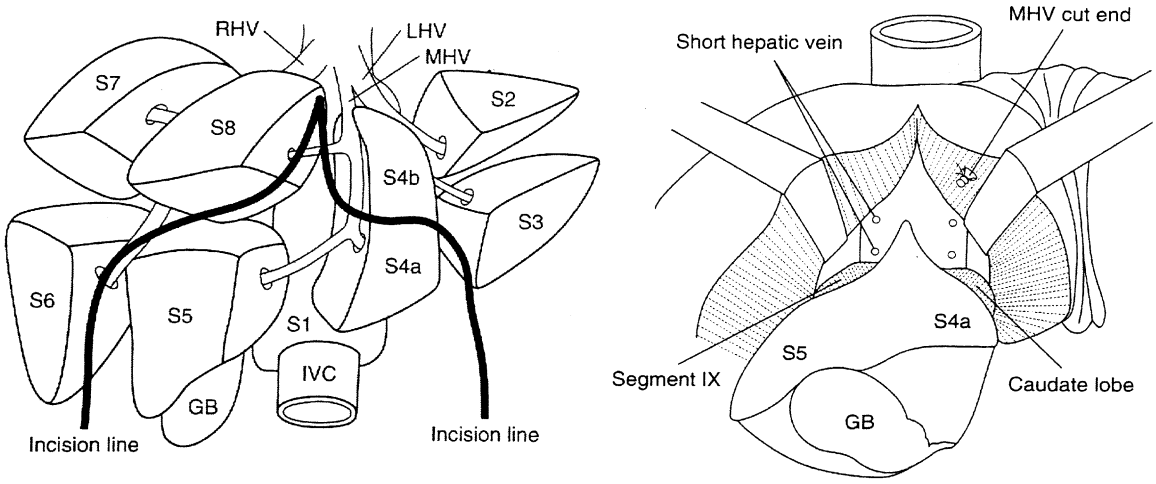

Fig. 1. A, Taj Mahal parenchymal incision line. GB = gallbladder; IVC = inferior vena cava; LHV = left hepatic vein; MHV = middle hepatic vein; RHV = right hepatic vein. **B**, Complete resection of S4a + S5 and total caudate lobe.

First Department of Surgery of Mie University, Mie, Japan. Of these 113 patients, 98 were treated surgically, but the other 15 were not, because they had advanced disease and were in poor health. Eighty-seven (88.8%) of the 98 patients underwent surgical resection, and these 87 patients were divided into two groups to compare outcomes of the treatment strategies during the early period (n = 62) and the late period (n = 25). We used the following operative procedures in the late period, choosing the procedure in each case according to the location and extent of the tumor: (1) PTPE with extended right hepatectomy; (2) extended left hepatectomy; and (3) for elderly patients and patients with poor liver function, S4a + S5 + S1 hepatectomy, which we refer to as the Taj Mahal liver parenchymal resection.[11] This new operative procedure minimizes parenchymal loss and likely decreases postoperative liver failure in comparison to central hepatic resection (S4a + S4b + S5 + S8) (Fig. 1). In addition, all patients underwent a total caudate lobectomy including the paracaval portion, referred to as segment IX according to the new Couinaud system[12,13] (Fig. 2), resection of segment S4a for curative purposes in addition to caudate lobectomy, and confirmation of negative margins by frozen-section biopsy of every cut end of the intrahepatic ducts in the remnant lobe. In no instance was bile duct resection alone used. This integrated policy was not applied in the early period. The operative procedures, postoperative complications, and outcomes in the two groups were compared.

We treated a total of 28 patients with hilar carcinoma in the late period. Of these 28 patients, 25 were treated by combined hepatectomy, but the other three were not because of their advanced disease; thus a resectability rate of 89.3% was achieved. These 25 patients consisted of 19 men and six women whose median age was 65.8 years (range 44 to 79 years). Twenty-two patients (88.0%) had obstructive jaundice. Tumors were classified as follows according to the Bismuth-Corlette classification: type 1 in two patients, type II in three, type IIIa in six, type IIIb in four, and type IV in 10. Surgical resections included extended right hepatectomy in nine cases (with pancreaticoduodenectomy in one), extended left hepatectomy in seven, and S4a + S5 + S1 (Taj Mahal) hepatectomy in nine (with pancreatic head resection and second-portion duodenectomy in one, pylorus-preserving pancreaticoduodenectomy in two, and pancreaticoduodenectomy in one). Our experience with these 25 consecutive hepatectomies is summarized in this report.

Statistical Analysis

The parameters were compared by using the chi-square test. The Kaplan-Meier method was used to

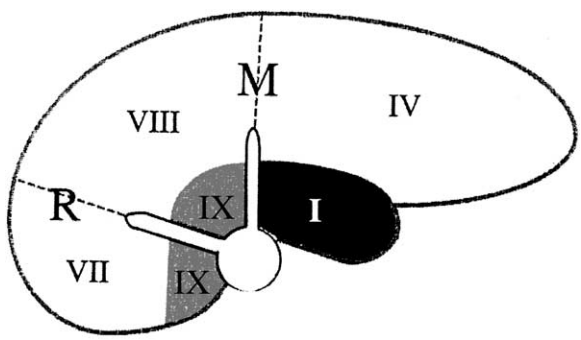

Fig. 2. Segment IX of the new Couinaud system (see ref. 13).

Table 1. Operative procedures in the 87 resected cases

Operative procedures	Early period (1976-1993) (n = 62)	Late period (1994-2000) (n = 25)
With hepatectomy*	40 (64.5%)	25 (100%)
Extended hemihepatectomy [S1]	14 [13]†	16 [16]†‡
Hemihepatectomy [S1]	13 [12]†	0
Central hepatectomy [S1]	8 [5]†	0
S4a + S5 resection [S1]	0	9 [9]‡
S1 resection alone	5‡	0
Without hepatectomy*	22 (35.5%)	0
Bile duct resection alone	19	0
Bile duct resection with PD	3	0
Total S1 resection*	35 (56.5%)	25 (100%)
Curative resection*	34 (54.8%)	22 (88.0%)

[S1] = including caudate lobectomy; PD = pancreaticoduodenectomy.
*$P < 0.01$, early period vs. late period.
†One patient with vascular resection.
‡One patient with pancreatoduodenectomy.

construct survival curves. Differences between survival curves were analyzed by the generalized Wilcoxon test, and a significant difference was defined as $P < 0.05$.

RESULTS

Surgical Procedure

Hepatectomy was performed in 65 (74.7%) of the 87 surgically resected patients—40 in the early period and 25 in the late period—and the difference between the two periods in terms of the number of patients undergoing hepatectomy was significant. Hepatectomy combined with vascular surgery was performed in more patients in the early period (n = 6) than in the late period (n = 1). Bile duct resection alone was performed in 22 of the 87 patients, all in the early period. Total caudate lobectomy that included the paracaval portion was performed in all patients in the late period, as opposed to caudate lobectomy alone in 35 patients (56.5%) in the early period. S4a + S5 + S1 hepatectomy was performed only in the late period. Curative resection (both macroscopically and microscopically negative margins) was achieved in 88.0% of patients in the late period as compared to only 54.8% in the early period; this difference in curative resection rates was significant (Table 1).

Morbidity and Mortality

Postoperative complications occurred in 24 (27.6%) of the 87 patients: 19 in the early period (30.6%) and five in the late period (20.0%); this difference between the two periods was not significant (Table 2). The most frequent complication was liver failure, which occurred in 10 patients and was more common in the early period (20.0%) than in the late period (8.0%).

Operative death (within 1 month) occurred in two cases (2.3%), and both deaths were caused by multiple organ failure. One of the deaths occurred during the early period in a patient who underwent extended right hepatectomy with resection of the caudate lobe and portal vein, and the other occurred in the late period in a patient treated by extended right hepatectomy with resection of the caudate lobe and pancreaticoduodenectomy.

Survival Rates

The overall cumulative 1-, 3-, and 5-year survival rates in the 87 resected patients were 59.1%, 34.1%, and 26.3%, respectively. The 1-, 3-, and 5-year survival rates in the early period were 52.5%, 27.1%, and 20.2% respectively, as opposed to 81.1%, 59.9%, and 49.9% in the late period, showing an improvement in outcome in the late period (Fig. 3).

Long-Term Survival

On the 87 surgically treated patients, 14 survived more than 5 years after the operation: 11 in the early period and three in the late period. The mode of treatment was extended left hepatectomy in nine patients, bile duct resection alone in four (with pancreaticoduodenectomy in 1), and independent caudate

Table 2. Major postoperative complications in the 87 resected cases

Complications	Early period (1976-1993)	Late period (1994-2000)
With hepatectomy	17 (42.5%)	5 (20.0%)
Liver failure	8 (20.0%)	2 (8.0%)
Leakage of hepaticojejunostomy	6	3
Wound infection	5	1
Multiple organ failure	3*	1*
Respiratory failure	2	0
Upper gastrointestinal bleeding	3	0
Intra-abdominal bleeding	1	0
Disseminated intravascular coagulation	1	0
Without hepatectomy	2 (9.1%)	0
Wound infection	1	0
Respiratory failure	1	0
TOTAL	19 (30.6%)	5 (20.0%)

*One patient died within 1 month after surgery.

lobe resection with pylorus-preserving pancreatoduodenectomy in one. All of them had tumor-free surgical margins. Four of the 14 patients had early carcinoma of the bile duct (pT1a or pT1b), and the other 10 patients had pT2 carcinoma with lymphatic permeation, venous invasion, or perineural infiltration. The histologic diagnosis was papillary adenocarcinoma in five cases, well-differentiated adenocarcinoma in five, and moderately differentiated adenocarcinoma in four. None of these long-term survivors had lymph node metastasis. Ten patients are still alive, three have died of tumor recurrence, and one died of other disease.

Experience With 25 Consecutive Hepatectomies in the Late Period

All of the patients treated by Taj Mahal hepatectomy were elderly, and their liver function was more impaired than that of the patients treated by extended right or left hepatectomy. Percutaneous transhepatic biliary drainage was performed to alleviate

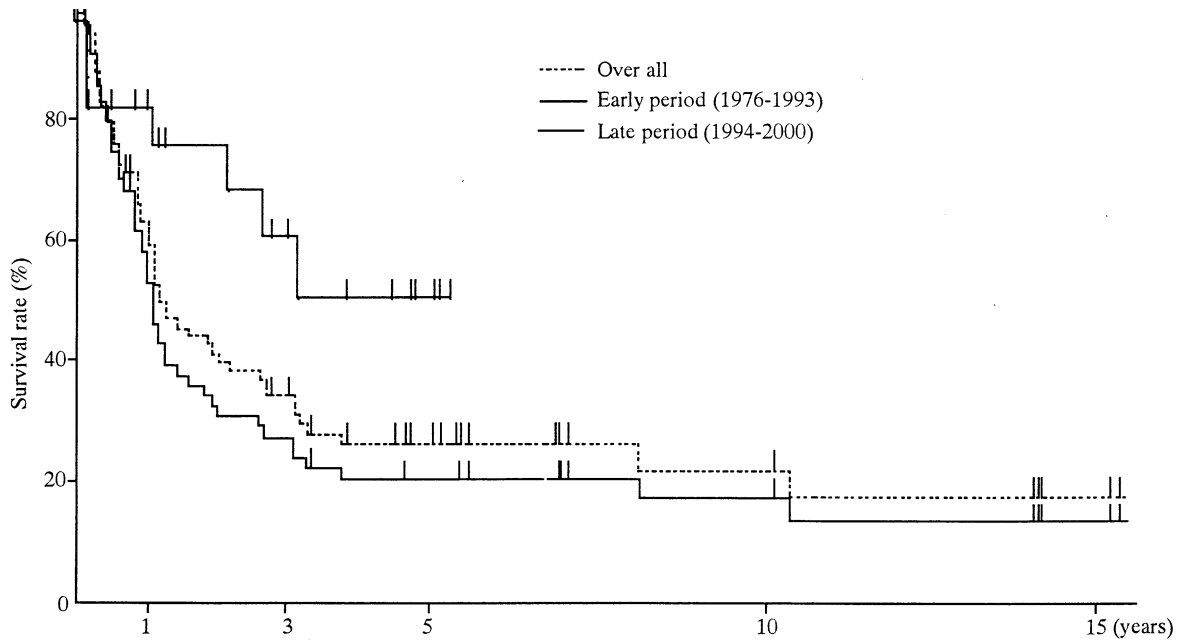

Fig. 3. Overall cumulative survival rate, and survival rates in the early and the late period.

Table 3. Surgical procedures and outcomes for hilar bile duct carcinoma in the late period (1994 to 2000)

	Extended right hepatectomy + S1	Extended left hepatectomy + S1	S4a + S5 + S1 resection
No. of patients	9	7	9
Age (yr)	64.4 ± 9.9	61.1 ± 7.9	69.7 ± 8.2
Sex (M:F)	7:2	6:1	6:3
PTBD	8 (88.9%)	7 (100%)	7 (77.8%)
PTPE	6 (66.7%)	0	0
Tumor type (Bismuth-Corlette)			
I	0	0	1
II	0	0	4
IIIa	5	1	0
IIIb	0	4	0
IV	4 (50.0%)	2 (28.6%)	4 (50.0%)
T-bilirubin (mg/ml)	0.8 ± 0.6	0.9 ± 0.4	0.5 ± 0.4
ICGR15 (%)	7.2 ± 3.6	8.5 ± 4.6	11.9 ± 4.2*
Curative resection	8 (88.9%)	6 (85.7%)	9 (100%)
Perioperative mortality	4†	0	0
Median survival time (mo)	11.7	34.0	20.0

PTBD = percutaneous transhepatic biliary drainage; PTPE = percutaneous transhepatic portal vein embolization.
*$P < 0.05$, Taj Mahal vs. extended right hepatectomy.
†Patients underwent PTPE preoperatively.

jaundice and evaluate the biliary system when necessary. PTPE was performed in six of the nine patients who underwent extended right hepatectomy. Extended right hepatectomy was usually performed in patients with Bismuth type IIIa tumors, extended left hepatectomy in those with type IIIb tumors, and Taj Mahal hepatectomy in those with type I and II tumors. Bismuth type IV tumors accounted for four (50%) of the cases treated by extended right hepatectomy, four (50%) of the cases treated by Taj Mahal hepatectomy, and two (28.6%) of the cases treated by extended left hepatectomy. A good curative resection rate was achieved with all of these hepatectomies in the late period. The postoperative courses of the four patients who underwent extended right hepatectomy with preoperative PTPE were complicated by methicillin-resistant *Staphylococcus aureus* infection (n = 2), cholangitis (n = 1), and bronchial asthma (n = 1) that ultimately led to liver failure or multiple organ failure. Among those patients who underwent extended right hepatectomy, only one operative death occurred (4%); the others died within 3 months of surgery (12%). There were no in-hospital deaths among patients who underwent extended left hepatectomy or Taj Mahal hepatectomy. As a result, the median survival times were markedly improved among those patients who had been treated with these procedures (34 months for extended left hepatectomy; 20.0 months for Taj Mahal hepatectomy) compared to those who had undergone extended right hepatectomy (11.7 months) (Table 3).

DISCUSSION

The results we achieved using the surgical protocol for hilar bile duct carcinoma in the late period in our series showed a high rate curative resection and an improved 5-year survival rate compared to results in the early period, reflecting the success of our latest policy for treating hilar bile duct carcinoma.

Right hepatectomy is generally performed if carcinoma is found in the right hepatic duct, with or without invasion of the right hepatic artery and/or the right portal vein. Similarly, left hepatectomy is performed if carcinoma is found in the left hepatic duct, with or without invasion of the left hepatic artery and/or the left portal vein. Carcinoma is considered unresectable if it is found in both the left and right hepatic ducts with invasion of the principal vessels. Although some advocate extended hepatectomy with contralateral vascular graft or live transplantation for these patients, the results have not been satisfactory.[10,14-16] However, when carcinoma is found in both the left and right hepatic ducts without any vascular invasion, the type of hepatectomy that offers the best chance of curative resection with an uneventful postoperative course remains a matter of controversy. Bengmark et al.[17] have recommended extended right hepatectomy because of the greater possibility of removing the tumor, and Iwasaki et al.[18] have recommended left hepatectomy because it facilitates tracing the right intrahepatic ducts. The fact remains that the volume of the left lobe of the liver is small (only 33.3% of the whole liver) and thus the left approach allows the minimum loss of parenchyma. By contrast,

more than two thirds of the functional hepatic mass is removed by extended right hepatectomy, and because postoperative hepatic insufficiency often occurs after this operation, it ultimately has a greater negative impact on overall survival time than left hepatectomy.[19] Similarly, a longer median survival time was observed after left hepatectomy (34.0 months) than after right hepatectomy (11.7 months) in the late period, and 9 (64.3%) of the 14 long-term survivors had been treated by left hepatectomy.

To prevent hepatic insufficiency after extended right hepatectomy, Makuuchi et al.[20] have been performing PTPE before extended right hepatectomy since 1990, and have reported good results. Based on their experience, the procedure has become popular in Japan, and it is now frequently performed before extended right hepatectomy. In 1995 Nagino et al.[21] recommended PTPE as an effective means of preventing postoperative hepatic failure in hilar bile duct carcinoma, and several other groups have also reported favorable results with PTPE.[22,23] We have achieved very good results with PTPE before extended right hepatectomy in 19 patients with hepatocellular carcinoma (n = 9), cholangiocellular carcinoma (n = 5), and metastatic liver disease (n = 5) in our series of 183 consecutive hepatectomies since 1994 (Table 4), but the results of PTPE have been disappointing in patients with hilar bile duct carcinoma. All four (66.6%) of the six patients with hilar bile duct carcinoma who underwent PTPE before extended resection died within 3 months after surgery. This served as a warning to us that we could not always depend on PTPE to be helpful in the treatment of hilar bile duct carcinoma. Whenever it seems that extended resection might be harmful, especially in elderly patients and patients with poor liver function, we now treat hilar bile duct carcinoma by Taj Mahal hepatectomy rather than performing PTPE and extended right hepatectomy. Such patients tolerate Taj Mahal hepatectomy well because it preserves a greater volume of liver parenchyma than extended right hepatectomy. Miyazaki et al.[24] described their results using a parenchymal-preserving hepatectomy (segment 1 and 4 resection) to achieve curative resection and reduce postoperative liver failure. The intent of our procedure is similar to that of Miyazaki et al.,[24] but we prefer to remove segment 5 instead of the superior portion of segment 4 for three reasons: (1) total caudate lobectomy including the paracaval portion of the liver parenchyma can be performed easily; (2) the cut surface becomes large, resembling an open book, allowing hepaticojejunostomy to be performed more easily and with a better field of view; and (3) the cut ends of the intrahepatic ducts on the right side (segments VI, VII, and VIII) can be more easily checked for negative margins. This procedure is employed in poor-risk patients when carcinoma is found in both hepatic ducts or has invaded predominantly the right hepatic duct with no vascular invasion. No serious postoperative complications have been observed after Taj Mahal hepatectomy, and the median survival rate has been much greater than that in patients treated by extended right hepatectomy with PTPE.

Table 4. Hepatectomy with PTPE outcomes in the late period (1994 to 2000)

Disease	Hepatectomy	PTPE	Mortality
Hepatocellular carcinoma	62	9	1 (11.1%)
Cholangiocellular carcinoma	16	5	0
Hilar bile duct carcinoma	25	6	4 (66.6%)
Cystic duct carcinoma	2	0	0
Gallbladder carcinoma	14	0	0
Metastatic carcinoma	33	5	0
Other	31	0	0
TOTAL	183	25	5

In a previous study[25] we demonstrated that the caudate lobe is frequently (42.3%) invaded by hilar carcinoma. Ogura and Kawarada[26] reported that caudate lobectomy combined with hepatectomy and extrahepatic bile duct resection increases the rate of curative resection and improves the survival rate. Nimura et al.[27] found microscopic cancer involvement in the bile ducts of the caudate lobe in resected specimens from 44 of the 46 patients who underwent curative caudate lobe resections. These reports have led us to routinely perform total caudate lobectomy including the paracaval portion in the late period, with the aim of thoroughly clearing carcinoma cells from the caudate lobe. In addition, our recent studies[28,29] have shown that the type 1 bile duct branches of the medial segment of the liver (B4) are located very close to the left bile duct branches of the caudate lobe (B1*l*), and they are frequently involved in hilar bile duct carcinoma. We have therefore been removing the S4a segment along with the caudate lobe in our recent patients. As a result of the integrated surgical strategy in the late period that was described earlier in this report, we have been able to achieve a curative resection rate of 86.9% and a 5-year survival rate of 49.9%. In 1998 we reported 1- and 3-year survival rates of 84.6% and 58.0%, respectively, of our series in the late period,[30] and it is now finally possible to report our 5-year survival rate in the year 2000.

In contrast, bile duct resection alone was performed in 22 (35.5%) of the patients in the early period. Because hilar bile duct carcinoma characteristically invades the liver and spreads through the periductal lymphatic vessels, the perineural spaces, and into the wall of the bile duct, curative resection was difficult to achieve with local resection procedures.[4–7] In actual practice, failure occurred in a high percentage of patients (76%) in the form of locoregional recurrence, even after formally curative extrahepatic bile duct resection.[5] Although aggressive hepatectomy[1,4,8–10] combined with vascular surgery[10,14] to treat hilar bile duct carcinomas has increased the rate of curative resection, because of the high perioperative morbidity and mortality rate associated with this procedure, it has failed to improve the overall outcome in hilar bile duct carcinoma.[8–10] Poor-risk patients were not considered candidates for extended hepatic resection with or without vascular resection, and there was no awareness of the concept of parenchyma-preserving hepatectomy or the need to remove segment S4a along with the caudate lobe in the early period. Consequently a greater number of cases of perioperative liver dysfunction and a significantly lower curative resection rate (54.8%) and 5-year survival rate (20.2%) were achieved in the early period in comparison with the late period.

Bismuth et al.[31] demonstrated a close correlation between tumor clearance at operation and outcome, and therefore emphasized the importance of achieving a tumor-free surgical margin. Hadjis et al.[1] reported that 15 of the 17 patients who died of disease recurrence had local recurrence. Shimada et al.[32] reported recurrence in the area of the hepaticojejunostomy sites as an important factor related to poor outcome. Thus, a negative surgical margin is clearly the most important factor in the long-term survival of patients with hilar bile duct carcinoma. Hayashi et al.[33] demonstrated that hilar bile duct carcinoma often (17 of 19 patients, 89.5%) and extensively invades the proximal intrahepatic ducts via an extramucosal route rather than by continuous mucosal involvement. We have therefore made it a policy to examine the cut end of each intrahepatic duct of the remnant lobe after resection, and to cut these ends repeatedly by dissecting into the parenchyma around the intrahepatic ducts whenever necessary until negative margins are confirmed by frozen-section biopsy. Launois et al.[34] applied a posterior intrahepatic approach to achieve curative resection, and the goal of their approach was similar to that of our policy. Although the reliability of frozen-section biopsy is a matter of controversy, we have achieved a survival of 5 years in three patients in the late period after confirming negative margins on frozen-section biopsy specimens of the cut ends, with a maximum of eight reconstructed intrahepatic bile ducts. Other factors that influence long-term survival after curative resection include lymph node metastasis, histologic tumor grade, tumor size, tumor invasion of the liver parenchyma, and tumor type.[35–38] When these factors are favorable, survival of 5 years or more is indeed possible. As was the case in other studies, low-grade tumors[36,37] and negative lymph node metastasis were observed in our long-term survivors.[35,36,38]

The role of liver transplantation in the treatment of hilar bile duct carcinoma[13,14] and improvement of the survival rate with additional adjuvant chemotherapy and radiation therapy after surgery has yet to be clearly defined.[39,40] Thus the only known means of improving the outcome of hilar bile duct carcinoma at the present time is to increase the curative resection rate. The most recently published comparative study[41] on the management of hilar bile duct carcinoma, in an American and a Japanese patient cohort, demonstrated that patients who had undergone resection with negative margins had the most favorable prognosis, regardless of ethnicity. However, aggressive hepatectomies with extended lymphadenectomy and vascular resections are not justified if they are associated with a significantly increased rate of surgical complications, and that is why we have emphasized preservation of the parenchyma to the extent that margin-negative resection allows.

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Ruminations of an Ordinary Hepatic Surgeon: A Journey Through the Pitfalls of Major Liver Resections

Thomas S. Helling, M.D.

Historically, major hepatic resections have been fraught with voluminous blood losses and, at times, high mortality rates. Improvements in patient selection and operative technique over the past 20 years have resulted in marked reduction in death and complications and have given the impression that liver surgery can be relatively effortless. Contrary to this belief, the present review illustrates some of the pitfalls and dangers of major hepatectomy and may serve to alert ordinary surgeons to approach this operation with a degree of trepidation and careful planning. Over a 22-year period, 147 liver resections were performed by one surgeon for solid liver tumors (range 0 to 21/yr). Of these, 101 were major hepatectomies comprising at least three anatomic segments (63 right, 24 left, 11 extended right, and 3 extended left) and form the basis for this report. The major resections were performed for benign disease in 16 patients and malignant tumors in 85 (24 primary and 61 metastatic lesions). All but one patient were noncirrhotic. Seventeen patients were more than 70 years and 84 were less than 70 years of age. There were five postoperative deaths among these 101 patients: two intraoperative (coagulopathy after venovenous bypass in 1 and air embolus in 1), two from postoperative liver failure, and one resulting from a myocardial infarction. Three deaths were in patients older than 70 (18%), and two were in patients younger than 70 (2%) ($P = 0.03$). Complications developed in 20 of 96 survivors, three patients required reoperation for postoperative bleeding, and nine patients had some duration of bile leakage. In contrast, among those undergoing "minor" hepatectomies (n = 46), there were no deaths and six (13%) patients had complications. In patients undergoing major hepatectomies, estimated blood loss was 3836 ± 3346 ml. Estimated blood loss was unaffected by experience (first 50 patients vs. second 51 patients) or use of the ultrasonic surgical aspirator, but has been reduced by the use of the Harmonic scalpel (2650 ± 2706.1 ml vs. 3997 ± 3405.8 ml, $P = 0.026$). The use of rapid-infusion systems aided in preventing intraoperative hypotension and hypothermia. Estimated blood loss was significantly greater than with minor anterior or lateral segmentectomies (n = 24) (3836 ± 3346 ml vs. 975 ± 518.8 ml, $P < 0.0001$). Hospital length of stay has been shortened, primarily by the use of closed suction drainage compared to open drainage (7.5 2 ± .4 days vs. 18.8 ± 8.4 days, $P < 0.0001$). Major hepatectomies continue to be formidable operations with the potential for copious blood loss and intraoperative instability. Proper patient selection, anesthesia support and availability of rapid-infusion technology, and familiarity with liver anatomy are important in keeping operative mortality and postoperative morbidity at an acceptable level. (J GASTROINTEST SURG 2002;6:625–629.)
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In their 1977 monograph on solid liver tumors, Foster and Berman,[1] in a review of 621 patients undergoing hepatectomy at 98 institutions, indicated that "the prose used to describe major hepatic resection was salted with emotional phrases that reflected the surgeon's monumental concern over what he considered to be an even more monumental task." The operative mortality rate in these patients was 25% for right and extended right hepatectomies and 9% for left hepatectomies. Thirty-two percent of the 82 deaths were due to intraoperative hemorrhage or the consequences thereof.[1] Paralleling this experience, Hanks et al.[2] noted a 42% mortality rate in seven patients undergoing major hepatic resections at Duke University from 1947 to 1969. Mean blood loss was 5700 ml. Subsequently, in 1982, Ryan et al.[3] reported a reduction in the mortality rate for major hepatic resections to 8% in 52 patients but found prolonged intraoperative hypotension in 37% of patients with a mean blood loss of 3400 ml. "Significant" postoperative complications developed in 44%. These investigators achieved better results with the

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use of a liver compression clamp and avoidance of a thoracoabdominal incision. Among 81 liver resections, 71 of them major, performed between 1976 and 1984, Ekberg et al.[4] described an operative mortality rate of 5% and median blood replacement of 8 units. Thirty-three percent of these patients developed postoperative complications, 17% of them "major." On a larger scale, Nadig et al.[5] compiled results of 444 hepatic resections performed at the Department of Veteran Affairs Hospitals between 1987 and 1992 and found an overall operative mortality rate of 12%; mortality was highest for those with hepatocelluar carcinoma (21 %) and lowest for those with colorectal metastases (4%). Clearly, improvements have occurred in patient selection and intraoperative technique to account for this reduction in mortality, and these improvements have allowed major hepatic resections to gain wider acceptance as treatment for solid liver tumors. Nevertheless, the observations of Foster and Berman[1] in reviewing operative records probably still hold true—that is, the description "in brief and controlled terms the details of what were apparently uneventful liver lobectomies for patients whose anesthesia records, in contrast, document the transfusion of enormous quantities of blood—with several episodes of cardiac arrest and massive resuscitation efforts. . ."[1] Herein is one surgeon's journey through 20 years of hepatic surgery with an honest portrayal (more typical than many published reports, it is feared) of the experience with, and pitfalls of, major liver resections for solid tumors.

MATERIAL AND METHODS

All patients undergoing hepatic resections for solid liver tumors from 1979 to 2000 by the author were included for analysis. Preoperative evaluation consisted of CT scans of the abdomen and chest (where indicated), MRI in indeterminate tumors, and/or ultrasonography of the liver, liver function tests (serum bilirubin, transaminases, and alkaline phosphatase), tumor markers (carcinoembryonic antigen α-fetoprotein), where indicated, and evaluation of any comorbid conditions. In the case of colorectal metastases, a metastatic evaluation of chest, abdominal, and pelvic CT scans, along with current colonoscopy results, was completed. After induction of anesthesia, venous access was obtained with large-bore catheters either in the antecubital, internal jugular, or subclavian vein. Arterial catheters were placed for continuous blood pressure monitoring. No attempt was made to keep central venous pressure low, as this was thought to endanger the patient should large blood losses occur. A standard bilateral subcostal incision with a midline extension or a "hockey stick" incision was made depending on adequacy of exposure. No patient required a thoracoabdominal incision, even those with bulky, right-sided tumors. The Thompson retractor system was employed in all cases. The hemiliver to be resected was fully mobilized by dividing diaphragmatic and retroperitoneal attachments. Since 1992, intraoperative ultrasonography has been used in all cases of metastatic disease to search for occult tumors and in selected other tumors to define portal and hepatic venous structures, particularly if tumors were in proximity to major hepatic veins or the inferior vena cava. The operative approach to major liver resections consisted first of inflow control by identification, ligation, and division of the ipsilateral portal vein, hepatic artery, and bile ducts (in all cases). Where possible, ipsilateral hepatic veins were ligated and divided before parenchymal dissection. If this was perceived as potentially dangerous because of poor exposure, the hepatic veins were dealt with last, after completion of the parenchymal dissection. The parenchymal dissection was undertaken along the line of vascular demarcation after inflow occlusion. In earlier years, the dissection was accomplished with a "finger fracture" technique, then with the Cavitron Ultrasonic Suction Aspirator (Valleylab, Boulder, Colorado), and more recently with the Harmonic scalpel. Individual vascular and biliary structures were ligated and divided as they were encountered. Bleeding from the cut surface was controlled by pressure from the assistant. Inflow occlusion to the contralateral liver by the Pringle maneuver was inconsistently used, and is now seldom used. There was no attempt made to purposefully keep central venous pressure low. The reverse Trendelenburg position was used to facilitate exposure. Total hepatic isolation by inflow and outflow occlusion with or without venovenous bypass was used in three patients. Intraoperative blood loss (estimated blood loss) was determined by the anesthesiologists. From 1990 on, blood replacement was by way of a rapid-infusion device (RISTM Rapid Infusion System, Haemonetics, Braintree, Massachusetts), which was capable of delivering blood warmed to 40° C at a maximal rate of 5 liters/min. In the first 29 resections, an open drainage system of Penrose drains was used. The remainder (72 patients) had drainage of the resected space with closed suction drains. Minor liver resections were performed without inflow occlusion but with the same technique in parenchymal dissection as was used for major hepatectomies. Drainage was employed in all cases. The first 24 patients had an "open" method of drainage that employed soft rubber (Penrose) drains in the manner described by Starzl et al.[6] The remainder of patients had closed suction drains placed, which were removed on postoperative day 3 or

4 unless bile drainage was observed. All patients undergoing major liver resections were observed overnight, at a minimum, in the postanesthesia care unit. Only those patients requiring further close monitoring were placed in the intensive care unit.

Results are expressed as mean ± standard deviation. Statistical analyses were determined using the unpaired Student's *t* test.

RESULTS

Over a 22-year period, 147 liver resections (range 0 to 21/yr) were performed by the author. Forty-six were minor resections consisting of subsegmental (n = 14), segmental (n = 7), bisegmental (n = 22), or nonanatomic "central" (n = 3) liver resections. One hundred one cases were major hepatectomies comprising at least three anatomic segments (63 right, 24 left, 11 extended right, and 3 extended left hepatectomies). Among these 101 patients, the indications for resection were benign disease in 16 and malignant tumors in 85 (24 primary and 61 metastatic lesions) (Table 1). All but one patient was noncirrhotic. The lone exception was a patient who had microscopic cirrhosis. Seventeen patients were over 70 and 84 were under 70 years of age. Overall mortality rate for the 147 patients was 3.4% (5 of 147). However, there were no deaths among those who had minor hepatic resections and five deaths (5%) among those who had major resections. Two deaths occurred intraoperatively, one from a presumed air embolus during an en bloc kidney–liver resection for a large renal cell carcinoma and one from a coagulopathy following reperfusion after total hepatic isolation and hemihepatectomy. Two patients died of liver failure on postoperative days 7 and 31, respectively. One patient died of a myocardial infarction on postoperative day 2 after an uneventful (900 ml blood loss) right hepatectomy. Three deaths occurred in patients over 70 (18 %) and two were in patients under 70 (2%) years of age ($P = 0.033$). Complications developed in 21 (22 %) of 96 surviving patients (Table 2). The most common complication was bile leakage lasting from 3 days to 8 months, including 7 (10%)of 72 patients in whom closed suction drainage was used. There were no complications attributed to the closed suction drains themselves, and none of the patients developed fluid collections in the right upper quadrant after removal of the closed suction drains. Three patients had postoperative bleeding and required reoperation.

Twenty-two patients had additional operative procedures at the time of hepatectomy (Table 3). The most common procedure was wedge resection of the contralateral liver lesions, which was performed in 10 patients.

Table 1. Indications for hepatectomy in 147 patients

Tumors	Major hepatectomy	Minor hepatectomy
Benign		
Hemangioma	8	4
Liver cell adenoma	0	3
Focal nodular hyperplasia	8	2
Malignant		
Primary		
Hepatocellular	15	5
Cholangiocarcinoma	8	4
Papillary carcinoma	1	0
Metastatic		
Colorectal	48	19
Leiomyosarcoma	1	4
Ovarian	3	2
Neuroendocrine	3	1
Breast	1	1
Renal	2	0
Gastric	1	0
Melanoma	1	0
Pancreatic	0	1

The estimated blood loss (EBL) for the 101 patients undergoing major hepatic resection was 3836 ± 3346 ml. For the first 50 patients the EBL was 3680 ± 2261 ml and for the second 51 patients the EBL was 3992 ± 4179 ml ($P = 0.50$). Ten patients had EBL greater than 8000 ml. In all patients, copious bleeding came from the middle hepatic vein, and in five of these 10 patients during removal of tumors near the origin of the middle and left hepatic veins and inferior vena cava. Two of these patients died in the intraoperative period. Twelve patients had an EBL less than 1000 ml, five in the first 50 patients (10%) and seven in the second 51 patients

Table 2. Complications in 101 major hepatic resections

Complications	No.
Postoperative bile drainage	9
Postoperative bleeding	3
Subphrenic abscess	3*
Pulmonary embolus	1
Wound hematoma	1
Liver insufficiency	1
Wound dehiscence	1
Wound infection	1
Pneumonia	1
Pleural effusion requiring thoracentesis	1

Survivors only, n = 96.
*All occurred in patients drained by the "open" method before 1990.

Table 3. Adjunctive surgical procedures in 101 patients undergoing major hepatic resections

Procedure	No. of patients
Subsegmental resection	10
Diaphragmatic resection (en bloc)	5
Adrenalectomy	2
Hepaticojejunostomy	2
Ileostomy closure	1
Right hemicolectomy	1
Distal pancreatectomy and splenectomy	1

(14%). The CUSA was used in 47 patients. There was no significant reduction in EBL in comparison to those patients whose resections were performed by "finger fracture" (n = 42) (4261 ± 4158 ml vs. 3695 ± 2275 ml, $P = 0.99$). When the Harmonic scalpel was used (n = 12), the EBL was significantly less (2650 ± 2706 ml vs. 39983 ± 406 ml, $P = 0.03$). In contrast, without manipulation of the major hepatic veins, as with minor hepatectomies, the EBL was substantially less. Those patients undergoing anterior or lateral segmentectomies (minor hepatic resections, n = 24), where larger hepatic veins were not encountered, had a mean EBL of 975 ± 519 ml ($P < 0.001$) in comparison to the EBL for the entire group of patients undergoing major hepatic resections.

Hospital length of stay for the entire group of 101 patients was 10.7 ± 7.0 days. When drainage of the hepatic bed was changed to closed drainage, the length of stay decreased significantly compared to the "open" drainage system (7.5 ± 2.4 days vs. 18.8 ± 8.4 days, $P < 0.001$).

DISCUSSION

In published reports over the past 12 years, major hepatic resection has been portrayed as a reasonably safe operation.[6–10] Operative mortality rates of 2% to 4% have been described, although major hepatic resections (three or more anatomic segments) were not necessarily separately discussed. In these series, minor hepatic resections comprised from 27% to 60% of cases. Mean EBL, when reported, did not exceed 1500 ml—even for major hepatectomies. In fact, Jamieson et al.[11] found that 10 of 21 patients undergoing a major hepatectomy did not require a blood transfusion. Serious complications were less than 5%, and postoperative liver failure or bleeding was distinctly uncommon. This optimism might lead to the conclusion that it is feasible for the ordinary general surgeon to perform major hepatic resections.

To the contrary, major hepatic resection continues to be a formidable operation. In this series, although operative mortality has been low (5%) and intraoperative mortality even lower (2%), a mean EBL of more than 3500 ml indicates an ever-present potential danger of exsanguination. Generally speaking, blood loss arose from major hepatic veins, primarily the middle hepatic vein, deep in the liver parenchyma, often unexpectedly. Meticulous inflow control before parenchymal dissection was desirable to avoid later injury to the contralateral portal vein, hepatic artery, and bile ducts; to demarcate the right and left hemilivers along the interlobar plane; and to reduce to some extent any subsequent bleeding. This was accomplished with relative ease and little blood loss. However, substantial bleeding still may occur from the major hepatic veins, usually the middle hepatic vein, even after control or ligation and division of right or left hepatic vein. The use of the Pringle maneuver had little effect, as retrograde bleeding from the vena cava could be torrential and was unaffected by further inflow control. Because of this concern, there was no conscious attempt to keep central venous pressure low for fear of exacerbating hypotension, should significant blood loss occur. In addition, a low central venous pressure might encourage air embolism if large hepatic veins were opened. The Trendelenburg position was not used because it seemed to make exposure of the liver more difficult. In fact, the reverse Trendelenburg position was favored for better exposure. Familiarity with hepatic anatomy deep within the liver and optimum exposure are essential to avoid repeated injury of the middle hepatic vein. Parenchymal dissection slightly to the right or left of this vein helped avoid unexpected avulsion of tributaries and resultant troublesome bleeding. Particularly dangerous were tumors near the origin of the major hepatic veins and inferior vena cava. Exposure in this area was less than ideal and proximal bleeding was difficult to control. In three patients, total vascular isolation was used for tumors in this location. Although this technique produced a bloodless field and relatively short (less than 60 minutes) warm ischemic times, rather impressive bleeding could still occur with reperfusion. The CUSA ultrasonic dissector provided better visualization of intraparenchymal vascular and biliary structures, but its use did not significantly decrease blood loss as Hodgson and DelGuercio[12] suggested it might. In contrast, the Harmonic scalpel, through its capability to coagulate small portal, arterial, and hepatic venous branches, provided better superficial hemostasis and lowered the EBL significantly. Use of the Harmonic scalpel deeper in the liver parenchyma often opened (and failed to coagulate) larger hepatic veins. Therefore its use was restricted to anterior and superficial dissection. It has been particularly valuable in minor anterior or lateral segmentectomies and

subsegmentectomies. Equally important in major hepatectomy was the availability of rapid-infusion devices with the capability of warming infused blood and fluids. A rapid-infusion system provided the ability to keep up with rather sudden blood loss and, by warming, forestalled development of hypothermia-induced coagulopathies. Once the hepatectomy was completed, bleeding from the cut surface usually stopped or was controlled with pressure and fine suture ligatures. Significant postoperative bleeding was uncommon, occurring in less than 4% of patients.

Almost one-half of the complications (9 of 21 patients) were due to transient biliary fistulas. In the first 29 patients, large Penrose drains were left in the space vacated by resected liver. This resulted in a long process of open drainage and wound irrigation to ensure healing of the potential space by secondary intention. As a result, hospital stay was prolonged (mean 18.8 ± 8.4 days) and persistent purulent drainage or bile fistulas occurred frequently (8 [28%] of 29 patients). Although not a contemporaneous comparison, with the introduction of closed suction drainage in 1990, hospital length of stay significantly decreased to a mean of 7.5 ± 2.4 days. Although other factors could have contributed, elimination of open wound irrigations clearly shortened hospitalization. Biliary leaks still developed in 10% of patients. Despite the report by Fong et al.[13] that drains were not necessary after hepatectomy, they were reliably able to drain bile leaks, they posed no danger to the patient, did not extend the hospital length of stay, and obviated the need for additional procedures should bile collections occur (which they probably would have in 10% of patients). Liver insufficiency developed in three patients postoperatively. Two died as a result. None were cirrhotic or septic, and the cause remained obscure.

Liver resection in the elderly poses a higher risk. The mortality rate for those over 70 years of age was significantly higher (18% vs. 2%). This was also found by Fortner and Lincer[14] (11% mortality, age over 64 years) and Koperna et al.[15] (25% mortality, age over 80 years). Although the most common cause of death in these two series was liver failure, one patient in this series died intraoperatively of coagulopathic bleeding, one from an unsuspected postoperative myocardial infarction, and one from unexplained postoperative liver failure (noncirrhotic). It would be advisable in elderly patients to ensure normal (noncirrhotic) liver function preoperatively, to rule out occult ischemic heart disease preoperatively, and to avoid heroic (extended) liver resections.

As opposed to "minor" hepatic resections (subsegmental or segmental resections) with no deaths and estimated blood losses usually less than 1 liter, major hepatectomies should be approached with careful thought given to patient selection, familiarity with hepatic anatomy, appropriate anesthesia support with rapid-infusion devices, and an attempt to control inflow and outflow before parenchymal dissection. With these caveats, operations of this magnitude can be performed with low mortality and morbidity, and the harrowing experiences reported by Foster and Berman[1] can be avoided. However, proper training is essential. Without it, major hepatic resections should not be performed by the "ordinary" general surgeon.

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An Unusual Case of Squamous Cell Carcinoma Arising at the Stomal Site: Case Report and Review of the Literature

P. Ramanujam, M.D., K.S. Venkatesh, M.D., F.R.C.S.(C.)

An unusual case of squamous cell carcinoma arising at the ileocutaneous stomal site is reported. The presenting symptoms were peristomal ulceration and bleeding. The patient was treated with wide local excision of the stoma and the peristomal skin, and relocation of the ileostomy. A search of the literature for other similar cases subsequently identified two additional cases that were reported in the literature in 1987 and 2000. (J GASTROINTEST SURG 2002;6:630–631.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Squamous cell carcinoma, ileostomy, ileocutaneous junction, ill-fitting appliances

Carcinoma developing at the ileocutaneous junction of an ileostomy is extremely rare.[1] This case is believed to be the second report of a primary squamous cell carcinoma of an ileostomy site. The first reported case was of a primary squamous cell carcinoma involving a skin-grafted ileostomy stoma.[1] The second reported case was of a primary squamous cell carcinoma involving a revised and re-matured stoma 41 years after a skin-grafted end ileostomy had been performed.[2] Five cases of primary adenocarcinoma of the ileostomy have been reported.[3–7]

CASE REPORT

A 76-year-old woman was seen in July of 1998 with peristomal discomfort and bleeding. The patient had undergone a total proctocolectomy for severe ulcerative colitis in 1947. The patient had had no problems with the stoma until 1 year before this presentation. At that time she noticed a small nonhealing peristomal ulcer that progressively grew larger. On examination, there was an ulcerated 4×3 cm lesion at the base of the stoma (Fig. 1).

There was no inguinal lymphadenopathy. The biopsy of the lesion showed a well-differentiated squamous cell carcinoma. Wide local excision with resection and relocation of the stoma was then performed (Fig. 2). Microscopic examination of the excised specimen showed tumor arising from the cutaneous junction of the ileostomy (Fig. 3). The patient had an uneventful recovery.

The patient was followed for a period of 28 months following the wide excision and relocation of the ileostomy. The patient died of congestive heart failure 28 months after the surgical procedure. The patient was disease free at the time of her death.

The patient had been wearing an old-fashioned, somewhat ill-fitting stomal appliance for many years. It is reasonable to assume that this appliance had caused chronic peristomal skin irritation with the resultant squamous cell carcinoma.

DISCUSSION

An ileostomy had been associated with significant postoperative complications before the development of the Brooke's type of everted stoma.[8] The technique of split-thickness skin grafting of the exposed ileal serosa was first described by Dragstedt et al.[9] These investigators devised the procedure to reduce peristomal serosal inflammation as well as skin irritation. This procedure was later abandoned by surgeons because of the delayed complication of stenosis from subdermal fibrosis.[10] Later, Monroe and Olwin[11] used a full-thickness abdominal flap as a graft to cover the serosa with some success.

It is reasonable to assume that this patient developed ulcerating squamous cell carcinoma as a result of chronic irritation from an old-fashioned, ill-fitting stomal appliance. Chronic irritation causing squamous cell carcinoma is well reported in the literature.[12–15] Squamous cell carcinoma has been reported

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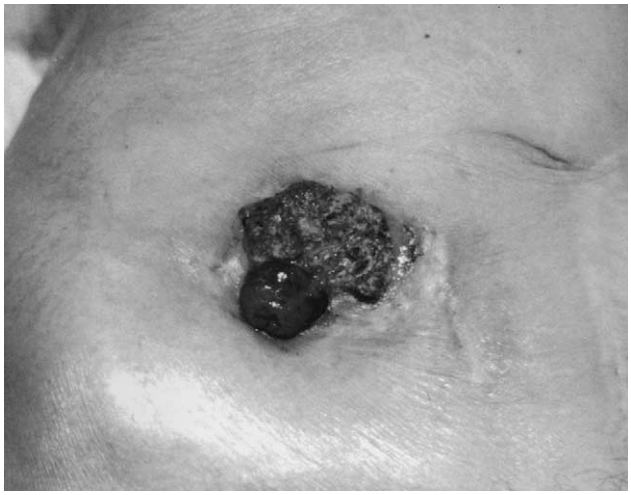

Fig. 1. A large ulcerating squamous cell carcinoma of the stomal site.

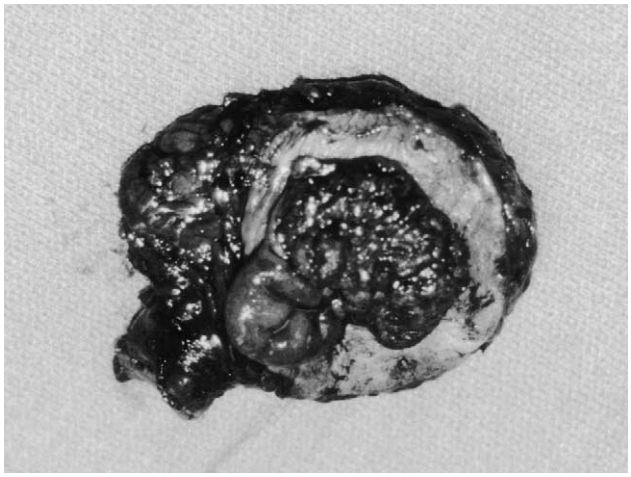

Fig. 3. Specimen showing the tumor widely excised with the stoma.

in association with ill-fitting dentures, burn scars,[13] pilonidal sinus,[14] chronic anal fistula, and hidradenitis suppurativa.[15] Even though chronic peristomal skin irritation is common, squamous cell carcinoma of the peristomal skin site is exceedingly rare.

CONCLUSION

Squamous cell carcinoma and adenocarcinoma presenting at the ileal and skin entrances appear to be locally invasive and slow growing.[6] Nonhealing peristomal ulcerations must be biopsied to rule out a malignancy. Wide local excision of the carcinoma and the stoma with the creation of a new stoma at a different site seems to be appropriate treatment.

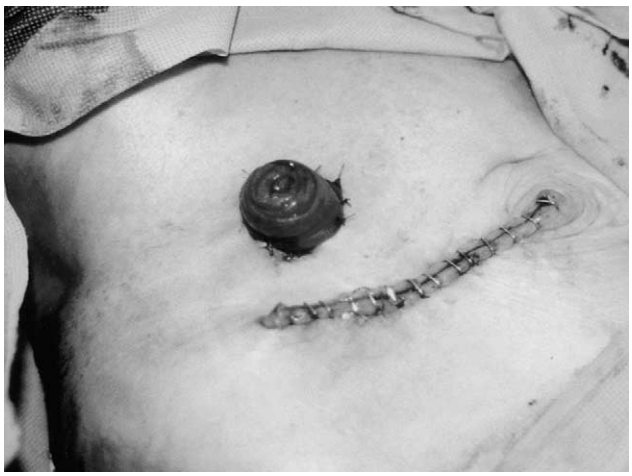

Fig. 2. Postoperative photograph showing wide excision with relocation of the stoma.

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Influence of Functional Bowel Disease on Outcome of Surgical Antireflux Procedures

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Patients with gastroesophageal reflux disease (GERD) have a coexisting diagnosis of functional bowel disease (FBD) in approximately 30% of cases. Symptom improvement after surgical therapy for GERD may be less in patients with FBD when compared to patients without this coexisting problem. A retrospective review of patients undergoing Nissen fundoplication between 1996 and 2000 evaluated patients with documented FBD or FBD symptoms to determine operative outcome. Poor postoperative outcome included recurrent heartburn, gas bloat syndrome, dysphagia requiring reoperation or dilation, or delay in resumption of normal diet. Bivariate comparison and multivariate logistic regression evaluated the independent impact of a documented diagnosis of FBD or preoperative symptoms of FBD on outcome. This study examined 155 patients: 32% reported having symptoms of FBD and 10% had a confirmed diagnosis of FBD. Poor postoperative outcomes occurred in 27%. Patients with a documented diagnosis of FBD were significantly more likely to have a poor outcome when compared to patients without symptoms of FBD (53% vs. 23%, $P = 0.01$). Patients with preoperative symptoms of FBD (but without a documented diagnosis of FBD) also had a higher incidence of poor outcome (5% vs. 23%, $P = 0.09$). Patients with FBD are at increased risk of poor results after antireflux surgery. Patients with these conditions should be counseled preoperatively regarding the potential for recurrent postoperative symptoms. (J GASTROINTEST SURG 2002;6:632–637.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Gastroesophageal reflux disease, functional bowel disease, irritable bowel syndrome, outcomes

The incidence of gastroesophageal reflux disease (GERD) is increasing.[1] Patients with GERD commonly present with symptoms of heartburn, chest pain, and acid taste; atypical presentations include asthma, hoarseness, and other pulmonary symptoms. GERD can result in serious complications including chronic pulmonary dysfunction, esophageal stricture, and esophageal cancer. Surgical treatment of GERD offers many patients durable and reliable relief of their symptoms.[2] Although recent studies have documented a significant improvement in disease-specific and generic quality-of-life indicators in patients treated medically and surgically for GERD-related symptoms,[3] other investigations have suggested that the complication rate after surgical treatment of GERD, particularly as it pertains to functional complaints including early satiety, bloating, excessive flatus, and inability to belch, may be significant.[4,5] In community-based studies, estimates of the incidence of gas bloat syndrome after Nissen fundoplication range from 8% to 50% and inability to belch from 43% to 80%.[5–8] Factors that may be predictive for morbidity or poor outcome after Nissen fundoplication have not been clearly defined.

Functional bowel disease (FBD) is a constellation of gastrointestinal complaints not explained by any identifiable structural or biochemical abnormalities. Patients with FBD suffer from upper, mid-, and lower abdominal symptoms including pain and altered bowel habits.[9] The actual pathogenesis of FBD is ill defined, but it has traditionally been viewed as a disorder of gastrointestinal motility.[10] Despite this traditional explanation for FBD, many patients with FBD have no identifiable motility abnormalities, de-

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spite the presence of significant symptoms.[11,12] Five constellations of symptoms have been found in patients with FBD, resulting in five defined subgroups of FBD: irritable bowel syndrome (IBS)-diarrhea, IBS-constipation, functional dyspepsia, dysmotility, and pain.[13] Patients with IBS typically complain of chronic or recurrent gastrointestinal symptoms including diarrhea, constipation, abdominal pain, and bloating. Functional dyspepsia is another subgroup of FBD in which patients have upper abdominal pain and other gastrointestinal symptoms centered in the upper abdomen and lower chest. Functional dyspepsia and symptoms of IBS coexist in 56% to 87% of subjects in a variety of population-based surveys.[9] Patients with all subgroups of FBD are nearly three times more likely to report symptoms of GERD than the general population.[12] A recent study involving patients with symptoms of GERD, but normal upper endoscopy and ambulatory esophageal pH monitoring, demonstrated a hypersensitivity to mechanical or chemical esophageal stimulation in nearly one third of these cases.[14] This observation suggests a link between the pathogenesis of FBD and heartburn in a subset of patients. This observation may have important clinical implications regarding responses to traditional therapy for GERD including gastric acid suppression and antireflux surgery.

We hypothesized that patients with coexisting GERD and FBD would be more prone to a poor surgical outcome when compared to patients without FBD. In addition, it is also reasonable to speculate that the development or worsening of functional complaints such as early satiety, abdominal pain, bloating, and/or excessive flatus after Nissen fundoplication may occur more commonly in those with preexisting FBD than in those without FBD.

METHODS

A retrospective review was conducted of the charts of all patients undergoing either open or laparoscopic Nissen fundoplication at the University of Michigan Medical Center over the 3½-year period between January 1996 and November 2000. This study was approved by the University of Michigan Institutional Review Board. All procedures were performed by one of four gastrointestinal surgeons at the university hospital, utilizing a similar operative technique. Before this investigation was begun, 40 laparoscopic Nissen fundoplications had been performed at our institution, thereby minimizing the effects of the learning curve. The average follow-up period was 31 months (range 6 to 69 years).

Basic demographic and clinical data were determined for each patient. Preoperative variables included age, sex, presenting symptoms, and results of diagnostic testing. Among patients undergoing operation, 98.7% had clinically proved reflux documented by pH probe testing or by endoscopically documented reflux esophagitis or Barrett's metaplasia. Operative records were examined to categorize the operation as having been performed as an open procedure or laparoscopically. Postoperative results and outcome, including the presence of complications, were based on documented examination by the primary clinician.

In addition to patients carrying a documented diagnosis of FBD, we identified additional patients with symptoms consistent with FBD. Patients were classified as having FBD if they reported a history of constipation, diarrhea, alternating constipation and diarrhea, irregular bowel habits, or chronic nonepigastric abdominal pain. Patients with a confirmed diagnosis of FBD were assessed as a separate subgroup of patients.

We included the following postoperative complications and symptoms in the definition of poor operative outcome: dysphagia requiring reoperation or dilation; recurrent heartburn; or complaints of gas bloat syndrome. Recurrent respiratory symptoms including cough or asthma were considered separately.

Statistical analysis was performed using two-tailed Student's t tests and χ^2 test of association where appropriate. A multivariate logistic regression analysis was also completed to identify independent effects of a documented diagnosis of FBD as compared to the larger group of patients with preoperative symptoms suggestive of FBD.

RESULTS

The results for 155 consecutive operative procedures are included in this analysis. The average age of the population was 45 years and 47% were men. Symptoms of FBD, including a documented diagnosis of FBD, were identified in 50 patients (32%); 15 of the patients in the FBD group (10%) had a documented diagnosis of FBD and these patients were analyzed as a separate subgroup (Table 1). Obesity was more commonly observed in patients with documented FBD (33% vs. 12%, $P = 0.01$) or with symptoms of FBD (26% vs. 12%, $P = 0.02$) when compared to patients without symptoms of FBD. There were no other significant differences in average age, sex distribution, percentage of smokers, or percentage of active alcohol users between patients with preoperative symptoms consistent with FBD, the subgroup of

Table 1. Demographic characteristics

Patient characteristics	Documented FBD patients	FBD symptom patients	Non-FBD patients
No. of patients	15	50	105
Age (yr)	41	44	46
Sex (% Male)	40	40	50
Current smoker (%)	26	14	15
Frequent alcohol user (%)	20	24	23
Obese (>100 pounds overweight) (%)	33*	26†	12

Patients with documented FBD are presented as a subgroup of patients with symptoms of FBD.
*$P = 0.03$ vs. non-FBD patients.
†$P = 0.03$ vs. non-FBD patients; all other differences nonsignificant ($P > 0.05$).

patients with documented FBD, and the non-FBD population undergoing surgical correction of GERD.

Typical presenting symptoms of GERD were similar in the patients with FBD and otherwise healthy patients. Heartburn or epigastric pain was reported by 93% of patients with documented FBD, 88% of patients with symptoms of FBD, and 81% of others, vomiting by 33%, 28%, and 23%, and asthma or cough by 26%, 42%, and 45%, respectively. Preoperative diagnostic studies included esophagogastroduodenoscopy demonstrating reflux esophagitis or Barrett's metaplasia in 60% of patients with documented FBD, 76% of patients with FBD symptoms, and 87% of the population with symptomatic GERD without FBD. Significant reflux was documented by positive pH probe in 66% of patients with documented FBD, 76% of patients with FBD symptoms, and 87% of others. Evidence of documented reflux by either study was found in 100% of patients with documented FBD, 98% of patients with FBD symptoms, and 99% of patients without FBD. Prevalence of symptoms, use of diagnostic testing, and the proportion of patients with documented reflux did not differ significantly among the patient populations. Patients underwent laparoscopic Nissen fundoplication (81%), open Nissen fundoplication (16%), or Toupet fundoplication (3%).

The overall operative success rate was 73% (Table 2). The most common poor postoperative outcomes were recurrent heartburn (13%), followed by gas bloat syndrome (10%) and cough (6%). Recurrent heartburn was confirmed by diagnostic testing in 60% of the symptomatic patients of whom three had a herniated wrap. The remaining patients with recurrent heartburn all reported significant symptomatic improvement with acid-reducing medical therapy. Operative complications were limited to a single perforation (0.6%) leading to the patient's death (0.6%). Fourteen patients had dysphagia requiring reintervention (9%); 71% of them were treated successfully with dilation alone.

Poor postoperative outcome related to gastrointestinal symptoms including delay in oral intake, dysphagia requiring reoperation or dilation, recurrent heartburn, or gas bloat syndrome occurred more often in patients with documented FBD when compared to patients without FBD (53% vs. 23%, $P = 0.01$). Similarly, patients with symptoms of FBD appeared more likely to have poor outcome (35% vs. 23%, $P = 0.09$). Recurrent respiratory symptoms including cough or asthma occurred in 4% of patients but did not vary significantly between groups. The increase in poor postoperative outcome due to gastrointestinal symptoms in patients with documented FBD or symptoms of FBD was largely due to an increase in the incidence of gas bloat syndrome (see Table 2). The odds of developing postoperative gas bloat syndrome in patients with documented FBD were 6.6 times higher than in patients without FBD ($P = 0.002$). Similarly, patients with FBD symptoms were 3.1 times more likely to develop gas bloat syndrome ($P = 0.03$). Although the presence of FBD did appear to predict an increase incidence of poor postoperative outcome related to gastrointestinal problems, the presence of FBD did not predict a greater incidence of recurrent cough or asthma.

Multivariable analysis examining the incidence of poor postoperative outcome revealed that documented FBD (odds ratio [OR] = 3.1, $P = 0.05$), female sex (OR = 2.0, $P = 0.06$), and obesity (OR = 2.4, $P = 0.06$) independently increase postoperative risk. After controlling for the effect of obesity and sex, FBD symptoms were no longer an independent predictor of poor postoperative outcome.

DISCUSSION

Although 73% of patients with GERD had prompt resolution of their symptoms after surgical repair, a substantial minority continued to have either gastrointestinal or respiratory symptoms. The majority of patients with residual symptoms had mild complaints including gas bloat syndrome or recurrent heartburn. Reoperation was required in only

Table 2. Postoperative outcome

Complications	IBS patients (%)	FBD patients (%)	Non-FBD patients (%)
Any poor postoperative outcomes (gastrointestinal)	53*	36†	23
Dysphagia requiring reintervention	6	8	10
Gas bloat	33‡	18§	6
Recurrent heartburn	13	14	12
Recurrent asthma/cough	6	8	8

*$P = 0.01$ vs. non-FBD patients.
†$P = 0.09$ vs. non-FBD patients.
‡$P = 0.001$ vs. non-FBD patients.
§$P = 0.02$.

6% of patients (3 patients had slipped wraps, 4 patients had dysphagia, one patient developed esophageal cancer, and one patient had recurrent reflux symptoms and was treated at an outside institution). These results are comparable to those of other large published series. Bais et al.,[15] in a prospective evaluation comparing open and laparoscopic antireflux procedures, reported an incidence of persistent dysphagia in 12% of patients randomized to laparoscopic Nissen fundoplication, recurrent GERD in 3.5%, and intrathoracic herniation in 3.5%. Other investigators have suggested that reflux symptoms often occur postoperatively despite successful procedures. Eubanks et al.[16] reported that 11% of 228 patients undergoing pH probe studies after Nissen fundoplication reported symptomatic reflux after their operative procedures. However, there appears to be a poor correlation between postoperative symptoms and documented reflux. In their study, although 93% of patients reported symptomatic improvement, 20% had abnormal DeMeester scores recorded on postoperative pH probe examination.

The incidence of recurrent gastrointestinal symptoms in this study appears to be more frequent in patients who have a history of documented FBD. This relationship is not evident among patients with recurrent respiratory symptoms. The persistence of symptoms suggests that the underlying pathology associated with FBD may diminish the effectiveness of surgical repair. Because of the retrospective nature of this study, it is difficult to determine whether the poor postoperative outcomes that were observed were actually related to a poor postoperative outcome versus a continuation of the patient's FBD complaints. FBD remains principally a clinical diagnosis that is based on patient-reported symptoms and an otherwise normal evaluation, which can often be extensive and includes upper and lower endoscopic evaluation, as well as CAT scans and other costly diagnostic tests. Although some investigators have reported correlations with physiologic data including rapid colonic transit time in patients with diarrhea-predominant IBS and increased sensitivity to rectal distention in patients with pain-predominant IBS, no consistent physiologic or anatomic abnormality has been documented in these patients.[10] To improve diagnostic accuracy, a variety of disease-specific and generic quality-of-life questionnaires have been used to identify patients with FBD and to follow the severity of illness through time.[17] The current study emphasizes the difficulties associated with a diagnosis of FBD. In many of the patients with poor postoperative outcomes in this study, these may have been due to a continuation of their symptoms related to FBD, which can often overlap significantly with symptoms of GERD. In the setting of FBD, it is important to appropriately counsel patients regarding likely outcomes after surgical treatment of any gastrointestinal problem.

Five constellations of symptoms have been found in patients with FBD: IBS-diarrhea, IBS-constipation, functional dyspepsia, dysmotility, and pain.[13] Patients presenting with FBD can suffer from upper, mid-, and/or lower abdominal symptoms including pain and altered bowel habits that cannot be explained by anatomic or biochemical factors.[9] Subgroups of FBD include both IBS and functional dyspepsia (reflux group). Patients with IBS typically complain of chronic or recurrent gastrointestinal symptoms including diarrhea, constipation, alternating constipation and diarrhea, abdominal pain, and bloating. Functional dyspepsia is another subgroup of FBD, and these patients typically complain of upper abdominal pain, as well as other gastrointestinal symptoms centered in the upper abdomen; symptoms in patients with functional dyspepsia often mimic typical symptoms of GERD. Functional dyspepsia and lower gastrointestinal IBS symptoms coexist in 56% to 87% of subjects in a

variety of population-based surveys.[9] Although they are rarely life-threatening, these conditions are widespread and have a significant impact on quality of life in up to 22% of Western populations.[18] Quality-of-life studies have demonstrated that FBD negatively affects employment, sexual functioning, leisure, travel, and diet. Patients who suffer from FBD report their health to be poor or fair 28% to 51% of the time.[19] These complaints often lead to further medical and surgical evaluation in an effort to improve patient quality of life. The frequent association of reflux and IBS symptomatology has led to referral for endoscopy, as well as other investigations to evaluate GERD symptoms. Subsequently those with documented reflux disease often undergo surgical therapy, principally Nissen fundoplication.

Although Nissen fundoplication has been largely successful in treating patients with GERD, a subgroup of patients who have a coexisting diagnosis of FBD appear to have greater than twice the incidence of postoperative gastrointestinal symptoms, particularly gas bloat syndrome, based on the data presented in the current investigation. This conclusion is consistent with the hypothesis that FBD represents a global, mild bowel dysmotility or hypersensitivity disorder that is unlikely to be altered by fundoplication. The current study suggests that patients with FBD who undergo surgical treatment for GERD are less likely than patients without FBD to derive significant improvement in their symptoms. Furthermore, patients with FBD may incur higher perioperative and postoperative costs related to delay in hospital discharge and reintervention resulting from recurrent symptoms or new gastrointestinal complaints after surgery.

The results of this retrospective study may be confounded by nonmeasured factors including coexisting psychologic illness and the degree and type of FBD. The study was further limited by its retrospective design and limited number of patients. We relied on indirect clinical evidence of FBD preoperatively and clinician observation postoperatively to identify complications and/or poor outcomes, both of which may be subject to bias. In addition, because of the small numbers in this study, as well as its retrospective nature, it was not possible to stratify the group with FBD into subtypes, aside from cases of documented FBD, which may lead to an underestimate of the impact of FBD on Nissen fundoplication outcomes. In light of this, we are currently planning a prospective study to further assess the impact of FBD on outcome after surgical treatment of GERD.

CONCLUSION

Nissen fundoplication, although successful for the majority of patients with GERD, may not offer the same benefit to patients with FBD. Patients with FBD need to be carefully counseled regarding the impact of Nissen fundoplication on their reflux symptoms and the significant potential for postoperative gastrointestinal disturbances including gas bloat syndrome.

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Effective Treatment of Rumination With Nissen Fundoplication

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Rumination is a syndrome characterized by the effortless regurgitation of recently ingested food. It has been linked to severe medical and psychosocial conditions including malnutrition, aspiration pneumonia, and complete social withdrawal. Psychotherapy, the current treatment modality for rumination, may improve symptoms but requires significant motivation and is rarely curative. We hypothesized that a complete fundoplication would eliminate, or at least impair, the ability to regurgitate gastric contents through the esophagogastric junction. We performed a Nissen fundoplication in five patients with a classic history of rumination. In all cases, symptoms had been resistant to medical and psychiatric intervention prior to fundoplication. Formal preoperative testing included esophageal manometry, 24-hour pH monitoring, endoscopy, and upper gastrointestinal barium swallow studies. All patients reported their primary symptom to be effortless recurrent postprandial regurgitation for 1 to 2 hours after meals consistent with rumination. Four (80%) of the five patients had low resting lower esophageal sphincter pressures with evidence of gastroesophageal reflux disease on 24-hour pH monitoring. All patients reported complete cessation of ruminating behavior after Nissen fundoplication. We report, for the first time, complete elimination of rumination symptoms after a Nissen fundoplication. Although further trials are needed to confirm our results, we recommend considering a Nissen fundoplication for treatment of rumination refractory to behavioral and medical interventions. (J GASTROINTEST SURG 2002;6:638–644.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Rumination, behavioral disorders, fundoplication, regurgitation

The term rumination refers to the effortless regurgitation of recently ingested food with subsequent remastication, followed by swallowing or spitting. It is estimated to occur in 6% to 10% of institutionalized mentally impaired persons, and is becoming more commonly recognized in persons with normal mental function.[1–4] As is the case with other rare diseases, rumination is underdiagnosed. Its symptoms are often ascribed to gastroparesis, chronic vomiting, or gastroesophageal reflux disease (GERD).[5] As a consequence, most patients see on average four to five physicians before the correct diagnosis is established.[5] Although it was initially believed to be of little consequence,[6] reports have linked rumination to serious medical complications including malnutrition, weight loss, dental decay, aspiration, choking, and pneumonia. Indeed, Konarski and Favell[7] estimated rumination to be the primary cause of death in 5% to 10% of ruminating individuals. Rumination can also have a damaging effect on one's psychosocial health, often leading to embarrassment and social isolation. Unfortunately, even when it is correctly diagnosed, treating rumination has proved to be challenging. Biofeedback and other behavioral techniques improve symptoms but require highly motivated individuals and are frequently not curative. Pharmacologic modalities have also produced disappointing results.

The physiologic mechanisms characterizing the ruminating event remain unclear. It has been thought that a defect of the lower esophageal sphincter (LES), the stomach, or the esophagus may be responsible for a predisposition to rumination.[5,8–13]

Fundoplication is the most common surgical treatment modality for GERD. It is widely accepted that fundoplication increases basal LES pressure[14–17] and

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may decrease transient LES relaxation.[17,18] For example, Ireland et al.[17] found a 50% decrease in the number of transient LES relaxations among 18 patients who had had a fundoplication. Because of these known effects of fundoplication and because fundoplication impairs vomiting and belching, particularly when it is long (i.e., >3 cm), we hypothesized that fundoplication might be an effective treatment for rumination. We have now used this procedure in five patients of normal intelligence who presented with rumination resistant to medical therapy. Because all of these patients underwent full esophageal and gastric functional studies, we were able to gain additional insights into the pathophysiology of this disease. This report summarizes the presentation, diagnosis, pathophysiology, surgical therapy, and outcomes in these five patients. To date, there are no reports of effective surgical therapy for this syndrome.

CASE REPORTS

Case 1

Patient R.F. was first seen as an 18-year-old man who had symptoms consistent with rumination since early childhood. His principal complaint was that during the first postprandial hour, food would suddenly reappear in his mouth. The regurgitated material tasted neither bitter nor sour and was subsequently reswallowed. He had been diagnosed as having rumination and had undergone behavioral therapy. He sought surgical intervention when medical therapy failed to control the problem and this behavior became socially embarrassing.

Preoperative pH studies revealed significant acid reflux, despite the absence of heartburn. He underwent a laparoscopic Nissen fundoplication. A moderate hiatal hernia was noted intraoperatively and repaired as a matter of course. Rumination resolved immediately after the operation, and the patient remained cured at 6 months' follow-up.

Case 2

Patient J.D., a 54-year-old, otherwise healthy woman, noted that after eating a meal, her abdomen would "spasm." She would belch three times and food would suddenly appear in her mouth. She would immediately reswallow the food and continue the cycle until the gastric contents acquired an acidic quality. The episodes never lasted longer than 2 hours. Although she admitted to significant life stressors, a formal psychiatric evaluation found no evidence of mental illness. She had been treated unsuccessfully with H_2 blockers. Promotility agents, used along with the H_2 blockers, induced projectile regurgitation.

On physical examination she was noted to have significant dental decay, but results of gastrointestinal studies showed no evidence of GERD (Table 1). The patient underwent a Nissen fundoplication. She returned to the clinic 2 weeks later tolerating a normal diet with no reports of rumination. Although we were unable to contact her for further follow-up, the patient has not returned to our clinic or to her referring gastroenterologist with any complaints since the operation.

Case 3

Patient K.M., a 44-year-old woman, had a history of rumination for 17 years. She reported regurgitating undigested food within 5 to 15 minutes after eating a meal. At no time did the food acquire an acid taste. Her rumination behavior ultimately led to such embarrassment that she declined to eat in any public setting.

Preoperative endoscopy revealed a small hiatal hernia and a wide-open gastroesophageal junction. The LES pressure was low and she had mild reflux, as shown by pH monitoring (see Table I). A Nissen fundoplication was performed with immediate relief of symptoms. The patient was contacted 1 year later and reported complete resolution of her rumination.

Case 4

Patient E.I., a 26-year old woman, reported a history of severe anorexia nervosa and bulimia since the age of 10. Although she denied currently engaging in dysfunctional eating behaviors, she admitted to spontaneously regurgitating undigested food after meals. She would repeatedly swallow and regurgitate this food, consistent with rumination. Within the past year, the episodes had become more troublesome, and she sought medical attention. The regurgitation was accompanied by debilitating gastric bloating, frequent belching, and dysphagia, but no heartburn (Fig. 1). Initial studies revealed a decreased LES pressure but normal acid exposure on 24-hour pH monitoring. She did, however, have spontaneous reflux observed on upper gastrointestinal barium studies (see Table 1). Prokinetic and acid suppression therapy provided minimal relief. The patient underwent a Nissen fundoplication.

Rumination was corrected immediately by the operation, and at 1-year follow-up she reported complete resolution of the rumination episodes. However, she continued to suffer from bloating, persistent obstipation, and the inability to belch. Repeat studies confirmed a functionally competent LES by manometry (pressure = 13 mm Hg and length = 4 cm), with the presence and amplitude of peristalsis essentially

Table 1. Preoperative evaluation of patients

Patients	Manometry	Upper GI series	24-hour pH	Gastric emptying	EGD
Case 1	LES: Pressure 5 mm Hg Total length 3 cm Abdominal length 1 cm Peristalsis: 100% Wave amplitude 55 mm Hg Wave duration 3 sec	Normal	Proximal 2.1% Distal 10.8% DeMeester score 53	Not performed	Flap valve laxity No esophagitis
Case 2	LES: Pressure 14 mm Hg Total length 3 cm Abdominal length 1 cm Peristalsis: 100% Wave amplitude 50 mm Hg Wave duration 3 sec	Not performed	Proximal 0.2% Distal 0.3% DeMeester score 3.3	Not performed	3 to 5 cm hiatal hernia
Case 3	LES: Pressure 8 mm Hg Total length 3 cm Abdominal length 3 cm Peristalsis: 100% Wave amplitude 90 mm Hg Wave duration 3 sec	Spontaneous reflux 3 to 5 cm hiatal hernia	Proximal 1.6% Distal 4.8% DeMeester score 18	Not performed	Wide-open gastroesophageal junction No esophagitis 3 to 5 cm hiatal hernia
Case 4	LES: Pressure 7 mm Hg Total length 4 cm Abdominal length 2 cm Peristalsis 100% Wave amplitude 85 mm Hg Wave duration 2.8 sec	Spontaneous reflux 3 to 5 cm hiatal hernia	Proximal 0.5% Distal 0.9% DeMeester score 6.1	Not performed	Normal
Case 5	LES: Pressure 8 mm Hg Total length 3 cm Abdominal length 3 cm Peristalsis: 100% Wave amplitude 130 mm Hg Wave duration 4 sec	3 to 5 cm hiatal hernia	Proximal 7.9% Distal 7.9% DeMeester score 29.4	Distal esophageal dysfunction with delayed emptying	Normal

Normal 24-hour pH values are less than 1% at the proximal probe, less than 4% at the distal probe, and a total DeMeester score of less than 14 (standard dual probe). EGD = esophagogastroduodenoscopy; GE = gastroesophageal; LES = lower esophageal sphincter.

unchanged (100% and 85 mm Hg). The fundoplication was well positioned without evidence of herniation on upper gastrointestinal studies. Although the operation successfully relieved the rumination, the postoperative complaints suggest a premorbid generalized gastrointestinal dysmotility syndrome.

Case 5

Patient J.M., a 61-year-old woman, reported regurgitating and swallowing undigested food after meals for 5 years. Each episode occurred approximately 10 to 15 minutes after eating, and was accompanied by abdominal distention. She also had a secondary complaint of heartburn. Although antacids and H_2 blockers relieved her heartburn, the rumination continued and she sought surgical intervention. Preoperative studies revealed a hypotensive LES with complete relaxation and normal esophageal body peristalsis, abnormal esophageal acid exposure on 24-hour pH monitoring, a small hiatal hernia, and poor clearance of the distal esophagus, as shown by radionuclide measurements (see Table 1). She did complain of occasional dysphagia, but this was not a primary symptom. The patient subsequently underwent a Nissen fundoplication with no complications.

She did quite well, with complete resolution of the rumination and heartburn. Six months after the operation, however, she developed dysphagia and presented with a 20-pound weight loss. Although 24-hour pH monitoring confirmed resolution of the GERD (0.7% proximal and 0.9% distal acid exposure), an upper gastrointestinal study revealed a small herniation of the wrap with mild obstruction in the distal esophagus that required an operation to redo the fundoplication.

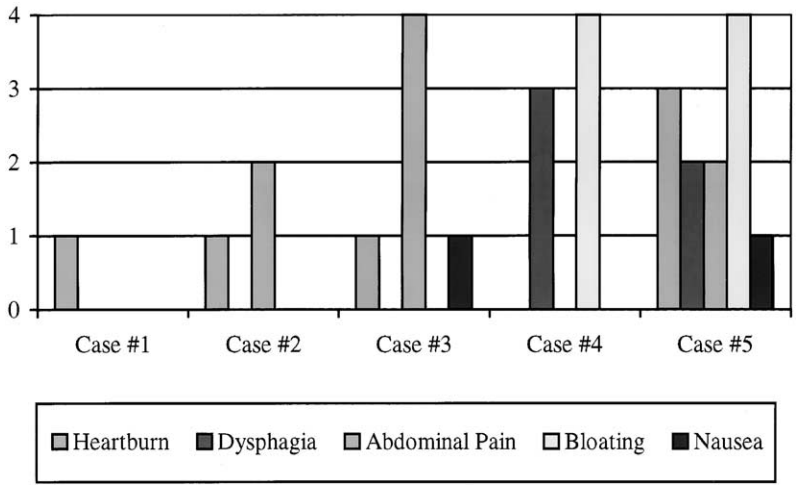

Fig. 1. Frequency of presenting symptoms in the five patients with rumination (1 = once a month; 2 = once a week; 3 = once a day; 4 = several times a day).

DISCUSSION

Diagnosis of Rumination

The Multinational Working Teams to Develop Diagnostic Criteria for Functional Gastrointestinal Disorders (Rome II) classifies rumination as a "functional esophageal disorder."[19] These disorders present with specific symptoms that typify esophageal diseases, yet they lack structural or metabolic abnormalities. The diagnostic criteria for rumination include the following for at least 12 weeks within the last 12 months:

1. Persistent regurgitation of recently ingested food with subsequent remastication and swallowing
2. Absence of nausea and vomiting
3. Cessation of the process when food becomes acidic
4. Absence of pathologic GERD (defined as evidence of esophagitis or abnormal esophageal exposure during 24-hour pH monitoring), achalasia, or other motility disorder recognized as the primary disorder

O'Brien et al.[5] investigated further the clinical features of rumination in one of the largest comprehensive studies of 38 adult patients with rumination. As in the Rome II classification, all patients experienced repetitive regurgitation of nonacidic undigested food. Most episodes began within 10 minutes of ingestion of a meal and terminated within 1 to 2 hours. Unlike vomiting, rumination was effortless and rarely associated with retching or nausea. On regurgitation, patients made a conscious decision to either swallow or spit out the food. In addition to symptoms stated in the Rome II definition, patients reported heartburn, nausea, abdominal pain, belching, bloating, and hiccups.

Each of our patients reported classic symptoms of rumination in accordance with the Rome II classification. Common associated complaints included abdominal pain, belching, bloating, and heartburn as described by other investigators.[5,20] One patient reported a history of anorexia nervosa and bulimia, which is fairly common among patients with rumination.[5,21–24] O'Brien et al.[5] found that 17% of female patients with rumination had a history of bulimia. They postulated that rumination might be a learned behavior, whereby shortening of the sphincter, which occurs when intragastric pressure increases with a full stomach, facilitates LES relaxation.

Pathophysiology of Rumination

The physiologic mechanisms characterizing the ruminating event remain unclear. Unlike ruminating animals, humans do not use an antiperistaltic action to propel food along the esophagus back to the mouth. In fact, esophageal motility appears to be completely intact and peristalsis is normal. Several case studies have recorded gastrointestinal pressure spikes secondary to abdominal wall contractions with simultaneous relaxation of the LES associated with episodes of regurgitation.[8–10] Unfortunately, a direct relationship between gastric pressure spikes and LES relaxation is not found consistently among patients with the rumination syndrome. O'Brien et al.[5] studied 38 patients suffering from rumination and noted LES relaxation with regurgitation, yet reported gas-

tric pressure spikes in only 33% of patients. Smout et al.[11] recorded transient LES relaxation in only 44% of reflux episodes with related abdominal pressure spike. In a recent study, gastroesophageal motor and sensory function were investigated in 24 patients, 12 with rumination and 12 control subjects.[12,13] Those with rumination experienced heightened sensitivity and more prominent LES relaxation in response to gastric distention compared to control subjects, suggesting visceral afferent hypersensitivity. Although no consistent abnormality has been detected in rumination, all studies report either a hypotensive LES pressure or transient relaxation of the LES in response to increased gastric pressure or distention.

Three of our patients (60%) had abnormal acid exposure on pH studies. This finding is not surprising, given the presence of LES dysfunction. Although prior studies of patients with rumination have frequently omitted 24-hour pH monitoring, there is evidence that patients with rumination have a higher incidence of abnormal acid exposure than those without rumination.[25] Is it possible that our patients had GERD rather than rumination? Several features of their presentation suggest that, although the reflux could be an associated manifestation, rumination was the primary problem. First, heartburn was reported only occasionally or not at all (see Fig. 1). Also, nocturnal reflux was absent on 24-hour pH monitoring and regurgitant material lacked an acidic quality, both of which are highly suggestive of rumination.

Preoperative evaluation revealed four patients with decreased resting LES tone, but no other manometric abnormalities. As previously discussed, this has been noted in other series and would in part account for the effortless, spontaneous regurgitation that accompanies gastric distention in patients with rumination. It also explains the correlation with abnormal reflux on 24-hour pH monitoring.

Treatment of Rumination

Early treatment of infants and mentally impaired patients with rumination included dietary experimentation and physical restraints. Included among the latter were nostril plugging, wiring the jaw closed, arm splints (to prevent finger sucking), and insertion of inflatable devices into the esophagus after eating. Aversion techniques such as electrical shock, scolding, and the application of unpleasant tastes to the tongue had also been recommended and have, understandably, been met with resistance because of ethical considerations.[26]

More recently the treatment of choice has been psychotherapy. A few investigators report improvement in symptoms with behavioral and psychotherapeutic interventions, but few have reported complete cessation of symptoms.[5,8,9,20] Shay et al.[8] described the successful use of biofeedback therapy, instructing patients to "practice" relaxing the abdominal muscles before, during, and after meals. After eight training sessions, they reported 80% improvement, with the only residual symptom being occasional heartburn. Although there may be a role for such behavioral techniques in alleviating rumination symptoms, researchers face at least two major limitations: the need for highly motivated, intelligent individuals and their inconsistent success rates.

Surgical treatment for rumination has been reported on one occasion. Brown[27] described a 34-year-old housewife with postprandial regurgitation. Despite having features of hysteria and schizophrenia on psychiatric evaluation, she refused psychotherapy. The patient underwent a hiatal herniorrhaphy, pyloroplasty, and vagotomy for a suspected hiatal hernia discovered on x-ray examination. A fundoplication was not performed. Her symptoms returned, unabated, 1 month later causing "great embarrassment and social withdrawal."

Our study describes the diagnostic and therapeutic features of five patients with rumination who were treated with a Nissen fundoplication. Unlike previously reported treatment modalities, all five patients treated in this manner reported complete cessation of their ruminating behavior. Three patients (Cases 1 to 3) had few other significant gastrointestinal complaints (see Fig. 1). In fact, we asked each patient specifically about the frequency of the following gastrointestinal-related symptoms: heartburn, regurgitation, dysphagia, abdominal pain, belching, bloating, nausea, chest pain, odynophagia, globus, and aspiration. Each patient had heartburn that occurred no more than once a month. Two patients had abdominal pain. In only one of them was it common, and the pain improved after the operation. A Nissen fundoplication relieved rumination in each of these patients, and because this was the predominant symptom, all were satisfied with the results. The remaining two patients, however, had more pronounced coexisting symptoms.

Case 4 initially complained of frequent dysphagia and bloating in addition to rumination. Her history was complicated by anorexia and bulimia for which a psychiatric evaluation was carried out to ensure that her eating disorder had been effectively treated. The Nissen fundoplication eliminated her rumination. A year later, however, she presented with worsening postprandial bloating. We concluded she had a concurrent gastric dysmotility disorder, given the supportive evidence for normal gastric emptying in patients

with rumination.[9,20,28] The persistent symptoms in this patient should not detract from the fact that fundoplication was effective in relieving rumination, but it should be emphasized that both the patient and the surgeon should have realistic expectations of which symptoms will improve with Nissen fundoplication. Although gastric motility usually improves with fundoplication, symptoms associated with gastroparesis may occasionally persist. We also recommend caution when treating patients with a history of bulimia, both to ensure that the diagnosis is correct and because vomiting may lead to disruption and herniation of the wrap. In addition, because there is evidence that rumination ceases in patients who successfully gain control over their eating habits, a trial of behavioral therapy should also be carried out before surgery is considered.[22,23]

The last patient (Case 5) presented with heartburn, dysphagia, abdominal pain, and bloating. We thought a Nissen fundoplication was ideal for this patient, as it would simultaneously treat her rumination and heartburn. She responded well, with complete resolution of both symptoms. Unfortunately she returned 6 months later with more prominent dysphagia and weight loss. Although dysphagia is a common transient postoperative complication after Nissen fundoplication, it usually resolves within the first 2 months.[29,30] Reevaluation with an upper gastrointestinal barium swallow study revealed a herniation of her wrap. After endoscopic dilation failed to relieve her symptoms, she underwent a reoperation to reduce and redo the fundoplication. Although she presented preoperatively with mild dysphagia and delayed esophageal clearance, it is difficult to know how much, if any, these findings contributed to her postoperative dysphagia.

CONCLUSION

We have presented five patients diagnosed with classic rumination who, after failure of medical management, were treated with a Nissen fundoplication. Our study confirms previous suggestions that an incompetent cardia may play a role in this disease. The therapeutic approach we recommend, which has not previously been described, is based on the restoration of cardioesophageal competence, the creation of a flap valve, and the enhancement of LES pressure. The procedure yielded good results with elimination of rumination in all patients. The effectiveness of this procedure and the consistent elimination of the problem in all patients suggests that a Nissen fundoplication should be considered for patients in whom rumination causes severe psychosocial or medical problems and in whom behavior modification and medical treatment have failed.

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Effect of Duodenal Diversion on Low-Grade Dysplasia in Patients With Barrett's Esophagus: Analysis of 37 Patients

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It is well known that in patients with Barrett's esophagus (BE), even after antireflux surgery, intestinal metaplasia can progress to dysplasia or even adenocarcinoma. However, the opposite—that is regression of dysplastic changes to intestinal metaplasia after antireflux surgery—has been documented in only a few reports. The objective of this study was to determine the effect of a duodenal diversion operation on low-grade dysplasia in patients with BE. Thirty-seven patients with either short-segment (n = 12) or long-segment (n = 25) BE underwent antireflux surgery plus either a duodenal switch procedure (13 patients) or a partial distal gastrectomy with Roux-en-Y gastrojejunal anastomosis (24 patients). All of them were subjected to complete clinical, endoscopic, histologic, manometric, and 24-hour pH testing, and 24-hour monitoring of the bile exposure in distal esophagus. There were no deaths in this series, and morbidity occurred in only one patient (2.7%). Manometric assessment after surgery showed a significant increase in sphincter pressure, abdominal length, and total length ($P < 0.001$). Acid reflux showed a significant decrease after surgery, and duodenal reflux was completely abolished in all except one patient. Follow-up in all patients was longer than 24 months (mean 60 months). Three to four endoscopic procedures were performed after surgery in each patient, and several biopsy specimens were taken distal to the squamocolumnar junction during each endoscopic procedure. Eleven patients (91%) with short-segment BE demonstrated histologic regression to either cardiac mucosa or nondysplastic intestinal metaplasia. Among the 25 patients with long-segment BE, there was a 62.5% rate of histologic regression to nondysplastic epithelium when the length of BE measured between 31 and 99 mm and 33% histologic regression when the length of BE was 101 mm or more. There were no cases of progression to high-grade dysplasia or adenocarcinoma. The endoscopic length of the columnar-lined esophagus did not change late after surgery. In 65% of patients with BE, antireflux surgery, gastric acid reduction, and duodenal diversion produced histologic regression of low-grade dysplasia to nondysplastic mucosa. This effect was even more pronounced when the length of BE was shorter. It seems to be permanent, and no progression to high-grade dysplasia or adenocarcinoma has occurred. (J GASTROINTEST SURG 2002;6:645–652.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Barrett's esophagus, low-grade dysplasia, duodenal diversion

We have recently demonstrated that classic antireflux surgery in patients with long-segment (>3 cm) Barrett's esophagus (BE) is plagued by a high rate of failure when long-term follow-up (>8 years) is conducted and several objective parameters are employed to assess this failure.[1,2] It is also well known that even after antireflux surgery, the specialized columnar epithelium with intestinal metaplasia can progress to dysplastic changes and even adenocarcinoma.[3–12] In contrast, very few studies report the opposite effect—that is, regression of dysplastic changes to nondysplastic intestinal metaplasia after antireflux surgery. We have found only four reports that mention this reversal.[9,12–14] In particular, DeMeester et al.[12] and Low et al.[14] have presented recent data on regression of low-grade dysplasia after Nissen fundoplication in seven patients and four patients, respectively.

Over the past decade, we have performed two different types of operations in patients with BE; these operations consist of antireflux surgery and reduction of gastric acid by highly selective vagotomy or by vagotomy and antrectomy and complete duodenal diversion through a Roux-en-Y loop 60 cm in length.[15,16] A

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total of 325 patients with BE have been subjected to these operations including 37 patients (11.4%) who had low-grade dysplasia at the time of surgery. The purpose of the present prospective study was to determine the effect of both operations on low-grade dysplasia in these 37 patients with BE.

MATERIAL AND METHODS

Patients

Thirty-seven patients were included in this prospective study, which was begun in January 1989 and ended in December 2000. The 18 men and 19 women had a mean age of 57.3 years (range 35 to 75 years). All patients had symptoms of gastroesophageal reflux with a mean duration of symptoms of 154 months (range 96 to 360 months). Twelve patients (32.4%) had short-segment (<3 cm) BE, whereas 25 patients (67.6%) had long-segment (>3 cm) BE. All patients had intestinal metaplasia distal to the squamo-columnar junction with cardiac mucosa. Only patients with low-grade dysplasia were included in the study and patients with high-grade dysplasia and adenocarcinoma were excluded. Nine patients (24%) had previously undergone antireflux surgery that failed, whereas 28 patients had no prior operations. All of these patients had been treated for 1 year with omeprazole (20 to 40 mg/day), but low-grade dysplasia persisted. None of the patients was operated immediately after the initial diagnosis of low-grade dysplasia.

Endoscopic Examination

All endoscopic procedures were performed by two of us (A.C. and I.B.) using an Olympus GIF XQ-20 endoscope. Special care was taken to measure the exact location of the squamo-columnar junction at the beginning and at the end of the procedure, avoiding the "push" and "pull" effects of the endoscope. This procedure was performed in all patients twice before and several times after surgery (at 12 months after surgery and every 1 or 2 years thereafter). For the present study, a special biopsy protocol was designed in which two biopsy samples were taken from the antrum and, in all patients with short-segment Barrett's esophagus, four-quadrant biopsy specimens were taken 5 mm distal to the squamo-columnar junction and the same procedure was repeated 2 cm distal. In patients with long-segment Barrett's esophagus, four-quadrant biopsy specimens were taken every 2 cm from the squamo-columnar junction to the lower esophageal spincter. For the present study, patients were divided into the following three groups according to the endoscopic length of the specialized columnar epithelium: (1) short-segment BE, when the length measured 10 to 30 mm; (2) long-segment BE, when the length measured 31 to 99 mm; and (3) extralong-segment BE, when the length measured 100 mm or more.

Histologic Analysis

Several biopsy specimens were taken from each patient at each endoscopic procedure. These specimens were immediately submerged in 10% formalin solution and sent for histologic examination. Samples were stained with hematoxylin and eosin and Alcian blue, and the type of epithelium lining the distal esophagus was carefully determined (cardiac or fundic), including the presence of intestinal metaplasia. Cardiac mucosa was defined by the presence of mucus-secreting columnar cells. Intestinal metaplasia was defined by the presence of goblet cells. For the present protocol, and in order to avoid misdiagnosis of dysplasia due to inflammatory and degenerative changes, endoscopy and biopsy were repeated before surgery to reconfirm the presence of dysplasia. Only patients with low-grade dysplasia were included,[17–19] and patients with an uncertain or indefinite grade of dysplasia were excluded.

Manometric Evaluation

Manometric testing was carried out after a 12-hour fast with patients in the supine position. The complete details of this procedure have been fully explained in previous reports.[15,20,21] Three manometric characteristics of the lower esophageal sphincter were determined: resting pressure, total length, and abdominal length. The latter measurement was taken from the distal end of the sphincter up to the respiratory inversion point, which is the level at which the end-expiratory pressure changes from a positive to a negative deflection.[21,22] A mechanically incompetent sphincter was defined by the presence of one of the following parameters: lower esophageal spincter pressure less than or equal to 6 mm Hg, total length less than 20 mm, and abdominal length less than 10 mm.[22,23] The location of the distal and proximal ends of the lower esophageal sphincter was also measured in centimeters from the incisors. The amplitude of the distal esophageal contractile waves was also determined in mm Hg. This test was performed before and 1 year after surgery.

24-Hour Intraesophageal pH

This test was performed after a 12-hour fast,[24,25] introducing the catheter through the nose until the

stomach was reached (Digitrapper; Synectics, Sweden). The catheter was then placed 5 cm above the manometric upper border of the lower esophageal spincter (manometry is always done before this procedure). Among the six different parameters that can be evaluated, the most useful and practical is the total percentage of time during which the intraesophageal pH remains below 4, this being our normal value less than 4% of the time during a 24-hour period (55 minutes). This test was carried out before and 12 months after surgery.

24-Hour Monitoring of Esophageal Exposure to Duodenal Juice

This procedure was developed to measure spectrophotometrically the intraluminal bilirubin concentration.[26–28] It consists of a portable opticoelectronic data logger (Bilitec 2000, Synectics) connected to a fiberoptic probe that is passed transnasally and positioned 5 cm proximal to the lower esophageal spincter. The complete details have been extensively published elsewhere.[1,15] The final calculation is based on the percentage of time that bilirubin is measured in the esophagus, with an absorbance greater than 0.2 being our normal value less than 2% of the time (28 minutes).

Statistical Analysis

For statistical evaluation, Fisher's exact test, chi-square test, and Mann-Whitney test were employed, with a value of $P < 0.05$ considered significant.

Surgical Treatment

All patients were subjected to an antireflux procedure (Nissen fundoplication in 22 patients and posterior gastropexy with calibration of the cardia in 15 patients). In 13 patients a duodenal switch procedure was performed (calibration of the cardia in 9 and Nissen fundoplication in 4) with highly selective vagotomy, plus an end-to-end duodenojejunostomy with Roux-en-Y loop.[15] In 24 patients truncal vagotomy (Nissen fundoplication in 18 and calibration of the cardia in 6), partial gastrectomy, and a Roux-en-Y loop were performed.[16] All nine of the patients who had a failed antireflux operation were subjected to a second antireflux procedure.

Definition of Regression

Patients with intestinal metaplasia and low-grade dysplasia were considered to have histologic regression if the following criteria were met: dysplasia was no longer present within the mucosa with intestinal metaplasia (loss of low-grade dysplasia), and cardiac mucosa was present on two consecutive endoscopic examinations and biopsy specimens (loss of intestinal metaplasia). Endoscopic regression was defined as a decrease of at least 3 cm in the length of the columnar-lined segment of the distal esophagus.

RESULTS

There were no operative deaths and no postoperative complications, except for one patient who had stricture of the gastrojejunal anastomosis, which was managed with endoscopic dilitation and a nasojejunal feeding tube for 1 month. There were no instances of delayed gastric emptying, and all patients were Visick grade I or II late after surgery.

Erosive esophagitis was present proximal to the squamo-columnar junction in 20 patients (54%). Peptic ulcers of the esophagus were present in two patients with short-segment BE (15%) and in 10 patients with long-segment BE (42%). Peptic stricture was demonstrated in two patients with long-segment BE. After surgery, multiple endoscopic control examinations demonstrated healing of esophagitis and peptic ulcers in all patients who underwent vagotomy plus gastrectomy, with no recurrence of symptoms up to the late control period (60 months). However, among the 13 patients who were subjected to the duodenal switch procedure, five had a recurrence of reflux symptoms without endoscopic esophagitis; this correlated with 24-hour pH studies demonstrating above-normal values in all five. These patients are being treated long term with protein pump inhibitors treatment. Four of them have shown regression to intestinal metaplasia.

The main manometric features of the lower esophageal spincter and esophageal waves before and after surgery are shown in Table 1. There was a significant increase in the resting pressure, total length, and abdominal length of the spincter. A significant decrease in the percentage of incompetent spincter was seen. The amplitude of the waves at the distal esophagus remained unchanged after surgery. The values for acid and duodenal reflux at the distal esophagus before and after surgery are shown in Table 2. There was a significant decrease in acid reflux to the esophagus after both types of operations ($P < 0.0001$). However, 55% of the patients subjected to highly selective vagotomy and the duodenal switch operation still had above-normal acid reflux values, whereas only 8.3% of patients who underwent vagotomy and gastrectomy had abnormal acid reflux ($P < 0.001$). In contrast, duodenal exposure of the distal

Table 1. Manometric studies before and after duodenal diversion

	Before surgery (n = 35)	After surgery (n = 23)	*P* value
LES pressure (mm Hg)	8.1 ± 4.5	12.6 ± 5.5	<0.01
≤6 mm Hg	19 (54%)	2 (8.7%)	
Total length of LES (mm)	27.4 ± 11	37 ± 11	<0.01
Abdominal length of LES (mm)	6.2 ± 6.3	11 ± 5.7	<0.006
<10 mm	22 (63%)	3 (13%)	
% Incompetent LES	26 (74%)	5 (22%)	<0.001
Amplitude of distal esophageal waves (mm Hg)	37.6 ± 18	39.5 ± 24	>0.8

LES = lower esophageal sphincter.

esophagus was completely abolished by the Roux-en-Y loop ($P < 0.0001$) in 16 (94%) of 17 patients assessed late after surgery.

The effect of duodenal diversion on low-grade dysplasia (histologic regression) is shown in Table 3. All 37 patients were for a late control follow-up (more than 24 months after surgery). Among 12 patients with short-segment BE, low-grade dysplasia regressed in 11 of them (91%). However, five patients had regression to intestinal metaplasia (41%), whereas loss of intestinal metaplasia and regression to cardiac mucosa occurred in six patients (50%). The mean time for regression to cardiac mucosa or intestinal metaplasia was similar. After this event, patients continued with further follow-up, with more than three endoscopic and biopsy studies in each case. Only one patient with low-grade dysplasia kept returning for follow-up over the next 8 years. The endoscopic length of the columnar epithelium did not change late after surgery. There was no progression to high-grade dysplasia or adenocarcinoma.

Among 16 patients with long-segment BE measuring between 31 and 99 mm, similar changes were observed. Regression to cardiac mucosa occurred in two patients (12.5%), whereas regression to intestinal metaplasia was demonstrated in eight patients (50%). The mean time for regression to either cardiac mucosa or intestinal metaplasia was similar. Persistence of low-grade dysplasia was observed in six patients (37.5%) at up to 6 years' follow-up. Not one patient had progression to high-grade dysplasia or adenocarcinoma. The mean length of the specialized columnar epithelium was similar, independent of its behavior. Among nine patients with extralong-segment BE, measuring 100 mm or more, no regression to cardiac mucosa was documented. Three patients (33%) showed regression to intestinal metaplasia at a mean time of 40 months after surgery. Persistence of low-grade dysplasia was observed in six patients (67%) at up to 80 months follow up. Not one patient had progression to high-grade dysplasia or adenocarcinoma.

The relationship between the length of the BE and the percentage of loss of low-grade dysplasia after duodenal diversion is shown in Fig. 1. There was an inverse correlation between the endoscopic length

Table 2. Acid and duodenal reflux at the distal esophagus before and after duodenal diversion

	Before surgery	After surgery	*P* value
24 hr esophageal pH monitoring			
(% of time with pH <4 in 24 hr)			
No. of cases <4%			
Duodenal switch (n = 11)	38.6 ± 21.5 (A)	5.4 ± 3.57 (B)	A vs. B < 0.0001
% Above normal	100	55	C vs. D < 0.0001
Vagotomy-gastrectomy (n = 12)	34.9 ± 22.8 (C)	1.3 ± 0.8	A vs. C > 0.69
% Above normal	100	8.3	B vs. D < 0.01
24 hr esophageal bilirubin monitoring			
(% Of time with bilirubin with absorbance >0.2)			
Duodenal switch (n = 7)	18.9 ± 6.3 (E)	0.81 ± 0.93 (F)	E vs. F < 0.0001
% Above normal	100	14	G vs. H < 0.0001
Vagotomy-gastrectomy (n = 10)	25.6 ± 120 (G)	0.74 ± 1.5 (H)	E vs. G > 0.29
% Above normal	100	0	F vs H > 0.9

Table 3. Effect of duodenal diversion on low-grade dysplasia (n = 37)

	Length of BE (mm)	Mean time for histologic regression (mo)	Mean further follow-up (mo)	Mean no. of postoperative endoscopies
Short-segment BE (n = 12)				
Regression to IM (n = 5)	23.0	24	32	3.4
Regression to cardiac mucosa (n = 6)	20.6	24	24	3.5
Persistence of LGD (n = 1)	15		96	4.0
Long-segment BE (30–99 mm; n = 16)				
Regression to cardiac mucosa (n = 2)	50.0	30	24	3.5
Regression to IM (n = 8)	60.6	33	24	3.6
Persistence of LGD (n = 6)	56.6	—	74	4.2
Progression to HGD (n = 0)	0	—	—	—
Extra–long segment BE (100 mm or more; n = 9)				
Regression to cardiac mucosa (n = 0)	—	—	—	—
Regression to IM (n = 3)	115	40	44	4
Persistence of LGD (n = 6)	122	—	80	4.5

BE = Barrett's esophagus; IM = intestinal metaplasia; LGD = low-grade dysplasia.

of BE and the histologic regression of dysplasia or intestinal metaplasia. Among patients with endoscopic short-segment BE, 91% had regression of low-grade dysplasia. Among patients with endoscopic long-segment BE, with a length between 31 and 100 mm, there was a 62.5% rate of disappearance of low-grade dysplasia, whereas this occurred in only 33% among patients with BE longer than 101 mm. No patient progressed to high-grade dysplasia or adenocarcinoma. The mean percentage of regression to nondysplastic epithelium was 69% after the duodenal switch operation and 63% after vagotomy plus gastrectomy ($P > 0.6$).

DISCUSSION

The results of the present prospective study suggest that among patients with BE and low-grade dysplasia, duodenal diversion produces histologic regression of this dysplasia in 24 (65%) of 37 patients with a follow-up of more than 24 months after surgery. Second, there is an inverse correlation between the endoscopic length of the columnar-lined esophagus and the probability of regression of low-grade dysplasia. Our study has some peculiarities, however; it is the only report to analyze the effects of total duodenal diversion in patients with BE and low-grade dysplasia; it included a large number of patients; follow-up was lengthy (60 months); there were several objective control examinations before and after surgery; and in each case at least three to four postoperative endoscopic specimens and several biopsy samples were analyzed during each procedure. In the surgical literature, there are four studies reporting cases of low-grade dysplasia that regressed to nondysplastic intestinal metaplasia or cardiac mucosa.[9,12–14] Skinner et al.,[13] in 1983, reported on 13 patients with BE who underwent a Belsey Mark IV procedure. Five of them had low-grade dysplasia and two showed regression at 4 years follow-up. McEntee et al.[9] evaluated 21 patients who had antireflux

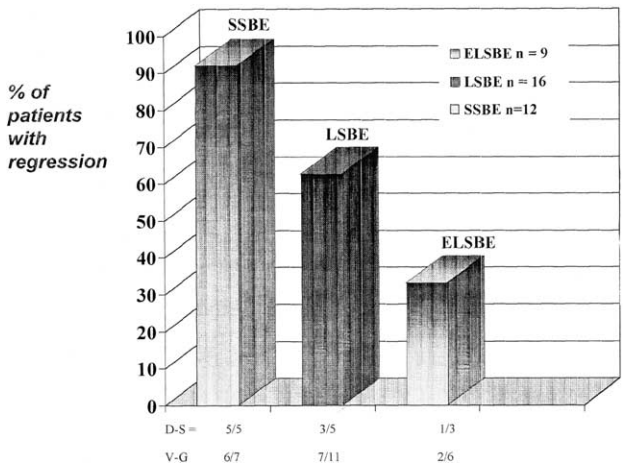

Fig. 1. Prevalence of histologic regression from low-grade dysplasia to nondysplastic epithelium in patients with Barrett's esophagus according to the endoscopic length of the specialized columnar epithelium. D-S = duodenal switch; ELSBE = extra–long segment Barrett's esophagus (≥100 mm); LSBE = long-segment Barrett's esophagus (31–99 mm); SSBE = short-segment Barrett's esophagus (≤30 mm); V-G = vagotomy-gastrectomy.

surgery (16 Nissen and 5 Angelchick procedures). In four of six patients with low-grade dysplasia, these investigators found regression at 2 years' follow-up. Low et al.,[14] in 1999, studied 14 patients with long-segment BE, who underwent laparoscopic antireflux surgery with a follow-up of 25 months, and reported that in four cases of low-grade dysplasia, there was histologic regression to nondysplastic intestinal metaplasia. The best report comes from DeMeester et al.,[12] who published their findings on the effects of antireflux surgery in 60 patients with BE. Among them, 15 patients had intestinal metaplasia of the cardia. One patient with dysplasia showed histologic regression to nondysplastic intestinal metaplasia. Among 45 patients with BE, nine had low-grade dysplasia, which showed histologic regression to nondysplastic intestinal metaplasia in six of them. Unfortunately it is not clearly stated whether 30 mm was the length of the BE or the mean length of the columnar-lined esophagus in DeMeester's study. In addition, in 11% of the patients, intestinal metaplasia progressed to low-grade dysplasia. No other objective parameters were evaluated after surgery in any of these reports, and the mean follow-up was 25 months.

In our study, with a mean follow-up of 60 months after surgery, three or four postoperative endoscopic examinations being performed and several biopsy specimens taken during each procedure in each patient, we demonstrated that duodenal diversion produced a permanent histologic regression of low-grade dysplasia in 65% of our cases, whereas progression to high-grade dysplasia or adenocarcinoma has not occurred. The mean time for regression to nondysplastic intestinal metaplasia or cardiac mucosa was quite consistent, being around 24 months after surgery, which is very similar to previously reported findings. Furthermore, what is very interesting is that the shorter the length of BE, the greater the probability of regression of low-grade dysplasia. In fact, among patients with short-segment BE, this regression occurred in 91%, whereas when the columnar-lined esophagus measured more than 100 mm in length, this regression was noted in only 33%. We know that one criticism of our findings is the possibility that we had sampling errors among our patients. Although it is not possible to avoid these errors completely, first we want to stress that all of our patients were evaluated by two of us, both of whom have vast experience with endoscopic procedures, and the same biopsy protocol was employed before and after surgery. Second, several biopsy specimens were taken from each patient every time endoscopy was performed. In patients with short-segment BE, four to eight specimens were taken each time, and in patients with long-segment BE, 12 to 14 specimens were taken. There is always a possibility of sampling error, but then the question is, how many specimens must be taken? There cannot be too many not only because of the risk of bleeding but also because patient discomfort is also an important consideration. Third, we performed at least three or four endoscopic procedures and took biopsy specimens in each case after surgery, performing these examinations five to seven times in several patients. Thus we believe our results truly reflect what occurred in each individual patient. We have not seen any previous surgical reports that take into account several objective parameters for each patient, with no loss of any patients to late follow-up.

The fact that after duodenal diversion there is a loss of low-grade dysplasia and even loss of intestinal metaplasia, but without regression or decrease in the length of the columnar epithelium lining the distal esophagus, suggests that the presence of cardiac mucosa seems to be a permanent, strong, and nonreversible type of metaplasia.[12] To the contrary, low-grade dysplasia and even intestinal metaplasia seem to be some of the more dynamic and not too permanent or strong epithelial changes, and these can be reversed after the elimination of reflux into the esophagus. Therefore it seems that the total duodenal diversion operation protects patients with BE from progressing to dysplasia or adenocarcinoma, and even produces histologic regression of dysplastic changes. Another interesting finding is the fact that both duodenal diversion procedures produced a similar percentage of regression. Duodenal switch resulted in 69% of regression, whereas vagotomy plus gastrectomy yielded 63% of regression. In both operations similar antireflux techniques were employed, and both involved a Roux-en-Y loop 60 cm in length. Total duodenal diversion was proved by the Bilitec test, which demonstrated complete elimination of bile reflux in 16 of 17 patients. In contrast, acid reflux values remained abnormal in 55% of patients after the duodenal switch procedure, but in only 8% after vagotomy plus gastrectomy, reflecting a greater suppression of gastric acid after the latter technique. These findings suggest that probably the combination of acid and duodenal reflux is an important pathogenic factor in the development of intestinal metaplasia and low-grade dysplasia, and decreasing it or eliminating it altogether could produce a histologic regression of both, which persists with no variation in the length of columnar epithelium with cardiac mucosa. It is well known that classic antireflux surgery decreases the probability of progression to high-grade dysplasia or adenocarcinoma compared to medical treatment.[6,7,10] But the current evi-

dence shows that even after antireflux surgery for BE, dysplasia or adenocarcinoma can occur.[3–12] Even in the report by DeMeester et al.[12] among patients demonstrating regression of nondysplastic intestinal metaplasia or low-grade dysplasia after antireflux surgery, 11% showed progression to low-grade dysplasia.

What are the differences then between our results and other reports concerning antireflux surgery in BE? There are two main differences. We, as do some other groups, always perform antireflux surgery in all of our patients. However, the lower esophageal spincter in patients with BE shows very severe structural damage, with a high percentage of patients demonstrating an incompetent lower esophageal sphincter[22,23] and a greatly dilated cardia or gastroesophageal junction.[29] Complete "normalization" or reestablishment of a normal lower esophageal sphincter is very difficult to achieve by means of any antireflux procedure after so many years of reflux and permanent damage. Therefore reflux to the esophagus can be greatly decreased but not eliminated completely and permanently, and what is worse is that years after surgery the lower esophageal sphincter can loose its strength and may return to the original preoperative incompetent condition.[2] This explains the high percentage of failures in patients with BE, even when their reflux has been controlled for 8 or 10 years after surgery.[1,2] When acid and bile reflux are measured 1 year after surgery,[30] Nissen fundoplication seems to be very effective in controlling acid and duodenal reflux into the distal esophagus. When these tests are performed 10 years after surgery,[1] the percentage of patients with positive reflux increases considerably. Therefore in our surgical procedures we try to achieve two main goals: (1) a significant decrease in gastric acid secretion by performing vagotomy and partial distal gastrectomy, and (2) permanent elimination of duodenal reflux by creating a long Roux-en-Y loop. It is well known that dysplasia and adenocarcinoma are closely related to reflux of duodenal content.[31–34] Therefore, even if the lower esophageal sphincter becomes incompetent again late after surgery, there is no harmful refluxate to the distal esophagus—that is, no acid or duodenal content can reflux. These are the reasons why this operation has not only produced a histologic regression of low-grade dysplasia or even nondysplastic intestinal metaplasia, but also why no progression to adenocarcinoma has occurred. In summary, duodenal diversion is extremely effective in controlling the presence of low-grade dysplasia in patients with BE. This effect is greater in patients with a short length of BE. This effect seems to be permanent, and no progression to high-grade dysplasia or adenocarcinoma has been seen.

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Erasmus: Paradigm of Renaissance Humanism
Stanley R. Friesen, Padova, Piccin Nuova Libraria, 2001, 164 pages.

We cannot underestimate the impact of humanism in the intellectual and cultural history of the West. Humanism engendered profound changes in the philosophical and cultural underpinnings of our society. As a consequence, the social and political fabric of Western society was fundamentally altered during the last millennium, while other societies that share our globe remained culturally pretty much unchanged.

Humanism began in intellectual efforts in the late Middle Ages in Europe to make ancient Greek texts more available to scholars by translating them into Latin. Doing the translations required a reexamination of the original Greek sources and of earlier translated versions. Errors were uncovered in these older interpretations. The unforeseen result of the correction of these errors was erosion of the authoritarian basis of societal governance, and an increasing threat to the Church and the princely rulers of Europe.

Erasmus (1466–1536) lived in a time of enormous change. Well educated and gifted with great energy and a superior intellect, he was an extraordinarily productive scholar. Although "publish or perish" was not yet an academic imperative, Erasmus published as though it were. His productivity was facilitated by the development of moveable type and the printing press, contemporary mechanical advances that allowed relatively inexpensive and rapid production of books.

A biographical examination of the work of Jerome, author of the *Vulgate Bible*, and a Latin translation of the *New Testament* were among the works that put Erasmus at the center of intellectual activities at the turn of the fifteenth century. In his publications and published correspondence, Erasmus espoused principles of tolerance for the ideas of others and, importantly, the ability of people to determine truth and falsehood by themselves. These attractive ideas were a major stimulus leading Luther to nail up his theses. It is said that Erasmus "laid the egg that Luther hatched."

All of this grand sweep of intellectual history and Erasmus' central role in the genesis of the Reformation is reviewed in detail in a tightly written book by Stanley Friesen, a well-known surgical scholar who has turned in retirement to issues of religious history that have long held fascination for him. Friesen focuses, more or less chronologically, on the life of Erasmus in thoroughly documented spare prose, recording not only his many publications but also the major events of his travels, and his interactions with other scholars as well as with the popes and princes of the time. There are, as well, descriptions of the influence of humanism in church music and the arts, with generous side trips into the roles of Linacre and Vesalius in overcoming the errors of Galenic medicine and into some details of the Copernicus-Paracelsus-Galileo story.

This is a book for readers who desire an understanding of the role of Renaissance humanism in the religious ferment of the time. It provides as well insights into the rationalism that led in the West to the ascendancy of democratic political structures and acceptance of the principles of science in new discovery.

Robert E. Condon, M.D., M.Sc.

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Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery Mini Fellowship Program, August 25–30, 2002; November 3–8, 2002; The University of Texas Southwestern Medical Center at Dallas. Fees: $10,000 (team of 2 physicians and 1 nurse); $5000 (physician); $1000 (nurse). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

AHPBA ANNOUNCEMENTS

November 2002: AASLD/AHPBA Surgical Forum, Boston, MA, November 1–5, 2002. This will be a liver-based program. Visit AHPBA.org for more information.

February 2003: 5th AASLD Biannual "Americas" Meeting, February 27–March 2, 2003. This will again be held at the Eden Roc Hotel in Miami, FL. The first day will be a postgraduate course chaired by C. Wright Pinson. Make this one with the family! Visit AHPBA.org for more information.

May 2004: 6th World Congress IHPBA Biannual Meeting, Washington, DC, May 27–June 2, 2004. The AHPBA hosts the IHPBA.

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