Esophagotomy During Laparoscopic Heller Myotomy Cannot Be Predicted by Preoperative Therapies and Does Not Influence Long-term Outcome

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The conventional wisdom is that inadvertent esophagotomy complicates laparoscopic Heller myotomy. This study was undertaken to determine if esophagotomy at myotomy can be predicted by preoperative therapy, and if esophagotomy and/or its repair jeopardizes outcomes. Of 222 laparoscopic Heller myotomies undertaken since 1992, inadvertent esophagotomy occurred in 16 patients (7%); 60 patients who underwent myotomy without esophagotomy were utilized for comparison. Dysphagia and reflux before/after myotomy were scored by patients on a Likert scale (0–5). The median (mean ± SD) follow-up after myotomy with esophagotomy was 38.8 months (31.6 ± 21.9 months) versus 46.3 months (51.0 ± 21.2 months) after myotomy alone. All esophagotomies were immediately recognized and repaired. Patients who experienced esophagotomy were similar to those who did not in application of Botox (56% vs. 77%) or dilation (44% vs. 65%), years of dysphagia (7.3 ± 5.4 vs. 7.4 ± 6.0), and mean preoperative dysphagia score (4.9 ± 0.4 vs. 4.8 ± 0.4). Esophagotomy led to longer hospitalizations (5.2 days ± 2.5 days vs. 1.5 days ± 0.7 days, $P < 0.05$) but not different postoperative dysphagia scores (1.5 ± 1.7 vs. 2.1 ± 1.4), reflux scores (1.4 ± 1.7 vs. 2.3 ± 1.3), or good or excellent outcomes (86% vs 84%). Esophagotomy during laparoscopic Heller myotomy is infrequent and cannot be predicted by preoperative therapy or duration or severity of dysphagia. Furthermore, complications after esophagotomy are infrequent and outcomes are indistinguishable from those of patients undergoing uneventful myotomy. (J GASTROINTEST SURG 2005;9:159–164)

KEY WORDS: Achalasia, Heller myotomy, esophagotomy, fundoplication

INTRODUCTION

Achalasia presents as dysphagia with regurgitation, heartburn, chest pain, and weight loss.[1] It is a rare primary motor disorder characterized by increased resting pressure with incomplete relaxation of the lower esophageal sphincter (LES) as well as uncoordinated contractions of the esophagus and, classically, aperistalsis. This is thought to be caused by a lack of nonadrenergic, noncholinergic inhibitory ganglion cells resulting in an imbalance of excitatory and inhibitory neurotransmission.[2,3]

Treatment focuses on weakening, dividing, or disrupting the constricting circular muscle fibers of the distal esophagus to incapacitate the LES. Modalities include medical therapy, endoscopic interventions including pneumatic dilation or botulinum injections, and surgery. Medical treatment, most often employing calcium channel blockers or nitrates, offers only limited temporary relief.[4–6] Endoscopic botulinum toxin (Botox) injected into the LES has been found to provide improved LES relaxation with

Presented at the Forty-Fifth Annual Meeting of The Society for Surgery of the Alimentary Tract, New Orleans, Louisiana, May 15–19, 2004 (poster presentation).
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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.10.015

relatively good efficacy; however, the results are uniformly short-lived, with only about 30% remaining palliated at 1 year.[7–10] Forceful pneumatic dilation of the LES results in good outcomes in 60% to 72% of patients but with a high recurrence rate, a definable perforation rate of 2% to 13%, and a risk of significant gastroesophageal reflux due to an incompetent LES in 30%.[1,10–12]

Surgery provides well-documented relief of dysphagia in over 90% of patients.[12–16] With the advent of the laparoscopic approach, the risk of complications is low and patients are treated with relatively little postoperative pain, short hospital stays, and rapid return to normal daily activities. With increasing frequency, surgery is being offered as first-line therapy for achalasia,[17] although most patients have been treated with endoscopic therapies at the time of referral. We, like others, have suggested a trend toward increased esophagotomy rates in patients with multiple preoperative endoscopic interventions.[17]

The long-term effect of esophagotomy during Heller myotomy remains unknown. The purpose of this study was to determine if esophagotomy during laparoscopic Heller myotomy can be predicted by the duration or severity of dysphagia or preoperative therapy with Botox or pneumatic dilation, and if esophagotomy and/or its repair affects long-term outcome following myotomy. Our hypotheses were that the duration or severity of dysphagia would not increase the incidence of esophagotomy and that preoperative therapy would increase the incidence of esophagotomy, but that the long-term outcome after myotomy would not be negatively impacted by myotomy.

MATERIALS AND METHODS

Preoperative Assessment

All patients underwent barium esophagram and esophageal manometry prior to laparoscopic Heller myotomy. The diagnosis of achalasia was confirmed in all patients. For all patients, barium esophagram demonstrated a dilated, aperistaltic proximal esophagus with a "bird's beak" narrowing distally, and esophageal manometry confirmed incomplete relaxation of the lower esophageal sphincter mechanism with an absence of esophageal peristalsis.

Operation

Our technique for laparoscopic Heller myotomy with concomitant endoscopy has been previously described.[16] Briefly, laparoscopic Heller myotomy was undertaken utilizing three 10 mm ports and two 5 mm ports. The first port, a Hasson cannula, was placed through the umbilicus and pneumoperitoneum was established. A second port was placed along the right anterior axillary line cephalad to the umbilicus. A fan retractor was utilized through this port to lift the liver off the anterior surface of the esophagus and stomach. The third port was placed in the subxiphoid position just below the liver edge. This port functioned as the videoscopic port for the remainder of the operation. The fourth and fifth ports, both 5 mm ports, were placed in the right and left mid-clavicular lines along the subcostal margins.

The epigastric fat pad was mobilized and the peritoneum and phrenoesophageal membrane directly over the esophagus were dissected sufficiently to identify and split the longitudinal muscle fibers of the lower esophagus. The anterior vagus nerve was identified and preserved. The circular muscle fibers were identified and myotomy undertaken using the 90°-angle hook cautery, extending 6 to 8 cm into the mediastinum and 0.5 to 1.0 cm onto the stomach. The trocar along the right mid-clavicular line was upsized to a 10 mm port and concomitant fundoplication was undertaken if there was a large hiatal hernia, if there was a patulous esophageal hiatus, or as part of the repair of an esophagotomy.

Concomitant per oral endoscopy was undertaken at the time of operation.[18] Gentle endoscopic esophageal insufflation was utilized to document adequacy of myotomy. After myotomy, the esophagus was tested for esophagotomy. This was done by instilling saline around the esophageal hiatus and intraesophageal insufflation. Esophagotomy was noted by the presence of air bubbles. Esophagotomies noted intraoperatively were closed with fine monofilament sutures. Anterior fundoplication (Dor fundoplication) was undertaken to buttress the esophageal repair.

Postoperative Management

On the day of operation, all patients undergoing uneventful myotomy underwent postoperative gastrografin esophagram followed by barium esophagram to detect occult esophageal perforations and to assess esophageal emptying. If no leak was present and esophageal emptying was swift, patients were started on clear liquid diets and discharged the following day on a full liquid diet with instructions to slowly advance their diet over the next 2 weeks. If slow emptying was seen during the esophagram, then patients were maintained on clear liquids in the hospital until the edema of the lower esophagus resolved, as determined by progressive improvement in their swallowing and/or repeat esophagram. Patients were discharged with instructions to advance their diets over the ensuing weeks, as tolerated. Patients were

followed in the outpatient clinic and by telephone. They were queried by an independent observer as to the extent of their dysphagia, if any, as well as other symptoms related to their swallowing. A Likert rating system for grading postoperative dysphagia and heartburn symptoms was utilized both preoperatively and postoperatively (Table 1).[17] Patients were also asked to rate their swallowing following myotomy as excellent (no dysphagia), good (much improved dysphagia), fair (mildly improved dysphagia), or poor (no improvement).[17]

Patients experiencing myotomy were managed similarly. However, they generally did not undergo esophagram the day of myotomy and hospitalization was prolonged, possibly unnecessarily, to avoid premature feeding and discharge.

Since 1992, 222 laparoscopic Heller myotomies have been undertaken. Inadvertent intraoperative esophagotomies have occurred in 16 patients, throughout the breadth of our experience. These 16 patients were compared to 60 concurrent patients, chosen otherwise arbitrarily from our database, who underwent laparoscopic myotomy without esophagotomy. Patients with or without esophagotomy were compared to determine differences in preoperative therapies, postoperative complications, pre- and postoperative symptoms, and long-term outcomes. Patients' data were maintained on an Excel 2002 spreadsheet (Microsoft, Redmond, WA) and were analyzed by χ^2 analysis, Fisher's exact test, Student's *t* test, or Mann-Whitney U test, when appropriate, using True Epistat (Epistat Services, Richardson, TX).

RESULTS

Patients experiencing or not experiencing esophagotomy were not different in age or presenting symptoms (Table 2). All patients presented with dysphagia. The duration and severity of dysphagia at presentation was likewise not different for patients undergoing uneventful myotomy or those experiencing esophagotomy at myotomy (Table 2). Notably, heartburn and regurgitation were significant complaints in approximately 80% before myotomy.

Endoscopic intervention has been performed in 83% of patients prior to referral for operative myotomy. Among the patients who experienced esophagotomy, 44% had received pneumatic dilation and 56% Botox. Among the patients who underwent myotomy without esophagotomy, 65% had received dilation and 77% Botox. Remarkably, 87% of the patients who underwent uneventful myotomy versus 62% of those who experienced esophagotomy had some type of either intervention preoperatively (Table 3).

Esophagotomy occurred in 16 patients throughout the breadth of our clinical experience. Injury ranged from merely a tiny air leak on endoscopic insufflation of the esophagus/stomach to one patient with three 1 cm esophagotomies and a 1 cm gastrotomy necessitating open repair, representing the only conversion to celiotomy in this experience. Nearly all injuries were small (≤5 mm) holes or tears. All were primarily repaired to the surgeon's satisfaction with fine polypropylene suture and buttressed with an anterior fundoplication.

Table 1. Dysphagia and heartburn Likert rating system

0	Never
1	Rarely
2	Monthly
3	Weekly
4	Daily
5	Every time I eat

Table 2. Demographic data and symptom presentation at the time of Heller myotomy

	Esophagotomy (n = 16)	No esophagotomy (n = 60)
Males/females	5/11	33/27
Age ± SD (y)	50 ± 17 (range 19–78)	50 ± 18 (range 12–80)
Symptoms		
Dysphagia	100%	100%
Heartburn	75%	82%
Regurgitation	81%	80%
Chest pain	38%	55%
Mean duration of symptoms (y)	7.3 ± 5.4	7.4 ± 6.0

Table 3. Preoperative endoscopic therapy prior to Heller myotomy

	Esophagotomy (n = 16)	No esophagotomy (n = 60)
Preoperative therapy		
Balloon dilation	44%	65%
Botox injection	56%	77%
Dilation and Botox	38%	55%
Dilation or Botox	62%	87%*
No dilation or Botox	38%	13%*

*More than patients experiencing esophagotomy, $P = 0.06$, Fisher's exact test.

Of 16 patients experiencing esophagotomy, three patients had undergone reoperative laparoscopic Heller myotomy for recurrent achalasia following previous myotomy. One patient had been treated by thoracotomy, esophagomyotomy, and Belsey Mark IV fundoplication while the other two had early failure of laparoscopic Heller myotomy. None of the patients without esophagotomy had undergone previous myotomy.

Seventeen concomitant procedures were undertaken in 16 patients in whom esophagotomy occurred. Sixteen of these procedures, by protocol, were fundoplications undertaken as part of the esophagorrhaphy (Table 4). All patients in whom esophagotomy occurred were treated, by protocol, with immediate primary repair and concomitant anterior fundoplication. One patient also underwent a concomitant esophageal diverticulectomy. This compares notably to 15 concomitant procedures undertaken in 13 of 60 patients undergoing uneventful laparoscopic Heller myotomy. Thirteen of the 15 concomitant procedures were fundoplications undertaken to correct a patulous hiatus and/or a notable hiatal hernia. Two patients also underwent esophageal diverticulectomy with fundoplication.

One patient required conversion to an open procedure in order to adequately repair three esophagotomies and one gastrotomy. This patient had not received any preoperative endoscopic therapy. For all other patients, all of whom had one or two esophagotomies, repair was undertaken laparoscopically. There were no conversions to open procedures for the laparoscopic Heller myotomies undertaken without esophagotomy (Table 4).

Mild complications occurred in four patients. Mild pneumonia developed in one patient following laparoscopic Heller myotomy. During otherwise uneventful myotomies, two patients developed CO_2 pneumothorax without lung injury treated with small tube thoracostomy, and one patient had brief intraoperative asystole without sequelae secondary to vasovagal response to pneumoperitoneum (Table 4). Patients incurring esophagotomy had significantly longer hospital stays (Table 4).

Table 4. Operative and postoperative data after Heller myotomy

	Esophagotomy (n = 16)	No esophagotomy (n = 60)
Concomitant procedure		
Fundoplication	100%	22%
Diverticulectomy	6%	3%
Conversion to open	1	0
Minor complications	1	3
Length of stay (d)	5.2 ± 2.5*	1.5 ± 0.7

*Longer than patients undergoing uneventful mytomy, $P < 0.001$, Mann-Whitney U test.

After Heller myotomy, patients were queried globally as to their subjective outcome based on symptoms. The length of follow-up was longer in patients undergoing uneventful laparoscopic Heller myotomy (Table 5).

Compared to preoperative scores, postoperative dysphagia scores were improved following laparoscopic Heller myotomy with or without esophagotomy. Heartburn scores statistically improved for those who underwent uneventful myotomy, but not for those who experienced esophagotomy (Table 5), although preoperative heartburn scores tended to be lower in patients who ultimately experienced esophagotomy.

Compared to patients experiencing esophagotomy, postoperative dysphagia and heartburn scores were nearly one point higher for the subset of patients who underwent fundoplication despite otherwise uneventful myotomy. There were no statistical differences, however, between the postoperative dysphagia scores and the heartburn scores of patients undergoing uneventful myotomy with fundoplication compared to those undergoing myotomy without fundoplication or myotomy with esophagotomy. The likelihood of an excellent or good outcome was not different for those experiencing esophagotomy and those who did not (Table 5). Magnitude of injury did not impact outcome.

Two patients in the esophagotomy group described their symptoms after surgery as poor. One of those patients had previously undergone laparoscopic myotomy and multiple endoscopic interventions (10 pneumatic dilations). The other had also undergone both Botox and dilation (two and five interventions, respectively). Of the four patients without esophagotomy who described their symptoms as poor, all had received preoperative endoscopic therapy as well.

One of the patients who incurred esophagotomy underwent postoperative pneumatic dilation to treat dysphagia without narrowing at the gastroesophageal junction. Of the patients who underwent uneventful myotomy, three underwent postoperative Botox injection and seven underwent postoperative dilation to treat symptoms of dysphagia without evidence of narrowing at the gastroesophageal junction. One patient underwent esophagectomy for severe dysphagia due to profound dysphagia thought to be the result of aperistalsis with an adequate myotomy.

DISCUSSION

Laparoscopic Heller myotomy is increasingly being utilized in the treatment of achalasia. Furthermore, we have shown that as surgeons progress along

Table 5. Subjective patient outcomes following Heller myotomy

	Esophagotomy (n = 16)	No esophagotomy (n = 60)	No esophagotomy with fundoplication (n = 13)
Follow-up (mo)	31.6 ± 21.9	51.0 ± 21.2	46.6 ± 15.8
Swallowing after myotomy			
Excellent	57%	47%	46%
Good	29%	37%	23%
Fair	0	8%	23%
Poor	14%	8%	8%
Dysphagia score			
Preoperative	4.9 ± 0.4	4.8 ± 0.4	4.7 ± 0.5
Postoperative	1.5 ± 1.7*	2.1 ± 1.4*	2.3 ± 1.7*
Heartburn score			
Preoperative	2.3 ± 1.7	3.1 ± 1.8	3.8 ± 1.6
Postoperative	1.4 ± 1.7	2.3 ± 1.3*	2.5 ± 1.5*

*Less than preoperative, $P < 0.05$, Mann-Whitney U test.

a learning curve, their patients have fewer complications and better outcomes after Heller myotomies.[21] After amassing a very large experience, we continue to see inadvertent esophagotomies, although possibly less frequently. Subjectively, we have to date felt that esophagotomies occur as a result of multiple preoperative therapies and hence a more difficult operation.[17] This study does not confirm a correlation between preoperative therapies and the likelihood of esophagotomies. Furthermore, we show that after myotomy, excellent and good outcomes are expected, even with inadvertent esophagotomy.

The patients in this series were mostly middle-aged men or women, presenting with severe dysphagia, heartburn, and postprandial regurgitation of undigested meals for over 7 years. The majority had previously received endoscopic interventions, with many undergoing both dilations and Botox injections. These interventions did not affect the incidence of esophagotomy. Rather, the patients who underwent uncomplicated myotomy were at least as likely, possibly more likely, to have received an endoscopic intervention than those who experienced esophagotomy with a trend toward statistical significance. It seems unlikely that those who previously received intervention had more difficult myotomies and esophagotomies were avoided only by more meticulous operations.

Anterior fundoplication was utilized in all patients in whom an esophagotomy occurred in order to buttress the repair. In patients undergoing uneventful myotomy, fundoplication was selectively applied in patients with hiatal hernia or patulous esophageal hiatus.[19,20] Anterior fundoplication is our fundoplication of choice. As such, fundoplication was utilized in less than one-quarter of patients.

Complications were uncommon and minor, but esophagotomy resulted in prolongation of hospitalization. The difference in hospital stay is likely the result of a combination of postoperative edema and slower return of functional swallowing as well as significant hesitance and concern on the part of the surgeon to discharge prematurely, particularly early in our experience.

With long-term follow-up, the outcomes of patients with or without esophagotomy were indistinguishable, nor did previous myotomy affect outcome. Among all patients, greater than four of five described their outcome as excellent or good. Likewise, dramatic reductions in dysphagia scores were noted, without significant heartburn. The lack of a statistically significant reduction in heartburn scores in patients who experienced esophagotomy, when compared to those who did not experience esophagotomy, seems to be related to lower scores preoperatively. Postoperative dysphagia and heartburn scores were similar between those who experienced esophagotomy and those who did not.

Patients undergoing uneventful myotomy with fundoplication had higher preoperative heartburn scores, which was consistent with findings at surgery, namely a patulous hiatus and/or a large hiatal hernia. Outcomes were similar to those without fundoplication and those incurring esophagotomy. Postoperative dysphagia and heartburn scores were similar as well. There were significant improvements in these scores postoperatively when compared to prior to surgery.

As noted, of the patients who described their symptoms after myotomy as poor, all had received either previous myotomy or endoscopic intervention. It cannot be inferred that these unsatisfactory outcomes

are related to preoperative therapy but it seems intuitive that results after reoperative myotomy will be suspect. As stated, we demonstrated no increased risk of esophagotomy after preoperative endoscopic therapy. Interestingly, the patient who incurred five esophagotomies had no preoperative endoscopic treatment.

It may be that those patients who had poor outcomes following myotomy after several preoperative interventions were those with more severe achalasia, however that might be quantitated. "Poor outcomes," whether due to complaints of heartburn or dysphagia, may be caused by a neuropathic defect inherent to achalasia, which may manifest as visceral sensory disturbances, including persistent dysphagia or heartburn. In our experience, when evaluated with 24-hour pH study, heartburn symptoms are almost never caused by pathologic reflux, despite poor acid clearance from the aperistaltic esophagus.[22,23]

The incidence of esophagotomy is low in this series of laparoscopic Heller myotomies. Esophagotomy has the risks of postoperative leak and infectious complications including sepsis, which was fortunately not seen. Because of the high proportion of patients referred with previous endoscopic interventions, it is impossible to examine a large enough number of patients who had not undergone any preoperative therapies for comparison. However, based on our data, it does not appear that patients who undergo preoperative interventions are at increased risk for esophagotomy. Additionally, those in whom esophagotomy occurs have outcomes that are essentially equivalent to those who undergo uncomplicated or uneventful myotomies. As such, fear of esophagotomy should not deter physicians from sending patients for early surgical intervention for severe achalasia, nor should it deter surgeons from attempting laparoscopic Heller myotomy in patients who have had multiple endoscopic therapies.

CONCLUSION

Laparoscopic Heller myotomy is a safe and effective treatment for patients with achalasia. Esophagotomy is infrequent with myotomy, even in patients previously treated with endoscopic therapies, such as dilation or Botox. In addition, those who undergo esophagotomy have long-term outcomes indistinguishable from those who undergo myotomy without esophagotomy.

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A Multidisciplinary Approach to the Treatment of Intestinal Failure

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Intestinal failure is most commonly treated by the administration of total parenteral nutrition (TPN). In some patients, however, surgical therapy may increase the ability to use the intestine for nutrition and thereby decrease the complications of TPN therapy. A multidisciplinary comprehensive intestinal failure program was initiated at the University of Nebraska Medical Center in October 2000. Here we describe the surgical approaches to patients with short bowel syndrome and the subsequent impact on the need for TPN and on survival. Fifty patients (children = 30, adults = 20) underwent surgical procedures to restore intestinal continuity (n = 5), repair enterocutaneous fistulas (n = 5), resect dysmotile or strictured/obstructed bowel segments or mesenteric desmoid tumors (n = 7), stricturoplasty (n = 2), Bianchi tapering and lengthening (n = 20), serial transverse enteroplasty (n = 8), and other operations (n = 8). Of these 50 patients, three patients did not require TPN after surgical intervention and seven had remnant small bowel anatomy that precluded TPN weaning (e.g., end duodenostomy) and were listed for transplantation or continued on full TPN support. Of the 40 remaining patients, most received the majority of calories from TPN at the time of referral, i.e., mean calories from TPN = 90%. Subsequent to the surgical and medical therapy, 26 (65%) have been completely weaned off TPN. In addition, 10 had substantial decreases in their TPN requirements (i.e., from 85% of calories from TPN at onset decreased to a median 35% of required calories at most recent follow-up). Four patients remained on the same amount of TPN support. Four of the seven patients listed for transplantation underwent successful transplantation. Despite the complications of short bowel syndrome, 86% (n = 43) of the patients are alive and well at a mean follow-up of 2 years. Patient deaths occurred primarily in those listed or eligible for transplantation and were related to advanced liver disease (n = 3), gastrointestinal hemorrhage (n = 1), or line sepsis (n = 1). Two other patients died, one from influenza A infection and one from unknown cause at home, months after complete discontinuation of TPN. In this series of patients with short bowel syndrome, surgical intervention led to weaning or discontinuation of TPN support in 85% of patients. An organized multidisciplinary approach to the patient with short bowel syndrome is recommended. (J GASTROINTEST SURG 2005;9:165–177)

KEY WORDS: Intestinal failure, short bowel syndrome, Bianchi, serial transverse enteroplasty (STEP), reversed segment, intestinal rehabilitation

INTRODUCTION

Intestinal failure defines a group of patients who have dysfunction of the small intestine that prevents absorption of adequate calories to support life, maintain body weight, or allow appropriate growth in children. Intestinal failure encompasses those patients with shortened bowel length (more commonly) and those with dysmotility syndromes.

In the 1960s and 1970s, novel surgical procedures designed to slow motility or improve nutritional absorption were developed in attempts to improve the survival of patients with short bowel syndrome.[1–5]

Presented at the Forty-Fifth Annual Meeting of The Society for Surgery of the Alimentary Tract, New Orleans, Louisiana, May 15–19, 2004 (oral presentation).

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.10.014

Although case reports exist of dramatic bowel adaptation and long-term survival with extremely short remnant small bowel length (i.e., 6 cm of jejunum), most patients with short bowel syndrome (SBS) in the absence of nutritional support died with severe malnutrition, weight loss, and dehydration.[6,7] Successful introduction of total parenteral nutrition (TPN) in the early 1970s dramatically altered the dismal survival in patients with extensive intestinal resections by providing nutritional support during the process of gradual adaptation.[8] For patients on TPN, the 1-year survival is generally good, ranging from 90% in children and young adults to 65% in older adults.[9] The difference between the expected survival in the normal population and patient survival on TPN is mostly from progression of the underlying disease. Some patients on TPN, however, develop life-threatening complications, including catheter-related bloodstream infections, venous thrombosis, and PN-associated liver disease. Many of these complications can be avoided or reversed if TPN can be discontinued.

In the early 1990s, intestinal transplantation was introduced and is now the standard of care for patients with intestinal failure who are failing TPN.[10–12] Patient survival after intestinal transplantation in the most recent era still does not match but approaches survival of patients dependent on TPN (i.e., 70% at 3 years vs. 60%–80 %, respectively).[13,14] Although intestinal transplantation is an excellent option for those patients with severe life-threatening complications of PN administration and no opportunity to discontinue TPN, transplantation requires long-term immunosuppression with its attendant risks and depends on the altruistic gift of organs, which cannot be predicted. The waiting list mortality, especially when the liver is irreversibly diseased, has been reported from 30% to 50%.[15] While continued efforts are being made to minimize this excessive waiting list mortality and the risks of immunosuppression, it seems prudent to maximize the function of the native small bowel whenever possible to avoid the need for TPN and thereby avoid or reverse the complications associated with it. Reexamination of autologous bowel reconstructive surgery and its role as an alternative to intestinal transplantation is therefore warranted.

In October 2000, individuals with a special interest and extensive experience in the treatment of intestinal failure at the University of Nebraska Medical Center developed a unique multidisciplinary Intestinal Rehabilitation Program (IRP). The IRP includes pediatric gastroenterologists, surgeons, adult gastroenterologists, dieticians, psychologists, and nurse coordinators. This multidisciplinary program was developed to evaluate, educate, and treat patients with intestinal failure with the goal of maximizing enteral tolerance and minimizing complications associated with TPN and the need for intestinal transplantation. The inpatient or outpatient evaluation is performed over a 3- to 5-day period during which the current caloric intake and distribution, baseline stool and urine output, prior medical and/or surgical therapies, remnant bowel length, caliber, and anatomy, and complications of SBS and/or TPN administration are defined. There was a period of initial collaboration with the Nutrition Restart Center and incorporation of many of the dietary recommendations and expertise into the medical management by our team.[16]

METHODS

Ninety patients were referred and evaluated by the IRP since October 2000. Thirty-one patients were initially referred for transplant evaluation (29% of intestinal transplant evaluations) and subsequently transferred to the IRP. Forty patients were managed with dietary manipulations, medications, and other medical care including 18 patients who underwent intensive inpatient TPN weaning.[17] This medically treated group will not be further discussed in this manuscript. Here we summarize the results of the autologous reconstructive surgeries performed. Summary data are reported as median (range).

Patient Demographics

Of the 90 patients evaluated by the IRP program, 50 were determined to have indications for surgical intervention to improve their intestinal function. This was a heterogenous group of patients that included 30 children and 20 adults, with median ages of 1.3 years (range 0.3–16 years) and 42 years (range 23–66 years), respectively. Table 1 delineates the

Table 1. Causes of intestinal failure in patients undergoing surgical therapy

	Pediatric (n = 30)	Adult (n = 20)
Gastroschisis	9	
Necrotizing enterocolitis/ thrombosis/ischemia	7	4
Volvulus	5	2
Pseudo-obstruction/ Hirschsprung's disease	2	1
Intestinal atresia	3	
Enterocutaneous fistula	2	1
Crohn's disease		3
Radiation enteritis		3
Desmoid tumor		3
Other	2	3

underlying diagnoses of the patients who underwent surgical intervention. Most of the patients undergoing surgical intervention had short bowel syndrome, although a few had normal bowel length with either dysmotility syndromes, mesenteric tumors, or proximal fistulas preventing adequate function. The average length of small bowel remnant in the children and adults (50 patients) was 31.5 cm (range 10–122 cm) and 76.5 cm (range 25–170 cm), respectively. The mean follow-up for the group overall to date is 2.0 years (range 0.4–3.7 years).

TPN Dependence

Forty-seven of the 50 (94%) patients were dependent on TPN at the time of surgical intervention. One child not on TPN had severe bacterial overgrowth due to a loop of dilated small intestine and had failed chronic antibiotic and steroid therapy, resulting in poor growth on large-volume tube feedings. Two adult patients had diarrhea and weight loss and recurrent intestinal obstructions from previous irradiation, although TPN had not been initiated prior to surgery. At the completion of surgical intervention, seven patients had anatomy or complications that prevented any TPN weaning and were referred for transplantation or maintained on TPN. These patients will be further discussed later in this paper. Of the remaining 40 patients, the majority of calories (>85%) were being supplied by TPN at the time of surgical intervention.

All patients in this program received dietary instructions, medical therapy, and psychologic counseling as needed. Dietary therapy was tailored to the anatomy and included some or all of the following: increased oral caloric intake, enteral tube feedings, and instruction on the short bowel syndrome diet.[16–19] Medications to slow gut motility, decrease acid hypersecretion, or increase absorption were added as needed (omeprazole, loperamide, tincture of opium, codeine, glutamine, or growth hormone).[17,20–23] Although a trial of glucagon-like peptide 2 is now underway and may prove more effective than glutamine and growth hormone in enhancing bowel adaptation, it was not available for use in this series of patients.[24,25]

Surgical interventions were considered in patients in whom all calories were being provided by TPN despite the presence of retained small bowel segments, those patients who developed jaundice (prior to severe liver decompensation), or when complications suggested the patients were at risk for death and alternatives to intestinal transplantation were likely to be successful. The most common indications were jaundice due to PN-associated cholestasis (40%), bacterial overgrowth, obstruction, enterocutaneous fistula, dilation and dysmotility of bowel segments, and poor enteral tolerance due to defunctionalized or bypassed small bowel. A number of patients had more than one indication for intervention.

Surgical Procedures

Twenty patients underwent the intestinal tapering and lengthening procedure as first described by Bianchi and modified by others (Fig. 1).[26,27] Eight patients (including three who had prior or simultaneous Bianchi procedures) underwent serial transverse enteroplasty (STEP) as previously described by Kim (Fig. 2).[28,29] Ten patients underwent repair of enterocutaneous fistulas and closure of ostomies in order to restore intestinal continuity. An additional 19 patients (including seven who had undergone another surgical intervention) underwent stricturoplasty, resection of obstructed or dysmotile bowel segments, tapering enteroplasty, formation of an ileostomy or colostomy, or creation of a reversed intestinal segment.

RESULTS

Survival

Actual patient survival after autologous surgical reconstruction is 86% with median follow-up of 2 years (range 0.3–3.7 years). Causes of death include line sepsis (n = 1), influenza infection (n = 1), liver failure/sepsis (n = 3), gastrointestinal hemorrhage secondary to gastric ulceration (n = 1), and unknown cause (n = 1) (Table 2).

TPN Dependence

Forty of the 47 patients dependent on TPN had anatomy that was amenable to PN weaning after surgical intervention. Twenty-six of these 40 patients (65%) initially on PN have been weaned completely off after surgery and have maintained appropriate growth velocity (children) and acceptable body weight (adults). In addition, 10 patients have had substantial decreases in their TPN dependence (i.e., 85% of calories from TPN at evaluation compared to 67% of calories enterally [range 60%–80%] at most recent follow-up). In 4 (10%) patients, minimal or no improvement was achieved in enteral function after surgery. The seven patients with anatomy not amenable to weaning of PN continued on TPN or were referred for intestinal transplantation. Three patients not on TPN prior to autologous bowel reconstruction remain off TPN with adequate control of the complications that prompted the surgical intervention.

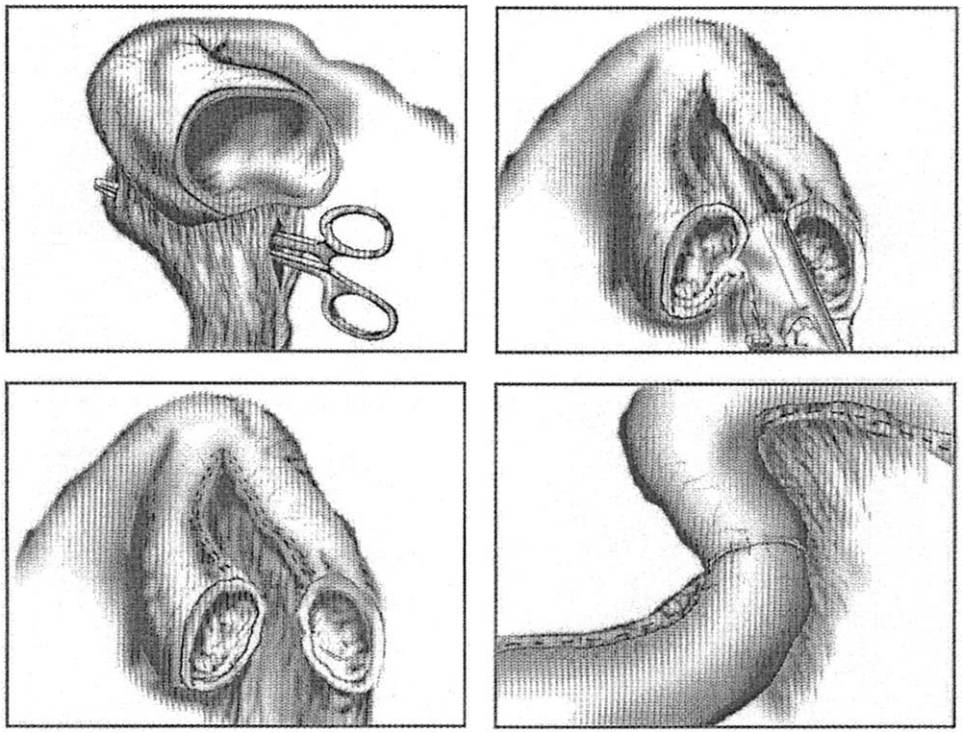

Fig. 1. The Bianchi procedure. (From Thompson JS. Surgical rehabilitation of intestine in short bowel syndrome. Surgery 2004;135:465–470. Reprinted with permission.)

Tapering and Lengthening Procedures

Bianchi. The median remnant bowel length in the 20 patients (including three adults) undergoing Bianchi lengthening was increased from 33 cm (range 16–90 cm) to 61 cm (range 29–130 cm). Indications for surgery in these 20 patients included jaundice with early or no portal hypertension (n = 10), poor enteral absorption despite all nonsurgical interventions (n = 6), and severe or recurrent bacterial overgrowth in dilated small bowel segments (n = 4). Ten of these 20 patients were severely cholestatic (median total bilirubin = 9.2 mg/dl [range 4.2–24 mg/dl]) at the time of surgery. Cholestasis completely resolved in 9 of the 10 and improved in 1 patient at the time of death from influenza A infection 5 months after surgery.

Nineteen of the 20 patients undergoing Bianchi procedures were on TPN, which supplied on average 76% of their caloric needs prior to surgery. Twelve of the 19 patients were completely weaned from their TPN (including 2 undergoing subsequent transplantation for surgical complications or loss of venous access) and 6 others (30%) were able to increase their enteral caloric intake to 68% (range 60%–80%) of their nutritional requirements with appropriate decreases in PN support. A 9-year-old boy not on TPN had severe recurrent bacterial overgrowth in a dilated small bowel segment resistant to medical therapy resulting in poor growth velocity. Postoperatively he demonstrated catch-up growth for height and weight despite a 40% decrease in his nighttime tube feedings.

Serial Transverse Enteroplasty. The serial transverse enteroplasty (STEP) procedure was performed in eight patients including three patients with prior or simultaneous Bianchi procedures included above. Indications for the STEP procedure were a short mesentery (n = 2), a second dilated loop removed from the site of simultaneous Bianchi lengthening or fistula repair in previous Bianchi loops (n = 3), and an alternative to simple tapering or Bianchi lengthening in dilated small bowel segments (n = 4). The remnant bowel length (median) in the five patients undergoing only the STEP was 62 cm (range 23–122 cm) initially, and the increases in length ranged from 12 to 15 cm. The increase in bowel length was limited in three patients because of the presence of fistulas between Bianchi loops (two patients) and shorter than anticipated bowel length (one patient scheduled for reversed jejunal segment). Cholestasis (total bilirubin = 5.4 mg/dl and 6.2 mg/dl) was present at the time of surgery in 2 (25%) patients, which resolved in 1 and contributed to sepsis and death 3 months after surgery in the other. As with the Bianchi procedure, more than 50% of the patients undergoing STEP procedures were weaned off their

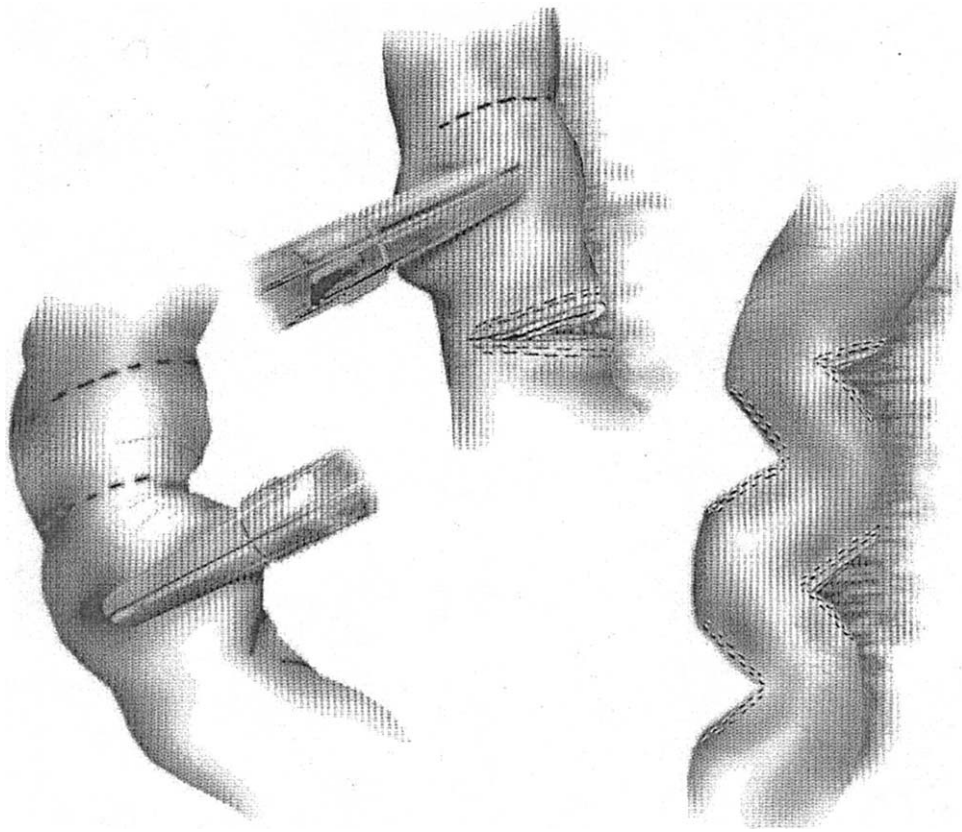

Fig. 2. Serial transverse enteroplasty (STEP). (From Thompson JS. Surgical rehabilitation of intestine in short bowel syndrome. Surgery 2004;135:465–470. Reprinted with permission.)

TPN completely and one had a significantly decreased need for TPN.

Recruit Bypassed or Unused Intestine. Ten patients underwent procedures to recruit bypassed intestine by closing fistulas (n = 5) and ostomies (n = 5). The median age of the seven children was 1.7 years (range 0.3–16 years), and the three adults were aged 43, 50, and 66 years. Eight of the 10 required 100% of their caloric needs from TPN prior to surgical intervention (the others required >85% of calories from PN) and 6 of the 10 were completely off TPN afterwards. Two patients are followed currently at a different center, but increased their enteral tolerance from 0% of required calories to 40% at the last follow-up (3 months after fistula repair). Two patients had no improvement in enteral tolerance. One jaundiced 4-month-old with 12 cm of remnant small bowel cleared her cholestasis after closure of her fistula, but she continues to have life-threatening fungal and resistant bacterial infections without substantial improvement in her enteral absorption and has been placed on the transplant waiting list (16 months old). An additional adult patient with prior abdominal radiation for endometrial sarcoma developed a recurrent fistula and has elected not to have further surgical intervention and is maintained on 100% TPN support.

Resection. Intestinal resection was performed for obstructions, dysmotility, and enteroenteric fistula in seven patients. Six of these patients were adults with a median age of 33 years (range 23–47 years). Although the selection of patients in this group is clearly not representative of all patients undergoing resection, only two showed improvement. One patient in this group was weaned completely from TPN after salvage transplantation and one patient had improved enteral tolerance (60% of caloric requirements at last follow-up). Four of the patients were referred for transplantation after resection; three due to complete enterectomies for desmoid tumors (n = 2) or lymphangioma (n = 1) and one after development of enterocutaneous fistulas and PN-associated liver disease. The latter patient, who developed fistulas, had prior radiation for treatment of a childhood Wilms' tumor, which likely contributed to the poor healing of the anastomosis. One patient declined transplant and died from liver failure/sepsis, one underwent combined liver small bowel transplantation (and is currently off TPN), and the other two died from

Table 2. Summary of surgical procedures and outcomes

Procedure	No. of patients (children/adults)	Transplant	Remnant SB length (cm)	Preoperative nutrition (TPN/part PN/enteral)	Postoperative nutrition (TPN/part PN/enteral)	Survival	Cause of death
Bianchi	20 (17/3)	L/SB (1) ISB (1)	33 cm before/61 cm after	17/2/1	1/7/12	18 (90%)	Line sepsis, influenza pneumonia
STEP	5 (2/3)	1 refused	62 cm before/79 cm after	4/1/0	1/1/3	4 (80%)	Liver failure
Restore continuity Fistula (5) Ostomy (5)	10 (7/3)	1 listed	38 cm (12–170)	8/2/0	2/2/6	9 (90%)	Unknown (possible dehydration or sepsis)
Resection	7 (1/6)	L/SB (1), 2 died on waiting list, 1 refused	60 cm (0–150) after		5/1/1	4 (57%)	Liver failure (2), gastrointestinal bleed
Other	8	L/SB (1)	100 cm (64–150)	5/1/2	1/0/7	8 (100%)	
Colectomy	*(1)*						
Stricturoplasty	*(1)*						
Ostomy	*(2)*						
Bowel revision	*(2)*						
Tapering	*(2)*						
Reversed segment	*(1)*						

SB = small bowel; TPN = full parenteral nutrition support; part = partial parenteral nutrition support; enteral = full enteral nutrition; L/SB = combined liver and small bowel transplant; ISB = isolated intestinal transplant.

Remnant small bowel lengths (measured or estimated) are reported as median (range) except for the Bianchi and STEP lengthening procedures, which are reported as the median before lengthening and median after lengthening measured intraoperatively.

liver failure/sepsis and gastrointestinal hemorrhage, respectively, while on the transplant waiting list.

Other Surgical Interventions

Nine adults and three children underwent other procedures, including reversed segment, ileostomy or colostomy to bypass nonfunctional bowel, takedown of a previous reversed proximal jejunal segment, simple tapering enteroplasty, and resection of a blind loop. Four of the adults underwent concomitant Bianchi, STEP, or ostomy closure. Two adults were not on TPN at the time of intervention, but their obstructive symptoms had resolved and preoperative weight loss had stabilized. The other 10 received 85% to 100% of their calories from PN at the time of surgery. Six of the eight, who have not been included elsewhere in this report (and 3 of 4 undergoing combined procedures) have been weaned off their TPN completely, including one jaundiced patient, who developed a postoperative enterocutaneous fistula and underwent liver/small bowel transplantation. Two patients have had no change in their TPN requirements (receiving 85%–100% of calories from PN). Radiation for a previous osteosarcoma and underlying Crohn's disease may have contributed to the persistent bowel dysfunction in these two patients after surgical intervention.

Transplantation

Seven patients were referred for intestinal transplantation from the IRP because of unreconstructable gastrointestinal tract (n = 3), complications after surgery in cholestatic patients (n = 2), no improvement in enteral function and recurrent life-threatening sepsis (n = 1), and loss of venous access more than 1 year after Bianchi (n = 1). Four of the 5 children placed on the transplant waiting list have undergone transplantation successfully with combined liver/small bowel allografts (n = 3) and isolated small bowel graft (n = 1) and 1 remains alive on the waiting list. Two adults placed on the waiting list died of sepsis complicated by liver failure in one and uncontrolled hemorrhage from a gastric ulcer in one. Two other adults with indications for transplantation refused transplant evaluation and both have died of sepsis and liver failure. Three patients with prior isolated liver transplantation are alive and one is completely off TPN.

DISCUSSION

There are several alternative interventions that may alter or improve intestinal function in a patient with short bowel syndrome (Fig. 3). First, the diet can be altered or medications added to manage stool output and flatulence allowing hyperphagia to compensate for the degree of malabsorption. Alternatively, autologous bowel reconstructive surgery can be performed. The third option for treatment of intestinal failure is intestinal transplantation, in which the native gut is replaced with a cadaveric graft. Each of the therapeutic options have specific indications. All patients are managed medically initially. Our medical management strategy has been previously described and will not be further detailed here.[17] In stable patients, slow gradual adaptation is followed for an indefinite period of time. In patients who develop complications or are unable to absorb any significant nutrition enterally (e.g., because of a proximal intestinal fistula), consideration is given to autologous bowel reconstructive surgery or transplantation.

Transplantation is usually considered the best option in the patient who has early but reversible liver disease, but no reasonable hope of being weaned from TPN and in those patients in whom the liver disease appears irreversible because of extensive portal hypertension.[30,31] The length and previous function of the remnant small bowel is considered in determining if combined liver small bowel graft is optimal or if the patient has enough remnant functional bowel that replacement of the liver alone could allow further adaptation and weaning from TPN.[32]

The group of patients that is the focus then of this paper had jaundice without extensive portal hypertension, proximal fistulas, focally or extensively dilated small bowel segments, or recurrent bacterial overgrowth and an adequate remnant length of small bowel to potentially be weaned from TPN. In these patients, we recommend further evaluation of nontransplant surgical therapy.

The published experience with autologous bowel reconstruction is somewhat limited. The earliest reports were published in the era shortly before the availability of TPN and were novel methods to try to decrease the extremely high mortality of patients with SBS. The first procedures introduced clinically were aimed at tapering dilated bowel segments, either by plication or excision of a portion of the bowel lumen along the antimesenteric border, usually using a surgical stapling device. These procedures were performed primarily in individuals who had undergone limited to moderate intestinal resections and to some extent had favorable factors for survival compared to the norm, but had focal or extensive bowel dilation leading to complications of bacterial overgrowth or sepsis.[33–35] The plication procedure has the theoretical advantage of not losing any of the mucosal absorptive surface, but complications previously

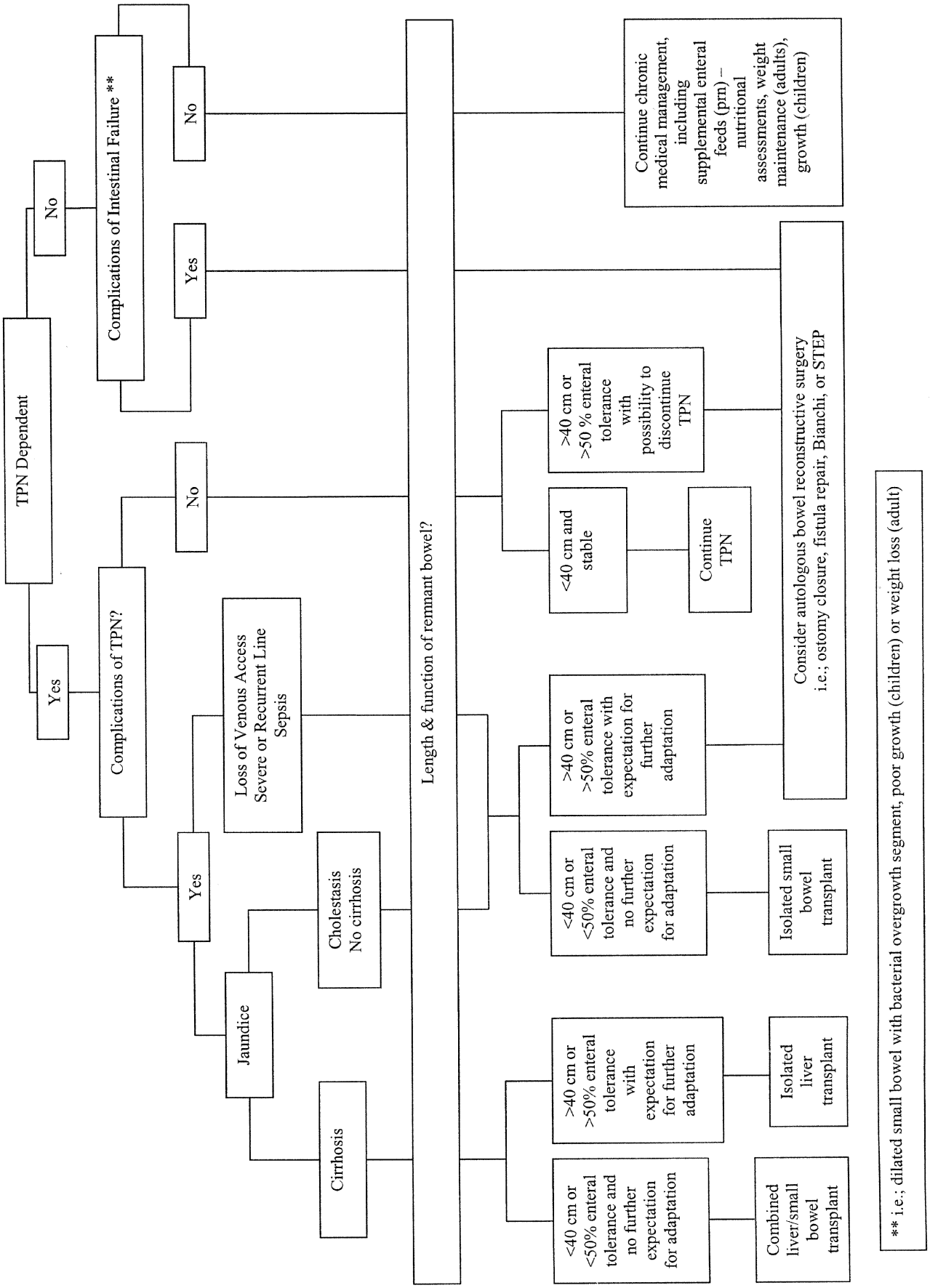

Fig. 3. Approach to the patient with intestinal failure.

reported include breakdown of the suture line with redilation or obstruction due to the extensive infolding of the bowel wall. The tapering enteroplasty on the other hand has a higher risk for leak caused by the actual excision of a portion of the bowel wall. In practice, the results appear to be quite similar. Despite the limited literature, it appears there is still a role for these procedures in selected patients with reasonably preserved lengths of remnant small bowel, especially with a short segment of severe bowel dilation complicated by symptomatic bacterial overgrowth or recurrent sepsis. In this series, we applied tapering enteroplasty in two patients with mixed results. One jaundiced 10-month-old female infant developed intestinal perforations after tapering enteroplasty, and after a very stormy recovery she successfully underwent salvage combined liver/small bowel transplantation. The other patient has been successfully weaned from TPN.

Other surgical approaches to SBS were aimed at controlling the rapid transit of nutrients from the stomach to the colon in order to improve mucosal contact time and nutrient absorption. Reversal of short segments of jejunum or ileum (i.e., antiperistaltic) have been described and are usually placed just proximal to the small bowel-colonic junction ranging in length from 3 to 8 cm.[36–39] Anecdotal reports of slowed transit time and improved absorption exist. Complications described are mostly attributed to nutritional complications of intestinal failure, but also include partial or complete obstruction. The application of this technique appears to be extremely limited. Risk of injury to and loss of even a short segment of intestine in the patient with very short remnant small bowel length might not be tolerable. In the current study, we performed a reversed intestinal segment in 2 patients with inflammatory bowel disease. One of these two patients was weaned from TPN although the other had no improvement.

Alternatively, the insertion of a partial colonic segment has been described to slow small bowel transit time.[40–42] The colonic interposition usually is placed approximately halfway through the remnant small bowel. The length of the interposed colon is variable and the usefulness of this technique in light of the few anecdotal reports remains unclear. We have no experience with this technique at the University of Nebraska.

This is the first series of the STEP procedure reported in the literature. In the previous patient report, the procedure was successfully performed after a prior Bianchi procedure.[29] In our two patients who had previously undergone Bianchi lengthening, we were unable to perform STEP to the degree anticipated because of the unexpected findings of interloop fistulas in both patients. One additional patient underwent STEP simultaneously in a loop of bowel with a shortened mesentery and separate from the loop lengthened by the Bianchi technique. Overall, we agree with the group from Boston that STEP should likely be reserved for a secondary procedure in patients that dilate after Bianchi lengthening. STEP was offered as a primary procedure in our series at times when the bowel mesentery was foreshortened or other anatomical considerations made a Bianchi procedure too risky.

The most frequently performed procedure in this series and the most common surgery reported in the literature for treatment of SBS is isoperistaltic intestinal lengthening as described by Bianchi. Benefits attributed to the lengthening procedure have included improved fat and/or d-xylose absorption, prolongation of transit time, and catch-up growth.[43–50] Absorptive studies have shown improvement after the Bianchi procedure, but they have been conducted in only a limited number of patients and some have suggested that the increased enteral tolerance is merely a result of hyperphagia, less bacterial overgrowth by eliminating the bowel dilation, and the natural bowel adaptation process.[51] Although we attribute the improvements in our patients to the surgery because we first maximized adaptation with dietary manipulations, we acknowledge the limitations of this study related to the absence of objective measures of improved absorption. Whether simple tapering enteroplasty would have had equal efficacy cannot be determined, but the preservation of absorptive mucosal surface area with the Bianchi, especially in the patients with remnant small bowel lengths less than 40 cm, is theoretically attractive. In lieu of absorptive studies, weaning or discontinuation of PN has been suggested as a surrogate marker for improved absorption. Weaning of PN must be done while maintaining weight stability in adults or appropriate growth in children. In previous reports of intestinal lengthening, the ability to wean from TPN varies considerably from 0% to 78% of patients.[47,52,53] These reports for the most part are superior to rates of weaning with medical therapy alone, which range from 12.5% to 18%.[54,55] Improvement in enteral tolerance in 80% of patients undergoing lengthening in this series compares favorably with other reports.

The timing of surgical intervention for SBS is controversial. Some have suggested that early intervention may yield improved results, although others suggest this may instead prevent full adaptation. The alternative proposed is waiting until no further advancement in feeding can be achieved.[52,56] Variations in the proposed "waiting time" have ranged from 4 to 6 weeks of stability to 6 months (in children) or 2 years (in adults) in which no further advancement

is made in enteral tolerance. No clear evidence for superiority of either approach exists; however, unnecessary intervention may lead to complications and we therefore choose to err on the side of caution. We have performed Bianchi and other autologous bowel reconstruction when patients have either not been able to achieve any further increases in enteral feeding on optimal diet and tube feedings with an appropriately dilated small bowel segment on radiographic imaging or have complications of PN administration or bowel dysfunction that suggest more urgency (i.e., liver dysfunction).

Previous reports suggest that lengthening procedures or other autologous bowel reconstruction should be avoided in patients with liver disease. The report from Pittsburgh suggests there is no role for Bianchi procedures in patients with intestinal failure.[57] In that study, Bianchi procedures were performed prior to referral and only patients that failed were later referred for intestinal transplantation.[57] Because of the selection bias, patients who benefited from autologous bowel surgery were excluded from the analysis. On the other hand, Georgeson et al. suggested that intestinal lengthening may be an alternative therapy to transplantation.[48] Weber likewise suggested that the Bianchi procedure should be offered to jaundiced patients without evidence of portal hypertension.[49] Further evidence to support the use of lengthening in the face of early liver disease is found in Bianchi's original series, in which all of the patients were jaundiced and no patient died perioperatively.[53] In 9 (out of 20) patients in the Bianchi report, cholestasis resolved and liver function returned to normal as enteral absorption improved. The reversibility of early PN-associated cholestasis even in the presence of bridging fibrosis or early cirrhosis has also been shown in our report of isolated intestinal transplantation.[30] Caution must be exercised, however, since half of the patients in the Bianchi series developed progressive liver failure leading to death. Today we would recommend that salvage with liver/intestinal transplantation be considered in such patients. Jaundice alone therefore should not be used as the sole criteria in deciding whether or not transplantation or autologous reconstruction should be performed. We recommend transplantation for patients with advanced cirrhosis (severe thrombocytopenia, ascites, and coagulopathy) and for the most part when the length of bowel is extremely short (perhaps <20 cm), although historical feeding tolerance is an important part of the decision making. In this series, we have chosen patients for nontransplant surgery who have jaundice and at times splenomegaly, but for the most part have bridging fibrosis or early cirrhosis without the other stigmata of chronic liver disease. In two patients with early complications, prompt resection of injured small bowel and listing for transplantation was successful. Close interactions between the intestinal rehabilitation and transplantation programs in our institution, extensive experience with management of the jaundiced patient, and the ease with which we could quickly move the patient to transplantation when needed are likely important factors in the good survival in our series.

The 2- and 5-year survival rates for patients with intestinal failure from nonmalignant conditions has been reported at 93% and 77%, respectively.[54] Mortality in previous studies of intestinal failure has been correlated with an end jejunostomy (compared to patients with colon in continuity), chronic obstruction, older age, need for parenteral nutrition (PN is associated with a 5.6-fold increased risk for death), and the development of liver disease.[14,54,55,58] Here we have found that taking down jejunostomies, relieving obstruction, lengthening, tapering, and other autologous reconstruction was successful in achieving enteral independence in more than 50% of patients, and an additional 30% had substantial decrease in their need for TPN. In addition, this group achieved excellent survival (86%) at 2 years, which compares favorably to previous reports of survival rates after lengthening procedures that range from 45% to 78%.[50,53] In this series, there did not appear to be any impact on survival that was related to the length of remnant intestine; however, the power of the analysis was insufficient to identify a small difference given that most patients had very short remnant small bowel length. The most common reasons for failure to wean from TPN in our series were complete resection of intestine, underlying inflammatory bowel disease, or radiation enteritis. Others have identified inflammatory bowel disease and radiation enteritis as particularly difficult problems, and we concur and recommend caution in consideration of surgery in patients with these conditions.

Despite the risk for complications, surgical intervention can lead to excellent results and achievement of enteral autonomy in a large percentage of those selected. The high rate of enteral autonomy achieved in this series compares favorably with other reports. Surgical intervention leading to improved enteral tolerance can reverse PN-associated cholestasis, and we believe that cholestasis alone is not a contraindication for lengthening as others have suggested. A cautious approach is warranted, however, in that these patients require more intensive postoperative monitoring and must be quickly transitioned to transplantation if severe complications occur postoperatively.

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Discussion

Dr. Brad W. Warner (Cincinnati, OH): Debbie, congratulations, that was an excellent presentation. I think this report underscores the value of a multidisciplinary approach to a complex problem by a team comprised of health care professionals who are interested in this disease.

I had several questions, the first of which is, when do you take a patient with short gut and attempt an autologous reconstructive type of procedure? In some patients, I think you might be able to up front identify that they are not going to benefit, so they would go directly to transplantation. What are your cutoffs? Is there some sort of criteria that you use, such as percent enteral tolerance of nutrient or intestinal length? As you know, in Dr. Bianchi's own series, the cutoff for survival with his intestinal lengthening procedure was 40 cm of intestinal length. For patients whose intestinal length was shorter than this, you were essentially rearranging the deck chairs on the Titanic! In other words, you could lengthen their intestine slightly and possibly increase their enteral calories a little bit. However, there is little impact on overall outcome. So it sort of gets back to my original question, is there specific length or tolerance of enteral nutrient that would direct you to not offer a lengthening procedure?

The other concern that I have is about doing lengthening procedures in patients who have underlying jaundice. If bridging fibrosis is generally an indicator of irreversibility, have you had any patients who have really gone on with significant portal hypertension or other liver-related problems after correction of their intestinal length?

My final question relates to patients in your series who have over 100 cm of intestinal length. In most series, in patients whose intestinal length is over 100 cm, the likelihood that they are going to need TPN long-term is probably less than 5%. So what was unique about the patients in your series who had intestinal lengths over 100 cm? They weren't really short, but your data would suggest that they improved after an intestinal lengthening procedure. That seems to be a bit confusing.

Thank you again for a nice presentation.

Dr. Henry Pitt (Milwaukee, WI): Congratulations on excellent results in a very difficult patient population. Twenty years ago at this Society and at the AGA, Larry DenBesten, Joe Roslyn, and I presented a couple of papers showing that these adults and children have a very high incidence of gallstones, that they are oftentimes symptomatic and quite complicated. I was a little surprised to see that you did not have any cholecystectomies, and I wonder whether you do prophylactic cholecystectomy in this group of patients?

Dr. Keith Kelly (Scottsdale, AZ): These patients will tend to improve with time, even if they are not operated on, because of all the other things you are doing for them. How then can you ascribe the benefits to the surgery rather than just to improvement spontaneously?

Dr. Sudan: Thank you very much for all the comments and questions. I would like to start by answering Dr. Warner's question as to when do we choose reconstructive surgery and which patients go straight

to transplant and whether or not there was a specific length.

In all of the patients we have not strictly adhered to a specific length, and the history of enteral tolerance and the ability to wean is taken from a lot of different factors. It is difficult for me to describe specific criteria exactly, because it is such a heterogenous group of patients. I think a lot of it is the experience of the program and the people who are working in it who have helped us to choose these patients. There have been reports in the literature of patients with intestinal length as short as 5 cm weaning from TPN, and so we don't believe there is any absolute length criteria. At the same time, patients who had less than 40 cm, as you noted Bianchi had said, did poorly, and in our own experience have less of a chance to wean completely off TPN. But I think part of what I would like to emphasize in our program that is different from previous reports is that we had the option and were successful in offering transplantation to patients who had failed the Bianchi procedure or failed other reconstructive procedures. I think this is an important message, that we can salvage many of these patients with transplantation.

As far as jaundice, when do we choose reconstruction and when do we choose transplantation, I think the jaundiced patient is a very difficult patient, but if we do not see any evidence of bleeding, ascites, or other complications, and if the liver disease does not appear to be as advanced to end stage, I think these patients can very definitely benefit from autologous surgery. On the other hand, evidence of portal hypertension would usually lead directly to transplantation.

Regarding the few patients who had a long length of remnant bowel, more than 100 cm. I agree, usually these would not be considered all that short, but in our series they were patients who were fully dependent on TPN. These were all adult patients, not children, which I think is one factor since adults seem to require a longer length of bowel to become TPN independent than children and interestingly these were the few with whom we really made little progress even though the remnant length was so long. The underlying diseases, however, were Crohn's disease and radiation enteritis in these patients, and this was likely a large reason for our lack of success.

As to Dr. Pitt's question regarding gallstones, we also see frequent gallstones in the patients with short bowel syndrome and did have some patients who underwent cholecystectomy. I apologize, I did not include those numbers in the summary. They underwent cholecystectomy, however, in conjunction with their other procedures and not as a separate procedure, and perhaps this is why I had overlooked this. It is fairly common, especially in the jaundiced patient, for us to do a cholecystectomy at the same time as other reconstructive surgery.

Yes, many patients with short bowel syndrome, Dr. Kelly, do improve over time, but all of the patients that we included were in one of two categories and I would expect are a limited number of short bowel syndrome patients overall. Our patients had demonstrated that they were stable in their ability to wean for a period of time and were not making any progress before they underwent surgery or had indications for intestinal transplantation that we believed would not have allowed the patient to survive a long period of gradual adaptation, and this pushed us to do the surgery more quickly. An example of the latter would be the patients who had proximal fistulas and jaundice, who underwent an earlier surgery, compared to those with Bianchi, who had undergone the lengthening after a fairly prolonged period of time of adaptation. We did not do absorptive studies to demonstrate improvement, so I cannot prove that these patients benefited. Nonetheless, based on my experience in intestinal transplantation, I would argue that these jaundiced patients would not have survived more than 6 to 18 months without this intervention because they had the complications we see in patients who are listed, and we know that there is somewhere between 33% to 50% mortality on the waiting list. These patients had indications for transplantation, and what I am trying to show is that we feel there are a few, actually more than 80% of these patients, who can be salvaged with reconstructive surgeries instead.

On the other hand, we do not do reconstructive surgery on all short bowel syndrome patients, and as I noted earlier in my talk we have 40 patients that we treated medically in our program because we agreed that in the absence of complications they would continue with a slow gradual adaptation and we could expect them to eventually wean from their TPN. Finally, there were other patients who were instead listed initially for transplantation without nontransplant reconstructive surgery either because of very poor function of their remnant length and/or advanced liver disease, which suggested that surgical intervention was very unlikely to prevent the need for transplantation. We hope to do absorptive studies in the future in both our medically treated and surgically treated groups to help define how these surgeries are benefiting the patients.

Thank you very much for your questions and thank you for the privilege of presenting our results in this forum.

Prognostic Factors and Evaluation of Surgical Management of Hepatic Metastases From Colorectal Origin: A 10-Year Single-Institute Experience

Eduard L.A.R. Mutsaerts, M.D., Ph.D., Serge van Ruth, M.D., Ph.D., Frans A.N. Zoetmulder, M.D., Ph.D., Emiel J.T. Rutgers, M.D., Ph.D., F.R.C.S., Augustinus A.M. Hart, Ph.D., Frits van Coevorden, M.D., Ph.D.

The aim of this study was to determine prognostic factors and outcome after liver resection for colorectal metastases in 102 patients over a period of 10 years. A stepwise procedure using proportional hazard regression analysis was used to identify prognostic factors. Estimated survival at 2 years was 71%, and at 5 years, 29% (Kaplan-Meier). Of 19 patients with isolated liver recurrence, 6 had a second metastasectomy; 4 of the 6 are still alive. We found that the number of hepatic lesions on computed tomography ($P = 0.012$), the interval between resection of the primary colon tumor and the hepatic metastasectomy ($P = 0.012$), and synchronicity of the primary and the hepatic metastasis ($P = 0.048$) showed evidence of independent prognostic value regarding survival. Resection of hepatic colorectal metastases may result in long-term survival. Patients with recurrence after a first liver resection may benefit from a repeat metastasectomy. Our data suggest there is no strong predictor of survival. Survival seems to decrease with increasing number of metastases found on computed tomography. (J GASTROINTEST SURG 2005;9:178–186)

KEY WORDS: Hepatic, colorectal, metastases, prognostic factors, survival

In western Europe and the United States, colorectal cancer is the most frequent malignancy, and after lung cancer, it is the second cause of cancer death. In the Netherlands, up to 8500 patients are diagnosed with colorectal cancer each year.[1] When colorectal cancer is diagnosed, as many as 25% of the patients already have manifest liver metastases and another 50% experience a liver metastatic recurrence within the next 5 years.[2]

Hepatic metastases are usually of colorectal origin (70%). Without treatment, the prognosis of symptomatic disease is poor, with a median survival between 6 and 12 months; with chemotherapy alone, median survival is up to 18 months.[3–6] Surgical resection is the only approach that offers a chance of long-term survival and cure.[7] In the literature, 5-year survival rates of up to 40% are reported after complete metastasectomy in selected cases.[8] Only 20–25% of patients are deemed suitable for hepatic resection.[9]

Identifying prognostic factors can help to categorize different patient risk groups. This could be helpful in choosing the optimal treatment for an individual patient. However, the prognostic significance of various risk factors is still controversial.

The aim of this study was to evaluate the experience at a single institute regarding prognostic factors and surgical management of hepatic metastases of colorectal origin.

MATERIAL AND METHODS

Between January 1990 and December 1999, 102 patients were treated for their histologically proved

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.06.005

colorectal liver metastases. At time of treatment, there was primary tumor control and no extrahepatic disease.

The following data were recorded: sex, age, Dukes classification, synchronicity, interval between primary tumor and metastases, interval between diagnosis and treatment of metastases, number of lesions on computed tomography (CT), laterality on CT, maximum size of the lesion on CT, year of hepatectomy, preoperative chemotherapy, number of metastases in the specimen, maximum size of lesion in specimen, radicality, size of resection, cholecystectomy, and postoperative chemotherapy.

For overall survival, patients who died from any cause were counted as treatment failures; all other patients were censored at the date of their last follow-up. Time was measured from the date of metastasectomy.

Statistical Methods

A stepwise procedure with proportional hazard (PH) regression analysis[10] was used to identify prognostic factors (Table 1) with respect to overall survival. In the first stage, only preoperative characteristics were considered for inclusion. This part of the analysis is aimed at identifying factors that can help in making therapeutic decisions. In the second stage, perioperative and postoperative factors were also considered for inclusion. The resulting factors can be used for prognosis. Inclusion and exclusion limit for the *P* value was 0.15. Year of metastasectomy and treatment factors were also considered for inclusion to adjust for confounding caused by these factors if necessary. Nevertheless, the treatment factors were handled with care as inclusion might also result in overcorrection if the indication for treatment rather than the treatment itself is responsible for a relation of survival and the relation between treatment and indication is strong.

The variables of interval between primary tumor and metastasectomy, interval between diagnosis metastases and metastasectomy, number of metastatic lesions (both on CT and in the surgical specimen), and size of the largest lesion (both on CT and in the surgical specimen) either had a severely skewed distribution or contained a small number of extremely high values. To reduce the impact on the PH analysis, interval, delay, and size were logarithmically transformed, whereas patients with more than four lesions were combined into one category. Primary analysis was based on these newly defined variables, but the results were compared with those of an analysis based on the original variables.

In all analyses, interval and ordinal variables were primarily considered to be linearly related with log (hazard). However, at each step, the linearity of each

Table 1. Patient- and treatment-related variables

Variable	No. of patients
Gender* (male/female)	53/49
Age† (yr) (mean [SD/median/min–max])	61[11/63/29–81]
<50	19
50–59	23
60–69	35
⩾70	25
Dukes stage§	
A	1
B	30
C	71
Synchronicity*	
Synchronous (<3 mo)	43
Metachronous (⩾3 mo)	59
Internal PT to metastasectomy† (mo) (mean [SD/median/min–max])	18[20/12/0–97]
⩽3	22
4–12	30
13–24	28
>24	22
Internal diagnosis metastases to metastasectomy† (mo) (mean [SD/median/min–max])	4.1[6.1/2/0–44]
0–1	38
2–3	31
4–6	15
>6	18
No. of lesions (CT)§ (mean [SD/median/min–max])	2.0[1.3/2/1–9]
1	49
2	27
3	14
4	9
>4	3
Laterality (CT)* (Unilateral/Bilateral)	82/20
Size of maximum lesion (CT)† (mm) (mean [SD/median/min–max])	45[25/40/5–20]
<30	23
30–49	42
50–69	16
⩾70	21
Year of hepatectomy†	
1990–1992	21
1993–1995	32
1996–1997	26
1998–1999	23
Preoperative chemotherapy* (yes/no)	9/93
No. of metastases per specimen§ (mean [SD/median/min/max])	1.9[1.8/1/1–17]
1	57
2	23
3	15
4	4
>4	3

Continued

Table 1. Continued

Variable	No. of patients
Mean histologic size of maximum lesion in mm† (histologic) (mm) (mean [SD/median/min–max])	50[30/45/6–140]
<30	26
30–49	35
50–69	18
⩾70	23
Radicality‡	
Irradical	9
Margin <1 cm	38
Margin >1 cm	55
Size of resection* (major/minor)	84/18
Cholecystectomy‡	
Yes	81
No	9
Already done	12
Postoperative chemotherapy* (yes/no)	4/98

PT = primary tumor; CT = computed tomography scan.
Type as used in analysis: *Binary, †interval, ‡normal, §ordinal.

variable was tested; if nonlinearity was present ($P < 0.05$), the P value of linear plus nonlinear effect was used in that step for consideration of inclusion or exclusion. Nonlinearity was introduced by categorizing the variables as shown in Table 1. In addition, at the end of each step, the deviance residuals[11] (including a smoothing spline) were plotted against the variable considered for inclusion in the next step to verify linearity.

At each step, the assumption of proportional hazards was tested by plotting the weighted Schoenfeld residuals[12] against time. If these plots suggested a deviation from the proportionality assumption, this was investigated further by fitting a time-dependent model, using a variable × time interaction, where time might be transformed if the Schoenfeld residual plots suggested this.

These checks were always performed for new variables to be entered in the model. If this was judged to be a major prognostic variable, the same was done for the variables already in the model.

If these checks shed doubt about the proportionality assumption, then in the next steps these variables were used as stratification variables (with strata defined as in Table 1) rather than as covariates. Only when testing the variables themselves were they used as covariates.

Survival-type calculations were done using the product-limit method of Kaplan and Meier.[13] The SE values were calculated according to the method of Peto et al.[14]

General

The P values were adjusted for multiple comparisons only where explicitly stated. In those cases this was done using the procedure of Hommel.[15]

RESULTS

In our database, 102 patients formed the study group that was the subject of our analysis.

Morbidity and Mortality

Postoperative complications were seen in 27 patients (26%; Clopper-Pearson 95% confidence interval [CI], 18–36%). Table 2 lists the type of complications. Three (3%) patients died postoperatively; no relationship was found with preoperative comorbidity or surgical techniques.

Survival

For all 102 patients, median follow-up was 28 months (range, 1–121 months). Median follow-up of the 48 patients still alive, of whom 8 have evidence of disease, is 31 months (range, 5–121 months) versus 26 months (range, 1–91 months) for the 54 patients who died. Of the 54 patients who died, eventually 48 died from their colorectal cancer, 3 died postoperatively, and 3 died from unrelated other causes. Estimated survival at 2 years is 71% (SE, 5%) and at 5 years 29% (SE, 7%) (Fig. 1). Table 3 presents

Table 2. Postoperative morbidity and mortality

Type	(n)
Morbidity (n = 27)	
Wound infection	1 (1%)
Bile leakage	3 (3%)
Abscess	3 (3%)
Jaundice	5 (5%)
Bowel obstruction (ileus)	1 (1%)
Pneumonia	1 (1%)
Subfrenic collection	4 (4%)
Decubitus	1 (1%)
Pyelonephritis	1 (1%)
Pulmonary embolism	1 (1%)
Portal vein thrombosis	1 (1%)
Heart failure (dec. cordis)	1 (1%)
Atrium fibrillation	1 (1%)
Splenic bleeding	3 (3%)
Mortality (n = 3)	
Combined hepatic and renal failure (days)	48
Hepatic failure (days)	39
Perioperative bleeding	Operation

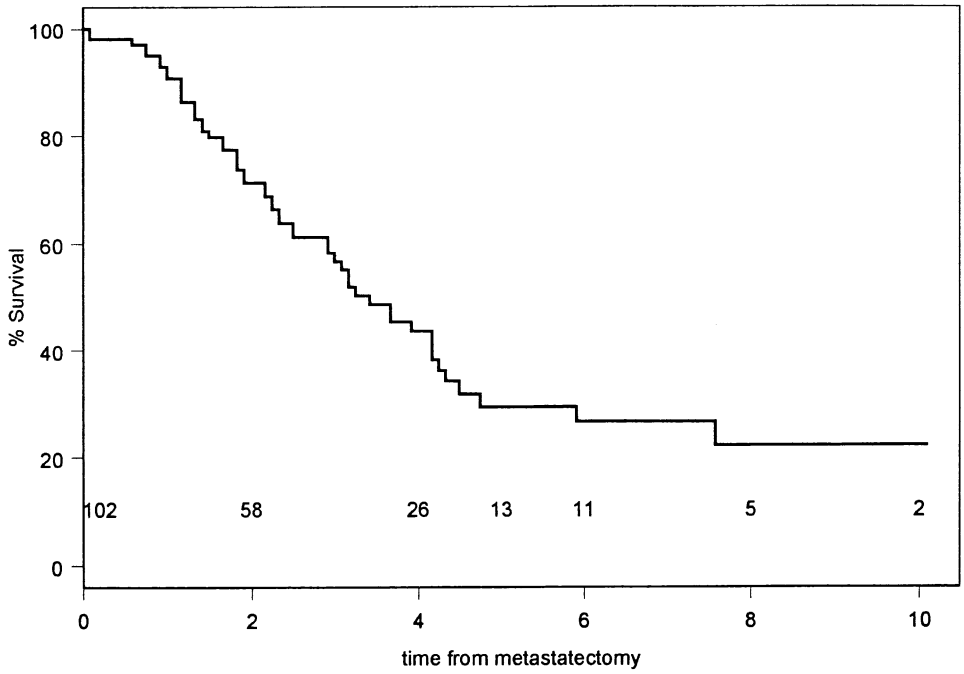

Fig. 1. Survival for all patients.

the results of the stepwise procedure to identify prognostic factors. For number of lesions on CT ($P = 0.012$), interval between primary and metastasectomy ($P = 0.016$, including nonlinearity), and synchronicity ($P = 0.048$), there is evidence of an independent prognostic value regarding survival. These P values are additionally adjusted for cholecystectomy and size of metastases on histology. The P values for these variables (0.080 and 0.13, adjusted for number of lesions on CT, interval between primary and metastasectomy [nonlinear], and synchronicity) are too high to provide evidence of a prognostic

Table 3. Survival, P values from stepwise proportional hazard analysis

Variable	Univariable	Multivariable	
		Preoperative variable	Preoperative + postoperative
Gender	0.26	0.16	0.27
Age	0.99	0.33	0.30
Dukes stage	0.52	0.37	0.83
Synchronicity	0.40	0.10*	**0.048***‡
Interval (In)	0.046†	0.021*†	**0.016***†‡
Diag-treat meta (In)	0.85	0.28	0.55
No. of lesions (CT)	0.0057	0.0090*	**0.012***‡
Laterality	0.37	0.80	0.80
Size (CT) (In)	0.86	0.36	0.78
Year	0.99	0.45	0.47
Preoperative chemotherapy	0.59	0.35	0.81
Size of resection	0.30	0.70	0.86
No. of metastases	0.026	0.65	0.88
Size max. meta (In)	0.74	0.24	0.13*
Radicality	0.41	0.40	0.68
Cholecystectomy	0.079	0.14	0.080*
Postoperative chemotherapy	0.64	0.53	0.70

*Underlines indicate covariates adjusted for.
†Includes nonlinearity.
‡Bold indicates significant values.

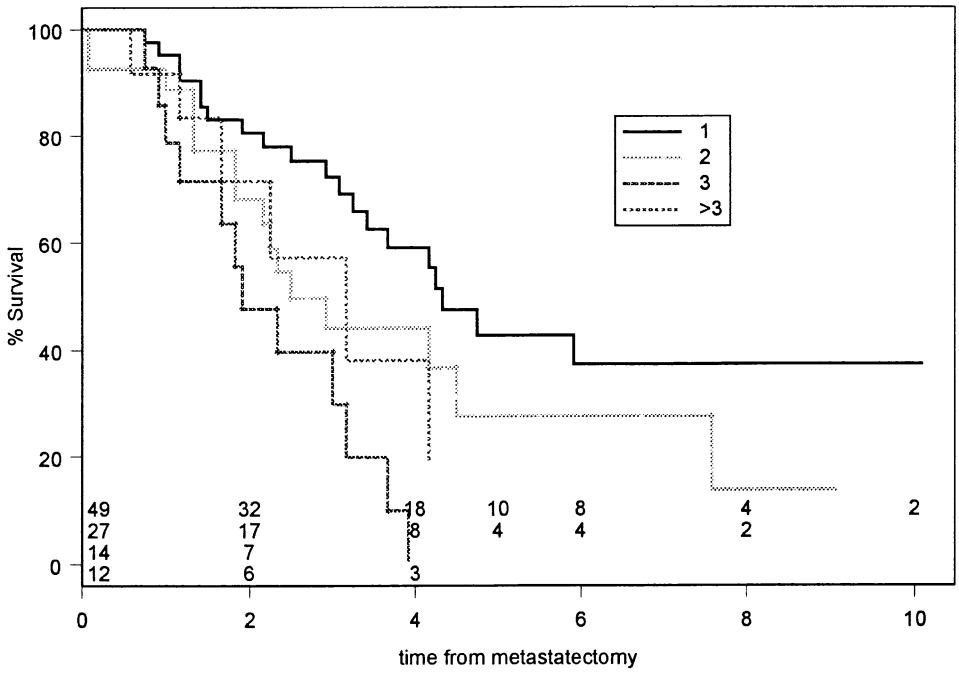

Fig. 2. Survival by number of metastases on computed tomography.

value regarding survival. However, when we adjust the *P* values at step 0 for the fact that a total of 17 *P* values are calculated, the *P* value for number of lesions at CT increases to 0.092, indicating weak evidence for the existence of an association between at least one variable and survival. There is no evidence for an association of more than one variable with survival.

Figure 2 presents the survival for three categories of number of lesions on CT. Estimated survival at 2 years is 80% (SE, 6%) for patients with one lesion, 68% (SE, 10%) for patients with two lesions, and 58% (SE, 11%) for patients with three or more lesions. At 5 years, survival is estimated to be 43% (SE, 9%) for one lesion, 28% (SE, 12%) for two lesions, and 0% for three or more lesions. Median survival (95% CI) is estimated to be 52 months (41–∞) for one lesion, 30 months (22–91) for two lesions, 23 months (14–38) for three lesions, and 38 months (20–∞) for four or more lesions. The estimated hazard of dying increases by a factor of 1.40 (95% CI, 1.10–1.77) per lesion (restricted to 5), unadjusted for other variables, and by 1.40 (1.08–1.81), adjusted for interval, synchronicity, cholecystectomy, and size of metastases as measured by pathologic examination. There is no evidence that the hazard ratio changes during follow-up (interaction with linear time: $P = 0.33$). Using the number of lesions as such, that is, without grouping more than four lesions in one category, generally gave lower *P* values ($P = 0.0001$ nonlinearly in step 0) but also evidence of nonlinearity ($P = 0.041$). This appeared to be entirely due to a patient with nine lesions, who died after 7 months.

Remarkably, the number of lesions on CT seems to be more informative than the number of metastases in the surgical specimen. In a PH model in which both are present (in addition to interval, synchronicity, cholecystectomy, and size of metastases as measured at pathology), the ln(hazard ratio) for number of metastases in the specimen is 0.03 (SE, 0.19; $P = 0.87$), whereas for the number of lesions on CT, an ln(hazard ratio) of 0.32 (SE, 0.18; $P = 0.073$) was found.

Survival After Recurrence

Sixty-three patients experienced a recurrence after metastasectomy, of whom 19 had recurrent liver metastases only (Fig. 3). Sixteen of the 63 patients underwent a second metastasectomy, in 7 of them accompanied by chemotherapy or radiotherapy. Twenty-six patients were treated with chemotherapy or radiotherapy without surgery, whereas 21 patients received no treatment for their recurrence. Fourteen of the 63 patients are still alive with a median follow-up of 10 months (range, 1–41 months) from treatment or diagnosis of the recurrence, whereas 49 died with a median follow-up of 13 months after diagnosis or start of treatment of the recurrent metastases. Estimated survival for the 63 patients is 28% (SE, 7%) at 2 years and 4% (SE, 4%)

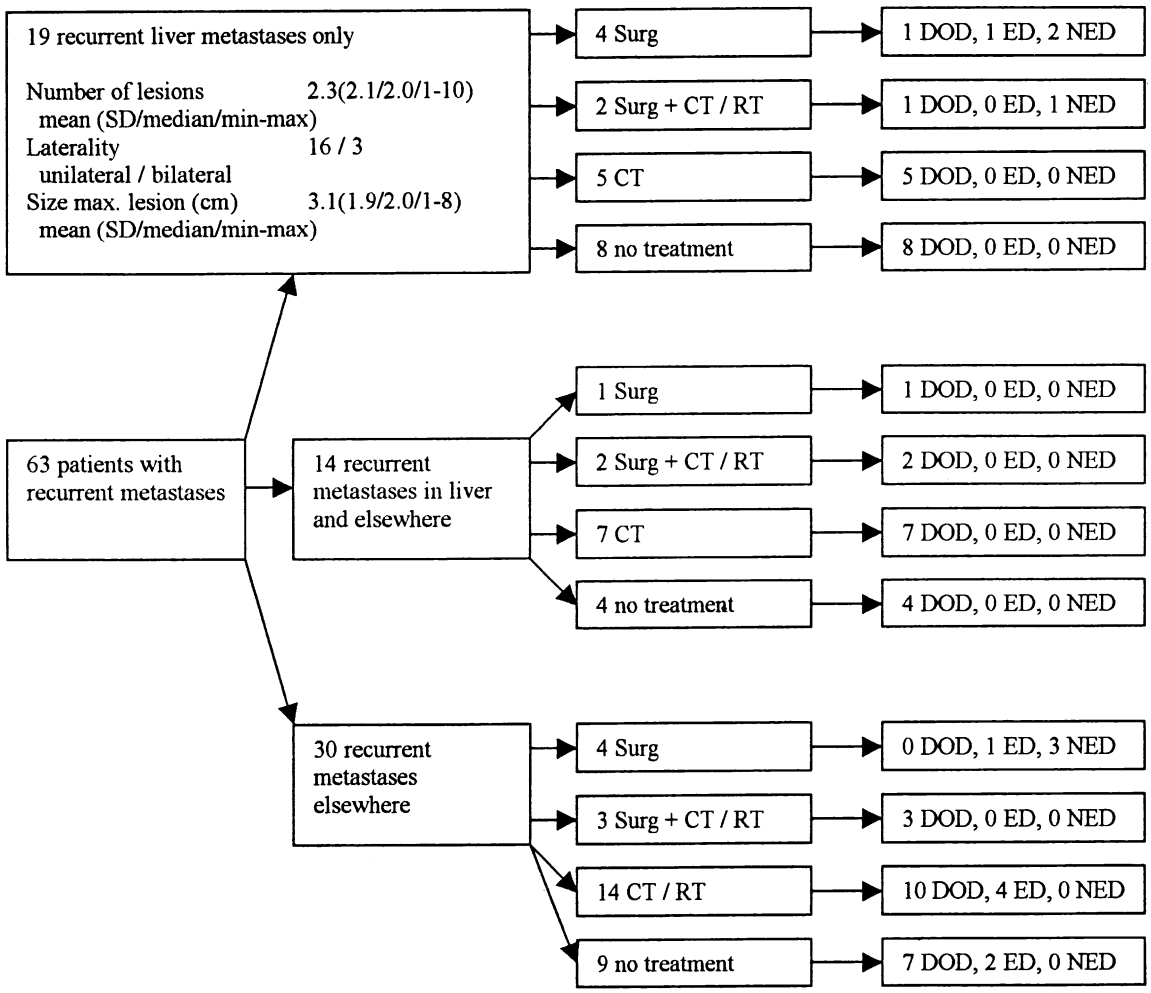

Fig. 3. Recurrent metastases: Location, treatment, and status at last follow-up.

at 5 years. The 16 patients with second metastasectomy had a 2-year survival of 76% (SE, 15%) and a 5-year survival of 19% (SE, 17%) (Fig. 4). Eight of them are still alive at 2, 8, 8, 8, 15, 16, 18, and 41 months after reoperative surgery. Of the eight patients who died, all except one did so after more than 1 year and five died after 2 years (at 26, 31, 37, 55, and 82 months).

When the 19 patients with liver recurrence only are considered, only four of them are still alive with a median follow-up of 11 months, whereas the remaining 15 died with a median follow-up of 13 months. Estimated survival for the 19 patients is 21% (SE, 11%) at 2 years and none yet at 5 years. For the six patients with a second metastasectomy in the liver, 2-year survival is 83% (SE, 24%) (Fig. 5). Four of the six are still alive at 8, 8, 15, and 41 months. The two patients who died did so after 2 and 37 months.

DISCUSSION

Resection of hepatic colorectal metastases in our experience results in a 5-year survival rate of 29%, comparable to data reported in the literature.[8,16,17] The postoperative morbidity and mortality rates of 26% and 3%, respectively, are in line with results of other groups.[8,18,19] These results support both the efficacy and safety of this type of treatment for

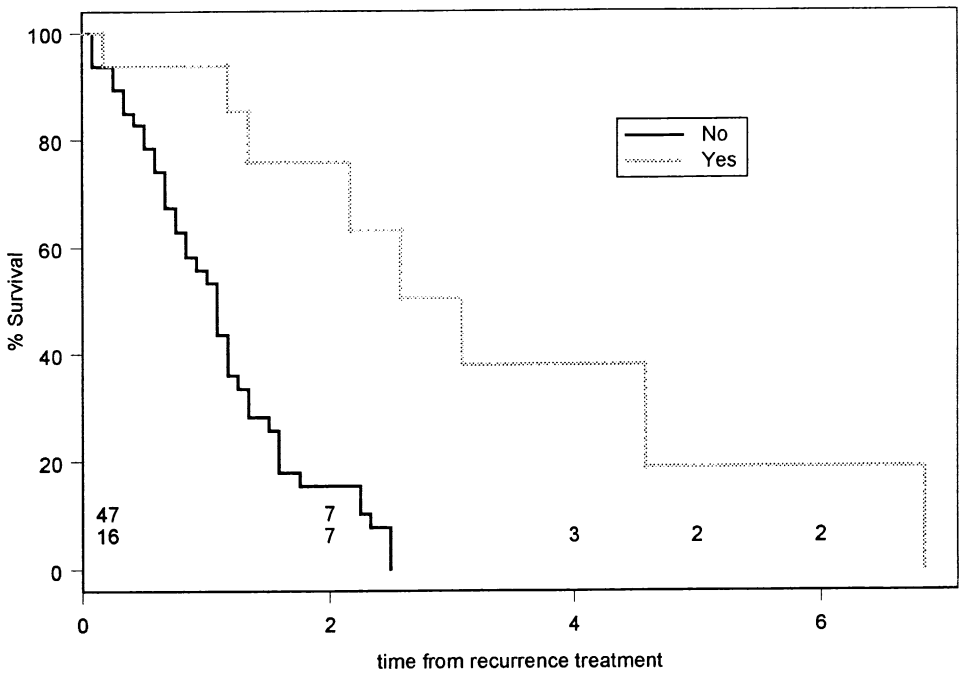

Fig. 4. Survival after recurrence and treatment by a second metastasectomy.

selected patients with colorectal metastases confined to the liver.

Identifying prognostic factors can help to individualize treatment. Various possible prognostic risk factors are still controversial.[16,18,20] The following factors are mentioned as predictors of poor long-term outcome: node-positive primary, short disease-free interval from primary to metastases, number of hepatic lesions, size of largest hepatic lesion greater than 5 cm, positive resection margin, extrahepatic disease, and CEA level greater than 200 ng/ml.[16] In our series, we found the number of lesions on CT,

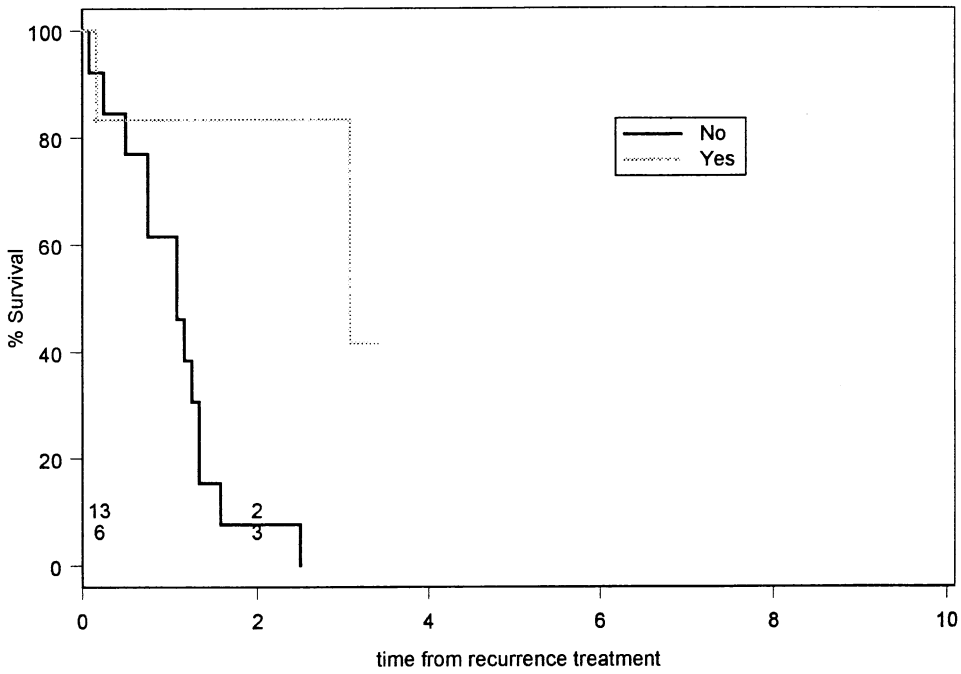

Fig. 5. Survival after liver recurrence only, and treatment by second metastasectomy.

disease-free interval between primary and metastasectomy, and synchronicity to be possible predictors of outcome.

Node positivity at the liver hilus during surgery has been considered extrahepatic disease and is as such an exclusion criterion for resection.

Remarkably, the number of lesions on CT seems to be more informative than the number of metastases in the surgical specimen. Generally, lesions found in the specimen, but not visualized on CT, are smaller than the smallest visible lesions seen on CT. This may indicate that not the number of lesions on CT scan but the ultimate number found in the resected specimen and size of the metastases are predictors of outcome. In our study, however, neither the number of lesions in the specimen nor the size of the largest lesion on CT scan or in the specimen was found to be of prognostic significance. The question arises of whether the number of lesions on CT will change as a predictor of outcome with the introduction of the current generation of CT screening. The sensitivity of the current preoperative radiologic work-up is superior to that available a decade ago. The current generation of helical CT screening and positron emission tomography may identify nodules in the range of 2–3 mm[21,22] instead of the minimal 7-mm slices that were made in the early 1990s. Where the difference in number of lesions found on CT or surgical specimen will decrease, the impact of the prognostic factor number of lesions on CT might be expected to diminish as number in the specimen is not a prognostic factor.

A frequently mentioned predictor of outcome is completeness of resection.[23] In our study, this was not found to be a prognostic factor ($P = 0.68$).

Over the years in the literature, the surgical approach has become more aggressive, aiming at clearance of the liver from all metastases, whenever resection was technically feasible. With a steady decline in the postoperative morbidity and mortality rate, the risk of increasing this rate again by more extensive surgery was accepted.[24–27] However, evidence of improved survival is equivocal. Although Scheele et al.[9] reported no changes of survival figures of the aggressive approach compared with those obtained from a conservative approach during the 1960s and 1970s, Hughes et al.[7] reported a 5-year survival rate in this patient group with more than three lesions of 18%, and other studies[8,24] reported a 5-year survival rate as high as 40–50%. In this study, almost no patient with three or more metastases survived longer than 4 years after metastasectomy. To improve results in this patient group, nonsurgical adjuvant treatment after liver resection needs to be considered.

The frequently reported independent factors regarding survival, synchronicity and interval between primary tumor and metastases, are highly associated to each other. Patients with synchronous liver metastases are considered to have a poor prognosis. In our study some evidence was found that synchronicity is a prognostic factor for survival ($P = 0.048$). Should these patients undergo a liver resection, and if so, when? Ballantyne and Quin[20] reviewed the literature on this issue and reported a 5-year survival rate of 0% but also of as high as 38%, with an average of 27%. They conclude that synchronous liver resections should only be offered after good patient selection, meaning metastatic disease limited to one lobe with a small diameter.

Asbun and Hughes[28] listed five prerequisites for simultaneous resection: (1) solitary lesion that can be removed by limited liver resection, (2) minimal blood loss and an uncomplicated bowel resection, (3) an incision that is also suitable for resection of the liver, (4) a patient who is fit enough to undergo both procedures, and (5) a surgeon who is comfortable in proceeding with the liver metastasectomy. However, in general it is thought that it is wiser to delay resection of the liver 6–8 weeks after the colorectal resection. In this period, the patient can recover and the surgeon can optimize further dissemination investigations. A delayed resection in limited metastatic disease will probably not have a significant influence on survival, as time to metastasectomy is not found to be a main determinant of survival of the colorectal cancer.[29] As these findings are not based on randomized comparisons, however, they should be interpreted with care. If multiple metastases are found at preoperative evaluation, the necessary surgery for the primary tumor can be combined with intraoperative ultrasound evaluation of the liver, often showing more extensive disease, not a suitable fit for surgical approach.

In this series, 63 patients experienced a recurrence after metastasectomy; of these, 19 patients developed a recurrence in the liver only (30%); comparable percentages are reported in other series.[7,30] Resection may provide for these patients again the only curative treatment option, with similar morbidity and mortality rates to a first liver resection.[30–32] Fig. 4 (recurrence anywhere) and Fig. 5 (recurrence in liver only) show a better survival for the selected group of patients with a surgical treatment versus patients who underwent chemotherapy or radiotherapy or no treatment. From the six patients with recurrent metastases confined to the liver who underwent a second metastasectomy (Fig. 5), 2-year survival was 83%, which is comparable to rates in the literature.[31] Of course, this outcome is a result of selection, but this

favorable survival result suggests that surgery might be a good option in selected cases of recurrent liver metastasis.

CONCLUSION

Adequate patient selection for surgical treatment of liver metastases of colorectal origin is paramount in achieving long-term survival. Resection of these hepatic metastases may result in long-term survival and cure. Even patients with multiple liver metastases or a recurrence after a first resection may benefit, provided good patient selection. In our series, we found no strong evidence for the existence of predictor(s) of survival. Liver metastasectomy is a relatively safe operation.

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Improvement of Postischemic Hepatic Microcirculation After Endothelin$_A$ Receptor Blockade—Endothelin Antagonism Influences Platelet-Endothelium Interactions

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Endothelin (ET) contributes to disturbances of hepatic microcirculation after ischemia/reperfusion (I/R) by causing vasoconstriction and enhancing leukocyte- and platelet-endothelium interactions. The aim of this study was to investigate a possible protective role of a selective endothelin$_A$ receptor antagonist (ET$_A$-RA) in this setting. In a rat model, warm ischemia of the left lateral liver lobe was induced for 90 minutes under intraperitoneal anesthesia with xylazine and ketamine. Groups of rats consisted of sham-operated (SO, n = 14), untreated ischemia (n = 14), and treatment with BSF208075 (5 mg/kg body weight IV, n = 14). The effect of the ET$_A$-RA on I/R was assessed by in vivo microscopy 20 to 90 minutes after reperfusion; by measurement of local tissue P_{O_2}, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glutathione *S*-transferase α levels, and by histologic investigation. In the untreated group, sinusoidal constriction to 69.4 ± 6.7% of diameters of SO rats was observed, leading to a significant decrease in perfusion rate (74.3 ± 2.1% of SO) and liver tissue P_{O_2} (43.5 ± 3.2% of SO) ($P < 0.05$). In addition, we found an increased percentage of stagnant leukocytes (142.9 ± 11.9%) and platelets (450.1 ± 62.3%) in sinusoids and in postsinusoidal venules ($P < 0.05$). Hepatocellular damage (AST and ALT increase to 1330 ± 157 U/L and 750 ± 125 U/L respectively; previously, 27.1 ± 3.5 U/L and 28.5 ± 3.6 U/L) was detected 6 hours after reperfusion ($P < 0.05$). Administration of the ET$_A$-RA before reperfusion significantly reduced I/R injury. Sinusoidal diameters were maintained (108.5 ± 6.6%), and perfusion rate (93.1 ± 1.8%) and tissue P_{O_2} (95.3 ± 5.7%) were significantly increased ($P < 0.05$). According to reduced leukocyte-endothelium interactions after therapy, both platelet rolling and adhesion were significantly reduced ($P < 0.05$). The number of stagnant platelets in sinusoids was 199.5 ± 12.3% of 50 ($P < 0.05$). After treatment, hepatocellular damage was decreased (AST and ALT levels after 6 hours of reperfusion: 513 ± 106 U/L and 309 ± 84 U/L, respectively; $P < 0.05$), and histologic changes were reduced in the long term. Our results provide evidence that the new therapeutic approach with an ET$_A$-RA is effective in reducing hepatic I/R injury. In addition to reduced leukocyte-endothelium interactions, the number of stagnant and rolling platelets in sinusoids and venules was significantly reduced. The reduction in microcirculatory damages is responsible for better organ outcome. (J GASTROINTEST SURG 2005;9:187–197)

KEY WORDS: Ischemia, reperfusion, liver, platelets, endothelin, receptor blockade

Liver injury caused by ischemia/reperfusion (I/R) is a complication of hepatic resectional surgery, liver transplantation, and hemorrhagic shock with fluid resuscitation. It has been recognized that the hepatic microcirculation represents a main target of I/R-induced hepatic injury.[1] In the liver, along with leukocyte accumulation, activation of Kupffer cells, swelling, and dysfunction of endothelial cells are concomitant features of the I/R process, which together enhance tissue damage.[2]

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This study was supported by a grant from the Else Kröner-Fresenius Stiftung and by a junior research fund of the Medical Faculty at the University of Leipzig.
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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.06.006

There is considerable evidence that platelets contribute to I/R injury in the heart,[3] lung,[4] and pancreas.[5] On activation, platelets are able to generate reactive oxygen species and nitric oxide (NO) as well as release proinflammatory mediators such as chemokines, cytokines, growth factors, and cytotoxic proteases.[6–9] Therefore, platelets have the potential to contribute to the manifestation of hepatic I/R injury. The first evidence of involvement of platelets in the development of I/R-induced liver injury was provided by the investigations of Cywes et al., who demonstrated platelet accumulation in the cold perfused rat liver using electron microscopy[10] as well as in the human liver using immunohistochemistry.[11] Recently, Khandoga et al.[12] demonstrated that platelets interact with the hepatic endothelium after 90 minutes of warm ischemia and 20 minutes of reperfusion and contribute to the development of hepatic microvascular and hepatocellular injury.

Endothelin-1 (ET-1) is a potent vasoconstrictor of hepatic microcirculation that is mainly produced by endothelial cells. In the intact liver, the constricting action of endothelin is in balance with the dilating action of NO, made constitutively by endothelial nitric oxide synthase (eNOS). It has been shown that production of ET-1 is controlled at the transcriptional level. Upregulation of prepro–ET-1 mRNA can be induced by numerous factors such as cytokines, angiotensin, thrombin, and transforming growth factor-β.[13] Released from endothelial cells, ET-1 mediates transient vasodilation that is followed by a profound and long-lasting vasoconstriction. On the other hand, ET-1 is able to induce an inflammatory response in human vascular smooth muscle cells by stimulating the synthesis and release not only of proinflammatory cytokines such as interleukin 6.[14] ET-1 mediates local injury but also systemic disease.[15]

Two distinct ET receptors have been identified and shown to be present on liver cells: ET_A and ET_B. ET_A receptor mediates the constrictive actions of ET-1. ET_B can potentially mediate both dilation and constriction but is mainly responsible for NO-mediated vasodilation.[16] ET_B receptors are expressed by all types of liver cells, whereas ET_A receptors were found on hepatocytes and hepatic stellate cells (HSCs) only.[17] Compared with other liver cells, HSCs have the greatest number of ET receptors.[17] Moreover, the ratio ET_A/ET_B is altered in activated HSCs,[18] suggesting the possibility that a change in the receptor subtype may contribute to the increased contractile potential of activated stellate cells.

The aim of this study was to evaluate whether the blockade of ET-1 action with the specific ET_A-RA BSF 208075 has beneficial effects in treating hepatic I/R injury, especially regarding microhemodynamics and platelet–endothelial cell interactions. We examined the acute effects of BSF208075 on microhemodynamics, as well as the long-term effects on liver function in a 1-week follow-up.

MATERIAL AND METHODS

Animals, Operative Procedure, and Monitoring

All of the experiments were conducted in accordance with local institutional guidelines for the care and use of laboratory animals. Forty-two inbred Wistar rats (250 to 300 g, female) were fasted for 12 hours and randomly divided into three experimental groups: sham operation (n = 14), untreated ischemia (n = 14), and treatment with the selective ET_A-RA BSF 208075 (Knoll AG, Ludwigshafen, Germany; 5.0 mg/kg body weight IV before reperfusion; n = 14). This dosage was chosen after preliminary tests in which dosages of 1, 5, and 10 mg/kg body weight were tested. Seven rats of each group were operated on and intravital microscopy was performed. The other seven rats of each group were used for tissue P_{O_2} measurements, laser Doppler flowmetry, and biochemical and histologic examinations in a 1-week follow-up. Rats received intraperitoneal anesthesia with xylazine and ketamine. Polyethylene catheters (PE 50, 0.28-mm internal diameter; Portex, Hythe, United Kingdom) were inserted into the right carotid artery and jugular vein. After a midline laparotomy, the blood supply to the left liver lobe was interrupted for 90 minutes by applying a microclamp to the vascular pedicle. The temperature of the ischemic liver was continuously controlled with a probe and maintained at about 37°C. Sham-operated animals were subjected to the identical surgical procedure with a brief (2-second) interruption of blood flow to the left liver lobe.

Platelet Separation

For intravital fluorescence microscopy, platelets were isolated from syngeneic donor rat whole blood and labeled with rhodamine-6G (50 μl of 0.05% per 1 ml of whole blood; MW 479; Sigma-Aldrich, Deisenhofen, Germany), as described by Massberg et al.[19] Before each infusion of platelets, the platelet count was assessed with a Coulter A ^{C}T Counter (Coulter Corp., Miami, FL). For our study, a total of 100×10^6 fluorescence-labeled platelets were infused intraarterially to achieve a labeled fraction in the recipient rat of approximately 10% of all circulating platelets.

Intravital Fluorescence Microscopy

The hepatic microcirculation was studied on the lower surface of the left liver lobe after infusion of labeled platelets during reperfusion, with the use of an intravital fluorescence microscope (Zeiss, Ober Kochem Germany) (eyepieces, ×10/20; objective, ×16/0.5 for water immersion; 100-W/2 HBO mercury lamp). The microscopic images were recorded with a CCD video camera (FK 6990-IQ; Cohu, Prospective Measurements, San Diego, CA) and transferred to a video system (S-VHS Panasonic AG 7330; Matsushita Electric Ind., Tokyo, Japan) for off-line evaluation. The following parameters were analyzed: sinusoidal perfusion rate (perfused sinusoids/total number of sinusoids observed), sinusoidal diameters (measured in 100 sinusoids per liver in the periportal zone, defined by dividing the sinusoid into three segments of equal length), and diameters of postsinusoidal venules.[20] Platelet–endothelial cell interactions were visualized on the liver surface in sinusoids and postsinusoidal venules. Fluorescent platelets were infused intra-arterially within a time period of 20 minutes after reperfusion, and 10 randomly chosen areas of the liver surface were visualized using a filter block (excitation, 530–560 nm; emission, >580 nm; Zeiss). Rhodamine-6G (0.1 ml, 0.05%) was then administered intravenously to quantify leukocyte–endothelial cell interactions within identical sinusoids and postsinusoidal venules. For assessment of leukocytes, labeled by systemic application of rhodamin-6G, an additional neutral density filter (5% transmission; Zeiss) was needed; hence, simultaneous visualization of previously applied platelets was impossible. After the intravenous injection of the plasma marker fluorescein isothiocyanate-labeled dextran (0.1 ml, 5%, MW 150,000; Sigma-Aldrich), sinusoidal perfusion was assessed (excitation, 450–490 nm; emission, >515 nm; Leitz).

Quantitative assessment of the microcirculatory parameters was performed off-line by computer-assisted analysis of the videotaped images using CAPIMAGE (Dr. Zeintl, Heidelberg, Germany). Rolling platelets and leukocytes were defined as cells crossing an imaginary perpendicular through the vessel at a velocity significantly lower than the centerline velocity in the microvessel. Their numbers are given as cells per second per vessel cross section. Platelets and leukocytes firmly attached to the endothelium for more than 20 seconds were counted as permanently adherent cells and quantified as the number of cells per square millimeter of endothelial surface, calculated from the diameter and length of the vessel segment observed.[19] In sinusoids, the number of accumulated ("stagnant") platelets and leukocytes was counted in the scanned acini and is given in [1/acinus]. The results are expressed as the number of stagnant platelets per acinus. Sinusoidal perfusion rate was quantified as a percentage of perfused sinusoids in each acinus from 7 to 10 analyzed per experiment.

Platelet Counts

Platelet counts in whole blood were determined using a Coulter A ^{C}T Counter (Coulter Corp.). Blood samples (50 μl) were taken from the carotid artery immediately before the induction of ischemia and after reperfusion before termination of the experiment. The data were standardized on a hematocrit of 0.45 and results are given as a ratio (percentage) of postoperative values to corresponding baseline values.

Polarographic tissue Po_2 Measurements

Hepatic tissue oxygenation was assessed by means of flexible polyethylene microcatheter Clark-type P_{O_2} probe (Licox System, GMS, Kiel-Mielkendorf, Germany), which was positioned beneath the glass slide on the surface of the liver as described by Mucke et al.[21] This allowed the Licox probe to integrate local tissue P_{O_2} values over the tissue area in contact with the 5-mm P_{O_2}-sensitive area near the catheter tip without interference with the ambient air (polarization voltage of 795 mV). On-line temperature compensation was performed with a temperature probe (type-K thermocouple probe; Licox System), which was also positioned between the hepatic surface and the glass slide. Measurements were performed during baseline, at the end of ischemia, and 30, 45, and 60 minutes after reperfusion.

Laser Doppler Flowmetry

Erythrocyte flux (AU [arbitrary units]) was assessed by means of laser Doppler flowmetry (DRT 4, semiconductor laser diode, 780–820 nm, 1.6 mW; Moor Instruments, Axminster, United Kingdom) at 10 sites of interest on the surface of the left liver lobe. Erythrocyte flux was calculated as the product of erythrocyte velocity and concentration within the tissue unit under investigation.[22] Measurements were performed during baseline, at the end of ischemia, and 15, 45, and 60 minutes after reperfusion. Values are given as percent of baseline.

Biochemistry

Preoperatively and again at 2, 6, and 24 hours after reperfusion and 2, 4, and 7 days after surgery, 200 μl blood was drawn via a jugular vein catheter for analysis of serum aspartate aminotransferase (AST),

alanine aminotransferase (ALT) and glutathione *S*-transferase α (α-GST) levels. AST and ALT were determined at 37°C by standard enzymatic techniques (micromethod, Ektachem-Kodak). Protein levels of α-GST were analyzed by enzyme-linked immunosorbent assay (HEPKIT-Alpha; Biotrin, Dublin, Ireland) according to the instructions provided.

Histology

Specimens were taken before liver manipulation and 6 hours, 2 days, and 7 days after reperfusion from the left lobe of the liver, fixed in 4% formaldehyde, embedded in paraffin, sectioned, and stained with hematoxylin-eosin. Histomorphologic alterations were semiquantitatively assessed by means of a scoring system from absent to severe. Impairment before organ manipulation was assessed by four parameters. Injury during warm ischemia, reperfusion, and follow-up was assessed by 10 parameters as described elsewhere.[23] Score points were assigned according to the importance of each parameter for organ function. Score values were given in percent of maximal attainable score points.

Statistical Analysis

All data are presented as mean ± SD. Statistical analysis was performed by one-way analysis of variance. If there were significant differences, the Bonferroni test was used for direct comparison of the groups. Values of $P < 0.05$ were considered significant.

RESULTS

Hemodynamic Parameters

Sham operation did not affect mean arterial pressure or heart rate over time. Animals subjected to ischemia experienced transient systemic hypotension during ischemia with only incomplete recovery of systemic blood pressure after 60 minutes of reperfusion compared with baseline ($P < 0.05$). Heart rate remained quite stable during ischemia but was significantly reduced during reperfusion ($P < 0.05$ versus baseline). However, ET_A-RA administration affected neither arterial pressure nor heart rate of ischemic rats (Table 1).

Table 1. Effect of ischemia and endothelin$_A$ receptor blockade on heart rate and blood pressure

	Baseline	90 min of ischemia	30 min after reperfusion
Mean arterial blood pressure (mm Hg)			
Sham	92 ± 3	87 ± 2	91 ± 8
Ischemia	91 ± 8	76 ± 5	84 ± 5
Ischemia + ET_A-RA	94 ± 8	83 ± 4	88 ± 6
Heart rate (bpm)			
Sham	418 ± 14	404 ± 8	414 ± 9
Ischemia	422 ± 12	414 ± 14	391 ± 9
Ischemia + ET_A-RA	415 ± 4	411 ± 14	402 ± 4

ET_A-RA = endothelin$_A$ receptor antagonist.
Values are given as mean ± SD. Sham operation did not affect mean arterial pressure or heart rate. In the ischemia group, transient systemic hypotension during ischemia with only incomplete recovery of systemic blood pressure after 60 minutes of reperfusion was seen. Heart rate remained quite stable during ischemia but was significantly reduced during reperfusion ($P < 0.05$ vs. baseline). ET_A-RA administration affected neither arterial pressure nor heart rate.

Hepatic Microcirculation

Diameters of sinusoids and postsinusoidal venules. In the sham-operated group, sinusoidal diameters of 8.4 ± 0.5 μm were measured. Taking this value as 100%, after ischemia followed by 20 minutes of reperfusion, the sinusoidal diameters in the nontreatment group were reduced to 69.4 ± 6.7% ($P < 0.05$). Response of postsinusoidal venule diameters to ischemia (76.2 ± 6.3% of sham group) was similar to the sinusoidal response. ET_A-RA treatment maintained sinusoidal (108.5 ± 6.6%) and postsinusoidal venule (103.2 ± 4.5%, $P < 0.05$ versus ischemia) diameters.

Platelet–endothelial cell interactions. Rhodamin-6G–labled platelets were analyzed in sinusoids and postsinusoidal venules. In sham-operated animals, only a few rolling platelets were registered in sinusoids (1.8 ± 0.1/acinus), and postsinusoidal venules (0.9 ± 0.1/s/mm). Likewise, the number of firmly adherent platelets was low under physiologic conditions in sinusoids (2.5 ± 0.3/acini), and venules (72.2 ± 6.2/mm^2). In contrast, 90 minutes of ischemia and 20 minutes of reperfusion caused significantly enhanced platelet–endothelial cell interactions in the rats. The number of rolling and permanently adherent platelets increased to 212.2 ± 12.3% and 484.2 ± 24.6%, respectively. In sinusoids, the number of stagnant platelets increased to 450% compared with the sham-operated group, whereas the number of rolling platelets remained at baseline (Fig. 1).

To determine the role of ET for platelet–endothelial cell interactions, the selective ET_A-RA was applied before reperfusion. After 90 minutes of ischemia followed by 20 minutes of reperfusion, both platelet rolling (110.6 ± 8.4% of sham group) and adhesion (123.5 ± 9.5% of sham group) were nearly absent in hepatic venules ($P < 0.05$ versus ischemia). The number of platelets stagnant in sinusoids in treated animals was still found significantly elevated compared with sham-operated animals (199.5 ± 12.3%; $P < 0.05$ versus ischemia).

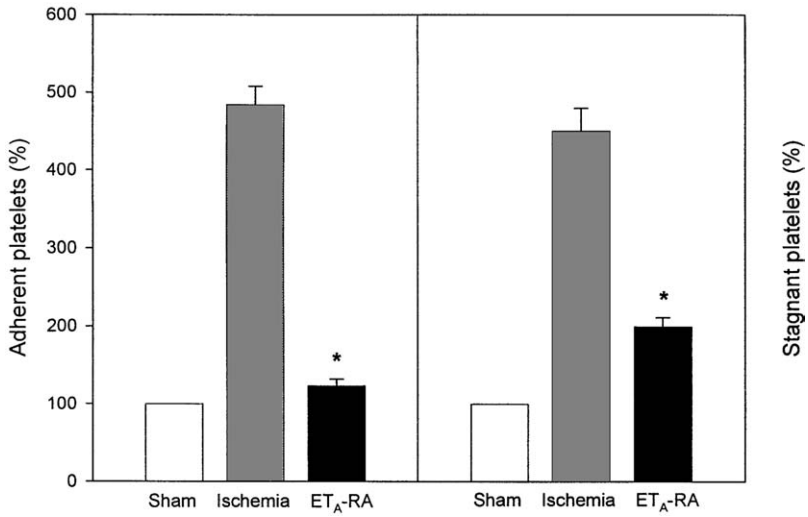

Fig. 1. Numbers of adherent platelets in postsinusoidal venules and stagnant platelets in sinusoids in sham-operated, ischemia, and treatment groups after 90 minutes of ischemia and 20 minutes of reperfusion. *Significant difference between ischemia and therapy groups ($P < 0.05$).

Leukocyte–endothelial cell interactions. Within sinusoids, the number of stagnant leukocytes was rather low (2.0 ± 0.4/acini). Ischemia significantly increased the number of stagnant leukocytes in sinusoids (142.9 ± 11.9%; $P < 0.05$). In postsinusoidal venules of sham-operated animals, only few rolling (1.8 ± 0.2 mm/s) and adherent (38.3 ± 8.1/mm^2). leukocytes were registered. In contrast, after 90 minutes of normothermic ischemia, the number of rolling (256.8 ± 18.1%) and firmly adherent (314.2 ± 17.2%) leukocytes was significantly increased.

The drug reduced the number of permanently stagnant leukocytes in sinusoids to 142.3 ± 11.5% of sham-operated animals ($P < 0.05$ versus ischemia). Within the postsinusoidal venules, a significant decrease in rolling (142.2 ± 14.9%) and permanently adherent (156.3 ± 16.3%) leukocytes was detected ($P < 0.05$ versus ischemia).

Sinusoidal perfusion. Sinusoidal perfusion was determined as an index of I/R-induced hepatic microvascular injury. The sinusoidal perfusion rate was 94.2 ± 1.8% in sham-operated animals, in contrast to 74.3 ± 2.1% after 90 minutes of normothermic ischemia followed by 20 minutes of reperfusion ($P < 0.05$). In ET_A-RA–treated animals, postischemic sinusoidal perfusion was ameliorated and showed values of 89.8 ± 1.3% ($P < 0.05$ versus ischemia).

Platelet Counts

Platelet count was determined in whole blood of animals before ischemia and after reperfusion. In sham-operated rats, 88.1 ± 15.3% of platelets (percent of baseline) were found in the systemic circulation at the end of the experiment. In contrast, the number of circulating platelets was markedly lower after 90 minutes of ischemia and 20 minutes of reperfusion (43.2 ± 11.3%). In the treatment group, 62.8 ± 8.2% of platelets were found in the systemic circulation.

Local Hepatic Tissue Po_2

In sham-operated animals, mean hepatic tissue Po_2 remained unchanged throughout the observation period (preoperative, 17.3 ± 2.2 mm Hg; 30 minutes, 18.2 ± 2.4 mm Hg; 60 minutes, 16.8 ± 1.9 mm Hg). In contrast, normothermic ischemia resulted in a decrease in Po_2 to mean values of 1.5 ± 0.5 mm Hg. Reestablishment of hepatic arterial and portal inflow did increase hepatic tissue Po_2 (30 minutes, 5.1 ± 2.4 mm Hg; 60 minutes, 8.0 ± 2.4 mm Hg, $P < 0.05$ versus sham) but failed to restore preischemic values (Fig. 2). ET_A-RA treatment did not change values during ischemia but led to fast restoration of tissue Po_2 to 11.5 ± 2.2 mm Hg after 30 minutes and 13.3 ± 2.4 mm Hg after 60 minutes of reperfusion ($P < 0.05$ versus ischemia).

Laser Doppler Flowmetry

Assessment of hepatic erythrocyte flux by laser Doppler flowmetry confirmed the results obtained from in vivo microscopic analysis. All groups

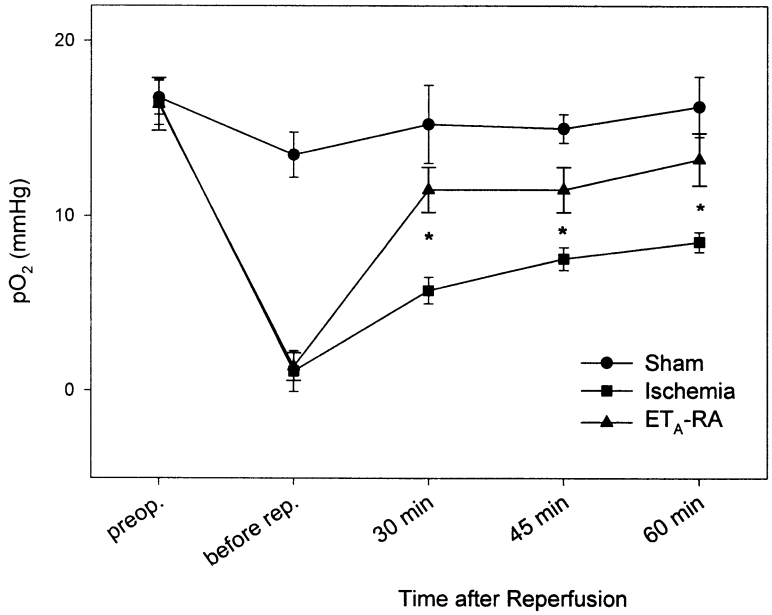

Fig. 2. Partial oxygen tension (P_{O_2}) of the left liver lobe before ischemia, at the end of ischemia, and 30, 45, and 60 minutes after reperfusion in the three investigated groups. Values are given as mean ± SD. *Significant difference between ischemia and therapy groups ($P < 0.05$). P_{O_2} was significantly higher 45 and 60 minutes after reperfusion in the therapy group compared with the ischemia group.

showed basal values of 590 ± 35 AU. In the sham-operated group, throughout the experiment values of 608 ± 36 AU were measured. Thirty minutes of normothermic ischemia resulted in a decrease in erythrocyte flux to 25 ± 6% of basal values. At 15, 45, and 60 minutes after reperfusion, values of 54 ± 10%, 60 ± 11%, and 86% ± 12% of basal values were found.

The ET_A-RA treatment averted the decrease in erythrocyte flux at 15, 45, and 60 minutes after reperfusion. Values of 89 ± 9%, 92 ± 10%, and 96 ± 9% were measured compared with baseline ($P < 0.05$ versus ischemia).

Liver Enzyme Activities

In sham-operated animals, 6 hours after reperfusion, due to operative stress AST (130.8 ± 14.6 U/L) and ALT (78.4 ± 18.1 U/L) values were significantly increased compared with basal levels (AST, 27.1 ± 3.5 U/L; ALT, 28.5 ± 3.6 U/L; $P < 0.05$). In the ischemia group, serum AST (1330.6 ± 157.7 U/L) and ALT (750.7 ± 125.8 U/L) levels increased significantly ($P < 0.05$) 6 hours after reperfusion, reflecting the substantial loss of hepatocellular integrity. In the treatment group, AST (613.7 ± 106.4 U/L; $P < 0.05$ vs. ischemia) and ALT (409.7 ± 124.5 U/L; $P < 0.05$) increase was reduced 6 hours after reperfusion, indicating hepatoprotection by the ET receptor blockade (Fig. 3). On comparison of the ischemia and therapy groups, at 24 hours after reperfusion, significantly lower AST values were measured in the treatment group ($P < 0.05$). On the second postoperative day, AST levels had normalized to baseline levels in all groups. The α-GST levels at 2 hours after reperfusion were elevated in nontreated and treated ischemic rats but did not differ significantly (2866 ± 452 μg/L vs. 2973 ± 337 μg/L). Six hours after reperfusion, α-GST levels in the treatment group were significantly reduced in comparison to the nontreated animals (417 ± 84 μg/L vs. 939 ± 102 μg/L; $P < 0.05$) (Fig. 4). Two days after reperfusion, α-GST levels in the ischemia and treatment groups returned to normal values.

Histology

Before liver manipulation, there was no evidence of relevant morphologic damage in either group. Six hours after reperfusion, histologic injury increased in both groups but was found to be significantly lower in the therapy group ($P < 0.05$). Slight increases in edematous injury (35%), reaction of the capsule of the liver (64%), and Kupffer cells (49%) were discovered in the therapy group. Histomorphologic alterations in the ischemia group included strongly developed interstitial and intracellular edema (57% and 90%, respectively), irregular trabecular disruption, hemorrhage, invasion of inflammatory cells, dilatation of

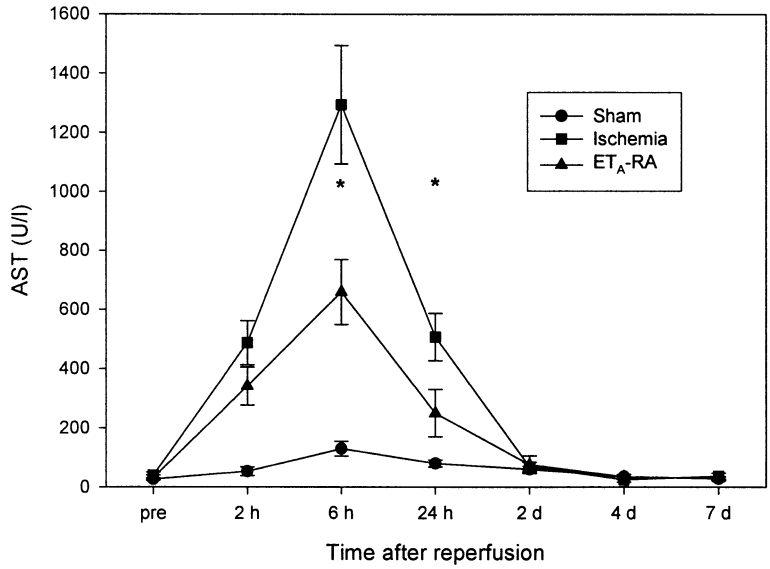

Fig. 3. Serum levels of aspartate aminotransferase before ischemia, at the end of ischemia, and from 2 hours to 7 days after reperfusion. Values are given as mean ± SD. *Significant difference between ischemia and therapy groups ($P < 0.05$). The serum levels were significantly lower 6 hours to 24 hours after reperfusion in the therapy group compared with the ischemia group.

the sinusoidal space, and sinusoidal congestion. Summarized injury in the sham-operated group was 25% versus 13% in therapy group ($P < 0.05$).

During follow-up (2 days postoperatively), an evident decrease in morphologic-pathologic alterations was observed in both groups in all investigated parameters. However, a significant difference in score values was still observed between the two groups (sham group, 15%; therapy group, 8%; $P < 0.05$). After 7 days, no difference in score values could be found between the groups.

DISCUSSION

In the current study, we provide evidence that the selective blockade of ET_A receptors during reperfusion after warm ischemia leads to improved hepatic microvascular blood flow. This beneficial effect was characterized by a significant reduction in the percentage of nonperfused acini and sinusoids, resulting in a more homogeneous tissue perfusion. In addition, decreases in both leukocyte- and platelet-endothelium interactions were observed, indicating improved microvascular perfusion.

After warm hepatic ischemia, various factors may contribute to localized disturbances observed in hepatic microvascular perfusion. As a consequence of an impaired transmembrane ion exchange during hypoxia, edema of hepatocytes and of sinusoidal endothelial cells with consecutive blood flow obstruction occurs and is paralleled by an increased intravascular hematocrit.[24] Additional endothelial cell damage occurs during reperfusion. Activation of Kupffer cells during this phase is followed by a secondary release of inflammatory mediators and oxygen radicals.[25] In addition to the morphologic injury to parenchymal and nonparenchymal cells, functional alterations of presinusoidal and intrasinusoidal blood flow regulation contribute to the disturbances observed after reperfusion.

Vasoconstriction is a factor involved in microcirculatory disturbance when reperfusion injury occurs after organ ischemia, and ET-1 is one of the most potent endothelium-derived constrictor agents.[26] ET-1 deeply influences the pathologic state in hepatic I/R injury by modulating local and systemic hemodynamics.[27–29] After hepatic ischemia, elevated ET plasma levels in the suprahepatic vena cava have been reported, indicating clearly that ET is produced in the liver.[28,30] Cytokines, such as interleukin 1 and tumor necrosis factor (TNF), are reported as potent stimulators of release of ET-1,[31] as well as anoxia and wall shear stress.[27,32] HSCs express ET receptors and show a strong contractile response to mediators such as ET-1, thromboxane A_2, and others.[33] A in vivo study demonstrated contraction of HSCs in normal liver after ET-1 stimulation by using intravital imaging,[34]

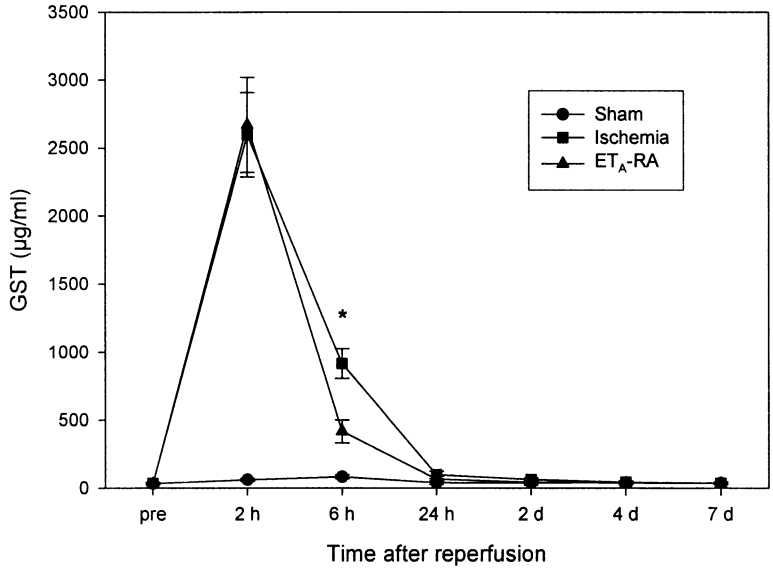

Fig. 4. Serum levels of glutathione *S*-transferase α before ischemia, at the end of ischemia, and from 2 hours to 7 days after reperfusion. Values are given as mean ± SD. *Significant difference between ischemia and therapy groups ($P < 0.05$). The serum levels were significantly lower 6 hours after reperfusion in the therapy group compared with the ischemia group.

suggesting that ET-1 may be involved in the regulation of liver blood flow under various pathophysiologic conditions.

Capillary perfusion failure is thought to be a key factor in the pathogenesis of reperfusion injury.[35] In the present study, we have demonstrated that the reperfusion period after 90 minutes of normothermic ischemia is associated with breakdown of blood flow in many sinusoids. The prophylactic treatment with the ET_A-RA could avoid these microcirculatory disturbances. An impact on leukocyte–endothelial cell interaction, as detected by a reduced number of sticking and rolling leukocytes, was observed in our analysis. The interaction of leukocytes with microvascular endothelium following tissue I/R is considered to precede migration into the tissue.[36] It has been suggested that a variety of specific adhesion molecules that are localized on endothelial and leukocyte membranes are involved in this multistep process. Selectins account for primary attachments (rolling) of leukocytes to the endothelium, whereas intercellular adhesion molecules, such as ICAM-1, and integrins on leukocyte surfaces (CD11/18) result in firm adhesion of leukocytes.[37] It has been shown that ET-1 stimulates several activation mechanisms on neutrophils. In vitro experiments suggest that ET-1 promotes adhesion of human neutrophils to cultured bovine endothelial cells as a result of an increased β_2-integrin expression on neutrophil surfaces.[38] Other investigators have demonstrated an upregulation of ICAM-1 and VCAM-1 (vascular cell adhesion molecule 1) expression in cerebromicrovascular human endothelial cell lines and in the vessels of the bowel induced by endothelins.[39,40] However, the reduction in leukocyte-endothelium interactions could also be a result of secondary effects of improved microhemodynamics.

More recently, there also is substantial evidence that suggests a role for platelets in contributing to I/R injury of various organs. Several studies reported the accumulation of platelets in the liver after cold[10,11] and warm[41] hepatic ischemia. Investigations using electron microscopy in a rat model of ex vivo liver perfusion found a correlation between the duration of cold ischemia and the degree of platelet sequestration in the liver tissue.[11] Likewise, in human livers, platelet accumulation was observed using immunostaining after transplantation.[10] In our in vivo study, the interactions of platelets with the postischemic hepatic microvascular endothelium were visualized and quantitatively analyzed using intravital fluorescence microscopy in sinusoids and postsinusoidal venules. Our data show that warm hepatic I/R induces platelet–endothelial cell interactions in all visible segments of the hepatic microvasculature. Activated platelets are able to release oxygen radicals and proinflammatory mediators such as serotonin, leukotrienes, platelet factor 4, and thromboxane A_2[6–9] and therefore might affect the postischemic sinusoidal perfusion.

After warm I/R, we observed a significant impairment of sinusoidal perfusion. In contrast, simultaneous with attenuated platelet and leukocyte adherence in the hepatic microvasculature, the sinusoidal perfusion rate was higher in animals with ET_A-RA treatment. Our study clearly demonstrates that the reduction in ALT and AST activities in rats after ET_A-RA treatment was associated with ameliorated sinusoidal perfusion, as well as attenuated platelet- and leukocyte–endothelial cell interactions. Although recent studies gave evidence that large numbers of neutrophils stagnant in sinusoids neither cause injury nor affect sinusoidal perfusion,[42,43] we were not able to clarify to what extent platelet accumulation in sinusoids might influence tissue damage. The mechanisms of sinusoidal platelet accumulation remain unclear and need further investigation. One could speculate that in addition to platelet stagnation in nonperfused sinusoids, interaction of platelets with endothelial ICAM-1 under low-flow conditions or capture of platelets by Kupffer cells may contribute to postischemic platelet accumulation in sinusoids. The reduction in platelet-endothelium interactions in the therapy group may be caused by a blockade of endothelin-induced platelet adherence or an activation of ET_B receptor subtype, which is responsible for the release of NO and, therefore, vasoprotection.[44,45]

Postischemic microcirculatory disturbances, that is, perfusion failure and microvascular accumulation of leukocytes, are thought to alter hepatic tissue oxygenation during postischemic reperfusion. Hepatic tissue P_{O_2} values were decreased to 1.5 mm Hg during ischemic periods and showed a slow recovery in the ischemic group. Treatment with the ET_A-RA inhibitor evoked a microcirculatory improvement measured by an increase in tissue oxygenation. It is known that oxygen supply in the early reperfusion period is the crucial factor for subsequent organ function.[46] In our model, we therefore were able to use measurement of local tissue P_{O_2} as a predictor of the effect of the therapy. The hepatic tissue damage that follows I/R is related to the following mechanisms: hypoxic damage during ischemia, injury to sinusoidal endothelial cells and hepatocytes after reperfusion, and microcirculatory disturbances secondary to endothelial cell damage. In this study, a sharp decline in hepatic tissue P_{O_2} was followed by a marked increase in serum AST and ALT levels at 6 hours after reperfusion. AST and ALT are commonly used as parameters of hepatocellular injury, but α-GST is a relatively new plasma marker that has not been frequently used. It has been reported that α-GST is a sensitive parameter for assessment of hepatocellular injury because of its distribution (80% of all α-GST is present in hepatocytes), high cytosolic concentration (5%), and shorter half-life (60 minutes). The present study confirms the sensitivity of α-GST, especially regarding reduced levels after therapy.[47,48] These data collectively suggest that ET can cause damage to the hepatic tissue due to hypoxia through alteration of the microcirculation. Increased ET levels in the ischemic group are associated with subsequent hepatocellular damage. Treatment with the ET_A-RA effectively reduced the ET-induced sinusoidal constriction; this was followed by an improved oxygen supply and reduced hepatocellular damage.

The laser flowmeter detected a significant improvement of hepatic tissue blood flow in the treatment group after the start of reperfusion. Kurihara et al.[49] reported that ET-1 produced only a mild decrease in hepatic microvascular flow as assessed by laser Doppler flowmetry. In contrast, we found a profound reduction in blood flow through the liver in the postischemic period and suggest that ET is largely responsible for this phenomenon. This thesis is supported by the improvement of erythrocyte flux in the therapy group.

CONCLUSION

We have clearly demonstrated that an ET_A-RA improves hepatic microcirculatory impairment and hepatic tissue oxygenation after warm hepatic I/R injury. The basic mechanism involved may be avoidance of sinusoidal constriction and a reduction in leukocyte- and platelet-endothelium interactions. For the first time, an influence of the ET system on the interactions between platelets and endothelial cells was described.

The blocking of ET_A receptors during reperfusion hence offers a successful means of hepatoprotection by the maintenance of microvascular integrity in the postischemic liver.

We thank Knoll (Ludwigshafen, Germany) for supplying BSF 208075.

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Hepatic Arterial Infusion After Curative Resection of Colorectal Cancer Metastases: A Meta-Analysis of Prospective Clinical Trials

Thomas E. Clancy, M.D., Elijah Dixon, M.D., Roy Perlis, M.D., Francis R. Sutherland, M.D., Michael J. Zinner, M.D.

The use of hepatic arterial infusion (HAI) for the delivery of chemotherapeutic agents to treat residual microscopic disease after curative hepatic resection for colorectal cancer metastases remains controversial. In recent years, a number of studies examining adjuvant HAI have shown conflicting results. A meta-analysis of prospective clinical trials was performed to determine if adjuvant HAI confers a survival benefit in this setting. Two reviewers independently performed a literature search of MEDLINE, PubMed, EMBASE, the Cochrane library, and the Cochrane Clinical Trials Registry. Prospective clinical trials comparing hepatic arterial chemotherapy after curative hepatic resection for colorectal cancer metastases against a control arm were included. Non–English-language publications were excluded. The outcome measure was survival difference at 1 and 2 years after surgery. Seven studies met the inclusion criteria, and all except one were randomized trials. The survival difference in months (positive values favoring the treatment arm) was 1.8 at 1 year (95% confidence interval, −4.9, 8.5) and 9.6 at 2 years (95% confidence interval, −2.2, 21.4). Neither was statistically significant (at 2 years, $P = 0.11$). Based on these findings, routine adjuvant HAI after curative resection for colorectal cancer of the liver cannot be recommended. However, given the trend toward a survival benefit at 2 years, further study is recommended. (J GASTROINTEST SURG 2005;9:198–206)

KEY WORDS: Hepatic artery chemotherapy, colorectal cancer, colorectal metastases, surgery

Of the more than 130,000 patients diagnosed annually with colorectal cancer in the United States,[1] liver metastases will ultimately be a primary determinant of survival in approximately 60%.[2] The median survival of patients with colorectal liver metastases is 12–24 months,[3] with few untreated patients surviving longer than 2 years. Therapeutic options for these patients are limited, and systemic chemotherapy has traditionally shown response rates of only 25–40%.[4–6] Newer regimens suggest response rates up to 50%, with slight but definite improvement in overall survival.[7]

Since the 1980s, the benefit of surgical resection of hepatic metastases has been well established in the literature.[8] An estimated 20% of patients with colorectal metastases to the liver have disease amenable to complete (R0) resection.[9] In fact, the ability to fully resect colorectal metastases limited to the liver is associated with a 5-year disease-free survival of 20–50% and an overall 5-year survival of 25–40%.[10–12] Unfortunately, recurrent disease develops in more than 60% of patients after presumed curative resection, with more than 50% of recurrences occurring in the liver.[13,14] Other authors have reported hepatic recurrence in more than 75% of patients after resection of liver metastases.[15] Given poor response rates to systemic chemotherapy, therapy of locoregional and systemic recurrence after R0 resection is limited if not amenable to further surgical extirpation.

The delivery of chemotherapeutic agents directly into the hepatic arterial system is based on the principle that liver metastases derive the majority of their

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.004

blood supply from the hepatic arterial rather than portal venous system.[16] Drug delivery via the hepatic artery might therefore allow higher doses to be delivered to a metastatic tumor, while minimizing systemic side effects. Early reports of hepatic arterial infusion (HAI) emerged in 1964,[17] with the description of an implantable hepatic artery pump in 1972[18] and the description of continuous infusion of medication via an implantable hepatic artery pump in 1980.[19] Early series[20] and multiple randomized controlled trials[21–29] have examined the use of HAI for chemotherapy for colorectal liver metastases. Reported response rates range from 40% to 60% with HAI. Impressive response rates, however, did not consistently extrapolate to improved survival, as patients often died from extrahepatic disease. A meta-analysis of the literature suggested only a mild survival benefit to HAI versus systemic chemotherapy in the setting of nonresectable colorectal metastases.[22]

Locoregional therapy with HAI of chemotherapy has been attempted in combination with resection of colorectal metastases to the liver for the purpose of treating micrometastases in the remaining liver, limiting hepatic recurrence, and preventing extrahepatic spread. Early reports[30] suggested a significant prolongation of median survival and a delay in hepatic recurrence with the use of postresection hepatic arterial 5-fluorouracil (5-FU). Based on the promising results of these nonrandomized studies, a number of investigators have undertaken prospective randomized studies to determine whether adjuvant hepatic arterial chemotherapy confers any benefit in the postresection setting.[24,31–36] Using varying chemotherapeutic schedules and somewhat different methodologies, these studies have shown discrepant results. Although some suggest an improvement in overall or disease-free survival with postresection HAI, others have shown no such benefit.

The lack of agreement in these studies, as well as the recognized toxicity and complications from HAI chemotherapy,[37] has prevented the universal adoption of this potentially beneficial technique. For this reason, this meta-analysis was undertaken to test the hypothesis that HAI of chemotherapy confers a survival advantage after hepatic resection of colorectal metastases.

METHODS

Inclusion and Exclusion Criteria

The QUOROM criteria,[38] which are published guidelines for reporting meta-analyses of randomized trials, were used in this analysis. Primary studies that prospectively compared HAI chemotherapy with some form of control arm for metastatic colorectal cancer that had been completely resected for cure (R0 resection) were considered for inclusion. Trials without a control arm were excluded. Only studies that presented survival information either numerically or in the form of a survival curve at 1 and 2 years were included. Any form of control arm was allowable provided it did not include HAI therapy. Only papers published in peer-reviewed journals and in the English language were included.

Identification of Trials and Search Strategies

We performed all searches in duplicate; final inclusion of articles was determined by consensus, and when this failed, the third author adjudicated. We searched multiple databases and resources including MEDLINE (PubMed), EMBASE, Cochrane Library, and the Cochrane Clinical Trials Registry; we exploded the search using the *related articles* term in PubMed. In addition, we contacted experts in the field and reviewed bibliographies to attempt to identify additional studies. Figure 1 outlines the results of our search strategy. We used the *limits* function in PubMed to limit our searches to English-language articles that were from randomized clinical trials or clinical trials. No year of publication limit was used.

Initially, 121 articles were identified; of these, 93 were excluded for a number of reasons (other topics, non–English language, retrospective in nature, no control arm, review, or meta-analysis). Of the remaining 28 articles, 21 were excluded (12 involved palliative therapy, 6 dealt with hepatocellular carcinoma, 2 were review articles, and 1 was not available). In total, seven articles were identified for inclusion.[24,32–36] Of these, six are prospective randomized trials, and one nonrandomized prospective clinical trial[34] was identified.

Data Extraction

All data extraction was performed in duplicate. Randomized controlled trial studies were scored for quality to assess validity using the Jadad scoring system,[39] which evaluates studies based on appropriate randomization, proper blinding, and an adequate description of withdrawals and dropouts. A standardized evidence table was used, and data were double entered. One- and 2-year survival percentages after randomization were extracted directly from the text where available or by extrapolation from the Kaplan-Meier curve; this methodology has been previously described.[22] In addition to study quality and survival information, information regarding

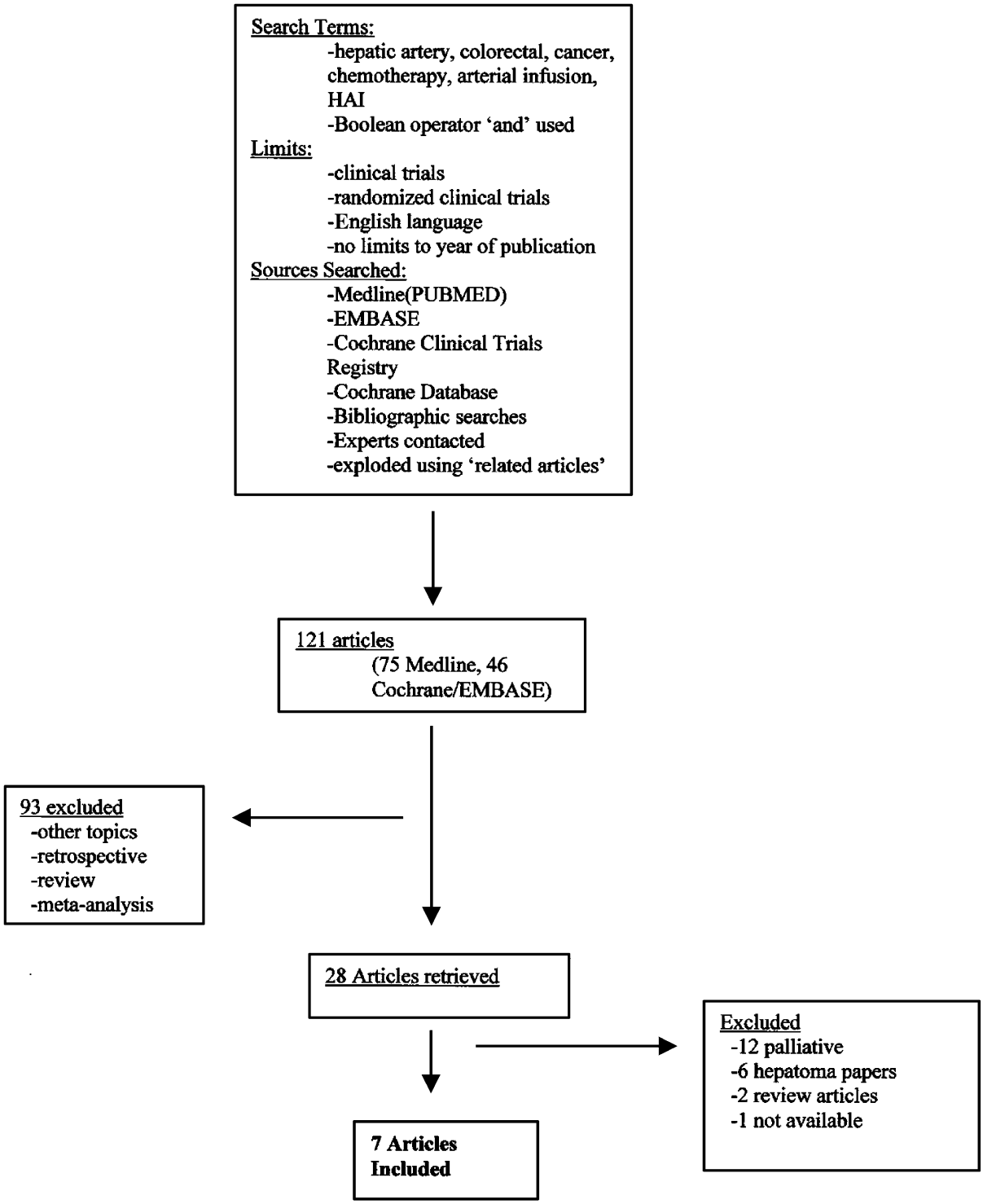

Fig. 1. Search strategy.

number of patients treated, agents and routes used, median survival, median disease-free survival, complication rates, and response rates were all extracted if presented. Standard deviation values of the difference in survival between the treatment and control arms were then derived from the calculated variance. An examination of crossover and intention-to-treat analysis was also performed.

Data Analysis

Given the small number of prospective trials on this topic, we did not distinguish between single-institution and multi-institution trials in our analysis. Surgical technique is not universally described and is assumed to be fairly uniform. Adjuvant protocols were different among the studies, and given this variation, a conservative meta-analytic approach was used. Examination of the pooled results was performed using the random-effects model for meta-analysis, which incorporates both within-study and between-study variance.[40–42] Finally, we performed a sensitivity analysis (a priori decision) as a means of assessing heterogeneity between studies; in sensitivity analysis, each study is sequentially removed from the analysis to determine its contribution to the overall effect size.

RESULTS

Details of study subjects and design are presented in Table 1. The studies varied widely in size, with a minimum of 19 subjects[36] and a maximum of 226.[24] Mean or median age, where reported, appeared to be consistent across studies, at or around 60 years.[24,31–36]

All of the included studies were prospective, non-blinded investigations of HAI chemotherapy versus some form of control. All except one[34] were randomized, and of similar quality (Jadad scores of 3 for all but Rudroff et al.[35] and Kusunoki et al.[34]). The studies differed somewhat in a number of details regarding treatment groups. Although all used some form of HAI 5-FU or 5-FU deoxyribonucleoside (FUDR [floxuridine]) with or without dexamethasone, two studies[34,36] also used adjunctive oral treatment. Duration of HAI treatment varied from 11 months[34] to 6 years.[32] Moreover, control groups also differed: two studies included no-treatment arms,[24,35] two included orally administered tegafur/uracil (UFT) or 5-FU,[34,36] and two included intravenous systemic chemotherapy.[32,33]

Survival rates at 1 and 2 years are presented in Table 2. One-year survival in the HAI group ranged from a minimum of 75%[35] to 100%.[34] Survival in the control group ranged from a minimum of 55%[35] to a maximum of 100%.[36] By 2 years, survival among HAI-treated patients ranged from 30%[35] to 90%,[34] and among control patients, from 50%[36] to 75%.[32]

Figure 2 displays the meta-analytic findings of survival difference between HAI and control groups using the seven prospective trials at 1 year, for the random-effects model. Figure 3 demonstrates survival differences and summary measures across the seven trials at 2 years for the random-effects model. Across the trials, overall survival difference for the HAI group compared with controls using a random-effects model was 1.8 months at 1 year postsurgery (95% confidence interval [CI], −4.8, 8.5; $P = 0.59$) and 9.6 months at 2 years postsurgery (95% CI −2.2, 21.4; $P = 0.11$).

Sensitivity analysis was to determine the contribution of each individual study to the overall effect size. No single study appeared to markedly influence the observed survival difference (data not shown). Removal of the ECOG study[31] and the study by Lorenz et al.[24] from analysis appeared to increase the overall effect size, although the survival difference at 1 and 2 years still did not appear to be statistically significant. These two trials both demonstrated[24,31] a negative impact on survival in the HAI-treated group at 2 years and were two of three[24,31,36] studies that reported a negative impact on survival for HAI at 1 year.

DISCUSSION

Surgical resection of colorectal metastases to the liver is a widely accepted practice, yielding 5-year survival rates of 20–50%.[10–12] However, the majority of these patients will ultimately die from recurrent disease, much of which occurs in the liver.[13] The use of HAI to exploit the preferential perfusion of metastases by the hepatic arterial system is a potentially promising strategy to control intrahepatic recurrence. The benefit of HAI chemotherapy after resection of colorectal liver metastases has not been universally demonstrated in the literature.

Meta-analytic techniques aim to synthesize results of related but independent studies for the purpose of increasing statistical power to detect treatment effects.[43] Several of the individual trials in this analysis suggested a survival benefit associated with the use of HAI chemotherapy after metastasectomy. Given that the reported survival benefits were small (10–25%), the individual trials examined in this analysis were underpowered to detect such a difference. For instance, to detect a 10% difference in survival with a type I error of 5% and power of only 80%, a trial would require 360 patients. No individual trial met this standard. Our analysis has demonstrated a small, but not significant, improvement in survival at 2 years for HAI chemotherapy after resection of colorectal liver metastases.

Review of the trials in this analysis shows some differences in adjuvant protocols used. One of the most promising individual trials in the literature was conducted by investigators at Memorial Sloan-Kettering Cancer Center,[33] who randomized 156 patients after resection of hepatic metastases to six cycles of

Table 1. Study characteristics

Reference	Year	n	N-HAI	Age (yr)	Jadad score	Outcome	HAI agent	HAI duration	Systemic agent	Systemic duration	Route
Kusunoki et al.[34]	2000	58	30	25–75	1	Survival 5 yr	5-FU pump/oral UFT	11 wk	Oral UFT	25 wk	Oral
Tono et al.[36]	2000	19	9	60	3	Survival 5 yr	5-FU pump/oral 5-FU	24 wk	Oral 5-FU	24 wk	Oral
Kemeny et al.[33]	1999	156	74	59 (28–79)	3	Overall survival	5-FU leucovorin-floxuridine/dexamethasone	12 wk (6 cycles)	5-FU/leucovorin	6 cycles (24 wk)	Oral
Lorenz et al.[24]	1998	226	113	61 (30–76)	3	Survival	5-FU/folinic acid	24 wk (6 cycles)	None	NA	NA
Kemeny et al.[31]	2002	75	30	60 (28–78)	3	Time to recurrence, hepatic disease-free survival	Floxuridine + oral 5-FU	4 cycles/8 cycles	None	NA	NA
Lygidakis et al.[32]	2001	122	62	61 (25–80)	3	Survival 5 yr	Mitomycin C/5-FU/folinate acid both IV/IA/IL-2 given IA	6 yr	Same IV except IL-2 given SC	6 yr	IV, SC
Rudroff et al.[35]	1999	30	14	58 (39–79)	2	Survival 5 yr	Mitomycin C/5-FU	16 wk (4 cycles)	None	NA	NA

5-FU = 5-fluorouracil; UFT = uracil-tegafur; IV = intravenously; SC = subcutaneously; IA = intra-arterially; IL = interleukin.

HAI with FUDR and dexamethasone plus intravenous fluorouracil versus 6 weeks of systemic therapy alone. Systemic therapy was used for all patients; patients were given systemic chemotherapy (5-FU and leucovorin) or systemic therapy plus HAI of FUDR and dexamethasone. These investigators demonstrated a small but significant improvement in 2-year survival (86% versus 72%, respectively) with the addition of locoregional therapy.

In one of the first published prospective trials investigating postresectional HAI, Lorenz and others[24] randomized 226 patients after complete resection of liver metastases to either HAI or resection only. No systemic chemotherapy was administered to either arm based on a belief from early studies demonstrating lack of efficacy of adjuvant chemotherapy in this setting.[44–46] Patient accrual was terminated when scheduled interim survival analysis was found to be possibly worse after HAI. The authors note a slightly higher rate of technical complications in pump placement and considerable toxicity (grade 3 and 4 toxicity) in 63% of treated patients. It is possible that this degree of treatment-related complications accounts for the lack of demonstrated survival benefit with HAI. Such morbidity may be more likely in a multicenter trial such as this one, where expertise is not as centralized as in the Memorial Sloan-Kettering Cancer Center[33] study.

A unique combination of systemic and locoregional chemotherapy was used by investigators in the Eastern Co-operative Oncology Group study.[31] Patients with one to three resectable colorectal metastases were randomized to surgery alone versus surgery followed by HAI FUDR and continuous-infusion 5-FU. A nonsignificant trend toward increased overall survival was observed for the chemotherapy arm, although intention-to treat analysis revealed poorer survival at 1 and 2 years with locoregional and systemic chemotherapy. The patients in this study were randomized preoperatively based on a prediction of resectability. Examination of patients in each arm suggests that censored patients in the treatment arm may have had a greater burden of disease, which could be reflected in decreased survival in an intention-to-treat analysis.

Smaller randomized studies have shown a similar range of results. Lygidakis and others[32] investigated the use of interleukin-2 plus standard chemotherapeutic medications via HAI versus systemic therapy alone in 122 postresection patients. Overall survival was significantly improved at 2 years with HAI (69% versus 47%). Two small studies from Japan demonstrated significant improvement in disease-free survival with HAI compared with systemic therapy

Table 2. One- and 2-year survival

		1 year				2 year			
Reference	Year	HAI survival	Control survival	Survival difference (mo)	95% CI	HAI survival	Control survival	Survival difference (mo)	95% CI
Kusunoki et al.[34]	2000	100	85	15	1–29	90	65	25	3–47
Tono et al.[36]	2000	88.9	100	−11.1	−31–9	77.8	50	27.8	−14–70
Kemeny et al.[33]	1999	95	91	4	−4–12	86	72	14	0–28
Lorenz et al.[24]	1998	85	91	−6	−17–7	58	71	−13	−21–3
Kemeny et al.[31]	2002	80	90	−10	−26–6	60	72	−12	−34–10
Lygidakis et al.[32]	2001	95	90	5	−5–15	92	75	17	3–31
Rudroff et al.[35]	1999	75	55	20	−14–54	30	55	25	−9–59

HAI = hepatic arterial infusion; CI = confidence interval.

alone.[34,36] These studies demonstrated either a significant improvement[34] or nonsignificant trend to improvement[36] in overall survival. Still, other small randomized studies have shown no significant difference in disease-free or overall survival with the use of HAI.[35]

In any meta-analysis or research synthesis, heterogeneity in the design of individual studies is an important consideration when attempting to form meaningful comparisons. As noted earlier, the primary source of heterogeneity in the studies examined lies in the use of adjuvant systemic therapy and varied systemic and HAI chemotherapy protocols. Ideally, regression techniques could be used to examine the effect of these differences on outcome. Unfortunately, the small number of trials available for this analysis precludes formal meta-regression.

Sensitivity analysis for 1-year survival did not demonstrate any single study that, when removed from analysis, would lead to a statistically significant effect size. Removal of the study by Lorenz et al.[24] changes our results slightly but not to statistical significance.

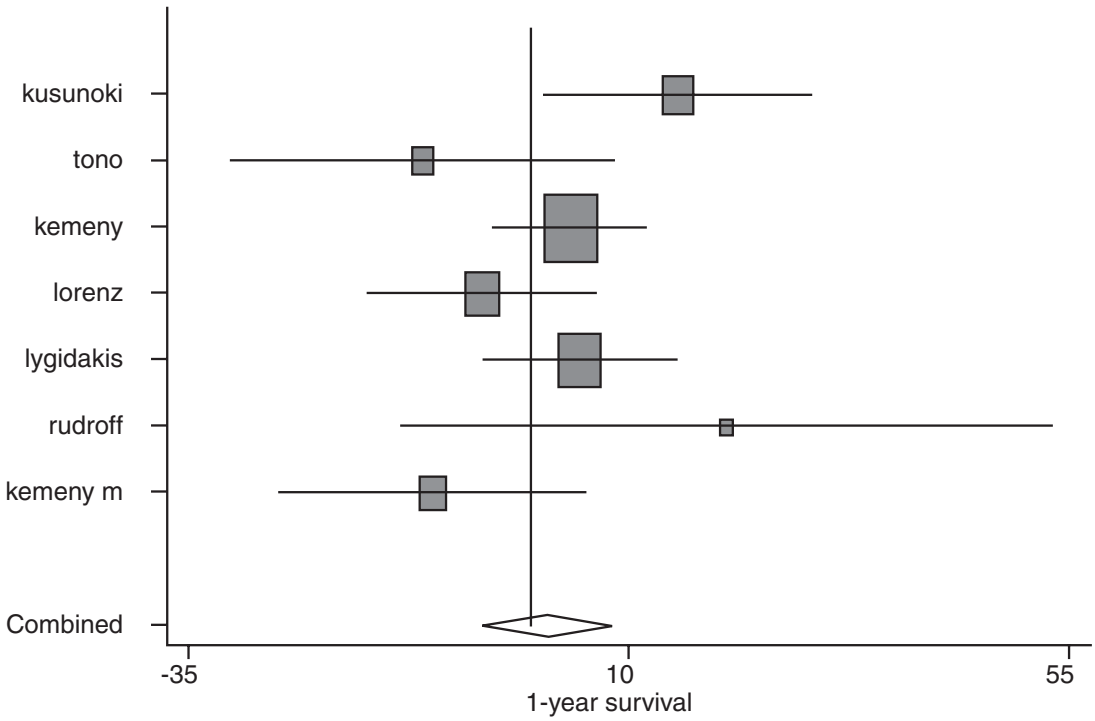

Fig. 2. Survival differences by treatment at 1 year (random-effects model). Time is in months. Central line represents 0 months (no difference in survival between treatments). Positive numbers represent improved survival with hepatic arterial infusion treatment. Mean survival difference for each study is presented, with 95% confidence intervals. The central box for each study represents relative study size. Combined effect is demonstrated at the bottom, with width indicating 95% confidence intervals.

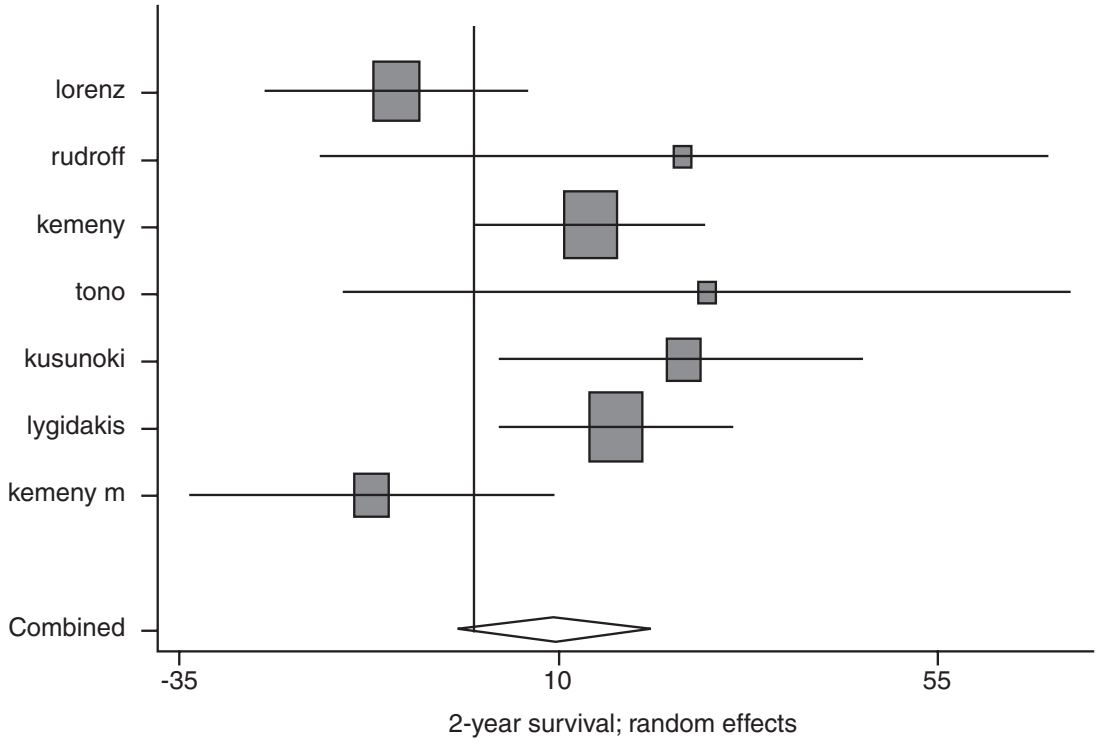

Fig. 3. Survival difference by treatment at 2 years (random-effects model). Time is in months. Central line represents 0 months (no difference in survival between treatments). Positive numbers represent improved survival with hepatic arterial infusion treatment. Mean survival difference for each study is presented, with 95% confidence intervals. The central box for each study represents relative study size. Combined effect is demonstrated at the bottom, with width indicating 95% confidence intervals.

The differences in systemic and regional chemotherapy used in this study or the higher-than expected complications and toxicity seen may account for the apparent decrease in survival with use of HAI. In addition, the study by Kusonoki et al.[34] was not randomized but was prospective. Inclusion or exclusion of these data did not significantly change our results in sensitivity analysis. Examination of sensitivity analysis at 2 years also suggests that the studies by Kemeny et al.[31] and Lorenz et al.[24] contribute most to an absence of observed difference. Although Lorenz et al.[24] may have greater-than-expected treatment-related morbidity from pump placement, Kemeny et al.[31] used systemic chemotherapy in the HAI group but not the comparison group. Still, it is unclear why the absence of systemic chemotherapy in controls would lead to decreased observed survival benefit with HAI. If systemic chemotherapy were to act in some way as an effect modifier of HAI therapy, the observed results might be expected; however, a plausible biologic mechanism for such an effect is not obvious.

The placement of an HAI device and subsequent HAI chemotherapy can be associated with serious complications. Kemeny and others[21] have reported hepatobiliary toxicity, including sclerosing cholangitis, in 6–25% of patients. Others[25,28,29,37] have documented biliary sclerosis in 20–40% of patients. The study by Kemeny et al.[21] used dexamethasone with the HAI regimen, and steroids may decrease hepatobiliary morbidity with HAI therapy. It is therefore possible that the observed treatment effect in this study is due in part to reduced morbidity from pump placement and use. Whether morbidity from HAI catheters contributes to decreased treatment effect in other studies is speculative; the primary data from each individual study are not available that would be required to comment on the outcome of HAI therapy independent of HAI pump complications.

Our analysis was limited to overall survival due to heterogeneity in how disease-free survival is measured and reported. We limited our analysis to overall survival at 1 and 2 years due to possible censoring of patients in the individual studies. For instance, Kemeny and others[33] reported approximately 91% follow-up at 2 years but only 55% follow-up at 5 years. Extrapolation of survival data in the setting of

significant censoring would provide an inappropriately low estimation of sample variance and deceptively narrow estimated confidence intervals. Hence, it is unlikely that meta-analysis of survival at 3 years or longer would provide a statistically meaningful result.

Overall survival at 1 and 2 years in our meta-analysis demonstrates confidence intervals that clearly include zero. It is therefore necessary to conclude that HAI after R0 liver resection of colorectal cancer metastases confers no survival benefit at 1 or 2 years. Of note, the mean survival after R0 resection of hepatic colorectal cancer metastases in these studies is generally longer than 3 years in both treatment arms. Given a trend toward increased survival with the use of HAI therapy, it is therefore possible that a significant treatment difference would be observed with longer follow-up.

Although 1- and 2-year overall survival appears to show an encouraging trend to improved survival with the use of HAI in this meta-analysis, survival differences do not reach statistical significance. Longer-term follow-up is warranted to determine whether a true survival benefit exists for overall survival. Our analysis does not examine or comment on hepatic disease-free survival, which may be significantly improved with HAI. Routine use of HAI after resection of colorectal metastases to the liver cannot be recommended based on this meta-analysis, but a trend toward improved survival suggests there is an important role for a properly powered clinical trial to further examine this topic.

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Osteoclast-Like Giant Cell Tumor of the Liver: A Rare Neoplasm With an Aggressive Clinical Course

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Osteoclast-like giant cell tumors (OCGTs) usually involve the bone and rarely affect the alimentary tract. Within the gastrointestinal tract the liver has been one of the most infrequently reported locations for this neoplasm to occur. In this article we report the occurrence of an OCGT arising in the liver of a 61-year-old woman. The patient presented with abdominal pain and a rapidly enlarging hepatic mass. Magnetic resonance imaging (MRI) indicated a multilocular solid lesion in the right lobe of the liver. A small extrahepatic lobulation at the lateral aspect of the lesion with penetration of the capsule was visible. Local extension into adjacent organs was not evident. Positron emission tomography (PET) did not indicate a tumor in the pancreas or elsewhere in the body. The tumor was removed by performing a formal right hepatic lobectomy. Histologic and immunohistochemical examinations revealed an OCGT. Within 3 months of the hemihepatectomy, widespread intraabdominal and pulmonary metastasis developed and the patient succumbed to her illness shortly thereafter. This report contributes further evidence to the aggressive biological behavior with regard to this rare neoplasm. The absence of metastatic disease indicated when using magnetic resonance imaging and positron emission tomography does not seem to change the overall dismal prognosis of this tumor. (J GASTROINTEST SURG 2005;9:207–214)

KEY WORDS: Liver tumor, osteoclast-like giant cell tumor, positron emission tomography

Osteoclast-like giant cell tumors (OCGTs)—histologically similar to giant cell tumors of bone—have been described in several extraskeletal sites.[1] In the alimentary tract, the pancreas seems to exhibit the highest predilection for this pathological lesion. After the description by Alguacil-Garcia and Weiland,[2] OCGTs of the pancreas have been recognized as a distinct clinicopathologic entity different from ductal adenocarcinoma. In general, OCGTs involving the gastrointestinal tract exhibit aggressive proliferation.[3,4] Nodal metastasis, the predominant mode of spread, is apparent in the majority of patients and the clinical course is usually dismal even after resection. Although approximately 32 occurrences of OCGTs arising in the pancreas have been reported,[4] there are only 4 instances described that study OCGTs of the liver.[5–8] We herein report the complete resection of an OCGT of the liver using positron emission tomography (PET) as one of the preoperative imaging modalities necessary to rule out metastatic disease. We discuss possible reasons for the early recurrence of the tumor with reference to the value of emerging preoperative imaging strategies and elicit particular attention to the clinical behavior regarding this rare neoplasm.

MATERIAL AND METHODS

A 61-year-old woman was admitted because of right upper quadrant pain that had persisted for 6 months. An ultrasound of the abdomen performed 4 months before admission demonstrated fatty infiltration of the liver and common bile duct (CBD) dilation to 1.3 cm. No liver lesions were noted at that point and her bilirubin level was within the normal range. The patient had undergone a laparoscopic cholecystectomy 5 years ago. Her past medical history was remarkable for coronary artery disease and hypertension. She had no history of hepatitis and denied alcohol and tobacco consumption or any family history attributable to liver disease. She exhibited no jaundice, anorexia, or weight loss. Endoscopic retrograde cholangiopancreatography (ERCP) performed 2

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.007

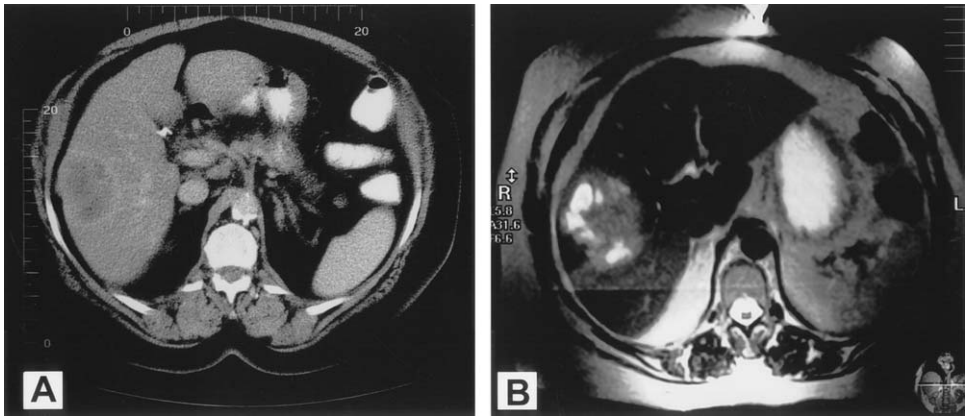

Fig. 1. Preoperative imaging observations. Abdominal computed tomography (CT) (**A**) reveals a heterogeneous solid mass in the right lobe of the liver. T1-weighted magnetic resonance imaging (MRI) (**B**) indicates multiple regions of fluid-like signals within the lesion representing cystic components or necrosis. There is dilatation of the common bile duct (CBD) to 1.8 cm.

months before admission confirmed CBD dilatation. The pancreatic duct system was normal. An endoscopic papillotomy performed during the examination failed to improve her symptoms. Contrast-enhanced computed tomography (CT) of the abdomen performed thereafter revealed a 6 cm right hepatic lobe heterogeneous solid mass (Fig. 1, *A*). The patient was subsequently referred to our institution for further evaluation.

Physical examination revealed a well-developed obese female with normal vital signs. Sclera were anicteric. Her abdomen was soft and nontender. There was no hepatomegaly, signs of chronic liver disease, or evidence of ascites.

Serum chemistries were within the normal range except for an alkaline phosphatase level of 170 IU/L. Serum alpha-fetoprotein, carcinoembryogenic antigen (CEA), and cancer antigen (CA) 19-9 were normal. Serology for hepatitis A, B, and C were negative.

Magnetic resonance imaging (MRI) of the abdomen confirmed an 8 × 8 × 10 cm mass within the right lobe of the liver involving segments V, VI, and VII (Fig. 1, *B*). The lesion was fairly well circumscribed with multiple regions of fluid-like signals on T1-weighted images suggestive of cystic components or necrosis. A small 2 × 2 cm extrahepatic component arising from segment VII without invasion of the abdominal wall was observed (Fig. 2, *A* and *B*). No other hepatic or pancreatic lesions were identified. Magnetic resonance cholangiopancreaticography (MRCP) confirmed the presence of CBD dilatation, but did not demonstrate any abnormality of the pancreatic duct system (Fig. 3, *A*). Whole body PET scanning using fluorine-18 fluorodeoxyglucose revealed increased uptake in the right lobe of the liver without any metabolically active lesion elsewhere (Fig. 3, *B*). A formal right hepatic lobectomy with en-bloc resection of the tumor, including 15 cm of

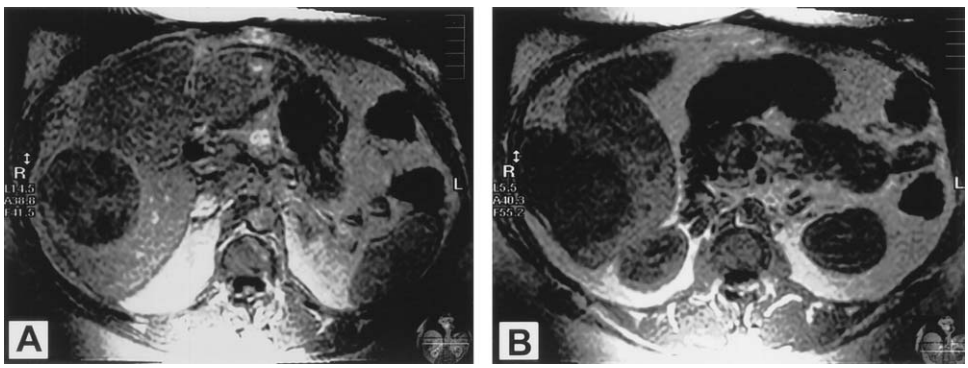

Fig. 2. T2-weighted magnetic resonance images (MRI) of the tumor. There is a 3 cm extrahepatic component (**A**) arising from the inferio-lateral margin of segment VII. The well-circumscript mass measuring 8×8×10 cm in diameter transgresses the hepatic capsule (**B**), but lacks invasion of the abdominal wall.

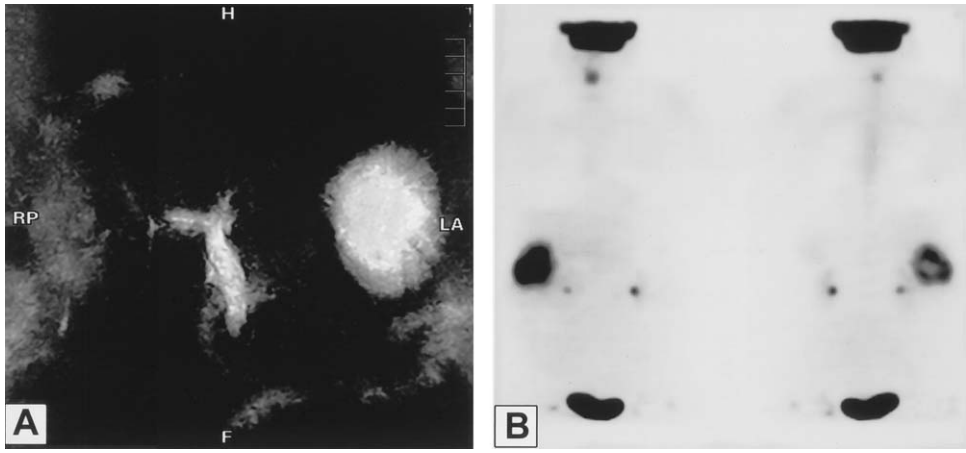

Fig. 3. Preoperative magnetic resonance cholangiopancreaticography (MRCP) and positron emission tomography (PET) scan observations. MRCP (**A**) demonstrates common bile duct (CBD) dilatation with normal pancreatic duct system. Whole body 18-fluorodeoxyglucose PET scanning (**B**) indicates a large metabolically active lesion in the lateral aspect of the right lobe of the liver without metabolic activity in the pancreas or elsewhere in the body (anterior and posterior view).

omentum adherent to the extrahepatic component, was performed. Macroscopic examination of the resected specimen revealed a white to brown irregular-shaped mass measuring 7 × 7 × 10 cm with multiple areas of necrosis and hemorrhage (Fig. 4). Microscopically, the tumor was composed of three cell types. Osteoclast-like giant cells (OCGCs), indistinguishable from osteoclasts of bone, were diffusely distributed throughout the tumor (Fig. 5, *A*). OCGCs displayed uniformly bland cytologic features. Their cytoplasm contained remnants of phagocytosed neutrophils and mononuclear tumor cells (Fig. 5, *B*). Pleomorphic large cells (PLC) were seen less frequently than OCGCs. These cells exhibited irregular pleomorphic and bizarre nuclei and they frequently demonstrated atypical mitosis. The third and largest component was the infiltrating mononuclear cell (MNC). Most of these cells were spindle-shaped and contained a single nucleus with varying degrees of cytological atypia. Immunohistochemically, OCGCs and infiltrating MNCs displayed divergent differentiation (Table 1). OCGCs were uniformly and strongly immunoreactive with the histiocyte–monocyte marker, cluster differentiation 68, (CD68) and the mesenchymal marker, vimentin (Fig. 5, *C* and *D*). They also exhibit weak staining with alpha-1-antitrypsin and alpha-1-chymotrypsin, but were negative for all other epithelial markers (Table 1). The infiltrating MNCs stained positive with alpha-1-antitrypsin and alpha-1-chymotrypsin (Fig. 5, *E* and *F*). The histopathological diagnosis indicated OCGT of the liver.

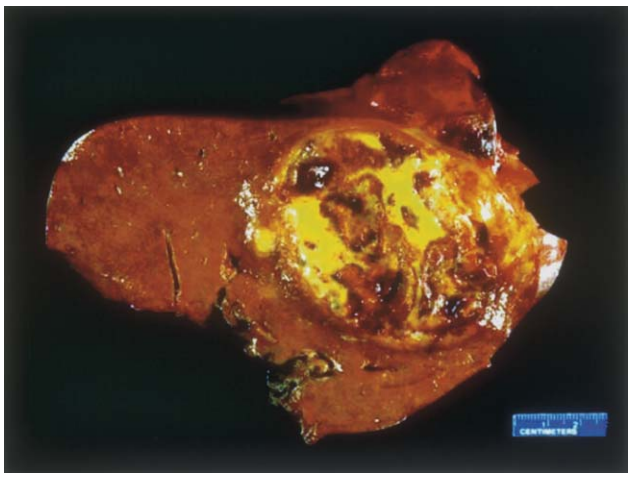

Fig. 4. Gross appearance of osteoclast-like giant cell tumors (OCGT) of the liver. The cut surface is solid, partly necrotic, and cystic with areas of hemorrhagic necrosis and fluid-filled locules.

All surgical margins including the resected omentum were free of tumor. Pericholedochal lymph nodes and peritoneal and mesenteric biopsies were negative for tumor. Her immediate postoperative convalescence was uneventful. The patient returned to the emergency department 3 months after the operation with fatigue and exertional dyspnea. Recurrence of the tumor was diagnosed using an abdominal CT that indicated widespread intraabdominal metastasis. A chest CT demonstrated pulmonary and mediastinal disease and the patient expired because of respiratory failure shortly thereafter.

DISCUSSION

In 1980, Munoz and associates[5] described an occurrence of OCGT of the liver, and since that time only 3 additional patients exhibiting this enigmatic

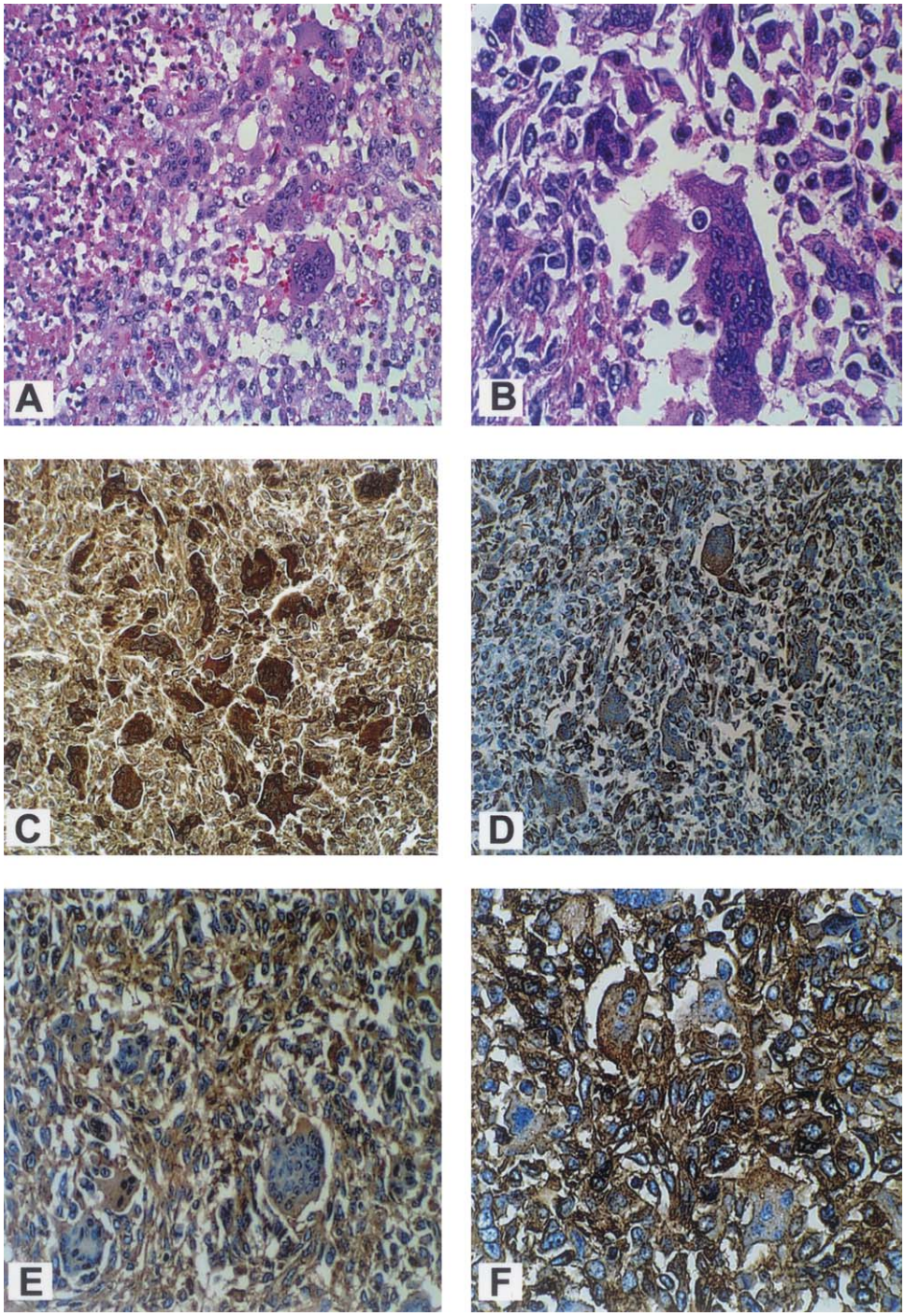

Fig. 5. Histological observations of the tumor. Numerous osteoclast-like giant cells (OCGCs) with bland cytological features (**A**) are intimately intermingled with infiltrating mononuclear cells (MNCs) displaying various degrees of cytological pleomorphism and atypical mitosis (hematoxylin and eosin [H&E] ×200). Dispersed throughout the tumor are infrequent pleomorphic large cells (PLCs) with bizarre nuclei. The cytoplasm of OCGCs occasionally contains remnants of phagocytosed MNCs (**B**, H&E, ×400). Immunohistochemical observations of the tumor. OCGCs exhibit strong immunoreactivity with cluster differentiation 68 (CD68) (**C**, CD68, ×200). Immunohistochemical stain for vimentin (**D**) indicates strong cytoplasmic staining of OCGCs and, to a lesser degree, of PLCs and MNCs (vimentin, ×200). MNCs and most of the PLCs of the tumor indicate strong expression of alpha-1-antitrypsin (**E**) and alpha-1-chymotrypsin (**F**). Some OCGCs also exhibit positive staining (alpha-1-antitrypsin and alpha-1-chymotrypsin, ×200).

Table 1. Immunohistochemical findings

Marker	Osteoclast-like giant cell tumor		
	OCGCs	PLCs	MNCs
Alpha-1-antitrypsin	++	+++	+++
Alpha-1-chymotrypsin	++	+++	+++
Alpha-fetoprotein	−	−	−
CEA	−	−	−
AE1-3 (cytokeratin)	−	−	−
HMW (CAM-52)	−	−	−
HMW	−	−	−
CK7	−	−	−
CK20	−	−	−
Vimentin	+++	++	+
CD68	+++	+	(+)

Expression is scored as follows: − = no cells are positive; (+) = less than 5% of the cells are positive; + = less than 25% of the cells are positive; ++ = 25%–50% of the cells are positive; +++ = greater than 50% of the cells are positive.
AE1-3 = anion exchanger 1-3; CAM-52 = chorioallantoic membrane 52; CD68 = cluster of differentiation 68; CEA = carcinoembryonic antigen; CK7 = creatine kinase 7; CK20 = creatine kinase 20; HMW = high molecular weight; MNCs = mononuclear cells; OCGCs = osteoclast-like giant cells; PLCs = pleomorphic large cells.

tumor have been reported at this location.[6–8] Much debate has focused on the origin and histogenesis of OCGTs, whereas the biological behavior of these tumors remains largely unknown.[1] Overall, the prognosis of OCGTs arising in the alimentary tract is unfavorable. Patients usually present with advanced disease and complete resection can rarely be performed. Leighton and Shum[3] and Shiozawa and associates[4] reviewed 20 and 32 patient cases of pancreatic OCGTs, respectively, and determined the median survival rates to be less than 1 year. Interval to death or disease progression ranged from 4 months to 5 years. Leighton and Shum[3] indicated nodal metastasis at operation in the majority of these patient cases and compared the outlook of OCGTs as similar to that of common ductal pancreatic carcinomas. All patients with OCGTs arising in the liver reported to date exhibit metastatic spread at the time of diagnosis or operation and outcome was dismal even after surgical resection (Table 2). In our study, the persistent CBD dilatation postpapillotomy, together with the fact that OCGTs occur more frequently in the pancreas, raised suspicion with regard to the presence of a primary or additional lesion in the head of the pancreas. However, the absence of elevated serum bilirubin or γ-glutamyl transpeptidase levels indicated using serum biochemistry, the absence of an abnormal pancreatic duct system indicated using MRCP and of a second extrahepatic metabolically active lesion indicated using PET scanning led us to conclude that the isolated CBD dilatation was of a nonobstructive nature unrelated to the OCGT and not caused by an additional intrapancreatic lesion. The observed CBD dilatation is presumably secondary and most likely attributable to the patient's prior cholecystectomy. In 5%–10% of the patients after cholecystectomy, nonobstructive functional dilatation of the bile duct system can be observed.[9]

Why the tumor recurred and spread so rapidly in such a short period of time is notable and worthy of discussion. Several reasons could account for the early recurrence and rapid progression of this tumor in our study: (1) The biological behavior of OCGTs arising in the liver might be similar to that of OCGTs arising in the pancreas which tend to be locally aggressive and have a high propensity to metastasize. (2) Referring to OCGTs of the pancreas, tumors expressing epithelial markers, similar to that in our study, are assumed to follow a more aggressive course.[10] (3) Although PET scanning is a useful adjunctive tool with regard to the staging of hepatocellular carcinoma, and, in particular, the detection of extrahepatic metastatic disease, it is known that small lesions or histologically low-grade lesions that are metabolically less active can be overlooked.[11,12] To date, there is no reported experience of radiotherapy or chemotherapy with regard to the management of these unusual malignancies. Hood and associates[8] described the occurrence of a 37-year-old female with OCGT of the liver who was treated with 5-fluorouracil and adriamycin, external beam radiation, and radioimmunotherapy (I-131 labeled antiferritin immunoglobulin [IgG]) for recurrent disease (Table 2). The tumor indicated an initial response as demonstrated by serial liver volume measurements, but the patient expired because of the disease progression 8 months after initial presentation. In our analysis after en-bloc resection with negative margins and the absence of nodal metastasis, a simple program of surveillance seems to be justified. However, acknowledging the radiosensitivity of giant cell tumors of bone, one may extrapolate the potential benefits in a neoadjuvant or adjuvant setting.

Another area of dispute concerns the striking morphological features and the exact histogenesis of the various tumor cells. Several recent observations now strongly support the concept that these giant cells represent a reactive infiltration of macrophages. The absence of any considerable cytological pleomorphism or atypia in all of the previous occurrences of hepatic OCGTs suggests that these cells do not represent an intrinsic tumor component. The observation of strong immunoreactivity with the histiocytic and mesenchymal marker CD68 and with vimentin both in our study and in most of the pancreatic

Table 2. Survey of OCGTs of the liver using literature data

Source	Age	Sex	Symptoms	Location and extent of tumor at presentation	Mixed histology	Treatment	Follow-up (months)
Munoz and associates[5]	87	M	Lethargy, weight loss	11 × 11 cm tumor in right lobe of liver with satellite nodules Metastasis to lung, adrenals, omentum Mesenteric and peripancreatic lymp nodes	None	Supportive—no surgery	Died because of liver failure on hospital day 32
Kuwano and associates[6]	54	M	General fatigue, weight loss	6 × 5 × 12 cm tumor in posterior area of right hepatic lobe invading right hemidiaphragm Lung metastasis	Conventional HCC and areas of osseous metaplasia	Posterior segmentectomy with resection of right diaphragm	Died on postoperative day 42 because of disease progression
Horie and associates[7]	66	M	Abdominal pain, hematemesis	Large tumor mass arising from inferior surface of the liver with compression and invasion of second portion of duodenum	None	Intraarterial mitomycin C infusions	Died on hospital day 42 because of disease progression
Hood and associates[8]	37	F	Abdominal and right shoulder pain	Large left hepatic lobe mass with invasion of anterior abdominal wall	Foci of HCC comprising less than 5% of tumor mass	Left hepatic lobectomy with partial resection of anterior abdominal wall Adjuvant 5-fluorouracil, adriamycin, external beam radiation, and antiferritin radioimmunotherapy	Died 8 months after initial presentation because of disease progression
Present study	61	F	Abdominal pain	8 × 8 × 12 cm mass in right lobe of liver with 2 × 2 cm extrahepatic component without abdominal wall invasion	None	Right hepatic lobectomy No adjuvant therapy	Died 3 months after surgery because of tumor recurrence

F = female; HCC = hepatocellular carcinoma; M = male; OCGTs = osteoclast-like giant cell tumors.

OGCTs supports the concept of macrophage derivation of these cells.[3] The most compelling evidence, however, for a nonepitheliogenic origin regarding these peculiar cells comes from genetic K-ras oncogene mutation analysis in pancreatic OCGTs. Using superselective microdissection techniques and one-step polymerase chain reaction (PCR) for K-ras oncogene mutations, a proven common early genetic event in carcinogenesis, it could be illustrated that only the infiltrating MNCs and none of the OCGCs harbor these mutations.[13] The immunoreactivity of OCGCs with the epithelial markers alpha-1-antitrypsin and alpha-1-chymotrypsin observed in our analysis and in the case of Hood and associates [8] seems to contradict a monocytic–histiocytic origin of these cells. However, this might be caused by phagocytosis of tumor cells by the OCGCs, a phenomenon which had been observed previously.[8,13,14] It is now believed that OCGCs are bone-marrow derived monocytes that are secondarily recruited into the tumor.[14] In fact, in the event that OCGT arises from the right hepatic duct, the diapedesis of OCGCs out of the intravascular space and into the interstitium of the tumor can be observed.[15]

Conversely to the OCGCs, the infiltrating MNCs display considerable pleomorphism and neoplastic features are considered to represent the intrinsic tumor component. Our observations regarding immunohistochemical reactivity with alpha-1-antitrypsin and alpha-1-chymotrypsin are consistent with the observations of Hood and associates[8] and support an epithelial origin. In pancreatic OCGTs, infiltrating MNCs indicate the same K-ras oncogene mutations as adjacent ductal carcinoma cells.[14] Referring to previously described occurrences of OCGTs of the liver (Table 2), the synchronous occurrence of OCGT and conventional hepatocellular carcinoma (HCC) observed was in two of the previously described reports of OCGT arising in the liver. This synchronous occurrence in epithelial-containing organs and the presence with some of them that exhibit a bona-fide carcinomatous component supports an epithelial origin and proves that infiltrating MNCs represent a dedifferentiated carcinoma. These are clinically relevant conclusions because given the epithelial origin of the mononuclear tumor cell population, it might be reasonable to consider agents such as gemcitabin as treatment for metastatic disease or palliation of disease recurrence.

In summary, contrary to the previously described instances we reported, a patient with OCGT of the liver where extensive preoperative multimodality imaging, using MRI and PET scanning to rule out metastasis or other extrahepatic pathology, indicated locoregional disease amenable to resection. The early recurrence of the tumor after complete resection indicated an aggressive clinical behavior with regard to this rare neoplasm. Patients with OCGT of the liver might be more beneficially served by the implementation of a nonoperative approach considering the dismal outlook of this neoplasm. Embolization of the tumor might be used as a palliative measure with regard to pain control. Our observations regarding hyperintensity on T1-weighted and hypointensity on T2-weighted imaging with heterogenous enhancement of the tumor on gadolinium-enhanced MRI is different from the usual MR appearance of HCC in North America.[16] However, at the present time, the lack of established MR criteria and the variance in MR observations depending on the histopathologic grade of patients with HCC does not allow a diagnosis of OCGT of the liver based solely on MRI.[16,17] It is important that future reports detail imaging observations, treatment modalities, patterns of spread, and clinical outcome to improve the prognosis with regard to this uncommon tumor.

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Case Report: Serial Percutaneous Cholangioscopy With Laser Ablation for the Management of Locally Recurrent Biliary Intraductal Papillary Mucinous Tumor

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We present a case of serial cholangioscopic laser fulguration of a biliary recurrence of pancreatic intraductal papillary mucinous tumor in a 76-year-old man. Through established percutaneous biliary drain tracts, the aseptic use of a standard 6.9 F ureteroscope and holmium laser fiber facilitated visual ablation within the biliary tree. Quarterly cholangioscopic laser ablation provided safe and effective local control without biliary infectious complications. This case appears to be the first treatment of recurrent intrabiliary intraductal papillary mucinous tumor by serial antegrade choledocoscopy and laser photocoagulation. Effective local control appears possible with minimal morbidity. Standard ureteroscopic equipment facilitates safe and efficient percutaneous antegrade choledocoscopy. (J GASTROINTEST SURG 2005;9:215–218)

KEY WORDS: Biliary intraductal papillary mucinous tumor, endoscopy, thermal ablation

A 76-year-old Caucasian man presented in June 2000 with fever and lethargy. On evaluation, he was noted to have a multiloculated hepatic abscess. A concomitant 1-cm pancreatic head lesion that appeared cystic was noted at the time of presentation; however, the patient manifested no signs of biliary obstruction. Percutaneous hepatic abscess drainage was unsuccessful, and the patient required operative drainage.

After complete recovery, the patient underwent evaluation of the mass in the pancreatic head, and ultimately resection was recommended. The patient elected for observation but then developed obstructive jaundice 6 months later. He underwent endoscopic retrograde cholangiopancreatography (ERCP), demonstrating distal biliary obstruction from a possible malignant process. He was treated with a pancreaticoduodenectomy and recovered without complication. Pathologic examination revealed a noninvasive intraductal papillary mucinous tumor (IPMT) (Fig. 1, *A*). All surgical margins were negative, including the ampulla of Vater and 19 resected lymph nodes.

Two years after surgery, the patient returned with jaundice and biliary obstruction. Percutaneous left and right bile duct drainage was obtained after failed endoscopic drainage. The initial cholangiographic appearance was most consistent with biliary stones, thought to be secondary to possible biliary anastomotic stricture. Follow-up cholangiography demonstrated papillary filling defects (Fig. 2). After adequate drain tract maturation, nondilated antegrade cholangioscopy with a 6.9 F ureteroscope (Olympus; America, Inc., Melville, NY) was performed via the right biliary ductal system. Immediate visualization of the papillary lesions (Fig. 3) was noted with biopsy,

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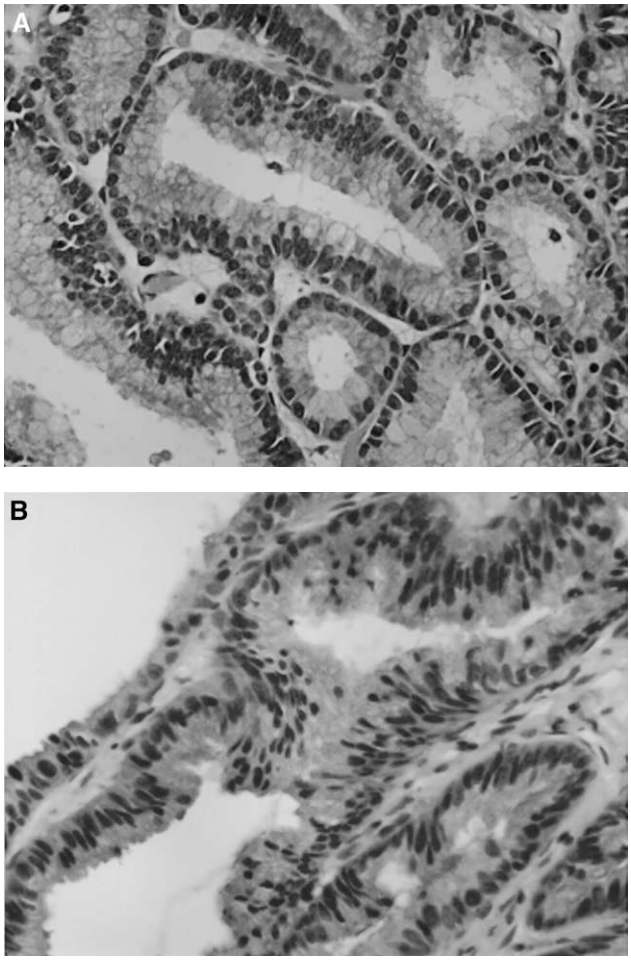

Fig. 1. (**A**) Histology of primary pancreatic tumor. Papillary tumor is lined by dysplastic tall columnar epithelium of mucin-producing type, with varying degrees of nuclear crowding and stratification. Papillae with narrow fibrovascular cores demonstrate focal architectural and cytologic atypia of mild-moderate degree. (**B**) Comparison histology of recurrent intrabiliary intraductal papillary mucinous tumor recurrence demonstrating characteristics of the primary lesion.

proving recurrence of the IPMT (Fig. 1, *B*). With the patient's underlying comorbidities and overall performance status, he was not thought to be a good candidate for an extended hepatic resection. Holmium laser (Trimedyne, Inc., Irvine, CA) fulguration (8 W) to the lesion and base of all papillae was visually demonstrated before replacing the biliary drains. Serial antegrade cholangioscopy demonstrated recurrent intrabiliary IPMT lesions. Quarterly antegrade biliary endoscopic laser fulguration has provided excellent local disease control for more than 1 year. The patient has had no complications from local disease progression. He remains with normal hepatic synthetic function and has these procedures performed on an outpatient basis.

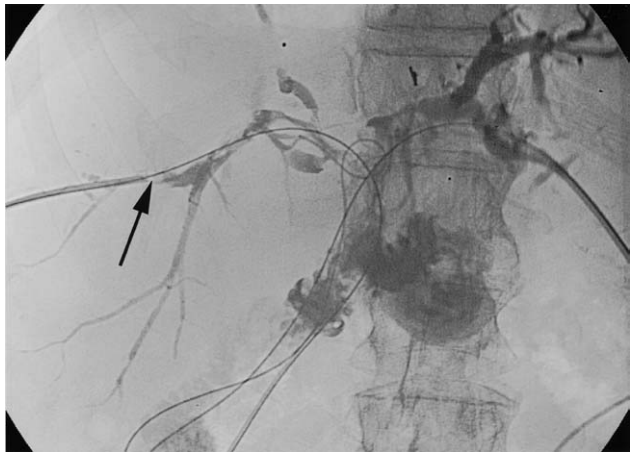

Fig. 2. Antegrade percutaneous cholangiography with visualization of an intraluminal papillary lesion (*arrow*).

DISCUSSION

IPMT is an uncommon cystic malignant lesion of the main pancreatic duct or its primary branches. The spectrum and nomenclature of cystic pancreatic epithelial lesions are, at best, confusing, but IPMT is a moderately dysplastic lesion of uncertain malignant potential.[1] Delays in diagnosis portend poorer outcomes, but early successes are observed after complete surgical resection of noninvasive lesions.[1,2] Patients often present with pain; however, nausea, vomiting, diarrhea, chronic or acute pancreatitis, and

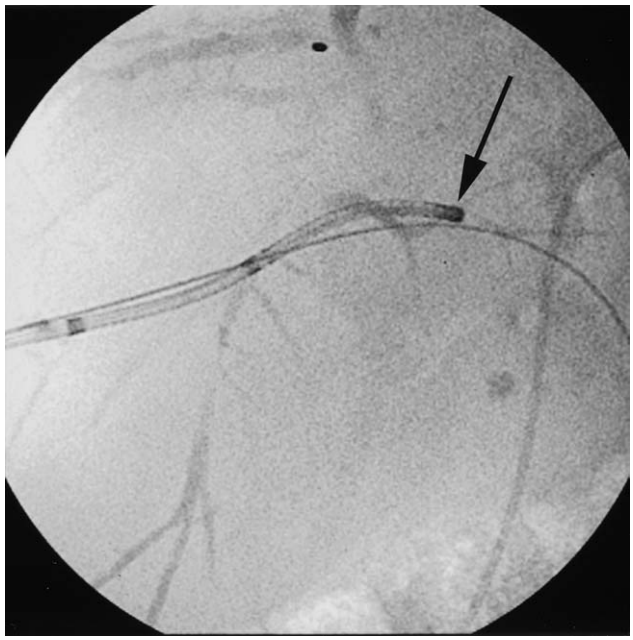

Fig. 3. Antegrade biliary endoscopy used to facilitate laser fulguration of papillary lesions (*arrow* denotes tip of ureteroscope used for biliary endoscopy).

jaundice can also be observed.[1,2] Unlike other pancreatic malignancies, alcohol abuse and smoking are not customary in patients with IPMT; nevertheless, one in five may present with overt diabetes mellitus as an indicator of pancreatic insufficiency.[1,2] Reliable diagnosis can be completed with computed tomography or ultrasonography, with ERCP, positron emission tomography scanning, or magnetic resonance imaging being useful in select cases.[1,2] Endoscopic identification of mucus extrusion from a dilated ampulla is considered pathognomonic for IPMT.[1]

Histologically, IPMT is characterized by papillary fronds, typically lined by dysplastic tall columnar epithelium of mucin-producing type and varying degrees of nuclear crowding and stratification. Papillae with narrow fibrovascular cores may demonstrate focal architectural and cytologic atypia of mild-moderate degree.[1,3] Intrahepatic and extrahepatic biliary ductal recurrences share this histology.[4,5]

IPMT of the biliary tree has been reported, with radiographic characteristics of the disease including papillary impressions within biliary tree dilation and elongated, cordlike filling defects indicative of mucus stranding.[6]

Once identified, surgical resection is the recommended treatment of choice, with select cases necessitating observation secondary to comorbid illness.[7,8] The first biliary mucin-secreting papillary lesion found simultaneously with a pancreatic IPMT was reported in 2000. Being designated histologically as an IPMT of the bile duct, successful distal pancreatic and left hepatic lobe resection resulted in an asymptomatic 10-month follow-up. Somogyi et al.[9] report resection of a hepatic duct after retrograde cholangioscopy localized an IPMT lesion; however, follow-up was not reported. Ishida and colleagues[10] also report concomitant intrahepatic IPMT and a multiloculated cystic IPMT of the pancreas; a benign outcome was noted 10 months after pancreateic resection and left hepatic lobectomy.

Remarkable homology of IPMT with the mucin-hypersecreting bile duct tumor is also reported, with the latter lesion being surgically resected in a series of nine patients. As reported by Kim and colleagues,[11] each of the nine patients was diagnosed on ERCP evaluation. Five patients underwent cholangioscopy for further understanding of the local extent and for preoperative planning. No endoscopic therapeutic manipulations were reported. One patient underwent exploratory laparotomy and biopsy for gross peritoneal carcinomatosis, subsequently dying from septic cholangitis. Of the remaining eight patients, seven were alive at the time of publication (follow-up range, 8–42 months), with the final patient having recurrent disease at 18 months.

Surgical resection is curative in many noninvasive pancreatic IPMT cases, but recurrence is seen in up to 8% (mean diagnosis at 40 months). However, invasive disease recurs in up to 91% at 3 years.[7] In addition, invasive IPMT reduces the 2.5-year survival rate from 93% to 24%.[12] Vigilance with clinical and radiographic follow-up appears mandatory in all cases.

Both transpapillary retrograde and percutaneous antegrade biliary endoscopy are well reported. Specific diagnosis and localization of IPMT via retrograde cholangioscopy and pancreatoscopy are also described.[9,13] Percutaneous transhepatic choledochoscopy for laser photocoagulation delivery to biliary malignancy was initially reported in 1987 by Classen et al.[14] Meng and others[15] report the serial use of choledochoscopy for laser ablation of recurrent biliary papillomatosis. Similar to our case, laser ablation after complete endoscopic evaluation, via an established T-tube tract, proved successful in this disease process.

Ponchon et al.[16] reported the largest contemporary series and the technique of successful antegrade choledocoscopy cases for various biliary findings. Each patient obtained preoperative biliary drainage via either transhepatic or T-tube drain, with 123 consecutive patients undergoing 161 procedures. Biliary duct stenosis, gallstone extraction with or without lithotripsy, and laser photocoagulation for intraductal adenoma or cholangiocarcinoma are discussed. Although one recurrent adenoma (of three) is noted in their series, this pathology appears initially favorable to laser photocoagulation therapy. Conversely, cholangiocarcinoma presents as an unfavorable lesion for laser fulguration. Each of eight cases of cholangiocarcinoma warranted high levels of laser energy (30 W) for any significant grossly visualized lesion, with every case demonstrating disease progression on cholangiography after only 4 months of follow-up. Although adenomas are reported, IPMT lesions were not encountered in this series.

CONCLUSION

To our knowledge, this case is the first report of recurrent intrabiliary IPMT locally managed by serial antegrade cholangioscopy and laser photocoagulation. Early palliation appears possible with this technique. Although local control can be obtained with this procedure, one must also consider definitive treatment of the underlying malignancy with methods such as partial hepatectomy or bile duct resection when possible. Endoscopic fulguration of IPMT is readily performed, with lesions being susceptible to

holmium laser energy. Frank and comprehensive patient counseling for surgical care of IPMT is necessary as the natural history of this disease is not well known. Finally, current standard ureteroscopic equipment facilitates safe and efficient percutaneous antegrade choledocoscopy.

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Extrinsic Denervation Alters Postprandial Absorption of Glucose and Glutamine in the Ileum: Implications for Small Bowel Transplantation

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In the postprandial period, augmentation of absorption of water, electrolytes, and taurocholate is believed to occur in the ileum. The role of extrinsic innervation in this postprandial augmentation has not been well studied and may be an important concept in small bowel transplantation. Our aim was to investigate extrinsic neural mechanisms mediating postprandial absorptive patterns. The study hypothesis was that postprandial augmentation of absorption in the ileum is blunted in transplanted (extrinsically denervated) bowel. Ileal absorption was studied in six dogs with an 80-cm in situ ileal segment via a triple-lumen perfusion technique using an iso-osmolar, ileal-like electrolyte solution alone and containing either glucose 2.5 mM, glutamine 2.5 mM, oleic acid 5 mM, or taurocholate 5 mM. Net absorptive fluxes of each substrate, as well as water and electrolytes, were measured in both the fasted state and after a 400-Kcal mixed meal before and at 2 and 12 weeks after our validated model of complete extrinsic denervation of the jejunoileum. At baseline, there were no differences in absorption of water, electrolytes, or any nutrient postprandially compared with the fasted state. Two weeks after extrinsic denervation, absorption of glucose at both 1 and 2 hours postprandially was decreased compared with absorption during fasting. Glutamine absorption was also decreased at 2 hours postprandially. At 12 weeks after extrinsic denervation, net postprandial absorption of glucose and glutamine returned toward normal and was not different from fasting absorption. No differences were noted in postprandial absorption of oleic acid or taurocholate at any time point. Decreases in absorption of nutrients postprandially after extrinsic denervation (which is necessitated by small bowel transplantation) may play an important role in post-transplant enteric absorptive dysfunction. The previously described postprandial augmentation in net absorption may be a function of enterically isolated gut and does not appear to occur in the in situ ileum. (J GASTROINTEST SURG 2005;9:219–226)

KEY WORDS: Postprandial absorption, extrinsic denervation, small bowel transplantation, glucose absorption, fat absorption, glutamine absorption, bile acid absorption

Enteric absorptive dysfunction complicates small bowel transplantation (SBT).[1–3] Previous studies have demonstrated transient decreases in absorption of water and nutrients in canine models of SBT.[4,5] Few formal studies, however, have investigated absorption in the postprandial, or "fed," state in the extrinsically denervated or transplanted bowel. Physiologic studies have demonstrated that absorption of water and nutrients is augmented in the small intestine after a meal.[6,7] Whether postprandial net absorption is affected by the conditions obligated by SBT, including extrinsic denervation of the graft, ischemia/reperfusion injury, lymphatic disruption, immunosuppressive medications, and immune phenomena, remains poorly understood.

The aim of our study was to determine the role of extrinsic innervation in mediating postprandial absorptive patterns. Our goals were of both physiologic

Presented in part at the Forty-Third Annual Meeting of The Society for Surgery of the Alimentary Tract and The American Gastroenterological Association, San Francisco, California, May 19–22, 2002, during Digestive Disease Week (poster presentation).
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Supported in part by a grant from the National Institutes of Health (NIH RO1 39337) (to M.G.S.) and the Department of Surgery, Mayo Clinic.
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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.04.007

and clinical interest, extending the translational investigations at our laboratory into the role of extrinsic innervation in controlling and/or modulating enteric function, as well as exploring absorptive function in a large animal model of intestinal (auto) transplantation. Our previous work showed that extrinsic denervation of the jejunoileum induced an early diarrhea that resolved 6–8 weeks postoperatively,[8] associated with a transient decrease in net absorption of water, electrolytes, and simple nutrients from the in situ jejunum and ileum at 2 weeks that resolved by 8 weeks postoperatively.[4,5] Based on previous studies,[6,7] we assumed that postprandial augmentation of absorption would occur in the in situ ileum and hypothesized that postprandial absorption would be altered in the extrinsically denervated bowel. We used our previously validated canine model of intestinal autotransplantation[8] to study absorptive function of the extrinsically denervated gut devoid of confounding factors of immune phenomena and ischemia/reperfusion injury. In doing so, we found (surprisingly) that postprandial augmentation of net absorption did not occur in the in situ ileum.

MATERIAL AND METHODS

Overall Design

Six dogs underwent baseline in vivo experiments of ileal absorption of water, electrolytes, and four simple nutrients (glucose, glutamine, taurocholate, and oleic acid), as well as measurements of ileal transit in both fasting and postprandial states. After the completion of baseline studies, these dogs underwent complete in situ extrinsic denervation of the jejunoileum and were restudied 2 and 12 weeks postoperatively with identical experiments of absorption and transit in vivo.

Animal Preparation

Surgical procedures, postoperative care, and subsequent conduct of experiments were performed with approval by the Animal Care and Use Committee of the Mayo Foundation in accordance with the guidelines of the National Institutes of Health and the U.S. Public Health Service policy on the humane use and care of laboratory animals. All dogs were fasted 12 hours before surgical procedures.

Catheter and cannula insertion. Six healthy female mongrel dogs (weight 14–22 kg) were anesthetized with intravenous sodium methohexital induction (12.5 mg/kg) and maintained on inhaled halothane (Ayerst Laboratories, New York, NY). Dogs underwent a midline celiotomy and placement of an ileal infusion catheter (internal diameter 1.5 mm), an ileal aspiration catheter (internal diameter 3.0 mm), and a modified Thomas cannula (internal diameter 1 cm). These two catheters were positioned at 115 cm and 100 cm, proximal to the ileocecal junction; the cannula was placed 80 cm distal to the second catheter and thus 20 cm proximal to the ileocecal junction, thereby providing an 80-cm test segment of distal ileum. The proximal ends of the infusion and aspiration catheters were fixed with cement in a metal cannula; this cannula and the distal ileal modified Thomas cannula were exteriorized through the abdominal wall. This configuration allows for a "triple-lumen" perfusion technique[9] consisting of a 15-cm mixing segment and an 80-cm study segment, similar in principle to our previous studies[4,5,10,11]; this type of experimental setup has been well described and illustrated previously.[4] Postoperatively, dogs were administered intramuscular butorphanol for pain control and maintained on parenteral fluid and electrolytes for 3 days before ad libitum feeding was allowed. Baseline absorptive and transit experiments (see later) were performed after allowing 2 weeks for recovery.

Extrinsic denervation. After completion of baseline experiments, a second celiotomy was performed, and all dogs underwent our model of in situ neural isolation of the jejunoileum, as described and illustrated previously in depth.[8] This surgical preparation establishes a complete extrinsic denervation as well as disruption of intrinsic neural and lymphatic continuity to the jejunoileum without interruption or occlusion of the primary blood supply during surgery; this preparation avoids any ischemia/reperfusion injury. In brief, all mesenteric, lymphatic, neural, and connective tissues at the base of the small bowel mesentery traveling to the jejunoileum were transected except for the superior mesenteric artery and vein. The artery and vein were carefully skeletonized with the aid of optical magnification by stripping investing adventitia and associated neural elements from the vessel walls for 1–2 cm. The proximal jejunum, just distal to the ligament of Treitz, and the distal ileum 5 cm proximal to the ileocecal junction were then transected to complete the intrinsic neural disruption. Intestinal continuity was restored by end-to-end jejunojejunostomy and end-to-end ileoileostomy. After recovery, absorptive and transit experiments were repeated at 2 and 12 weeks postoperatively (see later).

Absorption experiments. All dogs were fasted 12 hours overnight before each experiment. Fully conscious dogs, resting in a Pavlov sling, were studied before (at baseline, 0 weeks) and at 2 and 12 weeks after extrinsic denervation using a modification of the

triple-lumen perfusion system.[4,5] Each experiment began with gentle flushing of the ileal segment with infusate to remove intraluminal mucous and debris. The infusate, designed to reproduce the electrolytic milieu of the ileum, was a warmed (39° C), iso-osmolar electrolyte solution (in mEq/L: sodium 140, potassium 5, chloride 110, bicarbonate 35) containing 5 g/L of the nonabsorbable volume marker polyethylene glycol (PEG) (molecular weight, 3,350 Da) labeled with ^{14}C-PEG (5 μCi/L). Separate experiments were performed using the perfusate alone or perfusate containing one of four solute nutrients labeled with ^{3}H (see later). After flushing, the test solutions were infused continuously via the proximal ileal catheter at a continuous rate of 5 ml/min. Luminal samples were aspirated from the second catheter (15 cm distally) at a constant rate of 1 ml/min using a withdrawal pump (Harvard Apparatus Co., Dover, MA). The effluent from the end of the 80-cm test segment was collected by gravity flow via the distal ileal cannula. A 1-hour equilibration period was allowed to establish steady state dynamics, based on previous experiments.[4,5,10,11] Thereafter, samples from the proximal catheter and distal cannula were collected during four subsequent consecutive 1-hour intervals for analysis. The dogs were studied in the first 2 hours in the fasted state; dogs were then fed a 400-Kcal meal of pureed pork liver (200 g) and cream (120 ml) and studied for an additional 2 hours. Separate experiments were conducted using five different test solutions composed of the infusate alone or infusate containing one of the following four nutrients: 2.5 mM glucose, 2.5 mM glutamine, 5 mM taurocholate (the primary bile acid in the dog), or 5 mM oleic acid. The latter solute was delivered as a bile salt emulsion (to allow absorption independent of emulsification) by adding desiccated, unfractionated bovine bile (11.8 mM bile salts) to control for potential alterations in bile flow after denervation and to allow fat absorption. Each test nutrient was labeled with ^{3}H at 10 μCi/L. The low concentrations of the solutes glucose and glutamine were chosen to evaluate primarily carrier-mediated active transport (as opposed to diffusion) based on their coefficients of absorption. Each test solution was evaluated twice in each dog at each time point (baseline and 2 weeks and 12 weeks after denervation).

Transit studies. Transit studies were conducted during infusion of the electrolyte solution alone. After steady state had been reached, a single aliquot of 2 μCi of ^{3}H-PEG (2 ml) was infused as a bolus via the aspiration catheter to evaluate transit during fasting. Effluent was collected from the distal cannula in 5-minute intervals. After sampling of the effluent for ^{3}H-PEG concentration, the remainder of the effluent was pooled for analysis of absorption. Infusion of a single aliquot of ^{3}H-PEG was repeated after ingestion of the meal, again with collection of effluent in 5-minute intervals and pooling of effluent for absorptive experiments after sampling for ^{3}H-PEG concentration. Transit studies during fasting and after feeding were performed twice at each time point (baseline and 2 weeks and 12 weeks after denervation).

Analytic Methodology

All samples were analyzed in duplicate and run within days of the experiment. Concentrations of the nonabsorbable markers, ^{14}C-PEG and ^{3}H-PEG, and of the solutes of interest, ^{3}H-glucose, ^{3}H-glutamine, ^{3}H-taurocholate, and ^{3}H-oleic acid, were measured by dual-label scintillation techniques. Sodium and potassium concentrations were measured by flame photometry, and chloride concentrations, by chloridimetry.

Analysis of absorptive data. Net absorption of water, glucose, glutamine, oleic acid, and taurocholate was determined using principles of the triple-lumen perfusion technique, as described previously.[4,5] The first hour of infusion was used to allow establishment of steady state conditions (i.e., the amount of nonabsorbable marker entering the study segment per unit time equaled the amount of marker leaving the distal end of the segment). Net absorption of water for each experimental interval was calculated as net absorptive flux ($\mu l \cdot cm^{-1} \cdot min^{-1}$) from the difference in volume entering and leaving the 80-cm jejunal test segment as calculated by changes in concentrations of the nonabsorbable volume marker ^{14}C-PEG between the proximal ileal aspiration site and the distal ileal diverting cannula using standard formulas for an 80-cm test segment.[7,9–13] It should be noted that this triple-lumen technique allows for and takes into consideration potential inflow into the 80-cm test segment of ileum of proximal ileal content (succous). The mixing segment between the (proximal) infusion catheter and the (15 cm distal) aspiration catheter allows measurement of "corrected" actual volume entering the test segment as well as "corrected" actual concentrations of electrolytes and substrates entering the segment. Absorption is then calculated as net absorption by differences in concentrations between the start (proximal aspiration catheter) and end (distal ileal cannula) of the test segment. Positive values for net flux represent net absorption, whereas negative values represent net secretion. Net absorptive fluxes for glucose, glutamine, taurocholate, oleic acid, and water were determined for each experimental time interval using corrections based on the changes in concentrations

of ^{14}C-PEG, ^{3}H-solute, and standard formulas for the 80-cm test segment.[4,5]

The individual mean values of net absorption for the first two of the four separate consecutive 1-hour intervals per experiment were determined, and these mean values for the two duplicate experiments were likewise determined in each dog, representing the fasting absorption values. The results for the third hour were calculated as mean values for the two duplicate experiments, representing absorption in the first postprandial hour. Fourth hour results, with mean values for the two duplicate experiments, represented absorption in the second hour after the meal. Grand mean values across dogs in the fasted state, the first postprandial hour, and the second postprandial hour were calculated for the basal, 2-week, and 12-week time points.

Analysis of transit data. Transit time was calculated based on timed recovery of ^{3}H-PEG from the distal ileal cannula after bolus administration of the marker in the proximal aspiration catheter (start of the 80-cm study segment). The tota1 ^{3}H-PEG collected was tracked and compared with that infused. The first time interval at which more than 50% of total counts were collected was designated the half-time of transit (t_{50}). Tests in which less than 90% of the counts were retrieved were considered invalid.

Statistical Analysis

Mean net absorptive fluxes and t_{50} within groups were compared for all dogs across the time points (baseline, 2 weeks, and 12 weeks) during fasting and after feeding using analysis of variance (ANOVA) and a subsequent Student's *t* test for paired data with probability adjusted according to the Bonferroni correction for multiple related comparisons when appropriate. Similarly, at each time point, differences between measurements during fasting and after feeding were compared. Data in the text are presented as mean ± SEM values.

RESULTS

Health and General Characteristics of Dogs

All dogs tolerated catheter and cannula placement and subsequent extrinsic denervation, maintained a good appetite, and remained active and healthy. After extrinsic denervation, all dogs developed a watery diarrhea that returned to a soft, partially formed stool in 6–8 weeks. At 3 weeks postoperatively, all dogs had lost weight after extrinsic denervation (preoperative weight 17.3 ± 0.6 kg; 3-week postoperative weight 16.8 ± 0.6 kg; $P = 0.03$); however, all except one dog had returned to or exceeded preoperative weight by the end of the study.

Net Absorption

Water. During the baseline (time 0 weeks) measurements before extrinsic denervation of the jejunoileum, there were no differences in net ileal absorption of water in the postprandial period compared with fasting absorption (Fig. 1). Specifically, there was no postprandial augmentation of absorption of water in either the first or second postprandial hours compared with the fasting (preprandial) measurements. Similarly, when studied at 2 and 12 weeks after extrinsic denervation, no postprandial augmentation was evident. Although the mean net absorptive flux of water ($\mu l \cdot cm^{-1} \cdot min^{-1}$) during fasting appeared to decrease from baseline to 2 and 12 weeks after extrinsic denervation (19.7 ± 1.9 to 17.4 ± 2.9 to 18.6 ± 3.6), the changes were not statistically different (ANOVA $P = 0.86$). Similarly, differences in postprandial net absorptive fluxes also did not differ across the time points (P values > 0.05).

Electrolytes. Similar to water absorption, net ileal absorptive fluxes of sodium and chloride did not differ between fasting and postprandial periods at baseline or at the 2- and 12-week time points after extrinsic

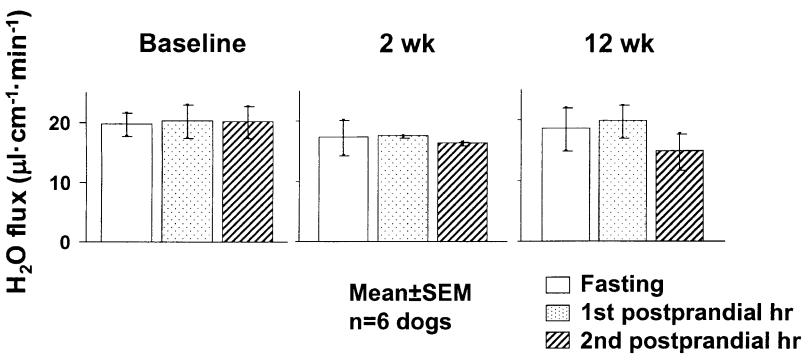

Fig. 1. Effect of extrinsic denervation of jejunoileum on canine ileal postprandial absorption of water.

denervation (Table 1). The net fluxes of sodium and chloride also did not differ across time points when compared during either fasting or the postprandial hours (ANOVA $P >> 0.05$).

There were minor changes in net absorptive fluxes of potassium. The net fluxes tended to decrease at the 2- and 12-week time points; significant differences compared with baseline measurements were only noted at the 12-week time point in the postprandial measurements. A mean positive net absorptive flux of potassium (at baseline) changed to a mean negative net absorptive flux (at 12 weeks after extrinsic denervation); these changes were, however, small.

Substrates. In contrast to net absorption of water and electrolytes, ileal absorption of several substrates did show differences. During the baseline measurements (time 0 weeks), net absorption of glucose did not differ postprandially from fasting values (Fig. 2); that is, there was no postprandial augmentation in absorption. However, at the 2-week time point, postprandial absorption of glucose actually decreased (ANOVA $P < 0.02$) during both the first ($P < 0.025$) and second ($P < 0.05$) hours. This decrease in postprandial absorption in glucose did not persist at the 12-week time point. Similar changes were seen with ileal absorption of glutamine (Fig. 2). Specifically, during baseline, there was no postprandial augmentation of glutamine absorption, but at 2 weeks after extrinsic denervation, net absorption of glutamine decreased postprandially (ANOVA $P < 0.06$) and especially in the second postprandial hour ($P < 0.025$). As with glucose, this decrease also did not persist at the 12-week time point.

Net ileal absorption of oleic acid and taurocholate showed a different pattern from glucose and glutamine. There were no changes in net ileal absorption of either substrate postprandially at any time point (Table 2). Although the mean values of net absorption of taurocholate appeared to be less in the first and second postprandial hours at the 2- and 12-week time points, the variances (SEM) were large, and no statistically significant changes were reached. In contrast, several changes were evident when comparing net absorption before and after extrinsic denervation. For oleic acid, net ileal absorption was less after extrinsic denervation (ANOVA $P < 0.05$) and specifically was less ($P < 0.025$) at the 12-week time point compared with baseline. For taurocholate, overall decreases in net absorption (ANOVA $P < 0.05$) also occurred at the 2- and 12-week time points during each condition (fasting, first postprandial hour, and second postprandial hour) compared with time 0 weeks.

Table 1. Effect of Extrinsic Denervation of Jejunoileum on Net Ileal Absorption of Electrolytes

	Net absorption		
		After denervation	
	Baseline	2 wk	12 wk
Sodium*			
Fasting	2.7 ± 0.4	2.4 ± 0.5	2.5 ± 0.6
Postprandial			
Hour 1	2.8 ± 0.4	2.5 ± 0.3	2.4 ± 0.5
Hour 2	3.0 ± 0.4	2.4 ± 0.5	2.0 ± 0.4
Potassium ($\times 10^{-1}$)*			
Fasting	0.6 ± 0.1	0.1 ± 0.3	−0.3 ± 0.5
Postprandial			
Hour 1	0.8 ± 0.2	0.2 ± 0.3	−0.2 ± 0.4†
Hour 2	0.7 ± 0.1	0.1 ± 0.3	−0.3 ± 0.4†
Chloride*			
Fasting	2.2 ± 0.2	2.0 ± 0.3	2.1 ± 0.4
Postprandial			
Hour 1	2.1 ± 0.3	2.0 ± 0.2	1.9 ± 0.4
Hour 2	2.3 ± 0.3	2.1 ± 0.3	1.9 ± 0.3

*Values are given as mmol·cm^{-1}·min^{-1} unless otherwise noted; data are mean ± SEM; n = 6 dogs.
†Differs from baseline, $P < 0.025$ (Bonferroni correction for two separate comparisons).

Transit Times

Transit times through the 80-cm segment were measured during fasting and during the first postprandial hour at the three time points (Table 3). No differences were noted either across time points or between fasting and postprandial conditions.

DISCUSSION

This study yielded two observations of physiologic and potential translational/clinical importance. First, of physiologic interest, we were unable to demonstrate a postprandial augmentation of the net absorption of water, electrolytes, or simple nutrients (glucose, glutamine, oleic acid, and the bile salt taurocholate) in the in situ canine ileum. Second, chronic complete extrinsic denervation of the jejunoileum, a model of jejunoileal autotransplantation (devoid of the confounding factors of ischemia/reperfusion injury or immunologic phenomena) led to a decrease in net ileal absorption of glucose and glutamine postprandially. This latter finding may have translational relevance in the field of intestinal transplantation, helping to explain some of the observations of enteric dysfunction after SBT.

At our laboratory, we first described postprandial augmentation in net absorption of water and electrolytes from the canine jejunum in 1981.[6] This postprandial absorptive augmentation was partially

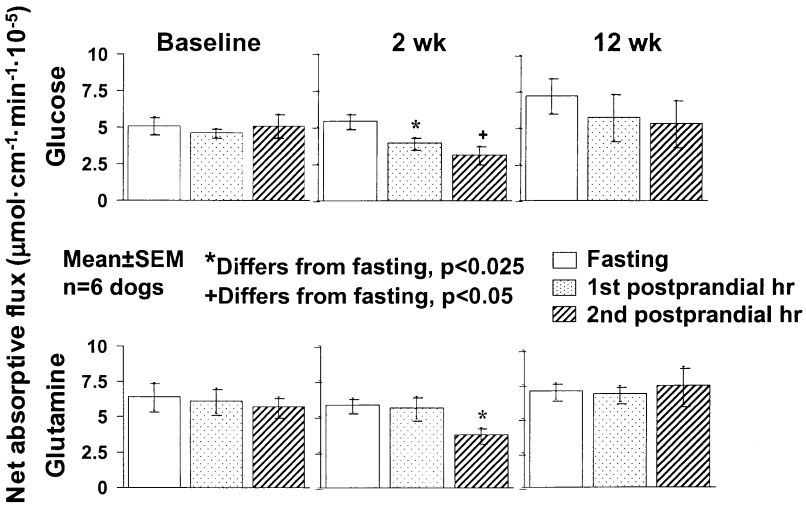

Fig. 2. Effect of extrinsic denervation of jejunoileum on canine ileal absorption of glucose and glutamine.

preserved in autotransplanted jejunum, suggesting that both neural and non-neural mechanism(s) mediate the response. Subsequently, several other groups confirmed this apparent physiologic response[14,15] and went on to show that it appears to be mediated by an increase in activity of brush border Na^+/H^+ exchanger at the level of the enterocyte membrane.[12] The current study appears to contradict these previous studies. However, all the studies previous to our current study were performed in enterically isolated, modified Thiry-Vella loops perfused with an electrolyte solution from which net absorption was measured. Our current study was performed in the in situ ileum specifically to avoid any confounding effects of chronic enteric/isolation necessitated by Thiry-Vella loops. There is precedent for similar concerns regarding making conclusions about changes in enteric absorptive function based on studies in enterically isolated segments. Indeed, our initial work on absorption from enterically isolated small bowel loops in dogs after extrinsic denervation failed to show any early (2 weeks) or late (8 or 12 weeks) effects on net absorption of water, electrolytes, or simple nutrients.[13,16] However, when subsequent experiments were carried out in the in situ jejunum[17] and ileum,[18] marked changes in net absorption were noted early after extrinsic denervation, consistent with the known watery diarrhea that occurs after extrinsic denervation. These studies called into question the conclusions regarding absorptive function or dysfunction based on measurements of absorption in enterically isolated loops of small bowel. These disparate results between in situ and enterically isolated segments are probably related to the lack of enteric content and loss of its trophic effects in the enterically isolated intestinal loops.[19] Lack of trophic factors such as nutrients, pancreatobiliary secretions, and intraluminal growth factors and the possibility of bacterial overgrowth may affect mucosal absorptive function in a nonphysiologic manner. Furthermore,

Table 2. Effect of extrinsic denervation of jejunoileum on net ileal absorption of oleic acid and taurocholate

Time after extrinsic denervation	Net absorption		
	Baseline	After denervation	
		2 wk	12 wk
Oleic acid			
Fasting*	1.1 ± 0.2	0.6 ± 0.2	0.6 ± 0.2†
Postprandial			
Hour 1	0.8 ± 0.1	0.7 ± 0.1	0.6 ± 0.2
Hour 2	0.7 ± 0.1	0.8 ± 0.1	0.6 ± 0.2
Taurocholate			
Fasting*	1.9 ± 0.2	1.1 ± 0.3†	1.2 ± 0.1
Postprandial			
Hour 1	2.1 ± 0.5	0.7 ± 0.3†	0.5 ± 0.4
Hour 2	2.4 ± 0.8	0.3 ± 0.3	0.5 ± 0.4

Values given as $mmol \cdot cm^{-1} \cdot min^{-4}$; data are mean ± SEM; n = 6 dogs.
*Differs across time points, analysis of variance, $P < 0.05$.
†Differs from baseline under same condition, $P < 0.025$.

Table 3. Transit time ($t_{1/2}$) through ileal loop

	Baseline	After denervation	
		2 wk	12 wk
Fasting	15 ± 3	14 ± 4	17 ± 6
Postprandial	11 ± 2	14 ± 2	17 ± 5

Values given in minutes; mean ± SEM; n = 6 dogs.

chronic enteric isolation of small bowel segments leads to a "disuse" atrophy that alters normal physiologic function.[19] Although one might question the effect of intestinal transection (disruption of myoneural continuity) that is necessitated by enteric isolation, in our experiment, intestinal continuity was also necessitated by our model of in situ neural isolation.

Our study also addressed the role of extrinsic innervation in postprandial absorption. The study was designed to determine whether extrinsic innervation plays a role in mediating postprandial augmentation in net absorptions. Net ileal absorption of glucose and glutamine in the early postprandial period was decreased. These decreases in absorption were not a nonspecific global event, because there was no postprandial effect on absorption of oleic acid or taurocholate at any time point. Also, there were no gross changes in transit after feeding that might explain a decrease in absorption. In addition, although we did not evaluate intestinal morphology in this experiment, we have shown previously that gross mucosal morphology does not change with this preparation.[20]

Our previous work and that of others have repeatedly shown a marked weight loss after in situ neural isolation (extrinsic denervation) of the jejunoileum[13,21,22] and after jejunoileal autotransplantation.[23,24] The primary cause or causes of this weight loss have remained elusive. Multiple studies of net absorptive function in the whole dog[14] and specifically in jejunum[17,25] and ileum[18,26] have shown statistically significant although relatively minor decreases on baseline absorption during fasting that do not appear great enough alone to explain either the profuse watery diarrhea or the weight loss that are so prominent in the first 2 to 3 weeks after these models of small bowel autotransplantation. The decrease in net absorption of the simple solutes (glucose, glutamine) in the early postprandial period may help to explain these previous observations. Also of interest is the finding that this postprandial decrease is transient. Early postprandial net absorption had returned to normal when measured at 12 weeks after extrinsic denervation, a time when the watery diarrhea had also resolved and the dogs had regained the weight they lost in the early postoperative period. This postprandial decrease in net absorption may have translational importance in the field of clinical SBT. Weight loss and diarrhea occur after SBT in humans, and the mechanism(s) remains largely unknown.[27,28]

Several limitations of our study must be acknowledged. First, strong conclusions about absorptive function based on using both a constant perfusion technique and an artificial electrolyte solution have limitations. Transit of luminal content through the small intestine occurs via bolus movement.[29] In addition, postprandial absorption occurs from luminal content composed of nutrients within enteric chyme; bile, pancreatic secretions, mucus, and complex nutrients all may affect absorptive function differently than simple electrolyte solutions. Second, we evaluated postprandial absorption for only the first 2 hours after the meal. We chose this time interval based on earlier studies mentioned above that showed that the postprandial augmentation in absorption was evident within the first hour after feeding. Whether postprandial absorption remains decreased at times after the first 2 hours remains unknown. Further, our study evaluated absorption in the ileum. As the vast majority of nutrient absorption occurs in the proximal small intestine, evaluation of absorptive function in the distal small bowel may not reflect global overall absorptive fluxes. Third, our test solutions contained at most 2.5 mM glucose. Other studies of postprandial augmentation of absorption have used solutions containing glucose. We, however, saw no augmentation in the solution containing 2.5 mM glucose. It remains possible that driving the sodium/glucose cotransport system may also affect paracellular uptake of water. Finally, our experimental canine preparation was designed specifically to examine the effect of extrinsic denervation. Whether the disruption of lymphatic continuity plays a role in this change seems unlikely but is at least possible. Also, direct translation to the clinical situation of human SBT is of potential importance, but other factors not present in our study may be equally or more important in altering absorptive function, such as ischemia/reperfusion injury, immune rejection, and pharmacologic effects of immunosuppression, all of which are known to affect absorptive function.[27]

Our experiment was designed to examine changes in net absorption postprandially after extrinsic denervation. The causes of the decrease in postprandial absorption remain unknown, and our experimental model in the dog in vivo cannot differentiate changes in mucosal transport systems (transporter expression, activity, etc.) or alterations in paracellular flow. Our previous in vitro work did show decreases secondary to extrinsic denervation in active transport of glucose and glutamine under basal conditions[25,26]; whether further alterations occur in the first 2 postprandial hours remains unknown.

In summary, our study showed that postprandial augmentation of net absorption of water, electrolytes, and simple nutrients did not occur in the neurally intact (or extrinsically denervated) in situ canine ileum. Also, extrinsic denervation of the jejunoileum led to a transient decrease in the early postprandial absorption of glucose and glutamine when measured

2 weeks postdenervation that returned toward normal when reevaluated at 12 weeks postdenervation. These observations are of physiologic interest and may be of translational clinical value in the field of SBT.

The authors thank Deborah Frank for her expert assistance in the preparation of the manuscript.

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α- and β-Adrenergic Receptor Mechanisms in Spontaneous Contractile Activity of Rat Ileal Longitudinal Smooth Muscle

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Gastrointestinal motility is influenced by adrenergic modulation. Our aim was to identify specific subtypes of adrenergic receptors involved in inhibitory mechanisms that modulate gut smooth muscle contractile activity. Muscle strips of rat ileal longitudinal muscle were evaluated for spontaneous contractile activity and for equimolar dose-responses (10^{-7} to 3×10^{-5} M) to the adrenergic agents norepinephrine (nonselective agonist), phenylephrine (α_1-agonist), clonidine (α_2-agonist), prenalterol (β_1-agonist), ritodrine (β_2-agonist), and ZD7114 (β_3-agonist) in the presence and absence of tetrodotoxin (nonselective nerve blocker). Norepinephrine (3×10^{-5} M) inhibited 65 ± 6% (mean ± SEM) of spontaneous contractile activity. The same molar dose of ritodrine, phenylephrine, or ZD7114 resulted in less inhibition (46 ± 7%, 31 ± 5%, and 39 ± 3%, respectively; $P < 0.05$). The calculated molar concentration of ZD7114 needed to induce 50% inhibition was similar to that of norepinephrine, whereas higher concentrations of phenylephrine or ritodrine were required. Clonidine and prenalterol had no effect on contractile activity. Blockade of intramural neural transmission by tetrodotoxin affected the responses to ritodrine and phenylephrine (but not to norepinephrine or ZD7114), suggesting that these agents exert part of their effects via neurally mediated enteric pathways. Our results suggest that adrenergic modulation of contractile activity in the rat ileum is mediated primarily by muscular β_3-, β_2-, and α_1-receptor mechanisms; the latter two also involve neural pathways. (J GASTROINTEST SURG 2005;9:227–235)

KEY WORDS: Contractility, motility, ileum, rat, in vitro, adrenergic, adrenergic receptor, α-adrenergic receptors, β-adrenergic receptors

Coordination and modulation of gastrointestinal motor activity are dependent on the interaction of two complex neural inputs: the enteric nervous system, which is completely intrinsic within the bowel wall, and the central nervous system, sending its influences through the extrinsic nerves to the gut (vagal, sympathetic).[1] Interactions between the central nervous system and the enteric nervous system are important in gastrointestinal responses to stress, eating, and behavior.[2]

Vagal motor pathways modulate mainly the upper gastrointestinal tract and the distal colon and rectum. In the small bowel, vagal inputs are supplied to myenteric neurons.[3] These enteric neurons influence the generation of motor patterns.

The intestinal sympathetic nervous system consists of nerve cell bodies located in the prevertebral ganglia with their postganglionic fibers entering the gut. No adrenergic nerve cell bodies are present in the gut wall.[1] Most, if not all, sympathetic postganglionic fibers affecting motility are thought to synapse in the enteric nervous system and not directly on smooth muscle cells. Indeed, adrenergic nerves do not synapse directly on nonsphincter muscle cells in the gut.[4]

Presented in part at the Forty-Third Annual Meeting of The Society for Surgery of the Alimentary Tract, San Francisco, California, May 19–22, 2002 (poster presentation).

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Supported by Nycomed AG Switzerland, Ethicon, Switzerland, and the Swiss National Science Foundation (B.M.B.; Nr. 31-61583.00).

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.012

Despite the predominant, direct adrenergic input to the enteric nervous system, we found strong, adrenergically mediated inhibitory motor mechanisms in rat jejunum and ileum occurring preferentially at the level of these smooth muscle cells rather than in the enteric nervous system[5,6]; these effects appeared to be independent of input from the enteric nervous system.

Therefore, one approach to target gastrointestinal motility disorders through adrenergic pathways would be to direct the pharmacologic therapy at the receptors occurring in the gut on smooth muscle cells. To date, therapeutic approaches targeting adrenergic pathways in the gastrointestinal tract have not been very successful, in part because of substantial cardiovascular side effects of the agents used.[7]

Therefore, mechanisms involved in modulating contractile activity of the gut mediated by specific subtypes of adrenergic receptors are of considerable interest. Our first aim was to identify which adrenergic receptor subtypes mediate inhibition of spontaneous contractile activity. Second, we wanted to determine if these receptor-specific mechanisms were mediated at the level of the smooth muscle and/or via the enteric nervous system. Our hypothesis was that both α_1- and β_2-receptor mechanisms mediate the inhibitory responses and that these mechanisms are active directly at the level of the smooth muscle and not indirectly via effects mediated through the enteric nervous system.

METHODS

Preparation of Tissue

Procedures and animal care were performed according to the guidelines of the Department of Agriculture of the Canton of Bern, Switzerland. Male Wistar rats were used in all experiments. Anesthesia was achieved with intraperitoneal sodium pentobarbital (5 mg/100 g; Abbott Laboratories, North Chicago, IL). A 5-cm segment of the ileum was removed beginning 2 cm orad to the ileocecal valve and stored in cold Krebs-Ringer buffer (concentration in mM: NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0, calcium disodium edetate 0.26, and glucose 11.1). The distal end of the specimen was marked.

Recording of Contractile Activity

The segment of the distal ileum was immersed in chilled, modified Krebs-Ringer bicarbonate solution and opened along the mesenteric border. The tissue was pinned flat in a Petri dish, and eight full-thickness muscle strips per rat were prepared in the direction of the longitudinal muscle. Silk loops were tied at both ends of the strips. The muscles were suspended vertically in 5-ml organ chambers (Radnoti Glass Technology Inc., Monrovia, CA) filled with modified Krebs-Ringer bicarbonate solution maintained at 37.5° C and bubbled with 95% O_2 and 5% CO_2 (Carbagas, Bern, Switzerland). The lower end of the muscle strip was connected to a fixed glass hook in the chamber, and the upper end was attached to a noncompliant force transducer (Radnoti Glass Technology Inc.), thereby allowing measurement of isometric force.

Experimental Design

After an equilibration period of 80–90 minutes with change of the buffer solution every 20–25 minutes, each strip was stretched incrementally at 10- to 15-minute intervals to its optimal length (L_o). L_o is defined as the length beyond which further stretching did not increase the amplitude of spontaneous contractions. The entire experiment was then performed at this L_o; strips without spontaneous activity were not used (2% of all muscle strips).

After recording of baseline spontaneous activity, one substance was administered per chamber in a cumulative manner every 10 minutes. Norepinephrine (NE) was chosen as the nonselective adrenergic agonist; phenylephrine and clonidine as α_1- and α_2-selective agonists; and prenalterol, ritodrine, and ZD7114, as β_1-, β_2-, and β_3-selective agonists, respectively. Drugs were added in cumulative doses (10^{-7} to 3×10^{-5} M) every 10 minutes. The highest dose used was 3×10^{-5} M according to our previous work using only NE.[5,6] One chamber contained a control strip to confirm stable activity during the duration of the experiment, and the final chamber contained a spare strip.

After the dose-response experiment, the chambers were washed 4 times with modified Krebs-Ringer buffer. When spontaneous contractions returned to baseline activity, tetrodotoxin (TTX; 10^{-6} M) was added to every chamber. TTX is thought to abolish most all enteric neural input by blocking neuronal sodium channels. After a 15- to 20-minute equilibration, the same dose-response experiment was repeated in each chamber with the same agonist.

At the conclusion of the experiment, the length of each strip between the two ties of silk loops and wet weight was measured.

Data Analysis

Total spontaneous contractile activity was quantified as the integral of the generated force ($g \times$ time as total area under the contractile curve) measured

for 5 minutes at L_o, whereas responses to adrenergic agonists were quantified by measuring the integral of force for 5 minutes immediately after drug administration. The integral of force was calculated by computerized methodology using special software (AcqKnowledge, Biopac Systems, Inc., Goleta, CA), normalized per millimeter squared of cross-sectional area (CSA) for each muscle strip.

The CSA was calculated using the following equation:

$$\text{CSA (mm}^2\text{)} = \text{Tissue wet weight (mg)/Tissue length (mm)} \times \text{Tissue density (mg/mm}^3\text{)}$$

Tissue length and weight were measured at the end of the experiment, and smooth muscle tissue density was assumed to be 1.05 mg/mm.[3,8]

The dose-response curve for each agonist was obtained by defining spontaneous contractile activity as 100%. To quantify these dose-response curves, the negative of the natural log (In) of the equipotent concentration that caused a 50% response (EC_{50}) was estimated for each agonist based on the dose-response curve. A greater EC_{50} represents a smaller concentration of an agonist needed to induce 50% inhibition of spontaneous activity.

Values are presented as mean ± SEM. Student's *t* tests with a Bonferroni correction were used to compare the effects of each specific agonist with spontaneous activity at all doses and with the respective effect of NE. The effect of TTX on spontaneous activity, on EC_{50}, and on each dose of the respective agonist was evaluated in the same way.

Drugs

L-Phenylephrine hydrochloride, clonidine hydrochloride, ritodrine hydrochloride, and norepinephrine bitartarate salt were purchased from Sigma (St. Louis, MO). Prenalterol and ZD7114 hydrochloride were purchased from Astra Zeneca (Södertälje, Sweden). TTX was purchased from Juro (Luzern, Switzerland).

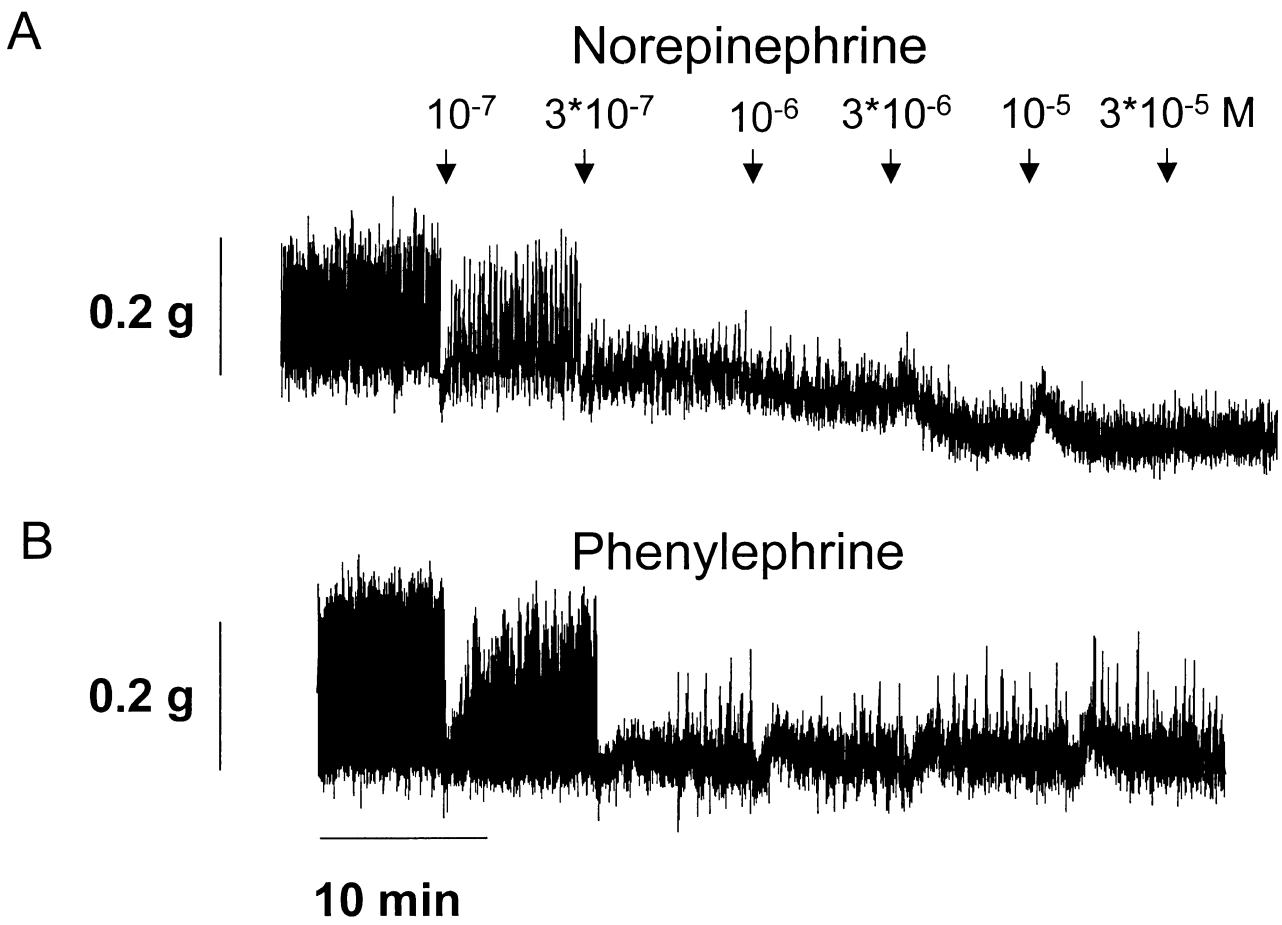


Fig. 1. Effect of norepinephrine (**A**) and phenylephrine (α_2) (**B**) on spontaneous activity. Cumulatively administered molar doses of agents caused a dose-dependent decrease in contractile activity.

RESULTS

Spontaneous Contractile Activity

Spontaneous phasic contractile activity was recorded shortly after suspending the muscle strips in the organ chambers. After the addition of TTX (after the first adrenergic dose-response experiments, washout, and restoration of spontaneous activity), contractile activity was reduced slightly from 77 ± 8 to 73 ± 8 (g/5 min/mm^2; $P < 0.01$).

Effect of Nonselective Adrenergic Stimulation

In all strips treated with NE, the amplitude and the baseline tone were reduced in a dose-dependent manner, whereas the frequency of contractions remained unchanged. At the higher doses, an initial increase in basal tone was observed (Fig. 1A). Inhibition of spontaneous contractile activity induced by the highest dose of norepinephrine (3×10^{-5} M) was $65 \pm 6\%$. Blocking all neural activity within the bowel wall with TTX (10^{-6} M) did not change the dose-response to NE (Table 1) nor the effect of the highest dose of NE on baseline tone (Table 2).

Effect of α-Agonists

Phenylephrine (α_1-agonist) inhibited contractile activity by reducing the amplitude but not the basal tone in a dose-dependent fashion (Fig. 1B). However, the EC_{50} was less than that for NE, and the inhibition (at 3×10^{-5} M) was less compared with an equimolar dose of norepinephrine (Table 1; Figs. 1, 2A). TTX had no effect on α_1-receptor–mediated inhibition induced by phenylephrine. However, if only changes in baseline tone were analyzed, TTX slightly increased the change of baseline tone induced by the highest dose of phenylephrine (3×10^{-5} M; $35 \pm 5\%$ versus $43 \pm 4\%$, $P < 0.05$; Table 2). Clonidine (α_2-agonist) with and without TTX had no demonstrable effect on contractile activity.

Table 2. Reduction of baseline tone induced by adrenergic agonist without or with tetrodotoxin (TTX; 10^{-6} M)

	Response to 3×10^{-5} M dose*	
	Without TTX	With TTX
Norepinephrine	75 ± 9	80 ± 6
Phenylephrine, α_1	35 ± 5	$43 \pm 4^{\dagger}$
Clonidine, α_2	7 ± 4	20 ± 4
Prenalterol, β_1	26 ± 4	32 ± 6
Ritodrine, β_2	66 ± 8	$45 \pm 6^{\dagger}$
ZD7114, β_3	58 ± 7	60 ± 7

*Values represent percent (mean ± SEM; n ⩾ 8 rats) reduction of baseline (one after the highest dose of agonist (3×10^{-5} M) compared with baseline tone before dose-response experiment (100%).
$^{\dagger}P < 0.05$ compared with without TTX.

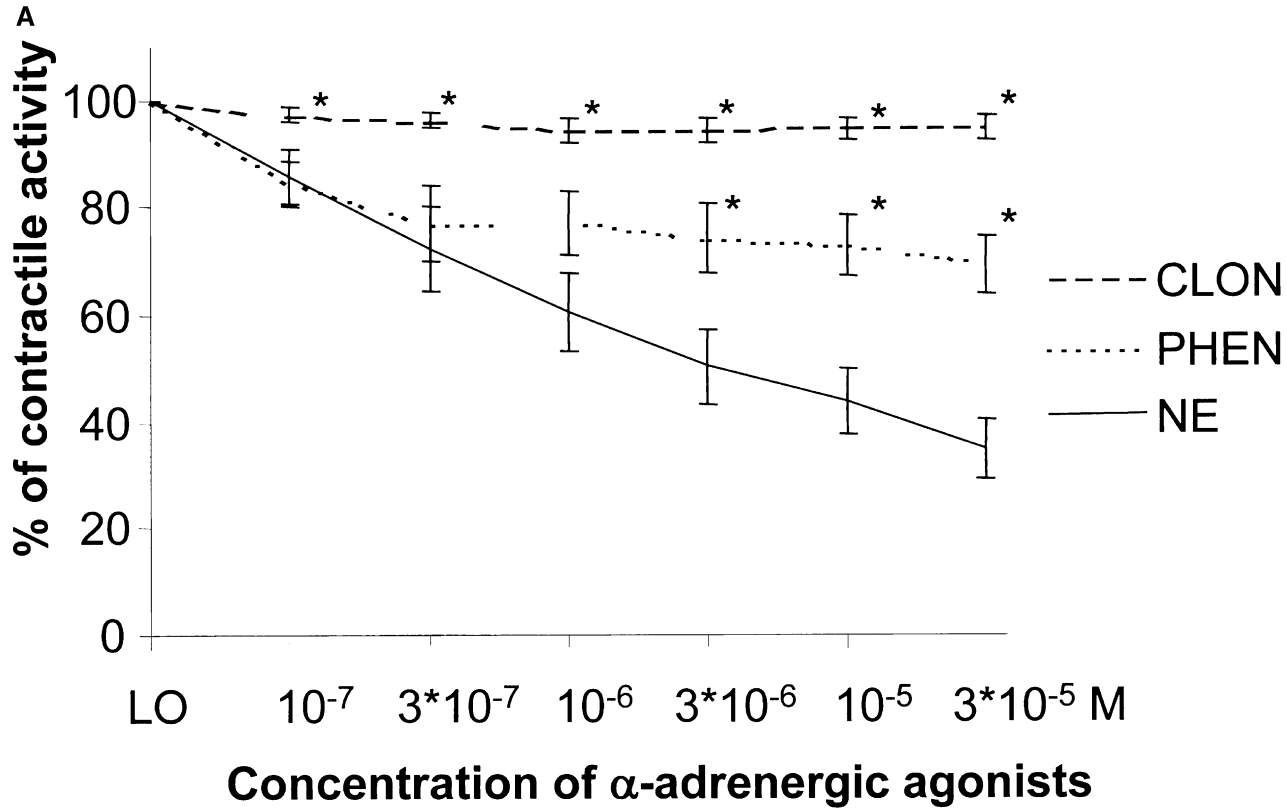
Effect of β-Agonists

Differing effects of the three β-adrenergic agonists were noted. Prenalterol (β_1-agonist) with or without TTX had no effect. In contrast, ritodrine (β_2-agonist) and ZD7114 (β_3-agonist) both induced a marked, dose-dependent effect with inhibitions of $39 \pm 3\%$ and $46 \pm 7\%$ at 3×10^{-5} M doses, respectively (Table 1, Figs. 2B, 3). TTX did not influence the dose-response of ZD7114 (β_3-agonist), but TTX reduced the inhibitory effect of 3×10^{-5} M ritodrine (β_2-agonist) from $46 \pm 7\%$ to $35 \pm 6\%$ ($P < 0.05$); the EC_{50}, however, did not change (Table 1). This decrease in inhibition seems to be due primarily to a lesser reduction in the basal tone (Fig. 4). Ritodrine (3×10^{-5} M; β_2-agonist) reduced basal tone by

Table 1. Inhibitory effect of selective adrenergic agonists on rat ileal longitudinal muscle without and with tetrodotoxin (TTX; 10^{-6} M)

	Response to 3×10^{-5} M dose*		EC_{50}	
	Without TTX	With TTX	Without TTX	With TTX
Norepinephrine	$65 \pm 6^{\dagger}$	$70 \pm 5^{\dagger}$	5 ± 0.3	5.3 ± 0.7
Phenylephrine, α_1	$31 \pm 5^{\dagger\ddagger}$	$30 \pm 6^{\dagger\ddagger}$	$1.5 \pm 0.7^{\ddagger}$	$2.3 \pm 1.2^{\ddagger}$
Clonidine, α_2	$5 \pm 3^{\ddagger}$	$13 \pm 7^{\ddagger}$	NA	NA
Prenalterol, β_1	$9 \pm 4^{\ddagger}$	$15 \pm 2^{\dagger\ddagger}$	NA	NA
Ritodrine, β_2	$46 \pm 7^{\dagger\ddagger}$	$35 \pm 6^{\dagger\ddagger\S}$	$3.5 \pm 0.4^{\ddagger}$	$3.0 \pm 0.6^{\ddagger}$
ZD7114, β_3	$39 \pm 3^{\dagger\ddagger}$	$42 \pm 4^{\dagger\ddagger}$	4.4 ± 0.6	4.4 ± 0.4

EC_{50} = calculated negative log of molar value resulting in 50% inhibition of spontaneous activity; NA = not applicable, because no inhibition was seen.
*Values given as percent inhibition, mean ± SEM; n ⩾ 8 rats.
$^{\dagger}P < 0.005$ compared with norepinephrine.
$^{\ddagger}P < 0.06$ compared with spontaneous activity before adding respective drug.
$^{\S}P < 0.05$ compared with same dose without TTX.



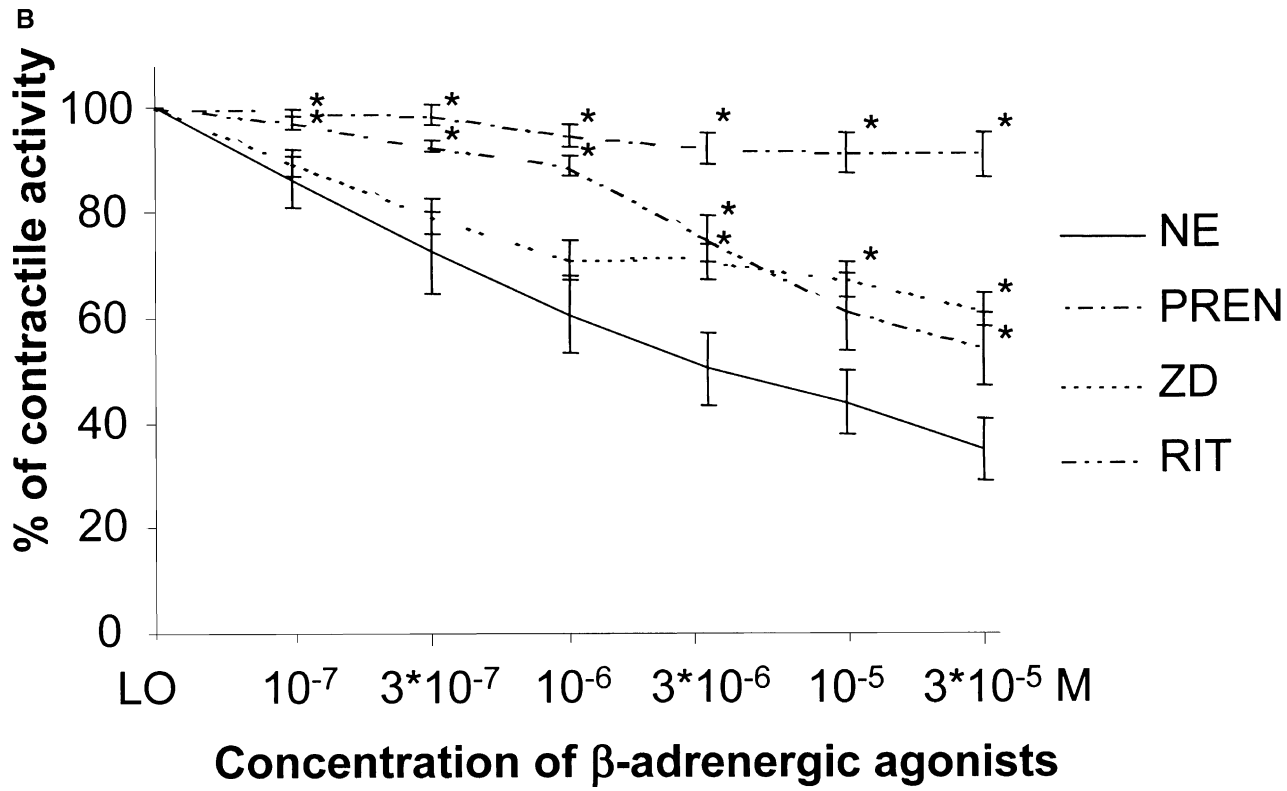


Fig. 2. Dose-responses of (**A**) clonidine (CLON) (α_1) and phenylephrine (PHEN) (α_2) and of (**B**) prenalterol (PREN) (β_1), ritodrine (RIT) (β_2) and ZD7114 (ZD) (β_3) compared with norepinephrine (NE). Values given as mean ± SEM; n = 9 rats. *$P < 0.05$ versus NE.

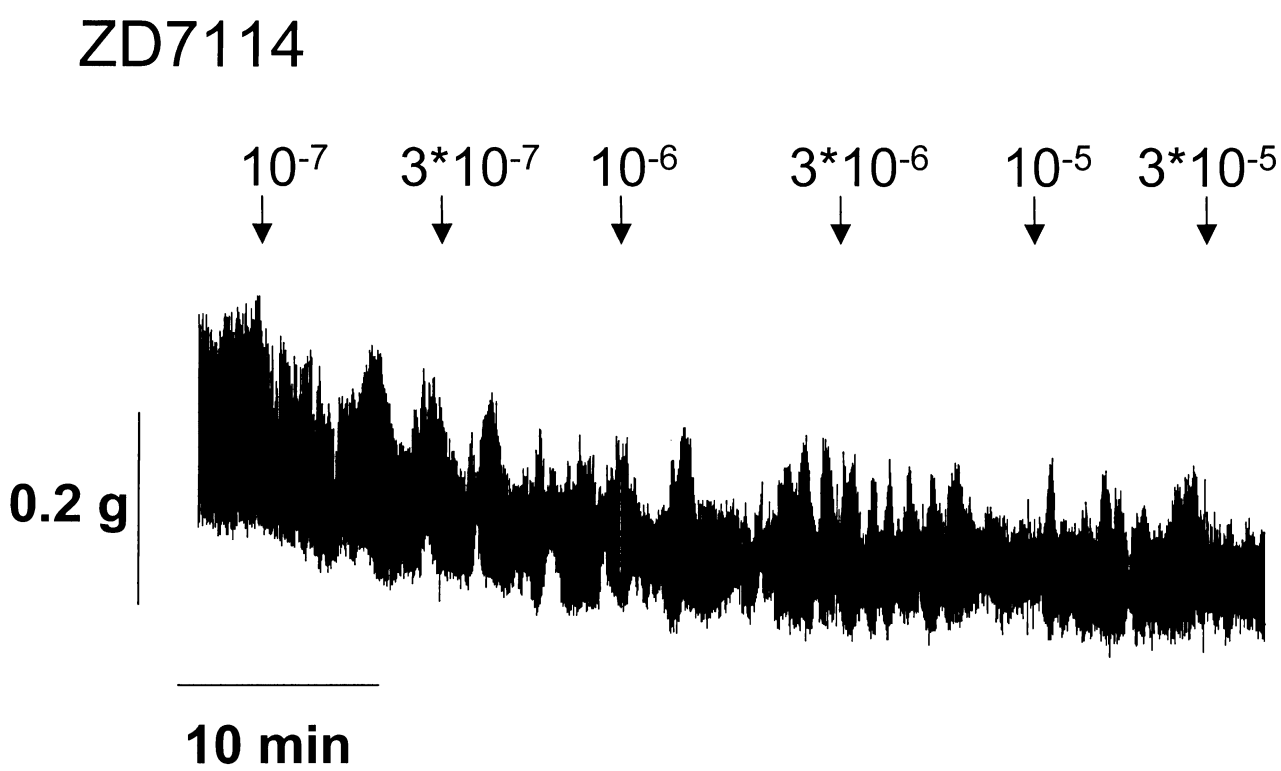


Fig. 3. Effect of ZD7114 (β_3) on spontaneous activity. ZD7114 was administered cumulatively and caused a dose-dependent decrease in basal tone and thus in contractile activity.

66 ± 8%. In the presence of TTX, the reduction in baseline tone was smaller (45 ± 6%, $P < 0.05$).

The EC_{50} for ZD7114 did not differ from the EC_{50} of NE (4.4 ± 0.6 versus 5.0 ± 0.3), suggesting a similar molar inhibitory effect by ZD7114. The EC_{50} of ritodrine and NE (3.5 ± 0.4 versus 5.0 ± 0.3, $P < 0.05$) differed; the dose-response curve for ritodrine was shifted to the right, compared with NE (Fig. 2B).

DISCUSSION

Our study was designed to characterize the involvement of specific adrenergic α_1-, α_2-, β_1-, β_2-, or β_3-receptor mechanisms in the inhibition of contractile activity of longitudinal smooth muscle in the rat ileum. These contractile responses are of particular interest, because modulation of gut motility via adrenergic pathways may represent a novel therapeutic target for motility disorders. This pharmacologic approach would require identification of specific receptor subtype mechanisms such that effects on intestinal contractile function can be targeted, possibly minimizing or even avoiding cardiovascular side effects.

Our main findings were that α_2- and β_1-receptor mechanisms do not appear to be involved in the adrenergic modulation of gut contractile activity in the rat, neither directly on the smooth muscle cells nor indirectly via the enteric nervous system. In contrast, α_1, β_2, and β_3 pathways reproduced, in part, the inhibition induced by norepinephrine, a nonselective, global adrenergic agonist. Blocking enteric neural activity within the muscle strip (with TTX 10^{-6} M) partially reduced the response of β_2-receptor and slightly increased the response of α_1-receptor stimulation, suggesting involvement of enteric neural mechanisms.

The involvement of α_1- but not α_2-receptors in the control of motor activity in the rat ileum is of special interest, because in general not much is known about the role of α-receptors in intestinal contractility. A case report of a patient with pheochromocytoma in whom paralytic ileus was treated successfully with the α-receptor antagonist phentolamine and later with prazosin (selective α_1-receptor agonist)[9] suggests that α-mechanisms may be involved in human small bowel contractile activity, whereas in an in vitro study in human tissue, α_2 pathways did not seem to play a role.[10] Therefore, it seems likely that in control of human small bowel contractility, α-adrenergic influence is dependent on α_1-receptors. This would be in accordance with our

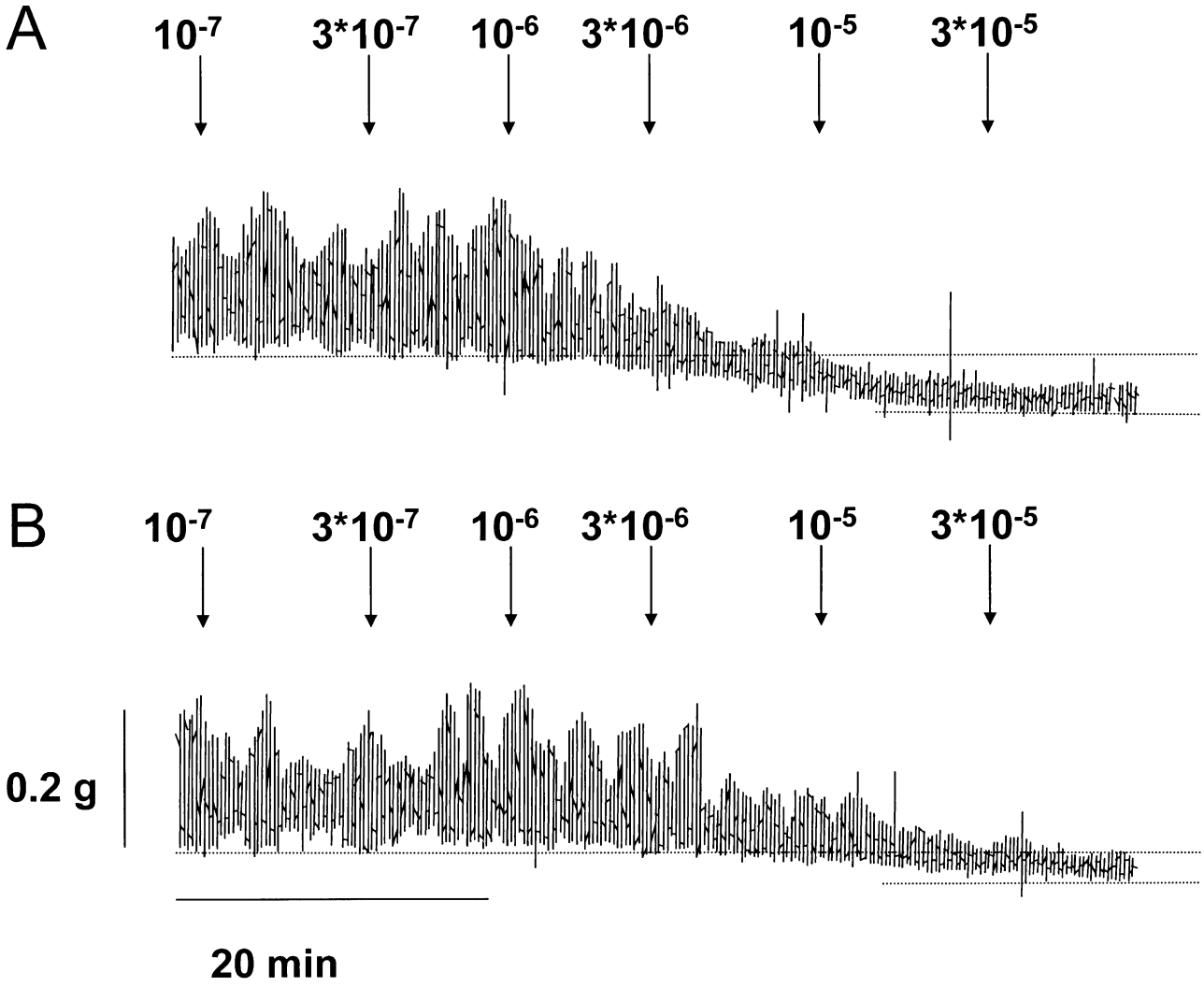


Fig. 4. (**A**) Effect of ritodrine (β_2) on spontaneous activity. Ritodrine was administered cumulatively and caused a dose-dependent decrease in contractile activity. (**B**) In presence of tetrodotoxin, the dose-dependent reduction in basal tone was smaller, thus reducing the overall inhibitory effect induced by ritodrine.

results in rat ileum where α_1 mechanisms but not α_2 pathways appear to influence contractile properties in vitro. However, in the gut of other species, the role of α-receptors is different: in guinea pig ileum, both α_1- and α_2-receptors mediate inhibition,[11] and in canine and mouse ileum and in rat colon, only α_2, not α_1, inhibitory mechanisms have been described.[12–14] In rabbit, α_1 mechanisms can be part of inhibitory pathways in other anatomic regions of the gut such as jejunum[15] and duodenum.[16] Because of marked species differences, broad generalizations between species must be made with caution.

Inhibitory mechanisms mediated by β_2-adrenergic receptors were identified in our study. This finding is consistent with results in rabbit ileum,[17] whereas in canine ileum, β_2 pathways had no influence on contractile activity.[12]

β_3-Receptors have been of particular interest because they seem to be abundantly present in gastrointestinal tissue.[18,19] Our results are in accordance with the data of Brown and Summers,[20] who showed that β_3 pathways play a major role in the inhibition of rat ileum. In guinea pig ileum, contractile activity is also inhibited by β_3-receptor stimulation,[21] whereas canine ileum does not seem to be influenced by β_3-receptors.[12]

As discussed earlier, β_2- and β_3-receptor–specific inhibition plays a role in inhibiting contractile activity, whereas β_1-receptor mechanisms do not appear to be involved in the inhibition of longitudinal muscle of the rat ileum. Our latter finding contrasts with data from Brown and Summers,[20] who reported a slight effect of β_1-receptor mechanisms in rat ileum. Differences in the muscle layers investigated and in

the experimental protocols, such as different substances that were used and conduction of the experiment in precontracted muscle strips, may explain some of these differences. We have shown previously that different contractile responses in circular versus longitudinal muscle layers are as important as are differences between anatomic regions of jejunum versus ileum.[22,23] In an in vivo study in canine ileum that supports our results, β_1-receptors were found to not be important.[12]

In our experiments, we tried to distinguish between muscle-related mechanisms and pathways involving the enteric nervous system, because under pathologic conditions, adrenergic mechanisms might be compromised at either level of control.[5,24,25] None of the specific adrenergic α_2-, β_1-, or β_3-receptor mechanisms were TTX sensitive, and therefore the pathways seem to be independent of the enteric nervous system. Interestingly, part of the β_2 and α_1 inhibition in our experiments appears to be modulated by presynaptic mechanisms. Blockade of neural β_2 mechanisms by TTX resulted in a lesser inhibition of contractile activity. This neurally mediated effect appears to occur via a reduction in baseline tone rather than a reduction in phasic activity. In contrast, the α_1-adrenergic effect appears to be related to a slight increase in baseline tone. The physiologic relevance of these findings as seen in our in vitro measurement of isometric contractions is not yet known. In other study designs, the distinction between muscle or neurally mediated inhibition was not made.[17] However, it is conceivable that part of the gastrointestinal motility disorders in neurologic diseases such as diabetic neuropathy or other postneurotomy syndromes (e.g., postvagotomy gastroparesis) are linked with an impaired modulation of contractile activity via β_2 and α_1 mechanisms. Thus, further studies are required.

CONCLUSION

Because none of the specific pathways alone reached the degree of inhibition achieved by NE, we conclude that adrenergic inhibition in rat ileum may be an additive effect of the three specific adrenergic mechanisms noted to inhibit contractile activity (α_1, β_2, and β_3). This concept of the involvement of several receptors in inhibitory mechanisms is supported by previous results in rabbit ileum[17] and by studies in human colon by Manara et al.[26] Possibly, the known plasticity of the gut may allow one receptor to take over for another receptor under various conditions. Hutchinson et al.[27] showed that β_1-adrenoceptors may compensate for β_3-adrenoceptors in adrenoceptor-mediated relaxation of ileal muscle from β_3-adrenoceptor knock-out mice, and Susulic et al.[28] Suggest that "cross-talk" might exist between β_3-adrenoceptors and β_1-adrenoceptor gene expression.

Our results, when compared with the literature, underline the high degree of variability not only in regional dependent differences (anatomic and muscle layer) but also between species. It is of interest that α_1-receptor mechanisms (but not α_2 pathways) played a role in our rat ileum study. The scarce data from the literature suggest a similar constellation of contractile α mechanisms in human small bowel. If this similarity is confirmed in the future, the rat ileum might be attractive to further model α_1 pathways in pathologic states.

For β_2- and β_3-receptors, species differences are evident as well, but we do not have comparable data for human ileum. Species differences, especially for β_3 pathways, would be of interest, because these receptors are abundantly present not only in adipose tissue but also in gastrointestinal tissue and therefore are of interest for the study of gastrointestinal motility.[29,30] To our knowledge the role of β_3-receptors in human contractility has not been carefully investigated in vitro.

Because of the species differences of adrenoceptor distribution and function, choosing the right animal model is crucial. This has been noted for cardiovascular studies[17] and will be the same for contractile studies of the gastrointestinal tract.

The authors thank Dr. M. G. Sarr for his valuable input to the manuscript.

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Comparative Study of Epithelial Gene Expression in the Small Intestine Among Total Proctocolectomized, Dietary Sodium-Depleted, and Aldosterone-Infused Rats

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We previously demonstrated enhanced plasma aldosterone, ileal activation of epithelial sodium channel (ENaC), and induction of 11β-hydroxysteroid dehydrogenase type 2 after total proctocolectomies in rats. However, factors other than circulating aldosterone may cause molecular induction associated with sodium transport. Sprague-Dawley rats were treated with sodium-deficient diets or subcutaneous aldosterone infusion for 4 weeks. Rats also underwent total proctocolectomies as positive control. We extracted epithelial RNA from the distal small intestine and compared mRNA expression of the α, β, and γ subunits of ENaC, prostasin, sodium glucose transporter 1 (*SGLT1*), and the α1 and β1 subunits of Na^+/K^+-ATPase among control, total proctocolectomized, dietary sodium-depleted, and aldosterone-infused rats by quantitative reverse transcription–polymerase chain reaction or Northern blotting. A significant increase in aldosterone was noted in sodium-depleted and aldosterone-infused rats. The induction of three subunits of ENaC and prostasin mRNA was observed in proctocolectomized, aldosterone-infused rats but not in dietary sodium-depleted rats. The levels of the α1 and β1 subunits of Na^+/K^+-ATPase were similar among the experimental groups. *SGLT1* mRNA was induced only in proctocolectomized rats. The molecular induction of ENaC, prostasin, and *SGLT1* is unique for total proctocolectomized rats. Aldosterone infusion can induce several essential molecules for sodium absorption, as seen in total proctocolectomy. (J GASTROINTEST SURG 2005;9:236–244)

KEY WORDS: Total proctocolectomy, ulcerative colitis, familial adenomatous polyposis, aldosterone, epithelial cells, intestinal adaptation

Total proctocolectomy followed by ileoanal (canal) anastomosis is established as a surgical treatment for ulcerative colitis and familial adenomatous polyposis.[1] The patients who undergo this procedure are cured of their diseases by the removal of the entire colon without receiving a permanent ileostomy. Nevertheless, the patients have persistent diarrhea and frequent bowel movements due to the lack of a colon.[2] Severe watery diarrhea and dehydration are frequent symptoms in those patients when they have acute or infectious enteritis. Dehydration is facilitated by a preexisting chronic deficit of body fluid and sodium.[3] The significance of subsequent renal compensation to keep homeostasis has been well addressed.[4] However, it is obvious that frequent bowel movements and watery diarrhea impair a patient's quality of life substantially after surgery.

In our previous study, adaptive or compensatory mechanisms for mitigating watery diarrhea were investigated using a total proctocolectomized model in rats.[5] We demonstrated the enhancement of plasma aldosterone, but not corticosterone, with chronologic

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Supported by Grants-in-Aid for Scientific Research 10557118 and 14657295 (K.F.) and 07457266 (I.S.) from the Ministry of Education, Science and Culture of Japan and by Kanae Foundation (K.F.).
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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.017

activation of the sodium transport mediated by epithelial sodium channel (ENaC) in the remnant ileum.[5] Because water homeostasis and electrolyte balance in the body are mainly regulated by the renin-angiotensin-aldosterone system in the gastrointestinal tract,[6] some of the molecular changes observed in the remnant small intestine may be similarly induced only by high levels of circulating aldosterone. Alternatively, a factor or multiple factors other than circulating aldosterone—such as dehydration, sodium deficit, or factors yet to be defined—may induce molecules associated with sodium transport in the remnant small intestine. In other words, it is unclear whether aldosterone induces almost all or a part of the molecular changes developing in epithelial cells of total proctocolectomized rats. Furthermore, if lower levels of aldosterone than those seen in total proctocolectomized rats could induce adaptive molecular changes, that might be better in the aspect of clinical application. Therefore, we compared gene expression in the distal small intestine among control, dietary sodium-depleted, aldosterone-infused, and total proctocolectomized rats. Dietary sodium deprivation has frequently been used to study the effect of sodium deficit and "endogenous" aldosterone on epithelial cell function without dehydration.[7–9] On the other hand, aldosterone is exogeneouly administered to investigate aldosterone-mediated sodium transport in the gut and kidney.[7,10,11]

We selected to study ENaC, Na^+/K^+-ATPase, prostasin, and sodium glucose transporter 1 (*SGLT1*) as essential molecules for sodium transport. ENaC and Na^+/K^+-ATPase have a major role in sodium absorption via entry through the luminal surface and extrusion from the basolateral side, respectively. Prostasin is a novel serine protease expressed in the rat kidney collecting duct that increases the activity of ENaC when prostasin and ENaC are coexpressed in *Xenopus* oocytes.[12] Therefore, prostasin may have a role in sodium transport in other epithelial tissues, including the remnant small intestine. Finally, the expression of *SGLT1* was investigated because this molecule is essential for glucose absorption and transports sodium along with glucose and water across the membrane against an electrical gradient in the small intestine.[13]

MATERIAL AND METHODS

Animals

Male Sprague-Dawley rats (8 weeks old) were housed in the animal room at Tohoku University Institute for Experimental Animals, Sendai, Japan, with a 12-hour light/dark cycle; they were fed a standard rat diet (Nippon Nosan, Yokohama, Japan) and allowed tap water ad libium. As control rats (n = 10), untreated rats at the age of 10 or 12 weeks were used throughout the series of experiments.

To establish models showing hyperaldosteronism, rats were subjected to a sodium-deficient diet (n = 8) or subcutaneous infusion of aldosterone (n = 6) for 4 weeks. A sodium-depleted diet was obtained from Funabashi Farm Co. (Funabashi, Japan) that contained 0% NaCl, 1.43% KCl, 50.27% corn starch, 23% casein, 10% sucrose, 5% corn oil, 4% cellulose, 1% UPS mineral without sodium and potassium, 1% UPS vitamin, and 0.3% DL-methionine. The rats were given free access to water and a sodium-depleted diet.

Alternatively, animals (weight, 250–300 g) fed the control diet were anesthetized with ether, and the osmotic pumps were placed in the subcutaneous space. D-Aldosterone (Sigma Chemical Co., St. Louis, MO) was dissolved with polyethylene glycol 400 and loaded into an osmotic pump (model 2ML4; Alza Co., Cupertino, CA). Aldosterone was administered at a dose of 80 μg/100 g/day continuously.[7,10] In our preliminary study, rats infused with polyethylene glycol alone exhibited no changes in parameters used in this study. Dietary sodium-depleted and aldosterone-infused rats underwent necropsy at 4 weeks after the treatment. Blood was immediately collected, and the small intestine was removed. As positive control, rats (250–300 g body weight) (n = 8) underwent total proctocolectomy as described previously.[5] The rats were maintained only by supplemented water for 3 days and then standard diets. Total proctocolectomized rats underwent necropsy at 4 (n = 6) or 8 (n = 2) weeks after their operation, and the small intestines were removed. The protocol for this project was approved by the Tohoku University Animal Care Committee.

Measurement of Plasma Aldosterone

Whole blood was collected from the abdominal aorta under anesthesia with ether between 12:00 A.M. and 2:00 P.M. (to avoid diurnal variation). Plasma was separated from whole blood via centrifugation at 3000 rpm for 10 minutes. The plasma aldosterone concentration was measured using ALDOSTERONE RIA KIT II (DAINABOT, Tokyo, Japan) and expressed as mean ± SE values.

Preparation of Total RNA From Purified Small Intestinal Epithelial Cells

Epithelial cells were separately isolated from 15-cm segments of the proximal, middle, and distal small intestine. After the removal of mucus in Hanks'

balanced salt solution (HBSS) containing dithiothreitol (DTT) (1.5 mg/ml), the mucosal tips were incubated 3 times in HBSS containing ethylenediaminetetraacetic acid (EDTA) (1 mM) for 45 minutes. At the end of each incubation, the supernatants were centrifuged at 1500 rpm for 5 minutes, and the resulting pellets were resuspended with RPMI 1640 (GIBCO BRL, Gaithersburg, MD). Both the purity and viability of the epithelial cells were assessed by staining with trypan blue and were consistently over 90% with a minimal contamination of mononuclear cells. The cells were pelleted and lysed with guanidium thiocyanate solution. RNA was extracted by cesium chloride gradient. The quantity and quality of the RNA were determined by absorbance at 260 nm and staining with ethidium bromide following gel electrophoresis.

Quantitative Reverse Transcription–Polymerase Chain Reaction

The amount of α, β, and γ subunits for ENaC and prostasin were measured by quantitative reverse transcription–polymerase chain reaction (RT-PCR). Complementary DNA was obtained from 1 μg total RNA in 20 μl RT buffer containing 50 mM Tris-HCl, pH 8.3, 55 mM KCl, 3 mM $MgCl_2$, 0.02 mM DTT, 0.5 mM dNTP, 62.5 mg/ml oligo(dT)12-18, and 100 units RNase H^- reverse transcriptase (GIBCO BRL) at 42°C for 60 minutes. The reaction mixture was heat-inactivated for 10 minutes at 90°C and diluted 4-fold with Tris-EDTA buffer. Two microliters of diluted RT mixture was used for mRNA quantification with QuantiTect SYBR Green PCR Kit (Quiagen K.K., Tokyo, Japan) and ABI GeneAmp 5700 (Applied Biosystems Japan, Tokyo, Japan) according to the manufacturer's protocol, in duplicate. The primer sequence for quantitative RT-PCR was determined with Primer Express software (PE Applied Biosystems, Foster City, CA) (Table 1). In each quantification with specific primer set, the dissociation curve of the amplified products displayed a single peak, demonstrating that only specific products were synthesized. Amplified products were preliminarily subcloned into a pCRII TOPO cloning vector with use of a TA cloning kit (Invitrogen, Tokyo, Japan). The sequence of inserted cDNA was confirmed using an AutoCycle Sequencing Kit (Pharmacia Biotech, Tokyo, Japan) and ALF Express DNA Sequencer (Pharmacia Biotech). The relative quantification of target and β-actin mRNAs was calculated using the comparative threshold cycle number for each sample fitted to a four-point standard curve. The standard curve was constructed using a serial dilution of total RNA extracted from colonic epithelial cells of control rats. The expression levels were normalized to β-actin mRNA. The amplification profile consisted of initial incubation at 50°C for 2 minutes, initial denaturation at 95°C for 10 minutes, followed by the specified 40 cycles of 94°C for 30 seconds, 50°C (for α and β subunits of ENaC), 55°C (for β-actin and prostasin), or 60°C (for γ subunit of ENaC) for 1 minute and 72°C for 1 minute.

Northern Blot Analysis

Twenty micrograms of total RNA was fractionated through electrophoresis on 1% agarose gels and transferred onto a Hybond-N+ nylon membrane (Amersham Pharmacia Biotech, Bucks, England). Complementary DNA of α1 and β1 subunits of Na^+/K^+-ATPase was kindly donated by Dr. Peter J. Fuller (Prince Henry's Medical Institute of Medical Research, Melbourne, Australia).[14] Rat glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) cDNA

Table 1. Primer sequence used for quantitative reverse transcription–polymerase chain reaction (PCR)

		Sequence	PCR product (bp)
ENaC-α	Up	5′-CGGAAGCCTTGTAGTGTGATCA-3′	103
	Down	5′-TCTGCAAGGACAGCATCTCG-3′	
ENaC-β	Up	5′-CCTCCCAACTATGACTCCCTGA-3′	169
	Down	5′-TGGCTCTTTGGACAAGGGC-3′	
ENaC-γ	Up	5′-ACGCTAACCCTGACTTAGCCTG-3′	152
	Down	5′-CTTGTCCCAATGTCAATGGTTG-3′	
Prostasin	Up	5′-ACCTTCTCCCGCTACATCAGAC-3′	255
	Down	5′-TCCCTTAACATAGCCAGCGC-3′	
SGLT1	Up	5′-CATCCTCTTCGCTATCAGCGTC-3′	361
	Down	5′-GATGCCGTTGATGTTCACCA-3′	
β-Actin	Up	5′-ACCACCACAGCTGAGAGGGA-3′	152
	Down	5′-CCGATAGTGATGACCTGACCG-3′	

ENaC = epithelial sodium channel.

was also prepared by PCR cloning as previously described elsewhere.[15] The protocol for probe labeling and Northern blotting was previously described.[16] The hybridization signals were visualized using a BAS system BioImage analyzer (Fuji, Tokyo, Japan).

Immunohistochemistry for α Subunit of ENaC

Short segments of 5 mm in length from the distal ileum were obtained from control, dietary sodium-depleted, and total proctocolectomized rats. Tissues were fixed in formalin and embedded in paraffin. We used a polyclonal antibody raised against ENaC-α subunit (Sigma-Aldrich Inc., St. Louis, MO) because the α subunit alone can form fully functional amiloride-sensitive sodium channels.[17,18] The sections were stained as previously described with minor modifications.[19] Briefly, the primary antibody was used at a dilution of 1:200. HRP-labeled anti-rabbit Fab′ fragment (HISTOFINE Simple Stain PO [MULTI], Nichirei, Tokyo, Japan) was used as second antibody. The antigen-antibody complex was visualized with 3,3′-diaminobenzidine (DAB) solution (1 mM DAB, 50 mM Tris-HCl buffer, pH 7.6, and 0.006% H_2O_2) and counterstained with hematoxylin. The specificity of the immunohistochemical staining was confirmed by replacing the primary antibody with normal rabbit IgG or phosphate-buffered saline.

Histologic Examination

A small segment of the distal ileum was obtained to investigate whether the mucosal architecture was altered by total proctocolectomy, aldosterone infusion, and/or breeding with sodium-depletion diet. Tissues were fixed in 10% buffered formalin and mounted in paraffin wax. Sections 3 μm thick were routinely stained with hematoxylin-eosin.

Statistical Analysis

All values are given as mean ± SE, with n representing the number of animals. Data were tested for significance by Scheffé's F test. Significance was accepted at $P < 0.05$.

RESULTS

Plasma Aldosterone Levels After Total Proctocolectomy, Treatment with a Sodium-Depleted Diet, or Treatment with Aldosterone Infusion

The plasma aldosterone level was 0.16 ± 0.06 ng/ml in control rats. Sodium-depleted and aldosterone-infused rats exhibited similar plasma aldosterone levels that were significantly higher (>10-fold) than those of control rats (Fig. 1).

Expression of the α, β, and γ Subunits of ENaC and Prostasin mRNA in the Distal Small Intestine

In both the proximal and middle small intestines, the expression of α, β, and γ subunit mRNAs of ENaC was not detected in any of the experimental groups examined (data not shown). When mRNA levels in the distal small intestine were compared among control, total proctocolectomized, dietary sodium-depleted, and aldosterone-infused rats, significant increases in the α, β, and γ subunit mRNAs were observed in total proctocolectomized and aldosterone-infused but not in dietary sodium-depleted rats (Fig. 2*A–C*). Interestingly, the expression of prostasin mRNA was also elevated in both the total proctocolectomized and aldosterone-infused rats but not in the dietary sodium-depleted rats (Fig. 2*D*). When total proctocolectomized and aldosterone-infused rats were compared, no significant difference was found in mRNA levels of three subunits of ENaC and prostasin. The dietary sodium-depleted rats exhibited levels of three subunits and prostasin mRNA comparable to those of control.

Protein Expression of α Subunit of ENaC in the Distal Small Intestine

When the colons of the control rats were stained with anti–α subunit antibody, the immunoreactivity was detected in the cytoplasm of the surface epithelia but not in the crypt cells (Fig. 3*A*). In the distal small intestine, we observed positive immunoreactivity in the cytoplasm of surface epithelia of the distal small

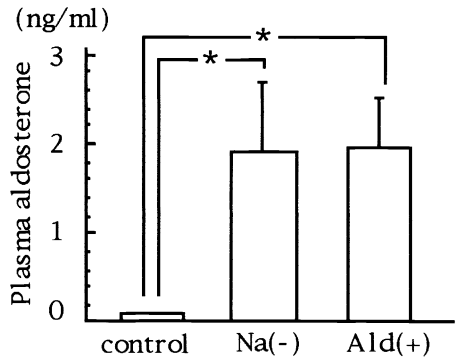

Fig. 1. Plasma aldosterone levels. Data are expressed as mean ± SE. *$P < 0.05$.

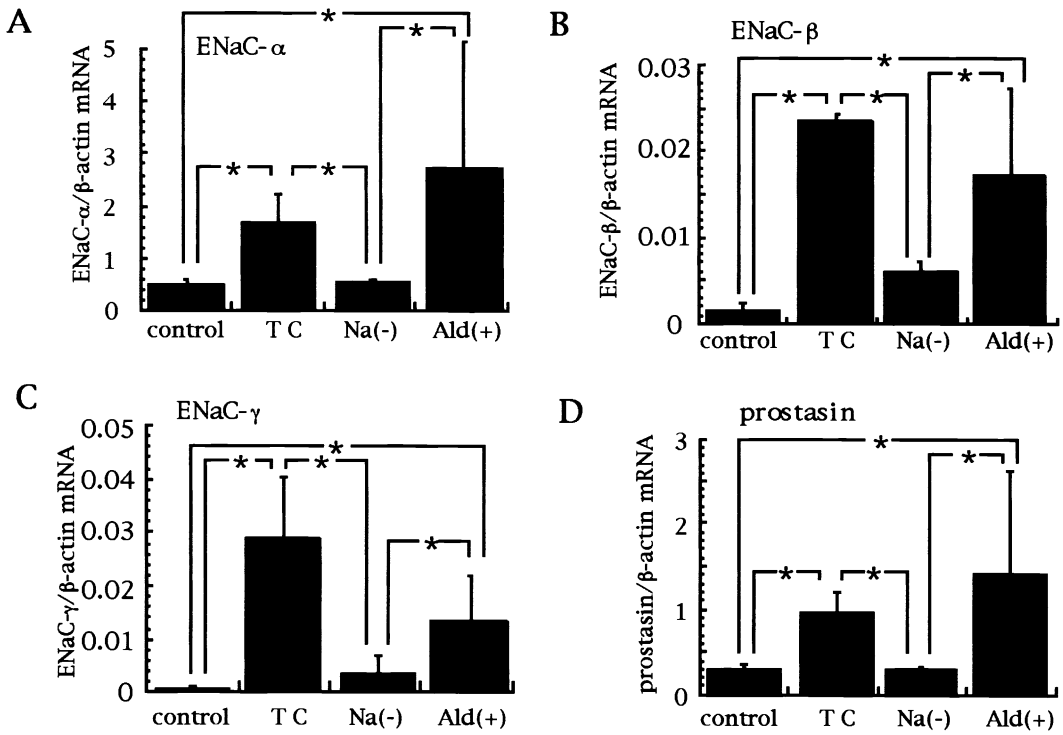

Fig. 2. Expression of epithelial sodium channel (ENaC) α subunit (**A**), β subunit (**B**), γ subunit (**C**), and prostasin (**D**) mRNA in epithelial cells from control, total proctocolectomized, dietary sodium-depleted, and aldosterone-infused rats. Epithelial RNA was obtained from the distal ileum 4 weeks after surgery or treatment. The amount of each mRNA was measured in duplicate. The expression levels were normalized to β-actin mRNA. TC = total proctocolectomy; Na(−) = dietary sodium depletion; Ald(+) = continuous aldosterone infusion. *$P < 0.05$, Significantly different values according to Scheffé's F test.

intestine only in the total proctocolectomized and aldosterone-infused rats (Fig. *3–D*). Positive immunoreactivity was limited to epithelial cells and absent in other cells of lamina propria. When normal rabbit IgG or phosphate-buffered saline was used instead of the primary antibody, no immunoreactivity was observed (data not shown).

Expression of Na^+/K^+-ATPase α1 and β1 Subunit mRNA in Intestinal Epithelial Cells

In contrast to the ENaC subunits, both α1 and β1 subunit mRNA of the Na^+/K^+-ATPase was constitutively expressed with 3.7 or 1.9 kb in epithelial cells of the proximal, middle, and distal small intestine. The expression of the α1 and β1 subunit

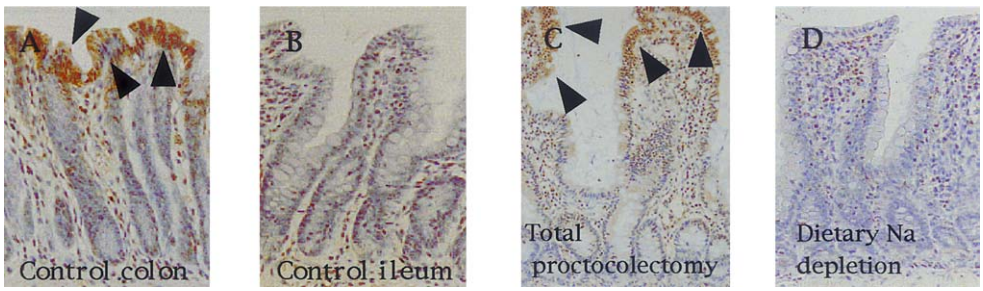

Fig. 3. In situ expression of epithelial sodium channel α subunit protein in the distal ileum of control (**B**), total proctocolectomized (**C**), and dietary sodium-depleted (**D**) rats (original magnification, ×150). The control colon was also stained with the antibody as a positive control (**A**). Immunoreactivity for the epithelial sodium channel α subunit was absent in control and dietary sodium-depleted rats and present in the cytoplasm of surface epithelia in total proctocolectomized rats. *Arrowheads*, positive staining.

mRNAs was stable following total proctocolectomy at 4, and even 8, weeks (Fig. 4*A*). Dietary sodium-depleted and aldosterone-infused rats also did not exhibit significant changes in α1 and β1 subunit mRNA expression in the distal small intestine (Fig. 4*B* and 4*C*).

Expression of *SGLT1* mRNA in the Distal Small Intestine

The induction of *SGLT1* mRNA was observed only in total proctocolectomized (3-fold increase), not in dietary sodium-depleted or aldosterone-infused rats (Fig. 5). Dietary sodium-depleted and aldosterone-infused rats exhibited levels of *SGLT1* mRNA comparable to those of control.

Histologic Examination of the Distal Small Intestine

Because adrenal steroids have been shown to change the mucosal architecture of the small intestine,[20] histologic examination of the distal small intestines from each of different groups was performed to investigate whether the changes in gene expression were related to morphologic changes in mucosa. We did not notice any histologic changes in villus height, crypt depth, or the ratio of globlet cells among control, total proctocolectomized, dietary sodium-depleted, and aldosterone-infused rats (data not shown).

DISCUSSION

Our final goal is to establish better management for the persistent diarrhea, latent electrolyte imbalance, and dehydration that develop in patients undergoing total proctocolectomies. We believe that analysis of the adaptation mechanisms in the small bowel as well as in the kidney after total proctocolectomies is the first step in the process of discovering novel therapies on the basis of pathophysiology. Rat models for human total proctocolectomy enabled us to investigate the roles of circulating aldosterone, ENaC, and 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in accelerated sodium absorption developing in the remnant ileum.[5,21] 11β-HSD2 converts glucocorticoids into the receptor-inactive metabolites, thus preventing the nonselective mineralocorticoid receptor from binding to glucocorticoids and determining the specificity of aldosterone for its receptor.[22–24]

Our previous data strongly suggest that aldosterone is a key hormone for adaptive and compensatory induction of the channel and the enzyme in total proctocolectomized rats. Those molecular inductions reflected functional activation of the amiloride-sensitive sodium channels and enhanced aldosterone reactivity in the remnant small intestine.[5,21] In humans, restorative proctocolectomies with ileal pouch-anal anastomoses and protective loop ileostomies significantly affect fluid, electrolyte, and acid-base balance. Huber et al.[4] reported that secondary hyperaldosteronism had an essential role for subsequent renal

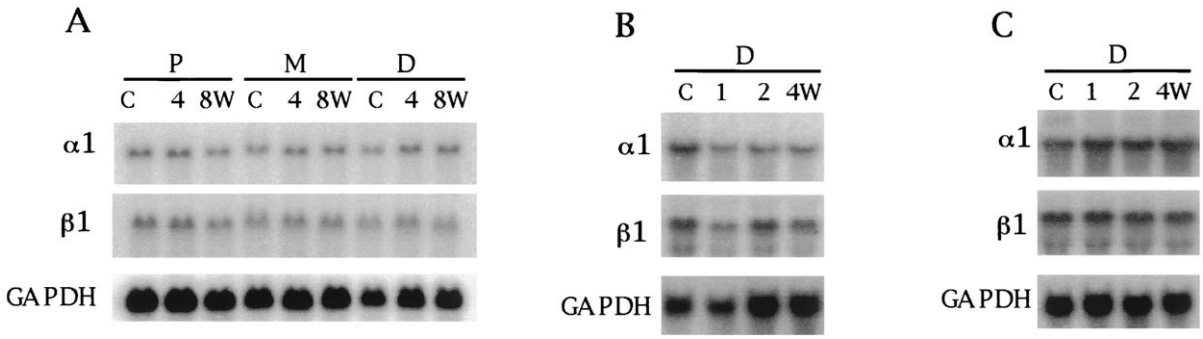

Fig. 4. mRNA expression of Na^+/K^+-ATPase in epithelial cells of the small intestine. (**A**) Epithelial RNA was obtained from the proximal (P), middle (M), and distal (D) small intestine of control (C) and total proctocolectomized rats at 4 weeks (4W) and 8 weeks (8W). The α1 (*top lanes*) and β1 (*middle lanes*) subunit cDNA was used as probes, respectively. The expression of *GAPDH* mRNA (*bottom lane*) was used as an internal standard. Similar results were obtained from two separate experiments. (**B** and **C**) Epithelial RNA was obtained from the distal ileum after the treatment with sodium-depleted diet (**B**) or continuous aldosterone infusion (**C**). The α1 (*top lanes*) and β1 (*middle lanes*) subunit cDNA, was used as probes, respectively. *GAPDH* cDNA was also hybridized as an internal standard (*bottom lanes*). Similar results were obtained from two separate experiments. Control rats, 1W, 2W, 4W = rats treated with sodium-depleted diet or continuous aldosterone infusion for 1, 2, or 4 weeks, respectively.

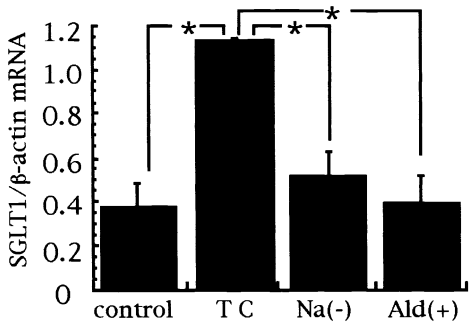

Fig. 5. Expression of *SGLT1* mRNA in epithelial cells from control, total proctocolectomized, dietary sodium-depleted, and aldosterone-infused rats. Epithelial RNA was obtained from the distal small intestine 4 weeks after treatment (surgery, diet, etc.). The amount of each mRNA was measured in duplicate. The expression levels were normalized to β-actin mRNA. TC = total proctocolectomy; Na(−) = dietary sodium depletion; Ald(+) = continuous aldosterone infusion. *$P < 0.05$, Significantly different values according to Scheffé's F test.

compensation, although the functional alteration in the remnant small intestine was not well addressed.

We initially investigated the expression of ENaC mRNA in the distal small intestine. The basic unit of ENaC consists of three subunits termed α, β, and γ.[17,25] The α subunit alone can form a fully functional amiloride-sensitive sodium channel, whereas the coexistence of β and γ subunits with α subunits leads to greater expression of amiloride-sensitive sodium conductance by the increasing surface delivery of ENaC.[17,18] In our previous study, we demonstrated mRNA induction of the three subunits only in the distal, not in the proximal or middle small intestine of total proctocolectomized rats using RNA extracted from the whole mucosa.[5] Therefore, we focused on those expressions in the distal small intestine using isolated epithelial cells. Aldosterone infusion similarly induced mRNA of the three subunits of ENaC in the distal small intestine, as was seen in total proctocolectomized rats. In contrast, dietary sodium-depleted rats showed constant levels of these mRNAs, although the aldosterone levels in aldosterone-infused and dietary sodium-depleted rats were comparable. It is unclear why the distal small intestines of dietary sodium-depleted rats did not exhibit induction of ENaC mRNA, because Will et al.[26] reported that sodium-depleted and aldosterone-infused rats similarly exhibited increases in amiloride-sensitive short circuit currents in the ileum. Therefore, activation of ENaC may be, at least in part, posttranscriptionally regulated by dietary sodium depletion.

Prostasin, a membrane-bound serine protease, was initially found in mammalian urine.[27] It has been shown that coexpression of prostasin and ENaC increases sodium transport in renal and bronchial epithelial cells and *Xenopus* oocytes.[12,28–31] Although the molecular roles of prostasin and ENaC in ENaC activation have not been elucidated, parallel expression of prostasin and ENaC may be essential for a physiologic response to enhanced aldosterone levels in epithelial cells of the distal small intestine. The induction of prostasin mRNA in total proctocolectomized and aldosterone-infused, but not sodium-depleted, rats suggests that more accelerated sodium transport may be present in the former two groups.

The Na^+/K^+-ATPase consists of two types of subunits, α and β, each of which has isoforms. It is widely accepted that epithelial cells essentially express α1 β1 heterodimers.[32] This enzyme is present at the basolateral membrane and actively extrudes sodium from cells into the interstitial milieu. In contrast to ENaC expression, the mRNA expression of the α1 and β1 subunits of Na^+/K^+-ATPase was stable in epithelial cells before and after the total proctocolectomies regardless of the site of the small intestine studied. Therefore, we hypothesize that the enzyme activity of Na^+/K^+-ATPase may be enhanced by post-transcriptional mechanisms and/or that Na^+/K^+-ATPase may originally have a wide range of capacity for sodium extrusion. Another possibility is that additional mechanisms of sodium extrusion may be present in the remnant small intestine. Similarly, treatment with a sodium-depleted diet and continuous aldosterone infusion did not alter α1 and β1 subunit mRNA levels. On the other hand, aldosterone induced the expression of the mRNAs of both ENaC and Na^+/K^+-ATPase subunits in the colon [11,33–35] or only ENaC[36] depending on the experimental conditions.

SGLT1 is a member of the cotransporter family that is expressed in the brush border membrane of the small intestine and is responsible for active glucose absorption across the brush border membrane. The transport of glucose is coupled to sodium transport down its electrochemical potential gradient across the plasma membrane.[37] We observed enhanced expression of *SGLT1* mRNA only in total proctocolectomized rats, which exhibited extremely high levels of plasma aldosterone compared with sodium-depleted and aldosterone-infused rats. In the chicken intestine, the reduction in sodium intake and aldosterone infusion decreased rather than increased the transport of α-methyl-D-glucoside.[38] Barfull et al.[39] speculated that the decrease in the hexose transport might be posttranscriptionally regulated under conditions of sodium restriction, because expression of *SGLT1* mRNA was stable before and

after the treatment for 2 weeks in the chicken intestine. The induction of *SGLT1* mRNA in the distal small intestine of total proctocolectomized rats may be due to extremely high levels of aldosterone[5] and/or other factors associated with the surgery, such as dehydration, malnutrition, and carbohydrate intake. It is well established that intestinal glucose transporter expression in rodents exhibits circadian periodicity[40] and induction by carbohydrate intake.[41]

Finally, we investigated the mucosal structure of the distal ileum because changes in the mucosal structure may affect the cellular differentiation and gene expression profiles. We did not find any alteration in morphology, in particular, after total proctocolectomy, demonstrating that epithelial cells in the distal ileum have a capacity to express ENaC and prsotasin mRNAs without remodeling the mucosal architecture. It is well documented that morphologic changes—such as villous atrophy increases in crypt depth, and goblet cell density—develop in the mucosa of ileal pouch.[42–44] Those morphologic alterations may affect the expression of multiple mRNAs, including ENaC, prostasin, and *SGLT1*, when the ileal pouch is constructed after total proctocolectomy.

The present study clearly demonstrates that any type of hyperaldosteronism is not necessarily accompanied by the molecular induction of ENaC, prostasin, and *SGLT1* in the rat distal small intestine. In humans, it is well known that some patients tolerate total proctocolectomies well while others do not, suggesting a possible difference in the degree of induction and/or functional activities of each molecule, probably due to the different genetic backgrounds. The present experiments do not provide adequate information regarding how aldosterone induces the ENaC subunit and prostasin mRNAs via aldosterone infusion and what other factors are associated with *SGLT1* mRNA induction in total proctocolectomized rats. Nonetheless, it appears that aldosterone infusion can lead to mRNA induction of several essential molecules for sodium absorption as seen in total proctocolectomy. We are concerned regarding whether those molecular changes in epithelial cells can be induced by drugs and reflect functional changes in sodium and water absorption.[45] New methods such as gene therapy may be required for local potentiation of mineralocorticoid action in the remnant small intestine.

The authors thank Prof. Yuichi Suzuki (University of Sizuoka, School of Food and Nutritional Science) and the late Prof. Jon Isenberg (University of California, San Diego) for fruitful discussion and advice on our project.

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The Role of Splenomesenteric Vein Anastomosis After Division of the Splenic Vein in Pancreatoduodenectomy

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Division of the splenic vein was performed in 29 patients who underwent pancreatoduodenectomy to achieve lymph node dissection and neural resection around the superior mesenteric artery. The basic protocol for the splenic vein reconstruction to reduce congestion of the spleen and stomach is as follows. When the inferior mesenteric vein (IMV) drained into the splenic vein, the confluence was preserved without reconstruction of the splenic vein. When the IMV drained into the superior mesenteric vein (SMV) or the splenomesenteric angle, the division of the IMV and spleno-IMV anastomosis were performed. In postoperative venography, nine patients showed downward flow (from the splenic vein to the IMV) and three patients showed upward flow (from the IMV to the splenic vein). Postoperative computed tomography scans showed venous dilatation and splenomegaly in the upward flow group; there were no patients in the downward flow group. In selected patients, splenic vein reconstruction is necessary to reduce congestion of the spleen and stomach. When the flow is downward, spleno-IMV flow should be preserved. When the flow is upward, spleno-SMV anastomosis is necessary instead of spleno-IMV anastomosis. (J GASTROINTEST SURG 2005;9:245–253)

KEY WORDS: Splenic vein, spleno-IMV anastomosis, pancreatoduodenectomy

Recent reports have demonstrated a reduction in the morbidity and mortality of pancreatoduodenectomy (PD) and an improvement in the 5-year actuarial survival of patients undergoing PD for pancreas head cancer.[1–3] In standard resection for pancreas head cancer, the lymph nodes at the right side and the proximal region of the superior mesenteric artery (SMA) must be dissected.[4–6] Furthermore, several authors have insisted that resection of the neural plexus around the SMA and extended lymph node dissection is necessary to improve the long-term survival of patients with advanced cancer.[7–12] On the other hand, such extended operations reduce the quality of life (QOL) because of intractable diarrhea and poor nutrition.[7] Therefore, to maintain the QOL of patients after pancreatic surgery, the approach of pylorus-preserving PD (PPPD) or only right-side resection of the neural plexus around the SMA has been adopted for patients with pancreas head cancer.[13,14]

These lymph node and neural plexus dissections are not easy to perform completely and safely because the root of the SMA is hidden by the overlying splenic vein. Because of this anatomic relationship, in our institute these dissections have been completed under the direct visual field through division of the splenic vein regardless of a possible combined resection of the portal vein. Division of the splenic vein sometimes induces splenomegaly, gastric varices, and variceal hemorrhage caused by regurgitation of the flow of the splenic vein, especially in PPPD. So in several cases, reconstruction of the splenic vein, such as a splenoinferior or splenosuperior mesenteric venous anastomosis, is needed. The purpose of this study is to clarify the indications for reconstruction of the splenic vein to reduce congestion of the spleen and stomach.

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.06.003

PATIENTS AND METHODS

Between May 1992 and December 2002, 60 patients with pancreas head cancer had undergone resection in the Second Department of Surgery, School of Medicine, Yokohama City University. PPPD was performed in 45 cases, and PD was performed in 15 cases. The operative procedure consisted of removal of the pancreatic tumor with dissection of the lymph nodes in the anterior and posterior pancreatoduodenal area, the area of the hepatoduodenal ligament, and the area around the common hepatic artery, the celiac trunk, and the SMA. The total neural plexus around the SMA was resected in 17 advanced cancers, right-side dissection was performed in 33 early cancers, and in 10 cases neural resection was not performed. The coronary vein was divided and the left gastric artery remained in both PPPD and PD. When the portal vein or the superior mesenteric vein (SMV) was macroscopically invaded by cancer, it was resected and reconstructed by end-to-end anastomosis (Fig. 1).

The splenic vein was divided in 29 of the 60 cases. In these cases, the lymph node dissection and resection of the neural plexus around the SMA were judged difficult because of the overlying splenic vein, or the splenic vein had to be resected with the SMV because of cancer invasion. Basically, the splenic vein reconstruction was performed as follows: when the inferior mesenteric vein (IMV) drained into the splenic vein apart from the spleno-SMV junction, the spleno-IMV confluence was preserved without reconstruction of the splenic vein during the division of the splenic vein. When the IMV drained into the SMV or the splenomesenteric angle, an anastomosis was made between the splenic vein and the SMV, the IMV, or the renal vein, with the expectation of downward venous flow going from the splenic vein to the SMV or the IMV. Anastomosis with the SMV or IMV was chosen because of the relatively short distances from the cut end of the splenic vein to the SMV and IMV.

The postoperative consequences of the venous flow from or to the spleen were observed on venography according to the celiac angiography in 12 patients

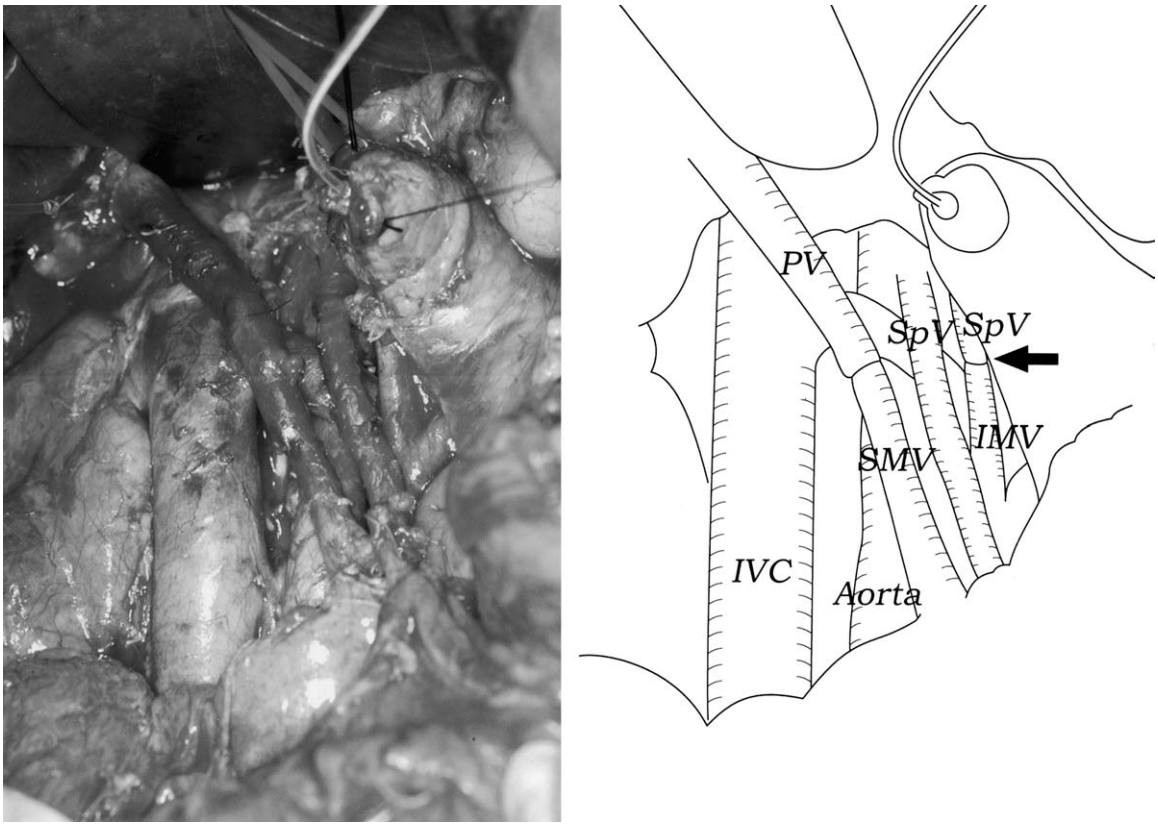

Fig. 1. During division of the splenic vein, the root of the superior mesenteric artery (SMA) and lateral side of the aorta can be recognized very well. Dissection of the lymph nodes around the SMA and in the lateral side of the aorta was performed completely and safely. The portal vein (PV) was reconstructed by end-to-end anastomosis. The splenic vein (SpV) was end-to-end anastomosed (*arrow*) to the inferior mesenteric vein (IMV). IVC = inferior vena cava; SMV = superior mesenteric vein.

who had spleno-IMV confluence or reconstructive anastomosis between the splenic vein and the IMV. Venous dilatation around the stomach and splenomegaly, which meant congestion of the stomach and the spleen, were evaluated on computed tomography (CT) scans in all 29 splenic vein resection patients. Hepatic steatosis was also evaluated on CT scans.

After receiving a full explanation of the purpose, procedure, and risks of the operation, all patients signed an informed consent statement.

RESULTS

Anatomic Pattern

Based on the surgical anatomy of 29 patients who underwent the splenic vein division, three anatomic patterns of the confluence between the splenic vein and the mesenteric vein were identified (Fig. 2). The IMV drained into the splenic vein (type A) in 14 patients (48.3%), into the SMV (type B) in 9 patients (31.0%), and into the splenomesenteric angle (type C) in 4 patients (13.8%). In the other 2 patients, the existence of the IMV was not confirmed.

Management

Management of the divided splenic vein in 29 patients was as follows: in 14 cases of type A, no reconstruction of the splenic vein was done in 13 patients, and end-to-side anastomosis between the splenic vein and the SMV was done in 1 patient; in 13 cases of types B and C, end-to-end anastomosis between the splenic vein and the IMV was done in 7 patients, end-to-side anastomosis between the splenic vein and the SMV was done in 3 patients, end-to-side anastomosis between the splenic vein and the left renal vein was done in 1 patient, and no reconstruction of the splenic vein was done in 2 patients (Table 1).

Table 1. Management after division of the splenic vein

Management	No. of patients
Type A (with spleno-IMV confluence) (n = 14)	
No vascular reconstruction	13
Vascular reconstruction between the SpV and the SMV	1
Type B and C (without spleno-IMV confluence) (n = 13)	
No vascular reconstruction	2
Vascular reconstruction between the SpV and the SMV	3
Vascular reconstruction between the SpV and the IMV	7
Vascular reconstruction between the SpV and the left renal vein	1
Anatomy of IMV unclear	2

IMV = inferior mesenteric vein; SpV = splenic vein; SMV = superior mesenteric vein.

Direction of the Splenic Venous Flow

Postoperative venography revealed four types of venous flow (Fig. 3). In type 1 (Fig. 4), the flow from the splenic vein passed through the anastomosis or the spleno-IMV confluence to the IMV and was delivered into the portal vein in six patients (50.0%). In type 2 (Fig. 5), the flow from the splenic vein passed to the IMV and drained into the systemic circulation

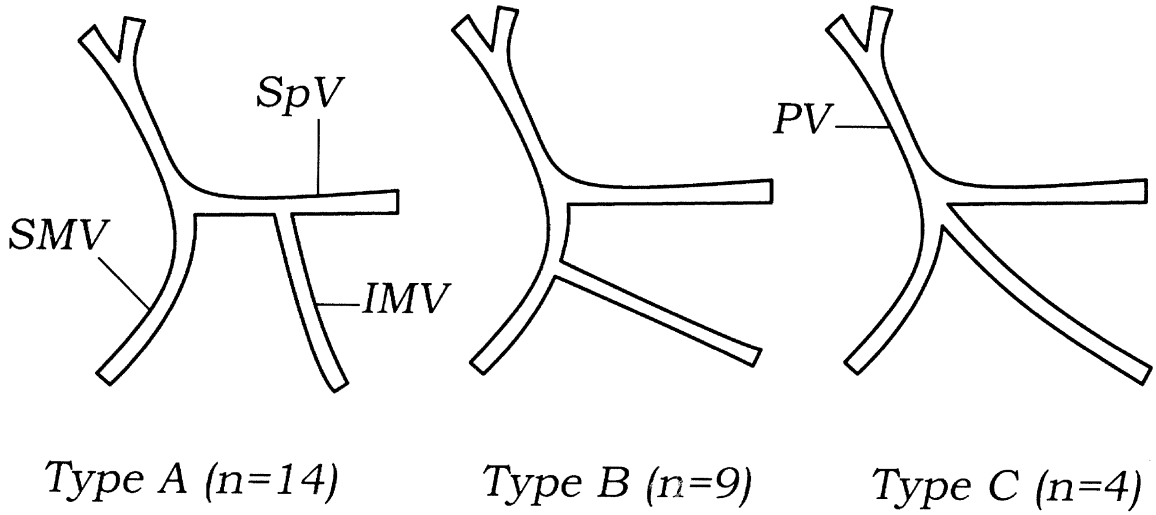

Fig. 2. There are three types of confluence between the splenic vein (SpV) and the inferior mesenteric vein (IMV). SMV = superior mesenteric vein; PV = portal vein.

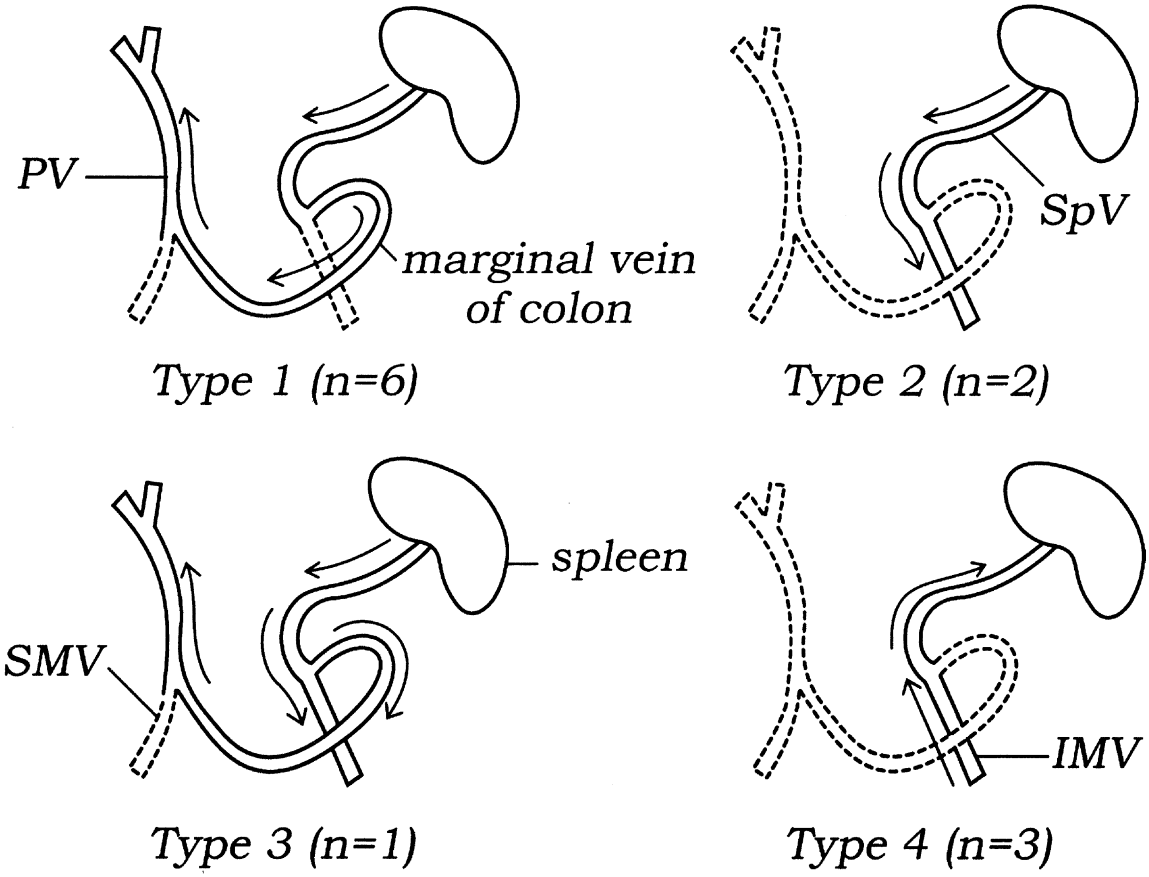

Fig. 3. There were four types of venous flow from the splenic vein (SpV) or inferior mesenteric vein (IMV) after the operation. Curved arrows indicate the direction of the blood flow. Types 1, 2, and 3 showed a downward flow of SpV. Type 4 showed an upward flow of SpV. PV = portal vein; SMV = superior mesenteric vein.

by collateral veins in two patients (16.7%). In type 3 (Fig. 6), the flow from the splenic vein passed to the IMV and flowed to the portal vein and the systemic circulation in one patient (8.3%). This type was a mixture of types 1 and 2. In type 4, the flow from the IMV passed to the splenic vein in three patients (25.0%). From this result, 9 of 12 patients showed a downward flow, such as types 1, 2, and 3. The other three patients showed an upward flow, such as type 4.

Varicose Vein and Splenomegaly

CT images after the operation showed neither venous dilatation nor splenomegaly in types 1, 2, and 3. However, these complications were observed in two patients of type 4 (two of three, or 66.7%) and in one patient without splenoinferior mesenteric venous confluence who had not undergone reconstruction of the splenic vein. All patients showing venous dilatation or splenomegaly were in the upward-flow group. In other patients, neither venous dilatation nor splenomegaly was observed (Table 2).

In none of the 29 patients, bleeding from the stomach due to congestion of the stomach occurred.

One patient without spleno-IMV confluence could not undergo reconstruction of the splenic vein. In this case, blood loss during operation had increased to 5200 ml because of congestion of the stomach and spleen. Therefore, distal gastrectomy had to be added to PPPD, which resulted in decreased portal vein pressure and prevention of gastric variceal congestion.

In another recent patient with spleno-IMV confluence, intraoperative color Doppler ultrasonography (US) after the division of the splenic vein showed that the venous flow from the IMV went to the splenic vein. Congestion of the stomach and the spleen appeared during the operation. Therefore, an end-to-side anastomosis between the splenic vein and the SMV was performed using the ovarian vein for bypass graft.

Hepatic Steatosis

Hepatic steatosis was found on CT images in 9 of 42 patients (21.4%) whose blood flow from the

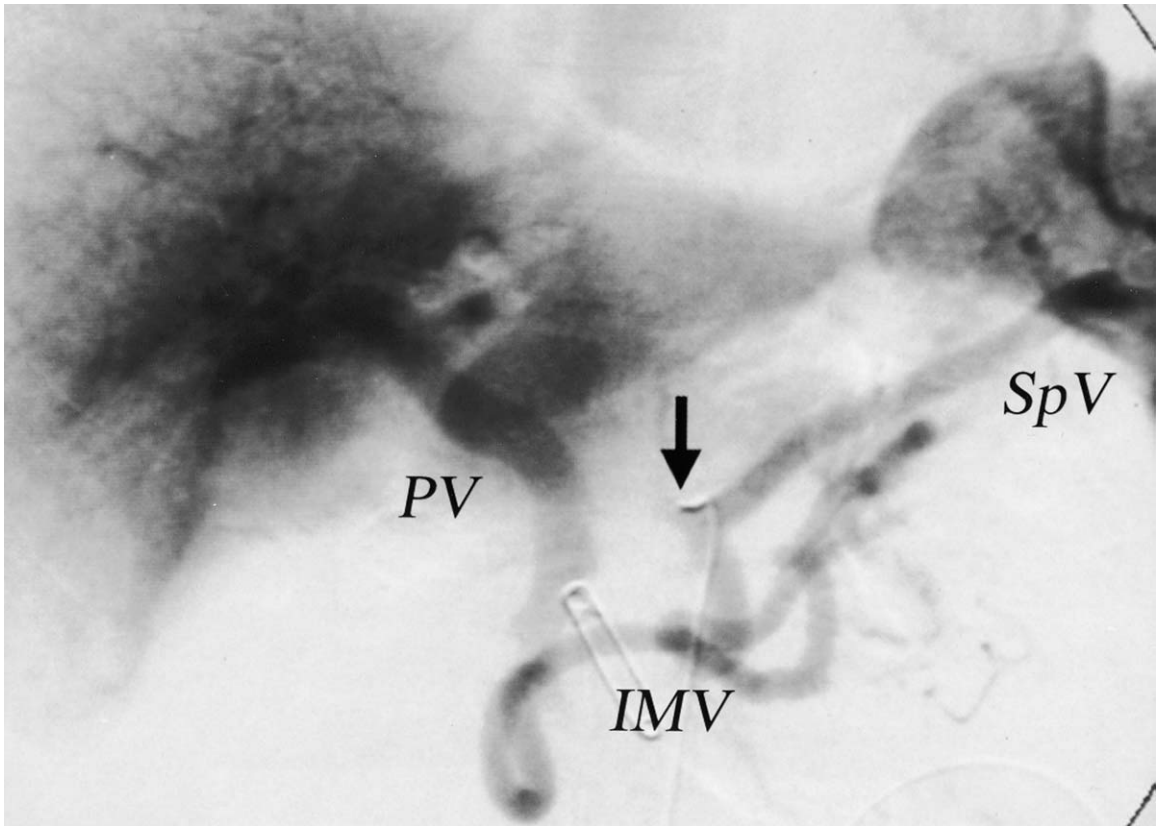

Fig. 4. The flow from the splenic vein (SpV) passed through the anastomosis or the splenoinferior mesenteric venous confluence *(arrow)* to the inferior mesenteric vein (IMV), and it was delivered into the portal vein (PV).

splenic vein drained directly into the portal vein, such as in types 1 and 3 with no division of the splenic vein, and in 4 of 7 patients (57.1%) with the blood flow of systemic diversion, such as in types 2 and 4 with anastomosis between the splenic vein and the left renal vein.

DISCUSSION

Retroperitoneal clearance and dissection of the lymph nodes and neural plexus around the SMA are considered inevitable to cure advanced pancreas head cancer. Hagihara[15] and Nagakawa et al.[11] reported that the incidence of metastasis to the lymph nodes around the SMA was higher than the incidence to the peripancreatic lymph nodes. However, these lymph node and neural plexus dissections, especially around the SMA, are not easy to perform completely and safely because the root of the SMA is hidden by the overlying splenic vein. During division of the splenic vein, we could see the root of the SMA and lateral side of the aorta very well, and we could dissect the lymph nodes and neural plexus around the SMA and lateral side of the aorta. Furthermore, we could partially preserve the neural plexus around the SMA, particularly in cases of early cancer. Intractable diarrhea was prevented, and we could maintain QOL after surgery.

There is disagreement about the necessity of splenic vein reconstruction after the division. Some surgeons do not anastomose between the splenic vein and the IMV or SMV regardless of PD or PPPD because they think that the venous flow from the spleen and stomach goes to the systemic vein or the SMV through the shunt of the short gastric veins and the esophageal veins.[16] However, splenic vein occlusion is sometimes accompanied by gastric varices and gastric variceal hemorrhage, which leads to treatment by surgical splenectomy or splenic arterial embolization.[17–19] Also, it has been reported that acute gastric mucosal hemorrhage occurred due to congestion of the stomach, especially after PPPD.[20] Therefore, it should be recognized that reconstruction of the divided splenic vein is sometimes necessary to avoid congestion of the stomach and spleen.

There are few reports on the postoperative consequences of the type of the venous flow that describe

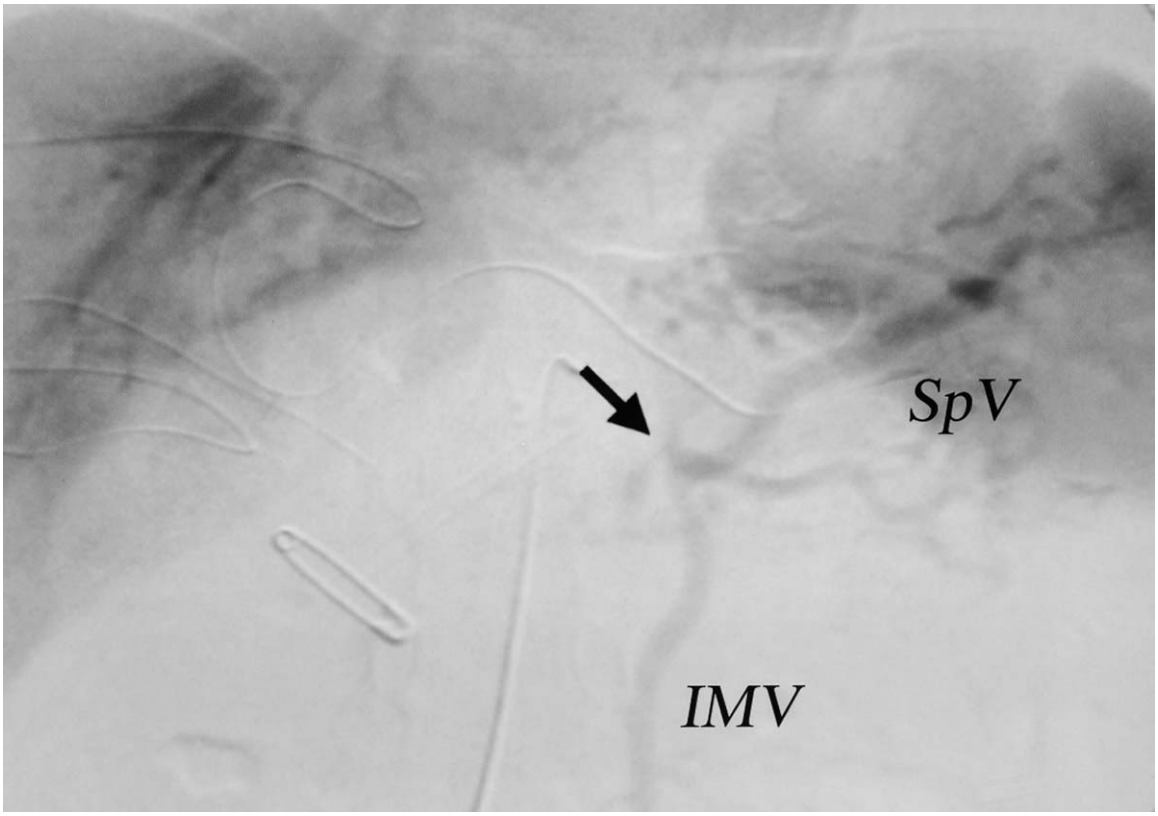

Fig. 5. Flow from the splenic vein (SpV) passed to the inferior mesenteric vein (IMV), and it drained into the systemic circulation. *Arrow*, Anastomosis or splenoinferior mesenteric venous confluence.

the relationship between varix, splenomegaly, and direction of the splenic vein. We have tried to clarify the significance of reconstruction of the splenic vein with the use of postoperative venograms of the portal circulation or CT images. There are three types of confluence between the IMV and the portal vein. Graf et al.[21] reported that the IMV drained into the splenic vein in 56%, into the SMV in 26%, and into the splenomesenteric angle in 18% of patients. In our study, the frequencies of these three types are similar to their data: 48.3%, 31.0%, and 13.8%, respectively.

Postoperative venography in splenic vein division cases with spleno-IMV anastomosis or preservation of the spleno-IMV confluence showed four types of flow of the splenic vein. Type 1 was the most common type. The flow from the splenic vein passed through the anastomosis or the spleno-IMV confluence to the IMV and then was delivered into the portal vein. Tamura et al.[22] also reported four cases of this type. Venous dilatation around the stomach and splenomegaly did not appear in type 1 on CT. Reconstruction of the splenic vein was considered to prevent congestion of the stomach and the spleen.

In type 2, the flow from the splenic vein passed to the IMV and drained into the systemic circulation via portosystemic shunts, because the inferior mesenteric–to–superior mesenteric collateral circulation was undeveloped. Venous dilatation around the stomach and splenomegaly were not observed on CT, although it might not be physiologic for insulin, glucagon, and other pancreatic hormones to be delivered into the systemic circulation. Hepatic steatosis occurred in 57.1% of the patients with systemic diversion and type 4, compared with 29.0% of the patients whose blood flow from the splenic vein drained into the portal vein, such as types 1 and 3. Although there was no significant difference between the two types of venous flow, hepatic steatosis had a tendency to increase in the patients with systemic diversion. The etiology of fatty liver is not clear, but it appears that the lower portal venous insulin/glucagon ratio is involved in preventing hepatic steatosis.[23–25] Further studies are necessary to clarify whether portal venous hormones such as insulin and glucagon or other nutritional states are related to the etiology of hepatic steatosis in these cases.

Type 3 was a mixture of types 1 and 2. The flow from the splenic vein passed to the IMV and then went

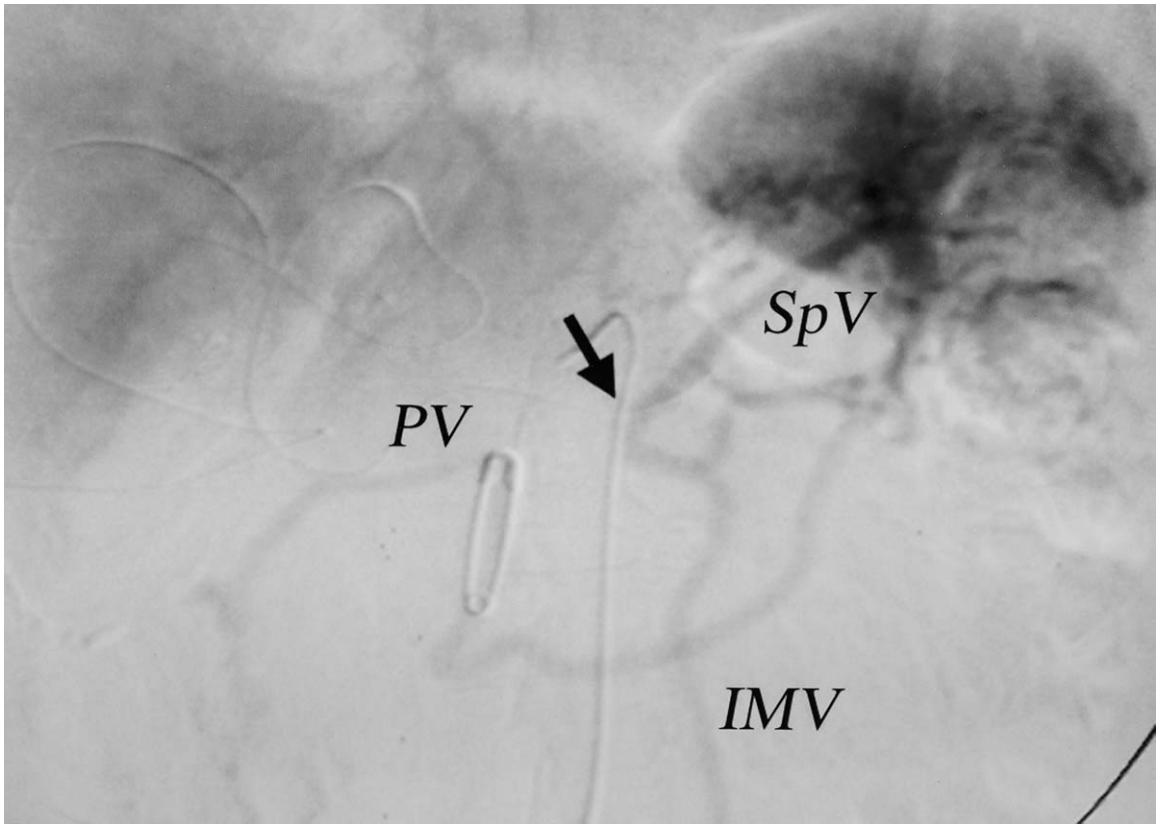

Fig. 6. Flow from the splenic vein (SpV) passed to the inferior mesenteric vein (IMV) and then went to the portal vein (PV) and the systemic circulation.

to both the portal vein and the systemic circulation. Venous dilatation around the stomach, splenomegaly, and hepatic steatosis did not appear.

In type 4, the flow from the IMV passed to the splenic vein, and it resulted in venous dilatation around the stomach and splenomegaly. When the venous pressure of the IMV is higher than the pressure in the splenic vein, an anastomosis between the splenic vein and the IMV should not be performed. In this type, an anastomosis between the splenic vein and the SMV is indicated.

After division of the splenic vein, the distance between the cut end of the splenic vein and the SMV had become too short to perform an end-to-side anastomosis. Therefore, we selected an end-to-end anastomosis between the splenic vein and the IMV. When spleno-IMV confluence existed, it was preserved, and reconstruction of the splenic vein was not needed. However, when the flow from the IMV drains into the splenic vein after division of the splenic vein, an end-to-side anastomosis between the splenic

Table 2. Venous dilation around the stomach and splenomegaly

	No. of venous dilatations	No. of splenomegaly procedures
Nondivided SpV (n = 31)	0	0
End-to-side anastomosis between the SpV and the SMV (n = 4)	0	0
Downward flow		
Type 1 (n = 6)	0	0
Type 2 (n = 2)	0	0
Type 3 (n = 1)	0	0
Upward flow		
Type 4 (n = 3)	2	2
No reconstruction without spleno-IMV confluence (n = 1)	1	1
Unclear of the direction of flow (n = 12)	0	0

SpV = splenic vein; SMV = superior mesenteric vein; IMV = inferior mesenteric vein.

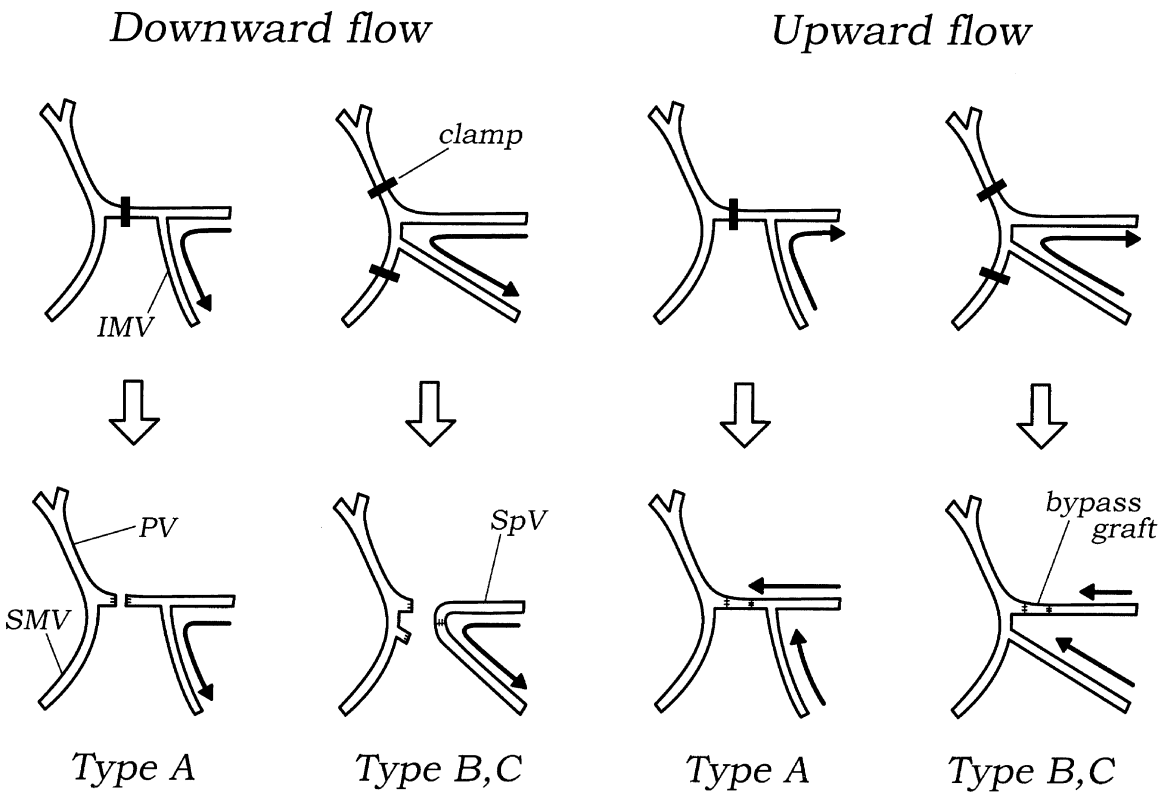

Fig. 7. The indication for reconstruction should be determined by the direction of the splenic venous flow during clamping the splenic vein (SpV) or the superior mesenteric vein (SMV) and the portal vein (PV). When the flow from the SpV runs to the inferior mesenteric vein (IMV) (a downward flow), the anastomosis between the SpV and the IMV should be performed. When the flow is opposite (an upward flow), the anastomosis between the SpV and the PV would be indicated, even if a bypass graft is needed. The direction of the flow of the splenic vein is assessed by intraoperative color flow imaging. When the change in splenic flow direction is observed during clamping the veins, which is appeared as the change of a color filling the vessel lumen, the flow is upward. *Arrow*, Direction of the flow.

vein and the SMV should be done using a bypass graft such as in the presented case, in which the ovarian vein was used for bypass graft.

How can we evaluate the direction of the flow of the splenic vein during the operation? Intraoperative color Doppler US can show the direction of the flow as a color filling the vessel lumen, and it is easy to do. In the future, intraoperative examination of the splenic flow by color flow imaging will be needed to decide if reconstruction of the splenic vein is indicated. The indication for reconstruction should be determined by the direction of the splenic venous flow during clamping the splenic vein or the portal vein and the SMV (Fig. 7).

In conclusion, reconstruction of the splenic vein or preservation of the splenoinferior mesenteric venous confluence after the division of the splenic vein is important in some patients to reduce congestion of the stomach and spleen. The necessity of reconstruction should be determined by the direction of the splenic venous flow during clamping the splenic vein or the SMV and the portal vein, which is examined by intraoperative color Doppler US.

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Peripancreatic Tuberculosis Mimicking Pancreatic Neoplasia

Eric S. Weiss, M.D., Walter M. Klein, M.D., Charles J. Yeo, M.D.

Tuberculosis of the pancreas and peripancreatic lymph nodes is an extremely rare disorder that has been reported with increased frequency in the past several years. Despite the fact that abdominal tuberculosis can generally be managed by pharmacotherapy alone, invasive procedures are often used before the establishment of the correct diagnosis, sometimes leading to unnecessary interventions and delayed treatment. To set the stage for our review, we first describe a case of a 31-year-old woman from India who initially presented with nonspecific symptoms and a pancreatic cystic lesion but was later diagnosed with peripancreatic tuberculosis. We then present a review of the current literature on peripancreatic and pancreatic tuberculosis, with a focus on diagnosis and management of the disease, but we also touch on issues such as epidemiology, infection control, and tissue acquisition. Finally, we offer clues that can be used to help identify patients who present with otherwise vague symptoms who may harbor pancreatic or peripancreatic tuberculosis. It is our hope that this case report and review of the literature will raise awareness and improve the management of this uncommon but serious disorder. (J GASTROINTEST SURG 2005;9:254–262)

KEY WORDS: Pancreas, tuberculosis, neoplasia

Tuberculosis (TB) of the pancreas and peripancreatic lymph nodes is a rare clinical entity that has been reported with increasing frequency in the scientific literature during the past 20 years. The exact cause of this increase is unknown, although experts point to a greater number of human immunodeficiency virus (HIV)-infected individuals, expanded use of immunosuppressant therapy, and increased globalization as possible explanations. Most cases of pancreatic TB are diagnosed only after tissue acquisition via biopsy or exploratory laparotomy, often when the clinician expected to find a noninfectious etiology for the patient's clinical symptoms. This is particularly important, because almost all cases of pancreatic TB are amenable to medical management. Clearly, heightened awareness of the presenting signs and symptoms of the disease, as well as knowledge of the common pitfalls in its diagnosis and treatment, could have a positive impact on the management of this unusual condition. To that end, we present a case of TB in the peripancreatic lymph nodes mimicking pancreatic neoplasia in a 31-year-old woman from India. In addition, we review the recent literature on pancreatic and peripancreatic TB, to increase awareness of the disease as well as to help guide physicians who evaluate and manage alimentary tract diseases.

CASE REPORT

The patient was a 31-year-old woman, originally from India, with a past medical history significant for pneumonia, iron deficiency anemia, and hiatal hernia. She initially presented to an outside hospital on February 27, 2003, with complaints of right-sided flank and chest pain. She described her pain as nonconstant and variable in severity. She denied weight loss, fever, chills, nausea, or vomiting. Her physical examination at the time was unremarkable and included normal respiratory, cardiovascular, and abdominal examinations. Her routine laboratory values were normal, including liver function tests. A computed tomography (CT) scan of the abdomen showed what was believed to be a cystic lesion in the head of the pancreas. Endoscopic retrograde cholangiopancreatography demonstrated normal pancreatic ductal anatomy, with no evidence of pancreatic or biliary abnormality.

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doi:10.1016/j.gassur.2004.06.010

She was referred to our institution for surgical evaluation on May 1, 2003. At this time, her symptoms and physical examination results remained unchanged and a CT scan (performed as a three-dimensional multidetector scan) revealed a low-density mass in the right side of the pancreas, possibly arising from the neck or uncinate process of the pancreas (Figs. 1, *A* and *B*). There also were two indeterminate cystic lesions visible within the liver parenchyma. There was no evidence of ascites, and all of the perihepatic and peripancreatic visceral vessels were patent. With the presumed diagnosis of a symptomatic cystic lesion of the pancreas, the decision was made to take the patient to the operating room for resection of the cystic lesion via either enucleation or partial pancreatectomy.

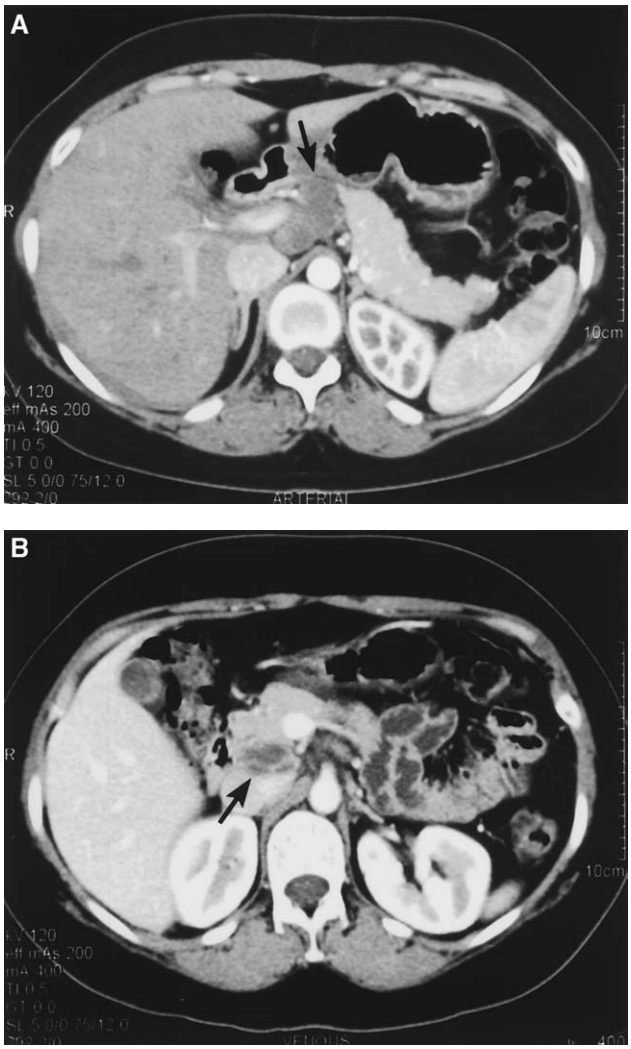

Fig. 1. Dual-phase (**A**, arterial; **B**, venous) spiral computed tomography scan of the pancreas demonstrating a cystic lesion apparently extending into or arising from the neck or uncinate process of the pancreas. For each image, the black arrow points to the large cystic mass in the pancreatic or peripancreatic region.

At abdominal exploration on May 27, 2003, there were multiple nodules present on the small bowel mesentery and on the intestinal serosa, in a miliary distribution. On further inspection, more miliary implants were found along the right fallopian tube and freely within the pelvis. One of these military lesions was excised and submitted to pathologic examinations. Two lesions found in the liver parenchyma were excised and sent for pathologic examination. When the pancreas was evaluated, it was found to be soft, with no palpable masses. However, an enlarged lymph node was identified just ventral and superior to the neck of the pancreas. Other enlarged lymph nodes were present in the peripancreatic area as well. The various specimens sent to pathology revealed granulomas with focal necrosis, suspicious for TB. In addition, the specimens were sent for culture and smear. With a grossly normal pancreas and the above information from frozen section, the decision was made to close the abdomen, without resection.

All pathology specimens were routinely processed (10% formalin), paraffin embedded, and stained with hematoxylin and eosin. Histopathologic examination demonstrated multiple granulomas with caseating necrosis, highly suspicious for an infectious process (Fig. 2). Examinations with special stains for fungi (GMS) and acid-fast organisms (Kinyoun, auramine/rhodamine) were negative. The initial smear of the enlarged peripancreatic lymph node demonstrated rare acid-fast bacilli. On postoperative day 17, *Mycobacterium tuberculosis* was isolated from the Bactec Middlebrook Medium specimen (Fig. 3). The organism was found to be susceptible to isonizide, rifampin, ethambutol, and pyrazinamide.

After the operation, the patient was placed in appropriate isolation with strict contact and droplet precautions. The patient consented to undergo an HIV antibody test, which was nonreactive on enzyme-linked immunosorbent assay. The serum CA-125 level was measured at 88 U/ml (normal, 0–35 U/ml). Finally, a thoracic CT scan revealed necrotic lymph nodes lateral to the left internal jugular vein, in the left superior mediastinum, and in the right midmediastinum and a 1.5 × 1.3-cm low-density lesion adjacent to the right pulmonary vein. The postoperative course was uncomplicated, and the patient was discharged on postoperative day 4 in stable condition, with instructions to take isoniazid, rifampin, ethambutol, and pyrazinamide. Before her discharge, her case was reported to the Maryland State Health Department. She has been followed and is currently doing well 1 year later, having completed her anti-TB therapy. Her right-sided flank and chest pain have resolved.

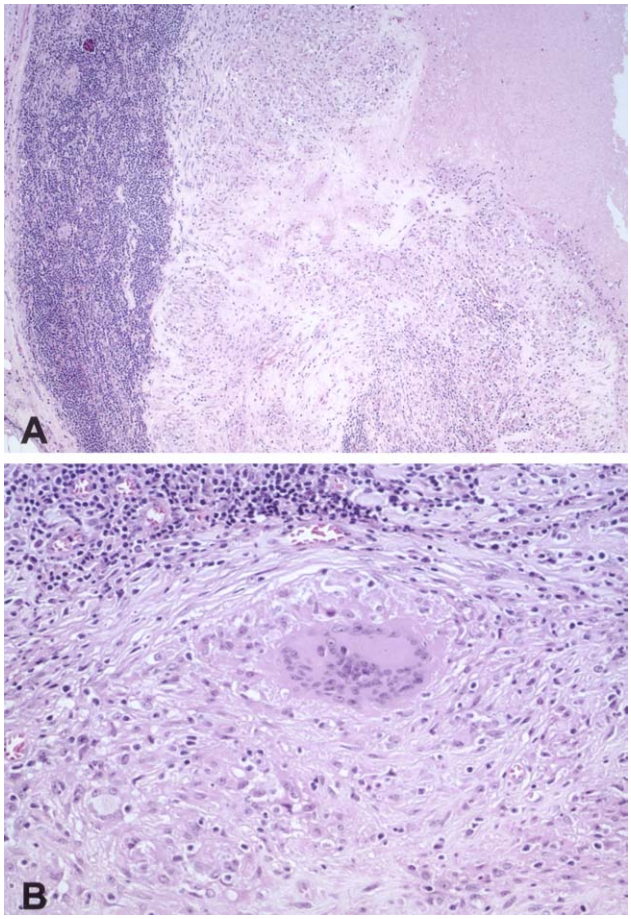

Fig. 2. (**A**) Low-power view of the peripancreatic lymph node demonstrating extensive subcapsular granulomatous inflammation with abundant central caseating necrosis (hematoxylin and eosin stain; original magnification, ×50). (**B**) High-power view of a single granuloma with numerous palisading histiocytes, lymphocytes, and a peripheral giant cell (hematoxylin and eosin stain; original magnification, ×160).

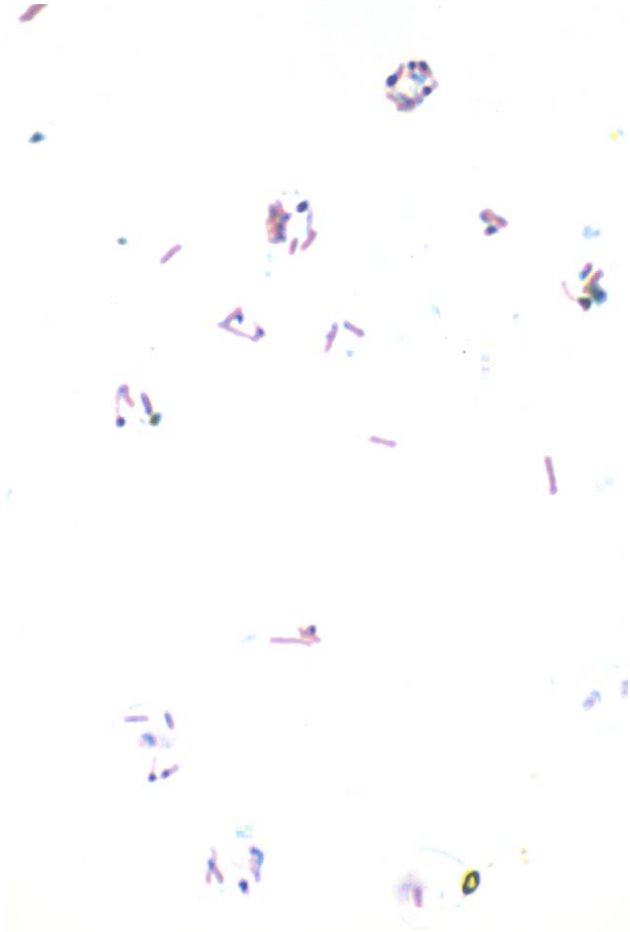

Fig. 3. Oil immersion photomicrograph of positive culture demonstrating numerous acid-fast positive bacterium consistent with *Mycobacterium tuberculosis* (Kinyoun stain; original magnification, ×400).

REVIEW

The present case illustrates an example of abdominal TB and, more specifically, peripancreatic TB. The disease is caused by the pathogen *M. tuberculosis*, a rod-shaped aerobic bacterium notable for its acid-fast staining properties. TB is a worldwide problem of impressive magnitude. In 1997, there were 7.96 million new cases of TB worldwide, leading to 1.87 million deaths.[1] For purposes of organizing the extent of the TB epidemic, the World Health Organization (WHO) divides the world's population into six defined global regions (rather than individual countries). The incidence, prevalence, and mortality of the disease vary greatly among these WHO regions (Table 1), and, notably, all forms of TB are continuing to increase in incidence in all regions.[2] The United States has not been immune to the devastating effects of the disease, as the national incidence of TB has steadily risen since 1980. In fact, between 1985 and 1992, there has been a 14% increase in cases of TB in the United States.[3] Proposed explanations for the rise include increased cases of HIV, expanded use of immunosuppressant therapy, globalization of the world's population, and increased transmission in environments such as prisons, homeless shelters, and nursing homes.

Although we most often associate TB with active pulmonary disease, primary abdominal TB is not uncommon, with varying incidence and prevalence among different countries. In 1986, for example, of the 22,768 reported cases of TB in the United States, only 0.58% were found to be located in the peritoneum.[4] In contrast, the prevalence of abdominal TB in developing countries has been estimated to be as high as 12%.[5] Although one might expect abdominal TB to be found in conjunction with active pulmonary TB, the percentage of cases where this association

Table 1. Incidence, prevalence, death rate, and percentage of HIV-positive individuals afflicted with TB, organized by WHO region

	Incidence*	Prevalence*	Death rate*	Percentage of HIV-positive persons affected
Africa	259	384	88	32
Southeast Asia	202	524	44	2
Eastern Mediterranean	129	258	30	3
West Pacific	120	230	22	0
America	52	72	8	6
Europe	51	73	7	2
Total	136	277	32	8

HIV = human immunodeficiency virus; TB = tuberculosis; WHO = World Health Organization.
Adapted from Dye et al.,[1] with permission.
*Data expressed per 100,000 population.

holds true is only 6–38%.[6] Abdominal TB is in fact quite distinct from pulmonary TB, more commonly affecting young adults (mean age in India, 31 years),[2] and likely due to ingestion rather than inhalation of the pathogenic organism. Once the offending organism is ingested and access to the gastrointestinal (GI) tract is gained, necrotic granulomas form in the intestine, which spread to the lymphatics in a miliary pattern affecting virtually every organ in the GI tract, including the pancreas.[7]

Although isolated abdominal TB is not uncommon, abdominal TB masquerading as pancreatic neoplasia is a very rare condition. Peripancreatic TB usually falls into one of four distinct clinical scenarios: the infection may (1) produce pancreatitis,[8] (2) cause obstructive jaundice,[5,9] (3) lead to GI bleeding,[10] or as in the present case, (4) mimic pancreatic neoplasia as a discrete mass.[7,11–19] This final presentation, the most common of the four, serves as the focus of the remaining discussion.

The reporting of TB mimicking pancreatic cancer began with Auerbach in 1944. In his seminal report, he described 1656 autopsies of tuberculous patients and identified 297 cases of miliary TB.[20] Only 14 cases had direct pancreatic involvement that may have mimicked neoplasia, and not a single case had isolated pancreatic involvement. Bhansali[21] reviewed 300 cases of miliary TB without finding any cases of pancreatic involvement. Recently, Franco-Paredes and colleagues[22] reported two cases of pancreatic TB and reviewed the current literature involving pancreatic TB among nonimmunosuppressed individuals. The authors found between 1980 and 2002 that 50 cases of pancreatic TB had been reported. Thirteen of these cases were categorized as pancreatic masses, mimicking pancreatic carcinoma. Since their report, our review in nonimmunosuppressed individuals identified an additional 25 cases of *pancreatic* TB presenting as discrete pancreatic masses (Table 2) and 42 cases of *peripancreatic* TB mimicking pancreatic masses (Table 3).

Despite the rarity of its occurrence, pancreatic TB masquerading as pancreatic cancer should not be overlooked. However, the diagnosis often proves to be extremely challenging, even for the most astute clinician. This is in part because the presentation of abdominal TB is slow and insidious, with nonspecific signs and symptoms. In the present case, for example, vague right flank and chest pain were the only presenting symptoms. Because it is true that patients most likely to develop pancreatic and peripancreatic TB are those with immunosuppression (such as HIV-positive individuals) or those who live in endemic areas,[23] in the absence of either of these characteristics, it can prove difficult to identify patients with pancreatic TB.

Uygur-Bayramicli and colleagues[24] described 31 patients with abdominal TB to identify reliable clinical characteristics of the disease (Table 4). Fourteen women and 17 men with a mean age of 34 years were diagnosed with abdominal TB over a 5-year period. In their series, only 19% of these patients had a personal history of previous TB, indicating that a past history of the disease may be helpful but certainly is not absolute. Although abdominal pain and weight loss were the most frequently cited complaints, 16 separate symptoms and signs were recorded, ranging from fever and night sweats to masses and perforation.[24] In a similar study, Al Muneff et al.[25] reviewed 46 cases of intra-abdominal TB in Saudi Arabia and reported 12 similar and equally nonspecific presenting signs and symptoms (Table 4). In Bhansali's[21] review of 300 patients with abdominal TB in India, males and females developed the disease with equal frequency, and although pain was again the most common presentation, the symptoms were wide ranging and nonspecific. Analysis of these three reviews reveal that although pain is a common presenting symptom, abdominal TB presents with a constellation of nonspecific signs and symptoms, making reliance on symptomatology alone for diagnosis ill advised and inappropriate.

Clearly, diagnostic studies must be used to diagnose effectively pancreatic TB. The diagnostic techniques used for evaluation of peripancreatic TB can be divided into two types: noninvasive and invasive. Noninvasive techniques rely mainly on CT, although magnetic resonance cholangiopancreatography and abdominal ultrasonography (US) have been frequently performed.

Table 2. Review of literature reporting pancreatic tuberculosis mimicking solitary pancreatic masses in nonimmunosuppresed individuals

Report of pancreatic tuberculosis	Cases of pancreatic tuberculosis/ total patients in study (n)	Type of study	Study population and presenting symptoms	Diagnostics	Management
Franco-Paredes et al.[22]	13/50	Retrospective review	Men and women 29–67 years old with multiple presentations	Many techniques	Medical and surgical management not specified
Chen et al.[5]	1/1	Case report	An 82-year-old man with right upper quadrant abdominal pain and obstructive jaundice	US and CT showing a hypoechoic mass in pancreatic head	Ex-lap with classic Whipple procedure followed by INH, RMP, and ETHAM × 6 mo
Chaudhry et al.[23]	9/345	Retrospective review	Eight men and 1 woman aged 17–45 years with abdominal pain, anorexia, and weight loss	Various imaging modalities leading to ex-laps in all 9 patients	INH, PZA, ETHAM, and RMP × 3 mo, followed by RMP and INH × 6 mo
D'Cruz et al.[11]	1/1	Case report	A 23-year-old man with abdominal pain, fever, and weight loss	US and CT showing pancreatic mass, FNA showing caseating granulomas	Medical management: RMP/ INH/PZA/ETHAM × 2 mo, RMP and INH × 7 additional mo
Demir et al.[12]	2/2	Case reports	1. A 32-year-old woman with weakness, fatigue, and pain	1. CT scan showing mass, biopsy during ex-lap	INH, RMP, and ETHAM × 6 mo, and INH and RMP alone for remaining 6 mo for each patient
			2. A 42-year-old woman with early satiety, fatigue, and weight loss	2. US showing mass, CT-guided FNA	
Fischer et al.[13]	1/1	Case report	A 65-year-old woman with abdominal pain, fever, and night sweats for 2 months	CT and ERCP showing mass leading to ex-lap	ETHAM, INH, and RMP × 2 mo, INH and RMP × 7 additional mo
Kouraklis et al.[31]	1/1	Case report	A 35-year-old woman with fever, chills, nausea/ vomiting, and pain	US, CT, UGI	Ex-lap with Whipple resection followed by ETHAM, RMP, and INH × 9 mo
Kwon et al.[14]	1/52	Prospective cohort	Not specified	Not specified	Not specified

(*Continued*)

Table 2. Continued

Report of pancreatic tuberculosis	Cases of pancreatic tuberculosis/ total patients in study (n)	Type of study	Study population and presenting symptoms	Diagnostics	Management
Liu et al.[15]	1/1	Case report	A 33-year-old man with epigastric pain, weight loss × 6 mo	Abdominal US showing mass leading to Ex-lap	Medical management, not specified
Panzuto et al.[32]	1/1	Case report	A 27-year-old man with weakness, fatigue, nausea/ vomiting, and weight loss	CT, MRI, and ex-lap	INH and RMP × 6 mo, PZA for first 10 weeks only
Ozden et al.[33]	1/1	Case report	A 40-year-old woman with recurrent cholangitis	CT, MRI showing mass encasing portal vein	INH, PZA, STREP, and RMP × 2 mo, ETHAM, INH, and RMP × 6 additional mo
Sanabe et al.[16]	1/1	Case report	A 63-year-old man with pain, likely pancreatic mass	CT, MRCP showing mass leading to distal pancreatectomy, gastrectomy, partial transverse colectomy	INH, ETHAM, and PZA; nonspecified course
Schneider et al.[17]	2/2	Case reports	1. A 30-year-old woman with crampy abdominal pain 2. A 70-year-old woman with nausea/vomiting and abdominal pain	1. CT and CT-guided FNA 2. Abdominal US and diagnostic ex-lap	PZA, STREP, ETHAM, and INH × 4 mo, INH, RMP, and ETHAM × 3 additional mo for each patient
Sinan et al.[7]	3/49	Retrospective review of CT findings	Not specified	Not specified	Not specified
Stock et al.[18]	1/1	Case report	A 64-year-old woman with epigastric pain, nausea/ vomiting, and diarrhea	ERCP/CT showing what was thought to be chronic pancreatitis leading to distal pancreatectomy	Distal pancreatectomy, with no medical management
Riaz et al.[19]	1/1	Case report	A 32-year-old man with jaundice, puritis, pain, fever, dark urine, and acholic stools	US and CT scan showing pancreatic head mass. Percutaneous US-guided FNA showing tuberculosis	Medical management not specified

Ex-lap = exploratory laparotomy; INH = isoniazide; RMP = rifampin; ETHAM = ethambutol; PZA = pyrazinamide; FNA = fine needle aspiration; CT = computed tomography; MRI = magnetic resonance imaging; US = ultrasound; ERCP = endoscopic retrograde cholangiopancreatography; MRCP = magnetic resonance cholangiopancreatography; UGI = upper gastrointestinal series; LUQ = left upper quadrant of abdomen.

Table 3. Review of literature reporting peripancreatic tuberculosis mimicking solitary pancreatic masses in nonimmunosuppressed individuals

Reports of pancreatic tuberculosis	Cases of peripancreatic tuberculosis/ total patients in study	Type of study	Study population and presenting symptoms	Diagnostics	Management
Brugge et al.[34]	1/1	Case report	A 28-year-old man with abdominal pain and fever	CT, FNA	Medical management unspecified
Hulnick et al.[6]	21/27	Retrospective review of CT findings	Men and women, mean age of 37 yr, with multiple symptoms	CT scans only	Multiple outcomes
Sinan et al.[7]	3/49	Retrospective review of CT findings	Men and women, mean age of 35 yr, with multiple presenting symptoms, including pain, fever, weight loss, mass, and diarrhea	CT scans only	Multiple outcomes
Xia et al.[35]	16/58	Presentation of 16 cases and retrospective review of 58 cases of pancreatic and peripancreatic tuberculosis in China	Men and women, mean age of 38 years, with abdominal mass, nausea/ vomiting, fever, pain, night sweats, and jaundice	CT, MRI, ERCP showing pancreatic masses	Variety of management techniques from surgical to medical

FNA = fine needle aspiration; CT = computed tomography; MRI = magnetic resonance imaging; ERCP = endoscopic retrograde cholangiopancreatography.

In a review of CT scans obtained on 49 patients with abdominal TB, Sinan et al.[7] found that the most common features were peritoneal involvement and lymphadenopathy. Pancreatic involvement typically appears as an enhancing hypodense mass or masses, with irregular borders. Because the differential diagnosis of a cystic pancreatic mass is broad and includes serous cystadenomas, mucinous cystic neoplasia, intraductal

Table 4. Presenting signs and symptoms of abdominal tuberculosis in three retrospective reviews

Symptoms	Presenting symptom in review by Uygur-Bayamicli et al.[24] of 32 cases in Turkey (%)	Presenting symptom in review by Al Muneff et al.[25] of 46 cases in Saudi Arabia (%)	Presenting symptom in review of 300 cases by Bhansali[12] in India (%)
Abdominal pain	51	70	100
Weight loss	51	70	24
Fever	13	73	49
Ascites	38	61	Not given
Diarrhea	32	Not given	15
Nausea/vomiting	16	Not given	29
Abdominal mass	3	13	60
Sweats	6	30	Not given
Change in bowel habits	Not given	39	
Mean age (yr)	34	46	Not given

Adapted from Uygur-Bayamicli et al.,[24] Al Muneff et al.,[25] and Bhansali,[21] with permission.

papillary mucinous neoplasms, pancreatic islet cell tumors, and pancreatic pseudocysts, among others, CT scans are often unreliable for diagnosis. To date, no studies have demonstrated a reliable imaging technique to accurately distinguish TB from other pancreatic pathology.

In contrast to noninvasive techniques, invasive diagnostic techniques can be used to obtain tissue for pathologic examination and thus are more reliable diagnostic tools. Endoscopic retrograde cholangiopancreatography may reveal tuberculous strictures of the pancreatic duct, which are often confused with exocrine tumors of the pancreatic head, thus further confusing the picture.[26] Techniques for biopsy include endoscopic US–guided biopsy, CT/US-guided percutaneous biopsy, and surgical biopsy (open or laparoscopic). A recent review demonstrated no difference in accuracy between these three techniques for biopsy of pancreatic masses.[27] D'Cruz and colleagues[11] recently reported the successful use of percutaneous US–guided fine needle aspiration to obtain pancreatic tissue and visualize caseating granulomas, thus preventing a need for open surgery. Unfortunately, in most cases in the literature, the diagnosis of peripancreatic TB was made only after exploratory laparotomy, as in the present case.

For a definitive diagnosis of peripancreatic TB, microbiological and/or histologic confirmation is needed. Direct smear for the detection of acid-fast organisms using ascitic fluid or a biopsy specimen is often unrewarding (sensitivity, 0–6%). Biopsy with direct visualization (using laparoscopy or laparotomy) is the best way to obtain tissue for histopathologic confirmation. Combined visual and histopathologic diagnosis has a high sensitivity, ranging from 85% to 100%.[28] Although the presence of caseating granulomas is highly suggestive of peripancreatic TB, definitive diagnosis mandates either microbiological or histologic confirmation. At times, positive cultures for the mycobacterium may require up to 4–6 weeks of growth.

Other entities can produce caseating granulomas and need to be considered in the differential diagnosis. These include sarcoidosis (which can produce a central zone of fibrinous necrosis, although noncaseating granulomas are more common), extraintestinal Crohn's disease with caseating granulomas, a fungal process such as coccidioidomycosis, and foreign body reaction. Often, clinical and radiologic correlations help to exclude these from consideration.

Once a tissue diagnosis has been made, the keys for management of TB rest on both the medical treatment for the affected individual and the prevention of infectious spread to unaffected individuals. Medical therapy generally consists of isoniazid and rifampin, with pyrazinamide and ethambutol added for severe or resistant cases. This four-drug regimen was deemed appropriate in the current case. In addition to anti-TB treatment, prevention of infectious spread is essential in the management of the disease. While in the hospital, the patient must be placed on strict airborne isolation and hospital staff must wear appropriate protective clothing to protect themselves and prevent spread. As was done in this case, all affected individuals must be reported to local health departments, so that previously exposed family members and close contacts can be identified, evaluated, and treated. Finally, patients should be tested for other factors that might increase the risk of TB infection, such as HIV and other immunodeficiency conditions. Strict adherence to prevention and control measures will help limit the rising incidence of TB in both the United States and worldwide.

CONCLUSIONS

The present case illustrates abdominal TB mimicking a pancreatic mass. Once the correct diagnosis was made, our patient was started on a four-drug regimen of anti-TB drugs, with improvement. However, as previously discussed, making the diagnosis of pancreatic TB often is extremely challenging. This is because patients present with symptoms and signs that both are nonspecific and mirror common pancreatic diseases. In addition, common imaging techniques such as CT and magnetic resonance imaging do not reliably distinguish infectious from noninfectious pancreatic masses.

TB is much more common in the U.S. immigrant population. Our patient was from India, which increased the possibility of TB as an etiology. A recent study examining 623 Dutch TB cases revealed that 17% were attributable to non-Dutch immigration.[29] There are also isolated reports of serum CA-125 levels being elevated with cases of abdominal TB, as seen in our patient.[30]

Pancreatic TB is a disease that is being reported with increased frequency. It is likely that this increase is reflective of a true increase in incidence of the disease, because other forms of TB continue to rise worldwide. By increasing our vigilance for this infectious etiology, we can decrease the morbidity associated with this unusual condition.

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Resection of a Cancer Developing in the Remnant Pancreas After a Pancreaticoduodenectomy for Pancreas Head Cancer

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We report a rare case of a curative resection performed on a carcinoma developing in the remnant pancreas at 3 years 7 months after a pancreaticoduodenectomy for pancreatic cancer. A 63-year-old man underwent a pancreaticoduodenectomy for pancreatic cancer on November 1999. Because the celiac trunk was occluded by atherosclerosis, an aortohepatic bypass with a saphenous vein graft was performed simultaneously. In May 2003, tumor marker levels increased, and a tumor was detected in the remnant pancreas on computed tomography. There were no findings such as invasion into the surrounding tissue or distant metastasis, and therefore we removed the remnant pancreas in July 2003. Histopathologically, the tumor consisted of a well-differentiated tubular adenocarcinoma and was limited to the pancreas. Moreover, the anastomotic site of the pancreaticojejunostomy was negative for cancer, and some foci of papillary hyperplasia and goblet cell metaplasia of the pancreatic ductal epithelium, which was thought to be the precursor of the pancreatic cancer, were seen. These findings suggested that the tumor was a second primary cancer developing in the remnant pancreas. This case provided suggestive evidence for the development of pancreatic cancer, and the surgical procedure for a pancreaticoduodenectomy with occlusion of the celiac trunk is discussed. (J GASTROINTEST SURG 2005;9:263–269)

KEY WORDS: Pancreatic cancer, remnant pancreas, surgery, occlusion of the celiac trunk, pancreaticoduodenectomy

Invasive ductal carcinoma of the pancreas has been one of the cancers with the poorest prognosis; only surgical resection is able to provide any cure. The most causative factor for the dismal prognosis of pancreatic cancer patients is the high recurrence rate of the cancer, even in those cases with a macroscopically curative resection. Furthermore, tumor recurrence generally leads to death within 1 to 3 months with rare exceptions, because effective strategies to prevent this recurrent disease have not yet been developed. To cure pancreatic cancer, it is essential to understand the basic mechanisms responsible for its carcinogenesis and development and then to establish modalities for earlier diagnosis.

In this case report, we describe a rare case of a patient who underwent resection for a tumor that developed in the remnant pancreas at 3 years 7 months after a pancreaticoduodenectomy for invasive ductal pancreatic cancer. Evidence will be presented regarding the precancerous lesion and the development of the pancreatic cancer. In addition, surgical issues will be discussed regarding patients with an occluded celiac trunk who must undergo a pancreaticoduodenectomy.

CASE REPORT

The patient was a 63-year-old man who underwent pancreaticoduodenectomy for pancreatic cancer at Tokyo Medical and Dental University Hospital, Faculty of Medicine, on November 25, 1999. Preoperative abdominal angiography showed that the celiac trunk was occluded by atherosclerosis, and therefore

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.016

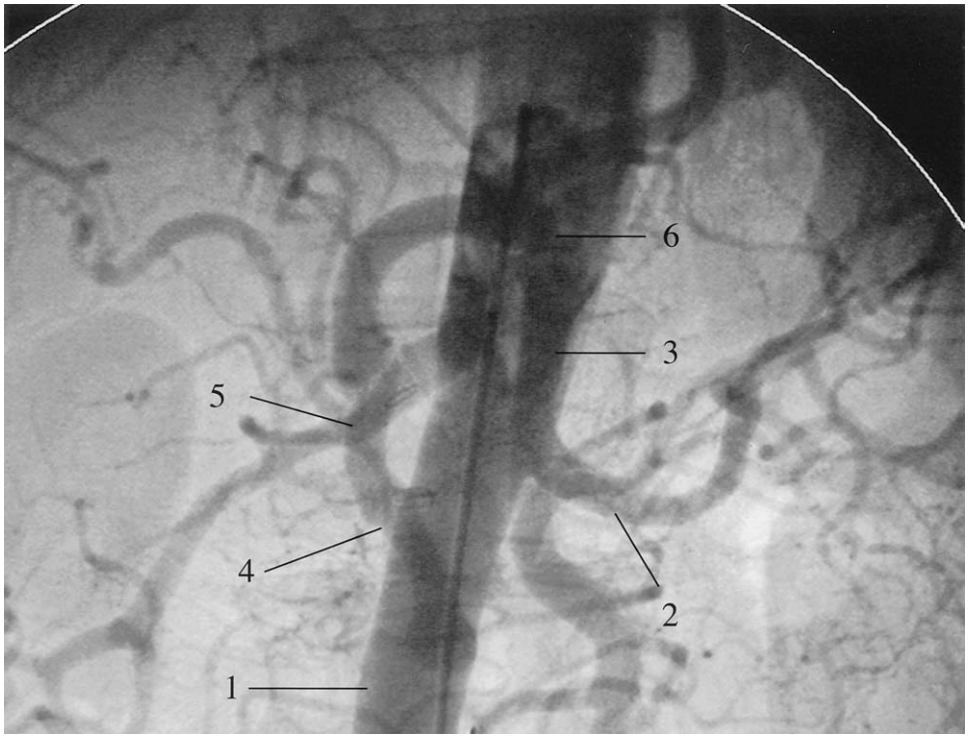

Fig. 1. Aortogram before the second operation. The bypass was made from the infrarenal aorta to the stump of the gastroduodenal artery using a saphenous vein graft. 1, Aorta; 2, left renal artery; 3, superior mesenteric artery; 4, aortohepatic bypass (saphenous vein graft); 5, stump of the gastroduodenal artery; and 6, celiac trunk (occluded).

we maintained the blood flow in the liver, stomach, and spleen by an aortohepatic bypass with a saphenous vein graft during the operation (Fig. 1). On histopathologic examination of the resected specimen, the cancer was diagnosed as a well to moderately differentiated tubular adenocarcinoma, pT3 pN0 pM0, and stage II.[1] Cancer cells were negative at the stump of the pancreas (Fig. 2). During the patient's follow-up in an outpatient clinic, the main pancreatic duct (MPD) of the remnant pancreas became dilated as shown on computed tomography (CT) in February 2003, and carbohydrate antigen 19-9 (CA19-9) was elevated to 56.1 U/ml (37 U/ml is the upper limit of the normal range) in May 2003. Therefore, recurrence of the pancreatic cancer was strongly suspected, and he was admitted at 3 years 7 months after the original pancreaticoduodenectomy. The CA19-9 level at admission decreased to normal limits after systemic chemotherapy with three courses of GEMZAR (gemcitabine hydrochloride; Eli Lilly Japan K.K., Kobe, Japan) at a dose of 1300 mg/body. However, the MPD of the remnant pancreas was still dilated, and the tumor protruded into the MPD near the pancreaticojejunostomy on abdominal CT (Fig. 3). The aortohepatic bypass was confirmed to be patent, and both common hepatic and splenic arteries were normally visualized on abdominal angiography. There were no findings of invasion into the tissue around the remnant pancreas, abdominal dissemination, lymph nodes, and distant metastasis, and therefore macroscopically complete removal of the tumor was expected. On July 10, 2003, the remnant pancreas including the pancreaticojejunostomy was removed together with the lymph nodes around the pancreas and the spleen. As expected, neither hepatic metastasis nor peritoneal dissemination was seen, and this was concluded to be a curative resection. In the resected specimen, the tumor was located near the pancreaticojejunostomy and was about 3 cm in diameter (Fig. 4). Histopathologically, the tumor consisted of a well-differentiated tubular adenocarcinoma that resembled the previous tumor, and there were findings of vascular invasion but no retroperitoneal invasion or lymph node metastasis. There were no cancer cells or atypical cells at the site of the pancreaticojejunostomy (Fig. 5). The tumor originated from a branch of the pancreatic duct near the MPD and was limited to the pancreatic parenchyma. Based

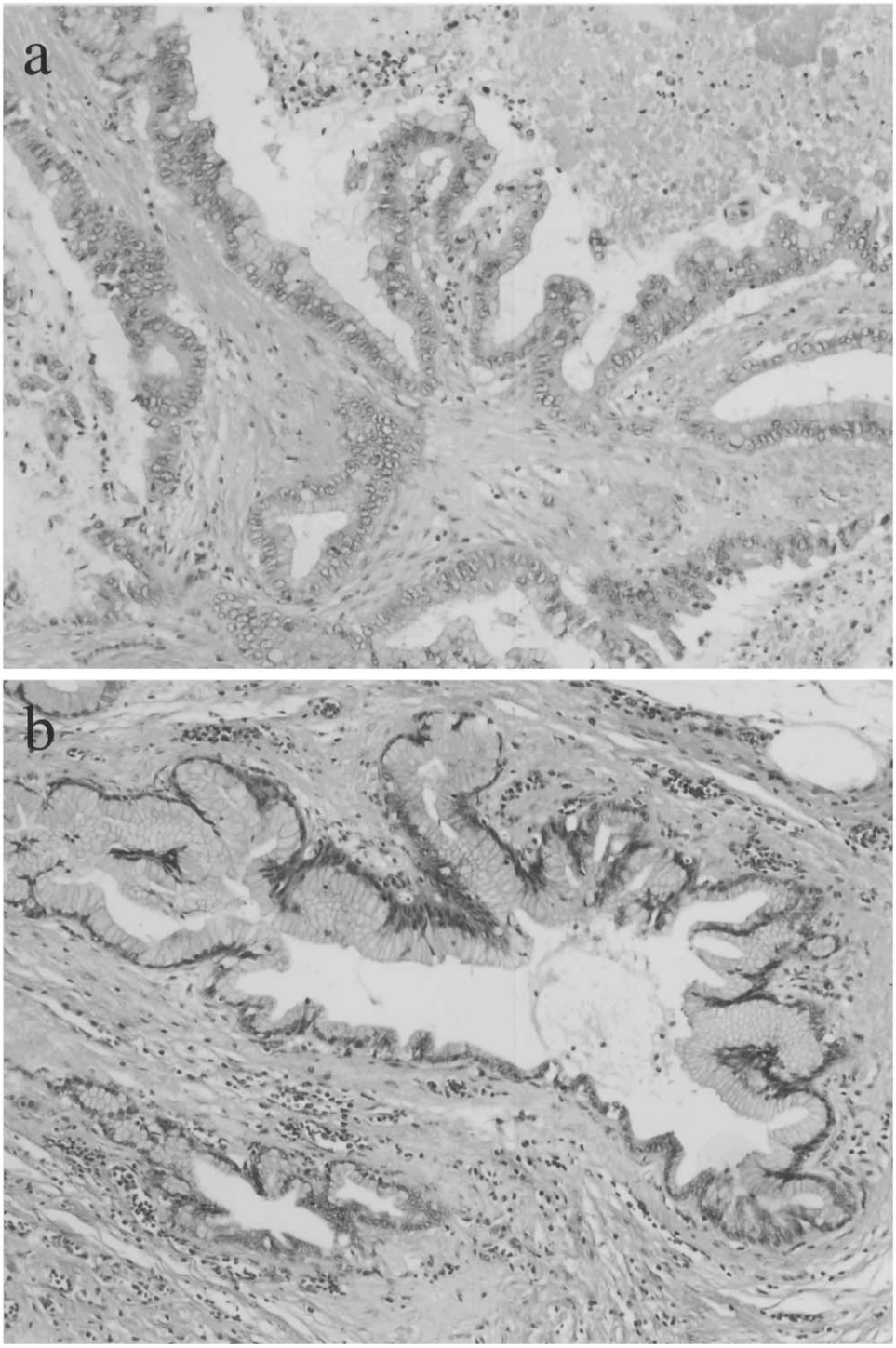

Fig. 2. (**a**) Histopathologic findings of resected specimen at the first operation. The cancer was diagnosed as a well to moderately differentiated tubular adenocarcinoma. (**b**) The surgical margin was negative for cancer cells, and hyperplasia of the pancreatic ductal epithelium was seen at the stump of the pancreas.

on the findings as mentioned here, we diagnosed the tumor as a metachronous primary cancer of the remnant pancreas. Moreover, some foci of low papillary hyperplasia and goblet cell metaplasia of the pancreatic duct epithelium were found in the resected specimen, which was also found in the first resected specimen (Fig. 6).

The postoperative course was uneventful, and the patient is still alive without any recurrence at 10 months after the second operation.

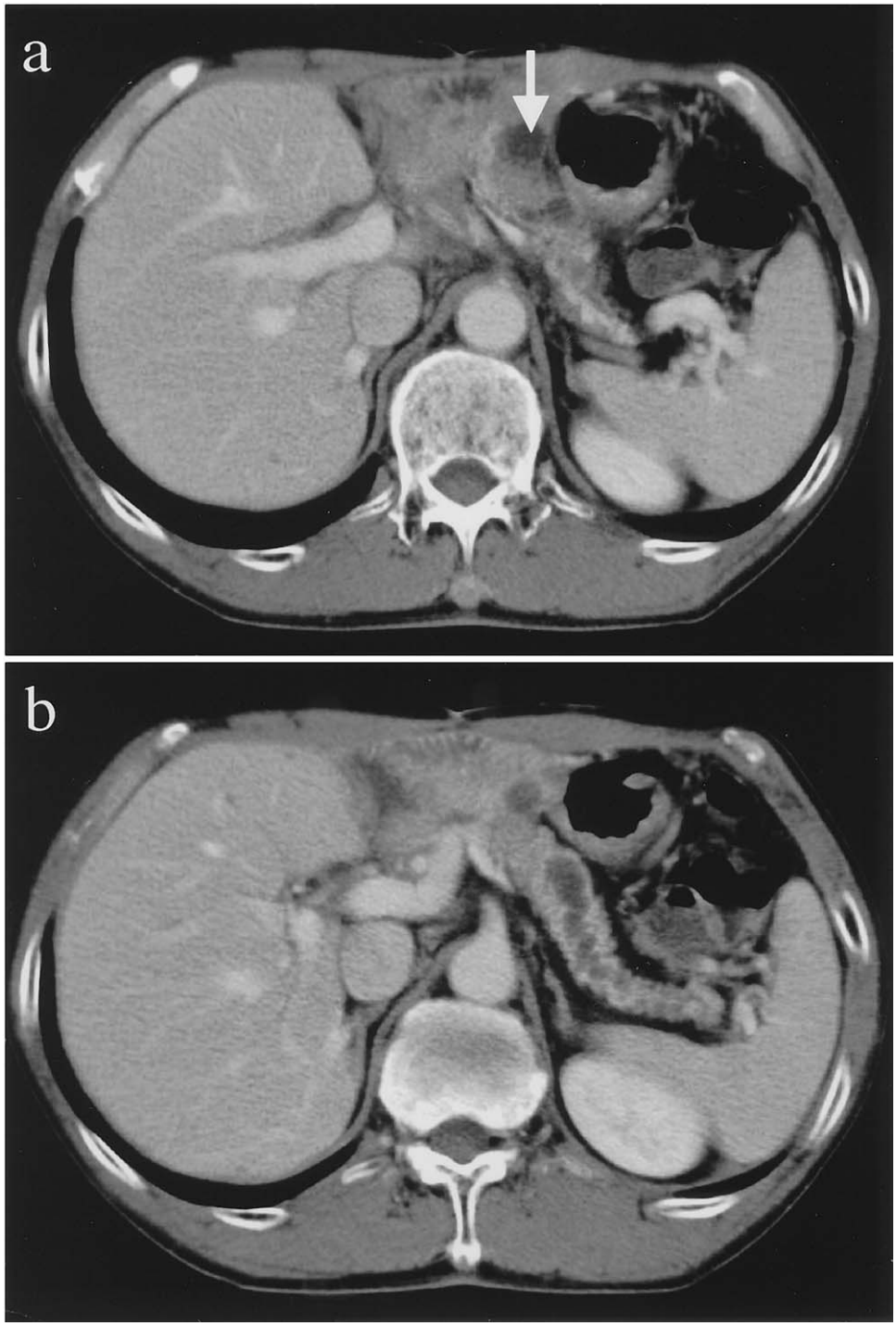

Fig. 3. Abdominal computed tomography. (**a**) The tumor (*arrow*), which protruded into the main pancreatic duct, was observed near the anastomotic site of the pancreaticojejunostomy. (**b**) The main pancreatic duct of the remnant pancreas was dilated.

DISCUSSION

Patients with pancreatic cancer still have a dismal prognosis. Although various treatments such as chemotherapy or radiation have been developed, surgical resection provides the only chance for a cure and long-term survival. However, even in those patients who undergo a surgical resection, the 5-year survival is approximately 20%,[2] and more than half of the patients had a relapse with the same cancer within 2

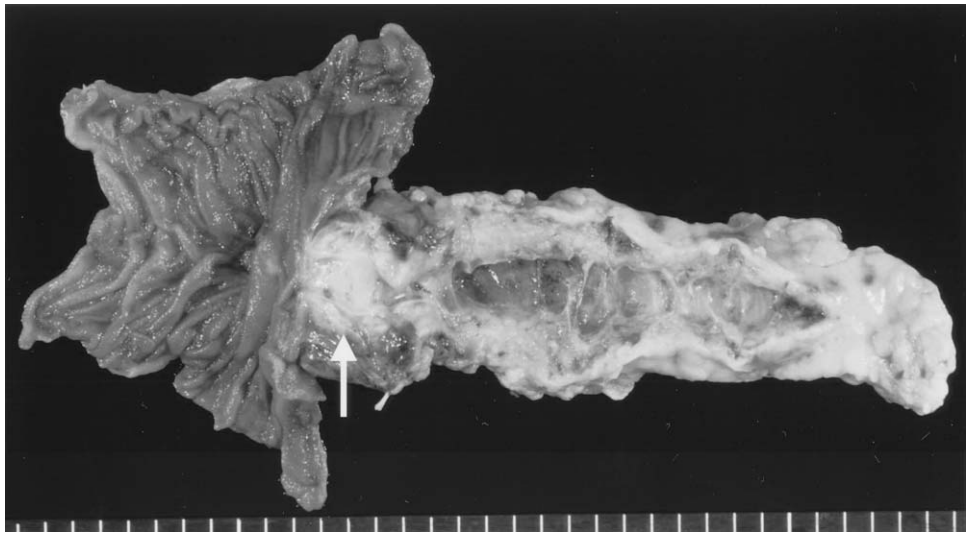

Fig. 4. The resected specimen from the second operation. There was a hard whitish tumor 3 cm in diameter near the anastomotic site of the pancreaticojejunostomy (*arrow*).

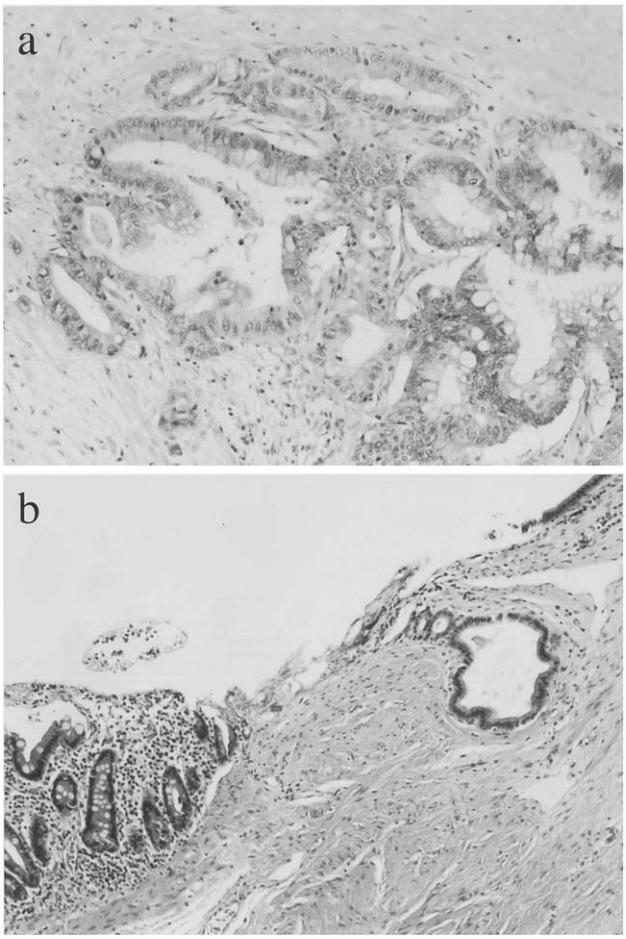

Fig. 5. Histopathologic findings of the resected specimen from the second operation. (**a**) The cancer was diagnosed as a well-differentiated tubular adenocarcinoma. (**b**) There were no cancer cells or atypical cells at the site of the pancreaticojejunostomy.

years after resection.[3–5] The most frequent recurrence patterns for pancreatic cancer after resection were local recurrence, hepatic metastasis, and peritoneal dissemination.[4–7]

In this case, the tumor developed near the anastomotic site of the pancreaticojejunostomy, but not the stump in the remnant pancreas, at 3 years 7 months after the pancreaticoduodenectomy for pancreatic cancer. The most interesting issue here is the mode of tumor development. There are two possibilities: local recurrence or a second primary cancer.

According to previous studies on the tumor factors associated with recurrence after the resection of a pancreatic cancer,[5,7,8] the possibility of local recurrence was thought to be quite low in this case because the second tumor exhibited no invasive characteristics into the surrounding tissue. In most cases with local recurrence, the tumor was far advanced, and there is usually no indication of surgical resection.

On the other hand, the findings given next strongly supported the idea that the tumor that developed in the remnant pancreas was a second primary cancer. First, the surgical margin at the first surgery was negative in the resected specimen, and there was neither atypical nor cancerous cells at the anastomotic site of the pancreatojejunostomy. Second, the tumor was limited to the remnant pancreas, and there was no indication that the tumor invaded into the adjacent tissue or into the remnant pancreas parenchyma. Third, some foci of papillary hyperplasia or goblet cell metaplasia in the ductal epithelium were found in both the first and second resected specimens. Papillary hyperplasia of the pancreatic ductal epithelium

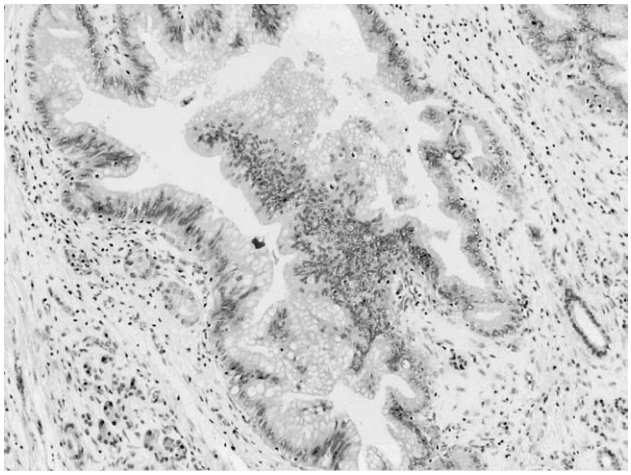

Fig. 6. Low papillary hyperplasia or goblet cell metaplasia in the remnant pancreatic ductal epithelium.

has been considered to be a precursor of infiltrating carcinomas.[9–12] In the literature, the time interval from these precursor lesions to an infiltrating carcinoma of the pancreas was reported to range from 17 months to 29 years.[11,12] Although there was a wide range in the latency period, the duration of 3 years 7 months in our case was thought to be reasonable.

Although it has been very difficult to distinguish between a recurrence and a second primary occurrence,[13–15] the molecular analysis and the clinicopathologic findings are useful in discriminating between a recurrent versus a second primary cancer.[16] It is well known that approximately 90% of pancreatic cancers have a point mutation of the *ras* gene with various mutation patterns, so different types of mutations between an initial and a second tumor strongly suggest a multicentric carcinogenesis. Unfortunately, we could not analyze for the *ras* gene because the specimen from the initial surgery was not stored.

In pancreatic cancer, multicentric lesions were found in 16% to 34% of patients.[17–20] Therefore, we can raise an alternative theory that a minute multicentric cancer was already present in the remnant pancreas at the initial surgery, because precancerous foci were seen in the resected specimen at that time. Although these two opinions seem different from each other, they are the same in terms of multicentric occurrence.

This case raised another interesting issue from a surgical standpoint. The celiac trunk was occluded by atherosclerosis, so we performed an aortohepatic bypass with a saphenous vein graft during the pancreaticoduodenectomy. Thompson et al.[21] reported that a high-grade stenosis or occlusion of the celiac trunk was present in 10.5% of the patients undergoing a visceral arteriogram. On the other hand, occlusion of the celiac trunk has been encountered in approximately 2% of those patients receiving a pancreaticoduodenectomy.[22] The causes of the occlusion of the celiac trunk were atherosclerosis,[22–24] extrinsic compression by the arcuate ligament,[22,25] and dense fibrotic tissue around the celiac axis.[26] In general, revascularization of the celiac trunk must be performed for atherosclerotic obstruction. In revascularization procedures, two methods such as bypass grafting of the occluded segment[22–24] and arterial reimplantation[21,22] have been reported. We performed an aortohepatic bypass from the infrarenal aorta to the stump of the gastroduodenal artery with a saphenous vein graft, and the bypass graft has been patent until now.

In summary, we present the rare case of a patient who underwent the removal of a cancer developing in the remnant pancreas at 3 years 7 months after pancreaticoduodenectomy for pancreatic cancer. This second cancer was thought to be another primary cancer rather than a recurrence based on the clinical and histopathologic findings. The present case might also provide insight into the role of precancerous lesions in the development of pancreatic cancer.

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Hypercalcemia and Pancreatic Endocrine Neoplasia With Elevated PTH-rP: Report of Two New Cases and Subject Review

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Humoral hypercalcemia of malignancy is widely associated with tumor production of parathyroid hormone related protein (PTH-rP). This peptide functions in endocrine, autocrine and paracrine mechanisms in a manner similar to PTH; increasing renal uptake of calcium, decreasing retention of phosphorous, and stimulating adenylate cyclase and phospholipase C. Although PTH-rP production has been well documented in neoplasms of the exocrine pancreas, we present here two cases of endocrine pancreatic neoplasms elaborating PTH-rP. We then review the literature of previous cases and delve into the pathophysiology of this peptide. (J GASTROINTEST SURG 2005;9:270–279)

KEY WORDS: PTH-rP, pancreatic endocrine neoplasm, hypercalcemia

INTRODUCTION

Cloned in 1987, parathyroid hormone–related protein (PTH-rP) is responsible for the most common paraneoplastic syndrome, humoral hypercalcemia of malignancy.[1] PRH-rP shares only limited homology with PTH; this peptide is larger than PTH and is localized to a different chromosome, the short arm of human chromosome 12.[2] Nonetheless, the common amino-terminus of PTH-rP binds to the same cell surface receptor in bone and kidney.[3] Such binding causes physiologic hypercalcemia, hypophosphatemia, increased urinary cAMP retention and the stimulation of adenylate cyclase and phospholipase C.[4–6] Two types of PTH/PTH-rP receptors have been identified: the *Type I* PTH/PTH-rP 1-34 receptor and the *Type II* PTH/PTH-rP 1-34 receptor.[3]

Importantly, PTH-rP is elaborated normally by multiple non-neoplastic tissues, including brain, hypothalamus, pituitary, thyroid, parathyroid, adrenal cortex, adrenal medulla, stomach mucosa, pancreatic islets, lactating and prolactin-stimulated mammary tissue, and skin.[7,8] The early death of PTH-rP receptor knockout and PTH-rP knockout mice speaks to the homeostatic importance of this factor.[9,10] In fact, the PTH-rP gene is expressed in virtually every cell and tissue in the body during normal development or adult life, including the beta cells of the pancreas.[11] This hormone has been demonstrated to function in traditional endocrine, paracrine and autocrine fashions, as well as "intracrine"-entering the nucleus directly after translation to promote proliferation or apoptosis.[11]

In addition, PTH-rP has been localized to many neoplasms not associated with hypercalcemia, such as neoplasms of the pancreas, skin, endocrine tissue, and mesothelium.[7] Thought to be neuroectodermal in origin, PTH-rP may modulate pancreatic islet growth by a protein kinase C–mediated mechanism.[12,13]

Besides its effects on calcium homeostasis, PTH-rP possesses other bioactivities. The amino terminus is a potent vasodilator, relaxing vascular tissue in an endothelium-independent manner, as well as increasing heart rate, contractility and coronary flow in rats.[14] This protein also appears to modulate the effects of transforming growth factor-β in bone culture.[15] Thus, as Ratcliffe wrote in 1997, "PTH-rP can be considered a polyhormone acting as a precursor for a number of regulatory peptides with autocrine, paracrine, and endocrine actions, and acting via specific cell surface receptors to produce a co-ordinated biological response."[16]

Tumors elaborating PTH-rP have been well documented in the literature. Among these are tumors of the exocrine pancreas. However, tumors of the

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.06.012

endocrine pancreas elaborating PTH-rP have been rare; only seven are recorded in the literature. We herein present two cases of well-differentiated islet cell tumors of the pancreas producing PTH-rP. We also provide a review of previous pancreatic cases (both endocrine and exocrine) and consider the pathophysiology of this unusual syndrome.

PATIENTS AND RESULTS

Case #1

A 38-year-old woman in her third trimester of pregnancy presented to her local hospital with anorexia, weight loss and obtundation in September of 2002. An emergency cesarean section was performed for fetal bradycardia, after which the patient remained in a coma for one week. Subsequent evaluation revealed a serum calcium level of 19.9 mg/dL (reference 8.8 – 10.5 mg/dL), and the patient developed acute renal failure. Computed tomography (CT) and magnetic resonance imaging of the abdomen and pelvis revealed a 7.0 × 3.5 cm right-sided pancreatic mass, in addition to two liver lesions measuring 6 cm and 5 cm in diameter, respectively. Investigation into the etiology of her hypercalcemia revealed a PTH-rP of 2.5 pmol/L (reference ⩽ 1.3 pmol/L).

A fine needle biopsy of the liver demonstrated metastatic clear cell, well-differentiated neuroendocrine carcinoma at the outside institution and later at Johns Hopkins Hospital (Fig. 1). The neoplasm was periodic acid-Schiff (PAS) positive, and stained with PAS diastase, but not with mucicarmine. Immunohistochemical labeling revealed 4+ positivity for cytokeratin (CK) AE1/AE3 and carcinoembryonic antigen (CEA), strong labeling (3-4+) for synapotophysin, 2-3+ positivity for CA 19-9 and 1+ for vimentin. Focal weak positivity was seen for CK20, S100-protein inhibin and alpha-1 antitrypsin. Tumor stains were negative for estrogen receptor (ER,) progesterone receptor (PR), TTF1 (a lung and thyroid carcinoma marker), CA 125, alpha fetoprotein, CD10 (a renal cell carcinoma marker), chromogranin, HMB45 and the hepatocellular cancer marker HepPar1.

The pathologic specimen was sent to Johns Hopkins, where the following stains were positive: PAS (cytoplasmic), PAS with diastase, pancytokeratin, CEA, CA 19-9, vimentin, synaptophysin, chromogranin, and focally for alpha-1-antitrypsin (Fig. 2). The neoplasm was negative for ER, PR, TTF-1, CD10, CA 125 and HMB45. These stains support a tumor of endocrine origin, specifically of pancreatic islet cells.

After control of the patient's serum calcium levels with bisphosphonates and resolution of her acute renal failure, the patient was discharged to a rehabilitation facility to receive four cycles of chemotherapy at 24-day intervals. She received paclitaxel, carboplatin and etoposide.

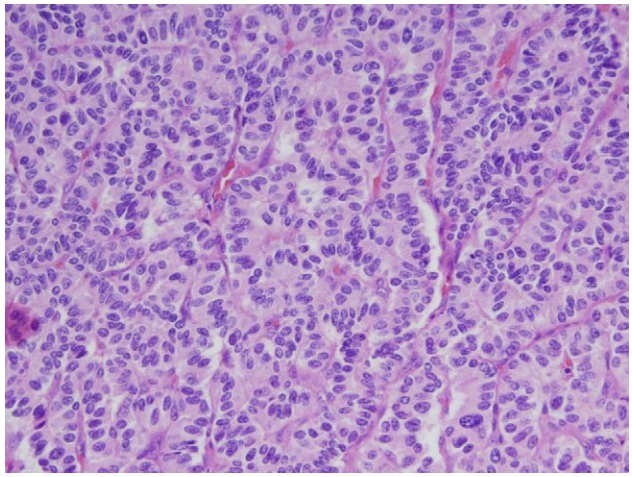

Fig. 1. Hematoxylin and eosin stain of pancreatic tumor at original magnification of ×40, for patient 1.

A CT scan after 4 cycles demonstrated that the hepatic lesions were slightly smaller, measuring 5 × 4.5 cm in the dome and 3.5 × 3 cm in the right lobe. No change in the pancreatic mass was seen. An octreotide scan demonstrated activity in the area of the pancreas but no metastatic activity. A bone scan was negative.

The patient was referred to the Johns Hopkins Hospital, and her disease was deemed surgically resectable in staged procedures. On April 24, 2003

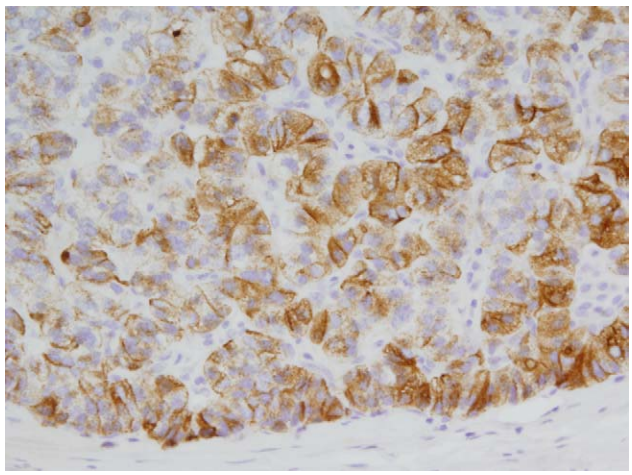

Fig. 2. Chromogranin stain of pancreatic tumor at original magnification of ×40 for patient 1. The strongly positive staining is consistent with a neuroendocrine tumor.

she underwent a pancreaticoduodenectomy, cholecystectomy, and intraoperative ultrasonography. On ultrasonographic examination, the two large hepatic metastases were confirmed to be in the right hepatic lobe. Given the scope of the planned pancreatic resection, it was decided to perform the liver resection in the future.

The specimen from this initial resection revealed a malignant, well-differentiated pancreatic endocrine neoplasm (PEN), measuring 6 cm at the greatest dimension. There was no vascular or perineural invasion, and the neoplasm did not involve the duodenum or distal common bile duct. The final resection margins were all negative. Immunohistochemical stains were strongly positive for synaptophysin, chromogranin and cytokeratins, with focal positivity for alpha-1-antitrypsin. These findings correlated well with the results of the previous liver biopsy specimens. The tumor involved one of eighteen resected lymph nodes.

Three months after the initial operation, the patient returned to the operating room for planned liver resection. Intraoperative ultrasonography and examination revealed no significant progression in disease or appearance of other metastases. Two large masses were identified in segments 7 and 8, each measuring approximately 5 cm in diameter (Fig. 3). Formal right hepatectomy was performed without complication. Pathologic examination of the liver lesions revealed metastatic well-differentiated neuroendocrine neoplasm, similar in appearance to the primary tumor, with negative margins. Postoperatively, calcium levels were in the normal range (9.1 mg/dl, normal, 8.4–10.5). The patient is alive and well, ably caring for her child.

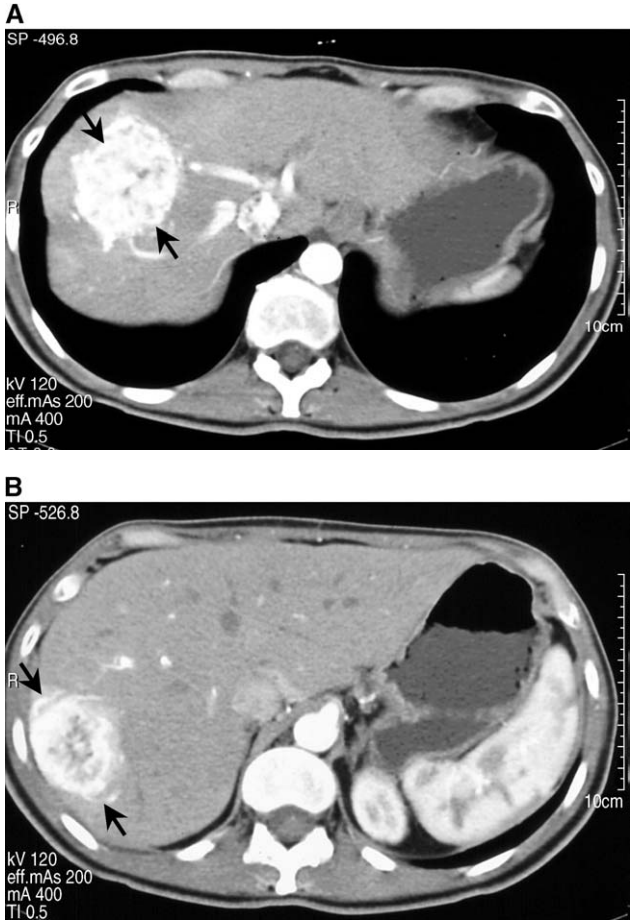

Fig. 3. Computed tomographic scans performed before resection of liver metastases in patient (**A**)1. Lesion in segment 8. (**B**) Lesion in segment 7. Note the magnitude of the feeding veins into the liver, consistent with arteriovenous shunting.

Case #2

A second patient presented to the Johns Hopkins Hospital for treatment of recurrent metastatic well-differentiated PEN. This 51-year-old man had presented 3 years previously to another institution after a 7-year history of diabetes, vomiting, weight loss, and non-productive cough. Evaluation at that time revealed an elevated calcium level and extensive tumor of the spleen and distal pancreas, which appeared consistent with islet cell tumor on CT-guided biopsy. Stains pointed towards a glucagonoma; indeed his pre-operative glucagon was somewhat elevated at 306 pg/mL (reference 20–100). Additionally, his PTH-rP was nearly 4 times normal at 4.9 pmol/L, and his calcium was high at 10.8 mg/dL, while his PTH was suppressed at 4 pg/mL (normal 10-65).

In June of 1995, he underwent a distal pancreatectomy, splenectomy, partial gastrectomy, and resection of a retroperitoneal nodule at the outside institution. Preoperatively and intraoperatively, a 4 cm mass was noted in the left lobe of the liver. This was not resected due to extensive intraoperative blood loss. Pathology from the other institution showed a PEN with positive margins, invasive into the spleen and serosa of the stomach. Five months later, he underwent a left lateral hepatic segmentectomy, wedge resection of the right lobe of the liver, and extensive dissection of celiac nodes. While the celiac nodes were benign, both the left lateral segment and right lobe were positive for metastatic well-differentiated PEN. Immunoperoxidase stain for glucagon was strongly positive, and stains for chromogranin were focally positive.

The patient was followed carefully postoperatively, and showed biochemical evidence of recurrence three years later in 1998, when his PTH-rP level was found to be 2.9 pmol/L and then 6.3 two months later (reference, <1.3 pmol/L), with a calcium level of

13.8. Moreover, his alkaline phosphatase levels rose persistently during this period. Of note, his glucagon levels were normal. Given these concerning laboratory values, an octreoscan was performed, revealing a focal area of increased uptake in the posterior segment of the right lobe of the liver. A subsequent MRI demonstrated a 6 × 8 cm mass in the area of previous resection, impinging on the left kidney and stomach remnant. Additionally, three 1-cm liver metastases were seen.

He was referred to the Johns Hopkins Hospital, where a CT scan showed a large heterogeneously enhancing mass in the left upper retroperitoneum measuring 10 × 10 × 8 cm, with probable involvement of the posterior stomach and left kidney and involvement of the left adrenal gland. (Fig. 4). Additionally, an 8 mm nodular focus was seen within the right hepatic lobe, suggestive of a metastasis.

He was subsequently taken to the operating room, where an exploratory laparotomy confirmed the CT and angiographic findings of a large left retroperitoneal tumor involving the left kidney and a metastatic focus in the liver. Additionally, five implantations were found on the peritoneal surface. The following procedures were performed: near total gastrectomy with Roux-en-Y esphagogastrojejunostomy, en bloc left nephroureteroadrenalectomy, resection of part of the left diaphragm, resection of portion of segment IV of liver, open cholecystectomy, and feeding jejunostomy.

Immediately postoperatively, the patient's calcium dipped to 6.4, but this normalized over the ensuing 10 days. His PTH-rP level decreased to 2.0 pmol/L (reference, 0.0–1.3), and his PTH increased to 92 pg/mL (reference 10–65), most likely

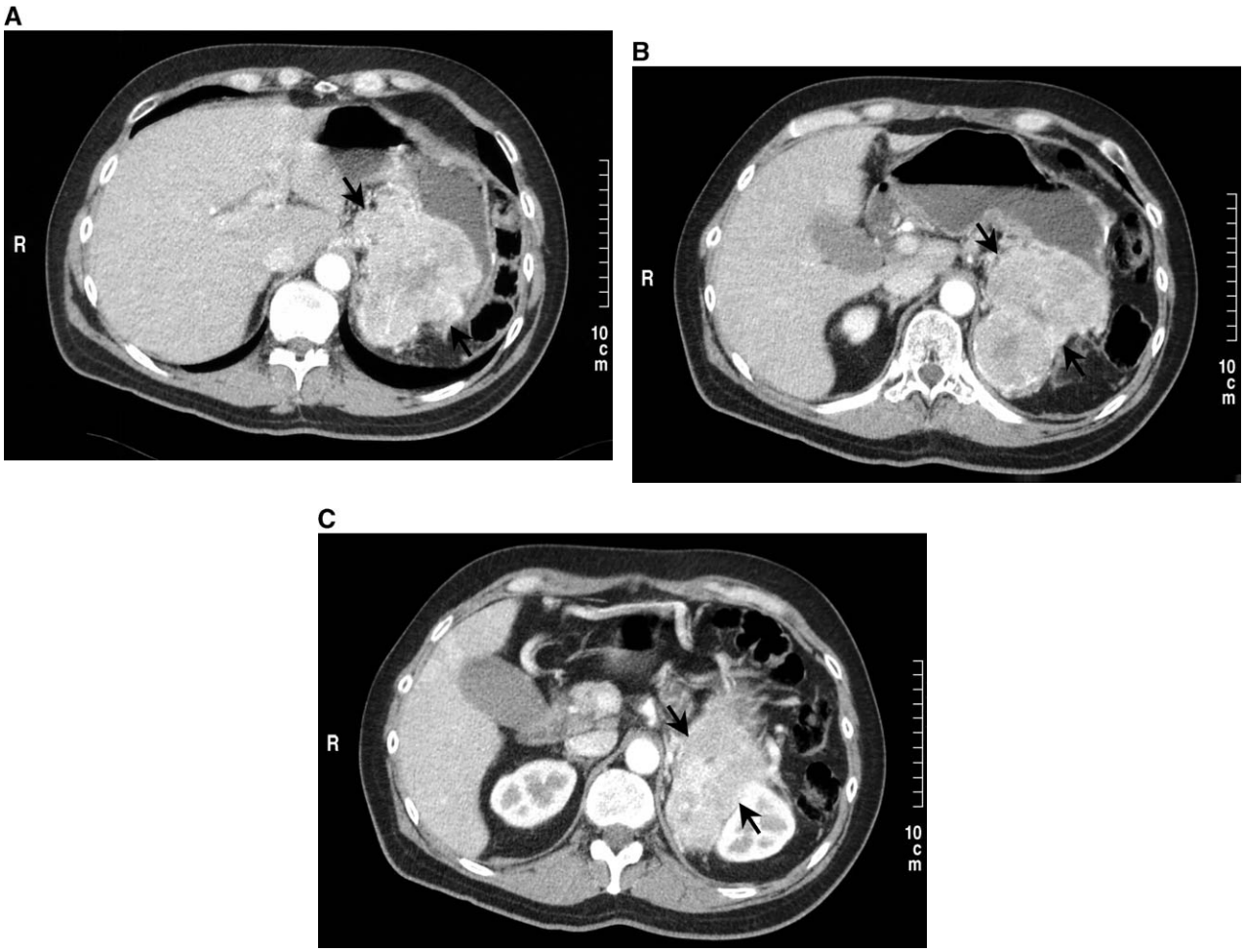

Fig. 4. Computer tomography scan performed before the resection of the large left upper retroperitoneal mass (*arrows*) in patient 2. Note the hypervascularity of the lesion and the large collaterals. The vascularity washes out in late phase. From a radiographic standpoint, the tumor appears consistent with (1) adrenal carcinoma, (2) nonfunctioning islet cell tumor, (3) retroperitoneal sarcoma, or (4) gastrointestinal stromal tumor.

to normalize the calcium level after the physiologic withdrawal of PTH-rP.

Histology confirmed that the 10-cm mass involving the left kidney and stomach was a well-differentiated PEN. Surgical margins were negative, excepting a focus of intravascular tumor at the distal margin. Four of the five sampled implants (omental, subpyloric omental, perinephric, left pericolon) as well as the liver segment were consistent with metastatic malignant islet cell tumor. Immunohistochemically, the tumor was diffusely positive for chromogranin and focally for somatostanin, but negative for serotonin, insulin, and glucagon.

Since surgery, he has required implantation of a microscopic brachytherapy elution device for liver metastases and the resection of pelvic masses. He has been readmitted once for hypercalcemia, treated effectively with hydration, diuresis, and bisphosphonates. He is alive with slowly progressing metastatic disease.

DISCUSSION

Although unusual, PTH-rP–producing neoplasms of the pancreas have been reported previously. Of note, most reported cases involve adenocarcinoma or undifferentiated exocrine pancreatic cancer, as opposed to the well-differentiated neuroendorine neoplasms described here. A review of the literature uncovered a first exocrine case reported in 1986 by Nagata and colleagues.[17] A 46-year-old woman presented with anorexia, lower abdominal pain, and dehydration. Laboratory work revealed a calcium of 17.6 mg/dL, a phosphorus of 3.2 mg/dL, and a PTH of 0. Unfortunately, the woman died; at autopsy, an undifferentiated carcinoma of the exocrine pancreas was discovered. Of note, this study occurred before the cloning of PTH-rP in 1987. The authors found that the protein isolated from the woman's tumor elicited an increase in adenylate cyclase activity, as confirmed by PTH-rP years later.

Bandyopadhyay et al. reported another case in 2003, also providing a literature review of six other documented cases of PTH-rP-producing tumors of the exocrine pancreas.[18] Table 1, adapted from their manuscript, details the laboratory values, tumor location, size, and pathology in these cases of exocrine tumors.

Table 2 presents the previous cases of endocrine tumors associated with elevated PTH-rP. Vair et al. reported a 47-year old woman with a pancreatic mass, refractory hypercalcemia and abnormally high "parathormone-like substance."[19] She had presented with left upper quadrant pain associated with fatigue and a 14 kg weight loss. Medical treatment of hypercalcemia was attempted; when this proved fruitless, the tumor was resected and found to be a well-differentiated PEN. The patient was alive and well two-years postoperatively with normalized serum calcium and PTH levels. Wynick et al.[20] followed with a woman who presented with right upper quadrant pain, polyuria and lethargy. Laboratory work revealed hypercalcemia and hypophosphatemia. A biopsy specimen stained positively for neuron specific enolase (a neuroendocrine marker) and PTH-rP; the pathology was consistent with a well-differentiated PEN. The patient was treated medically with octreotide and a low-calcium diet; at the time of publication, she was well and normocalcemic. Mitlak and colleagues presented a 77-year-old woman who presented with weakness, fatigue, confusion, hypercalcemia, hypophosphatemia and elevated PTH-rP. A CT scan of the abdomen revealed a large left upper quadrant mass and two hypervascular areas of the liver. A needle biopsy of the mass confirmed an islet cell tumor. At publication, she had undergone chemotherapy with recurrence of hypercalcemia.[21]

Miraliakbari et al. report a fourth case of pancreatic neuroendocrine tumor staining positive for PTH-rP. The calcium level in this 47-year-old woman was 16.6 mg/dL; her PTH level was 291 pg/mL (normal 50–340 pg/mL). Immunohistochemistry demonstrated tumor positivity for non-specific enolase and synaptophysin, as well as scattered positivity for serotonin, calcitonin, and alpha-subunit of glycoprotein hormones. The tumor also stained positively for PTH-rP. She was deemed unresectable with widespread recurrence and liver metastases after splenectomy, hemigastrectomy, and pancreatectomy.[7]

The same year, Williams et al. reported a 30-year-old man with abdominal discomfort who was found to have elevated calcium, suppressed PTH, a PTH-rP level almost ten times normal, and somatostanin of 5400 pmol/L (normal, $<$100 pmol/L). A pancreatic tumor was discovered on selective angiography. Tissue procured at laparotomy stained consistent with well-differentiated somatostatinoma, and the patient underwent chemotherapy and medical treatment for his metabolic abnormalities. At the time of report, his calcium level had normalized, although his PTH-rP remained elevated.[22]

Ratcliffe and colleagues report another neuroendocrine tumor of the pancreas associated with hypercalcemia attributed to PTH-rP production by the tumor. A 39-year-old woman presented with a 3-month history of malaise, 2 weeks of vomiting and thirst, and one week of constipation. His serum calcium level was twice normal and PTH-rP was 12.9 pmol/L (reference range, $<$0.2), while PTH was

Table 1. Summary of previous exocrine cases

Source	Year	Age	Sex	Pre-op Ca^{2+} (mg/dl) (normal)	Post-Op Ca^{2+} (mg/dl) (normal)	Pre-Op phosphorus (normal)	Post-Op phosphorus (mg/dl) (normal)	Pre-Op PTH (normal)	Post-Op PTH (normal)	Pre-Op PTH-rP (normal)	Post-Op PTH-rP (pmol/dL) (normal)	Tumor location	Tumor size	Pathology	Immunohisto-chemistry	Outcome
Nagata et al.[17]	1986	46	F	17.6	NA	3.2 mg/dl	NA	0	NA	NA	NA	Body of pancreas	NA	Pleomorphic undifferentiated carcinoma of exocrine pancreas	NA	Died
Birkeland et al.[26]	1992	60	M	13.2	NA	2.8 mg/dl	NA	0.7 pmol/L	NA	670 ng/L	NA	Body of pancreas	NA	Adenocarcinoma	NA	Died
Miraliakbari et al.[7]	1992	68	F	13.5 (8.7–10.6)	NA	NA	NA	66 pmol/L (17–92)	NA	NA	NA	Head of pancreas and extensive local spread	NA	Poorly differentiated adenocarcinoma	Positive for PTH-rP faintly positive to mucin stains. Negative for neuron-specific enolase, chromogranin, synaptophysin, calcitonin	Developed CHF and died
Tachibana et al.[27]	1994	56	M	15.0 (8.0–10.2)	NA	2.4 mg/dl (2.5–5.1)	NA	27.4 (6.5–59.7)	NA	950 pmol/L (<S)	NA	Uncinate process of pancreas	3.0 × 3.0 × 3.2 cm	Moderately to poorly differentiated adenocarcinoma	Positive for PTH-rP	Developed hepatic failure and died

Continued

Table 1. Continued

Source	Year	Age	Sex	Pre-op Ca^{2+} (mg/dl) (normal)	Post-Op Ca^{2+} (mg/dl) (normal)	Pre-Op phosphorus (normal)	Post-Op Phosphorus (mg/dl) (normal)	Pre-Op PTH (normal)	Post-Op PTH (normal)	Pre-Op PTH-rP (normal)	Post-Op PTH-rP (pmol/dL) (normal)	Tumor location	Tumor size	Pathology	Immunohisto-chemistry	Outcome
Yamamoto et al.[28]	1996	44	M	13.6 (8.0–10.2)	NA	3.3 mg/dl (2.5–5.1)	NA	4.9 pg/ml (10–55)	NA	118.4 pmol/L (13.8–55.3)	NA	Body and tail of pancreas	6.0 × 6.0 × 8.0 cm	Moderately differentiated adenocar-cinoma	Adenocarci-noma (moderately differentiated)	Died
Kakizaki et al.[25]	1998	61	M	13.2 (8.5–10.3)	NA	2.0 mg/dl (2.6–4.5)	NA	87.0 pg/ml (150–500)	NA	472.1 pmol/dl (16.2–64.7)	NA	Pancreatic head	NA	Undifferen-tiated car-cinoma originating from exo-crine pan-creas	Weak staining for PTH-rP Posi-tive: keratin, epithelial membrane antigen (EMA) Nega-tive: leuko-cyte common antigen (LCA), vimentin, NSE, chro-mogranin	Patient died from pro-gressive cancer; no surgery performed
Bandyopadhyay et al.[18]	2003	53	M	18	NA	1.54 mmol/L	NA	0.2 pmol/L (<7.3)	NA	19.4 pmol/L (0.7–2.6)	NA	Pancreatic head	NA	Poorly differen-tiated carcinoma	Positive for PTH-rP	Died

Adapted from Bandyopadhyay et al.[18]

Table 2. Summary of previous endocrine cases

Source	Year	Age	Sex	Pre-Op Ca^{2+} (mg/dl) (normal)	Post-Op Ca^{2+} (mg/dl) (normal)	Pre-Op phosphorus (normal)	Post-Op phosphorus (mg/dl) (normal)	Pre-Op PTH (normal)	Post-Op PTH (normal)	Pre-Op PTH+rP (normal)	Post-Op PTH+rP (pmol/dl) (normal)	Tumor locations	Tumor size
Vair et al.[19]	1987	47	F	4.14 mmol/L (2.16–2.63)	Hypo-calcemic	Normal	NA	291.0 pg/mL (<500)	NA	NA	NA	Body and tail of pancreas, infiltrating greater curvature of stomach	9 cm
Wynick et al.[20]	1990	37	F	3.46 mmol/L (2.2–2.6)	NA	0.48 mmpl/L (0.8–1.4)	NA	0	NA	17.5 pmol/L (<5)	NA	Tail of pancreas, liver metastases	5 × 4 cm
Mitlak et al.[21]	1991	77	F	12.1	NA	0.87 mmol/L	NA	3 ng/L	NA	440 ng/L (<35)	NA	Left upper quadrant	NA
Miraliakbari et al.[7]	1992	47	F	16.6 (8.7–10.6)	6.86 (8.7–10.6)	NA	NA	291.0 pg/mL (50–340)	NA	NA	NA	Pancreas extending to left kidney	11 × 7 × 7 cm
Williams et al.[22]	1992	30	M	4.04 mmol/L	2.53 mmol/L	1.25 mmol/L	NA	<0.8 pmol/L (0.9–5.4)	NA	20 pmol/L (<0.23)	3.9 pmol/L (<0.23)	Body and tail of pancreas, extending upwards into gastric	NA
Ratcliffe et al.[6]	1994	39	F	4.7 mmol/L (2.10–2.60)	Normal	1.09 mmol/L (0.8–1.4)	NA	1.1 pmol/L (0.9–5.4)	Normal	12.9 pmol/L (<0.2)	0.33–1.25 pmol/L (<0.2)	Body and neck of pancreas, lymph modes	12 × 12 × 9 cm
Kakizaki et al.[25]	2002	25	F	5.5 mmol/L (2.2–2.6)	2.3 mmol/L (2.2–2.6)	2.07 mmol/L (0.7–1.2)	NA	0	NA	3.9 pmol/L (<0.5)	0	Distal pancreas	9 cm

within normal limits. Ratcliffe used in-situ hybridization and immunohistochemistry to localize PTH-rP mRNA and peptide in the tumor. A tumor of 12 × 12 × 9 cm proportions was found emerging from the body and neck of the pancreas. After debulking, serum calcium normalized, and PTH-rP fell significantly.[6]

Notably, the most recent case of endocrine pancreatic neoplasm producing PTH-rP was described in a pregnant woman.[23] The authors note that severe hypercalcemia in the setting of pregnancy is rare; there are fewer than 150 cases reported in the world literature. Their patient, a 25-year-old female, presented at 29 weeks' gestation with an altered level of consciousness, and serum calcium twice the reference range. Like our patient (Case #1), she experienced renal failure, with a serum creatinine of 328 μmol/L (reference range, 60–110). Her serum phosphate was also double the normal range, but this was attributed to renal failure. After a workup that entertained the differential diagnoses of granulomatous disease, lymphoma, sarcoid, and myeloma, a full-body CT scan revealed a 9 cm pancreatic mass. Ultrasound-guided biopsy of this mass suggested a well-differentiated neuroendocrine tumor. After distal pancreatectomy and splenectomy, immunuocytochemical staining of the tumor was positive for PTH-rP antibody. The patient has done well since, with normalization of serum calcium and PTH-rP levels.

Evaluating Hypercalcemia

In considering the differential diagnosis for a patient with hypercalcemia, one should bear in mind that hyperparathyroidism accounts for over 90% of cases. On the other hand, a malignant diagnosis accounts for over 65% of hypercalcemia in inpatients.[24] In general, hypercalcemia may be due to increased bone resorption or increased calcium absorption. Less frequent causes attributable to increased bone resorption include hyperthyroidism, immobilization, Paget's disease of bone, the administration of estrogen or anti-estrogen in the treatment of patients with breast cancer, and hypervitaminosis A. Supraphysiologic calcium resorption may be induced by high oral calcium intake (the milk-alkali syndrome) coupled with low urinary excretion (i.e., chronic renal failure). In hypervitaminosis D, both bone resorption and increased calcium absorption lead to hypercalcemia. Other etiologies of increased calcium absorption include familial hypocalcemic hypercalcemia, sarcoidosis, tuberculosis and thiazide diuretics. Finally, miscellaneous causes of hypercalcemia include lithium ingestion, thiazide diuretics, pheochromocytoma, adrenal insufficiency, rhabdomyolysis and acute renal failure, theophylline toxicity, and congenital lactase deficiency.

CONCLUSIONS

Hypercalcemia is commonly associated with malignancy, being found in up to 10% of patients with advanced cancer. Such elevation in calcium level is due commonly to bone metastases (local osteolytic hypercalcemia), but may be due also to humoral hypercalcemia of malignancy. This entity, noted primarily in squamous cell carcinoma of the lung and larynx, is associated with elevated serum PTH-rP in more than 90% of patients.[22, 25] Here we report two cases of humoral hypercalcemia of malignancy caused by PTH-rP originating from pancreatic neuroendocrine tumors. These cases join the seven other documented PTH-rP-producing pancreatic neuroendocrine tumors in the literature.

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Current Concepts of Percutaneous Abscess Drainage in Postoperative Retention

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In recent years, percutaneous abscess drainage (PAD) of intraabdominal abscesses has become an important tool with regard to the treatment of intraabdominal sepsis. The aim of this study is to assess the value of PAD in the treatment of postoperative retentions. Between 1995 and 1999, the postoperative course of 3346 patients undergoing major abdominal surgery was analyzed. Mortality, morbidity, and comparison of different locations of intraabdominal abscesses were assessed. PAD was considered successful when the patient improved clinically within 24 hours, a decrease in the size of the abscess formation was noted, and complete recovery without further surgical intervention occurred. Out of 3346 operated patients, 174 (5.2%) were diagnosed as having an intraabdominal abscess formation and were treated by PAD. In 63 patients the abscess developed within the upper quadrants, in 66 patients the abscess developed within the lower quadrants, and in the remaining 45 patients the abscess developed within the retroperitoneal cavity or pelvis. The success rate of PAD was 85.6% with a morbidity rate of 4.6%. The least successful location for PAD was the left upper quadrant. Patients with abscess drainage in the right upper and lower quadrant experienced a high success rate. One patient died due to the PAD procedure. Unsuccessful PAD was closely related to an increase in mortality. In the case of intraabdominal abscess formation after visceral surgery, PAD should be the primary procedure. Attention should be paid to abscess formations in the left upper quadrant because there is an increased likelihood of complications caused by PAD. (J GASTROINTEST SURG 2005;9:280–283)

KEY WORDS: Percutaneous abscess drainage, intraabdominal abscess, postoperative complications

Percutaneous drainage (PAD) of intraabdominal abscess formations has been established as the predominant therapeutic tool with regard to the treatment of abdominal sepsis. A broad spectrum of indications reaching from temporary drainage (e.g., Crohn's disease),[1] to curative drainage (e.g., liver abscess),[2] and to postoperative abscess drainage is applied. The outcome of intraabdominal abscesses has improved over the last two decades because of the frequent use of PAD, advancements regarding surgical technology, and new antibiotic treatment regimens.[3,4] Undrained abdominal abscess formations still exhibit a mortality rate up to 90%, emphasizing the necessity for proper drainage.[5] Postoperative abscesses remain a serious and dangerous complication with a mortality rate of approximately 30%.[6] Because surgical drainage of postoperative abscesses was associated with a high mortality rate of 20%–40%,[7,8] it has been frequently replaced by PAD. This method has been demonstrated to be as effective as the surgical approach.[9–11]

The development of intraabdominal abscess formations after major abdominal surgery is not an uncommon complication and can be seen in up to 5% of the patients.[12] This retrospective study focuses on analyzing the outcome of PAD with regard to postoperative abscesses after abdominal surgery and link the outcome to the localization of the abscess.

MATERIAL AND METHODS

Between January 1995 and December 1999, the postoperative clinical course of 3346 patients after major abdominal surgery has been retrospectively analyzed. Diagnosis, localization, and PAD was guided

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.04.008

by computed tomography (CT). The indication for PAD was considered when the clinical course and morphologic signs on the CT scan demonstrated an abdominal retention. PAD was performed in close cooperation between the interventional radiologist and the surgeon.

The success of PAD was defined as clinical improvement within 24 hours, a morphologic decrease in the size of the abscess formation, and complete recovery without further surgical intervention. Persistent abscess formations despite PAD and the necessity of a reoperation for recovery were criteria that defined the nonsuccess of PAD. The localization of the primary abscess was defined by dividing the abdominal cavity into four quadrants (right upper, left upper, right lower, left lower), retroperitoneal cavity, and the pelvis. Morbidity and mortality caused by the PAD procedure were assessed and outcome data was analyzed with regard to PAD success and type of operation. All patients received antibiotics post-PAD that were ideally adapted to the bacteria indicated. Statistical analysis was analyzed by the χ^2 test.

All procedures were guided by CT and performed under local anesthesia after written informed consent was obtained. Catheters were placed into the abscess formation using the Seldinger technique or the coaxial technique. A multiple side hole catheter (Flexima regular all purpose; Boston Scientific [Med-Tech Division], Natick, MA) was used. Catheter sizes ranged from 8F to 16F according to the viscosity of the material. Initially, CT-guided diagnostic aspiration was performed and the material was examined for bacterial analysis. A proper drain was then situated and its placement was checked by CT. Once checked, it was anchored externally by suturing. Follow-up imaging studies were obtained without any specific protocols. The decision to obtain follow-up CT scan was based on the clinical course of the patient and the type and location of the abscess formation. The catheters were removed when the abscess formation was completely drained or indicated a considerable reduction in size on follow-up CT scan.

RESULTS

One hundred seventy-four patients out of 3346 patients (5.2%) required PAD for the treatment of a postoperative intraabdominal abscess. The majority (≅ 9%) of postoperative abscess complications occurred after hepatobiliary and pancreatic surgery (Table 1). In 63 patients the abscess formation was located in the right upper or lower quadrant, in 66 patients the abscess formation was located in the left quadrants, and in the remaining patients the abscess formation was located in the retroperitoneal cavity or pelvis (Table 2). PAD was successful in 85.6% (149 out of 174) of the patients. In 14.4% (25 out of 174) of the patients, PAD was not successful. This was caused by fistula-associated abscesses with major leakage in 8 patients, left subphrenic abscesses with involvement of the pancreas in 5 patients, nondrainable necrotic material in 3 patients, multiple abscess formations in 5 patients, and persistency despite drainage in 4 patients. The necessary reoperations were performed on the second to fifth day post-PAD.

PAD most likely failed when the abscess was located in the left upper quadrant (Table 2). Reoperation was performed in 12 out of 44 patients (27.3%) with an abscess in the left upper quadrant. The best success rate of PAD was achieved when abscesses were located in the right upper or lower quadrant. Reoperation in this subgroup was necessary in only 7.9% of the patients (5 out of 63). Complications due to PAD occurred in 4.6% of the patients (8 out of 174). Intestinal fistulas in 3 patients and intestinal bleeding in 5 patients required successful operative intervention. Intrahepatic bleeding with subsequent liver necrosis, which was attributable to PAD, caused the death of one patient. A total of 44 patients died postoperatively (1.2%). The mortality rate of all patients with intraabdominal abscess formations—independent of the therapeutic approach—was 8% (14 out of 174). Mortality rate was lower in patients with a successful PAD (6.7%) in contrast to patients requiring subsequent operation (16%). This was statistically significant (Table 3).

DISCUSSION

This study focuses on PAD as a postoperative intraabdominal abscess treatment. Because of its high

Table 1. Percutaneous abscess drainage (PAD) rate according to operated organs

Operations	n	PAD (n)	%
Esophagus	491	9	1.8
Gastric/duodenum	712	21	2.9
Hepatobiliary/pancreas	581	52	8.9
Colorectal	1151	67	5.8
Other	411	25	6.1
Total	3346	174	5.2

Table 2. Correlation of localization of postoperative abscess formations and success rate

Localization	n	Successful PAD n (%)	Unsuccessful PAD n (%)
Right upper quadrant	48	44 (92)	4 (8)
Right lower quadrant	15	14 (93)	1 (7)
Left upper quadrant	44	32 (73)	12 (27)
Left lower quadrant	22	19 (86)	3 (14)
Retroperitoneal cavity/pelvis	45	40 (89)	5 (11)
Total	174	149 (86)	25 (14)

PAD = percutaneous abscess drainage.

success rate, low incidence of procedure-associated complications, and moderate invasiveness PAD of intraabdominal abscess formations is the standard choice of care for abdominal sepsis. Success rates indicate greater than 80% in the literature (Table 4).[13–19] Our results correspond to these data. Complications usually occur in approximately 5% of the patients and procedure-associated lethality should be below 1%.

In our study, experienced interventional radiologists performed CT-guided PAD. The advantages of CT-guided drainage in contrast to ultrasound-guided PAD are the objective and reproducible documentation, improved localization, diagnosis by use of contrast medium, and effective planning of the PAD. A CT scan allows visualization of the entire abdomen despite the overlay of bowel or postoperative bandages. It is now the predominant imaging tool used for postoperative PAD.

As alluded to in this article, the best indications for PAD are encapsulated retentions in the paracolic, perihepatic, and subphrenic spaces on the right side. Limitations for PAD include so-called "complicated abscesses," such as retentions associated with extensive anastomotic leakage, multiple abscess formations, nondrainable necrotic material, and extended peritonitis. In these patients, primary surgical intervention is usually necessary. Secondary operations are required when PAD fails, which would mean that a patient exhibited no clinical improvement despite

Table 3. Mortality of successful PAD vs. unsuccessful PAD

Overall	14/174 (8.0%)
Successful PAD n = 149	101/149 (7.2%)
Unsuccessful PAD n =25	4/25 (16%)
	$p < 0.05$

PAD = percutaneous abscess drainage.

Table 4. Success rates and complication rates in published series of percutaneous absecess drainage

Author	Year	Success rate (%)	Complication (%)
Voros[13]	1996	92	7
Rothlin[14]	1998	85	3
Witzigmann[15]	1998	80	…
Dattola[16]	1999	93	5
Jansen[17]	1999	85	6.4
Our results	2003	85	4.6

PAD within 24–48 hours or that persistency of the retention remained. The majority of postoperative retentions (9%) occurred after hepatobiliary and pancreatic surgery.

The success rate of approximately 86% is concurrent with results published in the literature and also demonstrates the benefit of this noninvasive treatment for the patient. However, the limitations of PAD have to be considered during the initial diagnosis.[18,19] Patients with multiple abscess formations, extensive anastomotic leakages, pancreatic involvement, or nondrainable necrotic material indicate a substantial likelihood for subsequent secondary surgery.[20,21] These patients required careful monitoring so as not to postpone necessary surgery. Despite a high failure rate with these indications, PAD might be still be helpful for these patients. This is because PAD allows microbiologic analysis of the material as well as potential temporary relief for the patient with the possibility of a careful operation plan.

The type of operation, such as major pancreatic or hepatobiliary surgery, explains the predominant location of abscess formation in the upper quadrants. A close cooperation between the interventional radiologist and surgeon best ensures the adequate timing of a secondary operation. The indication for an invasive procedure remains an individual decision.

Special attention should be paid not only to the underlying type of operation, but also to the location of the abscess formation. In our study, the left upper quadrant was the most difficult location for a successful PAD and, considerably, often required surgical intervention (27%). This is probably caused by the high rate of complicated abscess formation in this area as well as to anatomic structures that prevent straightforward drainage (e.g., spleen, splenic artery, and left colic flexure) thus leading to complications such as bleeding or intestinal fistula. In addition, the size of the abscess formation also plays a role. Benoist and colleagues demonstrated that a diameter less than 5 cm is associated with a high failure rate on multivariate analysis as well as the lack of antibiotic

therapy.[22] All patients in our study routinely received antibiotics after PAD that were ideally adapted to the bacterial spectrum indicated.

The definition of success with PAD has been defined by Lambiase and associates.[23] Cure or success was considered when the patient returned to his or her normal health status caused before PAD. We used a similar definition of success that was adapted to the clinical situation combined with morphological reduction in size of the abscess. The second group of patients defined by Lambiase and associates demonstrated a temporizing effect after PAD, which means that there was clinical improvement of the patient before secondary surgery. This is a somewhat arbitrary definition, because the decision of whether to operate on a patient with an abscess who improves clinically or not is an individual choice based on the experience of the physician. We believe that our definition of success or nonsuccess is applicable and reproducible for postoperative retentions.

It is striking that patients who experienced successful PAD exhibited a lower mortality rate compared with patients who experienced unsuccessful PAD. This underlines the demand for prompt and successful drainage of abscess formations after abdominal operations. The persistency of infectious formations after an operation increases the likelihood of a complicated postoperative course with a substantial high rate of mortality—16% in our study.

PAD is an ideal example of a therapeutic tool that became standard care for the treatment of abdominal retention without evidence-based prospective randomized studies. Retrospective results have been compared with published historical controls using initial surgical intervention with regard to the treatment of intraabdominal abscesses. However, a prospective randomized trial comparing surgical intervention with PAD is not likely to be conducted in the future.

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A Technique for Emergency Liver Packing

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Control of liver hemorrhage may present a daunting clinical scenario. Use of liver packing techniques is highly effective to control bleeding but can result in significant recurrent bleeding with pack removal. Such bleeding is particularly a problem when large portions of the hepatic parenchymal surface and Glisson's capsule have been disrupted. We describe, herein, our approach to hepatic packing in scenarios where a large component of hepatic capsular disruption has occurred. Use of a non-stick bowel bag is employed on the disrupted liver surface, which, when removed, will not result in liver rebleeding. This technique has been used successfully in the management of five cases of severe liver injury with extensive capsular disruption. Familiarity with such an approach may facilitate management of similar liver injuries. (J GASTROINTEST SURG 2005;9:284–287)

KEY WORDS: Liver trauma, damage control, liver packing, hemangioma, hepatocellular

Hemorrhage from American Association for Surgery of Trauma (AAST) grade IV or V liver parenchymal injuries presents an extremely challenging clinical scenario. Liver bleeding occurs either after massive abdominal trauma or, rarely, from hepatic parenchyma rupture from rapidly expanding tumors, such as adenoma, hemangioma, or hepatocellular cancer.[1] When severe hemorrhage is associated with hemodynamic instability, it is an urgent situation with the development of shock. These clinical situations may be further complicated by additional injuries as well as the development of secondary metabolic complications, including coagulopathy, severe acidosis, and hypothermia. Familiarity with techniques for rapid and definitive control of liver hemorrhage, including hyperthermic coagulation, liver parenchymal mattress suture placement, vessel suture ligation, local procoagulant application, and indicated liver resection, is essential. For trauma patients, the use of liver packing as part of a damage control laparotomy has superseded urgent liver resection in the treatment of a number of liver injuries.[2] This technique allows the control of bleeding in a coagulopathic patient frequently with very advanced hepatic injuries. Of note, application of procoagulant tissue adhesives, fibrin sealants on the raw liver surface, followed by firm packing with laparotomy sponges may also improve hemostatic control.[3] At the time of pack removal, generally 1–3 days later when the patient is normothermic and not coagulopathic, clot disruption and excessive rebleeding frequently occur.[4] This recurrent bleeding may be particularly problematic when the initial hepatic injury involves a large disruption of Glisson's capsule, as a proportionately larger resultant bleeding area will result.

We report, herein, a modified technique for liver packing that enables easy, safe removal of the packs with preservation of the stable clot. The described technique has been used to control liver bleeding in five patients with massive hepatic hemorrhage (>8 unit transfusion requirements) from predominantly capsular disruption.

OPERATIVE TECHNIQUE

In the approach to extensive hepatic rupture, particularly involving the right hepatic lobe, we perform

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.11.003

a generous laparotomy, particularly extending the top of our incision to the xyphoid.[5] Rarely, the incision has been extended into the right chest through an anterior lateral transdiaphragmatic extension. Moreover, in all cases where significant liver disruption is noted, extensive liver mobilization of the right hepatic lobe exposing the bare area of the liver, and suprahepatic and infrahepatic inferior vena cava, is performed. In addition, division of the falciform ligament and the peritoneal attachments to the left lateral segment is completed. In our experience, mobilization of the right lobe of the liver is critical to understand the liver injury, assess potential associated vena caval injury, properly place liver sutures, obtain supra–vena caval or infra–vena caval control, and, if required, provide circumferential hepatic tamponade with packing.

Once major injury to vessels has been excluded or repaired, if the determination for liver packing is made due to continued extensive bleeding, or coagulopathy, we would begin by placing procoagulant tissue adhesives, fibrin sealants (i.e., collagen-based compounds, hydrogels, human or bovine thrombin-fibrin, Gelfoam [Pharmacia & Upjohn, Kalamazoo, MI], or Surgicel [Johnson & Johnson, New Brunswick, NJ]) on the raw liver surface.[6] Use of a Pringle maneuver, with/without vena caval control, may be considered to further decrease hepatic blood flow and hemorrhage.[7,8] Once the procoagulant is in place, the liver is "wrapped" by placing a sterile bowel bag around the liver. Packs are then placed firmly around the bag in a clockwise fashion from 6/7 o'clock to 5 o'clock to maintain pressure on the hepatic parenchyma and tamponade the bleeding (Fig. 1). Once any additional acute injuries such as bowel injury are excluded, the patient's abdomen then is closed by using a temporary abdominal closure technique. Our preference is to use the previously described technique of dynamic abdominal retention as it is both rapid to perform and inexpensively preserves abdominal domain.[7,9] After completion of the initial laparotomy, the patient is taken to the intensive care unit for a period about 24–72 hours, to allow the liver to recover and for the reversal of hypothermia and coagulopathy. After this period, the patient is returned to the operating room. Once the abdomen is open, the packs are removed. The bowel bag will be free from the liver and clot and can be easily removed from the liver surface without bleeding (Fig. 2). Then the right upper quadrant and liver are irrigated with normal saline or antibiotic solution. Of note, excess coagulant material will wash off easily without recurrent bleeding. Depending on the patient's condition,

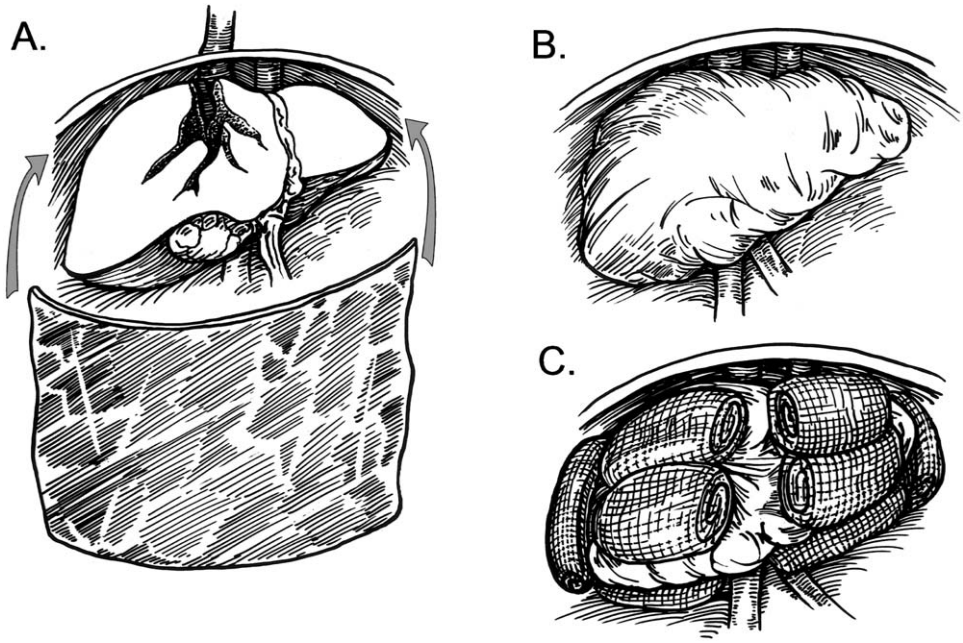

Fig. 1. Steps involved in liver packing with placement of bowel bag. After extensive mobilization of the liver and the placement of a procoagulant of choice, a square bowel bag is placed over the right and left lobes of the liver as far posteriorly as possible (**A**). The bag is then also folded under the liver (**B**). Abdominal sponges are then systematically packed around the liver beginning in the posterior hepatic space. The packing of sponges goes in a clockwise order starting at 6/7 o'clock position (adjacent to, but not on top of, the inferior vena cava or suprahepatic cava). The packing with sponges stops at 5 o'clock, without packing on top of the portal structures (**C**).

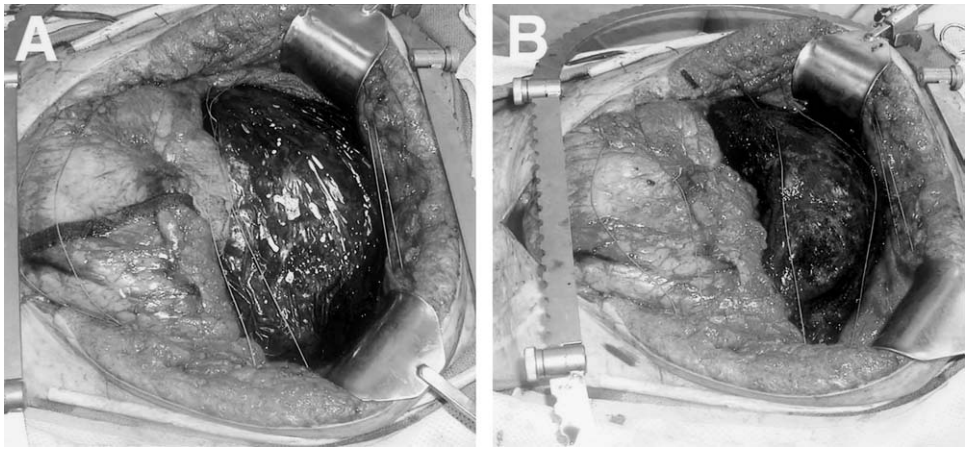

Fig. 2. Operative photograph demonstrating bowel bag 48 hours after placement following rupture of the right hepatic lobe and massive bleeding. (**A**) Photograph with bag in situ. (**B**) Photograph with bag removed from hepatic parenchyma. Note: Dynamic retention sutures were placed during the previous laparotomy to maintain abdominal domain.

either primary closure or delayed secondary closure of the abdominal incision may be used.

RESULTS

The described technique has been successfully used in five cases. In all cases, we observed control of the hemorrhage and minimal (<50 ml) subsequent bleeding once the packs were removed. Of note, we have selectively applied the described technique to the treatment of patients with a bleeding disruption of a large surface of the liver following direct control of larger bleeding vessels. Alternatively, such an approach may be considered in a patient undergoing a second-look with recurrent bleeding once conventionally placed packs are removed when definitive abdominal will be planned at a later date. Outcomes and etiology of bleeding in the five cases are summarized in Table 1.

Table 1. Outcomes of five cases in which plastic liver wrap with packing was used

Age/ gender	Etiology	Injury outcome
72/F	Idiopathic hepatic rupture	Closure after three explorations, discharged well
24/F	Hepatic adenomatosis rupture	Closure after two explorations, discharged well
47/M	Blunt trauma hepatic rupture	Closure after two explorations, discharged well
28/M	MVA blunt trauma hepatic rupture	Closure after two explorations, discharged well
32/F	MVA blunt trauma hepatic rupture	Closure after two explorations, discharged well

MVA = motor vehicle accident.

DISCUSSION

The successful management of liver trauma with the placement of abdominal packs was initially described by Feliciano, Mattox, and Jordan.[10] This technique has proved to be an extremely successful way to control liver bleeding due to major hepatic trauma or after the rupture of liver tumors.[2,4,11] The technique described herein provides the added benefit of easier, safe, subsequent pack removal and should be considered primarily when the problem encountered involves diffuse bleeding from disrupted liver parenchyma. In our experience, the removal of packs applied directly to the liver surface, particularly with the previous administration of procoagulant, will result in exfoliation and debridement of liver parenchyma with recurrent bleeding. It must be stressed that with the use of a bowel bag, no external adherence of the pack occurs to the clot and liver. The technique appears to work through the presence of procoagulants on the liver surface and the extensive parenchymal compression that the packing provides above the bag. Importantly, the ability of the liver to "regenerate" after parenchymal loss obviates concern for the possible loss of liver parenchyma from excessive packing pressure.[12]

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Benign Schwannoma of the Pancreas

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Reported cases of intrapancreatic schwannomas have recently increased in the literature. However, none of these cases were diagnosed clearly as schwannoma preoperatively. We herein describe the clinicopathologic findings of a solitary benign schwannoma occurring in the head of the pancreas. Additionally, the differential diagnosis versus other cystic- and solid-appearing pancreatic masses is briefly discussed. (J GASTROINTEST SURG 2005;9:288–290)

KEY WORDS: Schwannoma, pancreas, differential diagnosis

Schwannomas (neurilemoma, perineural fibroblastoma, neurinoma) are neurogenic tumors arising from the sheath of peripheral nerves in the soft tissues of the head and neck, extremities, mediastinum, and retroperitoneum.[1,2] The pancreas is an extremely unusual site of origin for these tumors.[2–5]

CASE REPORT

A 64-year-old previously healthy woman was incidentally discovered to have a hypoechoic mass in the head of the pancreas during a population screening program. The abdominal physical examination did not detect any marked change; and all laboratory data were normal, including tumor markers. The computed tomography (CT) scan showed a weak enhancement of the tumor. Magnetic resonance imaging (MRI) of the pancreas demonstrated the lesion with low intensity on T1-weighted images and marked enhancement after Gd-DTPA administration; a relatively high signal intensity was seen on T2-weighted images (Fig. 1, *A*, *B*). No liver mass or peripancreatic lymph node swelling was detected. The mass was hypervascular on angiography.

The laparotomy disclosed a solid, well-encapsulated tumor that was located in the head of the pancreas and had no signs of inflammation. Intraoperative frozen sectioning revealed a benign schwannoma; thus, we performed a simple enucleation of the tumor. The cut surface of the excised 2.5 × 2.0-cm tumor was pale yellow with foci of hemorrhage (Fig. 2). On microscopic examination, the lesion showed spindle cells with Antoni A and B patterns, strongly positive for S-100 protein.

After 2 years of follow-up, the patient has shown no evidence of recurrence or impairment of pancreatic endocrine or exocrine function.

DISCUSSION

A large number of schwannoma cases have been reported since 1910, when Verocay[6] reported it as a true tumor that stemmed from Schwann cells and that did not contain neuroganglion cells.

Schwannomas may be solitary or, more frequently, associated with von Recklinghausen disease.[2] Visceral locations of the tumor, arising from sympathetic and parasympathetic nervous fibers, are exceedingly rare,

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.057

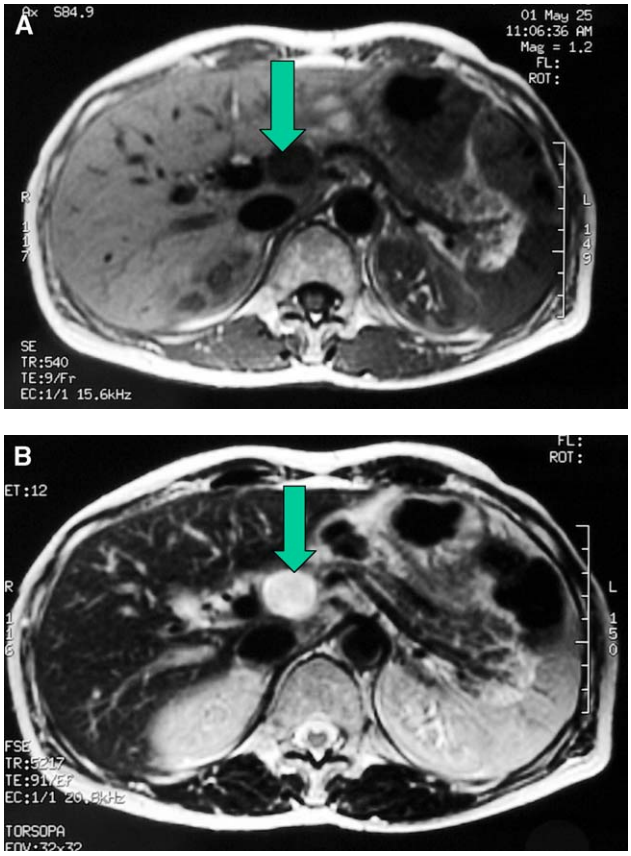

Fig. 1. Spin-echo MRI of the upper abdomen showing a round lesion in the head of the pancreas that appears hypointense on T1-weighted image (**A**), with very high signal intensity on T2-weighted image (**B**). There is no sign of infiltration of the surrounding tissues.

with the gastrointestinal tract being the most common site of involvement.[2]

In a PubMed search on this topic, we identified only 48 cases of pancreatic schwannoma reported from 1948 through 2004.[2–5] Patient age ranged from 35 to 87 years, with a nearly equal gender distribution, and the majority of the tumors were located in the head of the pancreas. Approximately two thirds showed cystic features on radiologic examination.

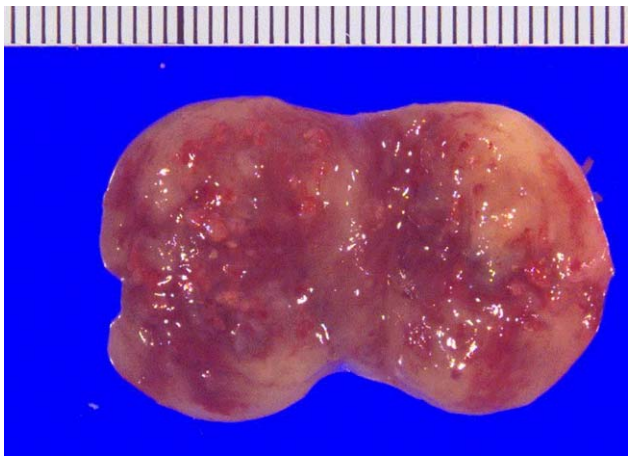

Fig. 2. Cut surface of the resected tumor (2.5 × 2.0 cm) showing it to be pale yellow with foci of hemorrhage.

The most important issue to be addressed is the difficulty in making the correct preoperative diagnosis.[6] In fact, large lesion with cystic degeneration can mimic a pancreatic pseudocyst at ultrasonic and CT or MRI examination. Pancreatic schwannomas, however, generally present in a clinically silent manner and are not preceded by an episode of pancreatitis. Biopsy of the wall can reveal the true diagnosis and prevent treatment by marsupialization.[3]

The differential diagnosis should also include adenocarcinoma, nonfunctioning islet cell tumor, and solid and cystic tumor and mucinous cystadenoma. The hyperintensity on the T2-weighted images, as well as the marked enhancement in comparison with the remainder of the gland found in schwannoma, enables differentiation from adenocarcinoma.[4] Nonfunctioning islet cell tumors, which are most often located in the body of the organ, are homogeneously hypodense in the texture at CT and therefore virtually undistinguishable from pancreatic schwannomas.[2] Mucinous cystic neoplasm contains larger cystic spaces; solid and cystic tumor tends to occur in young women and rarely exhibit calcifications.[2]

Moreover, the group of nonepithelial tumors of the pancreas with spindle cell features, such as solitary neurofibroma, can resemble schwannoma. However, schwannomas are frequently encapsulated, whereas neurofibromas are not.[7] Detection on MRI of a capsule visualized as a low-intensity rim along the margin of the tumor could therefore be used as a criterion to differentiate neurofibroma from schwannoma.[7] Accordingly, although the final diagnosis of schwannoma is based on pathologic examination of the tumor, radiologic imaging, particularly MRI, helps establish the benign nature of the lesion, define the anatomic location, and narrow the differential diagnosis. When possible, fine-needle aspiration cytology or intraoperative frozen sectioning may improve the accuracy of preoperative diagnosis.

Surgical resection is the treatment of choice in this type of tumor. However, given the benign course and exceedingly rare occurrence of malignant degeneration, a simple resection is recommended if this diagnosis could be established before an unnecessary large resection is done. Among the 48 previously reported cases, 31 underwent formal pancreatectomy.[2–5]

Recurrence after resection is very unusual, even if part of the capsule cannot be safely removed without causing damage to the underlying nerve or surrounding structures, and, therefore incomplete excision is occasionally warranted.[4]

In conclusion, we believe that the appearance of MRI plays an important role in the preoperative diagnosis of this disease. Despite the rarity, schwannoma must be considered as one possibility in the differential diagnosis of a solid and/or cystic mass arising in the pancreas.

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Review Article

Current Management of Esophageal Cancer

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ESOPHAGEAL CANCER: EAST AND WEST

From the outset, it is necessary to appreciate the divergence in epidemiologic pattern between the East and the West. The most striking finding on esophageal cancer in the past three decades was the dramatic rise in the incidence of adenocarcinomas of the lower esophagus and cardia in the West, which has surpassed squamous cell cancers as the predominant cell type.[1] In Asia, however, esophageal cancers, when diagnosed, are predominantly squamous cell in type and mostly located in the middle third of the esophagus. There has not been a noticeable rise in the incidence of adenocarcinoma of the esophagus and gastric cardia in published Asian data.

The exact reasons accounting for this difference are uncertain but are widely believed to be related to gastroesophageal reflux disease, obesity, and Barrett's esophagus,[2–4] which are uncommon in Asian populations.[5] The prevalence of *Helicobacter pylori* infection is decreasing in Europe and the United States, and this has been paralleled by an increasing incidence of gastroesophageal reflux disease and adenocarcinomas of the esophagus and of the gastroesophageal junction. These epidemiologic data suggest a protective role of *H. pylori* against reflux. The high prevalence of *H. pylori* infection in Eastern populations may guard against reflux and Barrett's esophagus, hence accounting for the differences in cancer cell type.[6] This association, however, remains controversial.

Regardless of the reasons for the difference in epidemiology, there are practical implications in management strategies. The Barrett's esophagus–dysplasia–cancer sequence, for instance, may allow surveillance programs to be instituted in Western countries, with the possibility of diagnosing the disease at a readily treatable stage.[7,8] High-grade dysplasia is amenable to surgical resection or other forms of ablative therapies, such as endoscopic mucosal resection or photodynamic therapy. There is evidence that patients with Barrett's esophagus who are recruited into surveillance programs have a better prognosis.[8] The optimal surveillance interval, its cost-effectiveness, the relative merits of the various treatment approaches, and the impact on the population at large are still debated.[9] In the East, except in very high incidence areas, population screening for squamous cell cancers is not cost-effective, especially when there is no good marker for the precancerous stage and early cancer, so most patients still present with symptomatic, advanced stage of disease.

In this review, we concentrate on discussing management issues for patients presenting with symptomatic esophageal cancer. Although the aims and treatment options are essentially the same for patients with squamous cell cancers or adenocarcinomas, selecting the most appropriate strategies is to a certain extent affected by many of the differences, such as those listed in Table 1. These are discussed where appropriate in this review. When the data from the literature are interpreted, it is important to be mindful of this epidemiologic difference between East and West.

STAGING AND STAGE-DIRECTED THERAPY

The objectives of staging are, first, to exclude patients with widespread metastatic disease for whom surgery is not going to be curative; second, to identify subgroups of patients for neoadjuvant therapies; and third, to provide quality control when clinical trials are performed. Traditional staging methods include

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.06.007

Table 1. Esophageal cancer: Some comparisons between East and West

	East	West
Cell type	Squamous cell cancer*	Adenocarcinoma
Location	Mid and lower esophagus	Lower esophagus/cardia
Main risk factors	Smoking and alcohol	Gastroesophageal reflux
	History of other upper aerodigestive tract cancers	Obesity
Socioeconomic status	Blue collar	White collar
Comorbid diseases	Pulmonary	Ischemic heart disease
	Cirrhosis	
Identifiable premalignant lesions	Dysplasia (but not of clinical use)?	Barrett's esophagus and dysplasia
Surgical approaches	Predominantly transthoracic	Transthoracic/transhiatal
Prognosis	Worse?	Better?

*In many series, adenocarcinomas of the gastric cardia are reported together, but the majority are Siewert type II and III cancers. True type I adenocarcinomas related to Barrett's esophagus are rare.

endoscopy/bronchoscopy, ultrasonography of the abdomen, and computer tomography (CT) scanning or magnetic resonance imaging (MRI) of the neck, thorax, and abdomen. Endoscopic ultrasonography (EUS) has become more widely available, certainly in specialized centers, and is regarded as the best staging modality for T stage and local-regional N stage. Lymph nodes that are typically identified as harboring metastatic disease are usually those that are greater than 5 mm and oval, that have an echo-poor pattern, and that have smooth borders.[10] The accuracy of determining T stage ranges between 85% and 90%, whereas nodal staging accuracy approximates 70% to 90%.[11,12] When EUS-guided fine needle aspiration cytology (EUS-FNA) is used, the diagnostic accuracy goes beyond 90%.[13] The neck is readily available for percutaneous ultrasound FNA of suspicious cervical lymph nodes,[14] but the celiac region is less accessible. EUS-FNA of celiac lymph nodes has been shown to be more diagnostic than CT and EUS without FNA.[15]

Positron-emission tomography (PET) with 18-F-fluoro-deoxy-D-glucose (FDG) is increasingly used and is of particular use in picking up distant nodal or systemic metastases. Sensitivity, specificity, and accuracy rates for the detection of distant metastases of 88%, 93%, and 91%, respectively, were reported, but local-regional staging of N1 disease seems much inferior to EUS.[16–19] A recent cost-benefit analysis that included EUS, CT, PET, and thoracoscopy/laparoscopy in staging showed that PET plus EUS-FNA was most effective but CT plus EUS-FNA was least expensive.[20]

Laparoscopy should be selectively used for lower third or gastric cardia cancers only as its value is minimal for more proximally located tumors.[21] Combined thoracoscopic and laparoscopic staging methods are accurate but are invasive. They are practiced in only limited number of centers and are unlikely to gain widespread support.[22]

Both overstaging and understaging have their drawbacks; the first may deny patients the possibility of curative treatment, and the second situation may result in undertreatment. Even with EUS, it is difficult to distinguish T1a (mucosal cancers) and T1b (submucosal cancers) disease; the latter is associated with a substantial chance of lymph node metastases (30–50%). Treating a T1b lesion with mucosal therapies such as endoscopic mucosal resection or photodynamic therapy may undertreat such patients. More difficulties arise with diagnosis of nodal metastases. The current diagnosis of nodal metastases mainly relies on enlarged nodes, and thus small nodes or early lymphatic spread will escape detection. Modification of the current staging system is also likely, as evidence is accumulating that the number of nodes, in addition to location, better stratifies prognosis.[23,24] Stage IV disease patients, by virtue of celiac lymph node involvement, may also have different prognostic implications compared with similarly staged patients with visceral organ metastases[24,25] and thus deserves more aggressive treatment. Current imaging techniques are unreliable in providing precise number and location of nodal metastases. Some surgeons would even regard lymph node status (especially local-regional ones) as unimportant for deciding whether a primary resection should be performed, because it cannot be predicted with sufficient accuracy; furthermore, regional nodes are resected routinely in esophagectomy.[26] Further advancement of techniques in EUS-FNA and in PET scans may increase the diagnostic accuracy but is unlikely to be precise, especially when tumor burden is low.

Patients with early tumors (T1-2 N0 M0) should do well with surgical resection alone, whereas for patients with metastatic stage IV disease to systemic

organs, the aim is obviously for palliation and surgical resection has little role. Chemoradiation or radiotherapy alone can be used for palliation of dysphagia, although their toxicity and duration of treatment have to be balanced against benefits and the expected short life-expectancy. Insertion of self-expanding metallic stents (SEMS) has become the preferred method in many institutions.[27] In patients with T3-4 Nx M0, Tx N1 M0, or Tx Nx M1(lym) disease, often regarded as suffering from "advanced" cancer, chemoradiation is often offered as the standard of care, despite the lack of conclusive data on the superiority of such treatments over surgical resection alone.[28] The assumption of benefit from a stage-directed therapy is intuitive and reasonable; the selection of patients for each treatment, however, is not necessarily evidence-based and requires further refinement. This is discussed further in the sections that follow.

PATIENT SELECTION FOR SURGICAL RESECTION

Surgical resection remains the mainstay treatment for patients with localized esophageal cancer. While in dedicated centers mortality after esophagectomy has been reduced to below 5%,[29–35] it still approximates 10% for most, especially when population data are studied.[36,37] The ability to perform a R0 resection, with clear resection margins, has been consistently shown to have the best prognosis. The role of palliative resections is becoming less significant, because other, less invasive methods of palliation exist. The primary aims of selecting patients for resection are therefore, first, to accurately assess the patient's physiologic reserve to withstand an esophagectomy and, second, to assess the tumor stage so that the chance of an R0 resection is maximized.

Risk Analysis for Esophagectomy

Assessing a patient's fitness is often based on the surgeons' experience and intuition, rather than an exact science. Objective scores to assess operative risk have been generated using various statistical methods to help patient selection.[38,39] One series of studies identified a compromised general status, poor cardiac, hepatic, and respiratory function as independent predictors of postoperative death. A composite risk score was established, validated, and, when applied in prospective patient selection, led to decrease in postoperative mortality rate from 9.4% to 1.6%.[33,39]

Objective risk scores like this have their practical drawbacks. These scores require a suitably large patient database to generate, and another group of patients for validation before it can be applied clinically. Problems arise when changes in surgical experience and management protocols take place with time; thus, the factors derived may become less relevant by the time they are put into clinical decision-making protocols. Scores that are applicable at one institution or population may not be useful at another. Patients with squamous cell cancers, such as those in Asian countries, may not have the same risk profile as those who have adenocarcinomas. The main risks for the former group seem to be pulmonary and hepatic, related to smoking and alcohol consumption, whereas for the latter group, cardiac risk factors may be more important.[33] It is also uncertain whether patient selection based on a "strict" mathematical scoring system is better than that of surgeons' and anesthesiologists' assessments alone. They are more likely to be complimentary to each other.

Patient Selection and Outcome

From the literature, it is uncertain what a "reasonable" rate of resection should be. Referral bias makes interpretation of data difficult. From a population standpoint, two regional studies in the United Kingdom showed that resection rates for esophageal cancer were 21%[40] and 31%.[41] In Hong Kong, the resection rate for the whole city is approximately 40%.[42] Resection rate can be much higher in some series, especially in those from Japan, reaching 70% to 80%.[31,43,44] There is most likely prereferral bias and selection. The meaning of resection rate alone is limited unless the nature of flow of patients is understood. Squamous cell cancers are also reported to have lower resection rates compared with adenocarcinomas.[33] This has implications when reports from the East and West are compared.

In studies that report on improvement of surgical results over time, more stringent patient selection often comes into play. The "composite risk score" already discussed led to reduction in mortality by strict "exclusion of high-risk patients from surgical resection."[33,39] In another study that spanned a 15-year period, although resection rates were not significantly different over time, the proportion of T4 tumors in the second half of the study period was half that in the earlier one, and R1/2 resections also were reduced from 14% to 6%.[31] So again, a selection bias was at least partly responsible for improved results. In the authors' institution, the introduction of chemoradiation therapy resulted in less palliative surgery, with more appropriate patient selection for resection. The resection rate is still around 55%, including patients referred from family physicians and self-referred patients from emergency department

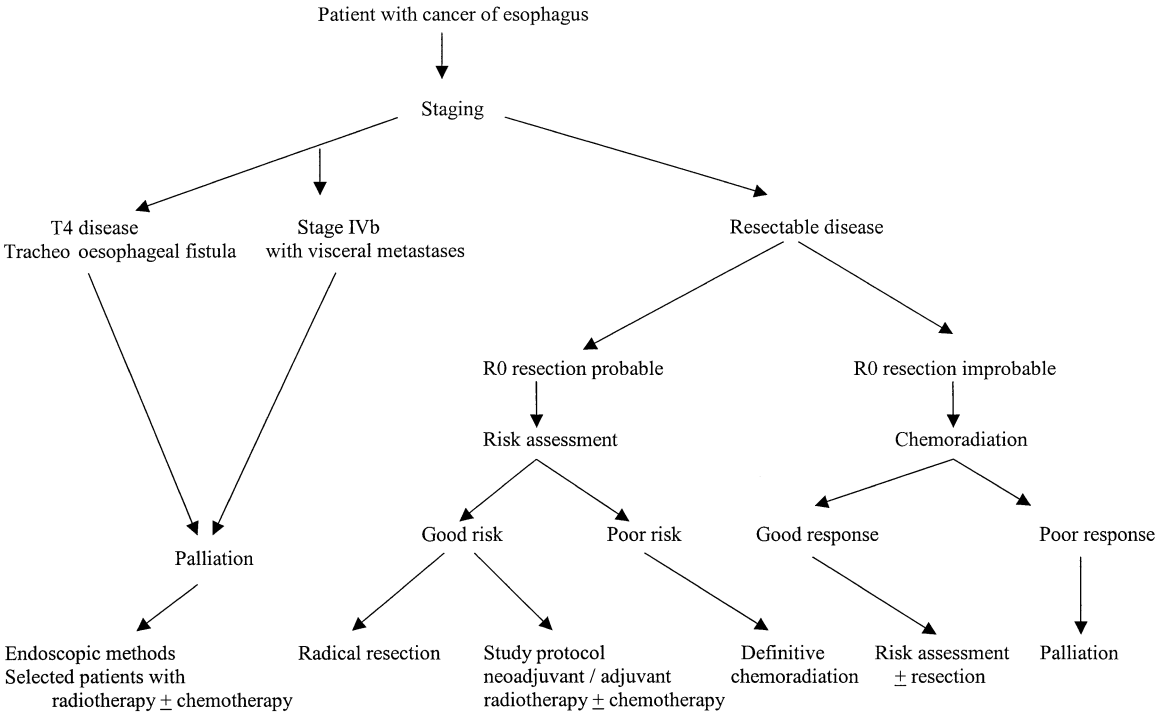

Fig. 1. Management algorithm for esophageal cancer at the University of Hong Kong Medical Center.

visits. The net result was an improvement in prognosis for the whole patient cohort.[30]

It thus is clear that accurate disease staging and risk assessment are desirable in the management decision-making process, with regard to patient selection for esophagectomy and combined modality treatments. The management algorithm from the authors' institute is shown (Fig. 1).

TECHNICAL ASPECTS OF ESOPHAGECTOMY

The results of selected series are shown in Table 2. It is observed that mortality rates in Asia, notably in China and Japan, are in general lower than those in Western countries. It is remarkable that a 30-day mortality rate of 4.6% could be achieved during 1952-1976 in China.[45] The reasons for that are not immediately apparent. Strict patient selection, surgical experience, and different patient risk profiles may all in part contribute.

Regardless of geography, results from both the East and West have improved. It would be expected that the techniques of esophagectomy should be critical in influencing postoperative outcome. There are many important variables involved in an esophagectomy, such as surgical access, the extent of resection and lymphadenectomy, the type and method of preparation of the esophageal substitute, pyloric drainage procedure, the route of reconstruction, and the technique of esophageal anastomosis. The most controversial are perhaps the choice of surgical access and the most appropriate extent of lymphadenectomy.[46,47] These considerations are interrelated as the surgical approach influences not only postoperative morbidity and mortality but also the ability to perform an extensive lymphadenectomy.

Transthoracic Versus Transhiatal Resection

Proponents of transhiatal resection believe that surgical resection for esophageal cancer is mostly palliative and a cure is a chance phenomenon for only those with very early tumors. The operating time is also shorter and postoperative morbidity is less.[48] Survival equivalent to that of transthoracic resection is claimed. Conversely, surgeons who practice transthoracic esophagectomy consider the open approach to be safer, with less chance of injury to the tracheobronchial tree, thoracic duct, recurrent laryngeal nerves, azygous vein, and aorta.[49] A more thorough lymphadenectomy leads to better staging and longer survival.

Clinical trials, whether randomized or nonrandomized, have not resolved the controversy. Two large meta-analyses concluded that the transthoracic approach probably resulted in higher perioperative morbidity and mortality rates, but long-term survival was not different.[50,51] Four randomized trials

Table 2. Selected reports on results after esophagectomy

Author/year	Resection technique	Study period	N	ADC to SCC (n) ratio	Anastomotic leakage (%)	Pulmonary complications (%)	Hospital mortality (%)	5-yr survival (%)
Akiyama et al.[43]	3-FL	1973–1993	717	0:717	—	31	5.2	42
Ellis et al.[180]	TTE/THE	1970–1994	454	303:139 (12 others)	6.4	6.6	3.7	24
Li and Yao[35]*	TTE/THE	1980–1994	17,815	2%:98%	3.9	—	3.9 (30-day)	28
Jamieson and Mathew[181]*	TTE/THE	1990–	11,398	—	11.7	—	11	Overall: 21.4 SCC: 21 ADC: 29
Orringer et al.[48]	THE	1976–1998	800	69% ADC	13	—	4.5	Overall: 23 SCC: 17 ADC: 24
Ando et al.[58]	3-FL/2-FL	1981–1995	419	0:419	13.8	22.4	7.9	40
Karl et al.[182]	TTE	1989–1993	143	115:16	3.5	14	2.1	Median 1.6 yr
Watanabe et al.[101]	3-FL/2-FL	1982–1994	353	0:353	—	—	—	3-FL: 48 2-FL: 23
Altorki and Skinner[85]	Enbloc	1988–1998	111	81:30	13.5	27	5.4	40
Collard et al.[183]	TTE/THE	1984–1997	324	158:160 (6 others)	—	31.3	5.2	35
Hagen et al.[29]	Enbloc	1982–2000	100	100:0	Colon: 12.5 Stomach: 10	30	6	52
Hulscher et al.[50]*	TTE/THE	1990–1999	7584	—	TTE: 7.2 THE: 13.6	TTE: 18.7 THE: 12.7	TTE: 9.2 THE: 5.7	TTE: 22 THE: 23
Shao et al.[34]	TTE/THE	1991–1998	3863	ESO + cardia	0.9	—	0.5 (30-day)	ESO: 40 Cardia: 21
Siewert et al.[33]	TTE/THE	1982–2000	1059	407:652	—	—	10 (30-day)	SCC: 30 ADC: 42
MRC 2002†	TTE/THE	1992–1998	802	2:1	S: 7 CS: 6	S: 15 CS: 16	S: 10 CS: 10 (30-day)	Median: S: 14 mo CS: 17 mo
Bailey et al.[37]	TTE/THE	1991–2001	1777	—	—	21	9.8 (30-day)	—
Liu et al.[45]‡	TTE/THE	1990–2000	6583	ESO + cardia	3.4	1.5	1.1	ESO: 23.9 Cardia: 17.6
Law et al.[184]	TTE/THE	1990–2001	421	0:421	3.1	15.9	4.8	27.5‡

3-FL = three-field lymphadenectomy; 2-FL = two-field lymphadenectomy; TTE = transthoracic esophagectomy; THE = transhiatal esophagectomy; enbloc = en bloc esophagectomy; ADC = adenocarcinoma; SCC = squamous cell cancer; S = surgery alone; CS = preoperative chemotherapy; MRC = Medical Research Council; ESO = esophageal cancer.
*Collective reviews.
†Multicenter trial.
‡Results selected from different time periods.

were published comparing the two approaches.[52–55] The largest compared 106 patients who underwent transhiatal esophagectomy with 114 patients who had the transthoracic approach for mid-lower third/cardia adenocarcinomas. Pulmonary complication rates were 27% in the former group compared with 57% in the latter. Ventilation time, intensive care, and hospital stay were longer in the transthoracic group. There were, however, no significant differences in in-hospital mortality at 2% and 4%. Significantly more lymph nodes were dissected in the transthoracic group (16 versus 31). There was a trend toward a survival benefit with the transthoracic approach at 5 years: disease-free survival was 27% compared with 39%, and overall survival was 29% compared with 39%.[52]

It is the authors' view that the transhiatal approach should only be selectively applied. In patients with advanced middle third tumors or in patients with tumors closely related to the tracheobronchial tree and especially after neoadjuvant radiation therapy, tumor infiltration and fibrosis may obliterate tissue planes and make blind dissection unsafe. As such, its application is more limited in the East. This should be taken into consideration before this approach is chosen.

Minimal Access Surgery

With the advent of minimal access surgery, various different approaches have been devised and studied in recent years, which include thoracoscopy, laparoscopy, mediastinoscopy, and open laparotomy and thoracotomy in various combinations.[56] The most popular is thoracoscopic esophagectomy with gastric mobilization via a laparotomy and cervical esophagogastrostomy.[57–67] Combining laparoscopic and thoracoscopic approaches has its advocates,[68–70] as does a totally laparoscopic approach.[71–73] The myriad of surgical methods implies a lack of consensus on which is superior. The results of selected series are shown in Tables 3 and 4.

Potentially serious intraoperative complications can occur; these include bleeding from the azygous vein[59] and from intercostal vessel,[63] injury to the aorta,[66,74] tracheobronchial tree,[60,61,75] and recurrent laryngeal nerve.[64] The lack of tactile control is probably a contributory factor. On the contrary, the increased magnification and excellent visualization offered by thoracoscopy might in fact help lessen complications. Less blood loss[57] and reduction in transient recurrent laryngeal nerve palsy from 80% to 18% were reported.[76]

For postoperative complications, similar anastomotic leak and respiratory complication rates, but shortened intensive care unit and hospital stay compared with historical controls, were shown in one study.[69] Another study reported that the incidence of pulmonary complications was reduced from 33% to 20% with thoracoscopic mobilization.[62] Osugi and colleagues[65,77] experienced longer operation duration, but reduction in vital capacity and performance status were less for the thoracoscopy group; the number of retrieved lymph nodes, blood loss, and morbidity were similar. In our studies, thoracoscopic esophagectomy was selectively applied to patients with elevated risk; but postoperative outcome was shown to be similar to those who underwent open thoracotomy, implying a benefit in high-risk patients.[57] Studies that include survival data report no difference with historical controls.

Except for the few studies mentioned, clear advantages of the minimal access methods could not be demonstrated, partly because the number of patients studied generally was too small to have sufficient statistical power to demonstrate a difference. There also are other reasons why benefits are difficult to confirm. With modern analgesic methods such as epidural analgesia, postoperative pain control is less of a problem.[78] The genesis of cardiopulmonary complications is multifactorial and does not depend solely on the size of the incision. Surgical trauma of the mediastinal dissection is also independent of the incision size. The benefit of smaller port sites compared with open thoracotomy may be offset by the lengthened time of single-lung anesthesia. A learning curve obviously exists for such complicated procedures.[76,79] The duration of the thoracoscopic procedure, blood loss, and the incidence of postoperative pulmonary infection were all less, and the number of mediastinal nodes retrieved was more, in the latter half of a group of 80 patients who underwent thoracoscopic esophagectomy.[79] Most reports to date reported only a limited number of patients. Only three reports had close to or more than 100 patients, each using a different technique.[65,67,68] Thus for most series, the full technical potential may not have been realized.

Patient selection in many series is evident. Two thirds of patients had cancer of stage II and below in two studies,[68,70] and in the series from Pittsburgh, 21% of patients had only high-grade dysplasia.[68] Selecting the most appropriate procedure for the different stages of esophageal cancer is controversial even with open surgery; it is even more difficult to determine the indication for the minimal access technique. It has been suggested that it is appropriate for stage IV disease, given that palliation is the aim, lymph node dissection is of secondary importance, and the potential benefits of laparoscopic or thoracoscopic approaches (shorter hospital stay, less pain, rapid recovery) are particularly beneficial.[72] For Barrett's

Table 3. Thoracoscopic esophagectomy, gastric mobilization via laparotomy, and cervical esophagogastrostomy

Author/year	N	Conversion (n)	Hoarseness (n)	Respiratory complication (n)	Anastomotic leakage (n)	Operating time (min)	Thoracoscopy time (min)	Blood loss (ml)	Lymph node dissected (n)	Mortality (n)	Survival (%)
Cuschieri[66]*	26	1	2	3	1	—	—	—	—	0	—
Gossot et al.[60]†	29	0	3	5	5	—	135	200	—	1	—
Akaishi et al.[62]	39	0	7	6	2	448	200	767	19.7 (mediastinum)	0	—
Dexter et al.[64]	24	2	8	13	2	—	183	—	13 (6-28)	3	—
Law et al.[123]	22	4	4	4	0	—	110	450	7	1‡	2 yr: 62 (TS) 63 (TT)
Kawahara et al.[61]§	23	0	5	2	1	—	111	163	29	0	1 yr: 78
Law et al.[58]‖	30	2	—	12	1	392	90	700	—	4	Median: 34 mo (TS) 16 mo (TT)
Smithers et al.[67]	160	20	—	39 (27%)	6	—	104	165 (TS)	11	8	Median: 29 mo 1 yr: 70 2 yr: 57 5 yr: 40
Osugi et al.[79]¶	94	10									
Early, n = 34			14%	29%	3%	—	278	428	29	0	55
Late, n = 46			15%	6.5%	0%	—	183	161	36	0	

TS = thoracoscopic resection; TT = transthoracic resection.
*Aortic injury in one patient.
†One patient with right bronchial injury.
‡One patient who was converted to open thoracotomy.
§One patient with tracheal injury.
‖For pharyngolaryngo-oesophagectomy only, four patients also had intrathoracic esophageal tumors.
¶With 5-cm minithoracotomy.

Table 4. Thoracoscopic esophagectomy and laparoscopic gastric mobilization

Author/year	N	Conversion	Hoarseness (n)	Respiratory complication	Anastomotic leakage	Operating time (min)	Thoracoscopy (min)	Blood loss (ml)	Lymph node dissected	Mortality	Survival (%)
Luketich et al.[68*]	222[†]	16	8	Pneumonia: 17	26	450	—	—	16 (10–51)	3 (30-day)	—
Nguyen et al.[69‡]	46	2.2%	1	—	8.7%	350	116	279	10.3	4.3%	3 yr: 57%

Figures represent number of patients unless otherwise stated
*Laparoscopic transhiatal esophageal mobilization in 8 patients.
[†]46 Patients with high-grade dysplasia.
[‡]Thoracoscopic and laparoscopic esophagectomy in 46 patients: 38 had cancer, 3 had high-grade dysplasia, 5 had benign disease.

esophagus with high-grade dysplasia, a minimally invasive approach also seems like a good choice, as the chance of lymphatic spread is minimal and oncologic concerns of inadequate lymphadenectomy are less. For patients with invasive but potentially curative cancer, it is most controversial. These techniques are perhaps more suitable for patients encountered in the West, because the tumors are located mainly in the lower esophagus; thus, dissection around the tracheobronchial area and recurrent laryngeal nerve is less hazardous. The lower esophagus is also more readily accessed via an open laparotomy or by laparoscopy. Another concern of minimal access techniques is port site recurrence.[57]

In the authors' practice, open resections are still preferred; thoracoscopic resections have mostly replaced-transhiatal approach and are selectively applied in patients with limited physiological reserve. Compared with the transhiatal method, the ability to dissect under direct visual control is advantageous. But just like for transhiatal esophagectomy, locally infiltrative tumors or postirradiated tumors in close proximity with the tracheobronchial tree are not favorable. Proof of the superiority over conventional transthoracic resection is not forthcoming. These techniques should not be attempted without training and mentorship and should be investigated further in centers with adequate experience with the open resections.

Extent of Resection: Axial and Lateral Margin

One of the most controversial aspects of treating gastrointestinal malignancies is the appropriate extent of resection to achieve the best outcome, and this debate is best exemplified by esophageal cancer.[80]

The need to obtain a clear axial and lateral margin is less controversial. It is clear that the chance of a histologic positive margin reduces with increasing distance at which the esophagus is transected away from the tumor edge[81] and that the frequency of anastomotic recurrence is a function of the length of proximal resection margin attained.[82] Positive lateral margin is associated with worse survival.[83,84] Obtaining a clear lateral margin is more difficult with esophageal cancer compared with other gastrointestinal malignancies, because of its anatomic position and adjacent indispensable structures. The concept of "en bloc" resection entails the removal of a "sheath" of tissue surrounding the esophagus to ensure complete tumor removal.[29,85] The site of the tumor has a bearing on the ability to perform such resections. For tumors below the tracheal bifurcation, wide lateral margins can be obtained, which could include the adjacent pericardium, periaortic tissue, thoracic duct, azygous vein, intercostal vessels, and the pleura on

both sides. For cancers in close proximity to the trachea, such resection is improbable except in T1 or T2 tumors. The concept is thus more applicable for Western patients, where most tumors are adenocarcinomas of the lower esophagus.

Extent of Resection: Lymphadenectomy

The rationale for extensive lymphadenectomy is that, first, lymphatic spread occurs early and widely in esophageal cancer. Between 8% and 30% of patients with tumors that reach the muscularis mucosa and 30% to 58% of tumors involving the submucosa have pathologic lymph nodes.[43] Second, more accurate pathologic staging can be obtained, which may guide further treatment. Third, local disease control is better; fourth, long-term survival is enhanced. Opponents to extensive lymphadenectomy claim that postoperative recovery is compromised, more thorough lymph node dissection merely leads to stage migration but does not improve prognosis, and long-term quality of life is affected as a result of morbidity, such as recurrent laryngeal nerve palsy.

Radical resections are considered superior in providing better local control.[85–88] In a detailed study of nodal metastases and recurrence for adenocarcinomas of the lower esophagus after en bloc esophagectomy, most of subsequent nodal recurrences were found outside the limits of dissection in the superior mediastinum or aortopulmonary window, suggesting that the recurrences arose from nodes along the recurrent laryngeal nerve that were not routinely removed.[86] It is claimed that local recurrence can be reduced to an impressive 5%.[85] Mediastinal disease, by contrast, is a common mode of recurrence after transhiatal resections without formal lymphadenectomy. In half the patients who developed recurrence after transhiatal resection, the initial site of recurrence is confined to the mediastinum.[89]

In Japan, a slightly different strategy of three-field lymphadenectomy (3-FL) has been selectively applied. This involves lymph node dissection of the abdomen, mediastinum, and bilateral neck. The overall rate of cervical lymph node metastases has been documented and is approximately 30%. In relation to the level of primary tumor, cervical lymph nodes are involved in 60%, 20%, and 12.5% of upper, middle, and lower third tumors, respectively.[43] Results from Japan have also prompted the introduction of similar strategies in the West, which yielded similar incidences of positive cervical lymph nodes.[32,88]

Studies on recurrence pattern provide some evidence against the routine practice of 3-FL. One would expect that if cervical lymphadenectomy were not carried out, then the incidence of subsequent cervical recurrence would correspond to the incidence of positive nodes found at the time of resection in similar patients who undergo three-field dissection. However, the incidence of cervical nodal recurrence is generally lower. In a study of 108 patients with R0 resections, 11% of patients had recurrent disease in the neck, and only 4% of patients had isolated cervical nodal recurrence. The higher incidences of mediastinal recurrence (25%) and systemic organ metastases (26%) further limited the role and justification of additional neck dissection.[90] A very similar study reported on 176 patients also documented a 6% incidence of cervical nodal recurrence, dwarfed by a local mediastinal recurrence rate of 21% and a systemic recurrence rate of 18%. Only two patients had isolated cervical nodal recurrence and underwent further neck dissection.[91] The relatively low incidence of cervical nodal recurrence and clinical relevance was also found for patients undergoing transhiatal resection. In a report of 149 patients with middle third and lower third tumors, cervical recurrence was found in 8.5% of patients. Again, the addition of a cervical lymphadenectomy was questioned.[92]

Enhanced survival rates are claimed after 3-FL compared with two-field lymphadenectomy (2-FL). The majority of reports, however, were nonrandomized studies. A nationwide survey from Japan reported significant differences in 5-year survival rates comparing 3-FL and 2-FL, for both N0 and N1 diseases (57% versus 45% and 33% versus 29%, respectively) in favor of the more extensive approach.[93] Two randomized trials have been published. The first showed a higher postoperative mortality rate for 2-FL and a survival advantage for 3-FL; in the second trial, 5-year survival rates were not statistically different for 3-FL (66.2%) and 2-FL (48%). In both studies, patient groups appeared highly selected and were not well matched, and adjuvant therapies were not controlled.[94,95]

These limited trials are therefore insufficient to prove an advantage with 3-FL. Subgroups of patients may benefit from 3-FL, but these groups are yet undefined. Studies are needed to further identify these patients. The chance of cervical nodal disease is determined to some extent by the presence or absence of nodal disease in the abdomen and/or mediastinum.[32] In one study, 11% of 63 patients without thoracic recurrent laryngeal nerve nodal involvement had metastatic cervical nodes, in contrast to 43% of 23 patients with thoracic recurrent laryngeal nerve nodal disease.[96] In another study, in patients without thoracic recurrent laryngeal nerve involvement, performance of 3-FL offered no survival advantage.[97] A sentinel concept is advanced, and molecular techniques such as reverse transcription–polymerase

chain reaction may help identify those patients with recurrent laryngeal nodes intraoperatively for additional neck dissection.[98]

The importance of the recurrent laryngeal nerve nodes is further realized when it is found that the value of 3-FL may not lie with the addition of a cervical phase but with the completeness of the superior mediastinal dissection along the recurrent laryngeal nerves. The need to preserve the recurrent laryngeal nerves, the vagal branches, and small arterial branches to the trachea and bronchi made dissection less complete.[99] It was observed that complete 2-FL that includes more extensive lymphadenectomy of the superior mediastinum performed from the thorax can in fact remove most relevant nodes in the neck. The added value of a separate approach to the neck in these patients is therefore minimal.[100] Furthermore, when such complete dissection has been carried out from below, 5-year survival rates were similar to patients who have a formal 3-FL and were better than those who underwent traditional 2-FL without recurrent laryngeal nerve lymphadenectomy.[101]

Although the benefits of 3-FL are undetermined, it can be carried out with low mortality rates, whether in Japan or in the West.[32,102] Morbidity rates, however, remain high, with anastomotic leaks of 19% to 30% and recurrent laryngeal nerve palsy reaching over 50% of patients.[102] Recurrent nerve palsy influences not only postoperative morbidity but also long-term quality of life in terms of speech, swallowing, and respiratory functions.[103] Tracheal ischemic necrosis also seems specific for 3-FL. Replacing 3-FL with neoadjuvant, adjuvant, or intraoperative radiotherapy[104] is an alternative, but their roles remain controversial.

COMBINED MULTIMODAL TREATMENT STRATEGIES

Radiotherapy Alone

The 5-year survival of patients treated with conventional external beam radiotherapy alone was less than 10%.[105,106] Encouraging results of a 22% to 33% 5-year survival rate were not duplicated.[107,108] Bias in patient selection was inherent in these studies, and an attempt by the Medical Research Council (MRC) at conducting a randomized trial comparing surgery with radiotherapy resulted in premature study termination for lack of recruitment.[109] Current evidences favor superiority of chemoradiation over radiotherapy alone; the latter is therefore reserved for palliation or for patients not suitable for chemotherapy.

Brachytherapy

Brachytherapy has been used as primary treatment for palliation or as a boost following external beam radiation. The main limitation of brachytherapy is the effective treatment distance. It seems an effective palliative mode of treatment in relieving dysphagia and bleeding. As a palliative modality, a local control rate of around 30% and a median survival of 6 months can be expected.[110] Main concerns are the development of radiation stricture and fistulas, whether used as palliation or as an intraluminal boost. Fistulae formation can occur in up to 14% of patients when used with chemotherapy and external radiotherapy, and treatment-related death rate can be up to 8%.[111] Given the significant toxicity of this treatment approach, caution is necessary, and guidelines for brachytherapy has been published.[112] There is at present no sufficient evidence that its addition to curative modalities can improve outcome.

Neoadjuvant Radiotherapy

Trials on neoadjuvant radiotherapy have failed to show increased resection rate or improved survival compared with surgery alone.[113–118] The European Organization for Research and Treatment of Cancer (EORTC) study suggested improved local disease control but no better long term outcome.[115] One study, which also involved chemotherapy, suggested a survival advantage imparted by preoperative radiotherapy but only in the pooled groups of patients receiving radiotherapy.[118] A Cochrane meta-analysis showed that if preoperative radiotherapy regimens do improve survival, then the effect is likely to be very modest with an absolute improvement in 5-year survival of around 3% to 4%.[119]

Adjuvant Radiotherapy

Postoperative radiotherapy was studied in four randomized trials[120–122]; all four studies demonstrated improved local disease control, especially reduction of tracheobronchial recurrence in the subgroup of patients with residual disease in the mediastinum after palliative resection.[121] The largest study published to date randomized 495 patients with intrathoracic squamous cell cancers.[122] Postoperative radiotherapy of 50 Gy to 60 Gy was administered to 220 patients to the entire mediastinum and bilateral supraclavicular fossa. The radiotherapy group had more male patients and more patients with positive lymph nodes. Per-protocol analysis showed no overall difference in 5-year survival at 31.7% for the surgery-alone group and 41.3% for the radiotherapy group. A benefit in the radiotherapy group was observed in stage III patients; 5-year survival rates were 13.1% and 35.1% ($P = 0.0027$). In patients with node-positive disease, difference in survival was of borderline significance. The chance of mediastinal, cervical lymph node and

anastomotic recurrences was also reduced. Survival benefit was not demonstrated for the other three trials. From these studies it seems reasonable to give postoperative radiotherapy to subgroups of patients, especially those who had palliative resections, to enhance local disease control. Suitable meta-analysis should be carried out to further enhance the statistical validity of the conclusions.

Neoadjuvant Chemotherapy

Eleven randomized trials were published studying the role of preoperative chemotherapy.[36, 118, 123–131] The two largest trials were the Intergroup trial (INT 0113) and the MRC trial. The first study randomized patients to undergo surgery alone or to have three cycles of cisplatin and 5-fluorouracil (5-FU) before surgery and, in those who had stable or responsive disease, two additional postoperative courses.[131] Of 440 eligible patients, 213 were assigned to the neoadjuvant group. The median survival was 14.9 months for the chemotherapy group compared with 16.1 months for the surgery group. Two-year survival rates were no different at 35% and 37%, respectively. The MRC trial (OE02) involved 802 patients and similar preoperative regimens with two courses of cisplatin and 5-FU.[36] Overall survival was better in the chemotherapy group. Median survival was 16.8 months versus 13.3 months (hazard ratio, 0.79; 95% confidence interval, 0.67–0.93; $P = 0.004$), and 2-year survival rates were 43% and 34%.

The differences in findings in these two studies are difficult to resolve. A higher dose of chemotherapy, as well as postoperative chemotherapy, was given in the Intergroup trial. Slightly more patients with adenocarcinomas were recruited in the MRC trial (66% versus 54%). Attempted resection was carried out in 92% of patients in the chemotherapy group and 97% in the surgery group in the MRC study, compared to respective values of 80% and 92% in the INT 0113. R0 resections rates, however, were similar at 60% (MRC) and 62% (INT,0113). There was significantly more delay to surgical resection in the INT 0113 trial: 93 days compared with 63 days. Nine percent of the patients in the MRC trial also had preoperative radiotherapy, whereas an unknown number in the American study had postoperative radiotherapy. The type of surgery in the MRC trial was also not controlled. The median survival of the surgery alone arm in the Intergroup trial (16.1 months) was equivalent to the chemotherapy arm in the MRC trial (16.8 months). The more intense chemotherapy regimen, and the delay in surgical resection could have adversely affected the outcome in the chemotherapy arm of the Intergroup trial. The reasons for the different conclusions between these two studies remain conjectural.

A meta-analysis was recently published, which included these two studies discussed above.[132] A total of 2051 patients were analyzed. Neoadjuvant therapy was found not to alter the rate of resection, rate of complete resection, or postoperative complications. The pooled clinical response was 36%, and pathologic complete response was only 3%. There appears to be a significant survival advantage for chemotherapy. At 3, 4, and 5 years, the increased survival was 21%, 24%, and 44%, respectively, reaching statistical significance only at 5 years (relative risk [RR] = 1.44; 95% confidence interval, 1.05–1.97; $P = 0.02$). It was estimated that 11 patients needed to be treated for one extra survivor at 5 years. It is also worth noting that all trials evaluated patients with squamous cell cancers except the Intergroup and MRC trial.

It seems that neoadjuvant chemotherapy may improve outcome in the long term, probably in subgroups of patients. It has been consistently shown that responders, especially the complete responders, fare far better than nonresponders. The latter even had worse prognosis compared with patients who had surgery alone, perhaps because of unnecessary delay to surgery.[123–125, 130, 131] It may be that in most studies the benefits in the responders were negated by the nonresponders.

Adjuvant Chemotherapy

Two studies were conducted by the Japanese Esophageal Oncology Group. The first trial compared postoperative cisplatin and vindesine chemotherapy with 50 Gy of radiotherapy.[133] In the second, a surgery-alone group was compared with the same chemotherapy.[134] Neither showed an advantage for adjuvant chemotherapy. A more recent report on 242 patients compared surgical resection with the addition of postoperative cisplatin and 5-FU.[135] The 5-year disease-free survival rate was significantly different at 45% with surgery alone and 55% with surgery plus chemotherapy. The overall 5-year overall survival rates, however, were not significantly different at 52% and 61%, respectively. The effect was more remarkable in the subgroup with lymph node metastasis. However, another small French study using, again, cisplatin and 5-FU as adjuvant therapy did not show advantage with chemotherapy.[136]

Neoadjuvant Chemoradiation

Several groups have explored chemoradiation as neoadjuvant therapy[118, 137–143] (Table 5). The radiation dose ranged from 20 Gy to 45.6 Gy. In five trials, only patients with squamous cell cancers were

Table 5. Randomized trials on neoadjuvant chemoradiation versus surgery alone

Author/year	N	Histology	Chemotherapy dose of radiation (cGy)	Complete response rate	Mortality (%)	Median survival (mo)	3-yr survival (%)
Nygaard et al.[118]							
S	41	SCC	Cisplatin, bleomycin	NA	13	7.5	9
CRT + S	47		3500		24	7.5	17
Apinop et al.[138]							
S	34	SCC	Cisplatin, fluorouracil	NA	15	7.4	20
CRT + S	35		4000		14	9.7	26
Le Prise et al.[137]							
S	41	SCC	Cisplatin, fluorouracil	12.5†	7	10	14
CRT + S	45		2000		8.5	10	19
Walsh et al.[139]							
S	55	Adeno	Cisplatin, fluorouracil	25%	8	11	6
C + S	58		4500		4	16	32 ($P < 0.05$)
Bosset et al.[140]							
S	139	SCC	Cisplatin	26%	4	19	34‡
C + S	143		3700		12.3	19	37
Burmeister et al.[143]							
S	128	SCC (39%)	Cisplatin, fluorouracil	15%	4.6*	22	32‡
C + S	128	Adeno (61%)	3500	SCC (26%) Adeno (9%)		19	34
Urba et al.[142]							
S	50	SCC (25%)	Cisplatin, vinblastine, fluorouracil	28%	2	17	16
C + S	50	Adeno (75%)	4500		7	17	30
Lee et al.[141]							
S	50	SCC	Cisplatin, fluorouracil	21%	NA	27	51
C + S	52		4560	(43%†)		28	49 (2 yr)

NA = not available; SCC = squamous cell cancers; Adeno = adenocarcinoma.
*Treatment-related mortality.
†In patients who had resection.
‡Extrapolated from graphs.

recruited[118,137,138,140,141]; two included mostly adenocarcinomas,[142,143] and one treated adenocarcinomas only.[139] Most of the studies recruited tumors up to stage III, although in one study, only stage I and II diseases were randomized.[140] A survival advantage with neoadjuvant chemoradiation over surgery alone was demonstrated only in one trial.[139] Three-year survival rates were 32% and 6% for the preoperative treatment group compared with surgery alone. This trial has been criticized on the grounds of inadequate preoperative staging, unclear surgical procedure, large number of protocol violations, and survival from the surgery group that was exceptionally poor. In the French study, the chemoradiation group had longer disease-free survival, a longer interval free of local disease, a lower rate of cancer-related deaths, and a higher frequency of curative resection, but overall survival was not different. Postoperative mortality was also higher for the treatment group (12.3% versus 3.6%), mainly related to respiratory and septic complications.[140] The most recent Australian trial also could not demonstrate survival advantage with combined treatment.[143] The results from these studies are conflicting and thus inconclusive. Despite this, the use of chemoradiation has increased; the Patterns of Care studies showed that preoperative chemoradiation therapy increased from 10.4% during 1992-1994 to 26.6% in 1996–1999. Interestingly, trimodal therapy was three times more common in patients with adenocarcinomas compared to those with squamous cell cancers.[144] Notwithstanding the lack of concrete data supporting such regimens, its use is commonplace. An Intergroup trial planned to include 620 patients to further address the role of neoadjuvant chemoradiation (CALGB 9781) was closed prematurely due to lack of accrual.

Chemoradiation as Definitive Therapy

The Radiation Therapy Oncology Group (RTOG 85-01) trial of chemoradiation versus radiotherapy provided convincing evidence of the superiority of chemoradiation.[32–34] The 5-year survival rate reported for the combined therapy group was 26% compared with 0% following radiotherapy (median survival, 14 months versus 9 months). Data on recurrence patterns showed that both local and distant disease control were superior with combined treatment. Local persistence of disease and recurrence was 47% compared with 65%. Intensification of radiation dose to beyond 50.4 Gy, whether by external beam[145] or by brachytherapy,[111] did not yield further advantage but yielded potential added complications.

A recent Cochrane meta-analysis of 13 randomized trials that compared chemoradiation with radiation confirmed the superiority of chemoradiation. Concurrent chemoradiation provides significant overall reduction in mortality at 1 to 2 years, an absolute reduction of death by 7%, and reduction in local persistence/recurrence rate by 12%. The downside is a 17% increase in grade 3-4 toxicities. Sequential chemoradiation provides no benefit, perhaps demonstrating the need to maximize the radiosensitizing properties of chemotherapy.[146]

The Role of Surgery

The RTOG 85-01 trial suggested that in patients with T1-3 N0-1 M0 disease, a 14% to 26% 5-year survival can be expected. The increased use of chemoradiation is shown both in the United States and even in Japan.[147–150] It has even been suggested that surgery may be of no additional value to chemoradiation and should be relegated as an "adjuvant" treatment.

Two clinical trials attempted to examine whether surgical resection was necessary after chemoradiation. A French study (FFCD 9102) was an equivalence trial that treated 455 patients with both squamous cell cancers and adenocarcinomas of stage T3-4 N0-1 M0 with two cycles of 5-FU, cisplatin, and concurrent radiation (46 Gy at 2 Gy/day or split course of 15 Gy at weeks 1 and 3). Only 259 patients who had at least a partial response were randomized to undergo immediate surgery or to have three additional cycles of chemotherapy with 20 Gy at 2 Gy/day or split course of 15 Gy. The death rate within 3 months after starting induction treatment was 9% for surgery group compared with 1% in the chemoradiation group ($P = 0.002$). Two-year survival rates were not different at 34% and 40%; median survival was 17.7 months and 19.3 months for surgical and nonsurgical groups, respectively. Patients in the surgical arm, however, less often required a stent (13% versus 27%, $P = 0.005$) or dilatations (22% versus 32%, $P = 0.07$).[151] Using the Spitzer index to study quality of life, there was no difference in the long term, but the surgery arm had transient deterioration in the immediate postoperative period.[152]

A German multicenter equivalence trial recruited 177 patients with squamous cell cancers (T3-4 N0-1 M0). Three cycles of 5-FU/leucovorin/etoposide/cisplatin were given followed by chemoradiation (cisplatin/etoposide plus 40 Gy). Resection was then performed. This was compared with a control group with the same chemotherapy, followed by definitive chemoradiation (cisplatin/etoposide plus >60 Gy). Treatment-related mortality rates were 10% in the surgical arm versus 3.5% in the nonsurgical arm. Local tumor control was worse in the nonsurgical arm, but median survival time and 3-year survival rates were not different at 16 months and 28% (surgical arm) versus 15 months and 20% (nonsurgical arm). Three-year survival rate was 35% in nonresponders undergoing complete tumor resection compared with 11% in nonresponders who did not undergo resection.[153] Both studies concluded that surgical resection may not be necessary after chemoradiation therapy.

It may be premature to negate the value of surgical resection. First, chemoradiation is by no means harmless, and surgical resection may not be as morbid as described. Treatment duration of chemoradiation is often long and compliance is problematic. Only 68% of the patients in the RTOG-8501 trial could complete the planned treatment.[154] In the control arm of INT 0123, acute grade 3 and 4 toxicity affected 43% and 26%, and long-term grade 3 and 4 toxicity affected 24% and 13%, of patients, respectively.[145] Chronic toxicity involved pericardial or myocardial injury, pleural effusion, and pneumonitis and could be responsible for late deaths.[155] Treatment-related mortality was 5% to 9% as reported by the Intergroup trials.[145,156] In studies that showed a benefit for chemoradiation or questioned the value of surgical resection, the results of the surgical arm were often suboptimal. In the FFCD 9102 trial, death rate within 3 months in the surgical arm was 9% compared with 1% in the nonsurgical arm[151]; in the German trial, again the mortality rates were 10% and 3.5%, respectively.[153] The early surgical deaths likely biased the long-term survival results. The Irish study of an unusually poor 6% 3-year survival was already described.[139] It has been consistently shown that good results from complex surgery like esophagectomy are much more likely in dedicated high-volume centers with high-volume surgeons, where mortality rate from surgery of 2% to 3% can be achieved.[29–33,157,158] Comparisons with nonoperative treatments will be

Table 6. Selected series showing local persistence/recurrence for resection and chemoradiation therapy

Author/year	N	Treatment	Local disease persistence/recurrence (%)
Dresner et al.[91]	176	TTE	21
Law et al.[57]	108	TTE/THE	25
Hulscher et al.[92]	137	THE	35
Cooper et al.[154]	61	Chemoradiation	45
Minsky et al.[156]	218	Chemoradiation 64.8 Gy/50.4 Gy	56/52

TTE = transthoracic resection; THE = transhiatal resection.

valid only when such results from surgery are integrated into clinical trials.

Second, local disease control with chemoradiation alone is suboptimal. It can be shown with increasing extent of lymphadenectomy that better local control is achieved with surgery; by comparison, nonoperative chemoradiation has a much higher local persistence/recurrence rate, greater than 50%[145] (Table 6). The relief of dysphagia is much more certain with surgical resection; the need to treat dysphagia with a stent occurred twice in the nonsurgical group in the FFCD 9102 trial.[151] Regardless of long-term survival, control of local disease is important, for local symptoms from recurrent tumor such as airway obstruction and fistulation are often distressing and very difficult to palliate.

Third, for the majority of patients treated by chemoradiation, residual disease exists. The pathologic complete response rate for most trials is in the area of 25%. Thus, it is logical to assume that surgical resection would enhance cure when residual disease is removed for most patients. In the German trial, the 3-year survival of nonresponding patients who underwent resection was 35% compared with 11% in those who did not.[153] Conversely, the role of surgery is less obvious in those with complete response. However ascertaining true complete response is difficult. Up to 41% of patients with a negative endoscopy have residual tumor in the surgical specimen, and 25% of the patients with residual disease in the surgical specimens were long-term survivors, suggesting a role for resection.[159] CT or EUS was no better in assessing response.[160,161] Recent studies using 18-FDG-PET scans showed promise,[17,162] but although PET scanning can more reliably distinguish responders and nonresponders, it is not accurate enough to pinpoint the complete pathologic responders.[163] Furthermore, as understanding of molecular mechanisms and techniques of diagnosis advance, the definition of "residual disease" will likely change. Tumors that contain no cancers on conventional histology are found to harbor micrometastases, and thus the true complete responders will be even less.[164] Whether surgical resection in these patients would enhance survival remains to be seen, although it seems a logical assumption.

Prediction of Response

Just as risk analysis plays a role in identifying appropriate patients for surgical resection, predictors for response to chemoradiation are invaluable. Multimodality treatments are toxic, time consuming, and costly. Many different predictors have been investigated, ranging from simple histology[165] to various molecular markers such as p53, proliferative cell nuclear antigen (PCNA), epithelium growth factor receptor (EGFR), Ki-67, cyclin D1, expression of thymidylate synthase, and microvessel density, in both tissue and serum. None are reliable and results cannot help clinical decision-making.[166] Metabolic imaging with PET scanning is promising, with its ability to predict response early in the course of treatment.[163]

It seems that cisplatin and 5-FU–based chemoradiation therapy has reached its therapeutic limit in treating esophageal cancer. More novel chemotherapeutic agents are being explored, including paclitaxel, docetaxel, the topoisomerase I inhibitor irinotecan (CPT-11), vinorelbine, gemcitabine, herceptin, oxaliplatin, and biomodulators such as interferon.[167] This remains a very active area of research. In addition, advances in techniques in radiation delivery, such as intensity-modulated radiotherapy, may further reduce radiation toxicity.[168]

ENDOSCOPIC PALLIATION

Endoscopic palliative treatments for more advanced tumors include placement of an esophageal prosthesis, laser therapy, intralesional injection of various substances, and photodynamic therapy. The two most commonly used techniques are insertion of prosthesis and laser therapy. Insertion of SEMS has become the preferred method in many institutions.[27,169] The smaller diameter of the delivery

mechanism makes aggressive predilatation of the tumor with the attendant complications unnecessary. These stents are more flexible than plastic prosthesis; membrane-covered versions are developed to seal esophago-airway fistulas and prevent tumor ingrowth. Three randomized trials were reported that compared the use of metallic stents with plastic prosthesis. Perforation, pneumonia, bleeding, and migration rates were significantly less with metallic stents. Because of the lower morbidity, metallic stents were also more cost-effective despite their higher initial cost.[170–172] The choice of various metallic stents depends on their individual characteristics, in terms of flexibility, tensile force, and degree of shortening on deployment in relation to the site of placement.

Main problems with SEMS are stent migration, tumor in-growth or overgrowth, and, if placed across the gastroesophageal junction, promotion of acid reflux. Placing uncovered stents across the cardia lessens the chance of migration, and newer stents are developed with a one-way flap valve to prevent reflux.[173] It has also been shown that "tumor" ingrowth is sometimes due to granulation tissue or hyperplastic reaction by the esophageal mucosa.[174] Patency can be achieved again by laser, argon beam application, or sometimes placement of a second stent within the first. Another problem of stent insertion concerns placement near the upper esophageal sphincter. Foreign body sensation, pain, odynophagia, and airway compression can be troublesome and demand accurate placement. This is illustrated in the situation when recurrent disease is found at the anastomosis or in the esophageal remnant after subtotal esophagectomy. Placement of SEMS is still possible and achieves good palliation.[175]

Compared with more conventional methods of palliation such as laser therapy, patients with SEMS spent less time in the hospital and required fewer reinterventions.[176]

Photodynamic therapy (PDT) is also effective in relieving dysphagia and bleeding from esophageal cancer. The depth of penetration and tumor necrosis after PDT is limited to about 5 mm and therefore has a low chance of perforation, compared with laser therapy, which is more operator dependent. One study that compared Nd:YAG laser with PDT showed that tumor response and palliation were similar, but PDT was easier and associated with significantly fewer perforations.[177] Disadvantages with PDT include photosensitivity, inability to relieve extrinsic compression, and the costs of specialized equipment. Stricture, especially in combination with radiotherapy and chemotherapy, can occur after PDT.[178]

FUTURE PERSPECTIVES

Advances have been made in the management of esophageal cancer; the onus is to select the most appropriate combination for individual patients. Surgeons play a central role in the treatment of this disease; how best to integrate surgical resection with nonoperative programs requires further definitions. Surgeons should aim at improving their results further, so that suboptimal outcome in operations is not used to compare with seemingly "safer" therapies. The technique and extent of surgical resection may change when more information is made available and should vary with patients and precise disease stage following thorough investigations. Chemoradiation therapy has certainly made a great impact on current management strategies,[30] but perhaps its overenthusiastic adoption and its presumed benefit have to be balanced against the lack of clear evidence of superiority over surgery.[179] Distant failure remains a major problem, and search for more effective systemic drugs must be a therapeutic target. Management strategies are going to evolve further, with improvements in molecular techniques and imaging methods and the introduction of more novel tumoricidal agents. The challenges for the future are to critically test strategies in a scientific, unbiased manner and to explore other innovative treatments.

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