Surgery for Achalasia: 1998

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Technical controversies abound regarding the surgical treatment of achalasia. To determine the value of a concomitant antireflux procedure, the best antireflux procedure, the correct length for gastric myotomy, the optimal surgical approach (thoracic or abdominal), and the equivalency of minimally invasive surgery, a literature review was carried out. The review is based on 23 articles on open transabdominal or transthoracic myotomy, 14 articles on laparoscopic myotomy, and four articles on thoracoscopic myotomy. Postoperative results of traditional open thoracic or transabdominal myotomy as determined by symptomatology were better with fundoplication than without fundoplication. The incidence of postoperative reflux as proved by pH monitoring was high in patients who had an open transabdominal myotomy without fundoplication. The type of antireflux procedure used and the length of gastric myotomy had little effect on results. The results of transthoracic Heller myotomy do not require a concomitant fundoplication. Laparoscopic and thoracoscopic myotomy had excellent results at short-term follow-up. A fundoplication must be added if the myotomy is performed transabdominally. A randomized prospective study is required to determine the best fundoplication and the extent of gastric myotomy. Although minimally invasive surgery for achalasia has excellent initial results, longer follow-up in a larger population of patients is needed. (J GASTROINTEST SURG 1999;3:447-455.)

KEY WORDS: Achalasia, surgery, current therapy

Achalasia is an uncommon esophageal motor disorder of uncertain origin. Absence or a decreased number of ganglion cells in the intramuscular plexus can be demonstrated and probably produces a motility dysfunction and resulting symptoms. The diagnosis is normally made by either manometry or esophagography, whereas pathologic study with endoscopic biopsy is usually of little use since nerve cells exist deep within the esophageal wall. The treatment for achalasia is basically a release of the nonrelaxing esophageal sphincter. Forceful dilatation with a pneumatic balloon is often the first choice followed by surgical treatment.

Esophageal myotomy was first introduced by Heller[1] in 1913. The various early operative methods emphasized elimination of the swallowing disturbance but disregarded the possibility of postoperative gastroesophageal reflux disease (GERD). The increased number of reports of postoperative "iatrogenic" reflux has encouraged many surgeons to perform an antireflux procedure in recent years. Some surgeons believe that an antireflux procedure should be added,[2,3] whereas others think that it is superfluous.[4,5] The type of fundoplication has also been debated. Some prefer an anterior Dor fundoplication and others a posterior Toupet fundoplication. Nissen and Belsey-Mark IV procedures have also been used with Heller myotomy.

The distal extent of the myotomy is a critical factor. Surgeons have concluded that inadequate division of the muscle wall results in postoperative dysphagia, and an excessively long myotomy may lead to GERD. Some surgeons prefer to extend the myotomy 1 cm beyond the gastroesophageal junction (GEJ),[6,7] whereas others recommend a 2 cm or longer extension.[8,9]

The optimal surgical approach has also been disputed. Both the transabdominal and transthoracic approaches have advantages. Controversies include optimal visualization and the degree of phrenoesophageal ligament dissection. Very often the approach is dependent on surgeon preference based on training, operative privileges, and experience.

The development of an endoscopic operation has made the surgical option for achalasia more popular.

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Laparoscopic Heller myotomy was first reported in 1991 by Shimi et al.[10] Since then many surgeons have performed this new procedure. The technique has not been standardized, however, as surgeons are still seeking the optimal method for preventing postoperative dysphagia and GERD.

Unfortunately, most reports on the efficacy of a particular technical aspect of Heller myotomy are complicated by multiple additional variables, some of which are controversial. These include appropriateness of 24-hour pH monitoring, patient postoperative symptom assessment, and length of follow-up. To clarify some of the technical controversies, a literature review was undertaken with the awareness that the additional variables mentioned require further study as well.

METHODS

Articles from 1966 to 1997 written in English and cited in MEDLINE Express were reviewed. The following criteria for study inclusion were used: postop-

Table I. Methods and results of myotomy with traditional open surgery for achalasia

Reference	Approach	Antireflux	No.	Follow-up (mo)	Gastric myotomy (cm)	Excellent or good results (%)	Postoperative abnormal pH
Björck et al.[11]	T	—	52		2	84.8	
	T	Belsey	6			100	
Black et al.[12]	A	—	53	48~	1~	83.0	
	A	Anterior	44			93.2	
Bonavina et al.[13]	A	Anterior	206		2	93.8	8.6% (7/81)
Csendes et al.[14]	A	Anterior	100	82*	0.5~1	97.9	19% (9/48)
Del Genio et al.[15]	A	Nissen	87	49.7*	2	100	0% (0/36)
Donahue et al.[16]	T	—	19	48*	0.5	63.2	
	A	Nissen	24	60*	2~3	95.8	0%
Ellis[17]	T	—	179	6~240, 108*	~1	73.7	
Gerzic et al.[18]	A	—	49	12~120	1~2	86.5	35.0% (13/37)
	A	Anterior	176				12.6% (16/126)
Jaakkola et al.[19]	T	—	34	46~290, 172*	2.1*	94	
	A	—	26	38~213, 105*	1.6*	48	
Jamieson et al.[20]	T	—	9	6~148	~1	100	
	T	Belsey	27		"Limited"	96	
Jara et al.[21]	T	—	145	12~323, 85*		48.0	
Little et al.[22]	T	Belsey	57	56*	1	84	0% (0/20)
Mansour et al.[23]	T	—	29	12~120		64	
	T	Belsey	8	3~24		100	
Mattioli et al.[24]	A	—	83	12~425, 193.3*	2~3	35.4	
	T	—	30	12~245, 137.3*	~1	43.4	
	A	Anterior	72	12~180, 86.9*	2~3	87.0	
Menzies Gow et al.[25]	T	—	102	12~264, 96*	2	93.2	
Muralidharan et al.[26]	T	—	90	12~228	1.5~2	92.3	
Okike et al.[27]	T	—	440	12~204	"Limited"	85	
	T	Belsey	12			75	
Pai et al.[28]	T	—	16	61*	0.5~2	94	
	T	Belsey	17			70	
Paricio et al.[29]	A	Posterior	48	64*	1	92	12.0% (3/25)
Picciocchi et al.[30]	A	—	16	60~216, 114*	1	56.3	36.3% (4/11)
	A	Anterior	58		2~3	89.7	8.8% (4/45)
Shoenut et al.[31]	T	—	15	6.3*	"A few mm"		40% (6/15)
Stipa et al.[32]	T	Belsey	43	81*		87.2	0% (0/5)
	A	Nissen	58	77*		83.1	
Tomlinson	A or T	—	39	6~28	2	69.3	
and Grant[33]	A	Nissen	35			94.1	
TOTALS			2504			82.6	15.0% (70/468)

T = transthoracic approach; A = transabdominal approach.
*Mean.

erative assessment of symptoms, studies comparing results with and without fundoplication, at least 50 or more patients for open myotomy publications, at least 10 or more patients for endoscopic myotomy publications, and the inclusion of postoperative pH monitoring results. Thus the review is based on 23 articles on transabdominal or transthoracic traditional open myotomy[11-33] (Table I), 14 articles on laparoscopic myotomy[15,34-46] (Table II), and four articles on thoracoscopic myotomy[36,47-49] (Table III). To avoid recounting patients, each article is taken from a different institution. Abstracts, pediatric series, cricopharyngeal achalasia, and secondary achalasia including Chagas' disease were excluded.

In this literature review, investigation was focused on five technical aspects of achalasia surgery: the value of a concomitant antireflux procedure, the best antireflux procedure, the optimal surgical approach (thoracic or abdominal), the correct length for gastric myotomy, and the equivalency of minimally invasive surgery. How these factors influence operative results is discussed. Postoperative symptoms were categorized as excellent (no symptoms) or good (mild symptoms) and fair (moderate symptoms) or poor (severe symptoms). For articles with other symptom classifications, equivalent categories to the preceding ones were created when possible. Postoperative pH monitoring was used to assess the reliability of postopera-

Table II. Surgical procedures and results of laparoscopic treatment for achalasia

Reference	No.	Follow-up (mo)	Antireflux	Gastric myotomy (cm)	Excellent or good results (%)	Postoperative abnormal pH
Anselmino et al.[34]	43	1~23, 11*	Anterior	1~1.5	95.8	5.7% (2/35)
Collard et al.[35]	12	14.4*	Anterior		91.7	0% (0/6)
Cuschieri[36]	12		1 anterior, 11 not performed	1~2	100	
Delgado et al.[37]	12	1~12, 3†	Anterior	0.5~1	91.7	0% (0/8)
Del Genio et al.[15]	57	29.6*	360 degree	2	100	0% (0/25)
Graham et al.[38]	26	7.1*	Anterior	2	95	14.3% (1/7)
Holzman et al.[39]	10	7~39	Not performed		90	
Hunter et al.[40]	40	12.5*	7 anterior, 32 posterior, 1 not performed	1	97.3	
Kathy et al.[41]	11		Anterior		100	
Mitchell et al.[42]	14	3~21, 12†	Anterior	0.5	85.7	0% (0/5)
Morino et al.[43]	21	3~55	Anterior	1	100	5.8% (1/17)
Peracchia et al.[44]	43	1~43, 17†	Anterior	1.5~2	97.5	8% (3/40)
Swanstrom	12	6~28, 16*	9 posterior,	2	100	66.7% (2/3)
and Pennings[45]			3 not performed		100	0% (0/9)
Vogt et al.[46]	20	1~47, 12*	18 posterior,	2~3	94.5	
			2 not performed		100	
TOTALS	333		(190 anterior, 59 posterior, 57 [360 degrees], 27 not performed)		96.6	5.8% (9/155)

*Mean.
†Median.

Table III. Methods and results of thoracoscopic esophagomyotomy for achalasia

Reference	No.	Follow-up (mo)	Antireflux	Gastric myotomy (cm)	Excellent or good results (%)	Postoperative abnormal pH
Cade and Martin[47]	12	1~12	Not performed	"Limited"	91.7	50% (2/4)
Cushieri[36]	23	6~31, 13*	Not performed	"Limited"	78.2	(4/?)
Maher[48]	21	1~52, 21†	Not performed	~1	90	0% (0/1)
Pellegrini et al.[49]	24		Not performed	0.5	88	60% (6/10)
TOTALS	80		(80 not performed)		86.3	53.3% (8/15)

*Median.
†Mean.

tive symptoms. The extent of gastric myotomy was categorized as 1 cm or less and more than 1 cm. The antireflux procedures evaluated included the Belsey-Mark IV, Dor, Toupet, and Nissen fundoplication. Infrequently performed procedures such as the Husfeldt, Collis, and Allison techniques were excluded. Only articles dealing with open myotomy were included for the assessment of a concomitant antireflux procedure, the best antireflux procedures, the correct length for gastric myotomy, and the optimal surgical approach. Heterogeneity of entry criteria and follow-up periods prevented statistical analysis. Articles on minimally invasive surgery were excluded from the comparisons because of their short follow-up and small patient numbers.

RESULTS

Traditional Open Myotomy

Methods and results of myotomy with traditional open surgery for achalasia are summarized in Table I. Most articles reported long-term follow-up. Symptom result classifications varied between publications and in some instances even within the individual article.

Postoperative symptom results of various open procedures categorized by the presence or absence of fundoplication and the extent of gastric myotomy are shown in Fig. 1. Myotomy with fundoplication consistently produced good results regardless of the extent of gastric myotomy, whereas results of transabdominal myotomy without an antireflux procedure were disappointing. The incidence of postoperative

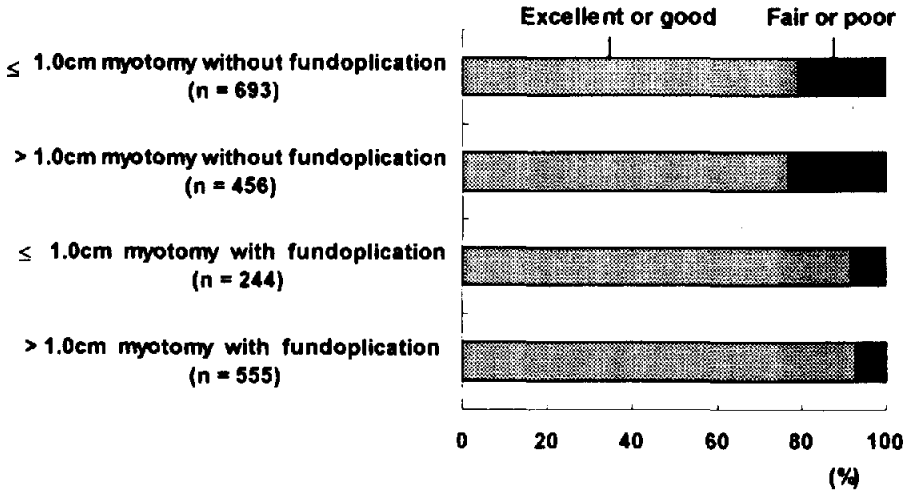

Fig. 1. Results of postoperative symptoms after traditional open myotomy for achalasia categorized by additional fundoplication and extent of gastric myotomy.

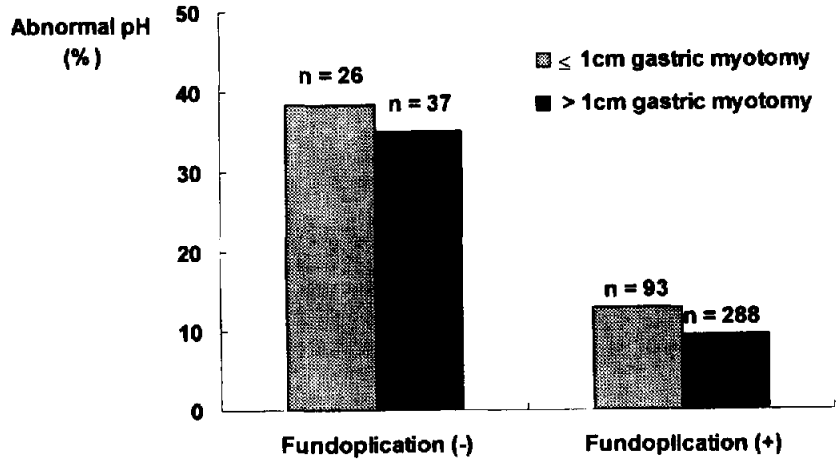

Fig. 2. Incidence of postoperative reflux after traditional open myotomy for achalasia categorized by additional fundoplication and extent of gastric myotomy.

reflux, proved by pH monitoring, was high in those who did not undergo an additional fundoplication regardless of the length of gastric myotomy (Fig. 2). Ten studies compared results between myotomy with and without fundoplication. Most reported that an additional fundoplication was beneficial,* whereas Okike et al.[27] and Pai et al.[28] demonstrated that myotomy without fundoplication was superior. Mattioli et al.[24] compared the long-term results of three different techniques. They concluded that long-term outcome for the transabdominal long gastric myotomy with Dor fundoplication was better than that for the transabdominal long gastric myotomy alone or the transthoracic short gastric myotomy alone.

Postoperative symptom results in patients categorized by type of fundoplication are shown in Fig. 3. The results were inferior in patients undergoing myotomy without fundoplication, especially when the transabdominal approach was employed. Although the Belsey-Mark IV procedure showed good results, it may be less satisfactory than the Dor, Toupet, or Nissen fundoplication.

The length of gastric myotomy extension did not influence postoperative results. Both postoperative symptomatology and pH monitoring results were better in myotomy with fundoplication irrespective of the length of gastric myotomy (Figs. 1 and 2).

The type of surgical approach influenced postoperative symptom results as well. When an additional fundoplication was employed, the transabdominal approach achieved better results than the transthoracic procedure. On the other hand, when an antireflux procedure was not concomitantly used, transabdominal surgery was unsatisfactory (Table IV). Transthoracic myotomy without fundoplication had acceptable results.

*References 11, 12, 16, 23, 24, 30, 33.

Table IV. Results of traditional open surgery categorized by extent of gastric myotomy, type of fundoplication, and surgical approach

Approach	Fundoplication	Gastric myotomy	No.	Excellent or good (%)	Postoperative abnormal pH
Transthoracic	Not performed	≤1 cm	677	79.8	6/15 (40%)
		>1 cm	294	91.6	
	Belsey	≤1 cm	96	86.1	0/20 (0%)
		>1 cm	29	82.4	
Transabdominal	Not performed	≤1 cm	16	56.3	4/11 (36.4%)
		>1 cm	162	52.9	13/37 (35.1%)
	Partial*	≤1 cm	148	96.0	12/73 (16.4%)
		>1 cm	380	91.8	27/252 (10.7%)
	Nissen	>1 cm	148	97.9	0/36 (0%)

*Dor and Toupet procedures are not separated since only one article has Toupet fundoplication in open myotomy that meets inclusion criteria.

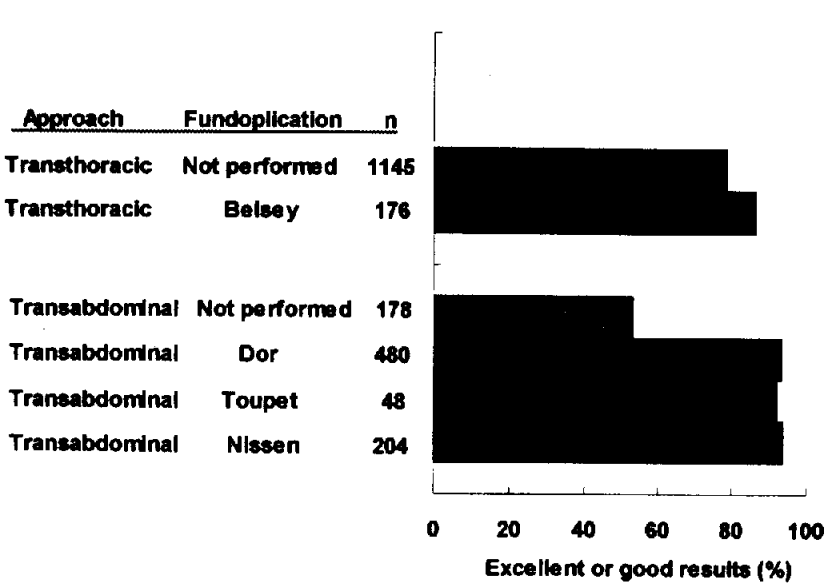

Fig. 3. Comparison of symptom results of open myotomy among various types of fundoplication.

Table V. Symptom results of minimally invasive surgery for achalasia categorized by type of fundoplication and surgical approach

Approach	Fundoplication	No.	Excellent or good results (%)
Thoracoscopy	Not performed	80	86.3
Laparoscopy	Not performed	26	96.2
	Dor	183	95.5
	Toupet	27	96.3
	Nissen	57	100

Minimally Invasive Surgery

The follow-up period after myotomy varies and is relatively short with the upper limit being 55 months. The symptomatic results of laparoscopic Heller myotomy were satisfactory (see Table II). Ninety-seven percent of patients had minimal or no complaints at short-term follow-up. Ten authors have reported the outcome of postoperative pH monitoring (see Table II). Anterior, posterior, and circumferential Nissen fundoplication achieved similar results with respect to postoperative symptomatology as shown in Table V. Patients without fundoplication (n = 27) did equally well on short-term follow-up. When fundoplication was applied, the incidence of abnormal findings on pH monitoring was low. Swanstrom and Pennings[45] reported that two of three patients undergoing myotomy without fundoplication had abnormal pH results, whereas none of nine patients had abnormal test results when posterior fundoplication was used concomitantly. However, the overall population of patients undergoing laparoscopic myotomy without fundoplication was too small for evaluation.

Twenty-six patients (7.8%) experienced a mucosal tear, perforation, or postoperative leakage. Ten of these patients underwent preoperative endoscopic dilatation of the distal esophagus. Conversion to open surgery was necessary in eight cases. The leading cause was mucosal perforation (n = 4) followed by obesity (n = 2) and bleeding from the liver (n = 2). Four cases of reoperation were reported. Three were for persistent dysphagia. One patient required repeat myotomy, one underwent esophagectomy and the other had a fundoplication takedown. One remaining patient underwent reoperation for postoperative bleeding. No deaths were reported.

Thoracoscopic myotomy is less commonly performed (see Table III). There are currently four publications on this topic and no long-term follow-up. Generally a concomitant fundoplication was not added and the gastric myotomy was short. The overall favorable outcome was 86%. The incidence of postoperative reflux documented by pH monitoring was 53.3% in 15 patients.

Symptom results of minimally invasive surgery are summarized in Table V. Despite short-term follow-up and a small population of patients, both thoracoscopic and laparoscopic myotomy showed satisfactory results. No conclusions concerning comparison of these techniques can be drawn at this time. Longer follow-up and more patient procedures are required.

DISCUSSION

Although statistical analysis of the referenced articles was avoided, patients undergoing myotomy without fundoplication were more likely to experience GERD postoperatively. However, the results varied from one institution to another. The type of fundoplication remains controversial. In fact, transabdominal partial and total fundoplications combined with myotomy have similar outcomes, both symptomatically and by pH monitoring. The Belsey-Mark IV procedure showed slightly inferior results. A comparison between the Toupet and Dor procedures could not be made in this investigation because of the small number of Toupet procedures.

The extent of gastric myotomy did not influence results as much as the presence or absence of a concomitant fundoplication. In patients who did not undergo fundoplication, a long myotomy clearly produced a higher incidence of postoperative gastroesophageal reflux. Results were consistently satisfactory when fundoplication was used regardless of the extent of gastric myotomy. There is, however, a question about accuracy of measurement as the distal extent of the lower esophageal sphincter is often difficult to localize. Identification of the GEJ is performed in various ways. Some identify the GEJ by observing a change from circular to oblique muscle orientation,* an increase in venous bleeding,[8] or a change in the fat pad position.[36] The completeness of myotomy can be assessed by several innovative methods. An intraesophageal balloon may be used to stretch the esopha-

*References 8, 34-36, 39, 43-45, 50, 51.

geal and gastric walls and thereby identify remaining circular muscle fibers for division.[34,44,51] Intraoperative esophagoscopy is widely used for determination of length and depth of myotomy.* Some surgeons use intraoperative manometry to determine myotomy adequacy.[15,43,52,53] Findings suggest that a greater curvature myotomy probably can be shorter than one placed on the lesser curvature side of the GEJ. If unequivocal criteria to identify the GEJ can be established, the extent of gastric myotomy can be more accurately studied. Agreement on the correct radial orientation of the myotomy would be helpful as well.

Surgical approach influenced the results. If a concomitant fundoplication was not used, transthoracic myotomy achieved better postoperative symptom results than transabdominal myotomy. There is evidence that the incidence of reflux after myotomy is higher for the transabdominal approach than for transthoracic myotomy.[54] This is presumably due to the increased dissection in the hiatal region required for the transabdominal operation. The phrenoesophageal ligament, which acts as an anchor for the lower esophageal sphincter mechanism, is more completely divided transabdominally.

The results of this literature review show that laparoscopic Heller myotomy for achalasia has a high percentage of favorable results. Resolution of symptoms is common probably because laparoscopic procedures offer excellent visualization of the esophageal wall, which assists the surgeon in performing a complete myotomy.[40,55] Microperforations are easily detected intraoperatively, and thus perioperative morbidity is low. Laparoscopic Heller myotomy is preferred over open transabdominal and thoracic myotomy because of the reduction in pain and recovery time. Long-term follow-up, however, is required before one can conclusively state that the laparoscopic repair is superior. Although thoracoscopic Heller myotomy showed favorable postoperative symptom results, follow-up has been short. The high incidence of postoperative positive pH monitoring scores may be misleading because patients experiencing postoperative symptoms were more likely to be selected for pH testing. In addition, the number of patients tested was small.

Ellis[17] has reported that 93% of patients undergoing transthoracic short esophagomyotomy without an antireflux procedure showed improvement, whereas others reported unsatisfactory results.[16,21,24] This may very well reflect experience and specifically the ability to accurately localize the distal extent of the lower esophageal sphincter. Surgeons have suggested that the Toupet fundoplication is effective because it helps keep the edges of the myotomy apart.[3,45] Swanstrom and Pennings[45] have presented excellent results of Heller myotomy with the Toupet fundoplication. However, a recent report from the same group has shown that there is a high incidence of recurrent GERD after laparoscopic Toupet fundoplication for patients with GERD.[56] Presumably the 270-degree fundoplication partially disrupted with time. Patients with a concomitant Nissen fundoplication had favorable results in the present investigation.

A concomitant Nissen fundoplication does require extra care, since unlike most GERD patients those with achalasia do not have esophageal motility. In fact, Topart et al.[57] reported recurrent dysphagia in 14 of 17 achalasia patients who underwent myotomy with a short Nissen fundoplication. However, Del Genio et al.[15] reported excellent results for a Nissen-Rossetti fundoplication with the use of intraoperative manometry. Initially they found that a normally calibrated fundoplication resulted in a high incidence of GER. Experience with this modality has led to the highest success rate reported. Donahue et al.[16] also have reported success with the "floppy" Nissen fundoplication in conjunction with a transabdominal myotomy.

Unfortunately, pH monitoring is not universally accepted as an accurate measurement of acid reflux in the postoperative myotomy patient. Esophageal motility is always impaired; therefore the length of reflux episodes may be misleading and with stasis of the distal esophagus food fermentation may lead to falsely high pH results. In addition, pH monitoring is not always associated with symptoms (patients with a high pH can be asymptomatic).[14,45] However, postoperative pH monitoring provided similar results to symptomatology in this review. Postoperative reflux may cause esophageal stricture, which is a devastating result and often leads to esophagectomy. Although considered controversial by some, pH monitoring does provide objectivity for the follow-up of patients who undergo myotomy.

Malthaner et el.[58] and Ellis[17] have reported that favorable results after myotomy tend to be inversely proportional to the length of follow-up. This clearly is the reason for the superior results associated with thoracoscopic myotomy vs. open myotomy. Therefore comparisons between the two operations are meaningless until long-term follow-up results are available.

CONCLUSION

Postoperative results were superior for myotomy with a concomitant fundoplication. The type of fundoplication had little influence on results. The length of gastric myotomy extension was important only if a fundoplication was not used. If a fundoplication is not employed, a transthoracic myotomy provides better

*References 15, 34, 38, 39, 42, 44, 46, 50, 51.

symptom control than the transabdominal operation. Further study is necessary for evaluation regarding the type of fundoplication and the extent of gastric myotomy. Minimally invasive surgery has shown satisfactory results at early follow-up. To determine the true efficacy of minimally invasive Heller myotomy, more patients and long-term follow-up are needed.

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Clinical Presentation and Evaluation of Malignant Pseudoachalasia

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Malignant pseudoachalasia can be indistinguishable from primary achalasia on routine clinical evaluation, often resulting in a delay in diagnosis. To better define the clinical features and appropriate management of this disease, the course of five patients discovered to have pseudoachalasia after being referred for a minimally invasive Heller myotomy was reviewed, as were 67 cases of pseudoachalasia previously reported in the literature. Patients with an occult malignancy tended to present with shorter durations of symptoms, greater weight loss, and at a more advanced age than patients with primary achalasia. Since contrast radiography and endoscopy frequently failed to differentiate these two diseases, persons with presumed achalasia meeting these criteria who are referred for minimally invasive surgery should undergo additional imaging to rule out an occult malignancy, since this condition cannot be reliably detected during the course of a thoracoscopic or laparoscopic esophagomyotomy. (J GASTROINTEST SURG 1999;3:456-461.)

KEY WORDS: Achalasia, pseudoachalasia, esophagus, adenocarcinoma

Primary achalasia is an idiopathic motility disorder of the esophagus characterized by aperistalsis of the esophageal body and incomplete or absent relaxation of the lower esophageal sphincter (LES) with swallowing. Pseudoachalasia occurs when a neoplasm involving the gastroesophageal junction leads to dysphagia, not through simple luminal obstruction but by rendering the LES nonfunctional in a fashion that manometrically mimics primary achalasia. The clinical presentation can be identical to that of idiopathic achalasia, often resulting in a substantial delay in diagnosis.

In the course of establishing minimally invasive esophagomyotomy as a treatment modality for achalasia at our institutions, five patients referred for such surgery were found instead to have pseudoachalasia. Four of these five patients underwent surgery with the initial intention of performing a Heller myotomy, demonstrating the difficulty often encountered in making an accurate diagnosis in these instances. To better define the distinguishing features and appropriate management of this disease, the clinical course of these five patients and all previously reported cases of achalasia due to cancer were reviewed and compared to a population undergoing a laparoscopic or thoracoscopic Heller myotomy for true achalasia.

METHODS

All five patients with pseudoachalasia were initially referred to one of two surgeons (C.A.P. or M.G.P.) for the purpose of undergoing a minimally invasive esophagomyotomy, and were ultimately found to have dysphagia on the basis of biopsy-proved tumor involvement of the gastroesophageal junction. Information on these patients was obtained through review of pertinent medical records, studies, and pathologic specimens.

All prior cases of pseudoachalasia due to malignancy reported in the English literature were reviewed. Reports were excluded when there was no documented anatomic involvement of the gastroesophageal junction with tumor, or when dysphagia was clearly due to simple obstruction and not LES dysfunction. Sixty-seven prior cases were ultimately included for review.[1-30] Analysis of each report in-

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cluded patient age, degree of weight loss, duration of symptoms, length of delay in diagnosis when applicable, tissue type of the culprit tumor, and the results of endoscopy, contrast imaging, and manometry. The records of 61 consecutive patients undergoing a minimally invasive Heller myotomy for achalasia at the University of Washington Medical Center from January 1994 to February 1998 were reviewed to determine each patient's age, duration of symptoms, and degree of weight loss. These patients were presumed to have primary achalasia based on postoperative follow-up ranging from 4 to 52 months. Records were unavailable for one person. Statistical comparisons between these patients and those with pseudoachalasia were performed using a two-tailed Student's *t* test.

RESULTS

Routine evaluation of patients referred for esophagomyotomy generally includes barium contrast radiography, manometry, and fiberoptic endoscopy, but none of these tests are uniformly effective in detecting subtle neoplasms causing pseudoachalasia. All five patients in the present series underwent barium contrast studies, and in no instance were the results of these studies suggestive of malignancy. Three patients had a classic "bird beak" esophagus on barium contrast studies (Fig. 1), whereas the other two patients had only mild esophageal dilation. When combined with the results from prior reports, only 12 (17%) of 70 patients had examinations suggestive of cancer. Moderate-to-severe esophageal dilation was observed in 70% of studies.

As might be expected, esophageal manometry was insensitive in detecting cancer and was deceptively suggestive of primary achalasia. All patients in the present series had an absence of peristalsis on esophageal manometry, and four of the five patients had incomplete or absent relaxation of the LES with swallowing. In one patient, limited tolerance to the examination precluded evaluation of the LES. When combined with the results from prior reports, peristalsis was absent in the 50 patients in whom it was studied, and incomplete relaxation of the LES was observed in all but one of the 49 patients in whom it was evaluated.

Upper gastrointestinal endoscopy was surprisingly insensitive to gastroesophageal tumors. All five patients in the present series underwent preoperative upper endoscopic examination with biopsies, and the findings were not suspicious for malignancy based either on the visualization of irregular mucosa or a positive tissue biopsy. When combined with the results from prior reports, only 32 of 72 initial upper endoscopies were suggestive of cancer based on these same criteria. Twelve additional patients had the diagnosis of cancer made on a subsequent endoscopic examination. Of the remaining 28 patients who had persistently nondiagnostic endoscopy, 10 patients were noted to have significant resistance to the endoscope at the gastroesophageal junction, either precluding passage entirely or requiring dilation or a pediatric endoscope to traverse the LES.

The difficulty in distinguishing pseudoachalasia from primary achalasia led to four of the five patients in our series being taken to the operating room for a planned esophageal myotomy. In two patients the diagnosis of a primary gastroesophageal "junctional" adenocarcinoma was made during the course of the surgery, based on intraoperative endoscopic and laparoscopic observation and biopsies prompted by the finding of induration at the gastroesophageal junction. Both patients underwent open resection of their tumors instead of a myotomy. In two other patients remote histories of resected adenocarcinoma of the breast in one and of resected cholangiocarcinoma in the other raised the suspicion of pseudoachalasia. In both cases findings suggestive of malignancy were

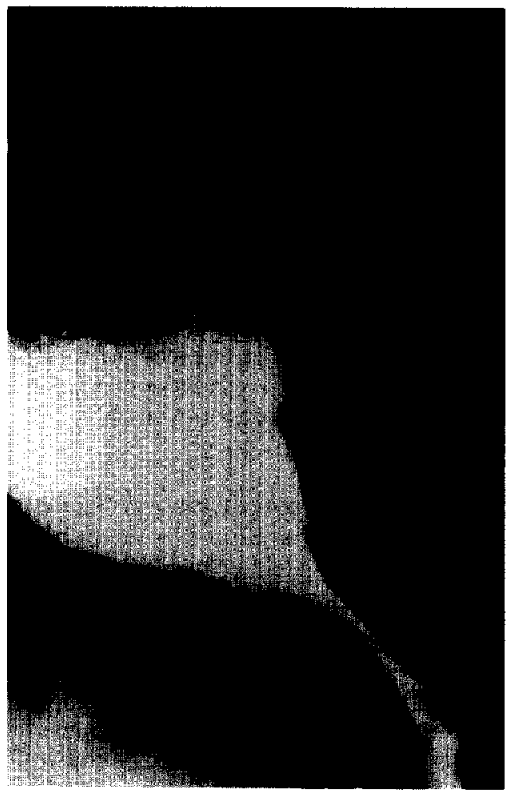

Fig. 1. Despite the classic findings of a dilated esophagus tapering to a narrow but smooth gastroesophageal junction suggestive of achalasia, this patient had a primary adenocarcinoma of the esophagus.

Fig. 2. Endoscopic ultrasonography revealed a submucosal tumor of the gastroesophageal junction in this patient, whose presentation was otherwise suggestive of primary achalasia. The tumor is seen as a large echolucent area extending from the 4-o'clock to 6-o'clock position. The lesion was not seen on several prior endoscopic examinations.

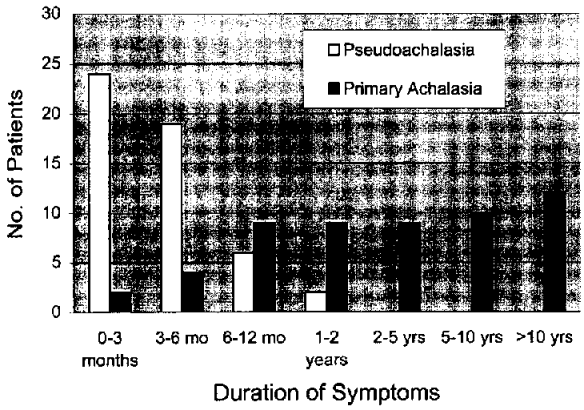

Fig. 3. Comparison of the duration of symptoms in patients with primary achalasia vs. malignant pseudoachalasia. (Studies in which this variable was not reported or was reported only as a mean for multiple patients were excluded.)

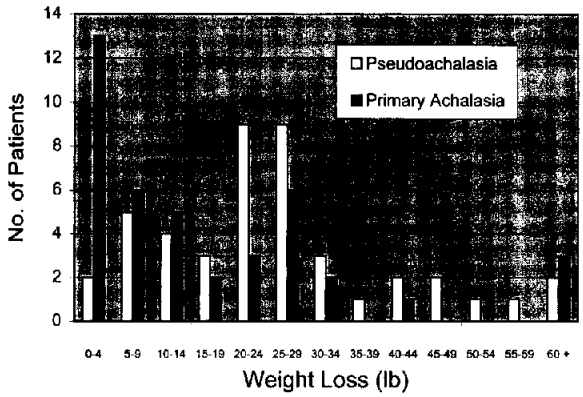

Fig. 4. Comparison of the degree of weight loss in patients with primary achalasia vs. malignant pseudoachalasia. (Studies in which this variable was not reported or was reported only as a mean for multiple patients were excluded.)

identified involving the gastroesophageal junction and diaphragm, but frozen-section examination of intraoperatively biopsied specimens revealed only benign tissue, and so esophageal myotomies were performed. The correct diagnosis was subsequently made on review of permanent histologic sections in one patient and on laparoscopy in the other patient, performed 1 month postoperatively when she presented with recurrent dysphagia. In both instances, biopsies of the gastroesophageal junction revealed metastatic adenocarcinoma.

Only one person with pseudoachalasia in the present series was identified preoperatively. The suspicion of tumor was raised because of a combination of clinical features including the patient's advanced age, substantial weight loss, brevity of symptoms, and a history of ovarian cancer resected 19 years previously. An endoscopic ultrasound examination was therefore performed and revealed a 2 cm submucosal mass of the distal esophagus (Fig. 2), which was subsequently confirmed on CT scan. The patient underwent enucleation of a leiomyoma with resolution of her symptoms.

Our general failure to make an accurate diagnosis preoperatively mirrors the previously reported experience with this disease. When the present series is combined with prior reports, 25 (35%) of 72 patients suffered a delay in diagnosis of their neoplasms of

Table I. Mean age, duration of symptoms, and weight loss in patients with primary achalasia and malignant pseudoachalasia

	Age (yr)	Duration of symptoms (mo)	Weight loss (pounds)
Pseudoachalasia (series)*	74	6.8	27.8
Pseudoachalasia (combined)†	64	5.1	25.2 (n = 65)
Primary achalasia‡	45	85.5 (n = 56)	18.1 (n = 44)
P value§	>0.001	>0.001	0.09

*Refers to patients in the current series only (n = 5).
†Refers to current series and all prior reports of pseudoachalasia (n = 72, except as noted).
‡Refers to patients undergoing minimally invasive esophagomyotomy (n = 60, except as noted).
§Two-tailed Student's *t* test.

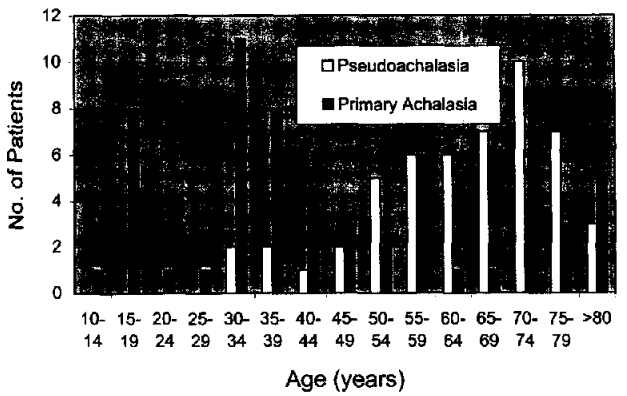

Fig. 5. Comparison of age in patients with primary achalasia vs. malignant pseudoachalasia. (Studies in which this variable was not reported or was reported only as a mean for multiple patients were excluded.)

more than 1 month. Forty-six patients suffered no such delay, and in one patient a clear determination could not be made.

To help clinicians make this often difficult diagnosis, the clinical parameters of advanced age, a short duration of symptoms, and significant weight loss have been historically advanced as suggestive of pseudoachalasia.[22,29] Findings consistent with this assertion were noted in comparing all patients with primary achalasia who underwent a minimally invasive Heller myotomy at the University of Washington to patients with pseudoachalasia (Table I). Duration of symptoms was a highly discriminatory variable, as pseudoachalasia generally presented within 6 months of onset, and primary achalasia rarely presented within that time frame (Fig. 3). Similarly, weight loss in excess of 35 pounds was highly suggestive of pseudoachalasia (Fig. 4). The broad and unpredictable distribution of ages in our primary achalasia cohort rendered this variable less helpful, except to note that pseudoachalasia is uncommon in patients less than 40 years of age (Fig. 5).

Table II. Culprit neoplasms in 67 previously reported cases of malignant pseudoachalasia

Diagnosis	No. of patients
Neoplasms of primary gastroesophageal origin	
Adenocarcinoma	47
Squamous cell carcinoma	5
Esophageal sarcoma	1
Gastric lymphoma	1
Neoplasms of nongastroesophageal origin	
Mesothelioma	5
Metastatic disease	4
Local extension from other primary malignancy	4

The predominance of primary adenocarcinoma as the culprit tumor in the present series reflects the results from prior studies. Adenocarcinoma of the gastroesophageal junction was the most frequent diagnosis among these patients, accounting for two thirds of all diagnoses (Table II). Potentially extramucosal tumors, such as sarcomas, mesotheliomas, and metastases, were also well represented.

DISCUSSION

In our experience and that of most others, secondary achalasia due to tumor infiltration of the gastroesophageal junction is easily confused with primary achalasia. Since the prevalence of pseudoachalasia ranges from 2.4% to 4.0% of the prevalence of primary achalasia,[12,22,23,31] it is a disease which most centers with an interest in esophageal function are likely to encounter, the incidence of which may increase with the rising incidence of adenocarcinoma of the gastroesophageal junction.[32] Reliance on manometry, contrast radiography, and endoscopy to detect all patients with malignant achalasia is naive. Previous reports suggest that one third of patients who have secondary achalasia due to cancer will suffer a delay in diagnosis because of the occult nature of these malignancies. Four of five patients in our own series were taken to the operating room for a Heller myotomy, suggesting that experience with this disorder does not confer immunity against its misdiagnosis.

The failure of the initial endoscopic examination to detect the culprit malignancies in so many patients with pseudoachalasia is striking, and may be due to

the types of cancers involved. Adenocarcinoma of the gastroesophageal junction, the most frequent diagnosis among all patients, often demonstrates a diffuse morphology, in which a well-defined tumor mass and mucosal ulceration are lacking.[33] Such tumors can involve the muscularis propria and the associated myenteric plexus, while evading endoscopic visualization. Nonmucosal tumors such as mesotheliomas, sarcomas, and metastases can clearly behave similarly.

Although the standard evaluation of patients thought to have achalasia will often fail to detect an occult cancer, a comparison between a historical cohort of patients with pseudoachalasia and one undergoing a Heller myotomy for true achalasia suggests that the suspicion of an unseen tumor can be raised by the clinical criteria of advanced age, significant weight loss, and a short duration of symptoms. Although patients undergoing a myotomy represent a subset of all patients with true achalasia, both the mean value and the distribution of patient age and weight loss in our control population were consistent with previously reported figures.[12,22,23,31,34-39] The average duration of symptoms in our patients with true achalasia (7 years) was substantially longer than the generally reported 2- to 5-year average,[34,35,38,39] although even these shorter periods are still markedly greater than those intervals seen in pseudoachalasia.

In addition to advanced age, short duration of symptoms, and significant weight loss, a history of malignancy or an unusually poor response to endoscopic modes of treatment are also consistent with the diagnosis of malignant pseudoachalasia. Also, in primary achalasia, the flexible endoscope should traverse the gastroesophageal junction with minimal pressure. Its failure to do so is highly suggestive of a cancer, regardless of whether abnormal mucosa is visualized or neoplastic tissue is obtained on biopsy. When the clinical presentation hints at malignancy that cannot be substantiated by routine evaluation, we advise endoscopic ultrasonography. Its efficacy in the local staging of esophageal cancer suggests a high sensitivity in detecting anatomic abnormalities of the esophageal and proximal gastric walls. Although CT scanning could play a similar role, it is not as accurate as endoscopic ultrasonography in determining the depth of esophageal tumors and so presumably would be less effective in detecting the presence of occult lesions.[40] It could be helpful, however, in demonstrating large extrinsic lesions or signs suggestive of widespread intra-abdominal or intrapleural tumor dissemination.

The need for accurate diagnosis in these patients cannot be overemphasized. When misdiagnosed with simple achalasia, these persons will eventually fail to respond to endoscopic modes of treatment and will be referred for esophagomyotomy. If the evolution of the minimally invasive approach to this operation parallels that of antireflux surgery, it will over the coming years supplant its open counterpart. However, our experience suggests that the inability to directly palpate induration and tumor bulk during such an operation will on occasion prevent accurate diagnosis of subtle malignancies, even when supplemented by intraoperative endoscopy and the liberal taking of biopsy specimens. Even if the correct diagnosis is made during surgery, immediate resection denies the patient a thoughtful and complete oncologic workup and precludes the increasingly popular administration of neoadjuvant therapy.[41]

CONCLUSION

Achalasia due to tumor involvement of the gastroesophageal junction can be very difficult to distinguish from primary achalasia on routine evaluation, often leading to a delay in diagnosis. Older patients who present with significant weight loss and a short duration of symptoms should be imaged with endoscopic ultrasonography to detect occult tumors of the gastroesophageal junction. Because of the difficulty in assessing these malignancies during minimally invasive surgery, preoperative diagnosis is of paramount importance.

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Serial Endoscopic Ultrasound in the Assessment of Response to Chemoradiotherapy for Carcinoma of the Esophagus

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The aim of the study was to assess whether endoscopic ultrasound (EUS) could accurately measure the locoregional response to chemoradiotherapy in patients with carcinoma of the esophagus. Seventeen patients with esophageal carcinoma underwent EUS examination before and on completion of chemoradiotherapy. The EUS findings were correlated with the results of histologic examination of the esophagectomy specimen. The accuracy of EUS in these patients was compared with the accuracy of EUS in a control group of 17 patients treated by surgery alone. In 16 of 17 patients EUS-determined tumor (T) stage was unchanged following treatment and in one patient there was T-stage progression. No patient demonstrated downstaging of the primary tumor according to classical EUS criteria. In 10 of 17 patients a reduction in maximum tumor depth of ≥2 mm was observed (range 2 to 18 mm). Histologic examination revealed that four patients with squamous cell carcinoma had experienced a complete pathologic response. These four patients had significantly lower posttreatment EUS tumor depths compared to patients without a complete response (5.0 vs. 9.0 mm; $P < 0.05$). Based on the post-treatment EUS examination, the accuracy was 59% for T stage and 59% for node (N) stage. The accuracy of EUS in patients treated by surgery alone was 94% for T stage and 94% for N stage, indicating a significant reduction in the accuracy of EUS in patients following chemoradiotherapy ($P < 0.05$). The accuracy of EUS examination in patients with carcinoma of the esophagus treated by chemoradiotherapy was poor. EUS did not detect downstaging of the primary tumor, even in the presence of a complete pathologic response. EUS assessment of maximum tumor depth was a better measure of response to therapy. (J GASTROINTEST SURG 1999;3:462-467.)

KEY WORDS: Endosonography, esophageal neoplasms, neoadjuvant therapy, radiotherapy

Recent evidence indicates that neoadjuvant therapy may confer a survival advantage to patients with esophageal carcinoma.[1-3] This has been demonstrated for patients with squamous cell carcinoma in uncontrolled prospective studies from Australia[2,3] and for those with adenocarcinoma in a randomized controlled trial from Ireland.[1] As a consequence, some centers now administer neoadjuvant therapy to patients with potentially resectable esophageal carcinoma. Few reported studies[4-7] have used endoscopic ultrasound (EUS), which is widely accepted as the optimal method for the evaluation of locoregional disease in esophageal cancer,[8] as a means of assessing response to treatment. In the current study we evaluated the accuracy of the assessment of locoregional response to chemoradiotherapy for carcinoma of the esophagus employing EUS as the primary imaging modality.

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PATIENTS AND METHODS

Over a 2-year period (May 1996 to April 1998), 17 patients (10 males and 7 females) receiving neoadjuvant therapy for T2-T3 N1 or T3 N0 esophageal carcinoma (American Joint Committee on Cancer/International Union Against Cancer classification[9]) underwent serial EUS assessment. The median age of the patients was 60 years (range 47 to 72 years). Histologic diagnosis was adenocarcinoma in 10 patients and squamous cell carcinoma in seven. Patients with systemic metastases identified on chest radiography or on computerized tomography of the thorax and abdomen were excluded. The first EUS assessment was performed the week before patients commenced neoadjuvant therapy and the second EUS assessment was performed within 14 days of completion of treatment.

During the same time period 17 patients with esophageal carcinoma underwent EUS staging followed by esophagectomy, but they did not receive preoperative chemoradiotherapy. These patients either had earlier stage disease (T1-T2 N0) or had requested immediate surgery. The pathology records of these patients were retrieved to determine the pTN stage in order to evaluate the accuracy of EUS in these control patients managed by surgery alone.

Symptom Assessment

Dysphagia was assessed prior to and on completion of treatment using a scoring system of 0 to 4 (Table I).

Endoscopic Ultrasound

Following administration of intravenous midazolam (5 to 10 mg), endoscopy was performed with the 9 mm Olympus P10 gastroscope (Keymed, Essex, United Kingdom), and the degree of luminal stenosis was assessed. EUS examination was undertaken with either the 13 mm Olympus UM-20 echoendoscope or the smaller 8 mm Olympus MH-908 esophagoprobe. Immediately before the introduction of the EUS scope, most patients were given 10 mg of intravenous nalbuphine.

The ultrasound examination began with an assessment of the celiac axis region, which was identified by following the splenic and hepatic arteries to their origin. The EUS probe was then withdrawn and the presence of perigastric or parahiatal nodes recorded. Finally, the primary esophageal tumor was assessed and an evaluation of the paraesophageal structures (lymph nodes, aorta, pericardium, and pleura) was made. Serial images of the primary esophageal tumor were obtained at 1 cm intervals, and the tumor depth was calculated at each level. The maximum tumor depth was recorded and its location from the incisors noted. Malignant nodes were defined by the following EUS criteria: a spherical shape, the presence of a distinct border, hypoechoic pattern, evidence of heterogeneity within the node, and a diameter of 6 mm or greater.[10,11] At least two of the coinvestigators were present at each EUS examination; the procedure was recorded on videotape and subsequently reviewed. The interpretation of the EUS findings thus represented a consensus opinion of at least two of the authors.

Table I. Dysphagia score

0 = Ability to swallow all solids unimpeded
1 = Difficulty in swallowing some hard solids such as bread or meat
2 = Ability to manage a semiliquid diet
3 = Ability to swallow liquids only
4 = Inability to swallow liquids and saliva

Chemoradiotherapy

Fourteen patients with tumor confined to the chest, that is, no infradiaphragmatic extension, received combined chemoradiotherapy. This comprised two cycles of cisplatin, 80 mg/m^2 (day 1), and continuous 5-fluorouracil infusion, 1 g/m^2/day (days 2 to 5). Radiotherapy (40 Gy) was started on day 1 of the first chemotherapy cycle and was delivered in 15 fractions over 3 weeks (days 1 to 5, 8 to 12, and 15 to 19). The second chemotherapy cycle was begun on day 28. The irradiated volume comprised the tumor and 3 cm margins proximally and distally. Radiotherapy was delivered in two phases. Phase I comprised 1866 cGy in seven fractions anteroposteriorly and posteroanteriorly. Phase II employed a three-field plan with an anterior and two posterolateral oblique fields in order to minimize radiation exposure of the spinal cord and lungs. All patients were treated on a 10 MV linear accelerator.

Three patients with adenocarcinoma and tumor extension into the cardia received chemotherapy alone. This was according to a modified Royal Marsden protocol.[12,13] This comprised four cycles of epirubicin, 50 mg/m^2, and cisplatin, 60 mg/m^2, together with a 12-week continuous infusion of 5-fluorouracil, 200 mg/m^2. The rationale for not administering radiotherapy to patients with tumor involvement of the cardia was the inability to deliver radiation uniformly because of the noncylindrical cross-section of this region.

Pathologic Findings

Esophagectomy specimens from the 17 patients who received chemoradiotherapy were examined to determine the pT and pN stages, and the presence of

a complete pathologic response was ascertained. No attempt was made to identify partial responses in the main tumor on the basis of pathologic findings. Although previous publications[14] have claimed that these responses can be identified by estimating the degree of intra- and extramural fibrosis, we do not have confidence in this. We do not believe it is possible to distinguish fibrosis that is a genuine tumor response to treatment from fibrosis that was part of the original host response to the primary tumor, or from fibrosis within non-neoplastic tissue that is induced by radiotherapy. All resected nodes were sectioned, measured, and evaluated for the presence of metastases. Because chemoradiotherapy induces lymph node atrophy, any extramural deposit greater than 3 mm in diameter, not in continuity with the main tumor mass, was also regarded as a lymph node deposit.[15]

RESULTS

Endoscopic ultrasound examination following neoadjuvant therapy showed no alteration in tumor stage for 16 patients and progression from T2 to T3 in one patient (Table II). In 11 patients EUS interpretation of the nodal staging was unchanged following chemoradiotherapy. Two patients showed progression from N0 to N1 and four patients showed regression from N1 to N0.

Table III summarizes the EUS findings and dysphagia scores before and after neoadjuvant therapy.

Table II. Comparison between endoscopic ultrasound and pathology findings

Diagnosis	Initial EUS	Final EUS	pTN	No. of nodes ≥6 mm*	No. of metastatic nodes ≥6 mm	Pathologic findings
SCC	T3 N0	T3 N0	T0 N0	2	0	Complete response
SCC	T3 N1	T3 N1	T0 N0	4	0	Complete response
SCC	T3 N1	T3 N0	T3 N0	2	0	
SCC	T3 N1	T3 N1	T0 N0	0		Complete response
SCC	T3 N1	T3 N0	T0 N0	3	0	Complete response
SCC	T3 N1	T3 N0	T3 N0	8	0	
SCC	T3 N1	T3 N1	T3 N1	5	1	Two nodes involved (17 × 12 mm and 5 × 4 mm)
AD	T2 N1	T2 N1	T1 N0	0		
AD	T2 N1	T2 N1	T2 N0	6	0	
AD	T2 N1	T3 N1	T3 N1	6	1	Single node involved (9 × 5 mm)
AD	T3 N0	T3 N0	T3 N0	0		
AD	T3 N0	T3 N1	T3 N1	0		Single node involved (1 × 1 mm)
AD	T3 N0	T3 N1	T2 N0	2	0	Extensive mural and extramural fibrosis
AD	T3 N1	T3 N0	T3 N1	3	3	Five nodes involved (3 ≥6 mm diameter)
AD	T3 N1	T3 N1	T1 N0	0		
AD	T3 N1	T3 N1	T3 N1	0		Single node involved (4 × 3 mm)
AD	T3 N1	T3 N1	T3 N1	1	1	Single node involved (6 × 6 mm)

SCC = squamous cell carcinoma; AD = adenocarcinoma; EUS = endoscopic ultrasound; pTN = pathologic stage.
*Number of nodes in resection specimens of ≥6 mm in diameter.

Table III. Comparison of endoscopic ultrasound–determined tumor depth, and length and dysphagia scores before and after neoadjuvant therapy according to tumor histology

	Before treatment	After treatment
Adenocarcinoma (n = 10)		
Depth (mm)	9.5 (8.0-20.3)	9.5 (7.5-12.5)
Length (cm)	6.5 (4.7-11.0)	6.0 (5.0-8.3)
Dysphagia score (median)	2.5	2.0*
Squamous cell carcinoma (n = 7)		
Depth (mm)	11.0 (10.0-15.0)	6.0 (4.0-8.0)†
Length (cm)	5.0 (3.0-5.0)	3.0 (2.0-6.0)
Dysphagia score (median)	2.0	1.0*

Values shown are medians and interquartile ranges.
*$P < 0.05$.
†$P = 0.06$ Wilcoxon matched-pairs test.

Patients in whom a complete pathologic response was observed had significantly reduced posttreatment tumor depths compared to patients in whom a complete response was not observed (median 5.0 mm vs. 9.0 mm; $P < 0.05$, Mann-Whitney U test) (Figs. 1 and 2).

Histologic examination of the resection specimens showed that four patients with squamous cell carcinoma had experienced a complete pathologic response (4 of 7 squamous cell carcinoma vs. 0 of 10 adenocarcinoma; $P < 0.05$, Fisher's exact test) (see Table II). Based on the final EUS examination, the accuracy for posttreatment tumor staging was 10 of 17 (59%) and for nodal staging it was 10 of 17 (59%). By comparison, the accuracy of EUS for the 17 patients who did not receive preoperative chemoradiotherapy was 16 of 17 (94%) for T stage and 16 of 17 (94%) for N stage, indicating a significant reduction in the accuracy of EUS following chemoradiotherapy ($P < 0.05$, Fisher's exact test).

Table II also shows the number of resected nodes that were 6 mm or more in diameter, irrespective of

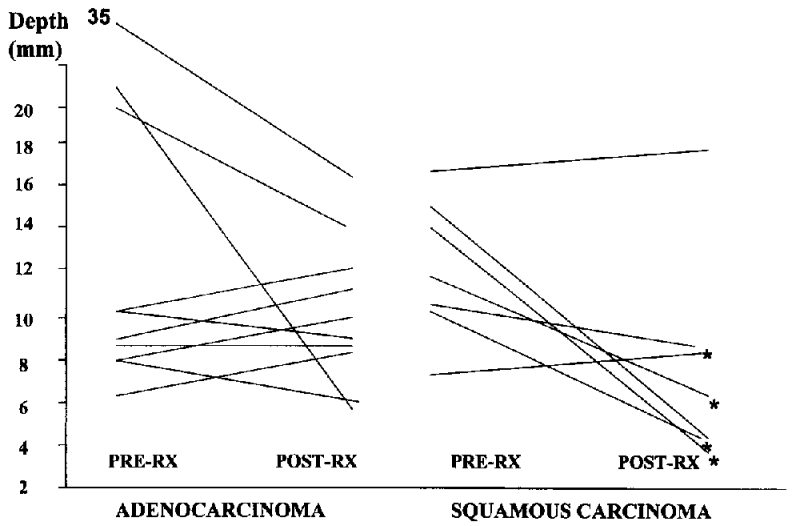

Fig. 1. Endoscopic ultrasound–determined tumor depth before *(PRE-RX)* and after *(POST-RX)* chemoradiotherapy according to tumor histology (adenocarcinoma vs. squamous cell carcinoma). * = Patients in whom a complete histologic response was observed.

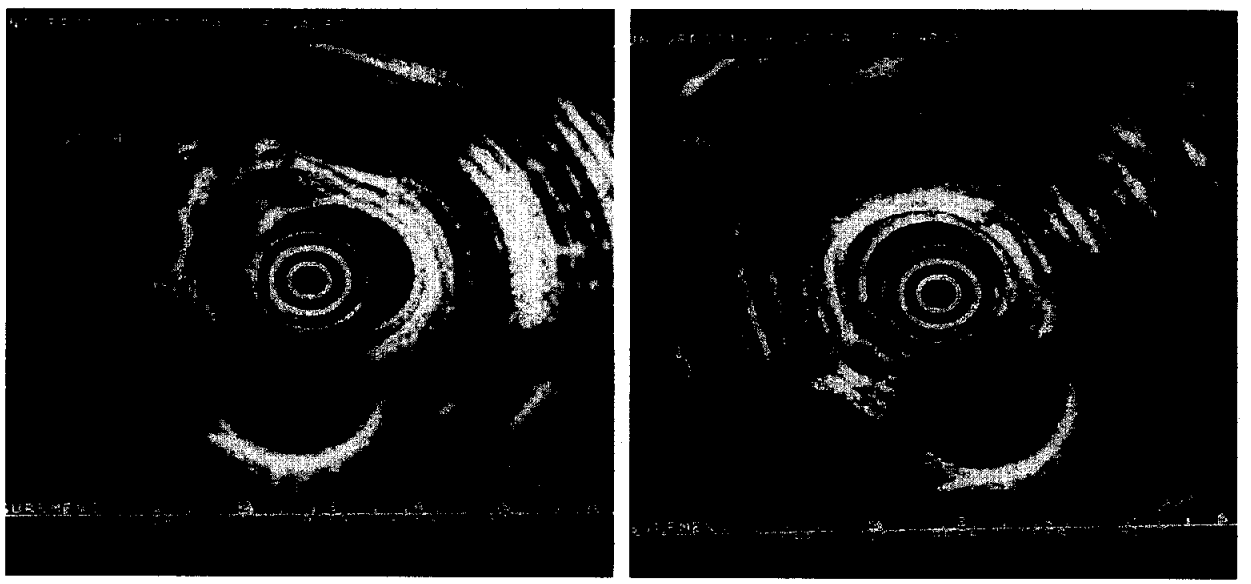

Fig. 2. Endoscopic ultrasound images from a patient with a T3 tumor. **A,** T3 hypoechoic tumor extending from the 7-o'clock to the 12-o'clock position before treatment with chemoradiotherapy. **B,** Only slight thickening of the esophageal wall without reconstitution of the normal echolayers. Examination of the esophagectomy specimen revealed a complete pathologic response.

whether or not they harbored metastases. This indicates that following chemoradiotherapy only 6 (14%) of 42 of the harvested nodes measuring 6 mm or more contained metastases.

DISCUSSION

The principal study findings were that following chemoradiotherapy the accuracy of EUS in staging locoregional disease was 59% for both T and N stage. By comparison, the accuracy of EUS for both T and N stage was 94% in the patients treated by surgery alone. These observations indicate that the accuracy of EUS is reduced in patients following chemoradiotherapy. Further, in all except one patient the EUS-determined T stage was unchanged following the course of treatment.

Patients with squamous cell carcinoma were significantly more likely to demonstrate a complete response to treatment compared to patients with adenocarcinoma. Each of the complete responders was staged T3 on posttreatment EUS examination, despite the absence of viable tumor in the esophagectomy specimens. However, these patients had significantly reduced tumor depths compared to the patients who did not show a complete response. This observation suggests that serial EUS measurement of tumor depth may be of value in the evaluation of locoregional response in patients with esophageal cancer and is worthy of further study.

The EUS-determined T stage did not show downstaging in any of the 17 patients after treatment, including the four patients in whom pathologic examination showed no residual tumor. Pathologically, in the patients with no viable tumor, the layers of the esophageal wall were not reconstituted but rather replaced by fibrous tissue. Hence it is not surprising that EUS examination showed loss of the normal wall echocharacteristics. EUS was unable to differentiate between a wall that was replaced by tumor and one that was replaced by fibrous tissue. We believe that this inevitably limits the ability of EUS to evaluate downstaging following therapy. Other investigators have failed to demonstrate any alteration in EUS-determined T staging following chemoradiotherapy.[4-7]

The accuracy of EUS for nodal disease following the administration of chemoradiotherapy was disappointing, with 7 (41%) of 17 patients staged incorrectly, suggesting that in this context the usual criteria for defining malignant nodes, including size 6 mm or greater, are inappropriate. This inaccuracy was due in part to an inability to identify metastases in small nodes outside the detection threshold of EUS and is likely to be related to atrophy of normal lymphoid tissue secondary to treatment. Additionally, in nodes retrieved from the specimen measuring 6 mm or more, metastatic deposits were identified less than 15% of the time with the remainder showing reactive changes only.

In our study, patients with squamous cell carcinoma who achieved a complete pathologic response had significantly decreased posttreatment tumor depths compared to patients in whom this response was not seen. Identification of patients who have a complete tumor response would permit the assignment of a prognosis, since these patients have been reported to have excellent 5-year survival rates, on the order of 70%.[2,3] Reduction of tumor depth as measured by posttreatment EUS would appear to be the best available method for identifying such a response. However, caution must be exercised since one of the four patients with squamous cell carcinoma and a posttreatment tumor depth of only 4 mm showed viable tumor within the resected esophagus. This implies that even in patients with an apparent complete response on EUS, surgical resection is mandatory.

Our findings are in keeping with the observations from other centers[16,17] showing a differential response according to histologic type, with squamous cell carcinoma responding more favorably than adenocarcinoma. It was disappointing that in patients with adenocarcinoma who were treated with regimens similar to those employed by Walsh et al.[1] and the Royal Marsden study,[12] we did not encounter the same frequency of complete tumor response as these other centers have reported. However, if reduction in tumor depth is an indicator of partial response, then 5 (50%) of 10 patients with adenocarcinoma would be classified in the oncologic literature as showing a partial response.

CONCLUSION

The accuracy of EUS in determining the T and N stage of esophageal cancer in patients treated with chemoradiotherapy was reduced compared to the accuracy in patients treated by surgery alone. Patients with squamous cell carcinoma were more likely to experience a complete response following therapy compared to patients with adenocarcinoma. EUS measurement of maximum tumor depth following treatment appears to be the best index of local response currently available.

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Lymph Node Micrometastases in Patients With Adenocarcinoma of the Esophagogastric Junction

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Recurrences of adenocarcinoma of the esophagogastric junction are frequent even in patients who are classified as pN0 after radical resection, suggesting that occult nodal metastases may have been missed on routine histologic examination. Immunohistochemical analysis using antibodies to cytokeratin was retrospectively performed in 1301 lymph nodes from 46 patients who underwent surgical resection for adenocarcinoma of the esophagogastric junction through a laparotomy and a right thoracotomy. Compared to routinely stained sections, the total number of metastatic lymph nodes was significantly ($P = 0.0001$) increased when both serial sectioning and anticytokeratin immunohistochemical analysis were performed. Overall 6 (33.3%) of the 18 patients previously considered N0 were recategorized as N1 for the presence of micrometastases to lesser curvature nodes. Three of these patients had recurrent disease within the first year of follow-up. Both the probability of survival or no recurrence and the disease-free survival were significantly greater in patients in whom the ratio of invaded to removed lymph nodes was less than 0.2. Anticytokeratin analysis identified occult nodal metastases in one third of our patients with adenocarcinoma of the esophagogastric junction. This modified tumor staging and had an impact on overall and disease-free survival. (J GASTROINTEST SURG 1999;3:468-476.)

KEY WORDS: Adenocarcinoma, esophagogastric junction, lymph node metastases, micrometastases, serial sections, anticytokeratin.

Lymph node status, which is usually determined by a single hematoxylin and eosin–stained section from each node, is at present the most powerful predictor of outcome in adenocarcinoma of the esophagogastric junction. Up to 77% of patients undergoing resection have metastasis to the abdominal and/or mediastinal lymph nodes, a factor that accounts for the dismal long-term survival.[1-3] It has been shown that involvement of both abdominal and mediastinal nodal compartments further decreases survival.[4] However, tumor recurrences are reported even in patients who are classified as pN0 after curative resection, suggesting that occult nodal metastases may have been missed on routine histologic examination.[5]

The aim of this study was to assess the following: (1) whether the rate of metastatic lymph nodes detected in the surgical specimen can be increased by routinely performing additional serial sectioning or immunohistochemical staining; and (2) whether the detection of micrometastases, consisting of a single carcinoma cell or a small cluster of carcinoma cells, may have some prognostic relevance.

MATERIAL AND METHODS

Patient Population

Forty-six consecutive patients with adenocarcinoma of the esophagogastric junction who underwent esophagogastric resection between April 1994 and July 1997 formed the study population. Persons older than 80 years and those with overt metastatic disease were excluded. There were 42 males and four females. The median age was 58 years (range 29 to 79 years); 16 patients were younger than 50 and 30 were older.

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According to Siewert's classification,[6] 24 tumors were type II (true cardia cancer), 19 were type I (distal esophageal), and three were type III (subcardial).

Surgical Technique

The operation was performed through a laparotomy and a right thoracotomy in all patients. The stomach was mobilized during the abdominal approach, and a stapled esophagogastric anastomosis was subsequently performed at the apex of the right chest after resection of the lesser curvature, the cardia, and the lower and middle esophagus. Lymphadenectomy included the celiac and infracarinal mediastinal nodes. Upper mediastinal nodes were routinely resected in patients with type I tumors.

Pathologic Analysis

All specimens were fixed in 10% formaldehyde solution, routinely processed, and embedded in paraffin. All of the original hematoxylin and eosin–stained sections were independently reviewed by two of us (S.F. and V.M.) to confirm tumor type according to Lauren's classification and tumor stage as outlined by the 1997 TNM classification of the International Union Against Cancer.[7] Tumors were characterized as esophageal or gastric according to the prevalent anatomic location, that is, the site where more than 50% of the tumor mass was located.

Lymph node metastases were grouped as follows, according to the classification proposed by Ishida et al.[8]: 0 = no carcinoma cells in any lymph nodes; 1 = only one discrete carcinoma cell; 2 = two or more discrete, nonaggregated carcinoma cells; 3 = in addition to discrete carcinoma cells, more than one carcinoma cell aggregation consisting of two or more cells; and 4 = metastatic tissue detectable by hematoxylin and eosin staining.

One paraffin block, representative of the tumor including the surrounding mucosa and all dissected lymph nodes, was selected from each patient. Additional serial sections, 3 μm in thickness, were collected onto slides coated with poly-L-lysine (Sigma Chemical Co., St. Louis, Mo.). One pair of adjacent slides was tested with anticytokeratins and stained with hematoxylin and eosin.

For the immunohistochemical analysis, a mixture of AE1 and AE3 monoclonal antibodies (Signet Laboratories, Inc., Dedham, Mass.) was used. A standard avidin-biotin peroxidase complex (ABC) technique was used.[9] Briefly, the slides were dewaxed, rehydrated, and microwave pretreated in citrate buffer (pH 6.1) (3 cycles of 5 minutes each at 780 W). After inhibition of the endogenous peroxidase activity with 3% hydrogen peroxide and extensive rinsing in TrIS-buffered saline (TBS), pH 7.6, the slides were subsequently incubated with 10% nonimmune human serum for 30 minutes at room temperature. After three rinsings in TBS, monoclonal antibodies AE1-AE3 (mixture of 20 μl AE-1:1 μl AE-3) were applied overnight at 4° C at 1:100 working dilution. After three rinsings in TBS, the secondary antibody (biotin-labeled antiserum against mouse IgG; Vector Labs, Burlingame, Calif.) was applied at 1:20 dilution for 50 minutes at room temperature. Finally, after three rinsings in TBS, the slides were incubated with ABC (Vector Labs) at 1:100 dilution for 50 minutes at room temperature. Monoclonal antibody/ABC mixtures were diluted with 0.05 mol/L TBS, pH 7.6.

The peroxidase activity was detected in a 0.03% 3-3′ diaminobenzidine tetrahydrochloride solution (Sigma Chemical) to which hydrogen peroxide was added. Slides were slightly counterstained with 30% Harris' hematoxylin solution. Negative controls sections were obtained by omitting the primary antibodies. Both carcinoma lesions and adjacent nonneoplastic tissues served as positive control sections. Subsequently all lymph node tissues tested for cytokeratin were examined and compared with the original hematoxylin and eosin–stained slides. The lymph nodes in which metastases were identified immunohistochemically but overlooked by the original hematoxylin and eosin staining were reevaluated to determine whether neoplastic cells were detectable in adjacent hematoxylin and eosin–stained preparations.

Statistical Methods

The prognostic relevance of the patients' baseline characteristics in terms of overall mortality or recurrence (all patients) and disease-free survival (patients with a complete resection) was assessed by means of survival analysis according to the Kaplan-Meier product limit estimate of the cumulative probability survival function.[10] We evaluated lymph node involvement on the basis of two criteria: presence or absence of nodal metastases ≤20% or >20% of involved lymph nodes. Other prognostic factors investigated included age at diagnosis, histologic grade, depth of tumor wall penetration, and clinical stage. The survival functions of the different classes of investigated variables were compared by means of the log-rank test, stratified and unstratified for histologic grade and tumor extension. It should be noted that because of the limited number of patients, only probability differences of 0.25 or greater can be demonstrated at a satisfactory level of power (0.80) by means of the log-rank test performed at a significance threshold of 0.05 (two-tailed).[11]

The percentages of positive lymph nodes determined by each of the three investigated methods (standard sections, serial sections, and immunohistochemical analysis) were compared after arc sine transformation by means of analysis of variance for repeated measures.[12] In addition, the agreement between the three procedures, pairwise considered, was assessed by means of Cohen's weighted kappa statistic.[13]

RESULTS

Surgical Outcomes

There were no deaths related to the operation itself. The overall morbidity rate was 15.2% and complications included pleural effusion in four patients, minimal anastomotic leakage (radiologic evidence only) in two, and axillary thrombophlebitis in one. As of the most recent follow-up, 23 patients were alive and disease free (median 18.5 months; range 4 to 52 months) and 23 patients had recurrent disease, 19 of whom have since died (median 12 months; range 4 to 27 months).

Pathologic Findings

The tumor measured between 1 and 3 cm in length in 18 patients, between 4 and 6 cm in 20 patients, and was longer than 7 cm in eight patients. Based on Lauren's classification, there were 38 intestinal and eight diffuse-type tumors. Staging according to the pTNM classification of the International Union Against Cancer is presented in Tables I and II for tumors considered to be esophageal (type I) and gastric (types II and III), respectively. A complete resection (R0) was achieved in 43 patients (93.5%), whereas microscopic residual tumor (R1) was left behind in three (6.5%).

Table I. Staging of 19 esophageal tumors (Siewert type I) and shifting of the pTNM classification resulting from the three investigated histologic methods

Tumor stage	pTNM classification	No. of patients		
		Standard	Serial	Anticytokeratin
I	T1N0M0	5	5	5
IIA	T2N0M0	1	1	1
	T3N0M0	4	4	3
III	T3N1M0	7	7	8
IV	Any T any N M1	2	2	2

Table II. Staging of 27 gastric tumors (Siewert types II and III) and shifting of the pTNM classification resulting from the three investigated histologic methods

Tumor stage	pTNM classification	No. of patients		
		Standard	Serial	Anticytokeratin
I	T1N0M0	1	1	1
IB	T2N0M0	3	0	0
II	T2N1M0	6	9*	8‡
	T3N0M0	3	2	1
IIIA	T2N2M0	1	1	1
	T3N1M0	4	5†	4
IIIB	T3N2M0	3	3	4§
IV	T1-T2-T3 N3 M0	2	2	2
	Any T any N M1	4	4	6‖

NOTE: All patients were moved from column 1 (Standard).
*Plus three T2N0M0 patients.
†Plus one T3N0M0 patient.
‡Plus two T2N0M0 patients.
§Plus one T3N0M0 patient.
‖Plus one T2N0M0 patient and one T3N0M0 patient.

Analysis of Lymph Nodes

A total of 1301 lymph nodes were examined, including both abdominal (n = 712 [54.7%]) and thoracic (n = 589 [45.3%]) nodes. Table III indicates the anatomic distribution of the lymph nodes. The mean number of resected lymph nodes was 28 (range 7 to 61). Table III also shows the absolute and relative frequencies of metastatic nodal involvement for the total and for each of the anatomic locations according to the three investigated histologic methods (i.e., standard hematoxylin and eosin, serial hematoxylin and eosin, and anticytokeratin). The proportion of micrometastases was similar in both intestinal and diffuse-type tumors.

Standard Sections. Twenty-eight patients (61%) had metastatic nodes, with a mean percentage of involved nodes for a single patient of 17.3% ± 20.8%. Tables I and II show the pTNM classification; eight of these individuals had only intra-abdominal metastases, three had only mediastinal metastases, and 17 had both intra-abdominal and mediastinal metastases. Eighteen patients (39%) were found to have no nodal metastases.

Serial Sections. Compared to routinely stained sections, the total number of metastatic lymph nodes increased from 199 (15.3%) to 212 (16.3%) in serial sections, with a significant ($P = 0.0001$) increase in the mean percentage of involved nodes (18.2% ± 21.0%) for a single patient. Four of the 18 patients previously considered N0 (22.2%) were recategorized as N1; two of them died after 4 and 16 months, respectively. Tables I and II indicate the shifting of the pTNM classification resulting from the new histologic analysis. One of the eight patients with nodal metastases only in the abdomen was found to also have micrometastases in the mediastinal compartment.

Anticytokeratin Immunohistochemistry. Compared to serial hematoxylin and eosin–stained sections, the total number of metastatic lymph nodes further increased from 212 (16.3%) to 255 (19.6% with anticytokeratin), with a significant ($P = 0.0001$) increase in the mean percentage of involved nodes (22.3% ± 22.7%) for a single patient. Single discrete cells were found in the marginal sinus and/or in the medullary sinus. Aggregations of carcinoma cells were found forming small nests or microtubules. In the single or clustered cells, the anticytokeratin immunoreaction was diffuse to the cytoplasm, mostly confined to the periphery (Figs. 1 and 2).

Six of the 18 patients previously classified as N0 by standard hematoxylin and eosin staining (33.3%) were recategorized as N1; three of them died after 4, 16, and 21 months of follow-up, respectively. Results of serial sectioning were confirmed by anticytokeratin analysis. In addition, two more patients considered N0 based on serial sections were recognized as N1; one of them died after 21 months of follow-up. According to the new pTNM classification of gastric tumors, one patient was shifted from N1 to N2 since immunohistochemical analysis allowed detection of seven involved nodes instead of five. Two (4.3%) of the 46 patients previously considered MX were reclassified M1 because of the detection of micrometastases in the peripancreatic nodes. Again, Tables I and II show the shifting of the pTNM classification based on the results of anticytokeratin analysis.

It is of interest that in this series, all newly diagnosed node-positive patients had metastases to lesser curvature nodes. Of the six patients with micrometastases, three showed evidence of recurrent disease within 12 months. Conversely, none of the nine patients with a minimum follow-up of 12 months after confirmed N0 classification at cytokeratin analysis had recurrent disease within a year.

Table III. Anatomic location of resected lymph nodes and prevalence of nodal metastases according to the three investigated histologic methods

Site	Resected nodes Total (%)	Nodal metastases Standard (%)	Serial (%)	Anticytokeratin (%)
Abdomen	712 (54.7)	123 (9.4)	129 (9.9)	167 (12.8)
Cardia	224 (17.2)	51 (3.9)	53 (4.1)	65 (5.0)
Lesser curvature	389 (29.9)	65 (5.0)	69 (5.3)	91 (7.0)
Celiac axis	63 (4.8)	2 (0.1)	2 (0.1)	2 (0.1)
Distant	36 (2.8)	5 (0.4)	5 (0.4)	9 (0.7)
Mediastinum	589 (45.3)	76 (5.8)	83 (6.4)	88 (6.8)
Lower	223 (17.2)	55 (4.2)	60 (4.6)	65 (5.0)
Middle	224 (17.2)	8 (0.6)	9 (0.7)	9 (0.7)
Upper	142 (10.9)	13 (1.0)	14 (1.1)	14 (1.1)
TOTALS	1301 (100)	199 (15.3)	212 (16.3)	255 (19.6)

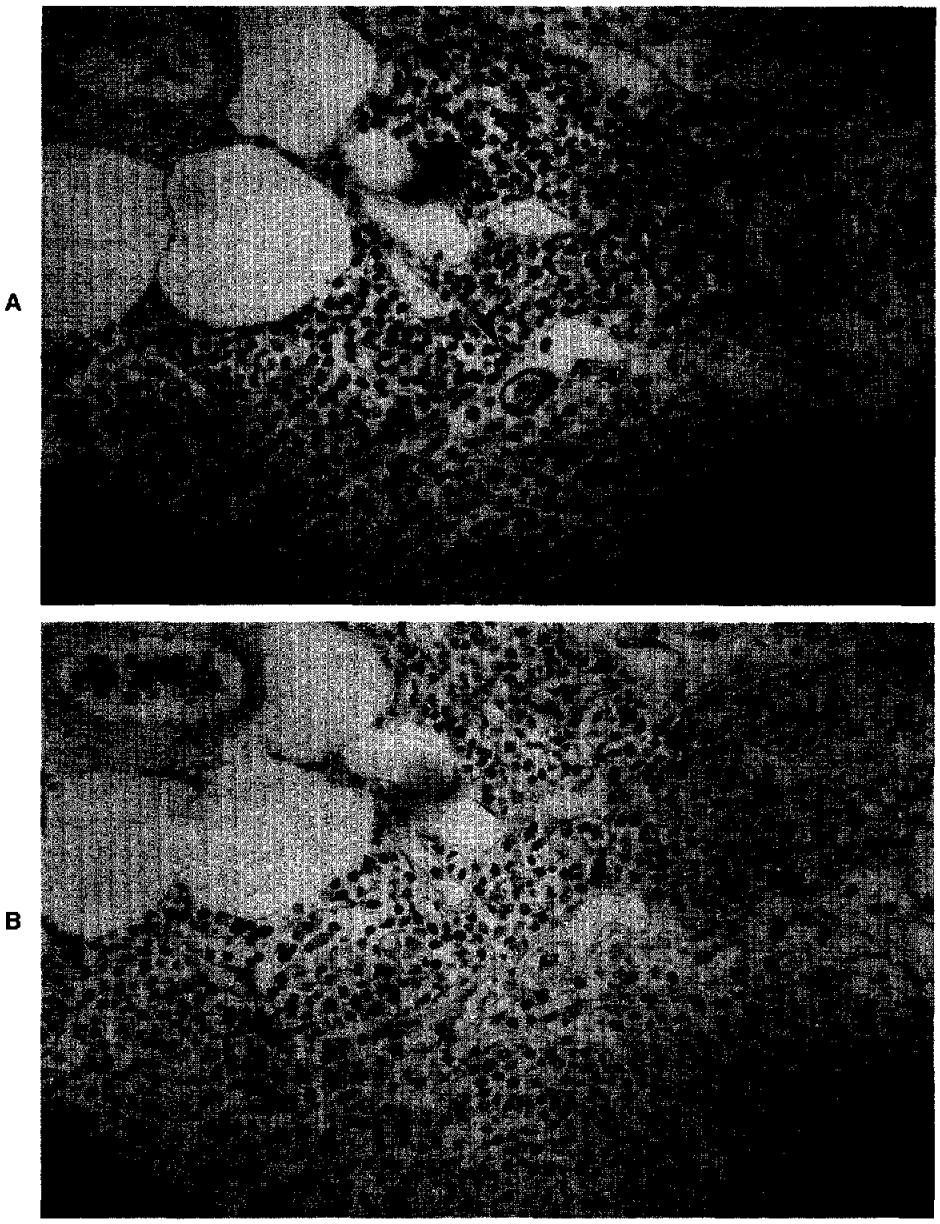

Fig. 1. A single cytokeratin-positive cell located in the medullary sinus of the lymph node (arrow) **(A)** that is not identifiable on the adjacent slide **(B).** (*A* and *B*, Hematoxylin and eosin stain; original magnification ×25.)

Analysis of Agreement

If we consider the agreement among the three methods, according to the five classes of Ishida et al.[8], we obtained a very high percentage of raw concordance (between 87% and 93.5%) and a very high value of weighted kappa statistic (between 0.845 and 0.956), particularly between standard and serial sections. However, two of the three patients classified as 1 according to serial sections (from 0 according to standard sections) died after 4 and 16 months of follow-up, respectively. Again, two out of four patients classified as 1 according to immunohistochemical analysis (changed from 0 according to standard sections) died after 4 and 21 months, respectively; in addition, one patient classified as 4 instead of 0 according to standard sections died after 16 months of follow-up. Finally, one patient classified as 0 according to serial sections and reclassified as 1 following immunohistochemical analysis died after 21 months; another patient reclassified as 4 instead of 1 died after 16 months.

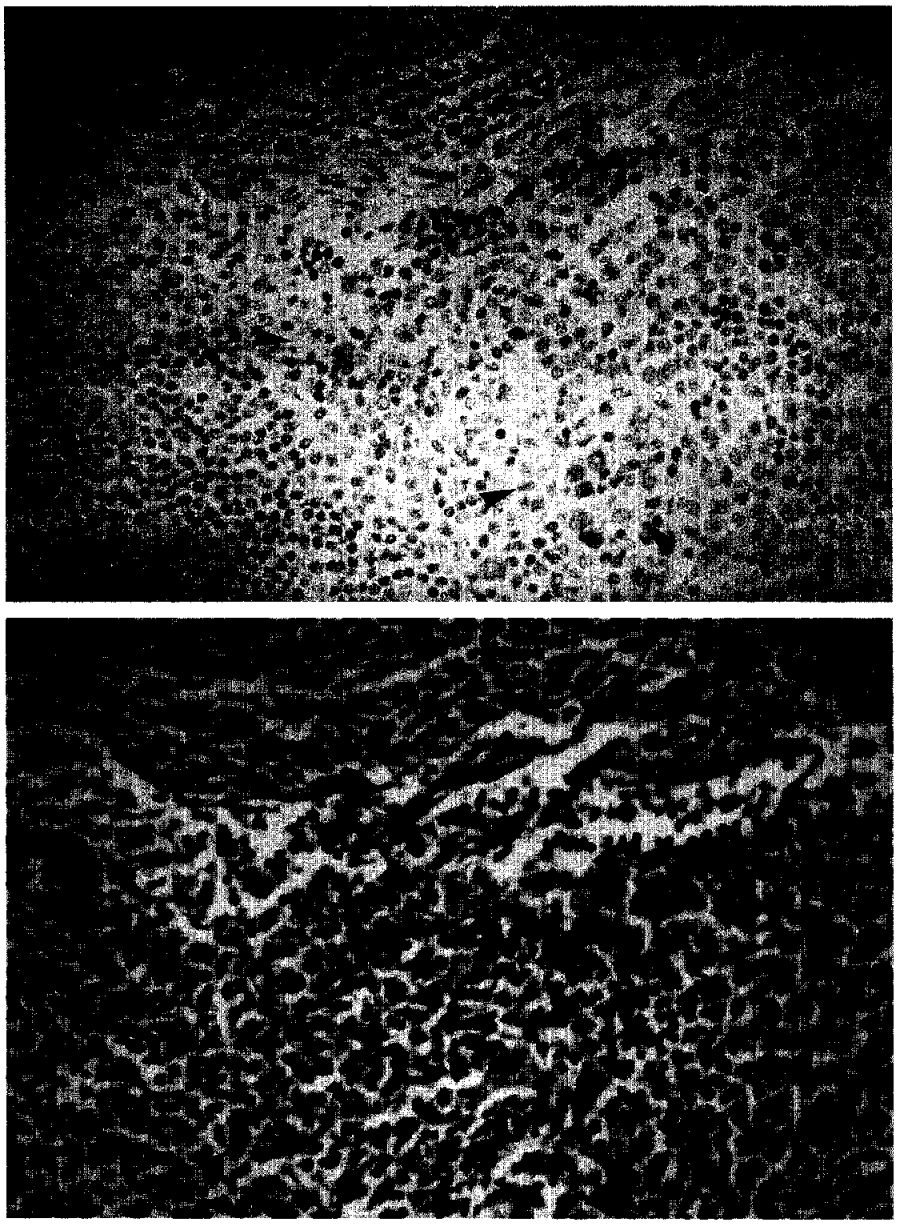

Fig. 2. Example of lymph node micrometastasis. Multiple neoplastic cytokeratin-positive cells (arrowheads) **(A)** within the lymph node parenchyma undetectable with hematoxylin and eosin stain **(B)** are shown. (*A* and *B*, Original magnification ×25.)

Analysis of Survival

Clinical Prognostic Factors. With regard to overall mortality or recurrence and disease-free survival, a nonstatistically significant prognostic value was found for patient age ($P = 0.7736$ and $P = 0.5656$, respectively), histologic grade ($P = 0.1568$ and $P = 0.2181$, respectively), and tumor stage ($P = 0.4563$ and $P = 0.5794$, respectively).

Standard Sections. The survival probability was higher in patients without nodal metastases ($P = 0.0381$). Even the disease-free survival probability was higher ($P = 0.0523$). Moreover, considering the percentage of lymph node involvement, both the probability of survival or no recurrence and the disease-free survival were significantly greater in patients in whom the ratio of invaded to removed lymph nodes was less than 20% ($P = 0.0173$ and $P = 0.0095$, respectively). Table IV shows the probability of overall survival or no recurrence with a 95% confidence interval (CI) at 36 months.

Serial Sections. The survival probability was higher in patients without nodal metastases ($P =$

0.0274). Even the disease-free survival probability was higher ($P = 0.0217$). Moreover, considering the percentage of lymph node involvement, both the probability of survival or no recurrence and the disease-free survival were significantly greater in patients in whom the ratio of invaded to removed lymph nodes was less than 20% ($P = 0.0092$ and $P = 0.0072$, respectively). Table IV shows the probability of overall survival or no recurrence with a 95% CI at 36 months.

Anticytokeratin Immunohistochemistry. The survival probability was higher in patients without nodal metastases ($P = 0.0533$). Even the disease-free survival probability was higher ($P = 0.0338$). Both the probability of survival and no recurrence and the disease-free survival were significantly greater in patients in whom the ratio of invaded to removed lymph nodes was less than 20% ($P = 0.0137$ and $P = 0.0105$). Table IV shows the probability of overall survival or no recurrence with a 95% CI at 36 months.

The impact of cytokeratin analysis on overall survival or recurrence is shown in Fig. 3. The poor prognosis of patients shown to have ≤20% of involved

Table IV. Cumulative probability of overall survival or no recurrence at 36 months by standard histologic analysis, serial sectioning, and immunohistochemistry

Variable	Standard		Serial		Anticytokeratin	
	95% CI	*P* value	95% CI	*P* value	95% CI	*P* value
% of involved nodes						
≤20%	0.48 (0.22-0.74)	0.0173	0.50 (0.22-0.78)	0.0092	0.50 (0.20-0.80)	0.0137
>20%	0.08 (0.00-0.24)		0.08 (0.00-0.24)		0.14 (0.00-0.30)	
No. of involved nodes						
0	0.50 (0.20-0.80)	0.0381	0.51 (0.15-0.87)	0.0274	0.53 (0.13-0.93)	0.0533
1 or more	0.15 (0.00-0.33)		0.16 (0.00-0.36)		0.20 (0.00-0.40)	

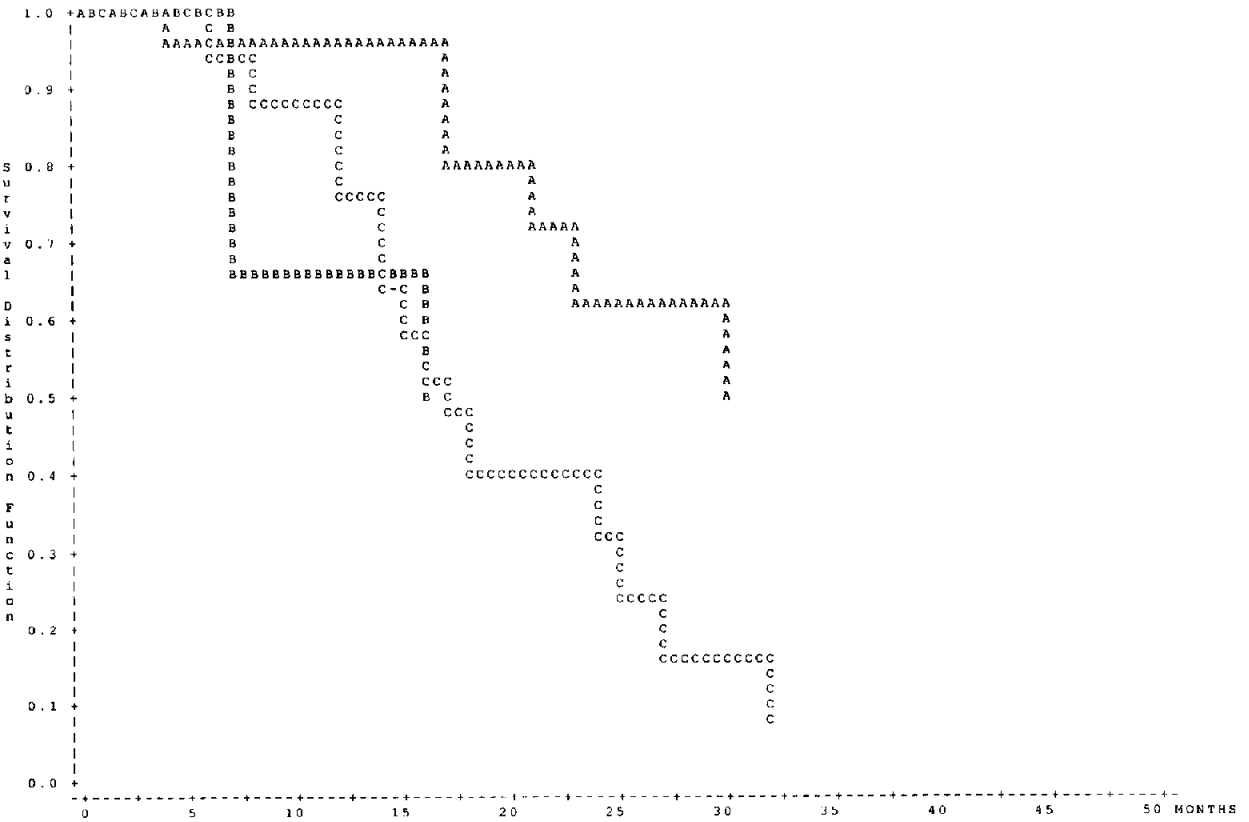

Fig. 3. Cumulative survival functions according to the percentage of lymph nodes involved (≤20% or >20%) on standard sections and anticytokeratin immunohistochemistry. (A = ≤20% for both; B = ≤20% for standard sections, >20% for anticytokeratin; C = ≥20% for both.)

nodes by standard sections and otherwise more than 20% by immunohistochemistry is evident (see Fig. 3, curve B). Indeed they have a similar survival pattern to that of patients with more than 20% of involved nodes as shown by both methods.

DISCUSSION

Surgical resection is still the mainstay of treatment for patients with adenocarcinoma of the esophagogastric junction. Long-term survival after resection depends mainly on complete local tumor removal and stage of the disease. Because nodal status is one of the single most critical factors affecting survival in these patients, extensive lymphadenectomy has been advocated to ensure removal of all metastatic nodes and to decrease the chance of regional recurrences.[3,14,15]

The results of the present study show that both the overall survival probability and the disease-free survival probability were lower in patients with nodal metastases. When the ratio of invaded to removed lymph nodes was greater than 20%, the survival probability was even lower.

This study also demonstrates the effectiveness of routine serial sections in detecting lymph node micrometastases. The addition of cytokeratin analysis further increases the diagnostic yield. Following this procedure, the nodal status changed in more than one third of our patients whose lymph nodes were judged not to be involved by tumor on routine histologic examination. In contrast to those patients confirmed to be N0 at cytokeratin analysis, all of whom were alive and disease free, half of the patients with nodal micrometastases had a recurrence of disease within a year.

Although the relatively small number of patients included in this series and the short follow-up do not allow for firm conclusions, it is evident from the present study that routine histologic examination underestimates metastases from adenocarcinoma of the esophagogastric junction. Therefore immunohistochemical analysis appears to be the procedure of choice to obtain the most accurate diagnostic assessment. From a theoretical standpoint, changes in tumor staging based on this method may aid in the selection of patients to be considered for adjuvant therapy.

The clinical relevance of micrometastases is a controversial issue. Immunohistochemical techniques have allowed the detection of occult metastases in a high percentage of patients with gastric adenocarcinoma.[5,8,16] However, it is still unclear whether the presence of individual or small clusters of tumor cells has a different prognostic impact. Siewert et al.[16] reported that the presence of three or more tumor cells in more than 10% of the lymph nodes was associated with a significantly shorter survival rate compared to the rates for other patients in the pN0 category. Ishida et al.[8] found that in patients with stage II gastric cancer, even the presence of single carcinoma cells in the nodes significantly worsened the prognosis. Izbicki et al.[17] noted a shorter relapse-free interval and a lower overall survival rate in patients with esophageal cancer and BER-EP4–positive cells in nodes free of tumor on routine histologic analysis. Although it may be true that single tumor cells can be removed by the host's immune response, it seems reasonable to advocate routine nodal dissection to diminish or eradicate residual cells with metastatic potential. The independent prognostic impact of the lymph node ratio and micrometastases supports the superiority of extended en bloc resection in patients with early disease.[18]

Despite the potential clinical value, both serial sectioning and immunohistochemistry appear to be too time consuming and expensive for routine use. In breast cancer the introduction of the sentinel lymph node biopsy holds promise for making serial sectioning and immunohistochemical analysis more cost-effective.[19] Whether a sentinel node exists in adenocarcinoma of the cardia is still open to question. Previous studies have shown that metastatic nodes from adenocarcinoma of the cardia are clustered around the lesser curvature and the lower mediastinum.[20,21] The finding that all of our patients with micrometastases had involvement of the lesser curvature nodes seems to confirm this observation and is of interest since serial sectioning and cytokeratin analysis could be restricted to this group of nodes in N0 patients.

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Asthma and Gastroesophageal Reflux: Fundoplication Decreases Need for Systemic Corticosteroids

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An association between gastroesophageal reflux (GER) and asthma has been suggested for many decades. Although antireflux therapy (medical and surgical) has been shown to be beneficial in patients with asthma, response to therapy has not been well quantified. The aim of this study was to evaluate long-term outcome in patients with asthma and associated GER undergoing fundoplication. From a database of more than 600 patients with GER treated surgically between 1991 and 1996, 39 patients with asthma as their primary indication for surgery were identified. Asthma symptom scores were determined using the National Asthma Education Program classification, and medication frequency scores were determined preoperatively and at latest follow-up (median follow-up 2.7 years). Comparisons were made using the Wilcoxon rank-sum test. Asthma symptom scores decreased significantly after antireflux surgery. More important, the medication scores for use of systemic corticosteroids decreased significantly postoperatively (2.2 preoperatively vs. 0.7 postoperatively; $P = 0.0001$). Of the nine patients who required daily oral corticosteroids, seven have discontinued treatment entirely (78%). In patients with asthma associated with GER, symptoms of asthma are improved following fundoplication. Especially important has been the ability to wean patients from systemic corticosteroids postoperatively. Fundoplication should be offered to those patients with GER-associated asthma, especially those who are steroid dependent. (J GASTROINTEST SURG 1999;3:477-482.)

KEY WORDS: Gastroesophageal reflux, GER, asthma, antireflux surgery, surgery, heartburn, reflux

An association between asthma and gastroesophageal reflux (GER) has been suggested since 1882, when Sir William Osler recommended that patients with asthma avoid eating large meals at bedtime to avoid worsening their asthma. Since that time considerable literature has accumulated substantiating this association. In fact, 33% to 90% of adult patients with asthma have clinical GER.[1] As many as 80% of patients with asthma will have abnormal intraesophageal pH studies[2-6] and approximately 40% have endoscopic evidence of esophagitis.[7] Up to 75% of asthmatic patients with GER will have improvement in pulmonary symptoms and peak inspiratory flow rates after 8 to 12 weeks of aggressive therapy with proton pump inhibitors or surgery.[8-12]

Laparoscopic antireflux surgery effectively controls GER eliminating symptoms and the need for chronic antisecretory medications in 95% of patients.[13-18] The aim of this study was to assess the clinical effectiveness of antireflux surgery (fundoplication) in patients whose primary indication for surgery is asthma associated with GER.

MATERIAL AND METHODS

Prospective data were collected on all patients undergoing operative treatment of GER. From a database of more than 600 patients with GER undergoing fundoplication between 1991 and 1996, 39 patients with asthma as the primary indication for surgery were identified. Asthma was defined according to the American Thoracic Society guidelines,[19] and all patients were referred by a pulmonologist or gastroenterologist specifically for management of

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GER-associated asthma. All patients were on a regimen of daily asthma medications and rated their asthma symptoms as severe or incapacitating despite intensive medical therapy with proton pump inhibitors and prokinetic agents. All patients had objective evidence of GER (esophagogastroduodenoscopic finding of esophagitis or abnormal acid reflux during 24-hour pH testing). Our approach for managing patients with asthma and GER is outlined in Fig. 1. GER symptom scores (heartburn, regurgitation, and dysphagia) (Table I), asthma symptom scores using the National Asthma Education Program scoring system[20] (Table II), and medication frequency scores (Table III) were determined immediately preoperatively and at latest follow-up (median 2.7 years) by examination, phone interview, or mailed questionnaire. Asthma medication was managed postoperatively by the referring pulmonologist or primary care physician.

Patients underwent either 360-degree Nissen fundoplication (n = 34) or 270-degree Toupet fundoplication (n = 5) using techniques already described.[14-16] There were no deaths and minor morbidity occurred in 20% of patients (two wound infections, one incisional hernia, and three patients with postoperative dysphagia requiring dilation).

Table I. Gastroesophageal reflux symptom scores

0	None
1	Mild but not bothersome
2	Occasionally interferes with daily activities
3	Frequently interferes with daily activities
4	Severe and incapacitating

Data were analyzed by Wilcoxon rank-sum test, exact test, and stepwise Cox regression. Results are reported as the mean. Results were considered significant if $P < 0.05$.

Table III. Medication frequency scores

0	None
1	Few times per year
2	Few times per month
3	Few times per week
4	Daily

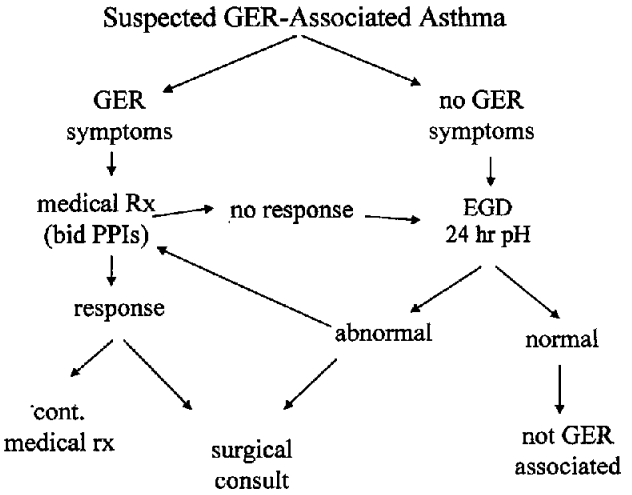

Fig. 1. Algorithm for management of patients with GER-associated asthma. GER = gastroesophageal reflux; PPIs = proton pump inhibitors; EGD = esophagogastroduodenoscopy.

Table II. Asthma symptom scores*

Score	0	1	2	3	4
Frequency of exacerbation	None	Rare	<1-2 times/wk	>1-2 times/wk Urgent treatment <3 times/yr	Daily wheezing, exacerbations frequent and often severe Urgent treatment >3 times/yr Hospitalization >2 times/yr with respiratory failure
Frequency of symptoms between exacerbations	None	Rare	Few	Cough and low-grade wheezing often present	Cough and low-grade wheezing almost always present
Degree of exercise tolerance	Excellent	Good	May not tolerate vigorous exercise	Diminished	Very poor
Nocturnal asthma	None	Rare	<1-2 times/mo	2-3 times/wk	Almost nightly
School or work attendance	N/A	Excellent	Good	Affected	Poor

*Classification of asthma by severity of symptoms as derived from the National Asthma Education Program, United States Department of Health and Human Services, Public Health Service, National Institutes of Health.[20]

RESULTS

Between 1991 and 1996, there were 39 patients who met the inclusion criteria for this study. The mean age of these 15 men and 24 women was 46 years (range 18 to 67 years). These patients experienced prolonged symptoms of asthma and GER prior to surgery with a median duration of asthma symptoms of 15 years (range 0.5 to 66 years) and GER symptoms of 8 years (range 0.5 to 47 years). In 49% of patients, symptoms of asthma preceded symptoms of GER, and in 33% of patients, GER symptoms preceded those of asthma. Eighteen percent of patients reported simultaneous onset of GER and asthma symptoms. Sixty-four percent of patients believed that there was a direct association between their reflux symptoms exacerbation of asthma, 13% thought there was no association, and 23% were unsure about any relationship.

Preoperatively all patients rated their asthma symptoms as severe and interfering with daily activities. Symptoms were frequently present and asthma exacerbations occurred several times each week. All patients were using asthma medications daily. GER symptoms were rated as severe and occasionally interfering with daily activities. All patients were taking daily proton pump inhibitors or H_2 blockers to control their GER symptoms.

At a median follow-up of 2.7 years (range 1 to 3.5 years), most asthma symptom scores decreased significantly after fundoplication (Fig. 2). Only work or school attendance showed no improvement postoperatively. Asthma medication frequency scores decreased significantly only for use of oral corticosteroids (Figs. 3 and 4). Use of oral bronchodilators decreased but did not reach statistical significance (3.0 vs. 1.1; $P = 0.054$). Of the 26 patients taking oral steroids preoperatively, 19 were able to decrease their use of steroids postoperatively, and 78% of patients taking daily oral steroids (7 of 9) were able to discontinue the use of oral steroids completely. GER symptom scores and medication frequency scores also decreased significantly postoperatively (Figs. 5 and 6).

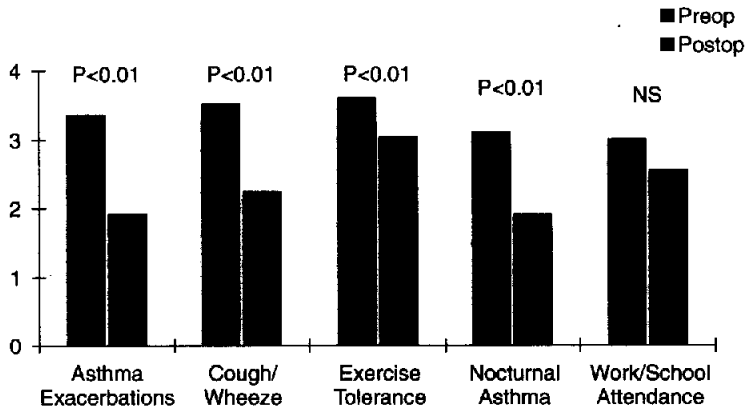

Fig. 2. Asthma symptom scores preoperatively and postoperatively. (NOTE: Scoring system derived from the National Asthma Education Program.[20] Values are means ± standard error of the mean [also applies to Figs. 3 to 6].)

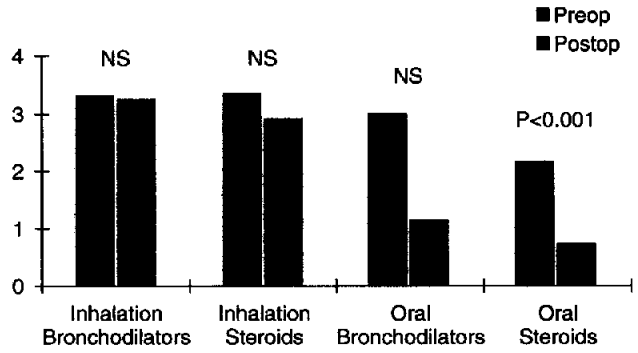

Fig. 3. Asthma medication frequency scores preoperatively and postoperatively.

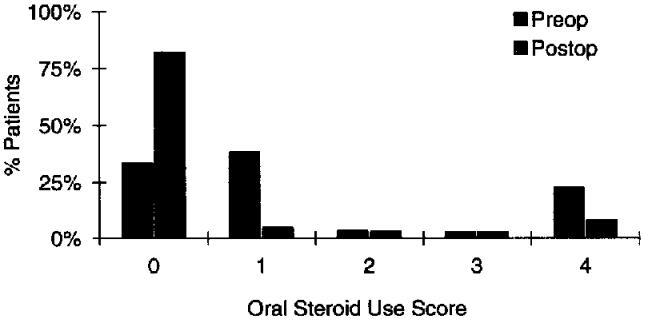

Fig. 4. Oral steroid use frequency scores preoperatively and postoperatively.

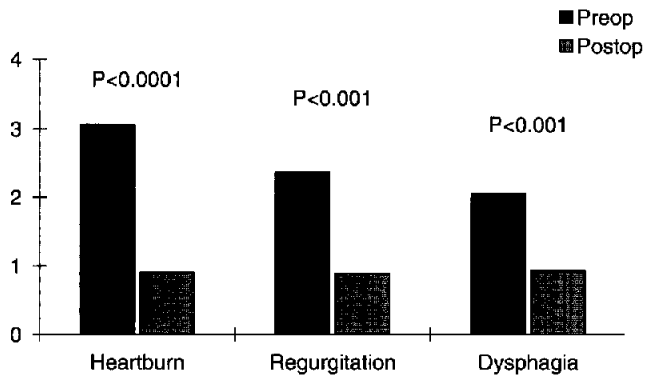

Fig. 5. Gastroesophageal reflux symptom scores preoperatively and postoperatively.

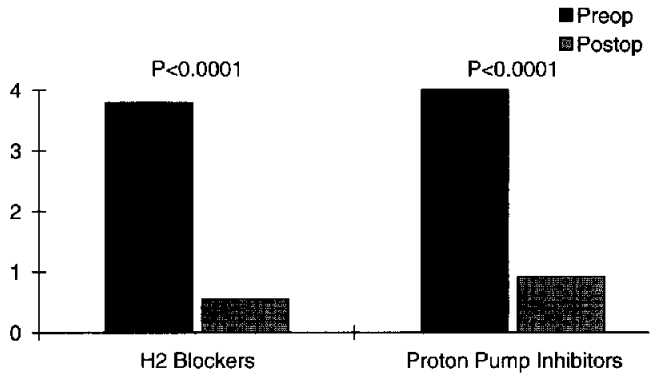

Fig. 6. Gastroesophageal reflux medication frequency scores preoperatively and postoperatively.

DISCUSSION

Nearly 20 million Americans suffer from asthma.[21] Among the many different triggers of asthma, one that is often overlooked is GER. The presence of GER in patients with asthma has been well described in both adults and children.[1,3,5,8,22-24] Up to 90% of adults with asthma will have symptomatic GER.[1] Although many patients with asthma complain of reflux symptoms, GER can be clinically silent in up to 24% of them.[25] With 40% of patients with asthma having endoscopic evidence of esophagitis[7] and nearly 80% having abnormal findings on intraesophageal 24-hour pH monitoring,[6] an association between these two conditions seems fairly clear. Despite this association, there remain gastroenterologists, pulmonologists, and surgeons who continue to overlook the potential impact of this association.

One of the reasons for this may be the absence of strong objective data documenting that treating GER will significantly improve asthma symptoms or pulmonary function in patients with GER-related asthma. Of nine clinical studies evaluating the effects of medical antireflux therapy on asthma,[8-10, 26-31] five showed improvement in pulmonary symptoms, whereas four showed no improvement despite maximal medical management of GER. Finding an objective response based on improved pulmonary function tests has been even less clear. Among these same nine studies, only three reports showed any objective improvement in pulmonary function as measured by standard pulmonary function tests. In contrast, operative treatment of GER-associated asthma has been very effective. In 10 uncontrolled studies evaluating the effect of antireflux surgery on asthma,* 66% to 100% of patients had improvement or elimination of their pulmonary symptoms postoperatively. Understanding the mechanisms by which GER may be contributing to asthma may help explain some of the differences between operative and medical management of GER-associated asthma.

Proposed mechanisms for GER-associated asthma include activation of a GER-induced vagally mediated reflex leading to bronchoconstriction, or microaspiration of gastric content with resulting airway inflammation and bronchoconstriction. Recent evidence suggests that mild esophageal acidification, even without gross esophagitis, activates reflex pathways that may aggravate or induce asthma.[37,38] Additionally, although medical management of GER neutralizes acid refluxate and promotes esophageal clearance, reflux continues, albeit a neutralized refluxate, which may still induce a neural reflex or lead to microaspiration. Only reestablishment of an effective antireflux barrier prevents reflux and thereby cures GER. It is with this in mind that we offer antireflux surgery to patients with asthma and associated GER.

In this study we identified patients whose primary indication for antireflux surgery was asthma. However, all patients had objective evidence of GER and met criteria for operative intervention based on GER alone. Ambulatory 24-hour pH monitoring in 21 patients confirmed abnormal GER. Those who did not undergo 24-hour pH testing had endoscopic evidence of GER and were treated after the time when 24-hour pH testing was always performed to confirm the diagnosis of GER. The outcome in all patients with regard to their GER symptoms and antireflux medication use parallels that of patients who have already been described following fundoplication for control of GER alone.[13-18,39]

Even though pulmonary function tests are considered important in assessing the success of asthma treatment,[19] we chose to assess the more direct clini-

*References 11, 12, 16, 23, 24, 32-36.

cal outcomes of symptom response and medication usage. Although this may be criticized for its lack of objective data, the impact that a patient's disease has on his or her symptoms and medication use is equally measurable, and the improvement in one's quality of life after treatment is vitally important. In nearly all categories of asthma symptoms, as measured by the National Asthma Education Program symptom scores,[20] fundoplication resulted in significant improvements. Only attendance at work or school was not improved following antireflux surgery. This parameter is difficult to interpret in light of the multifactorial nature of school or work attendance.

The impact of fundoplication on the use of asthma medications was less uniform but more dramatic. Most patients continued to rely on inhalation agents as they did preoperatively. Considering the long-term nature of asthma in most patients (median duration of symptoms 15 years), and the limited role a physician has in regulating these self-administered inhalation agents, this habit may be difficult to break. The changes in physician-regulated oral medication were dramatic. Although there appeared to be a decrease in the use of oral bronchodilators, this difference was not statistically significant ($P = 0.054$). Most impressive was the decrease in oral steroid use after fundoplication. Nineteen of 26 patients were able to decrease their use of oral corticosteroids, and 78% of patients who were taking oral corticosteroids daily were able to discontinue their use entirely. The more dramatic and statistically significant decrease in oral steroid use may reflect the aggressiveness of the referring physician to eliminate steroids, which are commonly thought to have more negative sequela than long-term bronchodilator use. Although we did not specifically address the impact of this decrease in oral steroid use on patients' long-term outcome or quality of life, clearly, allowing patients to decrease or stop the use of steroids and thereby avoid the long-term sequelae of chronic steroid use is extremely important.

CONCLUSION

GER-associated asthma is slowly becoming better recognized and accepted. Although medical management of GER may be effective, controlling reflux by correcting the mechanical cause of GER and reestablishing an antireflux barrier may be particularly important in asthma where small amounts of any refluxate may induce or promote bronchospasm. Fundoplication effectively decreases asthma symptoms and, more important, allows discontinuation of systemic corticosteriods in most patients with GER-associated asthma. Although the data presented herein do not specifically address the incidence of GER in patients with asthma, we believe all patients with asthma should be evaluated for GER, especially those with more severe steroid-dependent asthma. If asthma control is not complete with medical treatment of GER, or in those who wish an alternative to long-term medication dependence, surgical referral and fundoplication should be strongly considered.

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Correlations Between Esophageal Diseases and Manometric Length: A Study of 617 Patients

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The purpose of this study was to measure the length of the esophagus and assess its relationship to sex, weight, age, height, and various esophageal disorders. A retrospective analysis was undertaken of 617 esophageal manometric studies, which included 51 normal control subjects (27 males and 24 females) and 566 patients (297 males and 269 females) with esophageal disorders (50 with achalasia, 6 with diffuse esophageal spasm, 64 with strictures, 38 with nutcracker esophagus, 398 with gastroesophageal reflux disease [GERD] with positive 24-hour pH monitoring, and 66 with possible GERD but negative 24-hour pH monitoring). Manometry was performed in all of them by the station pull-through technique. The length of the esophagus was defined as the distance between the proximal end of the upper esophageal sphincter and the distal end of the lower esophageal sphincter. In the control group the mean (± standard deviation) length of the esophagus was 28.3 ± 2.41 cm. In patients with esophageal disorders the mean length of the esophagus was 28.0 ± 2.87 cm. Length of the esophagus is related to height but not to weight, sex, age, diffuse esophageal spasm, or nutcracker esophagus. Achalasia is associated with a longer esophagus, and GERD is associated with a shorter esophagus. Stricture is associated with a shorter esophagus, but this is in part due to the association between stricture and GERD. Patients with possible GERD but negative 24-hour pH monitoring have an esophageal length similar to that of GERD patients with positive 24-hour pH monitoring. Patients with GERD and stricture formation showed esophageal shortening in shorter patients. Achalasia, GERD, and GERD with stricture formation influence esophageal length. GERD-related strictures shorten the esophagus more significantly in short patients. (J GASTROINTEST SURG 1999;3:483-488.)

KEY WORDS: Esophageal, length, manometry

The average length of the esophagus in adults varies from 20 to 35 cm.[1,2] Postmortem studies showed esophageal length (the distance from the upper end of the cricopharyngeus muscle to the gastric mucosa) to be 22.8 ± 0.7 cm (mean ± standard error of the mean [SEM], range 18 to 26 cm).[3] In vivo measurement of esophageal length can be accomplished by use of external chest diameter as an index of esophageal length,[4] endoscopic visualization of the gastroesophageal junction,[5] and manometric analysis.[6] The influence of disease on esophageal length is particularly important in patients with achalasia and stricture formation. The elongated esophagus often seen with advanced achalasia influences treatment because excessive tortuosity renders myotomy ineffectual. The added length and resultant tortuosity diminish the benefit of a water column and gravity. Thus disruption of the lower esophageal sphincter is less beneficial. In patients with stricture formation, the surgical approach may be influenced by the overall esophageal length. Thoracic surgeons advocate a thoracotomy plus esophageal lengthening procedure for all patients with a short esophagus, whereas abdominal surgeons often attempt laparoscopic transhiatal esophageal mobilization followed by fundoplication. A retrospective analysis was undertaken to measure the entire length of the esophagus—the distance from the upper border of the upper esophageal

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sphincter to the lower border of the lower esophageal sphincter—and to assess its relationship to sex, weight, height, and various esophageal disorders.

METHODS

This study was a retrospective analysis of 617 esophageal manometric studies performed in the department of surgery at our institution. It included 51 normal control subjects (27 males and 24 females) and 566 patients (297 males and 269 females) with esophageal disorders (50 with achalasia, 6 with diffuse esophageal spasm, 64 with stricture, 38 with nutcracker esophagus, 398 with gastroesophageal reflux disease [GERD] with positive 24-hour pH monitoring, and 66 with possible GERD but negative 24-hour pH monitoring). The relationship between esophageal length and other parameters, including sex, height, weight, and age, as well as diagnosis, was studied using Student's *t* test and the Pearson and Spearman correlation coefficients with multiple regression.

Standard esophageal manometry was performed in all patients after an overnight fast. Medications known to interfere with gastrointestinal secretory or motor function were discontinued at least 48 hours before the study. A single-catheter assembly was used consisting of five polyethylene tubes bonded together with five lateral openings placed at 5 cm intervals from the distal end of the catheter and oriented radially around the circumference. The diameter of the lateral openings was 0.8 mm. The catheter was perfused with distilled water at a constant rate of 0.6 ml/min using a pneumohydraulic low-compliance perfusion pump (Arndorfer Medical Specialties, Greendale, Wis.). Each tube was connected to an external Statham pressure transducer (model P2306, Gould Instruments, Cleveland, Ohio) that had been calibrated using a mercury-filled manometer. Pressures were recorded by means of a Gould ES 1000 16-channel recorder (Gould Instruments) and printed on paper running at a velocity of 5 mm/sec. A belt pneumograph was positioned around the chest to record respiratory excursions. The assembly catheter was introduced through the nose. The lower and upper esophageal sphincters were localized by the station pull-through technique as the catheter was withdrawn at 1 cm intervals. The length of the esophagus was defined as the distance between the lower border of the lower esophageal sphincter and the upper border of the upper esophageal sphincter.

RESULTS

The means for age, weight, and height in the normal group (n = 51) are shown in Table I. Those same parameters for the group with esophageal disorders (n = 566) are presented in Table II. There was no difference between the mean (± standard deviation [SD]) length of the esophagus for the normal group (28.3 ± 2.41) and for the pooled group of patients with esophageal disorders (28.3 ± 2.87).

Table I. Values for the normal (control) group (n = 51)

Variable	Mean	SD	Minimum	Maximum
Age	39.2	16.3	20	83
Weight	173.1	40.6	108	298
Height	67.0	3.78	60	77
Length	28.3	2.41	24	37.8

Table II. Values for the group with esophageal disorders (n = 566)

Variable	Mean	SD	Minimum	Maximum
Age	48.9	14.8	20	88
Weight	183.9	40.3	80	397
Height	67.5	4.13	56	78
Length	28.0	2.87	19	38.6

In the normal group the Pearson and Spearman correlation coefficients showed that weight and age were not significantly related to length. A *t* test revealed a trend for longer esophagus length in males ($P < 0.12$), but multiple regression analysis showed that sex was not related to length after adjustment for height. There was no significant sex by height relationship as demonstrated in Fig. 1. Only height was a significant predictor of length (Pearson correlation coefficient $r = 0.387$, $P < 0.005$).

Multiple regression evaluation of the entire study group using height as a covariant showed that height and diagnosis are related to esophageal length. The relationship with height is highly significant ($P < 0.0001$), even after adjustment for all the diagnoses. Among the diagnoses, achalasia was found to be a significant ($P < 0.001$) predictor of length after adjustment for height and all the other diagnoses. GERD also appeared to have significant predictive value, although this is less clearly significant ($P < 0.04$). This observation was explored by taking each diagnosis by itself in comparison with the normal values in multivariate regression including height as a covariant (Table III). Patients with achalasia had a significantly longer esophagus than the normal subjects with a mean of 29.9 ± 3.13 cm ($P < 0.0015$). Patients with GERD as

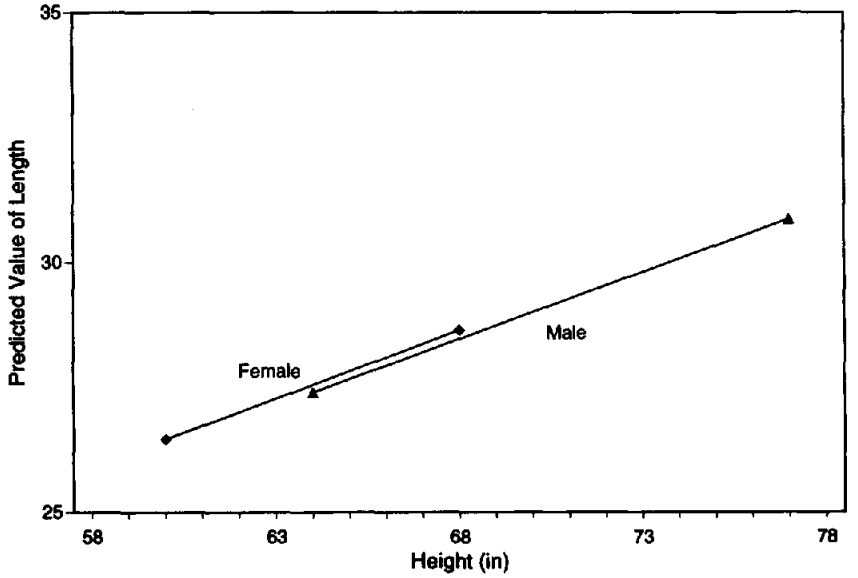

Fig. 1. Effect of sex on esophageal length after adjustment for height in 51 normal subjects (27 males and 24 females). Note that sex had no effect on esophageal length.

Table III. Values for each diagnosis after multivariate regression analysis

Diagnosis	No.	Mean	SD	t	*P* value
Normal	51	28.3	2.41		
Achalasia	50	29.9	3.13	3.26	0.0015
Diffuse esophageal spasm	6	29.9	4.49	1.03	0.31
Stricture	64	27.6	2.58	−2.36	0.021
Nutcracker	38	28.4	2.62	1.05	0.30
GERD	398	27.8	2.81	−1.98	0.05
Possible GERD/negative 24-hour pH monitoring	66	27.7	2.65	−0.91	0.37

diagnosed by positive 24-hour pH monitoring had a shorter esophagus than the normal subjects with a mean of 27.8 ± 2.81 cm ($P < 0.05$). Patients with possible GERD but negative 24-hour pH monitoring were similar to those with GERD in terms of length, with a mean of 27.7 ± 2.65 cm; however, since the sample size was smaller, the difference from normal values is not significant. Among patients with stricture, the length was shorter than that in control subjects, with a mean of 27.6 ± 2.58 cm ($P < 0.021$), but this relationship is partly due to the association between GERD and stricture. Patients with nutcracker esophagus had a normal length esophagus (mean 28.4 ± 2.62 cm). Patients with diffuse esophageal spasm had a longer than normal esophagus (mean 29.9 ± 4.49 cm); however, the results did not reach statistical significance ($P < 0.31$). In addition, the number of persons in the latter group was small (n = 6) so no reliable conclusion could be drawn.

Plots of predicted values of length by height, for normal subjects as well as patients with achalasia and GERD with and without stricture were made (Fig. 2). The predicted lengths were higher for patients with achalasia than for normal subjects and lower for patients with GERD (with and without stricture) than for normal subjects. However, although the lines for patients with achalasia and GERD without stricture were roughly parallel to the lines for normal subjects, the line for GERD with stricture had a steeper slope. Another regression analysis was performed for patients with GERD, predicting length from height, stricture, and height by stricture interaction. This analysis showed no significant difference in esophageal length between patients with and without stricture (mean length with stricture [n = 46] was 27.3 cm; mean length without stricture [n = 352] was 27.8 cm). However, there was a significant stricture by height interaction ($P < 0.05$).

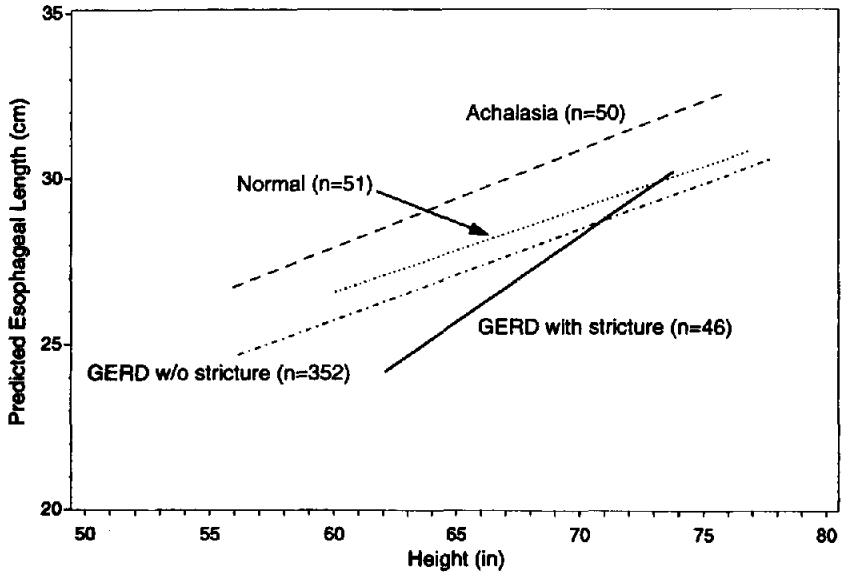

Fig. 2. Plot of predicted esophageal length by height for normal subjects and patients with achalasia, GERD with, and GERD without stricture. Note the steeper slope for GERD with stricture group.

DISCUSSION

The esophagus begins in the neck at the cricoid cartilage and passes through the thorax within the posterior mediastinum and extends for a few centimeters past the diaphragm to its junction with the stomach.[2] The ideal method for measuring esophageal length is controversial. A reliable reading is needed for all of the following: (1) patients with a short esophagus due to peptic stricture; (2) shortened esophagus found in patients with a failed antireflux procedure or paraesophageal hernia repair[7,8]; (3) selection of the best approach when esophagectomy is needed; (4) esophageal replacement procedures; and (5) insertion of a prosthesis or a nasogastric tube.[9]

Manometrically we measured esophageal length and its correlation with age, sex, weight, height, and specific esophageal disorders. Although in the literature esophageal length does show a correlation with height in children,[10,11] in adults this relationship is unclear.[3,5,12] However, our study showed a clearly significant positive relationship between esophageal length and height ($P < 0.0001$). Esophageal length did not correlate with either weight, sex, or age after adjustment for height.

A significant correlation was found between diagnosis and esophageal length. Patients with achalasia were found to have a longer esophagus. This may be due to dilatation and tortousity of the esophagus.[4,6] Patients with spastic conditions of the esophagus (diffuse esophageal spasm, nutcracker esophagus) tended to have an esophageal length that was comparable to that of normal subjects. Patients with GERD (positive 24-hour pH monitoring) had a shorter than normal esophagus ($P < 0.05$) as did patients with stricture ($P < 0.021$). GERD-related strictures tended to shorten esophageal length more significantly in shorter patients. In other words, GERD patients with strictures showed a greater increase in esophageal length per unit increase in height than those without strictures (Fig. 2). This finding to our knowledge has not been previously reported.

The observed stricture by height interaction was unexpected and intriguing but difficult to understand. First, consider the comparison between normal subjects and patients with GERD without stricture. They differed significantly in average height-adjusted esophageal length, but there was no interaction effect. The two height–esophageal length regression lines are basically parallel (Fig. 2). Assuming, for the purposes of this discussion, that these differences are effects of disease and that we can estimate the predisease esophageal length from the patient's height, we could say that GERD without stricture shortens the esophagus and the amount of shortening is independent of the predisease esophageal length. To make them not just parallel but equivalent, one can subtract a constant (about 2 cm) from all normal esophageal length values or add the same constant to all of the GERD without stricture esophageal lengths. Adding or subtracting a constant to "y" changes the intercept but not the slope of an xy regression line.

The comparison between normal subjects and patients with GERD-related stricture differs significantly in average esophageal length, and there is a significant interaction effect. The height—esophageal length regression lines are not parallel; they have different slopes. They cannot be made parallel by adding or subtracting constants. To make the normal height–esophageal length line parallel to the GERD-related stricture line, the normal esophageal length values must be multiplied by a constant. This is a mathematical equivalent of stretching them, for example, to 150% of their original length. Originally shorter esophagi change less with such stretching than do originally longer esophagi. That gives their regression line with height a steeper slope, such as that seen in GERD-related stricture, but it would also naturally increase the overall esophageal length for the group. The patients with GERD-related stricture have, on average, a shorter esophageal length not a longer one. To fix this, in addition to performing the above-mentioned manipulation, a constant must be subtracted as well in the GERD without stricture group.

GERD induces an inflammatory reaction in the esophagus causing stricture formation at the squamocolumnar junction. In cases of long-standing disease the inflammatory scarring and fibrosis are not solely confined to the mucosa but affect the entire thickness of the esophagus as well as the paraesophageal mediastinal tissues.[13,14] In some instances the stricture and esophagogastric junction ascend from the hiatus accounting for the shortening and inability to reduce the hernia. The concept of acquired short esophagus, although not accepted by all,[15] does exist in up to 14% of patients undergoing antireflux surgery.[16]

Questions concerning the accuracy of esophageal length measurements limit our ability to interpret these results. Manometric measurement of esophageal length, although more objective, is not without its limitations, especially in patients with scleroderma and Barrett's esophagus where the lower esophageal sphincter pressure may be so low that localization is difficult.[17] Previous studies have reported conflicting results. Bremner et al.[18] showed a strong correlation between esophageal length and height. In addition, esophageal length is reduced in patients with GERD as well as in those with stricture.[18,19] Qun Li et al.[6] measured esophageal body length as the distance from the upper margin of the lower esophageal sphincter to the high-pressure zone of the upper esophageal sphincter. This study demonstrated a poor correlation between esophageal length and weight or height but a significant correlation between esophageal length and sex. Among patients with esophageal disorders, those with achalasia showed a longer esophagus than others. Patients with GERD tended to have a longer esophagus and those with scleroderma to have a shorter esophagus, but the results did not reach statistical significance in either group. The authors stated that the result for scleroderma could be due to a type II error, as there were only 18 patients.

Endoscopy is readily available for measurement of esophageal length, as well as being the procedure most commonly used by surgeons and gastroenterologists, but it is crude and unreliable. Problems arise in locating the anatomic landmarks, especially in the presence of esophagitis, Barrett's esophagus, or hiatal hernia.[4,20] In addition, peristalsis and inexact identification of the upper esophageal sphincter create inherent inaccuracies with this method. Scapa et al.[21] measured esophageal length endoscopically as the distance from the incisor teeth to the esophagogastric mucosal junction. Among 758 patients, the majority (53%) had an esophageal length less than 38 cm indicating that esophageal length, per se, does not define the presence of hiatal hernia, which was present in 17.9%. Esophageal length significantly correlated with sex and height but not with weight, and patients with dyspeptic symptoms were shown to have a shorter esophagus than others.

The surgical management of the short esophagus is controversial inasmuch as many options are available, for example, dilatation and fundoplication, either through the abdomen or the chest, esophageal lengthening procedures such as the Collis gastroplasty, and an esophageal replacement technique using a variety of conduits.[22] The patient's height may influence the surgical approach on the basis of the data presented. A prospective trial of patients with GERD-related stricture with a wide range of heights is needed to test the postulate.

CONCLUSION

By means of manometry we found that esophageal length is associated with a patient's height and disease. We conclude that achalasia lengthens the esophagus, whereas GERD shortens the esophagus by a certain amount that is independent of the person's normal or original esophageal length estimated from height. Stricture-related GERD has the additional effect of lengthening the esophagus by a certain amount so that it is positively related to the person's normal esophageal length.

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Preoperative Esophageal Transit Studies Are a Useful Predictor of Dysphagia After Fundoplication

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Fundoplication performed for gastroesophageal reflux disease may be complicated by postoperative dysphagia despite successful reduction in reflux symptoms. This is more likely in those patients with reflux who have concurrent esophageal dysmotility. The aim of this study was to establish whether esophageal transit studies using a technetium-99m jello bolus (jello esophageal transit) could detect the presence of motility disorders preoperatively and hence predict surgical outcome. Transit studies in 33 healthy volunteers yielded a normal range of 2 to 24 seconds using ninety-fifth percentile distribution. In the second phase of the study, 26 patients accepted for laparoscopic fundoplication were enrolled: jello esophageal transit, manometry, and endoscopy were attempted preoperatively in all subjects. A clinical dysphagia score was assigned from a questionnaire. Six months after surgery, five patients had dysphagia and of these four were found to have abnormal preoperative jello esophageal transit, for a sensitivity of 80%. Of the 21 patients who had no dysphagia after surgery, 20 patients had normal preoperative jello esophageal transit, showing a specificity of 95%. This esophageal transit study is noninvasive, reliable, and sensitive. When performed prior to fundoplication, it appears to be of significant value in detecting a subtle functional motility disorder that predisposes to postoperative dysphagia. Jello esophageal transit may assist the surgeon in planning treatment of gastroesophageal reflux disease. (J GASTROINTEST SURG 1999; 3:489-495.)

KEY WORDS: Fundoplication, dysphagia, solid esophageal transit, dysmotility

Fundoplication, performed by either an open or a laparoscopic approach, is a well-accepted method of surgical control of gastroesophageal reflux disease (GERD).[1,2] Immediately after fundoplication, all patients have a mild transient dysphagia resulting from postsurgical swelling and inflammation, but most recover within 2 to 6 months after surgery as the inflammation subsides.[3-7] However, several studies summarized by Pope[6] found that 3% to 44% of patients experienced postoperative dysphagia.[6-8] Negre[7] found that 44% of patients had a slight degree of dysphagia at an average 6-year follow-up, whereas DeMeester et al.[8] reported an average of 15% and McKernan[4] reported 10% with dysphagia following the Nissen procedure. Pitcher et al.[5] reported 37% with mild dysphagia and 7% with persistent severe dysphagia, and Rattner and Brooks[9] reported 10% with dysphagia requiring dilatation after laparoscopic Nissen fundoplication. Our clinical experience has shown that approximately 5% of patients complain of significant dysphagia after laparoscopic Nissen fundoplication.

Preoperative esophageal manometry is widely recommended to detect any dysmotility, which may contribute to postoperative dysphagia.[10-13] However, we have found that patients with acceptable manometric results can develop dysphagia after laparoscopic fundoplication despite no signs of mechanical causes on gastroscopy. Kjellen et al.[14] found that acceptable manometric findings do not exclude the possibility of defective transport.

To assess swallowing after laparoscopic Nissen fundoplication, an objective test is required. In gastroenterologic practice, the clearance of a radioisotopically labeled liquid bolus is widely used to measure esophageal motor function.[15-19] In a pilot study in our unit, there was a poor correlation between dysphagia scores

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after laparoscopic fundoplication and the liquid transit study.

We reasoned that because patients after surgery have problems with solids rather than liquids, a test using a solid rather than a liquid bolus would be more appropriate in this context. Previous studies of solid transit have suggested that solid bolus is preferable in detecting clinically significant abnormalities of esophageal emptying.[14,20-22] Solid bolus transit varies depending on the makeup of the bolus, its viscosity or density, the swallow protocol, and the subject's position (supine or upright).[23-27,29,30] Kim et al.[23] used a jello bolus with a range of viscosities; an increase in viscosity resulted in a decrease in the percentage of activity emptied, that is, prolonged transit. Horowitz et al.[24] used labeled chicken liver in hamburger mince and reported a normal transit time of 7 to 94 seconds for an upright position. Kjellen and Svedberg[25] used a gelatin-based bolus but with a density of 1.0 g/cm^3, and reported a normal transit time of 3.5 to 7.4 seconds for the upright position. Although Wang et al.[26] used a jello bolus and protocol similar to that used by Kjellen and Svedberg,[25] but in the supine position, they reported a wider range of 20 ± 9.8 seconds compared to the 6.9 ± 1.4 seconds reported by Kjellen and Svedberg.[25] The large variation in normal ranges can be explained by the differences in bolus types, viscosity, and swallow protocols, all of which obviously need to be standardized before comparisons are possible.

Hsu et al.,[27] using a solid jello bolus in patients in the upright position, reported esophageal scintigraphy to be a sensitive method for determining esophageal motor function. The advantage over manometry and conventional radiography was its noninvasiveness and ability to quantify esophageal dysfunction. They suggested it may be a more sensitive indicator of defective esophageal transport than manometry. Maddern and Jamieson[28] reported that patients with dysphagia had slower esophageal emptying than patients without dysphagia and found a significant difference between normal control subjects and 73 patients with GERD.

The aim of this study was to establish whether a technetium-99m–labeled jello bolus could detect a functional motility disorder preoperatively, which would predict the patients most likely to suffer severe dysphagia after laparoscopic Nissen fundoplication despite a reduction in reflux symptoms.

MATERIAL AND METHODS

Study Groups

Over a period of 8 months, 26 patients with GERD (16 men and 10 women; age range 19 to 78 years) referred for laparoscopic fundoplication, who had no motility disorders or only minor nonspecific disorders of motility (24 by manometry and two on cine swallow after manometry failed), were recruited for this study. Prior to surgery, jello esophageal transport (JET) studies were performed. All subjects were requested to maintain a 3-day food diary and fill out symptom questionnaires before surgery and at 1 month, 3 months, and 6 months after surgery.

A control group of 33 healthy volunteers completed a symptom questionnaire to confirm that they had had no dysphagia and no clinical evidence of GERD in the previous month. They had JET studies performed to establish a normal range; 10 of these volunteers repeated the test 1 month later to check reproducibility. Seventeen of the 33 control subjects kept a 3-day food diary on two separate occasions to determine an acceptable variation for the puree texture content in a healthy person's diet.

The study protocol and the consent form were approved by the South Eastern Sydney Area Health Service Ethics Committee.

Details of Surgery

Operative technique was previously standardized in 100 patients by a single surgeon (D.R.H.). The surgery involved five ports using a 0-degree telescope, full mobilization of the distal esophagus, division of the upper short gastric vessels upward from the level of the splenic hilum and division of fascial attachments to create a large posterior window, posterior repair of hiatus performed using two to five sutures, and a loose 15 mm 360-degree fundoplication secured to the distal esophagus and by the lowest suture to the median arcuate ligament. No bougie was used, but a loose wrap was demonstrated by elevating the wrap anteriorly after trial placement of the first stitch.

Measurement of Jello Esophageal Transit

The jello bolus was prepared using commercially available jello crystals (0.07 g gelatin/g). Boiling water (3 ml) was added to two 5 ml beakers each containing 2 g of jello crystals. The mixture was stirred on a hot plate until the jello crystals completely dissolved; 20 MBq of technetium-99m pertechnetate was added to the jello and the mixture was poured into disposable teaspoons sprayed with a nonstick cooking oil to prevent the jello from adhering to the spoon. The spoons were then placed securely in a disposable container to prevent spillage and allowed to set for a minimum of 2 hours in a standard refrigerator. The radiation exposure to the patient from 20 MBq of technetium is extremely low and gave an effective dose of approximately 0.5 mSv. The viscosity of the prepared jello was 1×10^4 cP measured on two separate occasions.

For the test the subject was positioned sitting upright in front of a large field of view gamma camera fitted with a low-energy all-purpose collimator. A Co57 marker was placed on the subject's shoulder to indicate the level of the cricoid cartilage to indicate entry into the esophagus.

Dynamic computer acquisition was triggered at the beginning of the swallow at a rate of three frames per second for 100 seconds (128 × 128 matrix size). This information was stored and the study was repeated 5 minutes later with a second spoon.

To lubricate the esophagus, each subject was given 5 ml of water orally via a disposable syringe immediately before the administration of the jello. Subjects were instructed not to masticate and to swallow the jello as a single bolus. They were than asked to dry swallow every 20 seconds five times. If the bolus was stuck at the end of 100 seconds, the subject was given 50 ml of water to help clear the esophagus.

Analysis of Jello Esophageal Transit Data

A composite image was created, and the esophagus was drawn from the cricoid cartilage to the beginning of the stomach; the esophagus was then divided into three sections—proximal, middle, and distal. The JET study was excluded from analysis if the bolus stuck proximally or fragmented in the esophagus. This occurred in three subjects in the control group undergoing JET studies but in none of those in the GERD group. A time-activity curve was generated, and the total transit time was calculated by measuring an area under a manually selected range on that curve from when the bolus first entered the esophagus to when the bolus entered the stomach. This total activity was then divided by the maximum value in that range. To aid in interpretation, a condensed image was also generated. Each consecutive frame of the dynamic study was added side by side using a row summation technique. This condensed image, with time of the horizontal axis and the vertical axis representing the spatial arrangement of the jello, describes the entire dynamic transit of the radionuclide through the esophagus. An abnormal JET was assigned if either the first or second JET time was outside the control range.

Dysphagia Assessment

Swallowing was assessed subjectively using a questionnaire and a 3-day food diary completed by the subjects preoperatively and at prescribed intervals for 6 months after surgery. Subjects recording no episodes or one episode of dysphagia per month were considered normal, whereas subjects who had symptoms of dysphagia daily or a few episodes per week were considered abnormal.

Table I. Presentation of symptoms in 26 patients with GERD

Presentation	No.
Principle features	
Severe heartburn	21
Bleeding/anemia + large hernia	2
Severe chest pain + large hernia	1
Chest pain and regurgitation + large hernia	1
Dysphagia + large hernia	1
Additional prominent features	
Regurgitation	6
Previous stricture from dilatation	0

Table II. Endoscopy-defined characteristics in 26 patients with GERD

Hiatal hernia size (cm) characteristics	No.
0	6
1	5
2	5
3	0
4	4
5 or larger	4
Plus paraesophageal hernia	2
Endoscopic grade of esophagitis (Savary)	
0 + previous ulceration	1
0 + positive 24-hour pH	3
0 + paraesophageal hernia	2
1	7
2	8
3	4
4	1
Stricture	0

The 3-day food diary was recorded before surgery and at 1 month and 3 months after surgery. Dietary modification was assessed on the basis of the percentage of calories from puree and minced textured food in the total diet before and after surgery compared to control values.

The clinical characteristics of the 26 patients with GERD are presented in Tables I and II.

RESULTS

Control and Preoperative Jello Esophageal Transit Times

The normal range for JET, determined from the control group (n = 33), was 2 to 24 seconds using ninety-fifth percentile distribution (Fig. 1). Among the 10 volunteers who repeated the study, the reproducibility showed a mean difference of 1.6 ± 3 seconds (mean ± 1 standard deviation [SD]).

Preoperative Dysphagia

The diets of subjects preoperatively were not significantly different in puree/mince content from the diets of control subjects. This is a result of the large variation in the puree/mince content observed in the control diets 15% ± 9% (mean ± 1 SD). Subsequently dysphagia symptom scores from the questionnaire did not always correlate with the puree/mince texture content of the diet for individual subjects. These dysphagia parameters when compared separately to JET at the time of or in the week before the JET study also showed no correlation.

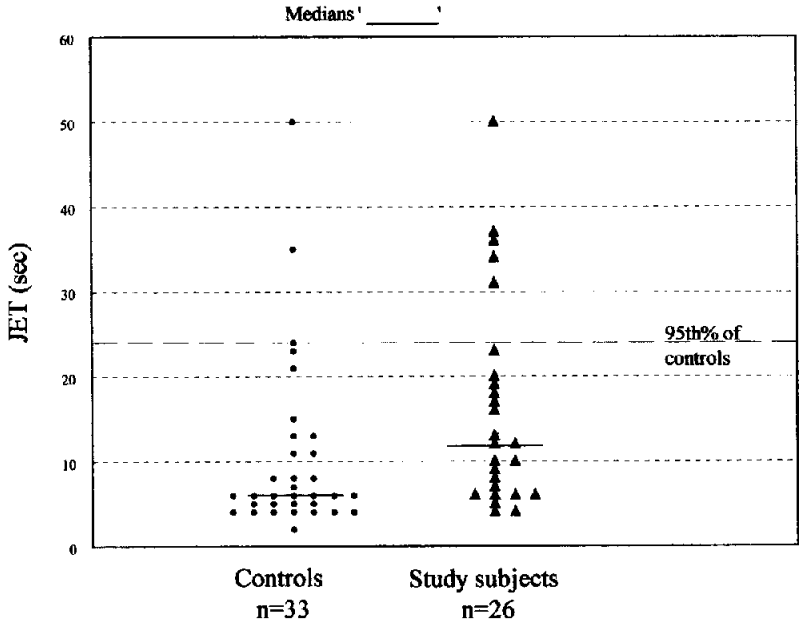

Fig. 1. Scatter plot of jello esophageal transit (JET) times in control subjects compared to GERD subjects preoperatively.

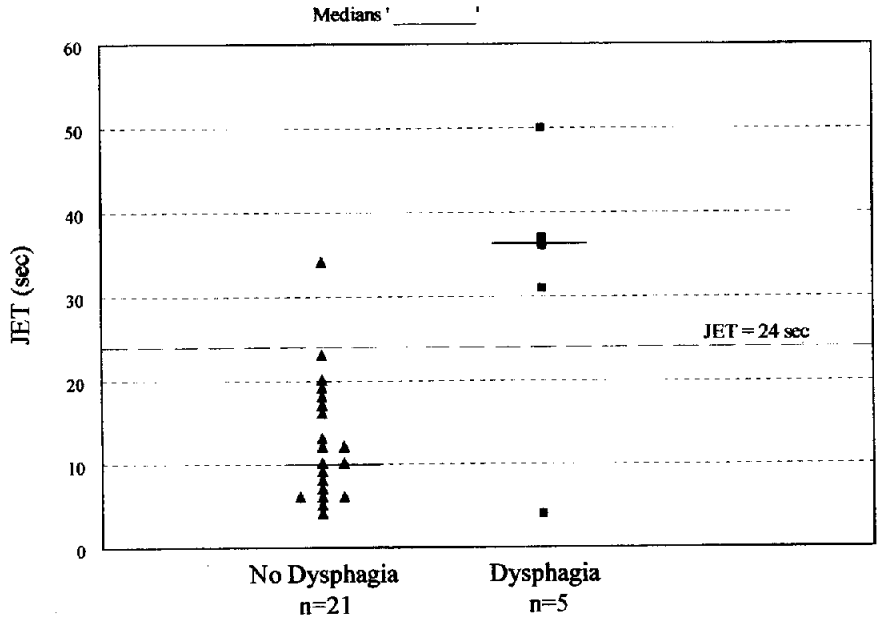

Fig. 2. Scatter plot of preoperative jello esophageal transit (JET) times comparing subjects with and without dysphagia 6 months after laparoscopic Nissen fundoplication.

Postoperative Outcome

Twenty-five of the 26 subjects had marked relief of GERD symptoms at 6 months after laparoscopic Nissen fundoplication. However, five subjects had moderate-to-severe postoperative dysphagia and 21 reported no dysphagia at 6 months after laparoscopic fundoplication (Fig. 2). Of the five subjects with postoperative dysphagia, one required reoperation, whereas the remaining four subjects had a dilatation against minimal resistance with little improvement. Results of postoperative subjective dysphagia assessment did not correlate with those of postoperative JET studies performed at the same time or week prior to the JET study.

Table IIIA. Preoperative jello esophageal transit (JET) vs. postoperative dysphagia

Preoperative JET	Postoperative dysphagia	
5 abnormal	4 yes	1 no
21 normal	1 yes	20 no

Table IIIB. Preoperative vs. postoperative dysphagia

Preoperative dysphagia	Postoperative dysphagia	
6 yes	2 yes	4 no
20 no	3 yes	17 no

Table IIIC. Preoperative manometry vs. postoperative dysphagia

Preoperative manometry	Postoperative dysphagia	
6 abnormal	2 yes	4 no
18 normal	2 yes	16 no
2 unsuccessful	1 yes	1 no

Predictive Value of Preoperative Measures

Comparisons have been made between preoperative JET, preoperative dysphagia, and manometry as predictors of postoperative dysphagia. (Tables IIIA, IIIB, and IIIC). Four of the five subjects with postoperative dysphagia had an abnormal JET study preoperatively.

The sensitivity of the JET study for predicting postoperative dysphagia is 80% (4 of 5 subjects), and the specificity of a normal study in detecting those who will do well after surgery is 95% (20 of 21 subjects). Review of the five subjects with abnormal preoperative JET times (see Table IV) in relation to details of manometry results shows no trend, although the number of subjects is very small.

By contrast, preoperative manometry was less reliable in predicting postoperative dysphagia (see Table IIIC). The sensitivity of manometry was 50% (2 of 4 subjects) whereas the specificity was 80% (16 of 20 subjects). Review of the six subjects with abnormal preoperative manometric findings (see Table IV) further illustrates its poor correlation with pre- and postoperative dysphagia and preoperative JET.

Table IV. Manometry details for six subjects with abnormal manometric findings and five subjects with abnormal jello esophageal transit (JET) times before laparoscopic Nissen fundoplication

Subject	Manometry Description	Preoperative dysphagia	JET	Postoperative dysphagia
Abnormal manometry				
1	High-amplitude contractions ~190 mm Hg	+	+	+
2	No sphincter, 60% propagation	−	+	+
3	Some repetitive contractions, no distal contractions	+	−	−
4	Low-amplitude contractions, 15 to 25 mm Hg (maximum 40 mm Hg)	−	−	−
5	Low-amplitude proximal contractions, no distal propagation, no sphincter	+	−	−
6	50% waves distally <40 mm Hg	−	−	−
Abnormal JET				
1	High-amplitude contractions ~190 mm Hg	+	+	+
2	No sphincter, 60% propagation	−	+	+
7	Normal	+	+	+
8	Failed	−	+	+
9	Normal	−	+	−

DISCUSSION

The normal range in this study of 2 to 24 seconds is broader than the range of 3.5 to 7.4 seconds reported by Kjellen and Svedberg.[25] However, their protocol differs somewhat from ours; they used a single labeled swallow, which was only repeated if the bolus stuck (stopped without further progression). This result was discarded from analysis if the second bolus did not stick. Only if the bolus stuck twice was it considered abnormal. Delay with the two boluses did not occur with our control subjects.

If we took an approach similar to that of Kjellen and Svedberg[25] and only included those transits that passed through the esophagus to the stomach over the period of the test, then our control range would be 2 to 20 seconds. This is still broader than the range achieved by Kjellen and Svedberg,[25] which may be explained by an additional protocol difference; they also included a 15 ml water bolus taken with the jello bolus, which is likely to increase transit perhaps similar to a liquid bolus. However, their solid bolus contained a higher percentage of gelatin than ours did, which would increase its viscosity and as one would expect from literature, should slow down transit.[27,29,30]

The study by Wang et al.,[26] which used a jello bolus preparation and protocol similar to those of Kjellen and Svedberg,[25] but with subjects in the supine position, also reported a wider control range. Wang et al.[26] did not report whether bolus obstruction occurred or if the test was repeated to check reproducibility. Therefore the lack of the specific protocol and measurement details makes comparisons between these results difficult. Based on our experience, if the bolus was chewed or partially disintegrated, then the resulting trail of isotope may register as a delayed transit. Therefore it is evident that a normal range needs to be determined independently for each laboratory using a set swallow protocol and standardized jello bolus preparation to ensure consistent viscosity.

Traditionally manometry has been used prior to fundoplication to detect and exclude those subjects with major dysmotility in an effort to reduce the risk of postoperative dysphagia.[10-13] Despite this precaution, dysphagia is a significant problem after surgery.[2,4,6-8,31] In our study, JET was clearly superior to standard manometry in predicting postoperative dysphagia. Because manometry has the capacity to identify specific motility disorders such as achalasia, its use may still be justified, but when patients with serious dysmotility are excluded, as in this sample, JET showed better sensitivity and specificity in predicting postoperative dysphagia than manometry.

Lundell et al.,[31] in a retrospective follow-up study of patients after fundoplication, found that preoperative scintigraphic measurement of esophageal emptying of a minced liver bolus correlated poorly with postoperative outcome. The difference between the study reported by Lundell et al. and our study probably derives from the differences in methodology. The good reproducibility shown in our study is similar to that reported by Kim et al.[23] By using jello boluses of different viscosity, Kim et al. also showed a direct relationship between percentage retention of the bolus and the viscosity. Puree or low-viscosity meals used to test transit may not accurately reflect impairment of transit.

Postoperative dysphagia can arise from both operative and nonoperative factors. The laparoscopic Nissen fundoplication had been performed in more than 100 patients by one surgeon (D.R.H.) prior to this study and included closure of the hiatus and division of short gastric vessels in all patients. All patients underwent gastroscopy at 3 months after surgery, and no mechanical cause such as hiatal stenosis or paraesophageal herniation was found to explain the dysphagia. This study shows that even when technical factors are controlled, there is a group of patients who are identifiable by JET, but not necessarily by manometry, in whom the rate of postoperative dysphagia is unacceptable. To date we do not know the capacity of JET to screen for serious dysmotility such as that associated with achalasia or scleroderma; this needs to be assessed before JET is used as the sole preoperative predictor. If JET identifies all patients with dysmotility, this subgroup could then be referred for manometry.

Further study is required to define the nature of the dysmotility shown by JET. Until then our results suggest that surgeons should avoid conventional laparoscopic Nissen fundoplication as treatment of GERD in the subgroup of patients with abnormal preoperative JET.

CONCLUSION

The JET study is a safe, noninvasive procedure that has good patient acceptance and is easy to perform. It enables both quantitative and qualitative assessment of esophageal transit and may identify a subgroup of patients in whom a modified surgical approach is required.

Measurements of jello viscosity were performed by the Department of Mechanical Engineering. University of Sydney, Australia. Esophageal manometry studies were conducted by the Department of Gastroenterology, St. George Hospital, Kogarah, Australia.

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Preoperative Biliary Drainage: Impact on Intraoperative Bile Cultures and Infectious Morbidity and Mortality After Pancreaticoduodenectomy

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Whether it is necessary to perform biliary drainage for obstructive jaundice before performing pancreaticoduodenectomy remains controversial. Our aim was to determine the impact of preoperative biliary drainage on intraoperative bile cultures and postoperative infectious morbidity and mortality following pancreaticoduodenectomy. We retrospectively analyzed 161 consecutive patients undergoing pancreaticoduodenectomy in whom intraoperative bile cultures were performed. Microorganisms were isolated from 58% of these intraoperative bile cultures, with 70% of them being polymicrobial. Postoperative morbidity was 47% and mortality was 5%. Postoperative infectious complications occurred in 29%, most commonly wound infection (14%) and intra-abdominal abscess (12%). Eighty-nine percent of patients with intra-abdominal abscess ($P = 0.003$) and 87% with wound infection ($P = 0.003$) had positive intraoperative bile cultures. Microorganisms in the bile were predictive of microorganisms in intraabdominal abscess (100%) and wound infection (69%). Multivariate analysis of preoperative and intraoperative variables demonstrated that preoperative biliary drainage was associated with positive intraoperative bile cultures ($P < 0.001$), postoperative infectious complications ($P = 0.022$), intra-abdominal abscess ($P = 0.061$), wound infection ($P = 0.045$), and death ($P = 0.021$). Preoperative biliary drainage increases the risk of positive intraoperative bile cultures, postoperative infectious morbidity, and death. Positive intraoperative bile cultures are associated with postoperative infectious complications and have similar microorganism profiles. These data suggest that preoperative biliary drainage should be avoided in candidates for pancreaticoduodenectomy. (J GASTROINTEST SURG 1999;3:496-505.)

KEY WORDS: Pancreaticoduodenectomy, biliary drainage, bile, bacteria, intra-abdominal abscess, wound infection

Marked elevation of serum bilirubin has previously been shown by some authors[1-6] but not others[7,8] to be an important risk factor for development of morbidity and mortality following operative treatment of biliary tract obstruction. Likewise, preoperative biliary drainage has not consistently been shown to improve postoperative outcome in patients with biliary tract obstruction.[9-15] It is well documented that both endoscopic and percutaneous biliary drainage procedures are associated with infectious complications such as cholangitis and bacteremia.[14,16-22] In this regard, pancreaticoduodenectomy is often accompanied by considerable postoperative morbidity despite a recent trend toward declining postoperative mortality.[23-31] It has long been a concern of ours that preoperative biliary drainage may have a negative impact on the outcome following pancreaticoduodenectomy. Preliminary data from our own institution have demonstrated an association between preoperative biliary drainage and cumulative wound and intra-abdominal complications.[32] However, studies in the literature specifically examining the effects of preoperative biliary drainage in patients undergoing pancreatic surgery for pancreatic and peripancreatic lesions are limited

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and their results are variable.* Therefore the purpose of this study was to determine the impact of preoperative biliary drainage on intraoperative bile cultures and postoperative infectious morbidity and mortality following pancreaticoduodenectomy.

MATERIAL AND METHODS

Patient Population

A total of 161 consecutive patients undergoing pancreaticoduodenectomy at Memorial Sloan-Kettering Cancer Center between January 1994 and January 1997 and from whom intraoperative bile cultures were obtained at the time of pancreaticoduodenectomy were identified from a prospectively collected pancreatic database. During the same time period, an additional 79 patients undergoing pancreaticoduodenectomy who did not have intraoperative bile cultures performed at the time of pancreaticoduodenectomy were identified from the prospectively collected pancreatic database.

Data Collection Variables

By retrospective chart review the following variables were collected: age, sex, history of jaundice, history of diabetes mellitus, preoperative biliary instrumentation, preoperative biliary drainage, preoperative pancreatic biopsy, history of fever and chills within 1 week of admission, preoperative total bilirubin level (mg/dl) on admission, pathologic diagnosis, intraoperative bile culture, type of pancreaticoduodenectomy performed, placement of an intraperitoneal drain(s) around the pancreaticojejunostomy or biliary-enteric anastomosis, placement of an intraoperative gastrostomy or feeding jejunostomy, operative time, intraoperative blood loss, intraoperative transfusion of red blood cells, postoperative infectious complications (intra-abdominal abscess [IAA], wound infection, urinary tract infection, bacteremia, pneumonia, catheter infection, *Clostridium difficile* diarrhea/colitis), other complications, hospital stay, and postoperative deaths.

Preoperative Biliary Instrumentation and Drainage Procedures

Biliary instrumentation was defined as cannulation of the biliary tract and included endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography, and operative cannulation by common bile duct exploration. Biliary drainage was defined as formation of a conduit between the biliary tract and either the gastrointestinal tract or an external collection system. This included endoscopic biliary stents, percutaneous external biliary drains, percutaneous internalized biliary stents, percutaneous cholecystostomy tubes, and operative biliary drainage prior to pancreaticoduodenectomy. Operative biliary drainage included T-tube choledochostomy, choledochojejunostomy, and choledochoduodenostomy.

Intraoperative Bile Cultures

An intraoperative bile culture was obtained at the time of pancreaticoduodenectomy when the bile duct was surgically divided. Intraoperative bile specimens for bacteriologic examination were routinely cultured and observed for 72 hours using three aerobic media (chocolate agar, colistin nalidixic acid agar, and MacConkey agar) and three anaerobic media (anaerobic blood agar, phenylethanol agar, and kanamycin/vancomycin blood agar). Intraoperative bile specimens were generally not specifically cultured for mycobacteria or viruses. Because *Candida* species and other rapidly growing yeasts will eventually grow in the bacterial cultures, special yeast cultures were generally not performed. However, the bacterial culture plates were held and observed for 72 hours to look for *Candida* species and other rapidly growing yeasts.

Evaluation of Postoperative Morbidity and Mortality

IAA was suspected postoperatively in any patient having persistent fever in the absence of wound, urinary, or pulmonary complications, or the development of unexplained clinical deterioration. Patients suspected of IAA underwent computed tomography (CT) of the abdomen and pelvis in an attempt to identify any localized intra-abdominal collection of fluid and gas that was suggestive of IAA. IAA fluid was obtained for culture at the time of CT-guided aspiration and drainage, at the time of reexploration and drainage, or from intraperitoneal drains placed in proximity to the pancreaticojejunostomy or biliary-enteric anastomosis at the time of pancreaticoduodenectomy. Wound infections were diagnosed clinically, with or without a wound culture. They involved the skin and/or subcutaneous tissue of the incision and were characterized by either purulent drainage from the incision, microorganisms isolated from a wound culture, or clinical signs and symptoms of infection (i.e., pain and tenderness, localized swelling, or erythema). Pancreatic leak was defined by an elevated amylase level in fluid obtained from intraperitoneal drains placed in proximity to the pancreaticojejunostomy or biliary-enteric anastomosis at the time

*References 9, 12, 13, 15, 25, 26, 28, 33-39.

of pancreaticoduodenectomy or in fluid obtained from CT-guided or operative intervention of all intra-abdominal fluid collections. Bile leak was defined clinically or by an elevated bilirubin level in fluid obtained from intraperitoneal drains placed in proximity to the pancreaticojejunostomy or biliary-enteric anastomosis at the time of pancreaticoduodenectomy or in fluid obtained from CT-guided or operative intervention of all intra-abdominal fluid collections. Postoperative death was defined as death within 30 days postoperatively or prior to discharge from the hospital.

Statistical Analysis

All statistical analyses were performed using the software program SPSS for Windows (version 8.0) from SPSS, Incorporated. One-way analysis of variance was used to compare the means of continuous variables. Pearson chi-square analysis with Yates' correction for continuity or Fisher's exact test, when appropriate, were used for univariate comparisons for all categorical variables analyzed. When multiple variables were determined to be statistically significant by univariate analysis, then all significant variables were entered into a logistic regression model for multivariate analysis to determine independent predictors of outcome. All preoperative, intraoperative, and postoperative variables examined by univariate and multivariate analyses are shown in Table I. A P value of ≤ 0.05 was considered statistically significant. Inclusion of those additional 79 patients undergoing pancreaticoduodenectomy who did not have an intraoperative bile culture performed at the time of pancreaticoduodenectomy into the statistical analyses did not significantly alter the results.

Table I. Preoperative, intraoperative, and postoperative variables examined by univariate and multivariate analyses

Preoperative
Age
Sex
History of jaundice
History of diabetes mellitus
History of fever and chills within 1 week of admission
Pancreatic biopsy
Biliary instrumentation
Biliary drainage
Total bilirubin level on admission
Benign vs. malignant disease
Intraoperative
Operation (SPD vs. PPPD)
Intraperitoneal drain
Gastrostomy or jejunostomy
Operative time
Blood loss
Red blood cell transfusion
Postoperative
Intra-abdominal abscess
Bacteremia
Urinary tract infection
Wound infection
Pneumonia
Catheter infection
C. difficile diarrhea/colitis
Pancreatic leak
Bile leak
Intra-abdominal sterile fluid collection
Upper gastrointestinal bleeding
Delayed gastric emptying
Paralytic ileum

PPPD = pylorus-preserving pancreaticoduodenectomy; SPD = standard pancreaticoduodenectomy.

RESULTS

Preoperative Variables

The median age was 68 years (range 28 to 87 years). Ninety-two patients (57%) were men and 69 patients (43%) were women. One hundred twenty-two patients (76%) had a history of jaundice. Thirty-five patients (22%) had a history of diabetes mellitus. Twenty-two patients (14%) had a history of fever and chills within 1 week of admission. Twenty-one patients (13%) underwent preoperative pancreatic biopsy. Median preoperative total bilirubin level was 2.0 mg/dl (range 0.2 to 38.4 mg/dl) on admission.

Preoperative Biliary Instrumentation and Drainage

One hundred twenty-five patients (78%) underwent preoperative biliary instrumentation (Table II). A total of 178 preoperative biliary instrumentation

Table II. Method and number of preoperative biliary instrumentation procedures performed in 125 patients*

	Number of each type of PBI procedure performed		
Type of PBI	First PBI (n = 125)	Second PBI (n = 41)	Third PBI (n = 12)
ERCP	118 (94%)	24 (59%)	5 (42%)
PTHC	1 (1%)	15 (37%)	7 (58%)
CBDE	6 (5%)	2 (5%)	0 (0%)

CBDE = common bile duct exploration; ERCP = endoscopic retrograde cholangiopancreatography; PBI = preoperative biliary instrumentation; PTHC = percutaneous transhepatic cholangiography.
*Eighty-four patients underwent one biliary instrumentation procedure, 29 patients underwent two, and 12 patients underwent three.

procedures were performed. Eighty-four patients underwent one biliary instrumentation procedure, 29 patients underwent two biliary instrumentation procedures, and 12 patients underwent three biliary instrumentation procedures. Overall, ERCP was performed in 83% of cases, percutaneous transhepatic cholangiography in 13% of cases, and common bile duct exploration in 4% of cases. Age ($P = 0.786$), sex ($P = 0.682$), preoperative pancreatic biopsy ($P = 0.311$), history of fever and chills within 1 week of admission ($P = 0.183$), preoperative total bilirubin level on admission ($P = 0.599$), and pathologic diagnosis ($P = 0.301$) were not significantly different among those patients who underwent preoperative biliary instrumentation and those who did not. History of jaundice ($P = 0.003$) and history of diabetes mellitus ($P = 0.037$) were significantly different among those patients who underwent preoperative biliary instrumentation and those who did not by univariate analysis. Multivariate analysis of those two preoperative variables by a logistic regression model disclosed that only a history of jaundice ($P = 0.004$) was independently associated with preoperative biliary instrumentation. A history of diabetes mellitus ($P = 0.063$) approached statistical significance by multivariate analysis.

Ninety-four patients (58%) underwent preoperative biliary drainage at the time of preoperative biliary instrumentation (Table III). A total of 119 preoperative biliary drainage procedures were performed. Seventy-two patients underwent one biliary drainage procedure, 19 patients underwent two, and three patients underwent three. Seventy-four biliary drainage procedures were done at the time of the first biliary instrumentation procedure, 35 were done at the time of the second biliary instrumentation procedure, and 10 were done at the time of the third biliary instrumentation procedure. Overall, endoscopic biliary drainage was performed in 73% of cases, percutaneous biliary drainage in 20% of cases, and operative drainage prior to pancreaticoduodenectomy in 7% of cases. Age ($P = 0.146$), sex ($P = 0.299$), history of diabetes mellitus ($P = 0.115$), preoperative pancreatic biopsy ($P = 0.718$), preoperative total bilirubin level on admission ($P = 0.125$), and pathologic diagnosis ($P = 0.560$) were not significantly different among those patients undergoing preoperative biliary drainage and those who did not. History of jaundice ($P = 0.007$) and history of fever and chills within 1 week of admission ($P = 0.064$) were significantly different among those patients undergoing preoperative biliary drainage and those who did not by univariate analysis. Multivariate analysis of those two preoperative variables by a logistic regression model disclosed that only a history of jaundice ($P = 0.006$) was independently associated with preoperative biliary drainage. A history or fever and chills within 1 week of admission ($P = 0.076$) approached statistical significance by multivariate analysis.

Table III. Method and number of preoperative biliary drainage procedures performed at the time of each preoperative biliary instrumentation in 94 patients*

	Number of each type of PBD procedure performed at the time of each PBI procedure		
Type of PBD	At first PBI (n = 74)	At second PBI (n = 35)	At third PBI (n = 10)
ES	67 (91%)	18 (51%)	2 (20%)
EBD	1 (1%)	15 (43%)	3 (30%)
IS	0 (0%)	0 (0%)	4 (40%)
PCCT	0 (0%)	0 (0%)	1 (10%)
TTCD	3 (4%)	1 (3%)	0 (0%)
CDJ	1 (1%)	0 (0%)	0 (0%)
CDD	2 (3%)	1 (3%)	0 (0%)

CDD = choledochoduodenostomy; CDJ = choledochojejunostomy; ES = endoscopic biliary stent; EBD = percutaneous external biliary drain; IS = percutaneous internalized stent; PCCT = percutaneous cholecystostomy tube; PBD = preoperative biliary drainage; PBI = preoperative biliary instrumentation; TTCD = T-tube choledochostomy.

*Seventy-two patients underwent one biliary drainage procedure, 19 patients underwent two, and three patients underwent three.

Intraoperative Variables

One hundred thirty-six patients (85%) underwent a standard pancreaticoduodenectomy and 25 patients (15%) underwent a pylorus-preserving pancreaticoduodenectomy. Pancreaticoduodenectomy was performed for a variety of histopathologic diagnoses (Table IV). Median total operating time was 325 minutes (range 175 to 727 minutes). In 86 patients (53%) diagnostic laparoscopy was performed during the

Table IV. Histopathologic diagnosis in 161 patients undergoing pancreaticoduodenectomy

Histopathology	No. of patients (%)
Adenocarcinoma	
Pancreas	90 (56)
Ampulla	22 (14)
Distal common bile duct	16 (10)
Duodenum	6 (4)
Chronic pancreatitis	13 (8)
Pancreatic endocrine neoplasm	3 (2)
Metastatic tumors	2 (1)
Intraductal papillary mucinous neoplasm of the pancreas	2 (1)
Gastrointestinal stromal tumor	2 (1)
Miscellaneous	5 (3)

same anesthesia before proceeding with the pancreaticoduodenectomy. Median laparoscopy time was 30 minutes (range 7 to 100 minutes). Median intraoperative blood loss was 900 ml (range 100 to 3500 ml). Median transfusion of red blood cells was 0 units (range 0 to 12 units). One hundred twenty-two patients (76%) had an intraperitoneal drain placed in proximity to the pancreaticojejunostomy or biliary-enteric anastomosis at the time of pancreaticoduodenectomy. Thirty-six (22%) had a gastrostomy or feeding jejunostomy placed at the time of pancreaticoduodenectomy. One hundred fifty-seven patients (98%) received perioperative antibiotics.

Intraoperative Bile Cultures

Ninety-four (58%) of the intraoperative bile cultures grew microorganisms (Table V). Seventy percent (66 of 94) of the positive intraoperative bile cultures were polymicrobial. The most common microorganisms isolated from the intraoperative bile culture were *Enterococcus* species (53%), *Streptococcus viridans* (28%), *Klebsiella* species (23%), *Enterobacter* species (20%), *Escherichia coli* (13%), yeast (11%), *Citrobacter* species (10%), and *Bacteroides* species (9%).

Preoperative biliary instrumentation ($P < 0.001$), preoperative biliary drainage ($P < 0.001$), and a preoperative total bilirubin level less than or equal to 2.0 mg/dl ($P = 0.009$) were determined to be statistically significant variables associated with a positive intraoperative bile culture by univariate analysis. Benign pancreatic or peripancreatic disease ($P = 0.075$) approached statistical significance by univariate analysis. Multivariate analysis of those four preoperative variables by a logistic regression model disclosed that only preoperative biliary drainage ($P < 0.001$) was an independent predictor of a positive intraoperative bile culture. A preoperative total bilirubin level less than or equal to 2.0 mg/dl ($P = 0.060$) approached statistical significance by multivariate analysis. The specific type of preoperative biliary drainage procedure performed (nonoperative vs. operative, $P = 0.340$; endoscopic vs. percutaneous, $P = 0.135$), as well as the number of preoperative biliary drainage procedures performed (one vs. two or more, $P = 0.508$), did not change the association between a positive intraoperative bile culture and preoperative biliary drainage.

Table V. Microorganisms isolated from the bile of 94 patients with a positive intraoperative bile culture

Microorganism	No. of positive cultures (%)
Enterococcus species	50 (53)
Streptococcus viridans	26 (28)
Klebsiella species	22 (23)
Enterobacter species	19 (20)
Escherichia coli	12 (13)
Yeast	10 (11)
Citrobacter species	9 (10)
Bacteroides species	8 (9)
Clostridium perfringens	7 (7)
Pseudomonas species	6 (6)
Coagulase-negative staphylococcus	6 (6)
Lactobacillus species	5 (5)
Serratia species	4 (4)
Streptococcus species	4 (4)
Candida albicans	3 (3)
Staphylococcus aureus	2 (2)
Morganella morganii	2 (2)
Hemophilus parainfluenzae	2 (2)
Pantoe agglomerans	2 (2)
Hafnia alvei	2 (2)
Proteus species	1 (1)
Micrococcus species	1 (1)
Diphtheroids	1 (1)

Postoperative Complications

One or more postoperative complications (morbidity) developed in 47% (75 of 161) of all patients. All postoperative complications are shown in Table VI. Postoperative infectious complications occurred

Table VI. Postoperative complications in 161 pancreaticoduodenectomies

Postoperative complications	No. of patients (%)
Any complication (morbidity)	75 (47)
Infectious complications	47 (29)
Wound infection	23 (14)
Intra-abdominal abscess	19 (12)
Delayed gastric emptying	15 (9)
Pancreatic leak	14 (9)
Intra-abdominal sterile fluid collection	11 (7)
Urinary tract infection	10 (6)
Upper gastrointestinal bleeding	8 (5)
Bacteremia	7 (4)
Catheter infection	7 (4)
Pneumonia	4 (3)
Paralytic ileus	4 (3)
C. difficile diarrhea/colitis	4 (3)
Bile leak	2 (1)
Tachyarrhythmia	2 (1)
Cerebrovascular accident	2 (1)
Intra-abdominal bleeding	2 (1)
Myocardial infarction	1 (0.5)
Deep venous thrombosis	1 (0.5)
Hepatic necrosis/failure	1 (0.5)
Cecal infarction	1 (0.5)
Small bowel infarction	1 (0.5)
Small bowel obstruction	1 (0.5)
Incarcerated inguinal hernia	1 (0.5)

in 29% (47 of 161) of all patients. Preoperative biliary drainage ($P = 0.001$) and preoperative biliary instrumentation ($P = 0.023$) were determined to be statistically significant variables associated with postoperative infectious complications by univariate analysis. Multivariate analysis of those two preoperative variables by a logistic regression model disclosed that only preoperative biliary drainage ($P = 0.022$) was an independent predictor of infectious complications. The specific type of preoperative biliary drainage procedure performed (nonoperative vs. operative, $P = 0.708$; endoscopic vs. percutaneous, $P = 0.466$), as well as the number of preoperative biliary drainage procedures performed (one vs. two or more, $P = 0.675$), did not change the association between infectious complications and preoperative biliary drainage. Median postoperative hospital stay was 11 days (range 4 to 52 days).

Intra-abdominal Abscess. IAA developed in 12% (19 of 161) of patients. IAA was diagnosed by CT of the abdomen in 18 patients and at autopsy in one. Eighty-nine percent (17 of 19) of patients with an IAA had a positive intraoperative bile culture ($P = 0.003$). Cultures were obtained from the IAA in 16 of 19 patients. The microorganisms cultured from the IAAs are shown in Table VII. Eighty-eight percent (14 of 16) of the IAA cultures were polymicrobial. The most common microorganisms isolated from the IAA were *Enterococcus* species (63%), *Streptococcus viridans* (38%), *Bacteroides* species (38%), coagulase-negative staphylococcus (25%), *Enterobacter* species (19%), *Escherichia coli* (19%), yeast (19%), *Klebsiella* species (19%), and *Pseudomonas* species (19%). Fourteen of the 16 patients with culture-proved IAA had a positive intraoperative bile culture. All 14 of these patients (100%) had one or more of the same microorganism(s) in both the intraoperative bile culture and the IAA culture.

Preoperative biliary drainage ($P < 0.001$) and preoperative biliary instrumentation ($P = 0.008$) were determined to be statistically significant variables associated with IAA by univariate analysis. Multivariate analysis of those two preoperative variables by a logistic regression model disclosed that only preoperative biliary drainage ($P = 0.061$) approached statistical significance as an independent predictor of IAA. The specific type of preoperative biliary drainage procedure performed (nonoperative vs. operative, $P = 0.646$; endoscopic vs. percutaneous, $P = 0.999$), as well as the number of preoperative biliary drainage procedures performed (one vs. two or more, $P = 0.999$), did not change the association between IAA and preoperative biliary drainage.

Wound Infection. Wound infection developed in 14% (23 of 61) of patients. Eighty-seven percent (20 of 23) of patients with a wound infection had a positive intraoperative bile culture ($P = 0.003$). Wound cultures were obtained from 18 of 23 wound infections. The microorganisms cultured from the wound infections are shown in Table VIII. Sixty-one percent (11 of 18) of wound infections were polymicrobial. The most common microorganisms isolated from wound infections were *Enterococcus* species (39%), *Staphylococcus aureus* (28%), *Enterobacter* species (22%), coagulase-negative staphylococcus (22%), *Klebsiella* species (17%), *Streptococcus viridans* (11%), diphtheroids (11%), and *Proteus* species (11%). Sixteen of the 18 patients with culture-proved wound infection had a positive intraoperative bile culture. Eleven (69%) of these 16 patients had one or more of the same microorganism(s) in both the intraoperative bile culture and the wound culture.

Table VII. Microorganisms isolated from 16 culture-proved intra-abdominal abscesses

Microorganisms	No. of positive cultures (%)
Enterococcus species	10 (63)
Streptococcus viridans	6 (38)
Bacteroides species	6 (38)
Coagulase-negative staphylococcus	4 (25)
Enterobacter species	3 (19)
Escherichia coli	3 (19)
Yeast	3 (19)
Klebsiella species	3 (19)
Pseudomonas species	3 (19)
Proteus species	2 (13)
Staphylococcus aureus	2 (13)
Citrobacter species	1 (6)
Streptococcus species	1 (6)
Candida albicans	1 (6)
Clostridium perfringens	1 (6)
Serratia species	1 (6)

Table VIII. Microorganisms isolated from 18 culture-proved wound infections

Microorganisms	No. of positive cultures (%)
Enterococcus species	7 (39)
Staphylococcus aureus	5 (28)
Enterobacter species	4 (22)
Coagulase-negative staphylococcus	4 (22)
Klebsiella species	3 (17)
Streptococcus viridans	2 (11)
Diphtheroids	2 (11)
Proteus species	2 (11)
Yeast	1 (6)
Citrobacter species	1 (6)
Hemophilus parainfluenzae	1 (6)
Bacteroides species	1 (6)
Morganella morganii	1 (6)

Preoperative biliary drainage ($P = 0.041$) was determined to be the only statistically significant variable associated with wound infection by univariate analysis. Placement of an intraperitoneal drain in proximity to the pancreaticojejunostomy or biliary-enteric anastomosis at the time of pancreaticoduodenectomy ($P = 0.069$) approached statistical significance by univariate analysis. Multivariate analysis of those two variables by a logistic regression model disclosed that only preoperative biliary drainage ($P = 0.045$) was an independent predictor of wound infection. The specific type of preoperative biliary drainage procedure performed (nonoperative vs. operative, $P = 0.177$; endoscopic vs. percutaneous, $P = 0.999$), as well as the number of preoperative biliary drainage procedures performed (one vs. two or more, $P = 0.757$), did not change the association between wound infection and preoperative biliary drainage.

Other Postoperative Infectious Complications. Urinary tract infections ($P = 0.524$), pneumonia ($P = 0.142$), bacteremia ($P = 0.999$), and catheter infections ($P = 0.700$) were not associated with positive intraoperative bile cultures.

Postoperative Deaths

There were eight postoperative deaths among the 161 patients undergoing pancreaticoduodenectomies, for a postoperative mortality rate of 5%. Preoperative biliary drainage was determined to be the only statistically significant preoperative or intraoperative variable associated with postoperative death ($P = 0.021$) by univariate analysis. The specific type of preoperative biliary drainage procedure performed (nonoperative vs. operative, $P = 0.523$; endoscopic vs. percutaneous, $P = 0.999$), as well as the number of preoperative biliary drainage procedures performed (one vs. two or more, $P = 0.676$), did not change the association between postoperative death and preoperative biliary drainage. IAA was determined to be the only statistically significant postoperative complication associated with postoperative death ($P = 0.054$) by univariate analysis.

DISCUSSION

In the present study, the incidence of postoperative infectious morbidity and mortality following pancreaticoduodenectomy is consistent with that of most large series reported in the literature.[23-31] We have clearly shown an association between preoperative biliary drainage and positive intraoperative bile cultures, postoperative infectious morbidity, and death. Likewise, we have clearly documented an association between positive intraoperative bile cultures and postoperative infectious complications, with similar microorganism profiles. Taken together these findings suggest that preoperative biliary drainage is an initiating event that leads to bacterial overgrowth in the biliary tract and subsequent development of infectious morbidity and mortality following pancreaticoduodenectomy.

The presence of bacteria in the bile of patients undergoing biliary tract surgery has long been recognized to be associated with an increased incidence of postoperative infectious complications.[40-45] Likewise, these studies have demonstrated that the specific microorganisms isolated from the bile and from postoperative infectious complications of individual patients are virtually identical. In surgically treated pancreatic diseases, this relationship has been less well characterized. Blenkharn and Blumgart[46] have previously shown that postoperative infectious complications following pancreatic surgery for both malignant and benign disease correlate closely with the presence of bacteria in the bile.

Studies in the literature specifically examining the effects of preoperative biliary drainage in patients undergoing pancreatic surgery for pancreatic and peripancreatic lesions are limited, and their results are extremely variable.* Those studies[9,12,13,15,33] comprised of small, heterogeneous groups of patients with pancreatic, peripancreatic, and biliary lesions, who have undergone biliary-enteric bypass far more often than pancreaticoduodenectomy, have generally shown no effect of preoperative biliary drainage on outcome following pancreaticoduodenectomy, with the exception of one study that showed a reduction in postoperative morbidity[9] and two studies that showed prolongation of hospitalization.[12,33] Likewise, studies looking exclusively at morbidity and mortality following pancreaticoduodenectomy have generally failed to show an association between preoperative biliary drainage and postoperative morbidity and mortality.[25,26,28,34,37] The results of many of these studies are difficult to interpret because of the lack of any critical analysis of preoperative biliary drainage in these reports.[26,34,37] Last, almost all studies have failed to address the relationship between the microorganism profiles of the intraoperative bile cultures and the postoperative infectious complications.†

Two studies that looked exclusively at morbidity and mortality following pancreaticoduodenectomy are worth mentioning in greater detail.[36,39] A retrospective study by Trede and Schwall[36] examined 285 consecutive patients undergoing pancreaticoduo-

*References 9, 12, 13, 15, 25, 26, 28, 33-39.
†References 9, 12, 13, 15, 25, 26, 28, 33, 34, 36, 37, 39.

denectomy for both malignant and benign pancreatic disease. They stated in their conclusions that patients undergoing preoperative biliary drainage had less postoperative morbidity and mortality, irrespective of the severity of jaundice. However, statistical analysis of their published data for the group of 150 patients with jaundice failed to show any overall statistical significance. A very recent retrospective study by Marcus et al.[39] examined 182 consecutive patients undergoing pancreaticoduodenectomy for both malignant and benign pancreatic disease. Prior to analyzing their data, they excluded 130 of the 182 consecutive patients undergoing pancreaticoduodenectomy for the following reasons: a bilirubin level less than 5 mg/dl (n = 83), biliary drainage procedures other than those done endoscopically (n = 43), and benign pathologic findings (n = 4). In those remaining 30 patients who did not undergo preoperative endoscopic biliary drainage for malignant biliary obstruction, as compared to those 22 patients who did, they found a marginally increased overall complication rate and prolonged hospitalization. Such a preselection process of eliminating 130 of 182 consecutive patients undergoing pancreaticoduodenectomy prior to data analysis for the above-described reasons makes it very difficult to interpret their results as they would apply to all 182 consecutive patients undergoing pancreaticoduodenectomies.

To date, there have been only two studies in the literature that have specifically examined preoperative biliary drainage and its effect on both intraoperative bile cultures and postoperative infectious morbidity and mortality in patients undergoing pancreaticoduodenectomy for pancreatic and peripancreatic malignancies.[35,38] In one such study by Lygidakis et al.,[35] 38 consecutive patients undergoing preoperative ERCP for obstructive jaundice secondary to pancreatic and peripancreatic carcinoma were prospectively randomized to either preoperative biliary drainage or no preoperative biliary drainage, followed by pancreaticoduodenectomy. Similar to our results, these investigators found that microorganisms cultured from the bile intraoperatively were virtually identical to those microorganisms cultured from postoperative infectious complications seen in the same patients. However, they found significantly fewer postoperative positive blood cultures in patients undergoing preoperative biliary drainage and no differences in IAA, wound infection, or mortality. They concluded that preoperative biliary drainage improved outcome and should be a prerequisite when pancreaticoduodenectomy is being considered. Their results regarding postoperative infectious morbidity and mortality differ considerably from those of our study in which patients undergoing preoperative biliary drainage had no difference in postoperative positive blood cultures, as well as significantly more IAA, wound infection, and postoperative mortality, as compared to those patients not undergoing preoperative biliary drainage. The small size of the study by Lygidakis et al.[35] is a potential explanation for the contrasting results between their study and ours.

In a recent study by Karsten et al.,[38] 241 consecutive patients undergoing preoperative ERCP for pancreatic or peripancreatic carcinoma with or without jaundice were retrospectively analyzed for the effect of preoperative biliary drainage on intraoperative bile cultures and postoperative infectious complications and death. In this study, 196 patients subsequently underwent pancreatic resection (163 pancreaticoduodenectomies and 33 total pancreatectomies), whereas 45 patients subsequently underwent biliary-enteric bypass. Similar to our results, these investigators found that microorganisms cultured from the bile intraoperatively were virtually identical to those microorganisms cultured from postoperative infectious complications. Likewise, they found that positive bile cultures were significantly more common in patients undergoing preoperative biliary drainage. However, in contrast to our findings, Karsten et al.[38] found that postoperative infectious morbidity and mortality were not different between the two groups. It is uncertain whether inclusion of patients undergoing total pancreatectomy and those undergoing biliary-enteric bypass for palliation, in addition to those undergoing pancreaticoduodenectomy, contributed to their contrasting results. It is possible, as suggested by Karsten et al.,[38] that the only way to definitively determine how preoperative biliary drainage affects outcome following pancreaticoduodenectomy would be to conduct a large prospective, randomized trial of biliary drainage versus no biliary drainage in patients with potentially resectable pancreatic and peripancreatic lesions and no history of antecedent biliary drainage. However, such a study is unlikely since a significant number of patients presenting to tertiary referral centers have undergone preoperative biliary instrumentation and drainage prior to presentation.

CONCLUSION

Preoperative biliary drainage increases the risk of developing positive intraoperative bile cultures and increased postoperative infectious morbidity and mortality following pancreaticoduodenectomy. Likewise, positive intraoperative bile cultures are associated with subsequent postoperative infectious complications and have strikingly similar microorganism profiles. Although biliary drainage has been shown to be appropriate, definitive therapy in the management

of biliary obstruction from unresectable pancreatic and peripancreatic malignancies, it is our belief that preoperative biliary drainage should be avoided whenever possible in patients who have potentially resectable lesions. Early consultation with a surgeon and utilization of helical CT technology and diagnostic laparoscopy to assist in determining resectability prior to considering biliary drainage may avoid such problems. Such a change in current preoperative management may have a favorable impact on patient outcome following pancreaticoduodenectomy.

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Magnetic Resonance Imaging With Magnetic Resonance Cholangiopancreatography Accurately Predicts Resectability of Pancreatic Carcinoma

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Accurate preoperative staging of pancreatic malignancy aids in directing appropriate therapy and avoids unnecessary invasive procedures. We evaluated the accuracy of magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) in determining resectability of pancreatic malignancy. Twenty-one patients with suspected pancreatic malignancy underwent dynamic, contrast-enhanced breath-hold MRI with MRCP prior to surgical evaluation. Results of this study were correlated with operative results and pathologic findings. The sensitivity, specificity, and accuracy of MRI with MRCP in detecting a mass, determining the nature of the mass, and predicting lymph node involvement and resectability were determined. MRI with MRCP correctly identified the presence of a pancreatic mass in all 21 of these patients. Following pathologic correlation, it was determined that MRI with MRCP was 81% accurate in determining the benign or malignant nature of the pancreatic mass and 43% accurate in predicting lymph node involvement. In predicting resectability, MRI with MRCP had a sensitivity of 100%, specificity of 83%, positive predictive value of 94%, negative predictive value of 100%, and accuracy of 95%. MRI with MRCP is an accurate, noninvasive technique in the preoperative evaluation of pancreatic malignancy. Information obtained from MRI with MRCP including identification of a mass and predicting tumor resectability may be of value in staging and avoiding unnecessary invasive diagnostic procedures in patients with pancreatic cancer. (J GASTROINTEST SURG 1999;3:506-511.)

KEY WORDS: Magnetic resonance imaging (MRI), pancreatic cancer, magnetic resonance cholangiopancreatography (MRCP)

Because of difficulties in early diagnosis, aggressiveness of pancreatic cancer, and lack of effective systemic therapies, only 1% to 4% of patients with adenocarcinoma of the pancreas will be alive 5 years after diagnosis.[1] Many patients considered to have resectable pancreatic malignancies based on preoperative imaging studies will be found to have unresectable disease at the time of surgery. Noninvasive modalities that have been used in the preoperative evaluation of patients with suspected pancreatic malignancy include CT scan and magnetic resonance imaging (MRI). Spiral CT is the most frequently used imaging modality in this disease and has generally been considered the test of choice because it gives high levels of pancreatic enhancement and lack of respiratory artifact.[2] MRI has been considered a second line of investigation for patients with pancreatic cancer. Some studies have demonstrated a limited ability for spiral CT to predict resectability of pancreatic malignancy, although the most recent data have demonstrated substantial improvements.[3,4] Technical advances in MRI, including the use of fast, breath-hold imaging techniques, magnetic resonance cholangiopancreatography (MRCP), and dynamic contrast-enhanced studies allow for thin-section studies of the pancreas. These advances have also provided improved staging results for MRI in the evaluation of pancreatic cancer, and in some studies better results than CT.[5,6] Our goal was to evaluate the accuracy of state-of-the-art MRI with MRCP in predicting resectability of pancreatic malignancy.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 21 patients undergoing MRI with MRCP for the eval-

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uation of suspected pancreatic malignancy from March 1996 to December 1997, who also underwent surgical exploration. During this time period, a total of 314 patients were referred for MRI with MRCP. Those studies done to evaluate biliary calculous disease, biliary strictures, and acute or chronic pancreatitis were excluded from this analysis. Follow-up was obtained on all patients undergoing MRI with MRCP during this time period.

All MRI examinations were performed on a 1.5 Tesla machine (Vision, Siemens Components Inc., Iselin, N.J.) equipped with a commercially available high-performance gradient system and a body phased-array coil. For MRCP, heavily T2-weighted coronal and axial images were obtained with 4 mm sections using a **H**alf-Fourier, **A**cquisition **S**ingle-shot **T**urbo spin-**E**cho (HASTE) sequence.[7,8] The matrix size was 160*256 and the field of view was ≤40 cm in all cases. Therefore in-plane spatial resolution was ≤2.5 mm × 1.5 mm. The repetition time (TR) was infinite, the echo time (TE) was 60 msec, and 160-degree refocusing pulses were used. With these parameters, 20 slices could be obtained in 18 seconds. In patients who could cooperate for a breath hold, an additional coronal projection sequence was used that generates images similar in appearance to conventional cholangiograms. This is a single-shot turbo spin echo with an infinite TR, a TE of 1100 msec, and a matrix of 240*256. Five 10 mm sections were obtained in a 20-second breath hold. Two separate sets of images were acquired. Both individual sections and maximum intensity projection data were used in the initial interpretations.

To visualize the pancreas with MRI, T1-weighted breath-hold gradient echo sequence (TR ≤190 msec, TE = 4.1 msec, flip angle = 70 to 90 degrees) images were obtained with a section thickness of 5 to 7 mm. Images were acquired prior to, 10 seconds, 40 seconds, and at 2 minutes following the administration of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist, Berlex laboratories, Wayne, N.J.) injected at approximately 2 ml/sec by hand bolus.

Spiral CT examinations were also performed in 11 of 21 patients. Quality contrast-enhanced spiral CT scans were available for review in 9 of 21 patients. Two patients had renal insufficiency and received only oral contrast medium for their CT scans. CT scans that were performed at outside institutions were not included in this study because of variations in technique and quality.

Findings from MRI with MRCP in these 21 patients were correlated with other study results, operative and pathologic findings. The ability of MRI with MRCP to detect a mass, determine mass size, and distinguish the nature of the mass was evaluated. Masses visualized on MRI with MRCP were characterized as malignant, benign, or indeterminate and correlated with pathologic findings. Malignant lesions were defined as discrete masses appearing hypointense with respect to background pancreatic parenchyma on postcontrast T1-weighted images. Benign lesions were defined as small simple cysts (<3 cm) or those fulfilling the criteria for a diagnosis of microcystic serous tumors, or when there was pancreatic ductal dilatation and no mass was seen. Indeterminate lesions were poorly defined areas of signal difference or morphologic distortion of the gland and no focal signal abnormality; larger cysts without septations or rim thickening were also considered indeterminate.

In resected specimens, the ability of MRI with MRCP to predict lymph node involvement with cancer was determined. Negative lymph nodes were defined radiologically as nodes smaller than 1 cm. In all patients, the accuracy of MRI with MRCP in predicting resectability was evaluated. Tumors were determined to be unresectable based on local vascular invasion or distant metastases. Resectable was defined as surgically removable with gross negative margins. Distant metastases were defined as clear evidence of liver metastases or peritoneal disease. Local invasion was defined as evidence of blood vessel encasement or thrombosis of the splenic, superior mesenteric, or portal veins.

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of MRI with MRCP in predicting resectability and lymph node involvement were calculated. In predicting resectability, true positives were defined as those patients who were resected and had no evidence of local vessel invasion or distant metastases on MRI with MRCP and in the operating room. True negatives were defined as those patients who on MRI with MRCP had evidence of local blood vessel encasement or intra-abdominal metastases and were subsequently confirmed at surgery. False positives were those thought to be resectable by MRI criteria who were not found to be resectable at surgery. False negatives were those thought not to be resectable by MRI criteria and were subsequently resected.

RESULTS

The median age of the 21 patients undergoing surgical exploration was 74 years (range 44 to 84 years). The predominant symptoms were jaundice (n = 10) and weight loss (n = 9) (Table I).

The predominant tumor type was ductal adenocarcinoma (n = 16) with two patients having papillary mucinous adenocarcinoma and one patient having a malignant islet cell carcinoma. Two patients had be-

Table I. Demographics and signs and symptoms of patients

Median age (yr)	74 (range 44-88)
Sex (M:F)	13:8
Signs and symptoms	
Jaundice	10
Weight loss	9
Abdominal pain	4
Anorexia	4
Gastric outlet obstruction	3
None	2
Diabetes	1
Fever	1
Pancreatitis	1

Table II. Histologic findings and location of pancreatic lesions

	No. of patients
Histologic type	
Ductal adenocarcinoma	16
Papillary mucinous adenocarcinoma	2
Malignant islet cell carcinoma	1
Macrocytic serous cystadenoma	1
Chronic pancreatitis	1
Lesion location	
Head of pancreas	16
Body	4
Tail	1

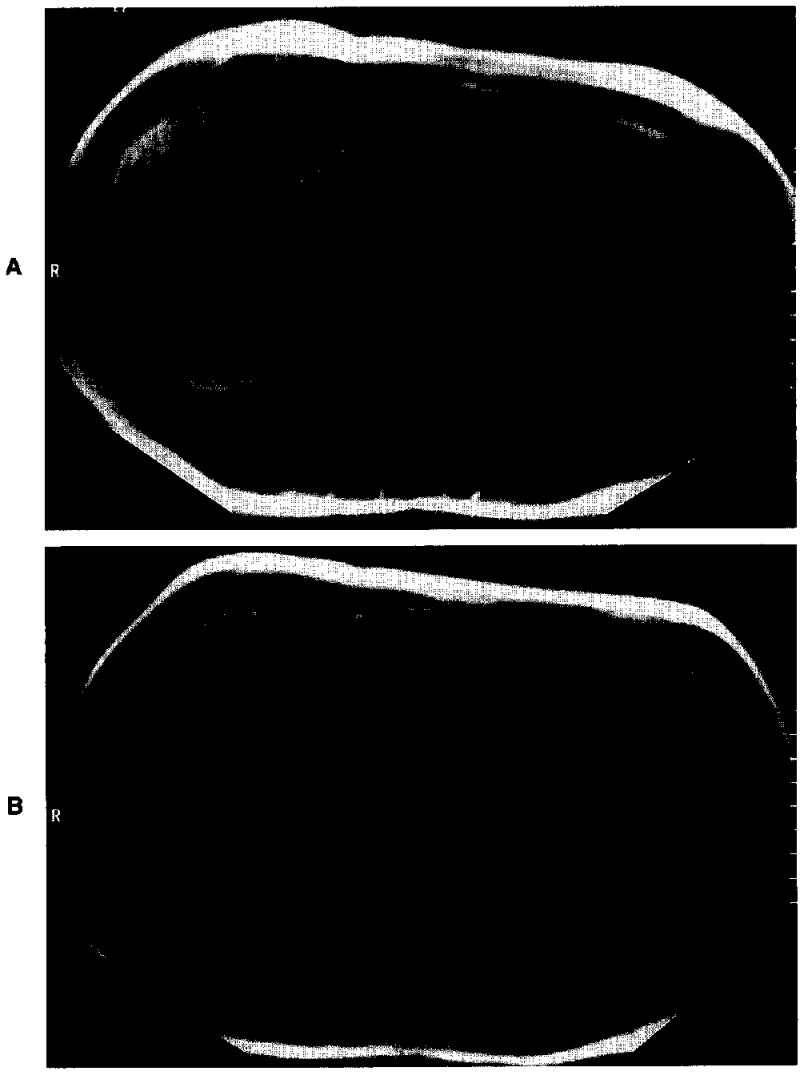

Fig. 1. Adenocarcinoma of the head of the pancreas resected at surgery. **A,** Postcontrast gradient echo T1-weighted image (repetition time/echo time/flip angle = 183 msec/4.1 msec/90 degrees) shows a mass confined to the head of the pancreas (arrow). The mass is hypointense compared to the higher signal intensity of the adjacent parenchyma. **B,** This image was obtained at a more superior level and shows dilatation of both the pancreatic duct (arrows) and the common bile duct (arrowhead).

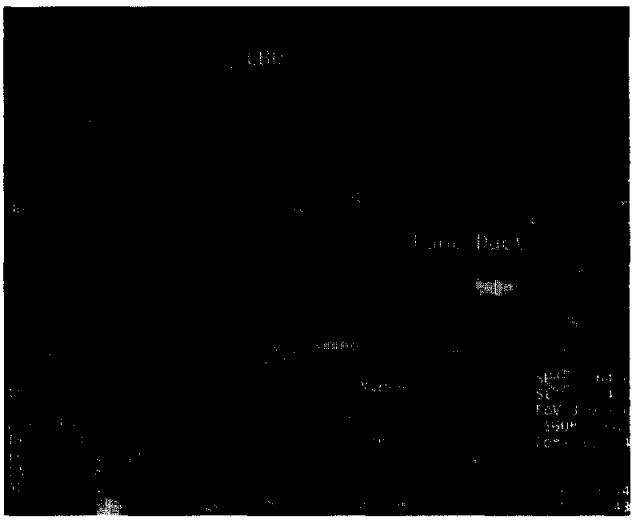

Fig. 2. Thin-section image from an MRCP using a heavily T2-weighted sequence. The pancreatic *(Panc)* duct and common bile duct *(CBD)* are dilated (arrows) and a mass (arrow) is seen at the confluence of the ducts.

nign disease with one patient having a macrocystic serous cystadenoma and one patient having focal pancreatitis in the head of the pancreas. Most patients had disease in the head of the pancreas (n = 16), whereas four patients had tumors in the body of the pancreas and one in the pancreatic tail (Table II).

MRI with MRCP detected a mass in 21 of 21 patients (Figs. 1 and 2). MRI with MRCP characterized the mass as malignant in 18 patients, indeterminate in two patients, and benign in one patient. In predicting malignancy, MRI with MRCP was correct in 17 of 18 patients. The one incorrect reading was in a patient with chronic focal pancreatitis in the head of the pancreas, who on gadolinium-enhanced T1-weighted images had a hypointense area in the head of the pancreas interpreted to be consistent with malignancy. This was found to be an inflammatory mass at pathologic analysis. Of the two masses characterized as being of indeterminate malignant potential by MRI with MRCP, on pathologic review one was benign and one was malignant. One was a patient with a cystic lesion in the head of the pancreas with few septations, and cystic malignancy could not be ruled out. On pathologic examination, this turned out to be a macrocystic serous cystadenoma. The other patient had only indirect signs of malignancy characterized by rounding of the uncinate process. This patient had a small carcinoma of the pancreatic head at pathologic evaluation. The one patient whose lesion was classified as benign on MRI with MRCP had a small, poorly defined mass in the pancreas and a dilated pancreatic duct thought to be due to chronic pancreatitis. This patient underwent endoscopic retrograde cholangiopancreatography (ERCP), which showed a narrowing in the pancreatic duct in the neck of the pancreas suspicious for malignancy. This patient underwent resection and at pathologic examination was shown to have an intraductal papillary mucinous lesion with two foci of microscopic invasive adenocarcinoma. Overall, in predicting the nature of the pancreatic mass, MRI with MRCP had an accuracy of 81%.

In two of the nine patients who had contrast-enhanced spiral CT scans, no definite mass was seen in the pancreas. Both of these patients had masses demonstrated by MRI with MRCP. Indirect evidence of pancreatic pathology, such as double ductal dilatation (n = 1) or intra- and extrahepatic duct dilatation (n = 1), was present in both cases on CT.

The mass size was evaluated on MRI examination and compared to the mass size at pathologic evaluation. The mean mass size by MRI evaluation was 2.7 ± 1.2 cm (range 1.5 to 6.0 cm), whereas at pathologic examination it was 3.9 ± 2.0 cm (range 1.0 to 9.0 cm) ($P = 0.08$).

The ability of MRI to determine lymph node involvement in the field of resection was determined. MRI did not detect positive nodes in any of the patients. Of 13 patients undergoing resection for malignant disease, eight had pathologically positive nodes, whereas five had pathologically negative nodes. Overall, for assessing lymph node involvement, MRI had a sensitivity of 0%, specificity of 100%, and accuracy of 43%.

At operation, 15 of the 21 patients had resection of all gross disease. Of those resected for malignant disease (n = 13), pathologic margins were negative in all but one patient. MRI with MRCP predicted that all 15 would be resectable. Six patients were not resected because of either liver metastases (n = 2), vascular invasion (n = 3), or peritoneal metastases (n = 1). MRI with MRCP correctly indicated nonresectability in five of these six patients. Despite MRI with MRCP findings, two of these patients underwent surgical exploration because they had evidence of gastric outlet obstruction. Unresectability was confirmed at operation in those cases, and a gastrojejunostomy was performed in each as a palliative measure. Three patients had an exploratory operation despite evidence of locally advanced disease on MRI with MRCP. None of these three patients were suitable candidates for resection, thus confirming the MRI findings. There was one patient who was predicted to be resectable by MRI, but this patient was found to have peritoneal metastases at the time of surgery. This is the one false positive. Overall, for predicting resectability, MRI had a sensitivity of 100% (15/15), specificity of 83% (5/6),

positive predictive value of 94% (15/16), and negative predictive value of 100% (5/5) with an accuracy of 95% (20/21).

DISCUSSION

In this retrospective series we have shown that MRI with MRCP is accurate in the preoperative identification of a pancreatic mass and the nature of the mass, and in predicting resectability of pancreatic malignancy. Accurate preoperative staging in pancreatic cancer allows for surgery to be avoided in patients with advanced disease. Furthermore, patients who are suitable for resection can be identified and new treatment protocols (i.e., neoadjuvant therapy) evaluated with respect to the stage of disease, for a better assessment of the outcomes of those protocols.

Noninvasive modalities that are utilized in the workup of a patient with a suspected pancreatic malignancy are sonography, CT scan, and MRI. Currently CT is the dominant noninvasive imaging modality used for the diagnosis and staging of pancreatic cancer.[9] Spiral CT in particular has been shown to provide good depiction of small vessels, high levels of pancreatic enhancement, and lack of respiratory artifact.[2] Despite this, the ability of spiral CT to predict resectability of pancreatic malignancies has been variable. In a small study, spiral CT had an 87% positive predictive value in indicating resectability of pancreatic carcinoma.[4] However, in the largest series published to date, 64 patients who underwent surgery for potentially resectable pancreatic adenocarcinoma were prospectively assessed for tumor resectability with spiral CT. Forty of 64 patients with pancreatic malignancy were found to have unresectable disease at surgery. Of these 40 patients, spiral CT enabled the correct diagnosis of unresectable disease in 21 (53%). Nineteen patients considered to have resectable disease at spiral CT were found to have unresectable disease at surgery.[3]

Laparoscopy has been advocated as an essential part of staging in pancreatic cancer because liver and peritoneal implants may be only a few millimeters in size and may be beyond the resolution of current imaging capabilities.[10] In our series the one case of peritoneal metastases went undetected by MRI. With further advances in noninvasive radiologic imaging,[11] the yield of laparoscopy, which is an invasive and expensive technique, may become smaller. Prospective trials are necessary comparing MRI with MRCP with laparoscopy to determine what, if any, advantage there is to laparoscopy over MRI.

Magnetic resonance abdominal imaging continues to evolve at a rapid pace. Advantages of MRI over CT include absence of ionizing radiation, multiplanar and three-dimensional display capability, and the ability to produce magnetic resonance angiograms.[12] In addition, magnetic resonance studies can incorporate an evaluation of the pancreatic duct and biliary tract with MRCP, which in some cases facilitates surgical planning. Furthermore, the contrast medium most effective for pancreatic magnetic resonance, gadopentetate dimeglumine, is non-nephrotoxic.[13] More recently there are data suggesting that MRI may have an advantage over CT for staging pancreatic malignancy.[6,14] However, there are few studies evaluating state-of-the-art MRI and its ability to predict resectability of pancreatic cancer. Trede et al.[14] evaluated five different modalities (ultrasound, MRI with MRCP, CT scan, visceral angiography, and ERCP) in their ability to predict resectability of suspected pancreatic malignancy. Only 24 (51%) of 47 patients who underwent operative exploration were resected. Of those resected, six had benign disease. Of the five modalities, state-of-the-art MRI was the most accurate in predicting lymph node involvement (80%) and overall resectability (96%). The results for detection of nodal disease are not supported by our study. In our series lymph node involvement was predicted accurately only 43% of the time. The stages of our tumors were not very advanced, as indicated by our resectability rate of 71% with a positive histologic margin rate of only 7%. The increased accuracy in the study by Trede et al.[14] may be due to either the advanced stage of many of the tumors leading to obvious nodal involvement or the large number of patients with benign disease and negative nodes who underwent evaluation. Nevertheless, the overall accuracy in predicting resectability in both studies was quite similar.

In addition to laparoscopy, another invasive technique that is now being used in the evaluation of patients with pancreatic carcinoma is endoscopic ultrasound. This modality has been found to be sensitive for detection of pancreatic tumors.[15,16] At present, whether endoscopic ultrasound is more sensitive than spiral CT or MRI is not known, as adequate studies to examine this have not been done. Although distant metastases must be demonstrated by other imaging modalities, the strength of endoscopic ultrasound may lie in its ability to predict local resectability.[17] Nevertheless, an MRI examination that is noninvasive and provides information pertaining to both local resectability and distant metastases appears to be a more attractive option than an invasive and limited examination such as endoscopic ultrasound. Other concerns in utilizing endoscopic ultrasound include the operator-dependent nature of this technique, the fact that

the uncinate process is not well visualized, and the time-consuming need for multiple images and angles to view the entire pancreas and periampullary region.

Most recently, positron emission tomography (PET) has been evaluated in the diagnosis and staging of pancreatic cancer. In a study of 22 patients with pancreatic cancer, PET scans failed (false negative) to reveal pancreatic tumors in four patients whose tumors were detected by CT scans. In addition, PET scans did not demonstrate any extrapancreatic disease not seen on thin-cut dynamic CT scans. Finally, PET scans did not demonstrate increased regional signal intensity in two patients who had microscopic disease in their peripancreatic lymph nodes.[18] Despite these poor results, further studies will define the role, if any, of PET in pancreatic cancer.

Ideally, preoperative imaging modalities in patients with suspected pancreatic carcinoma should be noninvasive and accurate. In this study MRI with MRCP had an overall accuracy of 95% in predicting resectability of pancreatic adenocarcinoma. Despite these results there are sparse data comparing state-of-the-art CT scans with MRI in predicting resectability of pancreatic carcinoma. In addition, the role of invasive staging techniques following accurate noninvasive imaging is unknown. Prospective studies are needed to compare modalities in order to determine the most accurate and cost-effective staging strategy.

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Squamous Cell Carcinoma of the Pancreas

Kamal M.F. Itani, M.D., Amir Karni, M.D., Linda Green, M.D.

Squamous cell carcinoma of the pancreas is a controversial entity. Although some reports show that it is metastatic from another source, others demonstrate that it is a primary tumor. Between 1988 and 1997, fourteen cases of pancreatic squamous cell carcinoma were identified in the records of our pathology department. In seven instances the features were consistent with squamous cell carcinoma with no adenomatous component. The records of six of these patients were available for review and constitute the basis for this report. Five patients were diagnosed by means of percutaneous CT-guided fine-needle aspiration, whereas the sixth patient was diagnosed using a transduodenal core needle biopsy. At the time of diagnosis four patients had lung lesions, three patients had liver lesions, and two patients had lytic bone lesions. One patient had a 6 cm esophageal lesion. Surgical intervention had no impact on treatment or palliation in one of the patients. Chemotherapy and radiation therapy, alone or in combination, were ineffective in all patients. Median survival from the time of diagnosis was 2 months. We conclude that in cases of squamous cell carcinoma of the pancreas, every effort should be made to exclude adenomatous components histologically within the tumor and to exclude another primary source of squamous cell carcinoma. This will allow a better understanding of this entity and a refinement of therapy. (J GASTROINTEST SURG 1999;3:512-515.)

KEY WORDS: Pancreas, squamous, carcinoma

The most common pancreatic malignancies arise from the exocrine ductal cells with more than 75% showing the classic adenomatous morphology. Reports of ductal carcinomas exhibiting a squamous or mixed adenosquamous morphology are rarely described in the medical literature with several reports giving a frequency of 0.5% to 4%.[1,2] In a review of 6668 cases of exocrine pancreatic cancers from various cancer registries between 1950 and 1985, the reported incidences of squamous and adenosquamous carcinomas were 36 cases (0.005%) and 68 cases (0.01%), respectively.[1]

In this report we review our experience with squamous cell carcinoma of the pancreas with emphasis on its unique diagnostic and pathologic features and clinical presentation, which can distinguish this entity from a primary lesion that has metastasized to the pancreas.

MATERIAL AND METHODS

The records of the pathology department at the Houston Veterans Affairs Medical Center were screened for all reports regarding the pancreas. Between 1988 and 1997, fourteen pancreatic squamous cell carcinomas were identified. All histologic material was reviewed by a single pathologist in all cases. In seven instances the features were consistent with squamous cell carcinoma of the pancreas, whereas the other seven had features that were more consistent with adenosquamous carcinomas. The records of six patients were available for review and constitute the basis for this report.

RESULTS

All patients in this study were men whose mean age was 65 years (range 38 to 80 years). There was no social or ethnic predilection (Table I). Chronic abdominal pain and weight loss were the predominant presenting symptoms; one patient had obstructive jaundice (Table I). CT scan of the abdomen performed in all six patients revealed large, complex tumors with necrotic cores located in the head of the pancreas (Fig. 1). Five patients with apparent metastatic disease were diagnosed by means of CT-guided fine-needle

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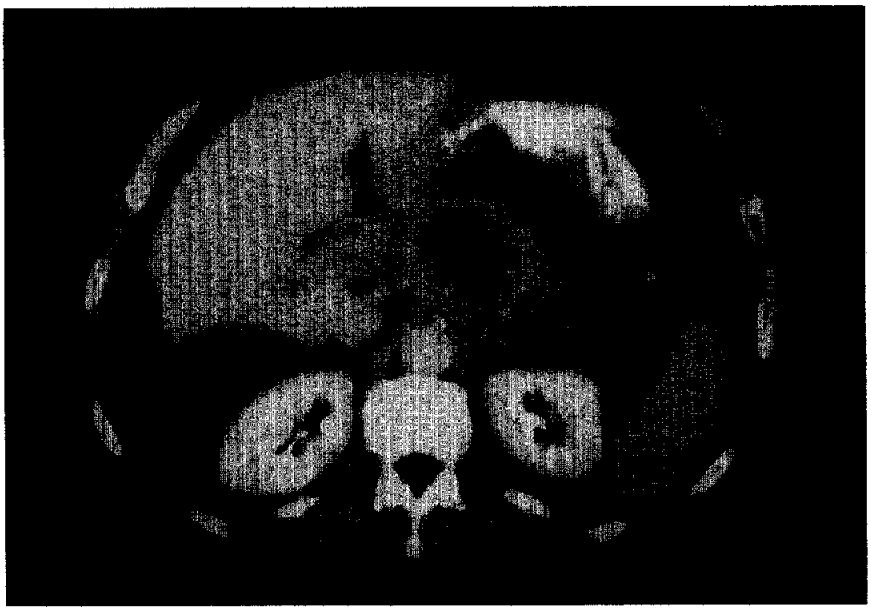

Fig. 1. CT scan of the abdomen of patient 1 shows a large opacified central mass with a fluid-filled cavity. These features were present in all patients and are characteristic of squamous cell carcinoma of the pancreas.

Table I. Clinical features of six patients with squamous cell pancreatic cancer

Patient	Age (yr)	Race	Sex	Symptoms	Diagnosis	Metastasis	Therapy	Survival* (mo)
1	68	White	M	Abdominal pain, weight loss	Transduodenal	None	Surgery	3
2	63	Hispanic	M	Abdominal pain, weight loss	FNA	Lung	Cisplatin/ 5-FU/radiation	1
3	80	Black	M	Abdominal pain, weight loss, jaundice	FNA	Lung, liver, bone	Cisplatin/ 5-FU/radiation	1.5
4	79	Black	M	Abdominal pain, weight loss	FNA	None	Radiation	3.5
5	63	White	M	Abdominal pain, weight loss	FNA	Lung, liver, bone	Cisplatin/ vinblastine	7
6	38	White	M	Abdominal pain, weight loss	FNA	Lung, liver	Radiation	1

FNA = fine-needle aspiration performed under CT guidance; 5-FU = 5-fluorouracil.
*From time of diagnosis.

aspiration. The only patient who underwent exploration was found to have a locally advanced unresectable tumor, and diagnosis was obtained by transduodenal core needle biopsy. In all cases the cells were keratinizing with eosinophilic cytoplasm on hematoxylin and eosin stain forming whorls or pearls with intercellular bridges (Fig. 2). The most common sites of metastasis were lung (4 patients), liver (3 patients), and bone (2 patients).

Patient 1 had a long history of drinking and cirrhosis of the liver but no history of pancreatitis. None of the other patients had pancreatic calcifications on CT scan or a history of pancreatitis. Patient 2 showed a 6 cm ulcer in the distal esophagus on upper gastrointestinal series.

Various treatment modalities were instituted including chemotherapy or radiation, alone or in combination. Chemotherapeutic agents included combinations of cisplatin with 5-fluorouracil or vinblastine (see Table I). The patient with obstructive jaundice was palliated with an endoscopically placed biliary stent. There were no long-term survivors. The me-

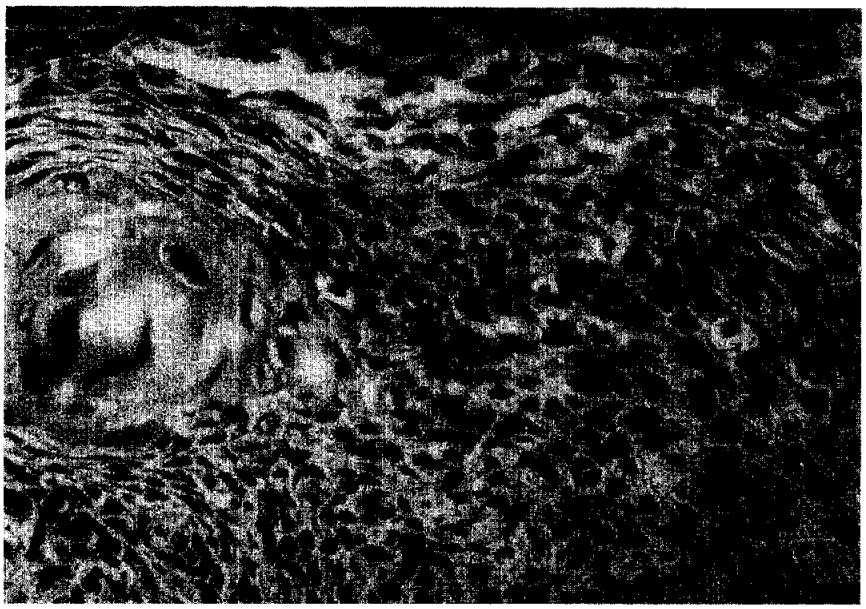

Fig. 2. Pancreatic biopsy of patient 1 shows normal architecture replaced by diffuse infiltrate of neoplastic cells with increased nucleus-to-cytoplasm ratios and large hyperchromatic irregular nuclei with prominent nucleoli. Focally, cells are keratinizing with eosinophilic cytoplasm forming whorls or pearls with intercellular bridges. (Hematoxylin and eosin stain, ×300.)

dian survival for all patients was 2 months (range 1 to 7 months).

DISCUSSION

In its normal state the pancreas is entirely devoid of squamous cells. During periods of inflammation such as in pancreatitis, it is not uncommon to observe squamous metaplasia of the ductal columnar cells.[3] In contrast to the relative frequency of squamous metaplasia, the transformation to squamous cell carcinoma is an unusual occurrence. The transformation has been described in two patients where squamous cell carcinoma was infiltrating a pancreatic pseudocyst[4] and in two others where pseudocysts were seen to coexist with squamous cell carcinoma.[5]

Patient 6 in our series had a significant history of drinking and cirrhosis of the liver discovered at surgery, but no history of pancreatitis. An extensive workup performed postoperatively did not reveal lesions elsewhere in the body.

Despite these reports, metastasis from other sites should always be excluded. Kolbusz et al.[6] reported one patient with asymptomatic esophageal squamous cell carcinoma masquerading as primary pancreatic carcinoma. Patient 2 in our series was also found to have a 6 cm esophageal ulcer on upper gastrointestinal series. Unfortunately, no biopsy of that lesion or postmortem examination was performed. In addition, four of our six patients had lung nodules with the assumption that these were pancreatic metastatic lesions. Although never reported before, the question of squamous cell carcinoma of the lung metastasizing to the pancreas should be entertained.

Histologically, several theories have been advanced for the development of the squamous component in patients with adenosquamous carcinoma. These include the theory of a primitive cell capable of differentiating into either squamous or glandular carcinoma, the theory of squamous metaplasia, and the theory of tumor collision.[7] Clinicopathologic[3] and immunohistochemical[8] studies have helped little in clearing the confusion raised by these theories with only one study showing that squamous cell carcinoma is squamous metaplasia of preexisting adenocarcinoma.[9] In the six cases reported herein, the absence of an adenomatous component in each one would support squamous metaplasia in reaction to chronic inflammation or metastasis from other sources to the pancreas.

Certain common clinical features found in our patients and described elsewhere support a primary pancreatic source. All cases described showed a large opacified mass on CT scan with a fluid-filled cavity consisting of necrotic keratinous debris. Symptoms are always vague consisting of abdominal discomfort

and weight loss (see Table I) with a tumor blush on angiography[10,11] and extravasation of contrast medium into the cystic component of the tumor on endoscopic retrograde cholangiopancreatography.[12] Responses to various chemotherapeutic agents and radiation therapy have been unequivocally poor with one report showing an objective response to bleomycin in one patient.[13]

CONCLUSION

We conclude that in patients diagnosed as having squamous cell carcinoma of the pancreas, a thorough histologic examination for an adenomatous component should be made. In cases where the tumor is of the pure squamous variety, a thorough search should be made for another possible primary lesion. If these potential sites are excluded, the diagnosis of primary squamous cell carcinoma of the pancreas should be entertained and a postmortem examination requested in each case. This should then relieve any doubt concerning a different primary source and ensure that the sample at the time of biopsy was adequate. Unless such a rigid protocol is followed, no advances will be made in defining this entity and developing proper therapy for it.

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Effect of Ileojejunal Transposition on Gastrointestinal Motility, Gastric Emptying, and Small Intestinal Transit in Dogs

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There is speculation that enteroglucagon and peptide YY are responsible for mediating the "ileal brake" known as a suppressive reaction of upper gastrointestinal motility and transit that is induced by the infusion of nutrients into the ileum. We studied changes in motility and transit in dogs with ileojejunal transposition in which the distal ileum is exposed to undigested nutrients. Nine adult mongrel dogs were equipped with strain gauge force transducers placed on the gastric body, antrum, duodenum, and proximal jejunum. Measurements of gastrointestinal motility, gastric emptying, and plasma levels of total glucagon-like immunoreactivity, immunoreactive glucagon, and peptide YY were obtained both before and after either ileojejunal transposition (5 dogs) or sham operation (4 dogs). Postprandial contractions in the gastric antrum and gastric emptying were significantly inhibited after ileojejunal transposition. The inhibitory effect of ileojejunal transposition on antral motor activity was found to correlate with the rise in plasma total glucagon-like immunoreactivity and peptide YY concentrations. However, plasma glucagon levels were unaffected by ileojejunal transposition. These results suggest that hypersecretion of enteroglucagon and peptide YY induced by ileojejunal transposition inhibits postprandial gastric motor function. (J GASTROINTEST SURG 1993;3:516-523.)

KEY WORDS: Ileojejunal transposition, enteroglucagon, peptide YY, gastrointestinal motility, gastric emptying

We have been elucidating the effect of ileojejunal transposition (IJT) on morphology and function of the small intestine.[1-3] IJT is an operative procedure that has been performed experimentally in rats and dogs; the ileal segment of the peristaltic direction is interposed into the proximal jejunum in the IJT operation. IJT induced hypertrophy of the jejunal mucosa as well as the interposed ileal mucosa and pancreas. We showed that plasma concentrations of enteroglucagon (EG) were significantly increased after IJT.[1-3] Thus IJT is considered a suitable model to induce hyperenteroglucagonemia, or hypertrophy of the small intestine and pancreas. However, the effects of IJT on upper gastrointestinal motility have not been reported thus far.

In 1972 Bloom[4] reported a patient with enteroglucagonoma who had severe constipation suggesting that EG had an inhibitory effect on gastrointestinal motility. Infusion of nutrients into the ileum is known to inhibit gastrointestinal motility and transit and to increase plasma concentrations of EG, peptide YY (PYY), or neurotensin (NT) in humans and dogs.[5-7] This inhibitory effect has been termed the "ileal brake," and the possibility has been raised that these peptides, which increase during ileal infusion, may mediate this response.[5-7] Because the interposed ileal segment is exposed to undigested nutrients in the IJT model, the same phenomenon as the ileal brake effect might be occurring in the IJT model. Therefore we hypothesized that the increase in plasma levels of EG and PYY would inhibit upper gastrointestinal motility and transit after IJT. An aim of the present study was to investigate the effects of IJT on upper gastrointestinal motility and transit and on plasma concentrations of EG and PYY.

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Parts of this study were presented at the Ninety-Fourth Annual Meeting of the American Gastroenterological Association, New Orleans, La., 1994, and published as an abstract in *Gastroenterology* 106:A550, 1994.
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MATERIAL AND METHODS

Preparation of Animals

Nine mongrel dogs (16 to 19 kg) of both sexes were used. The dogs were anesthetized with an intravenous injection of thiopental (25 mg/kg; Tanabe Seiyaku Co., Osaka, Japan) and inhalation of halothane (Takeda Chemical Industries, Osaka, Japan). They underwent laparotomy via a midline incision. Four strain gauge force transducers (F-12IS, Star Medical Inc., Tokyo, Japan) were sutured onto the serosal surface of the stomach, duodenum, and jejunum (Fig. 1). The transducer on the gastric body was placed on the side opposite the splenic hilum, the transducer on the gastric antrum was placed 4 cm proximal to the pyloric ring, the duodenal transducer was sutured at the level of the main pancreatic papilla, and the jejunal transducer was placed 10 cm distal to the ligament of Treitz. Lead wires from the transducers were exteriorized through a stab wound made between the scapulae through a subcutaneous tunnel and attached to a small connector as previously described.[8,9] A silicone tube (01-102, Create Medic Co., Ltd., Yokohama, Japan) was positioned in the superior vena cava via the right external jugular vein to withdraw blood samples. The lead wires, small connector, and tube were covered with a jacket to protect them against the dog's scratching. After one week of recovery, recording of gastrointestinal motility and blood sampling were performed. The IJT operation was performed by interposing the distal half of the ileum, except for the *terminal* 10 cm (one fourth of whole small intestine), into the proximal jejunum 15 cm distal to the ligament of Treitz in five dogs (IJT group) as previously reported[3] (Fig. 1). In the four dogs undergoing sham operation, the jejunum and ileum were transected and reanastomosed without transposition.

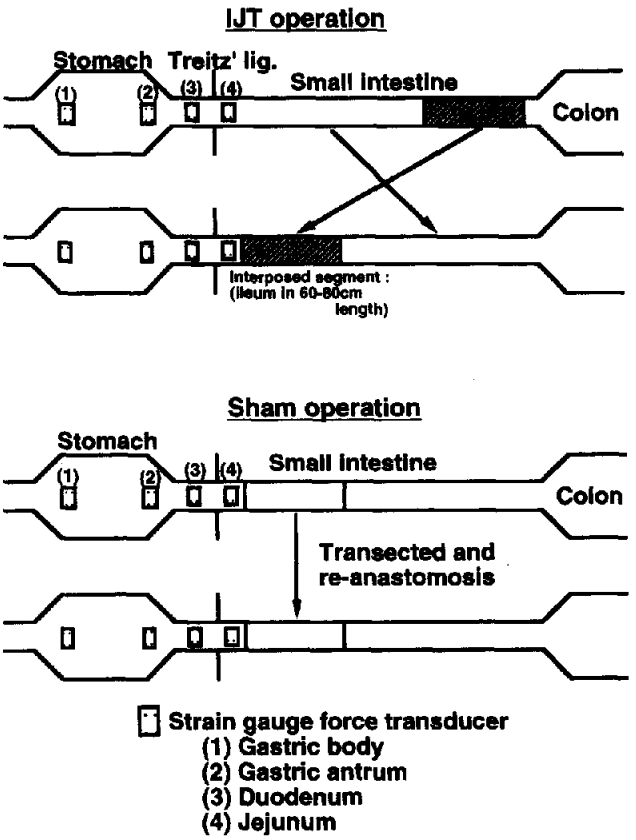

Fig. 1. Schema of the IJT and sham operation. In the IJT group, the distal ileum (60 to 80 cm in length) was transected and interposed into the proximal jejunum isoperistaltically 15 cm distal to the ligament of Treitz. In the sham group, the jejunum and ileum were transected and reanastomosed at the same portion of the anastomosis as in the IJT group.

Measurement of Body Weight

Body weights of all dogs were measured just before implantation of transducers and at the end of the experimental period, approximately 4 weeks after the IJT or sham operation.

Recording and Analysis of Gastrointestinal Motor Activity

Recording of gastrointestinal motility was performed 1 to 2 weeks after implantation of transducers and 4 to 5 weeks after IJT or sham operation. The dogs were housed in individual cages and given water ad libitum. Gastrointestinal motor activity was monitored continuously in a conscious condition. The dogs were fasted for 20 hours, after which their transducer lead wires were connected to an amplifier (MS-08S, Star Medical, Inc.) and activity was simultaneously recorded on both a computer (Eight Star, Star Medical Inc.) and a multichannel recorder (MS-0863, Graphtec Co., Tokyo, Japan). Motor activity was recorded until at least two interdigestive phase III contractions were observed. Then, during the phase I period, the first meal was given and postprandial motor patterns were recorded. When the motor pattern had returned to the fasting pattern and after two interdigestive phase III contractions were observed, the second meal was administered. Thereafter, recording of gastrointestinal motility was continued until at least two phase III contractions were observed. The dogs were fed a commercial diet that consisted of solid food (DS, Oriental Yeast Co., Tokyo. Japan; 15 g/kg body weight) and canned food (Vita One Crux, Japan Pet Food Co., Tokyo, Japan; 15 g/kg body weight) as their first and second meals. Solid food contained 25.9 g protein, 8.2 g lipid, and 7.6 g water and had 369 kcal per 100 g,

whereas canned food contained 10% protein, 5% lipids, and 82% water and had 85 calories/100 g.

Gastrointestinal motility was analyzed within the first 2 hours after feeding; the intensity of postprandial motility was calculated by totaling the areas between the baseline and the contraction waves at all transducer sites using a commercial computer program (Eight Star, Star Medical Inc.). The motor index was expressed as the ratio of postprandial intensity to the average values of intensity obtained from phase III contractions. During the entire monitoring period of gastrointestinal motility, the dogs were given two meals; therefore the postprandial motor index of each dog was represented by the average value of these two motor indexes.

Measurement of Gastric Emptying and Small Intestinal Transit

Gastric emptying and small intestinal transit were measured 1 to 2 weeks after implantation of transducers and again 4 to 5 weeks after IJT or sham operation. After 20 hours of fasting, dogs were given a test meal consisting of 200 g canned food and 50 g barium sulfate (Fushimi Pharmaceutical Company, Marugame, Japan). This canned food contained 10% protein, 5% lipids, and 82% water and had 85 kcal/100 g. The dogs were lifted onto a fluoroscopic table and placed in a supine position. The location of the meal/barium was observed through an x-ray/fluoroscopic system every 15 minutes until the intraluminal meal reached the colon. Gastric emptying was determined as the duration required for the meal mixed with barium to be completely expelled from the stomach, and small intestinal transit was defined as the time between when the meal began to enter the duodenum and when it began to appear in the colon.

Blood Sampling and Hormone Assays

During the continuous recording of gastrointestinal motility, blood samples were drawn from a silicone tube 5 minutes before the first test meal was given and again at 15, 30, 45, 60, 90, 120, 150, and 180 minutes postprandially. Blood samples were collected in ice-chilled glass tubes (NT-EA0205, Nipro Co., Osaka, Japan) containing ethylenediaminetetraacetic acid (EDTA; 1.25 mg/ml) and aprotinin (500 KIU/ml). The plasma was separated by centrifugation at 3000 rpm for 15 minutes and stored at −30° C until hormone assay.

The concentrations of plasma total glucagon–like immunoreactivity (total GLI) and plasma glucagon immunoreactivity were measured by radioimmunoassay using antiserum G25[10] and a Daiichi radioimmunoassay kit (Daiichi Radioisotope Association, Tokyo, Japan), respectively. The levels of plasma immunoreactive PYY were determined with a commercial PYY radioimmunoassay kit (RIK-7173, Peninsula Co., Belmont, Calif.) using plasma extracted by the method of Jorpes et al.[11] All sera were measured in duplicate.

Data Analysis

All values are expressed as the mean ± standard error. Paired Student's t test was used for all statistical analyses except for the plasma levels of gut hormones, and P values <0.05 were regarded as significant. The data for the plasma levels of gut hormones were analyzed by means of analysis of variance, and a P value <0.05 was considered significant.

RESULTS

Changes in Body Weight

The body weight before the first operation was 17.3 ± 0.5 kg in the sham group and 17.1 ± 0.5 kg in the IJT group. Before the animals were killed, their body weights were 16.6 ± 0.2 kg and 16.9 ± 0.6 kg, respectively. No significant differences were observed in preoperative and postoperative values between the IJT and sham groups.

Changes in Gastrointestinal Motility

Effect of IJT and Sham Operation on Upper Gastrointestinal Motility. Representative patterns of contractile waves recorded by strain gauge force transducers in sham-operated and IJT dogs are shown in Fig. 2. In the interdigestive state, the regular occurrence of phase III contractions was observed in all recording sites in both the sham and IJT groups. The cycle length of phase III contractions in the jejunum in the sham-operated dogs was 2.3 ± 0.6 hours and 2.4 ± 0.9 hours before and after the operation, respectively, and that in the IJT dogs was 2.1 ± 0.8 hours and 2.2 ± 0.9 hours before and after the operation, respectively; these four values were not different from each other. A test meal was given 20 minutes after the end of a phase III contraction; after feeding, continuous and regular waves characteristic of the postprandial state were observed in both groups.

Motor Index. In the IJT group the postoperative motor index of the gastric antrum was significantly depressed compared to preoperative levels, whereas in the sham group the motor indexes were similar before and after the operation (Fig. 3). The pre- and postoperative motor indexes of the duodenum and

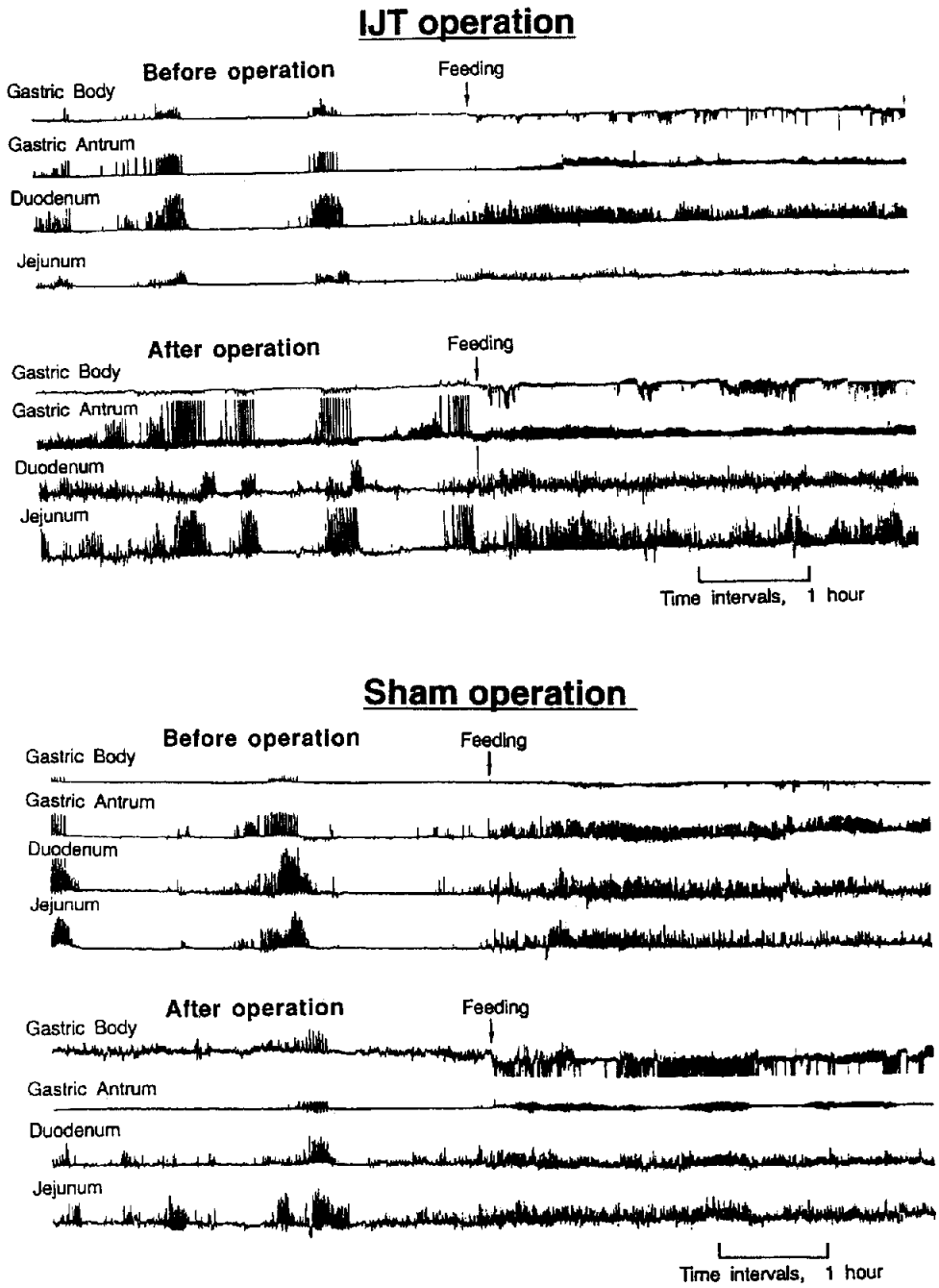

Fig. 2. Effect of the IJT and sham operation on upper gastrointestinal motility.

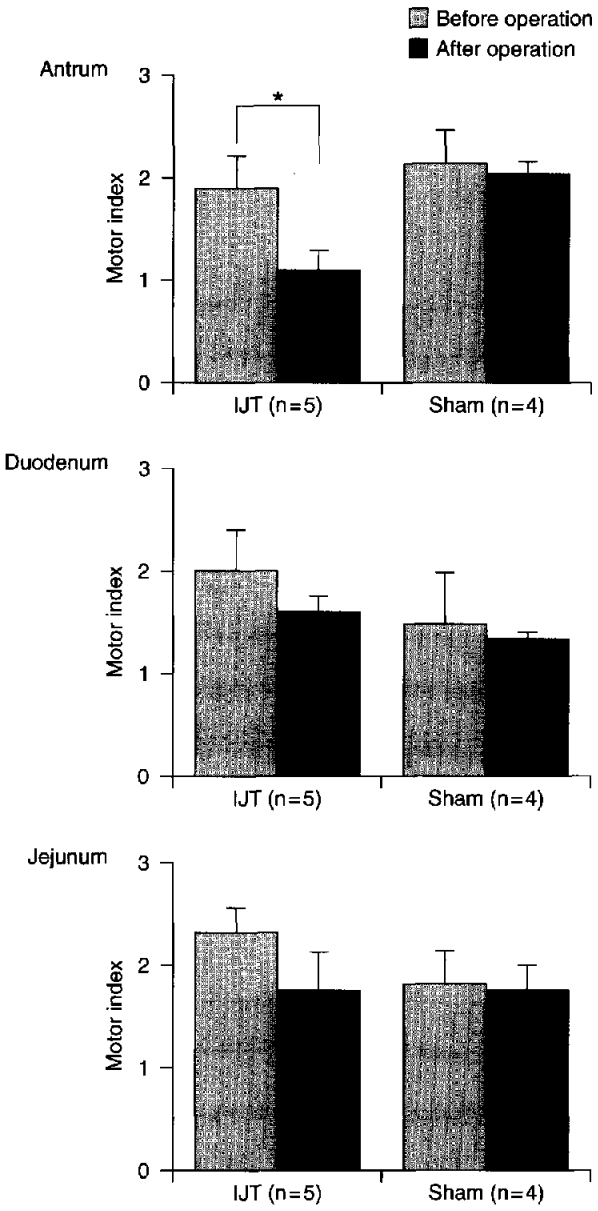

Fig. 3. Effect of the IJT and sham operation on the postprandial motor index. Values are mean ± standard error for five dogs in the IJT group and four dogs in the sham group. * = $P < 0.05$ compared to values before the operation.

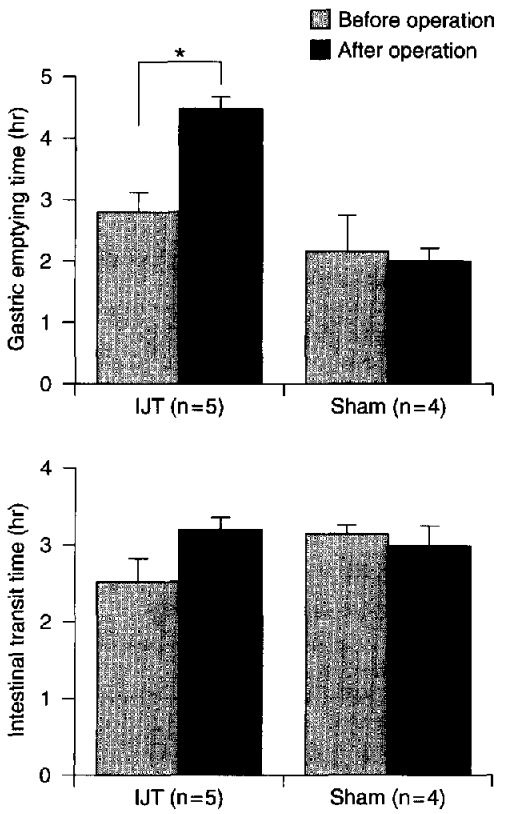

Fig. 4. Effect of the IJT and sham operation on gastric emptying time and small intestinal transit time. Values are mean ± standard error of the mean for five dogs in the IJT group and four dogs in the sham group. * = $P < 0.01$ compared to values before the operation.

jejunum showed no significant changes in either group.

Gastrointestinal Transit. In the IJT group, postoperative gastric emptying was significantly delayed compared to the preoperative value (Fig. 4). In contrast, in the sham group, the postoperative gastric emptying was not significantly different from the preoperative value. There were no significant postoperative changes in small intestinal transit in either group (Fig. 4).

Changes in Postprandial Gut Hormone Secretion

Changes in Plasma Levels of Gut Hormones. Before the IJT operation, the plasma level of total GLI was 1110 ± 40 pg/ml in the fasting state and increased gradually to a peak level of 2100 ± 150 pg/ml at 150 minutes after feeding. After the IJT operation, the plasma level of total GLI in the fasting state was 1940 ± 190 pg/ml and rose to a level of 6000 pg/ml by 90 minutes after feeding. Thus, under both fasting and postprandial conditions, postoperative plasma levels of total GLI were significantly elevated at all time points compared with preoperative levels. However, postoperative plasma levels of glucagon in the fasting and postprandial states did not differ significantly from preoperative levels (Fig. 5).

Before IJT, the plasma level of PYY was 15 ± 10 pg/ml in the fasting state and began to increase 30 minutes after feeding; levels peaked at 65 ± 11 pg/ml by 150 minutes, with a slight decline at 180 minutes. After IJT, the plasma level of PYY was increased to

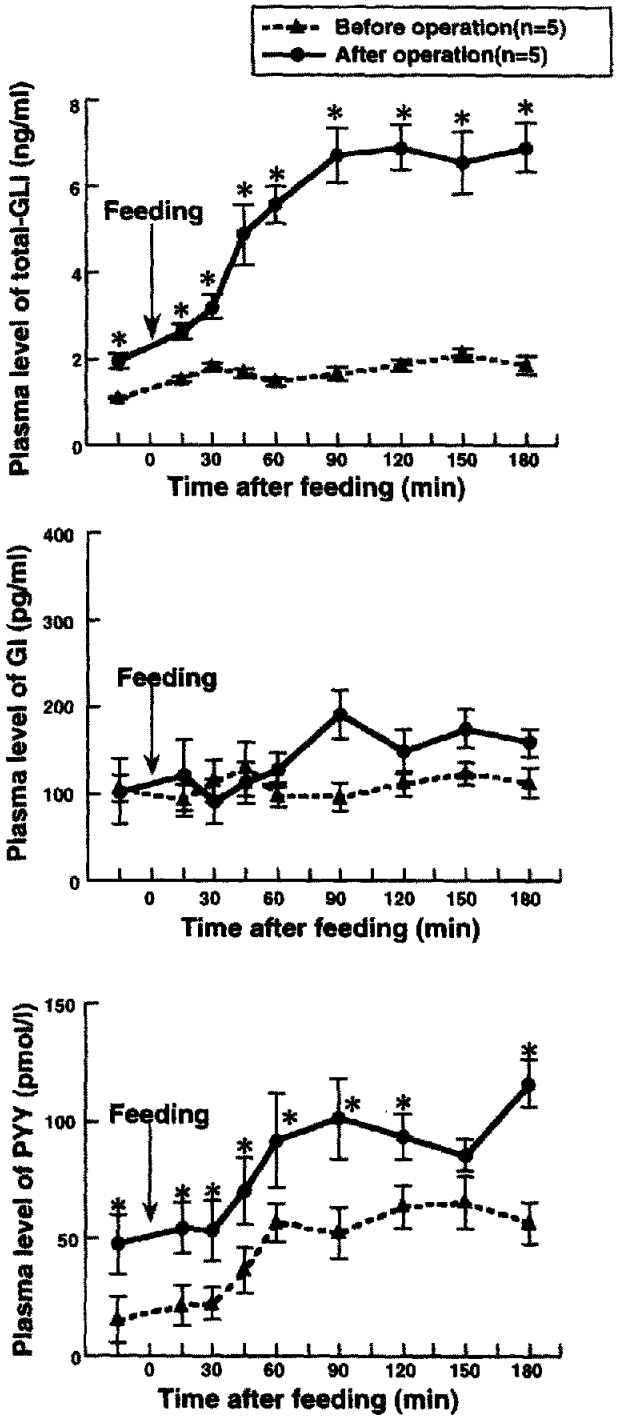

Fig. 5. Changes in plasma levels of gut hormones in the IJT group. Values are mean ± standard error of the mean for five dogs. * = $P < 0.05$ compared to values before the operation.

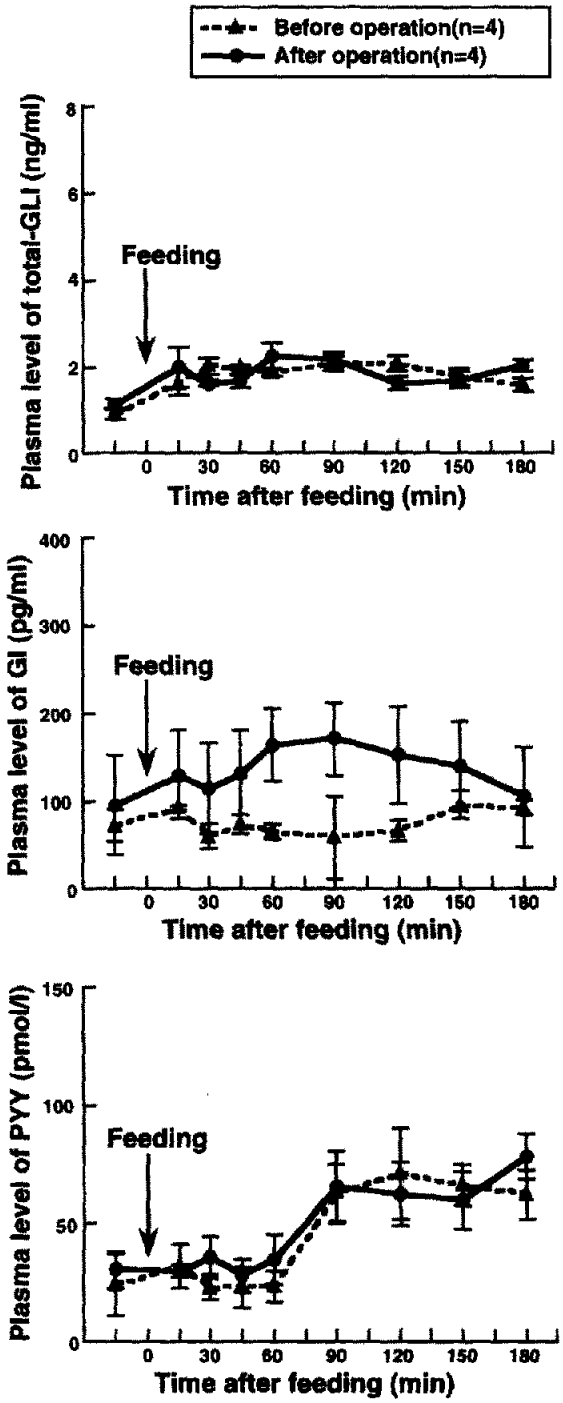

Fig. 6. Changes in plasma levels of gut hormones in the sham group. Values are mean ± standard error of the mean for four dogs.

47 ± 13 pg/ml in the fasting state compared to the preoperative level ($P < 0.05$). After feeding, plasma PYY began to rise after 30 minutes and reached 116 ± 10 pg/ml by 180 minutes, which was twice as high as the preoperative values. After IJT, postprandial plasma PYY levels were significantly increased compared to preoperative values at all time points except for 150 minutes (Fig. 5).

In the sham group, postoperative plasma levels of total GLI, glucagon, and PYY in both the fasting and postprandial states did not differ significantly from preoperative levels (Fig. 6).

Changes in Incremental Gut Hormone Response. In the IJT group, the cumulative increment of plasma total GLI for 3 hours after feeding was 313 ± 22 ng/ml and 1010 ± 94 ng/ml under pre- and postoperative conditions, respectively. Compared with the preoperative response, there was a significant postoperative increase in the cumulative increment of plasma total GLI ($P = 0.009$). Cumulative increments of plasma glucagon (0 to 180 minutes) after the IJT operation (20 ± 3 ng/ml) were not different from the preoperative level (26 ± 5 ng/ml. In the IJT group, pre- and postoperative cumulative increments of plasma PYY for 3 hours after feeding were 8.9 ± 1.7 ng/ml and 15.2 ± 2.3 ng/ml, respectively; no statistical difference was observed between these two values ($P = 0.024$).

In the sham group, pre- and postoperative cumulative increments of total GLI were 332 ± 36 ng/ml and 334 ± 28 ng/ml, respectively. Cumulative increments of glucagon (0 to 180 minutes) before and after the sham operation were 13 ± 3 ng/ml and 26 ± 9 ng/ml, respectively. In the sham group, pre- and postoperative cumulative increments of PYY were 8.8 ± 2.0 ng/ml and 9.2 ± 1.9 ng/ml, respectively. These data for incremental responses in the sham group indicated no difference between pre- and postoperative conditions.

DISCUSSION

In the present study, we showed that gastric but not small intestinal motility and transit was inhibited after feeding in the dogs with IJT. Plasma concentrations of EG and PYY were significantly increased after IJT compared to before IJT not only in the interdigestive state but also in the postprandial state. Hypersecretion of EG after IJT was presumed by the augmented levels of total GLI measured by an antiserum (G25), which reacts with both pancreatic glucagon and gut GLI, because the plasma levels of pancreatic glucagon were not altered by the IJT operation and were much lower than that of total GLI.

Previous studies have shown an inhibitory effect of intravenously injected synthetic PYY[12,13] and NT[14,15] on upper gastrointestinal motility. However, the effect of not only endogenous EG but also exogenous EG on gastrointestinal motility has not been studied thus far, because glicentin has not been available, which is the major constitutive peptide resulting from the processing of preproglucagon in the distal gut.

Recently, pure human glicentin was successfully synthesized.[16] We demonstrated that postprandial motor activity of the canine gastric antrum but not the small intestine was inhibited during intravenous infusion of glicentin as well as PYY and NT.[16] Therefore inhibitory effects of IJT on gastric motility and emptying must be mediated by these peptides. Increases in plasma concentrations of EG and PYY were considered to be associated with the exposure of the mucosa of the interposed ileal segment to the scarcely digested food; secretory cells of EG and PYY are abundant in the ileum.

We cannot conclude from the present study which peptide, EG or PYY, is more effective in the inhibition of gastric motility and emptying in dogs with IJT. An inhibitory effect of PYY on upper gastrointestinal motility has already been reported. Our study showed that exogenously injected EG also suppressed postprandial gastric motility, and the degree of inhibition induced by EG was not different from that induced by PYY.[16] We consider that both EG and PYY must play a role in the inhibition of gastric motility and emptying induced by IJT. Secretory cells of NT are also abundant in the ileum,[17] and exogenous NT inhibited gastric motility.[15,16] Moreover, Tsuchiya et al.[18] and Chu et al.[19] reported that hypersecretion of NT and hypertrophy of the pancreas and jejunal mucosa also occurred after the IJT operation in rats. Therefore hypersecretion of NT might be observed after the IJT operation in dogs. However, since we did not measure canine plasma levels of NT because of the lack of an appropriate measurement system, we could not exclude the role of NT in IJT-induced inhibition of gastric motility and emptying.

Inhibition of upper gastrointestinal motility and transit induced by infusion of nutrients into the ileum is called the ileal brake reflex.[5,6] Plasma concentrations of EG, PYY, or NT are known to increase during the occurrence of ileal brake, and these peptides are supposed to mediate the response. IJT might be a "chronic" model of the ileal brake, because an interposed segment of the ileum is frequently exposed to incompletely digested food. However, a significant difference between IJT and what is called the ileal brake is that duodenojejunal motility as well as gastric motility is inhibited in what is called the ileal brake; duodenojejunal motility and small intestinal transit were not significantly suppressed in dogs with IJT. This difference may be due to less pronounced stimulus to the mucosa of the interposed ileal segment in dogs with IJT. We speculate that perfusion of the intact ileum with pure nutrient might induce a stronger stimulus to the ileal mucosa compared to the stimulus occurring in the IJT model.

Although our method of measuring gastric emptying and small intestinal transit may have some disadvantage compared to the scintigraphic method, we believe that our method is reliable enough because the same method as ours was used in another recent study.[20]

CONCLUSION

Ileojejunal transposition inhibits postprandial gastric motility and emptying, but not small intestinal motility and transit, possibly through plasma EG and PYY secreted from the mucosa of the interposed ileal segment, although it is possible that unknown peptides other than EG and PYY are involved in IJT-induced motor responses in the stomach.

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Restoration of Myoelectrical Propagation Across a Jejunal Transection Using Microsurgical Anastomosis

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The aim of this study was to determine whether microsurgical anastomosis can restore propagation of jejunal pacesetter potentials (PPs) across a site of canine jejunal transection and preserve motility and transit in bowel distal to the transection. A complete jejunal transection with exact microsurgical anastomosis was performed in five dogs, while five dogs with intact jejunum and five dogs with complete transection and end-to-end conventional macrosurgical anastomosis were used as controls. Long-term recording electrodes and intraluminal, open-tipped pressure catheters were implanted in all dogs. The mean frequency of PPs decreased distal to the transection in both groups of transected dogs. However, aborad propagation of PPs across the anastomosis occurred episodically by 3 months in each dog that had a microsurgical anastomosis, but never occurred in any dog with a conventional macroanastomosis. Moreover, the motility and transit in bowel distal to the transection were unaltered in the dogs with a microsurgical anastomosis, whereas they decreased in the dogs with a macroanastomosis. The conclusion was that microsurgical anastomosis of transected canine jejunum restored episodic propagation of PPs across the anastomosis, and preserved motility and maintained transit in bowel distal to the anastomosis. The conventional macroanastomosis did none of these. (J GASTROINTEST SURG 1999;3:524-532.)

KEY WORDS: Intestinal transection, intestinal anastomosis, intestinal motility, intestinal transit, intestinal electrical activity.

Transection with anastomosis of the small bowel is one of the most commonly performed procedures in gastrointestinal surgery. The layers of the intestine are usually anastomosed using a hand-sewn, inverting, two-layered suturing technique. Although most subjects with such anastomoses appear clinically to recover well, the operation results in a failure of distal propagation of pacesetter potentials (PPs) from the proximal bowel across the transection site to the distal bowel. In dogs a permanent 25% decrease in the frequency of PPs in the bowel distal to the site of transection results.[1-3] In addition, lacking the dominant influence from the duodenal pacemaker, ectopic pacemakers arise in the distal bowel at sites 5 cm to 45 cm distal to the transection.[4] Bowel between the ectopic pacemaker and the transection site is driven in an orad direction, toward the stomach, by the pacemaker.[5] This slows transit and causes stasis in this segment of bowel, and can result in postprandial abdominal pain, nausea, and vomiting.[6]

Our hypothesis was that an exact end-to-end, layer-by-layer anastomosis of the bowel at the site of the transection using an operating microscope and microsurgical techniques would facilitate reestablishment of muscular and neural continuity at the site and so preserve electrical, motor, and transit patterns in the bowel distal to the transection. Our aim, thus, was to determine whether an exact end-to-end anastomosis using microsurgical techniques would restore propagation of PPs across a site of jejunal transection, and preserve motility and transit in the bowel distal to the transection.

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METHODS

These experiments were performed according to the guidelines set forth by the National Institutes of Health and were approved by the Mayo Clinic Institutional Animal Care and Use Committee.

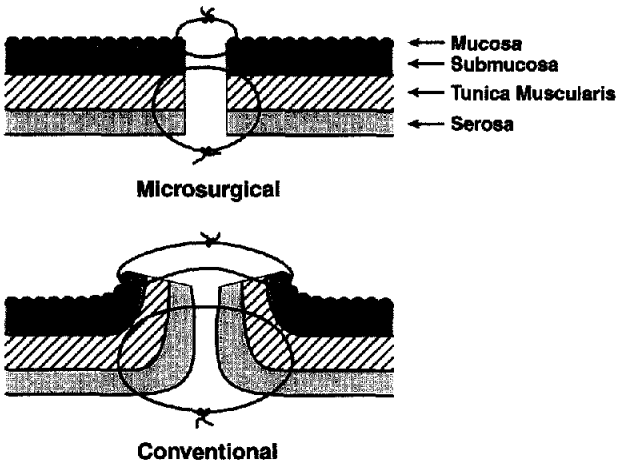

Fig. 1. Diagram of an exact end-to-end, microsurgical, jejunal anastomosis *(above)* and a conventional inverting, hand-sewn, macrosurgical jejunal anastomosis *(below)*.

Canine Experimental Preparations

Fifteen female mongrel dogs weighing between 16 and 22 kg were used in this study. All dogs were given a general anesthetic, and all operations were performed using sterile operative technique. In five dogs the proximal jejunum was transected 19 cm distal to the ligament of Treitz. The bowel was anastomosed in these dogs using an operating microscope and a microsurgical technique. Exact layer-by-layer, end-to-end anastomosis was done using continuous 7-0 polyglycolic acid sutures on the mucosal-submucosal layer and interrupted 7-0 Prolene sutures on the seromuscular layer (Fig. 1). In another five dogs a similar transection was done, but in these dogs a conventional inverting, hand-sewn, two-layered anastomosis (macroanastomosis) was performed using continuous 3-0 polyglycolic acid sutures on the inner layer and interrupted 3-0 silk sutures on the seromuscular layer. In the remaining five dogs no transection or anastomosis was performed.

Seven Ag/AgCl electrodes were sewn to the serosal surface of the jejunum of each dog at 4 cm intervals beginning 9 cm distal to the ligament of Treitz, so that three electrodes were positioned proximal and four distal to the site of transection and anastomosis in dogs with transection (Fig. 2). Four of the elec-

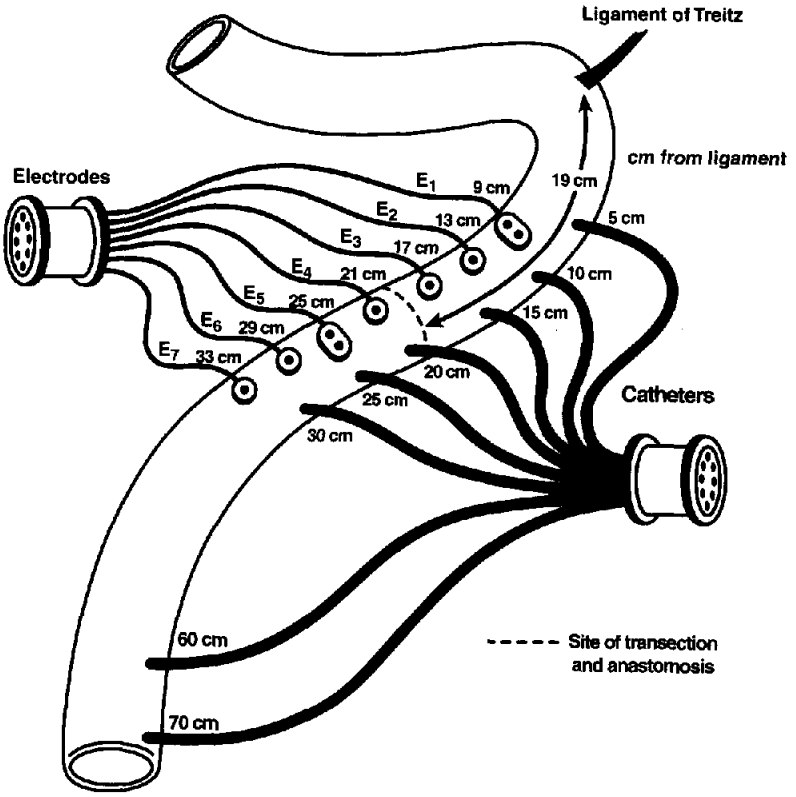

Fig. 2. Canine experimental preparation showing sites of jejunal electrode implantation, catheter implantation, and transection and anastomosis.

trodes were monopolar and two, those at the 9 cm and 25 cm sites, were bipolar. The electrodes were connected by insulated stainless steel wires to a multipin connector embedded in a stainless steel cannula. The cannula was positioned in and anchored to the left anterior abdominal wall.

Six manometric polyethylene catheters (inside diameter = 1 mm) were placed into the jejunal lumen through separate enterotomies in the bowel. These catheters were spaced 5 cm apart, beginning 5 cm distal to the ligament of Treitz, so that three were positioned proximal and three distal to the site of transection and anastomosis in dogs undergoing transection. In addition, a perfusion/aspiration system composed of two catheters was placed intraluminally so that the tips of the catheters were 60 cm and 70 cm distal to the ligament of Treitz. The manometric catheters and perfusion/aspiration catheters were cemented inside a stainless steel cannula and positioned in and anchored to the right anterior abdominal wall (see Fig. 2).

Conduct of Tests

Myoelectric and Manometric Recordings. Testing began 2 weeks postoperatively. Each dog had recordings of jejunal electrical activity and motility at monthly intervals for 3 months. The recordings were performed after an overnight 12-hour fast. The fully conscious dog was placed in a Pavlov stand and the seven electrodes were connected to an amplifier/computer acquisition system. The six manometric catheters were connected to an Arndorfer water perfusion system (Arndorfer Medical Specialties, Greendale, Wis.) with pressure transducers. The catheters were perfused with degassed water at 0.5 ml/min. Monopolar recordings were satisfactory from all electrodes, so only one pole of the bipolar electrodes was used during the recordings. The myoelectric signals were amplified using a six-channel analogue amplifier, and the manometric pressure signals were adapted for computer acquisition through the transducers. The analogue electrical and manometric signals were converted to digital signals that were sampled at 100 Hz and displayed on the VGA monitor. The data were stored and configured on the VAX system and on magnetic media. The study lasted 3 hours to allow a complete cycle of the interdigestive migrating myoelectric complex (MMC) to be recorded.

Jejunal Transit. On different days a transit study was performed on each dog in the fed state. To initiate a fed state in the bowel and to provide a flow of "chyme" that would allow measurement of transit, a nutrient infusion of Meritene (53% carbohydrate, 16% fat, 31% protein) was given to each dog through the manometric catheter located at 20 cm distal to the ligament of Treitz at a rate of 2.0 ml/min. A 0.9% NaCl solution with 5% polyethylene glycol (PEG), as a nonabsorbable marker, was perfused at a rate of 2 ml/min through the distal perfusion port located at 60 cm distal to the ligament of Treitz. After a 30-minute perfusion period to reach a "steady state," intestinal content was aspirated from the distal aspiration port at 70 cm distal to the ligament of Treitz in 10 ml aliquots for 30 minutes. With a steady state being reached, a bolus of a nonabsorbable marker, phenolsulfonphthalein (PSP), 0.125 mg in 0.5 ml volume, was instilled into the proximal perfusion port 20 cm distal to the ligament of Treitz and 1 cm distal to the transection site in the transected dogs. Sampling was continued from the distal aspiration catheter 50 cm downstream and content collected in 2 ml aliquots for 20 minutes. Aliquots were assayed for determination of PEG and PSP concentrations. Recovery of PSP was corrected for fractional intraluminal content recovered as determined by the fraction of PEG recovered. The time from bolus injection to recovery of half the PSP ($T_{1/2}$) was defined as the transit time through the 50 cm jejunal segment.

Postmortem Examination. After the completion of myoelectrical, motor, and transit studies, the animals were killed with an intravenous overdose of pentobarbital sodium (>70 mg/kg). The jejunal segment containing the anastomosis and a similar segment in dogs with intact bowel were carefully removed, inspected, and fixed in formalin. Microscopic sections of these intestinal segments were stained with hematoxylin and eosin for general structure, and with Masson's trichrome stain for fibrous tissue. The degree of approximation of the tunica muscularis and the myenteric plexus at the site of anastomoses were assessed.

Analysis of Data

Myoelectrical Data. Digitized myoelectric signals were analyzed using a VAX/VMS platform by a previously described method.[7] The parameters calculated were PP frequency and percentage of aborad PP propagation during phase 1 of the interdigestive MMC and during phase 3 of the complex. The phases of the interdigestive complex were identified visually using the criteria of Code and Marlett.[8] PP frequency was determined from the period of the individual PPs and expressed as cycles per minute (cpm). Aborad propagation of PPs was identified by assessing the relationship in time between PPs at adjacent electrodes. For example, when a PP at a proximal electrode was followed within 1.5 seconds by a PP at the next most distal electrode, a positive phase lag between the two electrodes was identified and aborad propagation was inferred. In contrast, when a PP at a distal electrode was followed within 1.5 seconds by a PP at the next

most proximal electrode, a negative phase lag was identified and orad PP propagation was inferred. The interval of 1.5 seconds was chosen because pacesetter potentials are propagated in health along the jejunum at a velocity ~5 to 10 cm/sec. Considering the 4 cm distance between electrodes, an individual PP should be detected by an adjacent electrode within 1.5 seconds, if it were being propagated to that electrode. When no propagation was occurring, PPs detected at adjacent electrodes were randomly associated in time. Under these circumstances, an equal chance (50%) was present that a given PP would be designated as propagating aborally or as propagating orally. The details of this method of analysis have been presented in an earlier report.[7]

The mean PP frequency and mean percentage of aborad PP propagation for each dog's 3-month study were calculated, and the overall means of each group of dogs compared using Student's *t* test for unpaired data.

Manometric Pressure Patterns. The manometric tracings were analyzed using the VAX system, and the pressure wave frequency and amplitude were determined. A motility index was calculated for each dog during phase 1 of the MMC and during phase 3 of the MMC, the phase of most vigorous contraction during fasting. The motility index was defined as MI = $\log_e$ (sum of the amplitudes × number of pressure waves + 1).

Transit. The time for one half of the PSP to reach the distal aspiration port was determined by first calculating the fraction of PEG recovered and then determining the percentage of PSP recovered. The time when one half of the PSP had been recovered was calculated.

Statistical Analysis. The mean PP frequency, percentage of aborad PP propagation, motility index, and $T_{1/2}$ transit time for each study on each of the 15 animals were determined, and the grand means were obtained for all five dogs in each of the three groups. Student's *t* test for unpaired data using the Bonferroni correction was applied. Only means that had a *P* value <0.05 were considered significantly different.

RESULTS

All dogs remained healthy through the experiment. They ate well, had no diarrhea, and maintained their weight during the 3-month testing period.

Intact Jejunum

The mean frequency of PPs ± standard deviation (SD) in the intact proximal jejunum of the control dogs during phase 1 of the MMC was 19.5 ± 0.5 cpm (Fig. 3 and Table I). The instantaneous PP frequency

Table I. Effect of transection and anastomosis on canine jejunal pacesetter potentials

Experimental group	Mean ± SD frequency of PPs (cpm)				Mean ± SD % of PPs classified as propagating aborally*					
	Phase 1 of MMC		Phase 3 of MMC		Phase 1 of MMC			Phase 3 of MMC		
	P	D	P	D	P	A	D	P	A	D
Intact bowel (n = 5 dogs)	19.5 ± 0.5	19.5 ± 0.5	19.8 ± 0.4	19.4 ± 0.7	91 ± 14	87 ± 11	88 ± 15	73 ± 3	70 ± 10	74 ± 11
Conventional macroanastomosis (n = 5 dogs)	19.6 ± 0.8	14.0 ± 1.5†	19.9 ± 0.5	14.0 ± 0.9†	86 ± 15	53 ± 5†	72 ± 17†	64 ± 14	53 ± 8†	76 ± 13
Microsurgical anastomosis (n = 5 dogs)	19.1 ± 0.5	13.6 ± 1†	18.8 ± 2	14.2 ± 1.0†	92 ± 10	66 ± 10†‡	64 ± 11†	69 ± 7	52 ± 5†	69 ± 11

PP = pacesetter potential; MMC = migrating myoelectric complex; P = proximal jejunum; A = midjejunum (intact bowel) or across site of midjejunal anastomosis (transected bowel); D = distal jejunum; SD = standard deviation.
*Only values >50% indicate true aboral PP propagation (see text); the greater the value, the more frequent the propagation.
†*P* <0.05 vs. intact bowel.
‡*P* <0.05 vs. macroanastomosis.

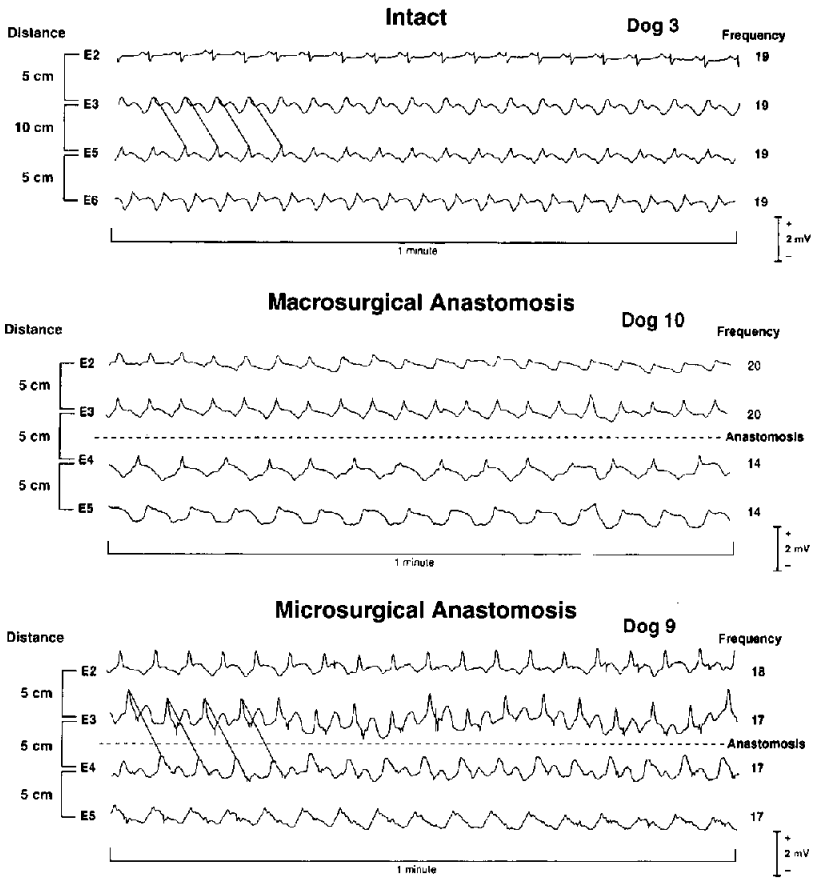

Fig. 3. Jejunal electrical recordings. Pacesetter potentials are propagated distally (slanted lines) along intact jejunum and across a jejunal microanastomosis, but not across a jejunal macroanastomosis. Distance = distance between electrodes *(E);* Frequency = pacesetter potential frequency (cpm).

at single electrode sites varied little over time (Fig. 4). Moreover, the frequency did not clearly differ from the most proximal site studied (20.5 ± 0.6 cpm) to the most distal site studied (19.1 ± 1.0 cpm; $P > 0.05$), 24 cm away. The phase lag between PPs detected by a proximal electrode and by the next most distal electrode 4 cm away also varied little over time (see Fig. 4), a positive pattern consistent with steady aboral propagation of PPs. The overall percentage of PPs propagating aborally during phase 1 of the MMC was 87% ± 11% (see Table I). Although fewer PPs appeared to propagate aborally during phase 3 of the MMC (70% ± 10%), the ability to detect such propagation was less accurate during phase 3. The mean ± SD motility index in the proximal jejunum during phase 1 was 8.1 ± 1.2 units, whereas that in the distal jejunum was 5.7 ± 2.5 units ($P > 0.05$; Table II). The motility index in the proximal jejunum increased to 11.6 ± 0.2 units during phase 3 ($\Delta = 3.5$ units; $P < 0.05$), whereas that in the distal jejunum increased to 10.4 ± 1.4 units ($\Delta = 4.7$ units; $P < 0.05$). The time required for 50% of a nonabsorbable marker to pass through the distal jejunum in the fed state was 5.6 ± 1.8 minutes.

Transection and Conventional Macroanastomosis

In contrast to the dogs with an intact jejunum, the frequency of PPs, during phase 1 of the MMC in dogs with a conventional macroanastomosis, decreased from 19.6 ± 0.8 cpm in bowel proximal to the anastomosis to 14.0 ± 1.5 cpm in bowel distal to the anastomosis ($P < 0.05$; see Table I and Fig. 3). Variation in the instantaneous frequency of the PPs in bowel distal to the anastomosis was greater than in the intact jejunum at a comparable location (see Fig. 4). PPs were not propagated either aborally or orally across the anastomoses. The phase lag between detection of a PP by an electrode proximal to the anastomosis and

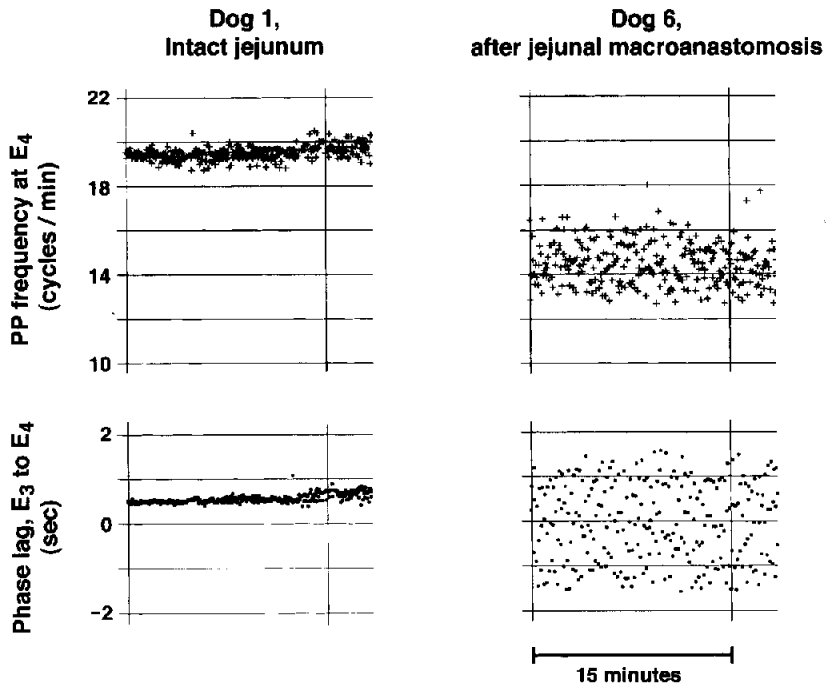

Fig. 4. Plot of the instantaneous frequency of jejunal pacesetter potentials *(PP) (above)* and the phase lag of PPs between electrodes *(E) (below)* against time in a dog with intact bowel *(left panel)* and in a dog after jejunal transection and macroanastomosis *(right panel)*. Electrodes E_3 and E_4 are 4 cm apart. In the transected dog, E_3 is 3 cm proximal to the transection and E_4 is 1 cm distal to it (see Fig. 2).

Table II. Effect of transection and anastomosis on canine jejunal motility

	Mean ± SD motility index (units)			
	Proximal jejunum		Distal jejunum*	
Experimental group	Phase 1 of MMC	Phase 3 of MMC	Phase 1 of MMC	Phase 3 of MMC
Intact bowel (n = 5)	8.1 ± 1.2	11.6 ± 2.0†	5.7 ± 2.5	10.4 ± 1.4†
Conventional macroanastomosis (n = 5)	9.7 ± 3.6	11.2 ± 1.3†	7.8 ± 1.5	8.2 ± 1.5‡
Microsurgical anastomosis (n = 5)	9.5 ± 3.4	11.9 ± 2.0†	7.4 ± 3.1	10.8 ± 1.4†

MMC = migrating myoelectric complex; SD = standard deviation.
*Distal to anastomosis in dogs with transection.
†Values differ from those of phase 1; $P < 0.05$.
‡Differs from values above and below; $P < 0.05$.

detection by an electrode distal to the anastomosis varied randomly, a finding consistent with lack of PP propagation across the anastomosis (see Fig. 4). Under these circumstances, our method of electronic analysis assigned 53% ± 5% of PPs to aborad propagation and 47% ± 5% to orad propagation, a random distribution reflecting no propagation. The mean motility indices in the jejunum proximal and distal to the transection during phase 1 of the MMC were similar to the corresponding values in dogs with intact jejunum ($P > 0.05$; see Table II). The mean motility index in bowel proximal to the transection and anastomosis increased from 9.7 ± 3.6 units during phase 1 to 11.2 ± 1.3 units during phase 3 of the MMC (Δ = 1.5 units), a change similar to that of the intact bowel ($P > 0.05$). In contrast, the index in bowel distal to the transection changed little during phase 3 (Δ = 0.4 units; $P > 0.05$) and was much less than the 4.7 unit change in intact bowel. In addition, jejunal transit in the fed state was slower in bowel distal to the transection in the dogs with conventional anastomosis ($T_{1/2}$ = 10.6 ± 3.6 min) than in the corresponding segment of bowel in dogs with intact bowel ($T_{1/2}$ = 5.6 ± 1.8 min; $P < 0.05$).

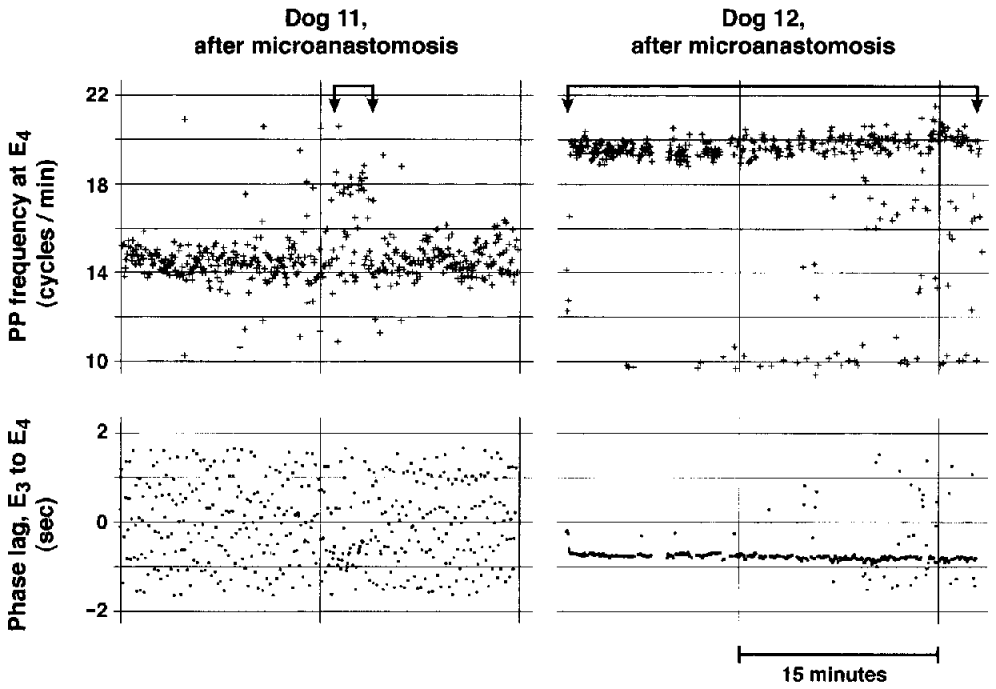

Fig. 5. Plot of the instantaneous frequency of jejunal pacesetter potentials *(PP) (above)* and the phase lag between PPs *(below)* against time in two dogs after jejunal transection and microanastomosis. Electrode E_3 is 3 cm proximal to the anastomosis and electrode E_4 is 1 cm distal to it (see Fig. 2). Connected arrows identify intervals consistent with PPs being propagated across the anastomosis.

Transection and Microsurgical Anastomosis

Microsurgical anastomosis preserved electrical activity, motility, and transit in bowel distal to the transection site better than did the hand-sewn, conventional macroanastomosis. The frequency of the PPs in phase 1 in bowel distal to the anastomosis did decrease with the microanastomosis to 13.6 ± 1 cpm (see Table I), and the instantaneous PP frequency usually varied more in the bowel distal to the anastomosis than in the intact jejunum (Figs. 4 and 5). However, by 3 months after operation, episodes of PP propagation across the anastomosis occurred in every dog. On these occasions, brief increases in PP frequency were found in the bowel just distal to the microanastomosis, and when this happened, the phase lags between PPs detected by electrodes proximal and distal to the anastomosis clustered and became nonrandom (Fig. 5, *left panel*). On other occasions, longer periods of increased PP frequency occurred in bowel distal to the anastomosis. These were accompanied by longer periods of steady PP phase lags across the anastomosis (Fig. 5, *right panel*). The electrical patterns in dogs with a microanastomosis then resembled those in dogs with an intact jejunum, except that these phase lags were sometimes negative (see Fig. 5).

The overall percentage of PPs crossing the anastomosis aborally during phase 1 of the MMC was 66% ± 10% in the dogs with a microscopic anastomosis, in contrast to the lack of propagation across the anastomosis present in the dogs with a macroanastomosis (53% ± 5%; $P < 0.05$). In addition, the mean motility indices during phase 1 of the MMC in bowel proximal and distal to the anastomosis in the dogs with a microanastomosis were similar to those of the control dogs ($P > 0.05$; Table II) and similar increases occurred during phase 3 ($P > 0.05$). Also, jejunal transit distal to the transection and anastomosis was changed little ($T_{1/2}$ = 7.3 ± 2.7 min) compared to the control dogs with intact bowel (5.7 ± 1.8 min; $P > 0.05$).

Postmortem Examination

Dogs with a conventional macroanastomosis showed fibrous thickening and some luminal narrowing on gross examination of the anastomosis. These findings were confirmed by histologic examination, which showed fibrous tissue separating the muscular and neural layers at the anastomosis and inversion of the bowel (Fig. 6). In contrast, little fibrous tissue was present at the site of anastomosis in the dogs with a

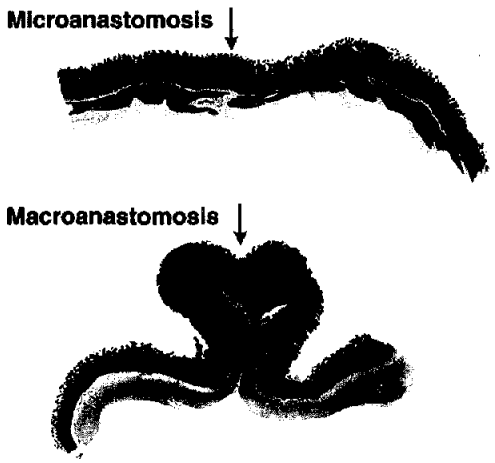

Fig. 6. Photomicrographs of a microsurgical jejunal anastomosis *(above)* and a conventional hand-sewn jejunal macroanastomosis *(below)*. Arrows = anastomotic sites. (Hematoxylin and eosin stain.)

microscopic anastomosis, and no narrowing of the lumen was detected. The tunica muscularis and myenteric plexus were approximated closely and accurately (see Fig. 4).

DISCUSSION

These experiments show that careful end-to-end, layer-by-layer microsurgical anastomosis after complete intestinal transection restored episodic propagation of PPs across the transection site and prevented the decreased motility and slowed transit found in dogs distal to a conventional inverting anastomosis. Propagation of PPs is thought to occur via the smooth muscle syncytium present in the tunica muscularis of the enteric wall. Complete intestinal transection disrupted the syncytium, but the microanastomosis must have restored it, at least in part, to allow episodic propagation to occur. The end-to-end approximation of the microanastomosis resulted in little scar tissue at the anastomotic site and restored the histology so that it more closely resembled that of the healthy bowel than did a macroanastomosis. Horgan et al.[9] found that few nerve fibers regenerate through scar tissue across a colorectal macroanastomosis in dogs. So by minimizing the deposition of scar tissue at the transection site with microanastomosis in this experiment, we likely increased the probability of muscular and neural regrowth. Also, Brookes et al.[10] found in guinea pigs that anally directed neurons reestablish communication across a carefully constructed colonic anastomosis, although at reduced levels. The microsurgical anastomosis apparently increased the probability of neuromuscular regrowth across the anastomosis by decreasing scar tissue and realigning the muscle and neural layers end to end.

The restoration of neuromuscular integrity after microsurgical anastomosis, however, was not complete. Only a small percentage of the PPs propagated across the transection site; the mean frequency of the PPs distal to the transection site (13.6 cpm) was less than in intact bowel (19.5 cpm). Nonetheless, restoration of the integrity of the neuromuscular layer with microanastomosis was of sufficient magnitude to result in preservation of motility during phase 3 of the MMC in bowel distal to the transection. Moreover, transit of content through bowel distal to the anastomosis was also preserved.

A surprising finding was that the direction of episodic PP propagation across the microanastomoses appeared on some occasions to be oral, toward the stomach, as shown in Fig. 6, rather than aboral toward the colon. Although orad propagation of PPs across the microanastomoses may have occurred, it is also possible that transection and anastomosis may have slowed the velocity of PP propagation across the operative site. Should propagation of PPs across the site have required more than 1.5 seconds, our method of analysis would have identified that the PPs were moving in an orad, not aborad, direction. Regardless of the explanation for these findings, however, our analysis of all tracings in all five dogs did identify a preponderance of aboral propagation across the microanastomoses, as shown in Table I. Moreover, propagation across the anastomosis in one direction or the other did occur in every dog with a microanastomosis, but never occurred in any dog with a macroanastomosis.

Whether the beneficial effects of microanastomosis were due solely to the episodic propagation of PPs or to restoration of neural connections across the site of transection is unknown. Others have shown in the guinea pig that reestablishment of neural pathways can occur across an anastomosis if the site of transection is carefully approximated.[10] The present experiments do not provide evidence as to whether disruption of neural integrity or muscular integrity was responsible for the decrease in motility distal to a transection and macroanastomosis. Partial restoration of muscular integrity apparently did occur in the dogs with a microanastomosis. Partial restoration of neural integrity, however, may also have occurred. Special neural stains and neural marker techniques would need to be used on the microanastomotic sites to explore this point further.

Patients who have intestinal transection and conventional macroanastomosis usually do not have symptoms or show overt signs of intestinal motor dysfunction after their operations. Apparently, the gas-

trointestinal tract is able to compensate for the changes produced by the transection, so that function is generally preserved and symptoms avoided. Nonetheless, the abnormalities we found in these tests are clearly present. They may contribute to adverse effects when motility is further impaired or transit slowed for additional reasons, for example, in patients with diabetes mellitus or those with myopathies or neuropathies of the bowel.

In summary, this experiment shows that a microsurgical anastomosis preserves electrical activity, motility, and transit in bowel distal to a transection and anastomosis better than a conventional handsewn, inverting macroanastomosis.

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Differences in Gastric Emptying Between Highly Selective Vagotomy and Posterior Truncal Vagotomy Combined With Anterior Seromyotomy

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Gastric emptying has been reported to be both delayed and unchanged following posterior truncal vagotomy combined with anterior seromyotomy (PTV + AS). When compared to highly selective vagotomy (HSV), our clinical experience was that PTV + AS not uncommonly produced postprandial distress. We studied gastric emptying of both liquids and solids 3 and 12 months following HSV and PTV + AS to determine what if any differences there were in gastric emptying between the two procedures. We compared these results with those from studies done in both normal subjects and unoperated duodenal ulcer patients. In 26 duodenal ulcer patients with perforation (n = 18) or bleeding (n = 8), who were treated with HSV (n = 10) or PTV + AS (n = 16), gastric emptying of liquids and solids was evaluated at 3 months and 12 months postoperatively. At 3 months, gastric emptying of liquids was delayed in both the HSV and PTV + AS groups as compared to values in both normal subjects and unoperated duodenal ulcer patients. The emptying of solids was markedly delayed by PTV + AS in contrast to HSV at 3 months (167.1 ± 28.4 minutes vs. 79.9 ± 16.7 minutes; $P < 0.05$). The lag duration was not affected. A limited number of patients studied at 12 months showed similar and near-normal emptying of solids in both the HSV and PTV + AS groups (67.5 ± 7.0 minutes vs. 70 ± 6.6 minutes). PTV + AS in contrast to HSV produces more marked delayed emptying of liquids and solids at 3 months; with time (1 year) these values return to near normal. (J GASTROINTEST SURG 1999;3:533-536.)

KEY WORDS: Highly selective vagotomy, gastric emptying, posterior truncal vagotomy with anterior seromyotomy

Two operations commonly used in the surgical treatment of duodenal ulcer disease are highly selective vagotomy (HSV)[1-3] and posterior truncal vagotomy combined with anterior seromyotomy (PTV + AS).[4-6] The latter procedure has also been adapted for use via a laparoscopic approach.[7-9] PTV + AS denervates not only the stomach but other portions of the gastrointestinal tract, in particular the duodenum, as well.[10,11]

Previous studies have shown no differences in the rates of gastric emptying of either solids or liquids between these two operations.[3,6,12] The drawbacks of these studies have been the experimental animals used[12] and the small number of patients studied,[6] which limited the significance of the findings. Our clinical experience has shown that although patients undergoing HSV predictably experienced no postprandial distress, patients undergoing PTV + AS had more variable responses. Some patients had considerable postprandial distress. These observations prompted the present studies.

The proximal 5 cm of the duodenum is considered to be a potent reflex inhibition site for gastric emptying.[13-15] A comparison of the effects of these two operations on gastric emptying provides an opportunity to evaluate the role of the posterior vagus in regulat-

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Table I. Emptying of liquids in normal subjects, unoperated duodenal ulcer patients, and patients undergoing HSV or PTV + AS 3 months postoperatively

	Normal (n = 9)	DU (n = 22)	HSV (n = 9)	PTV + AS (n = 16)
T20 (min)	14.2 ± 1.5	16.7 ± 2.8	10.7 ± 1.2	13.7 ± 0.9*
T40 (min)	17.3 ± 1.6	18.9 ± 1.0	21.9 ± 3.0	25.6 ± 2.4†‡
T60 (min)	20.7 ± 1.6	23.6 ± 3.2	29.2 ± 3.5†	33.6 ± 2.3†‡

DU = duodenal ulcers; HSV = highly selective vagotomy; PTV + AS = posterior truncal vagotomy combined with anterior seromyotomy; T20, T40, and T60 = half-time of 20, 40, and 60 minutes.
All values are means ± standard error of the mean.
*$P < 0.05$, HSV vs. PTV + AS.
†$P < 0.05$, normal subjects vs. DU, HSV, and PTV + AS patients.
‡$P < 0.05$, DU vs. HSV and PTV + AS.

ing the emptying of both solids and liquids. This comparison could help delineate vagal innervation of the duodenum in regulating gastric emptying.

METHODS

Patients who were to undergo surgical treatment of their duodenal ulcer disease by either of these two operations were recruited for this study, which was approved by the Human Studies Committee of the hospital. Indications for the operations were either perforation (n = 18) or bleeding (n = 8). Among the patients with perforations, 11 underwent PTV + AS and seven underwent HSV. In the group with bleeding ulcers, PTV + AS was performed in five patients and HSV in three. No patient had either obstruction or intractable pain. Patients were randomly assigned to undergo one of the two operations after it was first determined by the surgeon that either procedure was technically feasible. Both procedures were performed by the same surgical team.

Tests to measure gastric emptying of both solids[4] and liquids[5] were carried out 3 to 4 months after the operation. Emptying of solids was evaluated using technetium 99-DTPA–labeled microcapsules (1 to 2 mm) as a solid particle mixed in 300 ml of rice gruel (congee; protein, 20 cal; carbohydrates, 150 cal).[16] The solid emptying data were analyzed by means of a dual-phase model consisting of a lag phase and an emptying phase. The duration of the lag phase was determined as the interval between ingestion of the meal and the first appearance of detectable amounts of ^{99m}Tc-DTPA in the proximal small intestine.[17-19] The postlag solid emptying data were linearized by logistic transformation, and the slope of these data was used as an index of the speed of gastric emptying in the postlag period. The gastric emptying of liquids was evaluated after an overnight fast using a double-sampling technique (modified George test).[20] A 750 ml liquid cereal meal (protein, 2.56 g; carbohydrates, 38.93 g; fat, 0.91 g) was instilled into the stomach, after the residuum had been aspirated, through a radiopaque gastric tube. The tube had been inserted under fluoroscopic guidance into the body-antrum junction of the stomach. Samples of the gastric contents were aspirated at regular intervals and the concentrations of phenol red determined. A group of volunteers with no history of duodenal disease or other gastrointestinal problems (n = 35) served as control subjects. Duodenal ulcer patients with pain and or bleeding (n = 20) were studied as well.

In the liquid emptying studies, the half-time was the time required for half the volume to leave the stomach during the three periods of observation: 20, 40, and 60 minutes. The values were compared using the unpaired Student's t test. A comparison of the solid emptying results at 3 months was carried out by means of unpaired Student's t test; $P < 0.05$ was considered significant.

RESULTS

The data on the emptying of liquids in normal subjects, unoperated duodenal ulcer patients, and 3 months postoperatively in those treated with either HSV or PTV + AS are presented in Table I; corresponding data on the emptying of solids are presented in Table II. There was a difference in the early phase (20 minutes) of the gastric emptying of liquids (see Table I) between the PTV + AS and HSV groups (13.7 vs. 10.7 minutes). After 40 minutes, gastric emptying of liquids following PTV + AS was delayed compared to values in normal subjects and duodenal ulcer patients (25.6 minutes vs. 17.3 and 18.9 minutes, respectively). At 60 minutes it was delayed in patients undergoing both operations compared to values in normal subjects and unoperated duodenal ulcer patients.

The gastric emptying time of solids was markedly delayed by PTV + AS in contrast to HSV (167.1 vs.

Table II. Emptying of solids in normal subjects, unoperated duodenal ulcer patients, and patients undergoing HSV or PTV + AS (3 months postoperatively)

	Normal (n = 35)	DU (n = 20)	HSV (n = 10)	PTV + AS (n = 16)
Lag duration (min)	22.5 ± 2.1	34.4 ± 6.6	34.5 ± 8.8	44.0 ± 11.0
Emptying time (min)	82.5 ± 6.3	66.0 ± 4.7*	79.9 ± 16.7	167.1 ± 28.4*†‡

DU = duodenal ulcers; HSV = highly selective vagotomy; PTV + AS = posterior truncal vagotomy combined with anterior seromyotomy; T20, T40, and T60 = half-time of 20, 40, and 60 minutes.
All values are means ± standard error of the mean.
*P <0.05, normal subjects vs. DU, HSV, and PTV + AS patients.
†P <0.05, DU vs. HSV and PTV + AS.
‡P <0.05, HSV vs. PTV + AS.

Table III. Emptying of solids in normal subjects, unoperated duodenal ulcer patients, and patients undergoing HSV or PTV + AS (12 months postoperatively)

	Normal (n = 35)	DU (n = 20)	HSV (n = 4)	PTV + AS (n = 6)
Lag duration (min)	22.5 ± 2.1	34.4 ± 6.6	14.8 ± 4.8	11.0 ± 2.1†
Emptying time (min)	82.5 ± 6.3	66.0 ± 4.7*	67.5 ± 7.0	70.0 ± 6.6

DU = duodenal ulcers; HSV = highly selective vagotomy; PTV + AS = posterior truncal vagotomy combined with anterior seromyotomy; T20, T40, and T60 = half-time of 20, 40, and 60 minutes.
All values are means ± standard error of the mean.
*P <0.05, Normal subjects vs. DU, HSV, and PTV + AS patients.
†P <0.05, DU vs. HSV and PTV + AS.

79.9 minutes; P <0.05) (see Table II). The lag duration, namely, the time required for the first portion of the radiolabeled meal to appear in the duodenum, was unaffected by either HSV or PTV + AS.

A limited number of patients (HSV = 4; PTV + AS = 6) were studied 12 months or more later (Table III). At that time the values for gastric emptying of solids were similar in both the HSV and PTV + AS patients (67.5 vs. 70.0 minutes).

DISCUSSION

The findings in this study are at variance with those of a previous report but are consistent with our clinical observations. We noted that some patients in the early postoperative period following PTV + AS had symptoms suggesting gastric retention.

The gastric emptying of liquids and solids was delayed by PTV + AS in contrast to HSV at 3 months. Inasmuch as both procedures are equally effective in denervating the acid-bearing portions of the stomach, the difference in the emptying of solids is presumed to be related to the more extensive denervation of the remainder of the intestine by PTV + AS. The proximal portion of the duodenum in particular is thought to be the site for reflex inhibition of gastric emptying. Previous studies have shown that PTV + AS causes a partial denervation of this critical portion of the intestine, whereas HSV does not.

The mechanism by which the first portion of the duodenum may regulate gastric emptying of liquids and solids is not known. Osmoreceptors, fatty acids and caloric loads, and hormones such as gastrin, glucagon, insulin, somatostatin, cholecystokinin, and motilin[20-22] have been proposed as mechanisms for the mediation of this effect.

Previous investigators, noting the rapidity of the change in gastric emptying following experimental procedures, have postulated that duodenal regulation of gastric emptying is mediated through a neural mechanism.[23] Although hormonal changes were not evaluated in this study, the marked effects of the denervation produced by posterior truncal vagotomy, whether directly or in combination with a hormonal component, are evident 3 to 4 months postoperatively.[24] These changes in gastric emptying appear to improve with time. Some investigators have noted improvement in gastric emptying with time, whereas others have not.[25]

PTV + AS in contrast to HSV denervates the posterior antral nerve. In this and other previous studies, no differences have been noted in the lag time of emptying of solids early postoperatively (3 months). However, PTV + AS causes a marked delay of solid

emptying at 3 months. At 12 months both operations have shorter lag times (see Table III) but the same emptying times. This suggests that no physiologically important gastric sequelae occur as a result of denervation of the posterior antral nerve.

Denervation of the intestine beyond the duodenum may also be involved in causing the delayed emptying of solids. For example, denervation of the intestine as by bilateral truncal vagotomy is accompanied by decreased circulating levels of glucagon.[26]

The mechanism by which the gastric emptying of solids improved between 3 and 12 months is not known. Others have noted delayed gastric emptying in PTV + AS patients persisting beyond 4 years postoperatively.[25]

CONCLUSION

PTV + AS in contrast to HSV produces delayed gastric emptying of liquids and solids early postoperatively (3 months). This effect improves with time (1 year). Based on findings in previous investigations, this early delayed gastric emptying most likely results from denervation of the proximal duodenum by posterior truncal vagotomy.

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Liver Resection Using Total Vascular Exclusion, Scalpel Division of the Parenchyma, and a Simple Compression Technique for Hemostasis and Biliary Control

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Recent improvements in perioperative morbidity and long-term outcome following liver surgery have led surgeons to attempt larger and more technically challenging liver resections. Total vascular exclusion (TVE) of the liver during resection has been proposed as a technique that will facilitate these difficult resections while minimizing blood loss. Total vascular exclusion is performed by obtaining complete isolation of the vascular pedicle of the liver. Once the hepatic vein is clamped, rapid resections may be performed with a loss of only the blood volume contained within the liver itself. Safe performance of total vascular exclusion of the liver requires a thorough understanding of hepatic anatomy, patient selection criteria, and the physiologic changes incurred by hepatic exclusion and subsequent ischemia and reperfusion. The following report discusses these issues, gives a detailed description of the steps involved in obtaining safe total vascular exclusion, and presents a technique using rapid parenchymal excision with a scalpel and capsular compression to obtain hemostasis and prevent bile leaks. We briefly discuss our experience with 144 consecutive resections in which this technique was used. (J GASTROINTEST SURG 1999;3:537-542.)

KEY WORDS: Total vascular exclusion, liver, resection, hepatectomy, hemostasis, bile leak

Hepatic resection is widely accepted as an appropriate treatment for many benign and malignant liver conditions.[1-3] Increasing experience and good outcome in liver surgery have led many surgeons to attempt larger and more technically challenging resections. Because increased intraoperative blood loss is associated with higher perioperative morbidity and mortality and shorter long-term survival, minimizing blood loss is a primary concern for surgeons operating on the liver.[4]

Heaney and Humphreys[5] described a technique for total vascular exclusion (TVE) of the liver using an abdominothoracic approach in 1948. In 1966 the procedure was modified to include occlusion of the infra- and suprahepatic vena cava, porta hepatis, and infradiaphragmatic aorta.[6] This allowed safe excision of large hepatic tumors and minimized blood loss. The technique was modified Huguet et al.,[7] who used an abdominal approach. Huguet et al. described a technique for clamping the retrohepatic vena cava that also prevented flow from the lumbar and adrenal veins and did not always include aortic clamping. This caval occlusion was used in conjunction with porta hepatis occlusion. Several other authors have since demonstrated TVE of the liver to be a useful and safe method for the resection of difficult tumors with minimal blood loss.[1,2,4,8-10]

This article briefly reviews some specific anatomic considerations, physiologic concerns, and patient selection criteria. We then describe a modified technique for liver resection using TVE and rapid division of the parenchyma with a scalpel. Hemostasis is obtained by ligation of the hepatic artery prior to parenchymal division and suture compression of the cut parenchymal surface of the liver. Preresection control of the portal vein and hepatic vein is unnec-

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essary. Strict observance of technical details assures that total clamp time and blood loss will be minimal and outcomes will be optimized.

ANATOMIC CONCERNS

Proper exposure for difficult liver resections must be obtained in every case. It is rarely necessary to incorporate a thoracic incision and this should be avoided where possible to reduce postoperative morbidity. A bump placed behind the lower edge of the scapula, fixed upward retraction on the costal margin, and an incision that extends to the tip of the twelfth rib are necessary for optimal exposure (Fig. 1).

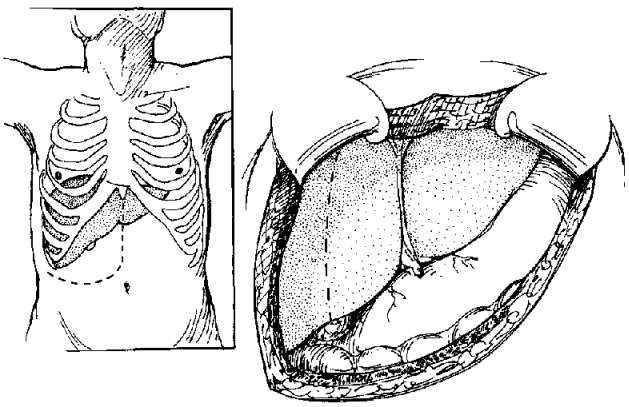

Fig. 1. Incision and exposure for hepatectomy. The subcostal extension is curved toward the tip of the twelfth rib. Fixed bilateral upper-hand and retraction gives good exposure of both lobes of the liver.

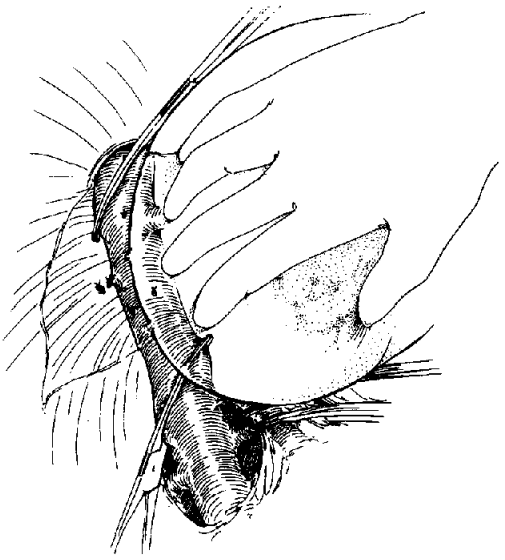

Fig. 2. The right side of the vena cava is exposed. Caudate branches, lumbar branches, and the right adrenal vein are divided. The porta hepatis is double clamped. Clamps are then placed across the vena cava above and below the hepatic veins.

The vascular pedicle of the liver is composed of the porta hepatis, with the portal vein and hepatic artery, and the hepatic vein confluence into the vena cava. There are several additional sources of collateral blood flow to the liver. Division of all hepatic ligaments and attachments to the diaphragm and control of caudate venous drainage to the cava will, however, eliminate these sources. Once fully mobilized, the liver is literally hanging on its primary vascular pedicle.

Blood flow into the liver is blocked by placing two vascular clamps on the porta hepatis. A replaced left hepatic artery, which is present in 20% of patients, must be clamped separately. Hepatic arterial perfusion is necessary for postresection parenchymal regeneration. Accessory arteries must be preserved. Accidental injury to an artery that is intended to perfuse the remnant lobe of the liver precludes safe resection.

Venous bleeding during transection of the liver parenchyma has several sources. The primary source is backflow from the hepatic veins and their tributaries. Other sources include caudate branches, the right adrenal vein, and lumbar segmental veins. A thorough dissection of the retrohepatic vena cava with vascular loops placed above and below the liver ensures primary caval control. The right adrenal vein must be ligated and preferably divided to free the vena cava and prevent tearing when the liver is elevated. Caudate branches may be divided prior to resection if this facilitates mobilization or safe parenchymal division. Remaining caudate and lumbar branches are controlled by proper clamp placement during exclusion (Fig. 2).

PHYSIOLOGIC CONCERNS

Clamping the vena cava creates a significant impairment of blood return to the heart. The hemodynamic effects include decreased venous return and decreased filling pressures resulting in smaller stroke volume and decreased cardiac output. To reduce the effects of decreased cardiac output, subdiaphragmatic aortic clamping has been attempted.[6,7] This does improve arterial perfusion of the upper body but is associated with increased postoperative morbidity. Subsequent work has demonstrated that aortic clamping did not affect tolerance of TVE.[2]

Before the vena cava is clamped, central filling pressures should be elevated to 12 to 15 mm Hg. A test clamping may determine the patient's ability to tolerate the procedure and guide the need for volume infusion; however, once the caval clamps have been in place for more than 5 minutes, it is unlikely

that the patient will tolerate release and a second caval clamping.

A concern that is more problematic is that of ischemia and reperfusion injury. The liver is a metabolically active organ and is sensitive to warm ischemia. Cell death may start to occur within a few minutes; however, most hepatocytes have adequate substrate to remain viable even after 60 to 90 minutes of warm ischemia. Huguet et al.[7,11] have demonstrated that patients with normal preoperative liver function can tolerate complete ischemia for up to 90 minutes. The incidence of hepatic failure appears to be more closely related to the volume and condition of the remnant liver.

Cirrhotic livers are thought to be less tolerant of ischemic insult than noncirrhotic livers. It has been demonstrated in a small group of selected patients with cirrhosis and normal preoperative hepatic function that patients can tolerate up to 60 minutes of ischemia with an acceptable morbidity.[10] Liver function was determined by total bilirubin level, prothrombin time, and the presence or absence of ascites.

There will obviously be a limit to the length of time that a liver can tolerate ischemia; however, it appears that in general this limit is beyond what is required for performance of a safe hepatic resection. Additionally, it is clear that a substantial portion of the intolerance to hepatic ischemia is related to the reperfusion injury. Work is currently underway to explore methods of reducing this secondary injury. If successful, we may be able to further extend the safe period of ischemia to which the liver can be exposed.

PATIENT SELECTION

Indications for resection under TVE include formal and extended lobectomy, paracaval resections, and hilar resections. It is unnecessary to perform TVE in most wedge resections. The technique for parenchymal closure described in this article depends on compressing the cut surface of the liver with a series of sutures incorporating both the anterior and posterior capsule of the liver. It is thus not possible to use this technique when performing a central resection (isolated segment I or IV and/or segments V and VIII).

Preoperative evaluation includes liver function tests, a nutritional assessment, and a renal assessment. In all patients a spiral CT scan is obtained and in many either a CT portogram or an arterial and venous phase angiogram is obtained to evaluate both vascular anatomy and tumor load. Additionally, the patient must be in a generally good state of health with acceptable cardiovascular and pulmonary function. Cirrhosis is considered a relative contraindication to TVE. If serum bilirubin is less than 2.0 mg/dl, the prothrombin time is less than 1.3 times the control value, serum albumin is greater than 30 mg/dl, and there is no evidence of ascites, TVE may still be considered. It is the volume of remaining functional liver that limits the extent of resection tolerated by patients with cirrhosis. The differential effect of TVE on normal vs. cirrhotic livers is not definitely worked out.

TECHNIQUE

The patient is positioned supine with a bump behind the lower edge of the right scapula. Intraoperative monitoring is via a radial arterial line and central venous line. Pulmonary arterial catheters are used selectively in patients with cardiopulmonary disease. Before the vena cava is clamped, it must be assured that the central venous pressure is between 12 and 15 mm Hg.

The incision is a variation of a right subcostal incision (see Fig. 1). The midline portion extends from the subxyphoid process to just above the umbilicus and then curves to the right, toward the tip of the twelth rib. A fixed retractor is used with retraction upward on the costal margins.

The peritoneal cavity is examined for evidence of extrahepatic deposits of cancer. Intra-abdominal adhesions and the falciform ligament are divided. The liver is then mobilized by complete division of the left and right triangular ligaments and the coronary ligament. Division of the right coronary ligament and elevation of the diaphragm off the bare area of the liver exposes the right side of the suprahepatic vena cava and the right hepatic vein. A similar dissection of the left coronary ligament exposes the left side of the suprahepatic vena cava. The gastrohepatic ligament is divided over the caudate lobe, and opened superiorly to the diaphragm and inferiorly to the edge of the porta hepatis.

After complete anterior and lateral mobilization of the liver, a thorough ultrasound examination is performed. The number of lesions and their precise location relative to segmental anatomy is noted. Additional information that may be obtained includes the location of the portal and hepatic veins and their relation to the liver pathology. At this time a determination of resectability is made.

If the resection is to proceed, isolation of the retro- and infrahepatic vena cava is begun. The anterior surface of the infrahepatic vena cava is dissected by elevating the porta to the patient's left and the caudate lobe superiorly. Several caudate branches may be divided at this point to facilitate safe access to the infrahepatic vena cava. Attempts to encircle the vena cava should not be made until the left edge of the vena cava

is clearly visible. A large blunt clamp may be gently passed from the left side to place a vascular sling.

The right lobe of the liver is then rotated upward and to the patient's left for exposure of the right side of the vena cava (see Fig. 2). The peritoneal covering is carefully divided. The right adrenal vein is identified and divided to prevent tearing with retraction of the liver. This manuever allows full mobilization of the right side and posterior aspect of the vena cava.

Exposure of the left side of the vena cava is attained by retracting the free left lateral segment and the caudate lobe upward and to the patient's right and the stomach to the patient's left. The left edge of the vena cava is seen between the right crus of the diaphragm and the base of the caudate lobe. The peritoneum is carefully divided from the site of the infrahepatic caval encirclement to the caval diaphragmatic hiatus. Again a large blunt right-angled clamp is gently placed behind the suprahepatic vena cava. A finger on the right side of the vena cava should feel the tip of the clamp, but the clamp should then be advanced under direct vision. A vascular loop is placed. The liver is now prepared for complete vascular exclusion.

The hepatic arteries supplying the segments of the liver to be resected are now ligated and divided in the hilum. This division is critical to help reduce perfusion pressures on the cut surface of the liver. If we are performing a formal right hepatectomy, we start by resecting the gallbladder. The cystic duct stump may then be used as a handle to rotate the porta hepatis clockwise. Division of the peritoneum behind the cystic duct will usually expose the right hepatic artery. This is confirmed by a test clamp and by observing the line of demarcation on the surface of the liver. Similarly, the left hepatic artery may be identified in the left side of the hilum just inferior or posterior to the left hepatic duct. Accessory hepatic arteries to the remnant lobe of the liver must be isolated and preserved to assure regeneration of hepatic parenchyma.

We do not routinely dissect the portal vein or its primary branches in the hilum. If easily accessible, it is optional to ligate the right or left portal vein at this point in the dissection. These vessels are transected during parenchymal division and may be easily oversewn.

Once the liver is prepared, a TVE test clamp may be performed for up to 5 minutes to ensure that the patient will tolerate the procedure. When the clamps are placed for the final time, it must be assured that the tips of the clamp incorporate the entire vena cava and that they exclude any lumbar branches that may not have been divided. The order of clamping is the porta hepatis, followed by the infrahepatic vena cava, and finally the suprahepatic vena cava. This prevents congestion of the organ.

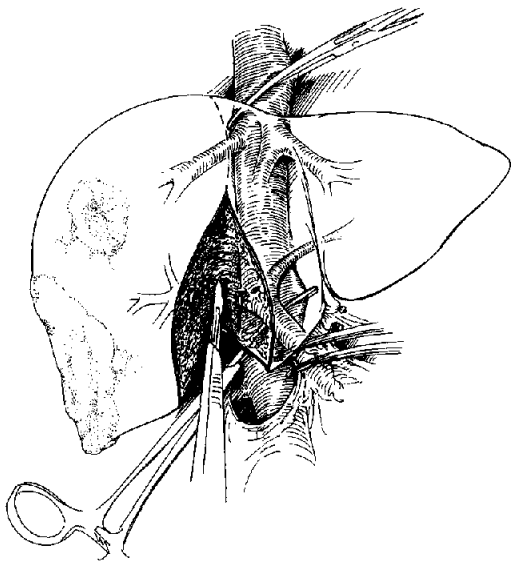

Fig. 3. The liver parenchyma is divided with a scalpel. Blood loss is limited to the intrahepatic volume and major structures are ligated at the cut surface of the parenchyma.

A line of parenchymal division is selected and scored on the peritoneum with electrocautery. Division of the parenchyma is performed with a scalpel (Fig. 3). If bleeding is minimal, the entire parenchymal incision and resection may be quickly performed. The liver may hold more than 500 ml of blood and thus some blood in the field is expected. Persistent bleeding is rarely encountered. If it does occur, it may be because the clamps have been placed inaccurately or nonocclusively. Compression of the cut surface of the liver prevents continued hemmorhage while the clamps are rechecked.

If a noncentral resection is being performed, we prefer to use a liver surface compression technique to control hemostasis and biliary leakage. Using this technique we simply oversew major vascular and biliary structures (larger than 2 mm) with figure-of-eight sutures and apply argon electrocautery to the remaining surface. The cut edges of the liver are then compressed, being rolled in toward each other. No. 1 monofilament absorbable sutures on large blunt needles are placed every 1 cm along the cut surface (Fig. 4.) These sutures are placed to incorporate both capsular edges of the liver and are used to compress the cut surface. Because these sutures may tear through, the edges of the liver must be held in approximation by an assistant during their placement. At completion the peritoneal edges appear to be pulled together like a book, compressing the cut surface of the liver and preventing bleeding and bile leaks. The portal and hepatic venous systems are low pressure and bleeding is

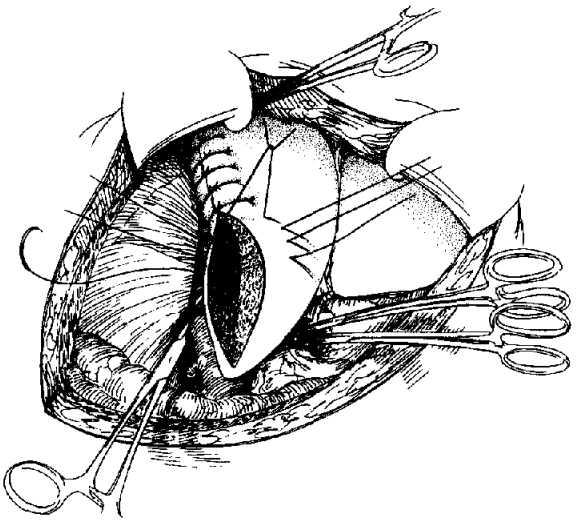

Fig. 4. An assistant rolls the liver edges toward one another while the surgeon places the capsular compression sutures. Stitches are placed 1 cm apart and 1 cm back from the cut edge of the capsule.

rarely a problem. It is occasionally necessary to place additional compression sutures.

If a central resection is being performed, we use the standard Bismuth techniques for vascular and biliary control with methodical oversewing of all identifiable vessels and ducts. This procedure takes longer, but surface compression is not feasible as it would obstruct flow to and from the pedicles.

Once hemostasis is assured, two large drains are placed at the site of the resection. The remnant liver must not lie in a position that twists its vascular pedicle. Although rarely necessary, a few sutures to reattach the triangular ligaments in the correct anatomic position will prevent rotation. The abdomen is closed in layers.

Postoperatively patients are usually monitored in the intensive care unit. Sedatives are minimized and early extubation is preferable. Hemoglobin levels, prothrombin times, liver function, and liver enzymes are checked daily for the first 3 days and then as necessary. The drains are removed when the patient is taking food by mouth with no evidence of bile leak.

CLINICAL EXPERIENCE

Clinical results using the preceding technique were previously published by Moussa et al.[3] Of the last 200 liver resections performed under the direction of the senior author (N.A.H.), TVE was used in 144. These were all major resections (three or more Couinaud segments) and included nine portal vein reconstructions, seven inferior vena cava reconstructions, and one hepatic artery reconstruction. Operative time averaged 5 hours (range 2.3 to 11.5 hours). Forty-eight percent of patients undergoing TVE required blood transfusion. We do not routinely use a cell saver. Average TVE clamp time was 31 minutes (range 27 to 75 minutes). Overall mortality was 5%, and there was a 16% major complication rate including five cases of liver failure, six cases of sepsis, and one postoperative myocardial infarction. Seven patients had bile leaks. All resolved without reoperation.

DISCUSSION

There are two primary techniques currently used in liver resection. They are the segment-oriented "Glissonian" approach, with an extensive hilar dissection prior to selective vascular control, and the TVE approach, which requires little hilar dissection and utilizes complete vascular control. Although the former is more widely used, TVE is gaining acceptance as a method of resection for difficult tumors.

There are a number of methods currently in use for parenchymal division and vascular and biliary control. The technique of crushing the parenchyma between the fingers or clamps, identifying structures, and ligating and dividing them is a secure but time-consuming process. Ultrasonic dissectors and hydrodissectors have been developed to obtain surface hemostasis, but vascular and biliary structures larger than 1 to 2 mm still require ligation and division. Stapling devices are expensive and their value in obtaining hemostasis and biliary control is still being evaluated.

Scalpel division of the parenchyma is rapid and accurate. If TVE is effective, major hepatic resections may be safely performed in 1 to 2 minutes. TVE prevents entrainment of air and thus air embolism. Arterial ligation in the hilum markedly reduces the perfusion pressure on the cut surface of the liver. Capsular compression only needs to overcome venous and biliary pressures. Figure-of-eight sutures on the cut surface are adequate to control structures larger than 2 mm. The primary portal vein and hepatic veins usually require a short running suture. Repairs or reconstructions of the portal vein, hepatic artery, and vena cava are rarely necessary but are facilitated by this bloodless field.

An additional value of the technique described above is its cost. There are no significant requirements for more advanced technology. This will certainly make this a more acceptable technique as cost containment further limits access to equipment and technology.

SUMMARY

We have described a technique for liver resection using TVE in which the hepatic parenchyma is divided with a scalpel, and vascular and biliary control is obtained intraparenchymally and by compression of the cut surface of the liver. Preresection division of arterial inflow is necessary to reduce perfusion pressure at the cut surface. This technique may be performed with an average clamp time approaching 30 minutes. Blood loss and ischemia/reperfusion injury are thus minimized. Perioperative complications appear to be comparable to most reports in the literature, especially considering the difficult nature of these resections. Great care must be taken to ensure complete vascular exclusion of the liver by proper dissection and placement of clamps. The technique is recommended for experienced liver surgeons undertaking difficult resections.

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Giant Colonic Diverticulum: A Rare Manifestation of a Common Disease

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Giant colonic diverticulum is a rare manifestation of a common disease primarily affecting patients over the age of 50 years. We reviewed all 81 cases of giant colonic diverticulum reported in the medical literature and present herein an additional case in a younger patient. Published reports were summarized with regard to current epidemiology, clinical aspects, diagnosis, pathogenesis, treatment, and complications. Giant colonic diverticulum can present as an acute, chronic, or incidental condition, or with complications. There are several suggested theories for the pathogenesis of giant colonic diverticulum, but none is universally satisfactory. A diagnosis can be made with plain films, barium enema, and CT scans. A combination of sigmoid resection and primary anastomosis was successful in 75% of the cases reported after the mid-1970s. More than 90% of giant colonic diverticula are found in the sigmoid colon. Sigmoid resection with primary anastomosis is the preferred treatment, although patients presenting with complications typically should be treated with Hartmann's procedure for free perforation or percutaneous drainage for a localized abscess. Because of the high risk of complications, we recommend segmental resection of the involved colon for those found incidentally. (J GASTROINTEST SURG 1999;3:543-548.)

KEY WORDS: Diverticular disease, giant colonic diverticulum, diverticulosis, cystic diverticulum

Giant colonic diverticulum is a rare manifestation of a common disease. Although diverticular disease is found in 35% of all persons 65 years of age in the Western world, fewer than 100 cases of giant colonic diverticulum have been documented. We searched the medical literature for reports of giant colonic diverticulum. Published reports were reviewed and summarized with regard to current epidemiology, clinical aspects, diagnosis, pathogenesis, treatment, and complications. Bonvin and Bonte[1] were the first to describe a giant colonic diverticulum in 1946. The first report in the English literature was provided 7 years later by Hughes and Green,[2] who describe a "solitary air cyst" arising from the antimesenteric border of the sigmoid colon. By the mid-1970s a dozen case reports had appeared in the literature,[3] and 20 years later 70 cases have been cited.[4] To date there are 81 reported cases of giant colonic diverticulum.[5] We report herein an additional case of giant colonic diverticulum affecting a younger patient.

CASE REPORT

A 43-year-old woman presented with a 6-month history of constant vague abdominal pain, mainly in the right lower quadrant. She denied having nausea, vomiting, changes in bowel habits and/or the genitourinary system, or weight loss. Her surgical history included an appendectomy and two ovarian cystectomies. Physical examination revealed scars from a McBurney's incision and a Phanensteil incision. No hernias were found, but a palpable, nontender mass in the right lower quadrant was present. Ultrasound examination of the pelvis revealed no solid mass or adnexal abnormalities. CT scan demonstrated an 8 cm air-filled mass in the right lower quadrant, which did not fill with enteric contrast material (Fig. 1). Barium enema showed sigmoid diverticulosis and the nonenhancing air-filled pocket (Fig. 2).

The patient subsequently underwent an exploratory laparotomy. An 8.5 × 6.0 cm air-filled cystic mass was found adherent to the sigmoid colon and mesentery of the distal ileum. We separated it from the small bowel mesentery, but it was intimately attached to the sigmoid colon (Fig. 3). Sigmoid colectomy with primary anastomosis was performed (Fig. 4). The patient was discharged on postoperative day 4

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Fig. 1. An 8 cm, air-filled mass is seen on CT scan. The mass was not enhanced by or filled with enteric contrast material.

Fig. 2. A barium enema revealed sigmoid diverticulosis and also showed the air-filled pocket that did not fill with barium.

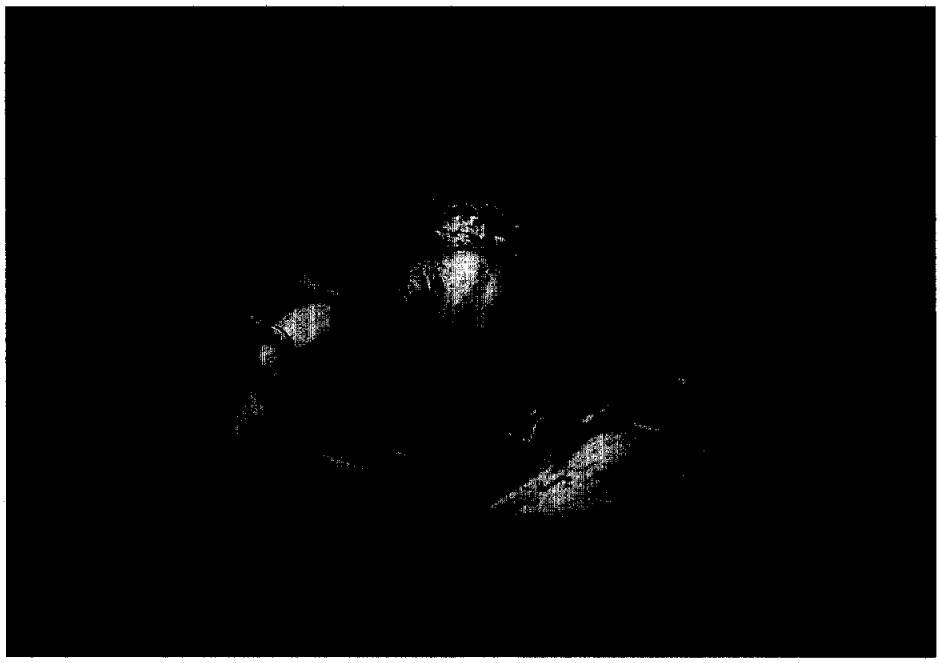

Fig. 3. An 8.5 × 6.0 cm air-filled cystic mass was adherent to the mesentery of the distal ileum but was intimately attached to the sigmoid colon.

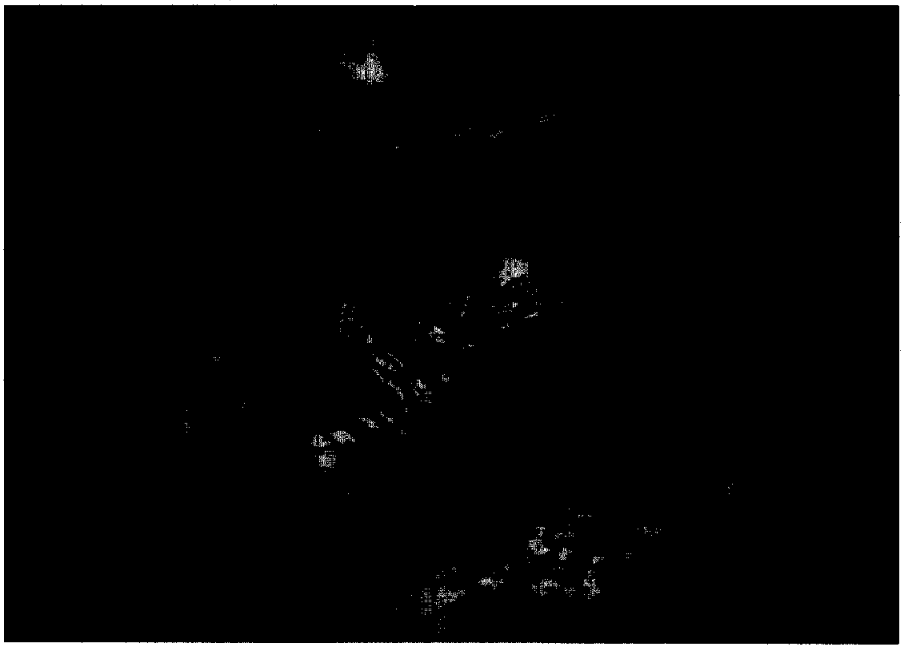

Fig. 4. After the mass was separated from the small bowel mesentery, sigmoid colectomy was performed.

after an uneventful recovery. Pathologic diagnosis was a giant cystic diverticulum of the sigmoid colon.

DISCUSSION

Presentation

Giant colonic diverticulum affects patients in the same age group as those with diverticular disease. The mean age is 65 years and there is a 60% male predominance. Age at presentation has ranged from 32[6] to 90[7] years, with only 10 cases reported in patients younger than 50.[2,6,8-15] More than 90% of giant colonic diverticula are located in the sigmoid colon, with concurrent diverticula found in at least 85% of patients.[5] Less than 5% are found in the transverse colon, and the remainder occur in the splenic flexure and descending colon.[4] There are three types of clinical presentations—acute, chronic, and incidental—and all occur with equal frequency.[13]

Acute Presentation. A giant colonic diverticulum can present acutely, similar to acute diverticulitis, causing nausea, fever, and left lower quadrant peritoneal irritation. A mass can be palpated in two thirds of these patients. This clinical picture has been attributed to acute changes in the size of the diverticulum.[16] This is supported by both the frequent finding of multiple adhesions to adjacent structures and the highly variable increase in size exhibited by these diverticula. Giant colonic diverticulum can progress over years, months, or even days. Melamed and Dantone[17] reported evolution from no diverticulum, to 3 cm, to a 6 cm size over a 6-month period, as well as complete emptying with evacuation. Ingram et al.[18] reported a giant colonic diverticulum that doubled in size within 24 hours. In one case the act of straining promoted the appearance and disappearance of the mass within a few hours.[16]

Chronic Presentation. An equal number of patients present with chronic symptoms of pain and bloating caused by tension from adhesions to adjacent structures. A palpable mass usually is present in these patients.

Complications or Incidental Presentation. The remaining cases are found incidentally on abdominal radiographs or present with complications. Of the 15% to 20% that are complicated presentations, two thirds are secondary to perforation, half of which are free intraperitoneal perforations.[4,5] Rare complications, with a single report of each, consist of focal wall infarction,[3] adenocarcinoma within the giant colonic diverticulum,[11] volvulus of the giant colonic diverticulum,[19] and partial small bowel obstruction.[7]

Radiologic diagnosis of giant colonic diverticulum is fairly distinct. Plain abdominal films show a large gas-filled cystic structure, usually in association with the sigmoid colon and displacing other intra-abdominal structures (Fig. 5). Barium enema usually reveals diverticulosis. Contrast within the diverticulum has been noted in 30%[11] to 60%[20] of cases. Likewise, abdominal CT reveals a gas-filled mass that may or may not show intimate association with the sigmoid colon. The size of the giant colonic diverticulum can range from 5 cm[21] to 29 cm,[22] with a wall thickness that is also quite variable, from 0.1[9] to 2 cm.[23] Typically colonoscopy adds little to the evaluation for two reasons: (1) it is probably a superfluous test with diagnosis apparent on radiologic examination and (2) because of the above-stated lack of defined communication with the bowel lumen. Furthermore, if continuity is present, the ostium is likely too small to be cannulated.

Fig. 5. A large, gas-filled cystic structure, usually in association with the sigmoid colon and displacing other intra-abdominal structures, can be seen on plain abdominal film.

The differential diagnosis of giant colonic diverticulum is shown in Table I. Cholecystoenteric fistulas can produce a gas-filled gallbladder but the gallbladder will rarely become as large as a giant colonic diverticulum. Furthermore, pneumobilia is often present and the gallbladder is typically contracted rather than distended.

Table I. Differential diagnosis of gas-filled intra-abdominal mass

Gallbladder
Cholecystoenteric fistula
Emphysematous cholecystitis
Pancreas
Infected pseudocyst
Small intestine
Meckel's diverticulum
Jejunoileal diverticulum
Duplications
Colon
Sigmoid/cecal volvulus
Giant colonic diverticulum
Duplication
Urinary bladder
Vesicoenteric fistula
Emphysematous cystitis
Pneumatosis cystoides intestinalis

Emphysematous cholecystis and cystitis both represent acute septic episodes that are readily distinguished from giant colonic diverticulum. Meckel's/jejunoileal diverticula are typically found in young patients, and continuity with the small intestine can be demonstrated with an upper gastrointestinal contrast study. Duplication cysts of the small and large bowel are also seen in the younger population, usually located on the antimesenteric border, and are more fusiform in shape. There is no communication with the bowel lumen and histologic examination reveals all four layers of the bowel wall. Pneumatosis cystoides intestinalis is a rare condition that is characterized by multiple gas-filled cysts in the wall of the alimentary tract. The exact mechanism of their formation is unclear. They can be distinguished from giant colonic diverticula in that they are always multiple, much smaller in size, and related to the mesenteric border. Histologic examination reveals a smooth muscle layer. Vesicoenteric fistulas can be ruled out because gas is readily voided and rarely noted on radiologic studies. Infected pancreatic pseudocysts are found in an entirely different location (retroperitoneal in the lesser sac) and within a completely separate clinical context. Sigmoid/cecal volvulus will present with an associated bowel obstruction and can quickly be ruled out by barium enema examination.

Pathogenesis

Several theories for the pathogenesis of giant colonic diverticulum have been offered, although none is universally satisfactory.

True Colonic Diverticulum. Seven reported cases of giant colonic diverticulum describe muscle within the cystic wall,[2, 24-26] and at least one giant colonic diverticulum with all four layers has been described.[25] This structurally resembles a duplication cyst, illustrating that both congenital and acquired diverticula can proceed to a giant colonic diverticulum.

Ball-Valve Mechanism. This was first proposed by Boijsen[26] and begins with a diverticulum whose communication with the lumen has been narrowed by inflammation. Gas can enter the diverticulum but not leave, thus precipitating an enlarging gas-filled mass. As this occurs, the mucosa degenerates either from inflammatory changes or pressure from trapped air.[26] This leaves a wall composed only of inflammatory tissue. This concept is in keeping with the histologic studies of Mehta et al.,[27] who reported dense fibrous tissue containing chronic inflammatory cells and foreign body giant cells in 42 of 44 specimens studied.

Contained Perforation. This is a variation of the preceding model. A ball-valve mechanism is maintained, yet the inciting event is proposed to be diverticular perforation that is contained locally. Subsequent inflammation and granulation tissue formation ensue, which is then diverticularized.[27] Many hold this theory to be implausible given that evidence of previous perforation is uncommon.[3] Furthermore, the ball-valve mechanism itself is questionable, as ostia larger than 2 cm have been discussed in several reports.[27]

Gas-Forming Organisms. This concept suggests that gas-forming organisms are responsible for diverticular distention after obliteration of an ostium. However, Asch et al.[8] could not find any growth when culturing contents of giant colonic diverticulum. Moore and Gold[28] found only moderate coliforms, and Harris et al.[29] found sterile fluid.

Management

In contrast to the obscure etiology of these diverticula, appropriate treatment is relatively clear. Surgical treatment is preferred, consisting of sigmoid resection and primary anastomosis. This has been accomplished successfully in 75% of cases reported thus far, including the present one, with no reported anastomotic leaks or reoperations. Diverticulectomy accounts for 25% of the procedures prior to the mid-1970s.[3] Despite its success, diverticulectomy is not recommended because of the surrounding inflammation and the possibility of a wide diverticular neck. Patients who present with complications should be evaluated and treated on an individual basis, typically with Hartmann's procedure for free perforation or percutaneous drainage for a localized abscess. Because of the substantial risk of complications, we recommend

segmental resection of the involved colon for diverticula found incidentally.

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Preservation Injury and Acute Rejection of Rat Intestinal Grafts: Protection Afforded By Pyruvate

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Pyruvate has been shown to prevent intestinal mucosal injury after ischemia-reperfusion. The aim of the present study was to determine whether pyruvate can (1) prevent postreperfusion mucosal injury occurring after intestinal preservation and subsequent transplantation and (2) exert a protective effect on the intestinal graft mucosa during acute rejection. Preservation mucosal injury was evaluated, after 2 hours of reperfusion, by comparing grafts transplanted in a rat syngeneic combination (ACI to ACI) after 2 hours of cold preservation using pyruvate (n = 6) or placebo (n = 6). Mucosal parameters obtained during acute rejection (allogeneic combination: ACI to Lewis) were compared between placebo-treated (n =6) and pyruvate-treated (n = 6) animals. Tissue injury was evaluated by histopathologic examination, oxygen free radical production by luminol-enhanced chemiluminescence, and degree of neutrophil infiltration by myeloperoxidase staining. After reperfusion of the preserved grafts and during acute rejection, mucosal oxygen free radical levels and the number of infiltrating neutrophils were significantly ($P < 0.05$) increased in the untreated grafts, whereas there was a statistically significant inhibition of these parameters in those treated with pyruvate. Mucosal injury, seen after reperfusion of the preserved grafts, was prevented by pyruvate. The histopathologic abnormalities observed in the untreated grafts during rejection were also significantly reduced by pyruvate. Treatment with pyruvate before cold preservation of intestinal grafts, in this rat model, reduced reperfusion mucosal injury, neutrophil infiltration, and oxygen free radical production. Oxygen free radicals were produced in the mucosa of the graft during acute rejection and their production was reduced by pyruvate, which exerted a protective effect on the rejecting allograft mucosa. (J GASTROINTEST SURG 1999;3:549-554.)

KEY WORDS: Small bowel transplantation, organ preservation, acute rejection, pyruvate, ischemia-reperfusion, oxygen free radical, chemiluminescence

Recent advances in clinical small bowel transplantation[1,2] suggest that this procedure might become a valid therapeutic alternative for patients with short bowel syndrome. The unavoidable period of hypothermic preservation (i.e., cold ischemia) and reperfusion of the intestinal graft is known to culminate in tissue injury.[3] We have previously shown that immediately after small bowel transplantation, mucosal injury is associated with an increased level of oxygen free radicals and with infiltration of activated neutrophils within the mucosa,[4] suggesting the importance of these events in the pathogenesis of such injury.

Acute rejection, a relatively frequent occurrence following small bowel transplantation, is also associated with mucosal injury. In this condition, the infiltrating immune cells are largely responsible for graft injury. Nevertheless, some of the histopathologic changes may be attributed to endothelial injury, which may result in ischemia of the graft, or to the activation of local enzymes or resident immunocytes. It has been recently shown that during acute rejection mucosal blood perfusion is decreased in the small bowel grafts.[5] The ischemic event is able to initiate the production of toxic oxygen free radicals,[6] which themselves could contribute to the observed mucosal injury.

The three-carbon compound pyruvate can scavenge oxygen free radicals by reacting with hydrogen peroxide to form water and carbon dioxide,[7] and

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can prevent oxygen free radical production by inhibiting superoxide formation.[8] We have previously demonstrated that pyruvate can prevent oxygen free radical formation, neutrophil infiltration, and mucosal injury after warm ischemia and reperfusion of the small bowel.[9] It stands to reason that pyruvate might exert a similar protective effect on the tissue injury seen after hypothermic small bowel preservation and reperfusion associated with transplantation and during acute rejection of intestinal allografts.

The aims of the present study were to evaluate the following: (1) whether pyruvate can prevent oxygen free radical formation, neutrophil infiltration, and mucosal injury after cold preservation and reperfusion of transplanted intestinal grafts; (2) whether oxygen free radicals are produced in the mucosa of the graft during acute rejection; and (3) whether pyruvate can prevent the formation of oxygen free radicals, thus exerting a protective effect on the ongoing rejection within the intestinal graft.

MATERIAL AND METHODS

Animals

Male ACI and Lewis rats (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) weighing 250 to 300 grams were used for this study. The animals were housed in the University of Pittsburgh animal care facilities, which are fully approved by the American Association for Accreditation of Laboratory Animal Care. The rats were anesthetized using methoxyflurane (Pittman-Moore, Inc., Mundelein, Ill.) for induction and sodium pentobarbital intraperitoneally (25 mg/kg; Abbott Laboratories, North Chicago, Ill.) for maintenance.

Posthypothermic Preservation Reperfusion Injury Model

Following harvest on a vascular pedicle, the small bowel grafts from ACI rats were stored in cold lactated Ringer's solution (4° C) and transplanted orthotopically into ACI recipients after 2 hours. Animals in group A (n = 6) were fed a liquid diet (No. 710027, Dyets Inc., Bethlehem, Pennsylvania) and used as controls, whereas animals in group B (n = 6) were treated with pyruvate. In the latter grup, 10 ml of the same liquid diet (No. 710027, Dyets Inc.) containing isoenergetic amounts of sodium pyruvate (0.32 g) was instilled intraluminally in the graft from 5 minutes before harvesting to the time of reperfusion. The final composition of this diet was exactly the same as reported in our previous study.[9]

Full-thickness small bowel sections were obtained before harvesting (control) and 120 minutes after revascularization of the graft, at which time the recipients were killed. The specimens were processed to evaluate morphology, the extent of neutrophilic infiltration, and oxygen free radical production.

Acute Rejection Model

Following harvest on a vascular pedicle, the small bowel grafts from ACI rats were stored in cold lactated Ringer's solution (4° C) and transplanted immediately into Lewis recipients. The duration of cold preservation was kept under 15 minutes in all the orthotopic allotransplants. Grafts obtained from control animals (group C; n = 6) were used to evaluate mucosal parameters occurring during acute rejection, whereas the effect of pyruvate was evaluated in grafts obtained from treated animals (group D; n = 6). Observations made on native ACI intestines (group E; n = 6) were recorded and served as baseline control data. Rats in group C (control) were fed 100 ml/day of liquid diet (No. 710027, Dyets Inc.), whereas animals in group D (pyruvate treatment) received 100 ml/day of liquid diet (No. 710027, Dyets Inc.) containing isoenergetic amounts of sodium pyruvate (0.32 g), from day 7 prior to harvesting (donor) to posttransplant day 6 (recipient).

At sacrifice, on posttransplant day 7, full-thickness small bowel sections were obtained. The specimens were processed for histologic study, the extent of neutrophilic infiltration, and oxygen free radical production.

Surgical Techniques

The technique used has been previously described.[4] In brief, the small bowel of the donor was harvested from the ligament of Treitz to the ileocecal valve with its vascular pedicle consisting of the superior mesenteric artery and the portal vein. The graft was removed, wrapped in saline-soaked gauze, and stored in cold (4° C) lactated Ringer's solution after the intestinal lumen was irrigated with 20 ml of cold (4° C) neomycin sulfate (Upjohn Company, Kalamazoo, Mich.) saline solution (0.5%). The graft was transplanted orthotopically using end-to-side anastomoses between the superior mesenteric artery and the infrarenal aorta and between the portal vein and the vena cava using 8-0 Prolene. All of the grafts appeared to be rapidly and completely reperfused immediately after revascularization. The time required to complete the vascular anastomoses was less than 30 minutes. The graft was immediately placed in gastrointestinal continuity by end-to-end intestinal anastomoses after the native small intestine was removed.

Tissue Preparation for Histologic Examination

The specimens were fixed in 10% buffered formalin and embedded in paraffin. Sections 4 μ thick were stained with hematoxylin and eosin. All specimens were analyzed by means of conventional light microscopy by a single pathologist (V.S.) to whom the status of the specimen was unknown. The histologic injury was evaluated on the basis of the following: degree of edema, mucosal separation from the basement membrane, extent of villous destruction, number of apoptotic figures, endothelial cell damage, leukocyte adhesion and infiltration, intravascular platelet aggregation, and number of Goblet cells.

Oxygen Free Radical Measurement

Oxygen free radical production was measured using luminol-enhanced chemiluminescence as previously described.[10] The technique is based on the affinity reaction of luminol (Sigma Co., St. Louis, Mo.) with oxygen free radicals, whereby light is emitted (chemiluminescence) and can be detected using photomultiplier tubes. In preparation, the mucosa was scraped from the intestine and placed immediately in a scintillation vial containing 1 ml of preoxygenated Krebs-Henseleit bicarbonate buffer. After 15 minutes, the tissue suspension was mixed with 1 ml of preoxygenated Krebs-Henseleit buffer containing luminol to obtain a final concentration of 100 μmol/L of luminol. The scintillation vial was placed in a Beckman LS 3801 liquid scintillation analyzer (Beckman Instruments, Inc., Fullerton, Calif.) operated in the out-of-coincidence mode. The photons emitted by the tissue suspension were counted for 5 minutes and the results analyzed by computer.

Background photon counts were subtracted from photon counts emitted by the tissue suspension. The protein content of each sample was determined using the method of Butcher and Lowry,[11] and the chemiluminescence data were recorded as counts per minute per milligram of protein.

Contamination of the tissue suspension with intestinal muscular cells was excluded by examining the histologic appearance of five different samples using standard immunohistochemical techniques with antirat actin monoclonal antibodies (Dako Corp., Carpinteria, Calif.).

Neutrophilic Infiltration

The neutrophilic infiltration of the intestinal mucosa was visualized by staining the cells containing the enzyme myeloperoxidase utilizing the Hanker-Yates reaction.[12] The specimens were immersed in OCT compound (Miles, Inc., Elkhart, Ind.), snap frozen in liquid nitrogen–quenched isopentane, and stored at −80° C until processed. Cross sections of the fixed intestine were cut at 25 μm with a cryostat (Reichart-Jung, Nussloch, Germany). The sections were mounted on gelatin-chrome alum–coated slides and air dried for 1 hour. The slides were then incubated with the Hanker-Yates reagent (Sigma) (1 mg/ml in 10 ml 0.1 mol/L TRIS buffer (pH 7.6) containing 10 μl of 3% H_2O_2) in a humidified box for 30 minutes. All of the sections were rinsed four times with Hanks' balanced salt solution and examined in a blinded fashion by light microscopy (Zeiss, Oberkochen, Germany). Stained cells were counted at 10× magnification using a reticulated screen, 1.2 mm × 1.2 mm, oriented so as to include a full thickness of the small bowel biopsies (mucosa, submucosa, muscularis, and serosa).

Statistical Analysis

Values are expressed as mean ± standard error of the mean (SEM). The normal distribution and Student's *t* tests were used to determine the significance of differences between the measurements. *P* values <0.05 were considered significant.

RESULTS

Mucosal oxygen free radical concentrations (mean percentage increase in chemiluminescence ± SEM) are shown in Fig. 1. After reperfusion of the hypothermically preserved grafts, there was approximately a sixfold increase in oxygen free radical concentrations in the untreated grafts compared to baseline values. Mucosal oxygen free radical production was significantly ($P < 0.05$) inhibited by pyruvate and maintained at near-normal values. In the allogeneic combination, acute rejection was confirmed by massive infiltration of leukocytes and apoptosis, endothelial cell damage, and a decrease in the number of Goblet cells. During acute rejection of the intestinal allograft, there was a significant ($P < 0.01$) increase of more than 10-fold in the oxygen free radical concentration in the untreated grafts compared to baseline values. Mucosal oxygen free radical production was significantly ($P < 0.05$) inhibited by pyruvate and maintained at approximately a twofold increase during acute rejection.

Mucosal levels of neutrophil infiltration (mean number of myeloperoxidase-positive cells in 1.2 × 1.2 mm ± SEM) are shown in Fig. 2. There was a marked increase in the number of neutrophils infiltrating the mucosa after reperfusion of the hypothermically preserved grafts ($P < 0.05$) and during acute rejection

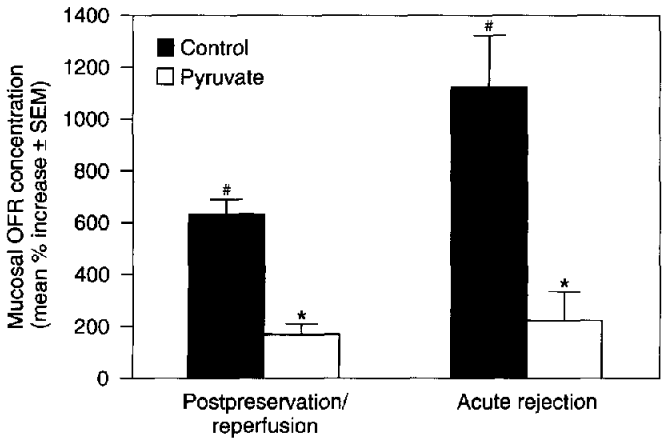

Fig. 1. Mucosal oxygen free radical *(OFR)* concentration (mean percentage of increase in chemiluminescence ± SEM). After reperfusion of the hypothermically preserved syngeneic grafts, there was approximately a sixfold increase in the OFR concentration in untreated grafts compared to baseline values. Mucosal OFR production was significantly inhibited by pyruvate and maintained at near-normal values. During acute rejection of intestinal allografts, there was a significant increase of more than 10-fold in the OFR concentration in placebo-treated grafts compared to baseline values. Mucosal OFR production was inhibited by pyruvate and maintained at approximately twice the baseline values during acute rejection. * = $P < 0.05$ vs. control; # = $P < 0.05$ vs. baseline.

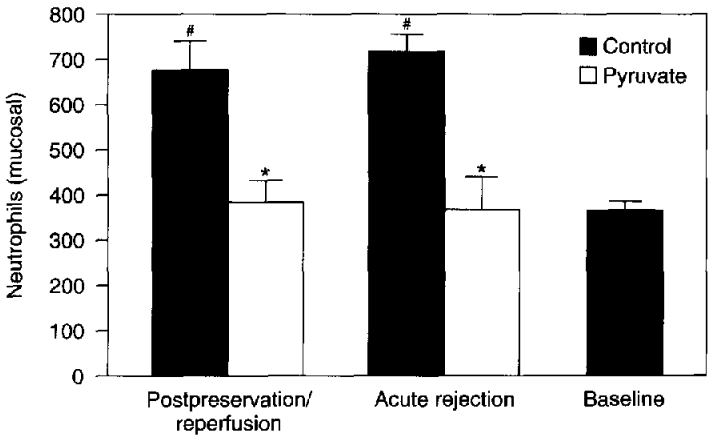

Fig. 2. Mucosal neutrophil infiltration (mean number of myeloperoxidase-positive cells in 1.2 mm × 1.2 mm at ×100 ± SEM). There was a marked increase in the number of neutrophils infiltrating the mucosa after reperfusion of the hypothermically preserved syngeneic grafts and during acute rejection compared to baseline values. This infiltration was significantly reduced by pyruvate. * = $P < 0.05$ vs. control; # = $P < 0.05$ vs. baseline.

($P < 0.05$) compared to baseline values. This infiltration was significantly ($P < 0.05$) reduced by pyruvate in both conditions.

After reperfusion of the hypothermically preserved grafts, the separation of the villous epithelium from the lamina propria extended almost the full length of the villi and in some sections destruction of the villous tips was also observed. In the grafts treated with pyruvate there was a marked decrease in edema and separation of the epithelium from the lamina propria was not observed.

During acute rejection an amelioration of the histopathologic abnormalities was seen in animals that received pyruvate. Graft sections obtained from this group showed a significant reduction in apoptotic figures, reduced endothelial cell damage, leukocyte adhesion, and intravascular platelet aggregation with preservation of Goblet cells, and increased mitotic

events as compared to untreated rejecting grafts. Pyruvate treatment reduced the intensity of mucosal injury but did not abrogate rejection completely; in fact, marked infiltration of leukocytes was present in all of the samples.

DISCUSSION

In this study we demonstrated that pyruvate exerted a protective effect on both posthypothermic preservation/reperfusion injury and acute rejection of intestinal grafts.

After hypothermic preservation and reperfusion of intestinal grafts, the amount of mucosal oxygen free radicals is increased, as we showed in a previous study[4] in which we observed a correlation between oxygen free radical mucosal levels and the degree of mucosal injury. This suggests that reactive oxygen intermediates play an important role in the pathogenesis of reperfusion injury after small bowel cold preservation (i.e., ischemia) and transplantation. The simple application of a supraphysiologic concentration of the natural metabolite pyruvate in the lumen of the intestinal graft effectively prevented formation of oxygen free radicals or scavenged them, maintaining the mucosal level of these reactive species only slightly above baseline values. In the present study we did not preserve the graft using intravascular solutions containing pyruvate, which could in theory increase the protective effect seen here.

The time of preservation used in this study was also relatively short (2 hours), and the evaluation of the status of the grafts was also performed relatively early (120 minutes after reperfusion), without information on survival.

The mechanism by which pyruvate protects the mucosa of the graft after reperfusion remains to be established. Oxygen free radicals can be produced by a large number of cells including neutrophils.[13] Tissue infiltration by neutrophils was also evaluated in this study, and indeed we observed an increased number of neutrophils 2 hours after reperfusion. Pyruvate significantly prevented this infiltration, and the neutrophils counted in the treated grafts were found to be equivalent in number to the resident cells in control intestines and were not activated. The Hanker-Yates reaction used in this study allows us to stain the enzyme myeloperoxidase within the cells. Activated (or degranulating) cells are easily distinguishable by a halo of stain around them, whereas the resident (or inactive) cells are usually smaller and stained within the cytoplasm only. The observation in our model that the neutrophils in the grafts treated with pyruvate were not active could indicate that pyruvate is inhibiting the formation of oxygen free radicals to a greater degree than is scavenging them after they are produced.

There is evidence that pyruvate can inhibit the formation of oxygen free radicals in isolated hepatic cells (data not published), and it is known that pyruvate can prevent oxygen free radical production by inhibiting superoxide formation.[8] An early scavenging activity of pyruvate on the oxygen free radicals, produced from the endothelial cells, could also explain the reduced infiltration and activation of neutrophils, since oxygen free radicals are known to represent a potential stimulus for the activation of these cells.[14]

During acute rejection of the intestinal allografts, we showed in this model that oxygen free radicals are produced in large amounts, with their level increased approximately 10-fold in the mucosa. The mechanism of formation of these radicals is not known. Acute rejection of intestinal allografts is characterized by an intensive leukocyte infiltration.[15] Macrophages and neutrophils are among the most numerous and when activated can both produce oxygen free radicals.[13,16] Although the increased level of mucosal oxygen free radicals observed could be the consequence of the activation of these infiltrating cells, we did not evaluate which cell population is responsible for oxygen free radical production.

We showed that in the animals treated systemically with pyruvate there is a significant reduction in the mucosal level of oxygen free radicals during acute rejection. This reduction is accompanied by an amelioration of the histologic findings suggesting that these two events, oxygen free radical formation and tissue injury, are related. We did not evaluate whether the reduced injury observed is a consequence of the decreased mucosal level of oxygen free radicals or whether pyruvate is preserving the tissue through a mechanism different from that of oxygen free radical scavenging or inhibition, which could result in a reduced inflammatory response and consequently reduced oxygen free radical production.

The observation in a previous study[5] that mucosal blood flow is reduced during acute rejection suggests that an ischemic (or hypoxic) component could also contribute to the mucosal injury observed. Histologic analysis of sections of the rejected intestinal graft showed increased endothelial damage, adhesion of leukocytes to the endothelium, and increased intravascular platelet aggregation. All of these factors could contribute to the reduced mucosal blood perfusion observed. Pyruvate treatment showed a beneficial effect on these abnormalities, reducing endothelial damage, adhesion of leukocytes to the endothelium, and intravascular platelet aggregation. We did not evaluate whether such protective effects also ameliorated mucosal blood perfusion during acute rejection.

There is also the possibility, currently under investigation in our laboratory, that pyruvate could protect the allograft being rejected by modulating the immune response.

The importance of mucosal integrity after reperfusion of the transplanted intestinal graft and during acute rejection is unquestionable. Sepsis and infection are still among the leading causes of complications and failure of this transplant.[1] Patients who receive intestinal grafts are given heavy doses of immunosuppressants, and the integrity of the graft mucosa could represent an important defense against the intestinal microflora. The protective effects of pyruvate in our two experimental models, and the fact that this compound is a natural metabolite with few known side effects in humans,[17] suggest that pyruvate could be of therapeutic value after small bowel transplantation.

We conclude that intraluminal treatment with pyruvate before cold preservation of intestinal graft, in this rat model, significantly reduced oxygen free radical production, neutrophil infiltration, and reperfusion mucosal injury. During acute rejection of rat intestinal allografts, oxygen free radicals are produced in the mucosa. Oxygen free radical production and neutrophil infiltration are reduced by pyruvate, which also exerts a protective effect on the intestinal mucosa during allograft rejection.

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Long-Term Results of Strictureplasty for Ileocolonic Anastomotic Recurrence in Crohn's Disease

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This study examined the outcome of strictureplasty for recurrence at the ileocolonic anastomosis after resection (ileocolonic strictureplasty) in Crohn's disease. The records of 42 patients who underwent ileocolonic strictureplasty between 1980 and 1997 were reviewed. The method of ileocolonic strictureplasty was Heineke-Mikulicz reconstruction for a short stricture (≤6 cm) in 41 patients and Finney reconstruction for a long stricture (20 cm) in one. Synchronous operations were performed for coexisting small bowel Crohn's disease in 17 patients: strictureplasty in eight, resection in two, and both in seven. Postoperatively there were two intra-abdominal abscesses, which were treated conservatively. There were no deaths. All except two patients had complete relief of symptoms after operation. Most of the patients who had preoperative weight loss gained weight (median gain +2.6 kg). After a median follow-up of 99 months, 24 patients (57%) had a symptomatic recurrence. Three patients were successfully managed by medical treatment. The other 21 patients (50%) required surgery for recurrence (20 for recurrence at the previous ileocolonic strictureplasty site). At present, two patients are symptomatic and currently receiving corticosteroid therapy. All other patients have had no recurrent symptoms. None of the patients have developed short bowel syndrome or small bowel carcinoma. Strictureplasty is a safe and efficacious procedure for ileocolonic anastomotic recurrence in Crohn's disease. (J GASTROINTEST SURG 1999;3:555-560.)

KEY WORDS: Strictureplasty, Crohn's disease, short bowel syndrome, ileocecal resection, ileocolonic resection, ileocolonic anastomotic recurrence, complications, reoperation

Most primary operations for Crohn's disease involve ileocecal or ileocolonic resection and anastomosis.[1-5] Recurrence at the ileocolonic anastomosis is common, and many patients require further surgical treatment.[1-5] In patients with minimal small bowel disease and adequate small bowel length, resection is the standard treatment for ileocolonic anastomotic recurrence. Although strictureplasty has become an accepted option for treatment of small bowel strictures conserving small bowel,[6-12] strictureplasty has also been recommended for ileocolonic anastomotic recurrence after ileocecal or ileocolonic resection. However, there have been only two published reports of strictureplasty for ileocolonic recurrence, and in these reports the number of patients was small and the duration of follow-up was short.[13,14] There have been no reports concerning the long-term results of ileocolonic strictureplasty.

This retrospective study reports the long-term outcome of 42 patients who underwent strictureplasty for ileocolonic anastomotic recurrence in Crohn's disease.

PATIENTS AND METHODS

Between June 1980 and October 1997, 42 patients underwent strictureplasty at the site of ileocolonic anastomotic recurrence (ileocolonic strictureplasty) after a previous ileocecal or ileocolonic resection for Crohn's disease at the General Hospital or Queen Elizabeth Hospital, Birmingham, United Kingdom. The medical records were reviewed, and patient characteristics, operative details, and surgical outcomes were defined for all patients.

After surgery, all the patients were followed up in our inflammatory bowel disease clinic at 3- to 6-month

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Table I. Patient characteristics

Median age at operation (range)	39 yr (17-66 yr)
Male:Female ratio	13:29
No. of previous operations	
1	15
2	9
3	10
4	4
5	2
6	2
Median duration between the last operation and ileocolonic strictureplasty (range)	77 mo (5-464 mo)

intervals for the first year and once a year thereafter. There were two late deaths unrelated to Crohn's disease. All other patients are currently being followed up in our inflammatory bowel disease clinic. Radiologic examinations of the bowel were performed in all patients with new symptoms. In view of the difficulty in defining recurrence clinically and radiologically, we have used further surgical treatment as the definitive end point. Cumulative reoperation rates were calculated by means of the Kaplan-Meier method.

RESULTS

Patient Characteristics

The indication for strictureplasty in all patients was recurrent obstructive symptoms due to ileocolonic anastomotic recurrence. Patient characteristics are shown in Table I. Eighteen patients (43%) had undergone multiple (≥3) operations for small bowel Crohn's disease before ileocolonic strictureplasty. The median duration between the last operation and ileocolonic strictureplasty was 77 months. Twenty-seven patients (64%) had preoperative weight loss (median loss 7 kg; range 1 to 18 kg). Fifteen patients (36%) were treated with corticosteroids (either adrenocorticotropic hormone or oral prednisolone) for at least 1 month immediately before surgery.

Operative Details

At laparotomy, three patients (7%) had a localized intra-abdominal abscess that was unrelated to the ileocolonic anastomotic recurrence. All sites of macroscopic Crohn's disease were inspected; strictures were identified by the passage of a 20 F Foley balloon catheter with the balloon inflated to produce a 2 cm sphere.

Short segmental fibrotic stricture has been treated by strictureplasty. Perforating diseases such as fistula and abscess, or long stricture (>20 cm), have been treated by resection. Heineke-Mikulicz strictureplasty was performed for a short ileocolonic stricture (≤6 cm) in 41 patients, and Finney strictureplasty was used for a long ileocolonic stricture (20 cm) in one. In both the Heineke-Mikulicz and Finney reconstructions, the anastomosis was made using one-layer continuous extramucosal 3/0 Vicryl (Ethicon Ltd., Edinburgh, U.K.) or PDS (Ethicon Ltd.) sutures.

Synchronous operations for coexisting small bowel Crohn's disease were performed in 17 patients (40%): strictureplasty in eight, resection in two, and both in seven. Either a Heineke-Mikulicz or Finney strictureplasty was performed for strictures in the proximal small bowel. In those not suitable for strictureplasty (long stricture, perforating disease-associated abscess or fistula), resection was performed. Synchronous resection was performed for perforating disease in three patients and for long strictures (>20 cm) in six patients. Two patients underwent covering loop ileostomy.

Early Results

There were no deaths. None of the patients developed anastomotic leaks or enteric fistulas. There were two localized intra-abdominal abscesses, which were treated conservatively. Other minor complications are listed in Table II. The median duration of postoperative stay was 8 days (range 4 to 107 days).

All except two patients had complete relief of symptoms after operation. The two patients whose symptoms were not relieved required further surgery within 6 months for recurrent disease at new sites (not previous operation sites). Only two patients required corticosteroids 1 year after operation.

Table II. Complications and duration of postoperative stay

Complications	
Anastomotic leak	0
Anastomotic hemorrhage	0
Intra-abdominal abscess	2 (5%)
Enteric fistula	0
Wound infection	3 (7%)
Chest infection	3 (7%)
Urinary tract infection	1 (2%)
Deaths	0
Median duration of postoperative stay (range) postoperative stay (range)	8 days (4-107 days)

Table III. Long-term results

Symptomatic recurrence	24 (57%)
Site of reoperation	
Previous ileocolonic strictureplasty site alone	10
Previous ileocolonic strictureplasty site and other sites*	10
Small bowel alone	1
Reoperation for recurrence at the previous ileocolonic strictureplasty site	20 (48%)
Repeat ileocolonic strictureplasty	9
Resection	10
Defunctioning ileostomy	1
Reoperation for recurrence at other sites	11 (26%)
Gastrojejunostomy	1
Small bowel strictureplasty	7
Small bowel resection	1
Sigmoid colectomy	1
Proctocolectomy	1

*Duodenum in one, small bowel in seven, sigmoid colon in one, total colon and rectum in one.

In 24 of the 27 patients who had preoperative weight loss, postoperative body weight was available. Twenty-two (92%) of the 24 patients gained weight postoperatively. The median weight gain 3 months postoperatively was +2.6 kg (range −6.0 to +17.5 kg).

Long-Term Results

Two patients died of unrelated disease during this study. No patients developed small bowel carcinoma. The median duration of follow-up was 99 months (range 5 to 190 months). Twenty-four patients (57%) had symptomatic recurrence (Table III). Three patients were successfully managed by medical treatment (corticosteroids) and required no surgery. The other 21 patients (50%) required surgery for recurrences. The sites of reoperation are shown in Table III. Twenty patients (48%) required surgery for recurrence at the previous ileocolonic strictureplasty site. The 5- and 10-year cumulative reoperation rates for recurrence at the site of previous ileocolonic strictureplasty were 44% (95% confidence interval [CI] = 28% to 61%) and 60% (95% CI = 42% to 78%), respectively (Fig. 1). Nine patients underwent repeat ileocolonic strictureplasty, 10 underwent resection, and one had defunctioning ileostomy alone. Eleven patients (26%) required surgery for recurrent disease at other sites: gastrojejunostomy in one, small bowel strictureplasty in seven, small bowel resection in one, sigmoid colectomy in one, and proctocolectomy in one.

Three of nine patients who underwent a second ileocolonic strictureplasty required further surgery for recurrence at the same site: a third ileocolonic strictureplasty in two and resection in one.

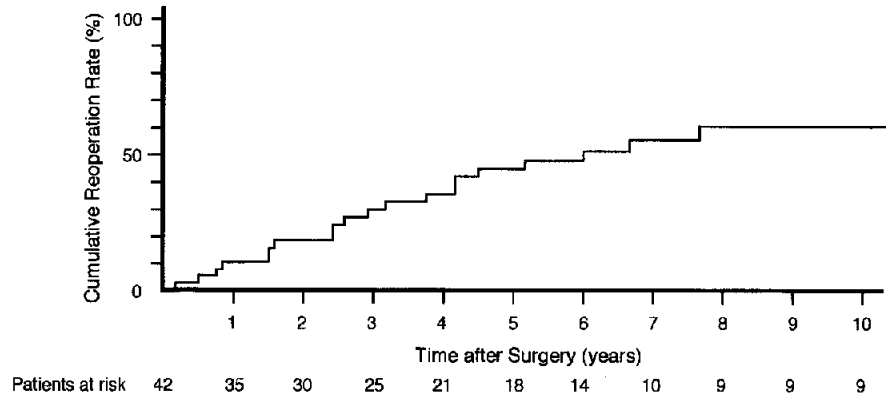

Fig. 1. Cumulative reoperation rate for recurrence at previous ileocolonic strictureplasty site.

None of the patients have developed short bowel syndrome. At present, two patients are symptomatic as a result of multiple small bowel disease, and they are now receiving corticosteroid therapy. All other patients have not had recurrent symptoms.

DISCUSSION

Most primary operations for ileocecal or ileocolonic Crohn's disease involve resection and anastomosis.[1-5] Rutgeerts et al.[5] reported that 46% of patients after ileocecal or ileocolonic resection had developed anastomotic recurrence after a follow-up of 3 years. In this unit 40% of patients who underwent ileocecal or ileocolonic resection required repeated resection, and 18% required two further resections. Thus ileocolonic anastomotic recurrence is common, and many patients require surgical treatment.[1-5] Repeated ileocolonic resection will reduce the length of small bowel and impair ileal function. Furthermore, repeated resections may lead to short gut syndrome, especially when patients have active small bowel disease and multiple previous small bowel resections. In 1986 Alexander-Williams et al.[15] from our unit advocated balloon dilatation for anastomotic strictures, but they were soon discouraged by perforation and by the experience of early stenosis. Other authors[16,17] reported that endoscopic balloon dilatation was a safe and effective option for selected patients with colonic strictures or strictures of an ileocolonic anastomosis in Crohn's disease.

Strictureplasty has become a useful surgical option in the management of localized short segmental small bowel Crohn's disease.[6-12] Sayfan et al.[12] found no significant difference in operation-free intervals following resection or strictureplasty for obstructive small bowel Crohn's disease and concluded that strictureplasty was an effective alternative to extensive or multiple resections for multifocal stenotic small bowel Crohn's disease. It seemed logical, therefore, to use this technique for ileocolonic recurrence. As is true of small bowel strictureplasty, ileocolonic strictureplasty is avoided in perforating disease if it is associated with a fistula or an abscess. We have used ileocolonic strictureplasty for a short anastomotic stricture. We are less enthusiastic than others about using the long Finney strictureplasty for long stricture since it will never function normally, and there is a risk that small bowel malignancy may be missed. A long stricture or perforating disease at the ileocolonic anastomosis has been treated by repeat resection in principle. In only one patient did we make an exception by treating a long ileocolonic stricture with Finney strictureplasty, since there was already a serious shortage of small bowel.

Because strictureplasty involves a suture line fashioned through macroscopic disease, there was concern about a possible increase in postoperative complications, especially septic complications such as leak, fistula, or abscess. However, many authors reported that the septic complication rate after strictureplasty was similar to that after bowel resection.[6-12] In this study after strictureplasty there were neither anastomotic leaks nor enteric fistulas. Two patients developed a localized intra-abdominal abscess, which was treated conservatively. There were no other serious complications. Thus in this study, as in others, strictureplasty was associated with a lower incidence of serious postoperative complications.

There have been only two published reports on the use of strictureplasty for ileocolonic anastomotic recurrence in Crohn's disease.[13,14] In 1991 Sharif and

Alexander-Williams[13] from our unit reported an audit of outcome in 24 patients who had ileocolonic strictureplasty. Only one patient had a stricture at the site of previous strictureplasty and underwent repeat strictureplasty. After a mean follow-up of 70.8 months, all 22 living patients had complete relief of symptoms at the time of the report. Tjandra and Fazio[14] reviewed 22 patients who had ileocolonic strictureplasty. Only two patients had symptomatic recurrences from new strictures at sites different from the ileocolonic region, and one needed reoperation for recurrence after a median follow-up of 2 years. There was no recurrence at the ileocolonic strictureplasty site. However, they stated that the long-term effectiveness of ileocolonic strictureplasty is not clear, and it is probably no better than that following repeat ileocolonic resection.

There have been no reports concerning the long-term results of ileocolonic strictureplasty. In this series, after a mean follow-up of 99 months, 20 patients (48%) required surgery for recurrence at the site of previous ileocolonic strictureplasty, and 11 patients (26%) required surgery for recurrence at a site different from the ileocolonic anastomosis. The reoperation rate after ileocolonic strictureplasty in this series was much higher than the two previous reports on ileocolonic strictureplasty.[13,14] This difference can be explained by the longer follow-up period in this study. It is difficult to conclude whether or not our long-term results of ileocolonic strictureplasty are favorable, since there is no comparable group. However, our reoperation rate after ileocolonic strictureplasty was similar to the 40% to 65% after ileocolonic resection in the published reports or recent study in our unit.[1-5] There was also no difference in the relief of symptoms between those two groups. Therefore we believe that the long-term results of ileocolonic strictureplasty are satisfactory.

In this series obstructive symptoms were completely relieved in all but two patients who required further surgery within 6 months. Most patients gained weight following surgery, and few patients required steroids 1 year after surgery. At present, two patients are symptomatic because of multiple sites of small bowel Crohn's disease, and they are now receiving medical treatment. All other patients are asymptomatic and in good health. None of the patients have developed short bowel syndrome.

One of the concerns raised by strictureplasty is the possibility of malignancy after surgery, because the segment of inflamed bowel is left in situ. Marchetti et al.[18] reported the first case of adenocarcinoma arising at a strictureplasty site in Crohn's disease. In the present study, none of the patients developed smal bowel carcinoma. The actual incidence of small bowel carcinoma in patients with Crohn's disease does not seem to be high. Biopsy of primary strictureplasty sites was not routinely done in this series. Surveillance is not feasible, but the possibility of carcinoma should be considered when symptoms recur in long-standing quiescent disease.

These results suggest that ileocolonic strictureplasty is associated with a low incidence of postoperative complications, and most patients are rapidly restored to health after strictureplasty. The reoperation rate after ileocolonic strictureplasty is similar to that after ileocolonic resection in the long term. In patients with minimal small bowel disease and adequate small bowel length, both repeat resection and strictureplasty may be appropriate treatments for a short ileocolonic anastomotic recurrence, provided it is not associated with a fistula or an abscess. In this study many patients underwent repeated operations for small bowel disease. Those patients will still require further surgery for recurrence at the ileocolonic anastomosis and in the small bowel. We conclude that ileocolonic strictureplasty has an important role in conserving gut in patients with anastomotic recurrence after ileocolonic resection, particularly those at risk of short bowel from active small bowel disease and/or multiple previous resections.

We wish to acknowledge the contribution of Professor J. Alexander-Williams, who provided many of the patients in this study.

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Surgical Resection of Gastric Cancer in the Octogenarian Population

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The medical records of 80 patients whose mean age was 81.1 years (range 80 to 94 years) were retrospectively evaluated for morbidity, mortality, and survival following gastric resection for gastric carcinoma. The overall 5-year survival of 68 patients who had undergone a total or subtotal gastrectomy for adenocarcinoma was 11%, with a mean and median survival of 25 and 17.5 months, respectively. In contrast, eight patients who did not undergo gastric resection for adenocarcinoma were found to have a mean and median survival of only 3.6 and 2.0 months, respectively. The 30-day perioperative morbidity and mortality rates for patients who had undergone gastric resection were 45.8% and 5.0%, respectively. The total gastric resection group had no perioperative deaths or anastomotic leaks. We conclude that with careful selection of patients and precise surgical technique, gastric resections can safely be performed in octogenarian patients with minimal morbidity and mortality. (J GASTROINTEST SURG 1999;3:561-564.)

KEY WORDS: Gastric cancer, gastrectomy, elderly, octogenarian, esophagojejunostomy

Although the incidence of gastric carcinoma has steadily declined in the United States, management of elderly patients with gastric carcinoma remains problematic. Chemotherapy and radiotherapy have little role in the treatment of gastric cancer, whereas surgical resection continues to be the treatment of choice. Morbidity and mortality rates following gastric resection in younger patients have been shown to range from 3% to 15%.[1-3]

Many surgeons believe that patients who present with gastric carcinoma in their eighth or ninth decade of life carry a morbidity, mortality, and life expectancy that are unacceptable when treated with aggressive surgical resection.

Despite evidence of improved survival and palliation with gastric resection,[1] many surgeons will opt for simple gastrointestinal bypass or gastrointestinal feeding procedures in their elderly patients. However, a number of institutions have reported that patients in their seventh decade have mortality rates of 3% to 9.6% following gastric resection for cancer.[3-5]

In contrast to other reports in the literature, this retrospective study compares and evaluates a true elderly group of patients, 80 years of age and older, who either underwent a gastric resection for carcinoma, a gastrointestinal bypass, or a gastrointestinal feeding procedure between 1981 and 1994. Postoperative complications, associated diagnoses, surgical procedures, morbidity, mortality, and survival are reviewed.

MATERIAL AND METHODS

Approval was obtained from the institution review board of the Kuakini Medical Center and Straub Clinic and Hospital, Honolulu, Hawaii. The medical records of all patients 80 years of age and older who had undergone surgical evaluation for a total or subtotal gastrectomy (after a pathologically proved diagnosis of gastric carcinoma) between January 1, 1981, and July 15, 1994, were retrospectively reviewed. Patients ranged in age from 80 to 94 years (Table I). Records from 80 patients were reviewed for postoperative complications, associated diagnoses, surgical procedures, morbidity, mortality, and survival.

Extent of surgical resection was determined at the time of abdominal exploration. When possible, a total

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or subtotal gastrectomy was performed to completely remove all microscopic carcinoma with intraoperative frozen sections. The decision whether to perform a gastric resection at the time of the abdominal exploration was at the discretion of the attending surgeon. All patients who had a subtotal gastrectomy (75% to 95% gastric resection) underwent a Billroth I or Billroth II reconstruction.

Patient follow-up consisted of 1- and 6-month visits postoperatively and annual or biannual examinations thereafter. Endoscopy and/or gastrointestinal contrast roentgenography was performed annually or biannually.

Table I. Age and sex of all patients

Age (yr)	Men	Women	Total	%
80-85	32	12	44	55
86-90	18	11	29	36
91-95	4	1	5	6
96-100	1	1	2	3
TOTAL	55	25	80	100

Table II. Comorbidity of all patients

Diagnosis	No. of patients
Hypertension	17
Heart disease	13
Diabetes mellitus	10
Anemia	9
Congestive heart failure	7
Atrial fibrillation	6
Chronic obstructive pulmonary disease	4
Recent myocardial infarction	3
Renal failure	3
Preoperative sepsis	1

The Scheffe-F test and single-classification analysis of variance was employed for all statistical analyses.

RESULTS

Thirty-seven percent of the patients presented with epigastric discomfort, 25% presented with anorexia, and another 25% presented with melena. Two patients presented without symptoms but were diagnosed with gastric carcinoma after routine follow-up endoscopy for a history of previously excised gastric polyps.

All patients underwent preoperative evaluation with endoscopy and/or gastrointestinal contrast roentgenography. Preoperative metastatic workup in selected patients consisted of routine laboratory tests, computerized tomography, and bone scans. All patients except for two, who were diagnosed intraoperatively, were taken to the operating room with a diagnosis of gastric carcinoma.

Histopathologic evaluation revealed 76 patients (95%) with adenocarcinoma, three patients with lymphoma, and one patient with a spindle cell gastric tumor.

Hypertension and heart disease (patients with documented coronary artery disease, stable on medical treatment) were found to be the most prevalent comorbidities. However, no specific comorbidity was found to be associated with an increase in patient perioperative morbidity or mortality (Table II).

Following gastric resection, patients with stage I adenocarcinoma (38%) were found to have a 27% overall 5-year survival with a mean and median survival with disease of 36 and 25 months, respectively (Table III). Stage III adenocarcinoma was diagnosed in 28% of the patients, with a mean and median survival with disease of 25 and 19 months, respectively (Table III). For all stages of disease, an overall 5-year survival of 11% was found.

Fourteen of the patients diagnosed with adenocarcinoma underwent a total gastrectomy with an esoph-

Table III. Stage of disease, survival, and disease-free interval in patients undergoing gastric resection for adenocarcinoma

Stage	No. of patients	%	Median survival with disease (mo)	Mean disease-free interval (mo)*
0	3	4	—	31
I	26	38	25	33.6
II	8	12	13	26
IIIA	11	16	14	8
IIIB	8	12	19	0
IV	12	18	5	0

*All stage 0 patients remained disease free at the end of follow-up.

agojejunostomy anastomosis. A survival range of 3 to 80 months, with a mean and median survival of 31 and 19 months, respectively, was found. Fifty-four patients with adenocarcinoma underwent a subtotal gastrectomy (10 with Billroth I and 44 with Billroth II reconstructive procedures), with a mean and median survival of 24 and 16 months, respectively.

Eight patients (10%) who underwent surgical exploration for gastric adenocarcinoma were found to have metastatic disease and therefore did not undergo gastric resection. These patients underwent either a gastrointestinal bypass (6 patients) or a gastrointestinal feeding procedure (2 patients). The mean and median survival with disease was 3.7 and 2.0 months, respectively, which is significantly less than that found in the 68 patients who underwent a gastric resection for adenocarcinoma with a mean and median survival of 25 and 17.5 months, respectively.

One of three patients diagnosed with gastric lymphoma died on postoperative day 10 following intra-abdominal sepsis, whereas the two other patients remain disease free at 12 and 24 months. One patient was diagnosed with a gastric spindle cell tumor and is disease free at 48 months.

Eighteen additional operative procedures (16 patients) were performed at the same setting as the gastric resection with no distinct adverse outcomes. Six patients had a cholecystectomy for cholelithiasis; six patients had splenectomies for large greater curvature tumors; two patients diagnosed with a second primary colon cancer underwent colon resection for stage I and stage II disease; one patient underwent repair of an expanding abdominal aortic aneurysm; and another patient underwent a splenectomy, partial pancreatectomy, and left nephrectomy for extensive disease.

In the octogenarian population presented here, the overall 30-day postoperative mortality rate was found to be 5%. Two patients died of postoperative sepsis, one patient died of pneumonia, and one patient died following a postoperative myocardial infarction. Table IV outlines all postoperative complications with their frequency of occurrence. No single morbidity was associated with an increase in mortality. The mean postoperative hospital duration was 18.2 days with a range of 6 to 57 days.

Table IV. Postoperative morbidity

Morbidity	No. of patients
Aspiration pneumonia	6
Gastric outlet obstruction	10
Pneumonia	6
Urinary tract infection	5
Prolonged ileus	4
Subphrenic abscess	3
Wound infection	1
Small bowel obstruction	2
Dumping syndrome	1
Anastomotic leak	1
Wound dehiscence	1

DISCUSSION

The incidence of gastric cancer in the United States has been steadily declining since the early part of this century. Over the past 50 years it has decreased from 25 to five per 100,000 patients. However, our experience with gastric cancer in Hawaii is considerably greater than in other regions of the United States because of the large Japanese population. Gastric carcinoma remains a major surgical dilemma in specific patient populations, especially those patients in their eighth or ninth decade of life.

In contrast to previous studies, we have evaluated a truly elderly population. The mean age of patients in this study was 81.1 years, with a range of 80 to 94 years. The average age is 7 years older than in previously reported series.[1,4-6] As shown in Table I, 30 patients (42%) are more than 85 years of age.

Surgical resection for gastric cancer continues to be the only effective treatment modality.[1,2,7-10] Ekbom et al.[1] reported on 144 patients (in their sixties or seventies) with gastric carcinoma who underwent either a gastric resection or gastrojejunostomy bypass. In that group of patients, gastrojejunostomy bypass proved to provide significantly less palliation, with little improvement in gastrointestinal complications and a higher postoperative mortality. In this study only one patient who underwent gastrointestinal bypass was palliated sufficiently to be discharged home prior to death. The remaining seven patients in the nonresected group remained hospitalized and died with persistent gastrointestinal ileus and unresolved gastric bypass obstruction. In contrast, nine patients with metastatic disease who underwent palliative resection were all discharged home before they died.

As a result of improved patient survival and palliation with gastric resection, a number of authorities have advocated, when conditions permit, performing an extensive gastrectomy.[1,2,10] The overall 5-year survival was 11%, which is similar to that reported in other retrospective studies of younger patient populations.[1,2,4,5] The mean and median survival for all stages was 25 and 17.5 months, respectively, which is significantly better than the mean and median survival with disease of 3.7 and 2.0 months, respectively, in the eight nonresected patients.

Although several reports have indicated mortality rates of 6% to 10% in elderly patients undergoing gastric resection, many surgeons may not offer gastric resection because of anticipated adverse results. Elderly patients alternatively are offered bypass procedures or feeding tube procedures because of their advanced age. Our experience, similar to other reports, suggests that this bias is not warranted. Djokovic and Hedley-Whyte[11] evaluated 500 patients over 80 years of age, who had undergone a variety of surgical procedures, with an overall mortality rate of 6.2%. Three recent retrospective studies have also shown that patients in their sixties and seventies can tolerate aggressive gastric resection with a mortality rate of 3% to 9.6%.[3-5] In comparison, the mortality rate for gastric resection in the general patient population has been shown to be 7%.[2,10]

In our series the most frequent morbidity was gastric outlet obstruction (Table IV). Aspiration and hospital-acquired pneumonia also occurred with increased frequency with one case of aspiration pneumonia resulting in a postoperative death. Of the 10 reported cases of gastric outlet obstructions, eight occurred within the gastrojejunostomy bypass group. Four postoperative deaths were found within the subtotal gastrectomy group; however, no deaths occurred in the total gastrectomy group.

The incidence of anastomotic leak following esophagojejunostomy has been reported to be as high as 21% with a mortality rate approaching 50%.[12] In this study a total of 14 esophagojejunostomy anastomoses were constructed with no clinical leaks noted. To minimize this severe complication, a patient's overall medical condition, extent of carcinoma, and attention to technical detail must be carefully considered when performing a total gastrectomy.

CONCLUSION

With careful patient selection and precise surgical technique, gastric resections can safely be performed in selected octogenarian patients with acceptable morbidity and mortality.

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