Presentation of the Founder's Medal to Dr. Lawrence Way

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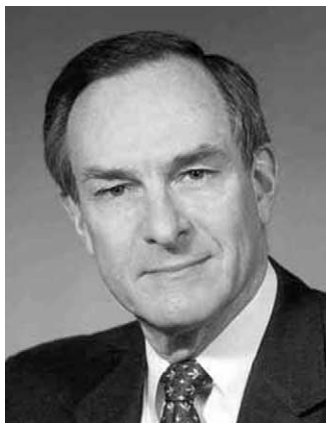
Some 25 years ago, the Board of Trustees of The Society for Surgery of the Alimentary Tract initiated a tradition that we continue today. Starting with Dr. William Silen from Boston, in 1976, the Board has honored every year one of the Society's senior members with the Founder's Medal. This medal, the highest recognition bestowed by the Board, is meant to be a tribute to someone who epitomizes what the Society stands for, a tribute to someone who has worked tirelessly to help advance the Society's cause. It is also a recognition of this person's unique contributions to the broader fields of education, research, and excellence in the delivery of patient care. We have since then conferred this award at the time of our Annual Scientific Meeting. Our elders believed that it was important to put a temporary halt to the frenzy of our scientific activities, and that instead of nourishing our intellect we should devote some time to the nourishment of the soul. Never has this been more important than in today's world. Indeed, our culture and our world are ever more demanding of our personal time and energy, and more concerned with increasing speed and efficiency in all its activities than with the individual's feelings and emotions. Thus stopping, if only for a few minutes, to feed the soul is appropriate and essential.

Today's recipient of the Founder's Medal is Dr. Lawrence Way. He is Professor of Surgery and Vice-Chairman of the Department of Surgery at the University of California San Francisco, and the director of their Videoscopic Surgery Center. The honor he receives today marks an illustrious career, which began at Cornell University with his graduation in 1955. In 1959 he obtained his M.D. degree from the University of Buffalo. From Buffalo, he moved to the University of California San Francisco for his internship and surgical training, and he has remained there, for the most part, ever since.

It was at the University of California that he met Dr. J. Engelbert Dunphy, who would become his mentor, his life-long friend, and I believe, the star that has always guided Dr. Way through his prestigious academic career. Shortly after Dr. Way completed his residency, Dr. Dunphy sent the young doctor to Los Angeles for 2 years to work under the guidance of Dr. Morton Grossman. It was then that Dr. Way fell in love with the physiology of the gastrointestinal tract, a passion he has kept alive ever since.



Dr. Lawrence Way

Dr. Way's academic work has centered on the study of the physiology and pathophysiology of the upper gut and the biliary tract, and on surgery of the biliary tract and pancreas. His name and landmark articles are constantly being cited by those who publish papers on pancreatic cancer, pancreatitis, common bile duct stones, bile duct injuries, Klatskin's tumor, and the like.

Dr. Way is a leader in the full sense of the word. Leaders inspire confidence, making people feel comfortable following in their paths. A leader must have vision, and the wisdom to choose the right path to achieve the mission. As someone who was privileged to work under his guidance for the first 15 years of his academic career, I can attest to that vision and to that wisdom. Somehow he always seemed able to see beyond the horizon and to embrace the right cause. I vividly remember when I arrived in San Francisco in 1978 and found that he was having a "Wang" machine installed in his office. For those of you who may have forgotten, that was the first version of a word processor. He made me start using it, which gave me several years' advantage over many of my contemporaries. I also remember the first version of a slide-making program that he forced us to incorporate. I remember the development of laparoscopic cholecystectomy and how he forced himself and all those who worked with him to become proficient in

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the use of this new technique. And, when it became clear that a laparoscopic cholecystectomy provided significant advantages, he pushed each one of us to apply this new method in our own fields. He was instrumental in the developing applications to the esophagus, the stomach, and the pancreas. Dr. Way is someone who does not fear change; rather he sees change as a challenge. If a change means an improvement, he welcomes the change. Perhaps it is in recognition of his vision and his ability to deal with change that he has been appointed to the Committee on Emerging Surgical Technology and Education of the American College of Surgeons, as well as to the Gastroenterology Devices Advisory Panel of the Food and Drug Administration.

Dr. Way has a passion for excellence. He sets high goals for himself and for those who work with him, and he forces himself and others to always move in that direction. His disciples, many of whom are here today, will remember what it was like when we had to prepare for Grand Rounds at the VA Hospital in San Francisco, and what it was like to write a manuscript, carry out experiments, and write grants. Nothing but the best was acceptable, and until the product was perfect you simply had to do it again, and again, and again.

As much as leadership and the pursuit of excellence are important aspects of Dr. Way's personality, the most notable characteristic is his ability as a teacher. He is the ultimate teacher, for he teaches with his own actions. Many of us have learned how to write simply by trying to emulate him. Many of us learned how to communicate by observing the way he did it. Many of us reinforced our integrity by observing the way he behaved. But if there is one place where he truly becomes the ultimate teacher, it is in the operating room. Again and again he is able to walk into the operating room, in the middle of trouble, help for just a few minutes, find the right solution, and leave. Only someone whom he has taught will ever know how much he has helped in those precious minutes while making the rest of the team in the operating room believe he was just passing by. Teaching of this sort changes the pupil's life forever.

Several years ago, shortly after I had moved away from San Francisco, I found myself helping a less experienced colleague in a difficult situation. As I was doing so, I was thinking, "What would Larry do if he were here?" When the problem was eventually corrected, I realized that some day this young surgeon might pass these tips on to someone else, and thus the effects of a true mentor tend to live forever. I read this quote somewhere and have kept it on the wall of my office as a reminder: "A teacher affects eternity...one can never tell where his influence stops." Dr. Way epitomizes that teacher.

Ladies and gentlemen, it is a great privilege to introduce to you the 2001 recipient of The Society for Surgery of the Alimentary Tract Founder's Medal, Dr. Lawrence Way.

Absence of Gastroesophageal Reflux Disease in a Majority of Patients Taking Acid Suppression Medications After Nissen Fundoplication

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Recent studies have shown that many patients use acid suppression medications after antireflux surgery. The aim of this study was to determine the frequency of gastroesophageal reflux disease in a cohort of surgically treated patients with postoperative symptoms and a high prevalence of acid suppression medication use. The study group consisted of 86 patients who had symptoms following Nissen fundoplication that were sufficient to merit evaluation with 24-hour distal esophageal pH monitoring. All completed a detailed symptom questionnaire. The mean postoperative follow-up period was 28 months (median 18 months). Thirty-seven patients (43%) were taking acid suppression medications after fundoplication. Only 23% (20 of 86) of all the patients and only 24% (9 of 37) of those taking acid suppression medications had abnormal esophageal acid exposure on the 24-hour pH study. Heartburn and regurgitation were the only symptoms that were significantly associated with an abnormal pH study. Endoscopic assessment of the fundoplication was the most significant factor associated with an abnormal pH study. Multivariable logistic regression analysis showed that patients with a disrupted, abnormally positioned fundoplication had a 52.6 times increased risk of abnormal esophageal acid exposure. Most patients who use acid suppression medications after antireflux surgery do not have abnormal esophageal acid exposure, and the use of these medications is thus often inappropriate. Because of the limited predictive power of symptoms, objective evidence of reflux disease should be obtained before prescribing acid suppression medication for patients who have undergone antireflux surgery.
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KEY WORDS: Antireflux surgery, Nissen fundoplication, gastroesophageal reflux disease, GERD, heartburn, laparoscopic surgery, antacids, proton pump inhibitors, H_2 receptor antagonists

Numerous studies have shown that antireflux surgery provides safe, effective, long-term control of reflux symptoms,[1–9] with normalization of esophageal exposure to both acid and nonacid gastric juice.[10] The quality of life after operation,[5,11–13] and the cost-effectiveness[14–16] of surgical therapy is comparable if not superior to medical therapy. Despite the demonstrated effectiveness of surgical therapy for gastroesophageal reflux disease (GERD), recent reports have called attention to the observation that many patients are prescribed acid suppression medications after antireflux surgery.[17,18] Spechler et al.[17] reported long-term follow-up findings for patients with complicated GERD enrolled in the Department of Veterans Affairs randomized trial of medical versus surgical therapies.[19,20] In the first report on the Veterans Affairs trial, almost half (46.9%) of the patients treated by fundoplication had taken antireflux medications at some time during the 11- to 13-year follow-up period.[17] In the second report, which has received considerable attention in the nonmedical press, 62% of the surgically treated patients had used medications.[20] A second study from the Mayo Clinic in Jacksonville, Florida, reported that 39% of 89 individuals who had undergone laparoscopic antireflux surgery had used antireflux medications. Of interest, only 51% of those taking medication had symptoms of heartburn or regurgitation. The reasons for taking

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medication in those without heartburn or regurgitation included abdominal pain (7 patients), bloating (2 patients), dysphagia (2 patients), and Barrett's esophagus, prevention of injury caused by nonsteroidal anti-inflammatory drugs, burning tongue, sore throat, "to help digestion," and unknown (1 patient each).[18] This list of symptoms suggests that the use of acid suppression medication may have been inappropriate for at least some of the patients.

The observation that many patients are using acid suppression medications after antireflux surgery has been used to imply that surgical therapy for GERD is often ineffective. Those holding this view assume that use of these medications after surgery is a sign of persistent or recurrent reflux disease, and is thus evidence of therapeutic failure. The aim of this study was to determine the frequency of, and predictive factors for, abnormal esophageal acid exposure in symptomatic patients who have undergone Nissen fundoplication. The high prevalence of antireflux medication use in our study cohort allowed us to additionally investigate the frequency of abnormal acid exposure in those patients taking acid suppression medications after operation.

PATIENTS AND METHODS

The clinical and esophageal physiology records of all patients who had been treated by Nissen fundoplication for GERD and who underwent postoperative 24-hour distal esophageal pH monitoring at the University of Southern California Department of Foregut Surgery between December 1991 and June 2000 were reviewed. Asymptomatic individuals who volunteered for postoperative studies as part of a follow-up study, those with more than one previous Nissen fundoplication, and those with a named motility disorder were excluded. The remaining study population consisted of 86 symptomatic patients.

Symptoms and Medication Use

All patients had postoperative symptoms that warranted detailed investigation, and all completed a structured symptom questionnaire at the time of their esophageal pH examinations. The symptoms of heartburn and chest pain were graded as 0 (none), 1 (minimal; occasional episodes), 2 (moderate; primary reason for medical visit), or 3 (severe; affects daily life). Regurgitation was graded as 0 (none), 1 (minimal; occasional episode after straining or large meal), 2 (moderate; predictable with position change or straining, or 3 (severe; affects daily life, possibly with a history of aspiration). Dysphagia was graded as 0 (none), 1 (occasionally with coarse foods; lasting a few seconds), 2 (moderate; requiring clearing with liquids), or 3 (severe; requiring a semiliquid diet and with a history of meat impaction). Patients were requested to identify the primary symptom driving their need for medical attention. The site of dysphagia was categorized as either pharyngeal or esophageal.

Similarly, a structured questionnaire was completed at the time of pH monitoring concerning the patients' use of medication, and additional information about past and present medication use was obtained from the patients' medical records.

pH Monitoring

All of the patients underwent 24-hour distal esophageal pH monitoring. The pH monitoring was performed as previously described, by positioning a glass pH electrode (Mui Scientific, Toronto, Ontario) 5 cm above the manometrically measured upper border of the lower esophageal sphincter.[21] The electrode was connected to a digital recording device (Microdigitrapper, Synectics Medical, Irving, Tex.), and pH was continually monitored for 24 hours. The patients' diets were limited to foods having a pH in the range 5 to 7. The stored data were transferred to a personal computer and analyzed with the use of a standard software package (Multigram, Gastrosoft, Irving, Tex.) according to our standard protocol. Patients were classified as having abnormal esophageal acid exposure if they had an esophageal pH less than 4 for more than 4.4% of the total period that the pH was monitored.[21]

Endoscopy

Upper gastrointestinal endoscopy was performed in 63 patients (73%). Esophagitis was graded according to the modified Savary-Miller system.[22] Patients were identified as having Barrett's esophagus by the presence of microscopic intestinal metaplasia in a macroscopic columnar-lined esophagus. The status of the Nissen fundoplication was assessed by the surgeon at the time of endoscopy and classified as either normal, disrupted, "slipped," abnormally twisted or "spiral," or "too tight." The status of the fundoplication was usually best assessed by a retroflex examination, looking proximally at the gastroesophageal junction from within the stomach.

Statistical Analysis

The proportions of patients with and without abnormal distal esophageal acid exposure were compared for each categorical factor using Fisher's exact

test. The ordinal data for length of postoperative follow-up were dichotomized and then also analyzed using Fisher's exact test. A stepwise forward binary logistic regression analysis was performed to identify significant predictive factors for the presence or absence of abnormal esophageal acid reflux. SPSS version 10.0.5 software (SPSS Inc., Chicago Ill.) was used for all statistical analyses.

RESULTS

The study population consisted of 48 men (56%) and 38 women (44%) who had a mean age of 47 years (range 20 to 75 years). Sixty patients (70%) had a laparoscopic Nissen fundoplication and 26 patients (30%) had an open operation. Thirty-nine patients (45%) had their Nissen fundoplication performed at the University of Southern California. The primary symptoms recorded by patients on the structured questionnaire were heartburn (37 patients, 43%), dysphagia (12 patients, 14%), epigastric pain (10 patients, 11.6%), chest pain (8 patients, 9.3%), regurgitation (5 patients, 5.8%), cough (3 patients, 3.5%), and other (9 patients, 12.8%). The mean interval between the operation and the pH investigation and symptom assessment was 27.8 months (median 18 months, range 0 to 192 months).

Twenty (23%) of the 86 post–Nissen fundoplication patients had abnormal distal esophageal acid exposure on the 24-hour pH examination. As shown in Table 1, there was no significant association between any of the following factors: sex, type of operation (laparoscopic vs. open), or length of postoperative follow-up, and the presence or absence of abnormal esophageal acid exposure.

Relationship With Acid Suppression Medication Use

During this postoperative period, 37 (43%) of the 86 patients had used acid suppression medications. The medications used were proton pump inhibitors (PPIs) in 25 patients (68% of those taking medications), H_2 receptor antagonists (H_2RAs) in 12 patients (32%), and antacids or other antireflux drugs in 12 patients (32%). Twelve patients were taking more than one class of medication.

Nine (24.3%) of the 37 patients using antireflux medications after operation had abnormal acid exposure (see Table 1). The proportion of patients with abnormal esophageal acid exposure in the group who has used medications (24.3%) was not significantly different from the proportion with abnormal acid exposure among the patients who had not used medications (11 [22.4%] of 49 patients; Fisher's exact test $P = 1.0$). Similarly, the specific use of PPI or H_2RA medications was not significantly associated with the presence of reflux disease ($P = 0.6$; see Table 1).

Relationship With Postoperative Symptoms

Details of the symptoms complained of are shown in Table 2. Abnormal distal esophageal acid

Table 1. Association of sex, operative factors, and use of medication with the presence of abnormal distal esophageal acid exposure on 24-hour pH monitoring after Nissen fundoplication

Factor	N (%)	Positive pH study N (%)	*P* value*
Male	48 (56)	10 (21)	0.61
Laparoscopic operation	60 (70)	11 (18)	0.16
Follow-up interval <median (18 mo)	43 (50)	9 (21)	0.8
Follow-up interval ≤12 mo	31 (36)	8 (26)	0.79
Follow-up interval ≤6 mo	11 (13)	3 (27)	0.71
Acid suppression medication use	37 (43)	9 (24)	1.0
Proton pump inhibitor or H_2RA use	33 (38)	9 (27)	0.6
Reflux esophagitis of any grade	24 (38)	8 (33)	0.4
Barrett's esophagus (Savary-Miller grade 5 reflux esophagitis)	18 (29)	8 (44)	0.06
Fundoplication abnormal†	24 (38)	11 (46)	0.018
Fundoplication not intact or in abnormal position‡	12 (19)	9 (75)	<0.001
Fundoplication intact and in normal position§	51 (81)	8 (16)	<0.001

NOTE: All percentages rounded to the nearest whole number.
*All *P* values calculated using Fisher's exact test (two-sided).
†Any abnormality in the appearance of the Nissen fundoplication on endoscopy (includes disrupted, abnormal position, "too tight," twisted, or spiral).
‡Nissen fundoplication judged on endoscopy to be either disrupted, herniated into the chest, or in an abnormal position around the stomach ("slipped" Nissen).
§Includes patients in whom the fundoplication was normal, "too tight," or twisted or spiral.

exposure was significantly more frequent among patients with heartburn compared to patients without heartburn. This was true for heartburn of any severity but was more significant for patients with moderately severe or severe heartburn or heartburn as their primary symptom. Patients with both heartburn and regurgitation were significantly more likely to have abnormal distal esophageal acid exposure. The strongest association with the presence or absence of abnormal esophageal acid reflux was with a primary symptom of either heartburn or regurgitation.

Forty-nine percent of patients had either heartburn (37 patients, 43%) or regurgitation (5 patients, 5.8%) as the primary symptom. Other primary symptoms included dysphagia (12 patients, 14.0%), chest pain (8 patients, 9.3%), epigastric pain (10 patients, 11.6%), cough (3 patients, 3.5%), and other (11 patients, 12.8%). Only 5 of the 44 patients with a primary symptom other than heartburn or regurgitation had abnormal esophageal acid exposure (see Table 2). Only one patient with dysphagia as the primary symptom and one patient with chest pain as the primary symptom had increased esophageal acid exposure. Neither chest pain nor dysphagia was significantly associated with a positive pH test (see Table 2).

Fifty of the 53 patients who complained of dysphagia were able to localize the site of the obstruction as being primarily pharyngeal or esophageal. Of these, 14 patients (28%) reported primarily pharyngeal dysphagia. The site of the dysphagia was not associated with the risk of increased distal esophageal acid exposure (pH test positive in 3 of 14 with pharyngeal localization vs. 10 of 36 for esophageal localization; $P = 0.73$, Fisher's exact test).

Relationship With Endoscopic Findings

No endoscopic abnormality was detected in 39 (61.9%) of the 63 patients who underwent postoperative endoscopy. Grade 1 esophagitis (single or multiple erosions on a single fold; erosions may be erythematous or exudative) was present in one patient and grade 2 esophagitis (multiple erosions affecting multiple folds; erosions may be confluent) was present in another patient. No patient had grade 3 esophagitis (multiple circumferential erosions). Four patients (6.3%) had residual distal esophageal stenoses and were classified as grade 4 esophagitis (ulcer or stenosis). Barrett's esophagus (grade 5 reflux esophagitis) was present in 18 patients (28.6%).

As shown in Table 1, there was no significant association between the presence of reflux esophagitis of any grade (including Barrett's esophagus) or the presence of Barrett's esophagus alone and an abnormal distal esophageal acid exposure. Increased esophageal acid exposure was seen only in the patients with Barrett's esophagus and occurred in 8 of the 18 patients with this endoscopic finding.

Table 2. Association of post–Nissen fundoplication symptoms with the presence of abnormal distal esophageal acid exposure on 24-hour pH monitoring

Symptom	Total N (%)	Positive pH study N (%)	*P* value*
Heartburn any severity	61 (71)	18 (30)	0.047
Heartburn moderately severe or severe	49 (57)	16 (33)	0.02
Heartburn primary symptom	37 (43)	13 (35)	0.04
Regurgitation any severity	50 (58)	15 (30)	0.12
Regurgitation moderately severe or severe	42 (49)	14 (33)	0.04
Regurgitation primary symptom	5 (6)	2 (40)	0.33
Heartburn and regurgitation	46 (53)	15 (33)	0.04
Heartburn and regurgitation both moderately severe or severe	33 (38)	12 (36)	0.04
Heartburn or regurgitation primary symptom	42 (49)	15 (36)	0.01
Not heartburn or regurgitation	21 (24)	2 (10)	0.14
Not moderately severe or severe heartburn or regurgitation	28 (33)	3 (11)	0.06
Heartburn or regurgitation not the primary symptom	44 (51)	5 (11)	0.01
Chest pain any severity	47 (55)	13 (28)	0.32
Chest pain moderately severe or severe	32 (37)	10 (31)	0.20
Chest pain primary symptom	8 (9)	1 (13)	0.68
Dysphagia any severity	53 (62)	14 (26)	0.44
Dysphagia moderately severe or severe	36 (42)	8 (22)	1.00
Dysphagia primary symptom	12 (14)	1 (8)	0.28

All percentages rounded to the nearest whole number.
*All *P* values calculated using Fisher's exact test (two-sided).

Relationship With Operative Factors

The appearance of the fundoplication was considered to be normal in 39 (61.9%) of the 63 patients who underwent postoperative endoscopy. Twelve of the 24 patients with an endoscopically abnormal fundoplication had either a disrupted (nonintact) fundoplication (3 patients) or a fundoplication that was intact but in an abnormal position (9 patients). In the latter patients it was misplaced distally as the so-called slipped Nissen in seven patients, and it had herniated above the diaphragm in two patients. The other 12 patients with an abnormal-appearing fundoplication had an intact and normally positioned fundoplication that was either too tight (4 patients) or had an abnormally twisted or spiral appearance (8 patients).

The endoscopic classification of the fundoplication was significantly associated with abnormal distal esophageal acid exposure (see Table 1). Patients with any endoscopic abnormality of the fundoplication had a statistically significant increased frequency of positive pH test results ($P = 0.018$), but the association was strongest for patients with a fundoplication that was either disrupted, herniated, or placed around the stomach ($P < 0.001$; see Table 1).

Regression Analysis

The factors entered into the binary logistic regression model for the presence or absence of abnormal esophageal acid exposure were (1) the presence of an intact, normally positioned fundoplication, (2) the presence of either heartburn or regurgitation as the primary symptom, and (3) the use of PPI or H_2RA medications. Other symptom-related factors were shown not to be independent of each other in a preliminary analysis. Although not a significant factor in univariate analysis, the use of PPI and H_2RA medications was included in the analysis because of the importance of this factor for this study. The inclusion of the status of the fundoplication in the model meant that the analysis was limited to the 63 patients who had undergone postoperative endoscopy.

An intact, normally positioned fundoplication was the most significant factor in the regression analysis and was highly associated with the presence or absence of abnormal esophageal acid exposure ($P < 0.001$, Table 3). The relative risk for abnormal reflux in the presence of an intact, normally positioned fundoplication was 0.019, equivalent to a 52.6 times decreased risk of having abnormal esophageal acid exposure (see Table 3). Heartburn or regurgitation as the primary symptom was also a significant predictor of the presence of abnormal esophageal acid exposure (see Table 3), but the use of PPI/H_2RA medications was not significantly associated with the presence of abnormal esophageal acid exposure (see Table 3).

DISCUSSION

The 86 patients in this study all had symptoms following a Nissen fundoplication that were severe enough to prompt both medical consultation and a 24-hour pH monitoring study. Forty-three percent of the patients had taken acid suppression medications of some type, and 38% had used PPI or H_2RA medications after their operations. Despite the symptomatic failure of surgical therapy in all patients, only 20 patients (23%) had abnormal distal esophageal acid exposure on 24-hour pH monitoring.

Abnormal esophageal acid exposure was detected in only 24% of the patients who had used acid suppression medications of any type, and in only 27% of those who had been using PPI or H_2RA medications. The use of these medications was not significantly associated with the presence of abnormal reflux on either a univariate or multivariate analysis. The use of acid suppression medications is thus likely to have been inappropriate in most of the patients taking the medications. Patients who used acid suppression medications were statistically no more likely to have recurrent or persistent reflux disease after surgery than patients who did not use these drugs. This is the first study of its type, and it is reasonable to assume that our findings apply to the postoperative cohorts reported by Spechler et al.[17,20] and Bammer et al.[18] The study by Spechler et al.[20] included data on the mean percentage of time that the pH was less than 4 on postoperative pH studies for some of the patients, but information on the frequency of positive pH tests was not reported. Our data indicate that the problem for most of the patients taking acid suppression medications after antireflux surgery in those studies was not failure of the surgery to prevent reflux but rather inappropriate administration of medications without objective evidence to support their use.

The present study indicates that a pH study is necessary to diagnose persistent or recurrent gastroesophageal reflux in patients who have undergone antireflux surgery. Symptoms were not a reliable guide to the presence of abnormal reflux. Most patients with heartburn did not have abnormal esophageal acid exposure even though heartburn, especially if moderately severe or severe, was significantly associated with the presence of abnormal esophageal acid exposure. The most significant association between symptoms and abnormal pH test results was with heartburn or regurgitation as the primary symptom. In the binary logistic regression analysis, patients with heartburn or regurgitation as the pri-

Table 3. Binary logistic regression analysis for factors associated with the presence or absence of abnormal distal esophageal acid exposure after Nissen fundoplication

	Relative risk	95% CI for relative risk	*P* value
Fundoplication intact and in normal position	0.019	0.002–0.174	<0.001
Primary symptom heartburn or regurgitation	5.748	1.092–30.255	0.039
PPI or H_2RA use	4.059	0.722–22.822	0.112

CI = confidence interval; H_2RA = Histamine-2 receptor antagonist; PPI = proton pump inhibitor.

mary symptom were found to have a 5.7 times increased risk of abnormal esophageal acid exposure compared to those with other primary symptoms. The unreliability of using even this strongest symptomatic predictor of abnormal reflux is shown by the finding that only 36% of those with a primary symptom of heartburn or regurgitation were found to have abnormal esophageal acid exposure.

More than half of the patients reported postoperative dysphagia, emphasizing that this study population is not representative of the normal Nissen fundoplication patient population. In a prospective evaluation of 100 patients who underwent laparoscopic Nissen fundoplication at our institution, the frequency of persistent troubling dysphagia was less than 5%.[5] The findings in this study show that dysphagia should not be considered a reflux symptom in patients who have undergone antireflux surgery.

Somewhat surprisingly, the presence or absence of reflux esophagitis was not associated with abnormal esophageal acid exposure. The explanation for this finding is that most of the patients (92%) were classified as having reflux esophagitis because they had either esophageal stenosis (grade 4 reflux esophagitis) or Barrett's esophagus (grade 5 esophagitis). The esophageal stenoses and Barrett's esophagus were present preoperatively and persisted after antireflux surgery despite adequate reflux control in most patients. "Pill esophagitis" can occur after Nissen fundoplication and can simulate erosive esophagitis due to reflux disease.

The status of the Nissen fundoplication, as assessed by retrograde endoscopy, was significantly associated with the results of the pH study. A significant association was found if any abnormality of the fundoplication was present, but on univariate and multivariate analyses the factor most significantly associated with the pH study was the presence of an intact, normally located fundoplication compared to a fundoplication that was either disrupted or abnormally located. Patients with a disrupted or abnormally positioned fundoplication had a 52.6 times increased risk of abnormal esophageal acid exposure, and 75% of the patients in this group had a positive pH study. Conversely, only 16% of the patients with an intact, normally positioned fundoplication had abnormal esophageal acid exposure.

These findings indicate the value of an endoscopic assessment of the fundoplication in patients with persistent postoperative symptoms. They also suggest that the endoscopy should be performed by a clinician who can reliably interpret the appearance of the fundoplication. The identification of a spiral or twisted fundoplication is indicative of an improper geometric construction of the fundoplication. Distinguishing between a properly constructed fundoplication and one that is abnormally twisted or spiral can be difficult for clinicians without considerable experience in the construction and follow-up of antireflux operations. Follow-up after antireflux surgery should therefore ideally be performed by the operating surgeon. Follow-up by surgeons rather than gastroenterologists is also likely to reduce the frequency of inappropriate use of acid suppression medication.

It is not possible in this retrospective study to be certain of the cause of the symptoms experienced by the patients who had normal pH studies. Most of the study population (55%) had their Nissen operations performed at another institution. Some of these patients from other centers were referred to our institution for esophageal physiology studies only and their other investigations, including endoscopy, were performed at the primary treatment center. Even when all of the investigations were performed at our institution, a definite diagnosis was sometimes not reached. Data regarding the final diagnosis in the patients who did not have GERD are therefore not presented.

Detailed investigations are sometimes required in patients with normal pH studies who have troubling symptoms after antireflux surgery. These investigations include assessment for delayed gastric emptying, duodenogastric reflux, and altered ambulatory esophageal or gastric motility. Many symptomatic patients who have a normal esophageal pH study will have abnormalities detected on these other tests that account for their symptoms. Other diagnoses that can cause postoperative symptoms that can be confused with reflux symptoms are gastritis, irritable bowel syndrome, and nonulcer dyspepsia. Symptoms from these diagnoses may have been present preoperatively but become more apparent after antireflux surgery has relieved the reflux symptoms.

CONCLUSION

Symptoms occurring after antireflux surgery are usually not caused by recurrent reflux disease. Although acid suppression medications are prescribed for many patients after antireflux surgery, most patients who are using these medications do not have persistent or recurrent GERD, as defined by abnormal esophageal acid exposure, and the use of these medications is thus often inappropriate. Objective evidence of abnormal esophageal acid exposure should be obtained before acid suppression medications are prescribed in postfundoplication patients. Although some symptoms, especially heartburn or regurgitation as the primary symptom, are significantly associated with abnormal esophageal acid exposure, neither symptoms nor the presence of endoscopic esophagitis can reliably be used to identify patients with abnormal reflux after fundoplication. Because of this, a 24-hour esophageal pH study is required to document the presence of reflux disease after antireflux surgery. The strongest predictor of the pH test result is the absence of an intact, normally positioned fundoplication, associated with a 50 times increased risk of abnormal esophageal acid exposure. The investigation of symptoms occurring after antireflux surgery should be undertaken by a clinician, preferably the operating surgeon, who is familiar with the normal and abnormal appearance of the fundoplication and who recognizes the need to diagnose the cause of patients' symptoms before treatment is prescribed.

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Discussion

Dr. J.G. Hunter (Portland, Ore.): You suggest in your conclusions that patients who have recurrent symptoms be tested with a pH probe before they are placed on medical therapy. Our practice has generally been to place them on medical therapy and then check for responsiveness. Did you look at the proportion of patients who were responsive to proton pump inhibitors as a predictor for a positive 24-hour pH study? As you know, most patients have no response to proton pump inhibitors when they are given the drug postoperatively, and I suspect their PTT studies would be normal.

Dr. Lord: We did not specifically look at that issue. The fact that these patients went on to have a 24-hour pH study after medical therapy indicates that they probably did not have an excellent symptomatic response to their acid suppression medications.

Dr. R. Bell (Englewood, Colo.): I think many gastroenterologists as well as many of us would consider esophagitis at repeat endoscopy to be fairly clear evidence of reflux, even if the pH test was normal. If you include those patients as having recurrent reflux, what percentage of the patients that you evaluated with symptoms actually had evidence of reflux by either endoscopy or pH testing?

Dr. Lord: The combination of endoscopic esophagitis with symptoms was not analyzed. However, in a univariate analysis, either symptoms alone or esophagitis alone predicted only a minority of the patients, typically one third. It is unlikely that even in combination you would be able to identify more than 50% of the patients with abnormal esophageal acid exposure, and a test that is not able to identify the majority of the patients who have abnormal esophageal acid exposure has only limited clinical value. The reason for the limited usefulness of reflux esophagitis as a predictive factor for abnormal reflux is that very few of our patients had erosive esophagitis indicative of reflux disease. Most of those classified as having reflux esophagitis had either a stenosis or Barrett's esophagus that was present preoperatively but persisted postoperatively. These are considered cases of grade 4 and 5 modified Savary-Miller reflux esophagitis, and those patients were thus classified as having reflux esophagitis in the study; however, our data show that their presence after antireflux surgery is not a sign of persistent or recurrent reflux disease. It is worth noting as well that although there were no definite cases of "pill" esophagitis in this study, this can be a cause of pH test–negative esophagitis, especially after antireflux surgery.

Dr. N.J. Soper (St. Louis, Mo.): I believe these findings help refute some of the data that have been in the lay press over the past few weeks, which is coming back to haunt us. It does beg a question, though. Here is a large group of patients with symptoms who are on medication, yet some of them have reflux. What did you determine to be the cause of the symptoms in most patients? Did you find gastritis or duodenitis, or do you think it is functional dyspepsia or something else that is occurring in this group of disgruntled postoperative patients?

Dr. Lord: That is a very good question; answering it was not a specific aim of this study, so I cannot give you the exact frequencies of the causes for the symptoms in these patients.

I can note, however, that although many of these patients report that they have heartburn, heartburn in the postoperative setting may not actually be heartburn. Substernal and epigastric discomfort can be confused with heartburn in this setting. Dr. DeMeester reports that if patients with supposed heartburn after antireflux surgery are specifically questioned, they will acknowledge that the characteristics of their symptoms are quite dissimilar to the characteristics of their preoperative heartburn. In particular, a burning characteristic typical of heartburn is often absent.

These patients often require specific tests, including tests for duodenogastroesophageal reflux, for abnormal gastric emptying, and for esophageal and gastric motility abnormalities that are evident on a prolonged 24-hour manometric examination but may not be detected by standard manometry. An abnormality that is responsible for the patient's symptoms is often detected by these tests. As you noted, gastritis and functional dyspepsia or irritable bowel syndrome are also common explanations for the symptoms. It can be a long and challenging process to identify the cause of the symptoms in some of these patients.

Dr. L.W. Way (San Francisco, Calif.): In your previous studies, you included patients with the diagnosis of reflux esophagitis who were referred for fundoplication, even in the absence of positive pH monitoring. In other words, you believe that some patients do have reflux and are candidates for surgery despite negative test results. Did all of these patients have preoperative tests that were positive, and what was the correlation between the preoperative tests and the subsequent findings in these patients?

Dr. Lord: Because most of the primary operations in this study were done outside the University of Southern California, the preoperative test results were not included in our analysis, and we did not attempt to obtain preoperative test data from either the University of Southern California or the other centers.

Computer-Enhanced vs. Standard Laparoscopic Antireflux Surgery

W. Scott Melvin, M.D., Bradley J. Needleman, M.D., Kevin R. Krause, M.D., Carol Schneider, B.S.N., E. Christopher Ellison, M.D.

Computer-assisted telesurgical devices have recently been approved in the United States for general surgery. To determine the safety and efficacy of these procedures, we performed a prospective trial of computer-enhanced "robotic" fundoplication compared to standard laparoscopic control procedures. Consecutive patients undergoing surgical treatment for gastroesophageal reflux were included. The operating surgeon worked at a console using a three-dimensional image and manipulated hand controls. Operative times, complications, and length of hospital stay were recorded. A standardized questionnaire was administered to evaluate symptoms. Twenty patients were entered into each group. There were no differences in age, preoperative weight, or sex. Operative times were significantly longer in the robot group (97 vs. 141 minutes). There were no complications and most patients went home the first postoperative day. At follow-up, symptoms were similar in both groups; however, there was a significant difference in the number of patients taking antisecretory medication—none in the robotic group but six in the laparoscopic group reported regular use. Computer-assisted laparoscopic antireflux surgery is safe. However, operative times are longer, with little difference in outcomes. At the current level of technology and experience, robotic antireflux surgery appears to offer little advantage over standard laparoscopic approaches. (J GASTROINTEST SURG 2002;6:11–16.)

KEY WORDS: Computer-assisted surgery, robotic surgery, fundoplication, Nissen, laparoscopic surgery

Laparoscopic Nissen fundoplication has emerged as the leading treatment for refractory gastroesophageal reflux disease (GERD). Reports of short- and long-term follow-up have demonstrated relatively good results, with surgery reducing symptoms and medication requirements and most patients expressing satisfaction with their outcome.[1–3] The modification of open fundoplication by the laparoscopic technique significantly reduced complication rates and markedly improved recovery times, currently making laparoscopy the standard for the performance of esophagogastric fundoplication. Despite the successes, laparoscopic manipulation is often hampered by rigid, nonarticulated instruments and a flat, two-dimensional image. These limitations have been addressed in a variety of new technical devices now available in the United States. In July 2000 the Food and Drug Administration (FDA) approved the use of the DaVinci (Intuitive Surgical, Mountainview, Calif.) computer-enhanced telemanipulator surgical instrument (robot). After our initial training experience, we designed a study to compare the use of this computer-enhanced telemanipulator device to the standard laparoscopic treatment of GERD.

METHODS

All patients referred to a single surgeon's practice with the diagnosis of GERD and selected for surgery were entered into a database. Referrals were from a variety of sources including gastroenterologists, primary care physicians, and other surgeons. The indications for operative intervention were continued symptoms of reflux including regurgitation, heartburn, and in some cases extraesophageal manifestations. All patients required medical therapy and had had symptoms of GERD for at least 6 months.

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Workup included esophagogastroduodenoscopy, video barium swallow, and in some cases 24-hour pH and manometric studies. Patients with previous surgery of the gastroesophageal junction, morbid obesity, and paraesophageal hernia were excluded from this study. Data collected included patient age, weight, sex, comorbid conditions, preoperative medications, and history of previous surgery. Perioperative data were recorded as well. Operative time was calculated from the time of skin incision to skin closure. "Robot" use time was calculated from the beginning of manipulation using the DaVinci device to the discontinuation of its use. Perioperative complications, length of hospital stay, and follow-up were recorded. All patient records were reviewed for evidence of further interventions, and a symptom survey was completed at the last follow-up visit or by phone interview by a single examiner. Patients were asked to respond to a series of questions concerning various symptoms. Specifically we determined whether patients had undergone additional esophagoscopy or dilatation, and whether they experienced dysphagia, bloating, regurgitation, or heartburn. The use of antisecretory medications was determined. Positive answers were indicated if patients responded that they had experienced symptoms or used medication to control heartburn symptoms on more than a weekly basis.

The control group consisted of patients entered into the antireflux database beginning 3 months before FDA approval and initiation of the prospective robot trial. The experimental group consisted of patients who presented to the office after the DaVinci surgical instrument was approved and who consented to a protocol approved by the human subjects committee at our institution. Identical data were collected throughout the follow-up period in both groups. Statistical analysis was carried out using the Student's t test, and significance was assigned for $P < 0.01$.

OPERATIVE TECHNIQUE

In all cases, after antibiotic prophylaxis, general anesthesia was used. All patients were placed in a leg-abducted, mild reverse Trendelenburg position. The initial access port was placed in the supraumbilical position and diagnostic laparoscopy was accomplished. For the standard laparoscopy group, a 5 mm right subcostal, a 5 mm epigastric, a 5 mm left subcostal, and an 11 mm midclavicular port were used. After retraction of the left lobe of the liver anteriorly, the gastroesophageal junction was dissected completely, including the retroesophageal space, under direct vision. The hiatal hernia was repaired in all patients using 0 nonabsorbable sutures. The proximal short gastric vessels were taken down in all cases to completely mobilize the gastric fundus, using Autosonix shears (U.S. Surgical, Norwalk, Conn.). A 360-degree fundoplication was created over a 56 Fr bougie, using interrupted 2-0 nonabsorbable sutures. Suturing was facilitated in this group by means of the Endostitch device (U.S. Surgical). A Toupet-type fundoplication was created in patients who demonstrated a lack of propagated peristalsis in the esophagus.

The operating room for the robotic cases was staffed by a team of nurses and technicians who were experienced in laparoscopic procedures. All personnel had undergone extensive training in a laboratory and clinical setting before beginning the robotic procedures. The surgeon had extensive experience in laparoscopic surgery and specifically had performed more than 500 laparoscopic antireflux procedures. For the robotic cases, a 12 mm epigastric port was placed for the endoscope. Two 7 mm ports that were dedicated to the DaVinci device were placed in the midline subxiphoid and the left midclavicular line below the costal margin. One 5 mm port in the right subcostal margin was used for liver retraction, and one 11 mm port in the left anterior axillary line was placed for accessory instruments and retractors. The surgeon sat at the control console within the same operating room and manipulated hand controls under three-dimensional image monitoring (Fig. 1). A bedside surgeon was in the sterile field and was responsible for changing instruments, retraction, extrainstrument manipulation, and passing sutures into the abdomen. The short gastric vessels were divided by the assistant using the Autosonix shears, and the mobilization was done by the primary surgeon with the DaVinci device. The second assistant was on the patient's right and was responsible for maintaining liver retraction. The surgeon controlled the two DaVinci working ports, including an electrocautery hook, grasper, scissors, dissector, needle driver, and a dual-optic 12 mm endoscope. Most dissection was done with 2:1 or 3:1 motion scaling. In all cases a 30-degree angled scope was used. Similar sutures were used for closure of the esophageal hiatus and wrap, using standard needles and sutures manipulated with the DaVinci device. Trocar sites larger than 10 mm were closed in each group.

RESULTS

Twenty patients in each group were included. Patient demographics were similar in the two groups (Table 1). In both groups there were 17 Nissen fun-

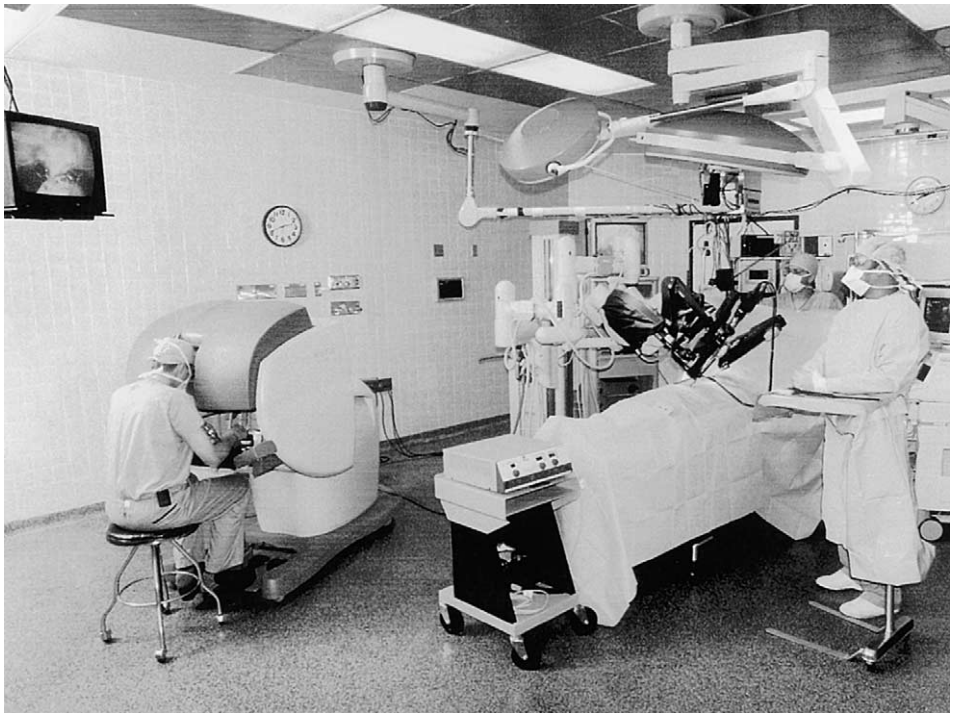

Fig. 1. Standard operating room layout using the DaVinci surgical telemanipulator device.

doplications and three Toupet fundoplications. There appeared to be very little difference between the patient characteristics in the preoperative period. There were no intraoperative or device-related complications. All operations were completed laparoscopically. The operative time was shorter in the laparoscopic group compared to the robotic group (97.1 minutes [range 45 to 168 minutes] vs. 140.9 minutes [range 88 to 271 minutes]; $P = 0.001$). This difference was decreased by eliminating the recorded operative times for the first 10 robotic fundoplications, but still remained significantly longer (97.1 vs. 131.1 minutes [range 99 to 173 minutes]; $P = 0.006$). The time recorded for the first 10 patients (150.6 minutes) was longer than that for the second 10 patients (131.1 minutes) but did not reach statistical significance. There were no complications recognized during the hospital stay. Most patients were discharged on postoperative day 1. One patient in the laparoscopic group and two patients in the robotic group were discharged on postoperative day 2 because of persistent nausea.

Table 1. Patient demographics

	Laparoscopic	Robotic
Age (yr)	49.6	42.9
Sex (% male)	35	65
Weight	181.1	195.5
Antireflux medication (%)	100	100

All patients were seen at least once within the first month after the surgical procedure. Two patients in each group were lost to longer follow-up, and all four of these patients were relatively symptom free at the time of the first postoperative visits. Patients' responses to the symptom survey are shown in Table 2. The follow-up period was longer for the control group (11.2 months vs. 6.7 months, with a range of 7 to 13 months and 4 to 10 months, respectively; $P < 0.001$). Most patients were relatively symptom free and only had mild or occasional symptoms. A significant difference was seen between the two groups in the number of patients taking daily antisecretory medication. Six of the 18 laparoscopic patients, compared to none of the 18 robotic patients, were taking daily medication. However, none of the six patients taking daily medications reported symptoms of heartburn while on medication. The only patient who underwent postoperative pH probe testing was a patient who required reoperation. This patient, who was in the control group, required reoperation for persistent reflux and underwent a redo laparoscopic Nissen fundoplication 6 months after her initial operation, with moderate relief of symptoms.

Table 2. Follow-up patient symptom survey

	Laparoscopic	Robotic
Number	20	20
Average follow-up (mo)	11.2	6.7*
Endoscopy	3	2
Dilation	1	1
Dysphagia	5	3
Heartburn	4	3
Regurgitation	4	0
Bloating	5	7
Reoperation	1	0
Antireflux medication (daily)	6	0*
No long-term follow-up	2	2

*$P < 0.001$.

DISCUSSION

A discussion of computer-assisted surgery (CAS) requires a clear understanding of the terminology. The device used in this study is truly a computer-enhanced "telemanipulator." The term telemanipulator or telesurgery implies that a distance has been interposed between the surgeon and the patient. In this setting the computer also enhances this interaction by the filtering of fine physiologic tremors and motion scaling. This differs from a true robotic device, which is technically defined as "a powered, computer-controlled manipulator with artificial sensing that can be reprogrammed to move and position tools to carry out a wide range of surgical tasks."[4] This describes such advanced devices as Robodoc (Integrated Surgical Supplies, Ltd., Sacramento, Calif.), a device designed for orthopedic surgery that is programmed to create a precise defect within the femoral shaft for placement of a prosthesis.[5] Although these technical terms accurately describe the instruments used, the term robotic or "robotic surgery" is popularly applied to a wide variety of telemanipulators and computer-controlled devices, such as surgical instrument holders, surgical assistants, and targeting mechanisms.

The feasibility of computer-enhanced telesurgery has been reported in a variety of clinical scenarios and operative techniques.[6, 7] Until now, no real comparison between CAS and traditional laparoscopic surgery has been made. The advantages of CAS are, in theory, significant. Clearly the high-resolution, three-dimensional optical system provides better depth perception and perhaps better definition of tissue planes than standard two-dimensional laparoscopic images. Multiarticulated instruments that rotate 360 degrees are more facile and can allow sutures and other instruments to be applied in a variety of angles and orientations that would be difficult with the use of typical, rigid laparoscopic instrumentation. However, the limitations of standard laparoscopic instrumentation have not necessarily limited innovative surgeons from performing most advanced intra-abdominal procedures. In many clinical scenarios, laparoscopic surgical procedures have become superior to open procedures, including such procedures as Nissen fundoplication.[8] Therefore the advantages of CAS may be less than originally thought for intra-abdominal laparoscopic procedures. CAS is most likely to offer significant benefit in such clinical scenarios as cardiac surgery, where fine motor skills and precise visualization do, in fact, enable a minimally invasive approach that has not been possible with existing technology. Early clinical evidence from trials within the United States and the European experience demonstrate the significant advantages of the minimally invasive approach, using advanced telemanipulation devices.[9]

This study demonstrates the effectiveness of CAS in the performance of an advanced laparoscopic operative procedure. However, it fails to demonstrate a significant superiority in the performance and outcome of the procedure. This comparison is made with the knowledge that CAS is truly in the infancy stage of its technology. Many technological advances have already improved the speed at which these devices can be set up and handle instrument changes. It is anticipated that in the very near future ongoing advances will, in fact, make this family of devices not only easier to use, but imperative to use, and perhaps even ubiquitous in all operating rooms. The operative experience with these types of devices is limited when compared to more than a decade of experience gained with advanced laparoscopic procedures, and specifically, laparoscopic antireflux procedures. Although in this study the first 20 cases are compared to standard laparoscopic instrumentation, it is imperative that any new technology be compared to what is considered standard therapy at that time. Skill may be acquired more rapidly with CAS than with standard laparoscopic instrumentation. In the novice surgeon, skill performance on a standardized test remains superior to that with standard laparoscopic instrumentation, even after training.[10] This difference may be eliminated in the experienced surgeon, and the true learning curve for such complex devices has not been well demonstrated.

We chose to evaluate the potential advantages of CAS over laparoscopy using antireflux surgery as a standard. The techniques are relatively well standardized, and the procedure requires advanced laparoscopic skills. Operative time is a reasonable parameter to evaluate when determining the efficacy of a

new instrument designed to facilitate an old operation; however, time does not always correlate with quality. Quality is difficult to assess directly, but quality may be inferred by the clinical outcome of the operation. The objective measurements of outcome are invasive and often require clinically unindicated interventions. Symptom relief, specifically heartburn and regurgitation, may correlate with reduction of acid reflux and therefore was used as a measure of quality.[1] The use of antisecretory medicine, although often recorded, does not seem to correlate well with reflux and may, in fact, be overutilized.[11] It was unexpected that there would be such a difference in the use of these medications between these two study groups, but it may relate to the difference in follow-up or other factors that are not as evident. Overall, at this time there appears to be no large difference in the clinical outcomes of the two surgical groups.

CONCLUSIONS

Laparoscopic approaches to gastroesophageal reflux have now become standard therapy for patients with disease refractory to standard medical therapy. Laparoscopic surgery offers the advantages of a well-documented and safe operation with generally good results. This study demonstrates the efficacy of performing advanced procedures using computer-assisted devices; however, at the current level of development these devices appear to offer no clear advantages in operative outcomes compared to standard laparoscopic approaches. Future advancements will increase the usefulness of computer-assisted surgery.

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Discussion

Dr. L. Way (San Francisco, Calif.): I think you have shown us your experience, but I am not sure we have gotten your opinion. I imagine you would like to have something objective to tell us and you are shying away from powerful conclusions, which I suppose you think is your responsibility. But what about your subjective reaction? Is this something that you enjoy doing? Do you think that the operation is more fun or technically better? What is your reaction to this initial experience?

Dr. W. Melvin: I deliberately did shy away from my subjective opinion. I currently do not use this instrument for standard antireflux surgery. I do not think it provides any significant advantage. I enjoy the proprioception and tactile sense of being able to feel what I am doing. I think there are some aspects in training that are important. It is more efficient use of my skills and the operating room time to not use it.

There are some cases where I think it does provide an advantage. One example is the Heller myotomy where the increased optics probably do offer an advantage. Having gone back and forth between the two now, that is one instance where I would use it, but on a day-to-day basis for most of the procedures we can do laparoscopically, I would not normally use this instrument.

Dr. B. Schirmer (Charlottesville, Va.): One of the limitations it seems now is the energy source. I currently per-

form all of my laparoscopic Nissen fundoplications with a Harmonic scalpel as the only energy source. Did you find only having the cautery to be a limitation?

Dr. Melvin: Absolutely, and I think that highlights the limitations and early stage of this technology. There is not an ultrasonic dissector at this time; one is under development. Currently, we are inserting standard laparoscopic Autosonix shears to take down the short gastric vessels, which is really making it a hybrid operation. As the technology expands and provides us with more instruments, it should make a big difference.

Dr. Schirmer: My other question has to do with the area of residency training. Obviously not all of our residents are going to go into general surgery and maybe the application of robots, right now this machine, is limited in general surgery, but for those trainees who are going to go on to areas such as cardiac surgery, this may be a very helpful thing for them to learn for their future careers.

What are you doing in terms of incorporating this into your residency training, and how many cases does it take before a resident or someone is able to at least learn the basics of it and begin climbing up on the learning curve?

Dr. Melvin: That is a very interesting question and something that I think about often, and I think that if you ask my residents Dr. Way's question, their subjective evaluation of it, they would respond without the cautious optimism that I expressed. They do not like it because it is stealing cases from them. It is hard enough to compete against other residents. Now they have to compete against a machine.

We have done some evaluation of skills testing to see how long it takes someone to develop competence. I do not know what the answer is. For the novice surgeon this instrument is probably easier to use; the skills acquisition is quicker than laparoscopic skills. There are a variety of different techniques and tests that we are currently working on to try and get them to develop their skills using the robot. We have one in the laboratory now and so we can use that in the laboratory setting, much like laparoscopy.

One other quick thing is this may allow simulators much easier. You can envision a device that does not have a bedside actuator, just reproduces motions on a computer.

Dr. K. Lillemoe (Baltimore, Md.): As you know, we have one of these devices, and I would echo your feelings that the residents are not very fond of the machine. Are there limitations, set by either the FDA or the manufacturer, that surgeons must have prior credentialing before they are actually allowed to use the device, which may hinder residency training?

Finally, the other question that you might not have specific data on, but you talked about, concerns the operative time being somewhat longer. My understanding is the turnover time for "back to back" cases with this device is also quite excessive, and I think in all fairness, since this time also goes into our operating room day planning, that it might be worth mentioning what your experience is with turnover time.

Dr. Melvin: I looked specifically at operating room time, which I will define as skin-to-skin. I think there is a significant increase in the turnover time as far as setting up the instruments, but as with any other complicated device in the operating room, the nurses have gotten better. But, as you know, turnover time is very nebulous, and so it was very difficult to quantify, and I decided not to report that.

As far as I know, there are no limitations that are imposed on us as far as credentialing. It is an institution-by-institution credentialing process as is the case for much of the new advanced technology, and that is a difficult issue when there has not yet been any precedent set, even at our institution. So it is a continuing problem, but there are no external limitations placed on us.

Dr. A. White (Bronx, NY): I was one of the four original surgeons in the Intuitive trial. My question is, did you have any opportunity or any episodes where you had machine shutdown, and if so, how did you handle it?

Dr. Melvin: The device is quite cumbersome, and although I did not show a good picture of the bedside instrument, it needs to be wheeled in, it blocks the surgeon's access to the patient, it blocks the anesthesiologist's access to the patient, and we actually held a couple of fire drills, as I called them, to see what would happen if we needed to move this device out of the way so we could actually get to the patient. We did not have any of the instruments lock up during any of these procedures. We had some glitches; many of those have been worked out. It seems quite durable at its current level of software. We have not had many machine complications or breakdowns, fortunately, and hopefully we will not in the future.

Laparoscopic Antireflux Surgery and Its Effect on Cough in Patients With Gastroesophageal Reflux Disease

David S. Thoman, M.D., Thomas T. Hui, M.D., Maria Spyrou, M.D., Edward H. Phillips, M.D., F.A.C.S.

In addition to heartburn and regurgitation, cough is a frequent nonspecific complaint of patients with gastroesophageal reflux disease. The incidence of alternative etiologies for patients with chronic cough who are undergoing antireflux surgery is not known. To determine this, and the response of chronic cough to fundoplication, we performed a retrospective review of 129 patients with proven gastroesophageal reflux referred for surgical therapy. Chronic cough was present in 37 (29%) preoperatively. No differences were found in age, sex, or preoperative manometric findings between those with and without chronic cough. Patients with cough had a higher number of lower esophageal reflux events on preoperative 24-hour pH testing, and were more likely to have persistent dysphagia after surgery. Fifty-nine percent of patients with cough had an alternative etiology for cough, compared to 36% of those without cough. Of the common alternative etiologies, only a history of postnasal drip occurred more frequently in those with cough. Complete resolution of cough occurred in 24 patients (64%), with another 10 (27%) reporting significant improvement. The average cough score improved significantly regardless of which coexisting etiology the patients may have had. Additionally, heartburn and regurgitation were improved in 94% of all patients. (J GASTROINTEST SURG 2002;6:17–21.)

KEY WORDS: Gastroesophageal reflux, chronic cough, laparoscopic fundoplication

Cough is one of the most common complaints for which people seek medical attention.[1] Gastroesophageal reflux disease (GERD) has been shown in multiple studies to be one of the most common causes of chronic cough in all age groups.[1–5] When cough and GERD occur concomitantly, the incidence of alternative etiologies for chronic cough has not been previously reported. Because relatively few series have reported on the response of chronic cough to laparoscopic antireflux surgery (LAS), we studied this patient cohort.

PATIENTS AND METHODS

A retrospective review was conducted in 137 consecutive unselected patients who underwent LAS between January 1, 1995 and May 31, 2000. Eight patients were lost to follow-up and not included in the analysis. A single surgical team performed all procedures. All preoperative and intraoperative data were collected concurrently. Physicians not directly involved in patient care collected data at 2 weeks and 6 weeks postoperatively. A telephone interview was then performed at an average of 27 months postoperatively (range 3 to 68 months).

Data selected for analysis included age, sex, preoperative symptoms, preoperative evaluations, indications for operation, and postoperative symptoms. The presence of asthma or postnasal drip was determined by patient interview alone; no further testing was performed. Laryngeal examination was not routinely performed. All patients had gastroesophageal reflux demonstrated by upper endoscopy or 24-hour pH monitoring. All patients underwent preoperative manometry.

Patients were considered to have chronic cough if it was nonproductive and had been present for at least 8 weeks. For analysis, patients were divided into

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Table 1. Age, sex, esophageal manometery, and 24-hour pH results in patients with (Group A) and without (Group B) preoperative cough

	Group A (cough)	Group B (no cough)	*P* value
Patients	37 (29%)	92 (71%)	
Average age (yr)	53	52	0.81
Sex (% male)	57	64	0.75
Mean lower esophageal sphincter pressure (mm Hg)	11.9	12.1	0.94
Mean upper esophageal body contraction (mm Hg)	65.8	69.7	0.63
Mean lower esophageal body contraction (mm Hg)	66.8	71.9	0.57
Average total lower esophageal time at pH <4	20.8	17.4	0.32
Average total upper esophageal time at pH <4	10.4	9.2	0.85
Average lower esophageal reflux episodes	95.2	52.1	0.004
Average upper esophageal reflux episodes	20.6	30.2	0.42

two groups on the basis of the presence (group A) or absence (group B) of preoperative chronic cough. A previously validated cough scoring system was used to determine response to surgery.[6] Patients were asked to rate the cough as follows according to how much it bothered them: 0 = not at all; 1 = mild; 2 = moderate; or 3 = severe. They were then asked about the frequency of the cough, which was graded as follows: 1 = once a month; 2 = once a week; 3 = two to four times a week; or 4 = daily. The scores were multiplied together resulting in a possible score ranging from 0 to 12.

During the initial years of the study, laparoscopic Nissen or Toupet fundoplication was performed on the basis of manometric findings. Later the Nissen fundoplication was used exclusively, adjusting the length of wrap for poor esophageal peristalsis.[7] The short gastric vessels were routinely divided in all patients. The esophagus was fully mobilized to ensure an adequate intra-abdominal length and the crura were approximated.

Parametric and nonparametric data were analyzed by means of paired *t*-test and Fisher's exact test, respectively.

RESULTS

A total of 129 patients underwent Nissen fundoplication, whereas eight patients underwent a modified Toupet fundoplication. Two patients undergoing Toupet fundoplication had cough preoperatively, and one of them improved postoperatively.

Demographic data, preoperative esophageal manometric findings, and results of 24-hour pH testing are shown in Table 1. There were no differences in esophageal manometry results between groups. Preoperative 24-hour pH results were obtained from 33 patients in Group A (89%) and 83 patients in Group B (90%). The percentage of time at pH<4 and the number of upper esophageal reflux episodes were equivalent. However, there were significantly more episodes of lower esophageal reflux in Group A. We did not analyze the temporal relation between cough and reflux during the 24-hour pH study.

Symptoms before and after surgery are shown in Table 2. Cough was rated the most significant complaint by 19 patients in Group A (51%). All of these patients, however, demonstrated at least one other typical reflux symptom. All symptoms were reduced significantly by LAS. The greatest symptomatic relief occurred with a decrease in heartburn and regurgitation. If patients who reported significant improvement in their coughs were considered cured, there would be a 93% reduction ($P < 0.0001$). One patient reported some initial improvement in cough with symptoms at 1 year equivalent to those present preoperatively. He was considered a nonresponder. Table 3 lists the number of patients in each group with common alternative etiologies for chronic cough.

Table 2. Effect of laparoscopic antireflux procedure on symptoms of gastroesophageal reflux disease

Symptom	Preoperative No. (%)	Postoperative No. (%)	% Reduction	*P* value
Heartburn	109 (85)	6 (5)	94	<0.0001
Regurgitation	100 (78)	7 (5)	94	<0.0001
Nausea	44 (34)	9 (7)	79	<0.0001
Dysphagia	36 (28)	17 (13)	54	0.023
Cough	37 (29)	13 (10)	66	0.002

Table 3. Common alternative etiologies for chronic cough compared between groups

Group	n	Smoking	Asthma	PND	ACE inhibition	Any cause
Group A (cough)	37 (29%)	10 (27%)	11 (30%)	12 (32%)	4 (11%)	22 (59%)
Group B (no cough)	92 (71%)	18 (20%)	15 (16%)	8 (9%)	18 (20%)	33 (36%)
P value (A vs. B)		0.49	0.24	0.009	0.44	0.17

ACE = angiotension-converting enzyme; PND = postnasal drip.

Only a self-reported history of postnasal drip occurred more frequently in those with cough.

Table 4 shows the average improvement in the cough score after surgery for each subgroup, and for group A as a whole. Significant improvement occurred in all subgroups. Complete resolution of cough occurred in 24 patients (65%), with another 10 (27%) reporting significant improvement. Of the 10 smokers reporting cough preoperatively, eight had complete resolution of their coughs after LAS. Three of these patients quit smoking postoperatively, which may have contributed to their improvement. Table 5 shows the incidence of other symptoms of GERD and their responses to LAS in both groups. Group A had a significantly lower reduction in dysphagia after LAS.

DISCUSSION

Chronic cough has been variously defined in the literature as that which persists for at least 3 to 8 weeks.[2] It is well accepted that 95% of chronic cough is the result of postnasal drip, asthma, GERD, smoking, bronchiectasis, or use of angiotensin-converting enzyme (ACE) inhibitors.[2] Multiple causes for chronic cough are reported to occur 18% to 62% of the time.[2,5] Despite this, a systematic diagnostic protocol has been repeatedly shown to be very effective in elucidating an etiology and directing effective treatment.[5] When GERD has been determined to be the cause of chronic cough, a trial of medical therapy is usually begun. Response rates with H_2 antagonists and/or prokinetics have ranged from 70% and 100%, with average response times of up to 6 months.[2] Larraine et al.[8] compared medical and surgical treatment in a randomized controlled fashion in patients with asthma and GERD. Although no difference was found between antireflux surgery and cimetidine, both groups showed significant improvement in pulmonary symptom scores, which included cough.

Several studies have reported on the efficacy of LAS in eliminating cough in patients with proven GERD (Table 6).[6,9–12] Allen and Anvari[6] performed LAS in 119 patients with GERD who had chronic cough despite maximal medical therapy with proton pump inhibitors. These patients were also carefully screened to ensure that other etiologies were not responsible. At 6-month follow-up, 83% were either cured or had significant improvement in their coughs. Patti et al.[9] recently reported complete resolution of cough in 19 (83%) of 23 patients in whom a correlation between cough and reflux was found during 24-hour pH monitoring, but in only 8 (57%) of 14 patients when this correlation was absent.

Our 29% incidence of chronic cough is somewhat higher than that reported in other large unselected series of patients with GERD.[9,11] This may be a result of more careful screening or a more liberal definition. We included any patient with a cough score greater than zero, whether it was considered nagging or not. Patients will not often volunteer cough as a symptom, assuming it to be unrelated to their heartburn. This is particularly true in patients with alternative etiologies, who believe they already have an explanation for their coughs.

Previous studies of cough and GERD have involved patients who have undergone careful evaluation in eliminating other possible causes of cough. We chose to evaluate patients referred primarily for treatment of their typical reflux symptoms, who on interview were also found to have a chronic cough. These unselected patients had a high frequency of

Table 4. Subgroup analysis of improvement in average cough score

	Average cough score (0–12)*					
	Smoking	Asthma	PND	ACE inhibitor	Any cause	All patients
Preoperative	8.2	8.6	8.4	8.0	8.4	9.2
Postoperative	0.4	1.0	1.4	1.0	0.8	1.2

Abbreviations as in Table 3.
*$P < 0.001$, for all subgroups.

Table 5. Symptoms of gastroesophageal reflux disease before (preop) and after (postop) fundoplication in patients with (Group A) and without (Group B) preoperative cough

	Group A (n = 37)	Group B (n = 92)	
Symptom	No. (%)	No. (%)	*P* value
Heartburn			
Preop	34 (92)	75 (82)	.77
Postop	1 (3)	5 (5)	1.0
%Reduction	97	94	.92
Regurgitation			
Preop	34 (92)	66 (72)	.39
Postop	3 (8)	4 (4)	.42
%Reduction	91	94	.91
Nausea			
Preop	14 (38)	30 (33)	.70
Postop	5 (14)	4 (4)	.13
%Reduction	63	88	.13
Dysphagia			
Preop	9 (24)	27 (29)	.83
Postop	7 (19)	10 (11)	.40
%Reduction	21	62	.0001

coexisting alternative etiologies for cough, which in most instances was thought to be the primary source. The disappearance of cough postoperatively was a pleasant side effect for many patients, most of whom continued to smoke, use ACE inhibitors, or suffer from asthma. It seems likely that many of the patients who had self-diagnosed postnasal drip were, in fact, suffering primarily from GERD.

The finding of a higher number of episodes of lower esophageal reflux in the patients with cough is consistent with a prior study by Irwin et al.[3] In comparing the results of 24-hour pH testing in 12 patients with cough to those in normal control subjects, a greater number of reflux events was the only positive finding. Two possibilities may account for this. First, a brief lower esophageal exposure to acid may trigger cough through a vagally mediated esophagobronchial reflex. Ing et al.,[13] in a double-blind, randomized, controlled fashion, found instillation of 0.1 nmol/L HCl in the distal esophagus to precipitate cough in patients previously diagnosed with GERD-related cough.[13] Second, it is well known that cough may trigger lower esophageal reflux through increased intra-abdominal pressure.

It has been previously suggested that respiratory symptoms are more often relieved by antireflux surgery when esophageal motor function is normal than when it is abnormal.[12] In our patients, preoperative manometry did not predict which patients would be cough-free after LAS. Perhaps cough, unlike other GERD-induced respiratory symptoms, behaves more like the typical reflux symptoms. This would seem reasonable if cough primarily resulted from lower esophageal acid exposure, which may not be the case with symptoms such as wheezing, hoarseness, choking, or asthma.

CONCLUSION

Patients with chronic cough and GERD are significantly improved by antireflux surgery even in the presence of coexisting etiologies.

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Table 6. Studies examining the efficacy of antireflux surgery in relieving symptoms secondary to gastroesophageal reflux disease

Reference	No. of patients	Symptom prevalence preoperatively (%)		Symptom reduction after LAS (%)		Median follow-up (mo)
		Heartburn	Cough	Heartburn	Cough	
Patti et al.[9] (2000)	340	100	11	91	74	28
Allen et al.[6] (1998)	178	84	69	93	83	6
Wetscher et al.[10] (1997)	21	100	86	95	67	6
Hunter et al.[11] (1996)	300	89	19	93	81	17
Johnson et al.[12] (1996)	118	100	34	86	76	36
Present study	129	85	29	94	93	27

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Discussion

Dr. M. Murr (Tampa, Fla.): What do you think is happening? You are correcting reflux, but some of the cough symptoms are not related to the actual reflux itself? What do you think is the mechanism of reducing cough in such a large number of patients?

Dr. D. Thoman: I think it just demonstrates how significant reflux is in producing cough. Even those patients with other etiologies, which you would think may persist postoperatively, improved their cough scores significantly.

Dr. M. Patti (San Francisco, Calif.): I have two questions. First, before the operation, did you try to establish a correlation between the cough index and the reflux, and was that a predicting factor for you? Second, after the operation, did you study again the patients who still had persistent cough to see if they still had reflux?

Dr. Thoman: We did not look at that preoperatively, as you reported recently. In terms of studying that information postoperatively, there were actually only three patients who had persistent severe cough postoperatively: one of them was studied and did not have reflux, and the other two were not studied.

Dr. V. Fink (Chicago, Ill.): Cough is a protective mechanism. You are taking away the cough regardless of the etiology, which would not be a good thing in most cases. In GERD it may help, and even then if there is aspiration, you may want to allow some coughing. So I question the value of taking away the cough.

Dr. Thoman: I agree that it is a protective mechanism, however, if you rid the patient of the reflux, there is no longer a need for the resultant cough. I think that is what we did for most patients.

Dr. Fink: But then if that patient should develop chronic bronchitis or use a great deal of tobacco and so forth, he or she may need the cough reflux.

Dr. Thoman: I am unaware of the incidence of those things postoperatively. We did nothing specifically to the cough mechanism.

Physiologic Mechanism and Preoperative Prediction of New-Onset Dysphagia After Laparoscopic Nissen Fundoplication

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The aim of this study was to determine whether preoperative physiologic factors can account for and be used to predict the development of postoperative dysphagia after laparoscopic Nissen fundoplication. One hundred sixty-three patients with gastroesophageal reflux disease underwent laparoscopic Nissen fundoplication with a median follow-up of 14 months (range 6 to 81 months). Preoperative dysphagia was present in 37% (60 of 163) and was relieved in all but five patients (92%). Female sex ($P = 0.01$) and the presence of a stricture ($P = 0.02$) were the only preoperative variables associated with the presence of preoperative dysphagia. Eight percent (8 of 103) of patients without preoperative dysphagia developed new-onset dysphagia, and of these 63% (5 of 8) had a normal lower esophageal sphincter (LES) (pressure >6 mm Hg; length >2 cm; abdominal length >1 cm). New-onset dysphagia was significantly more common in patients with a normal LES (22% [5 of 23] vs. 4% [3 of 80], $P = 001$). Patients with a normal LES had almost a sixfold increase in the risk of developing dysphagia as those with an abnormal LES (relative risk = 5.8). Only a preoperative normal LES ($P = 0.02$) or mean LES pressures ($P = 0.04$) were positively associated with the development of postoperative dysphagia. The severity of this dysphagia also showed a strong positive trend of increasing with mean preoperative LES pressures ($P = 0.07$). Finally, preoperative LES pressure significantly correlated with postoperative LES pressure ($r = 0.48$, $P = 0.01$) and with mean residual LES (nadir) pressure ($r = 0.33$, $P = 0.05$) offering insight into the mechanism of this dysphagia. In conclusion, preoperative LES parameters play a role in the development of dysphagia after laparoscopic Nissen fundoplication. Patients with a normal LES or high mean LES pressures are at increased risk for developing this complication and should be informed of this before laparoscopic Nissen fundoplication. (J GASTROINTEST SURG 2002;6:22–28.)

KEY WORDS: Gastroesophageal reflux disease, laparoscopic Nissen fundoplication, outcomes, dysphagia, postoperative complications

Laparoscopic Nissen fundoplication has become the surgical treatment of choice for gastroesophageal reflux disease (GERD), with medium-term success rates of 90% or more in the setting of typical symptoms of GERD.[1] Although a Nissen fundoplication will reliably and reproducibly relieve heartburn and regurgitation, 10% to 20% of patients will complain of postoperative side effects such as dysphagia, bloating, and excessive flatulence.[2,3] Preoperative dysphagia is common in patients with GERD, occurring in as many as 20% to 50% of patients, and usually resolves after antireflux surgery.[4–8] Severe persistent or new-onset dysphagia, on the other hand, is arguably one of the most feared sequelae of antireflux surgery. Although some degree of temporary dysphagia is common and perhaps even desirable immediately after laparoscopic Nissen fundoplication, 5% to 10% of patients will report persistent dysphagia when asked months or years later.[9] Ambiguity in when and how to measure postoperative dysphagia has resulted in a relatively wide range of reported incidences (2% to 44%), although most authors report rates between 5% and 10%.[10] Many patients with postoperative dysphagia have a readily identifiable mechanism, including a spiral, long, or tight fundoplication, or underlying esophageal motility abnormalities. Some, however, will complain of dysphagia even in the absence of these problems. In this circumstance its

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mechanism is unclear and, to date, no reliable means to predict its occurrence has been identified.[11] The aim of this study was to determine whether preoperative physiologic factors can account for postoperative dysphagia and whether those patients can be reliably predicted.

MATERIAL AND METHODS

Study Population

One hundred sixty-three patients with documented GERD by ambulatory 24-hour pH monitoring (DeMeester score >14.72) who had undergone laparoscopic Nissen fundoplication at the University of Southern California, Department of Surgery, Los Angeles, California, between 1991 and 1999 were included in this study. This study population included 119 men (73%) and 44 women (27%) with a median age of 48 years (range 15 to 78 years). Median follow-up was 14 months (range 6 to 81 months). All patients were preoperatively evaluated with a contrast video esophagram, esophagogastroduodenoscopy, esophageal manometry, and 24-hour ambulatory pH monitoring. Patients who had a normal DeMeester score (<14.72) on 24-hour ambulatory pH monitoring or were diagnosed with achalasia, scleroderma, nutcracker esophagus, diffuse esophageal spasm, or hypertensive lower esophageal sphincter (LES), those who had previously undergone foregut surgery, and those who were less than 6 months post surgery at follow-up were excluded from this study. Thirty-three patients had an esophageal stricture evident on either upper endoscopy or radiographic examination of the esophagus before surgery. Thirty-six patients had Barrett's esophagus; it was less than 3 cm in 17 and greater than 3 cm in 19 patients. Preoperative variables evaluated included patient age, sex, esophageal and LES manometric characteristics, ambulatory pH, endoscopic findings, radiologic findings, and preoperative symptoms.

Outcome Measures

The main outcomes measured were the persistence or development of dysphagia. All patients complaining of dysphagia were questioned by phone to validate scoring. Dysphagia was measured by means of a standard scoring system as follows: 0 = asymptomatic, no dysphagia; 1 = mild occasional dysphagia requiring no diet or life-style modifications; 2 = moderate dysphagia requiring diet and/or life-style modifications; 3 = severe dysphagia requiring medical intervention. Only patients reporting grade 2 or 3 dysphagia were recorded as having dysphagia for analysis in this study. Patients reporting grade 0 or 1 were considered normal. Sixty of the 163 had preoperative dysphagia. To eliminate any bias created by the presence of dysphagia before surgery, analysis of postoperative dysphagia was done in the 103 remaining patients.

For the purposes of assessing the risk of dysphagia, the following variables were evaluated: symptoms, esophagitis graded via the modified Savary-Miller criteria, stricture defined as either radiographic or endoscopic evidence of esophageal luminal narrowing, hiatal hernia, which was considered present if more than 2 cm separated the diaphragmatic crura endoscopically or radiographically, and esophageal body contraction amplitude and percentage of peristalsis.

Manometry

Esophageal manometry was performed, as previously described, using a low-compliance pneumohydraulic perfusion system consisting of an eight-lumen catheter.[12] The specific parameters measured included the following: LES resting pressure, which was measured at the respiratory inversion point, overall LES length, abdominal LES length, LES relaxation, esophageal length, esophageal body contraction amplitudes, morphology and progression, upper esophageal sphincter resting pressure, overall length, and function. Normal LES characteristics were defined as a mean pressure greater than 6 mm Hg and less than 26 mm Hg, a total length greater than 2 cm, and an abdominal length greater than 1 cm. The LES was considered normal when all three of these were within the normal range and incompetent if any one of these was below the lower limit of normal. Fifty-two patients had a second esophageal motility evaluation during the workup of recurrent or new foregut symptoms after a laparoscopic Nissen fundoplication and were available for comparison studies.

Twenty-Four-Hour Ambulatory pH

Twenty-four-hour pH monitoring was performed as previously described by positioning the pH measuring electrode 5 cm above the manometrically measured upper border of the LES.[13] The electrode was connected to a digital recording device (Microdigitrapper, Medtronic Functional Diagnostics, Minneapolis, Minn.), and pH was monitored for 24 hours. Sampling frequency was four times per second.

Surgical Technique

All surgical procedures were performed using a uniform, previously published operative technique.[14] Briefly, this included crural closure, full mobilization

of the gastric fundus including division of the short gastric vessels, and construction of a 1 to 2 cm "short, floppy" fundoplication over a 60 F bougie.

Statistics

Univariate analysis was accomplished using Fisher's exact test for nominal data, unpaired *t* tests and logistic regression analysis for continuous variables, and one-way analysis of variance for comparison of three or more mean values. Correlation coefficients were calculated by the method of Pearson. A *P* value less than or equal to 0.05 was considered significant. Statistical analysis was performed using SPSS version 7.5 (Statistical Package for Social Science, Chicago, Ill.).

RESULTS

Dysphagia Before Surgery

Dysphagia was present in 37% (60 of 163) of patients before surgery and was the primary complaint in 20% (12 of 60). It was relieved in all but five patients (92%). Univariate analysis identified the presence of a stricture ($P = 0.02$) and female sex ($P = 0.01$) as risk factors for the presence of preoperative dysphagia (Table 1). Sixty-one percent (20 of 33) of patients with a peptic stricture and 52% (23 of 44) of women complained of dysphagia before surgery. There was no significant correlation between the symptoms of preoperative and postoperative dysphagia ($P = 0.86$) (Table 2).

Table 1. Risk factor analysis for preoperative dysphagia (n = 163)

Risk factors	Significance
Sex (female)	$P = 0.01$
Age	NS
Height	NS
Weight	NS
Symptoms	NS
Esophageal manometric length	NS
Esophagitis	NS
Stricture	$P = 0.02$
Barrett's esophagus	NS
Length of Barrett's esophagus	NS
Hiatal hernia	NS
Size hiatal hernia	NS
pH score	NS
LES competence	NS
Mean LES pressure	NS
Total LES length	NS
Abdominal LES length	NS

NS = not significant.

Dysphagia After Surgery

Eight percent (13 of 163) of patients experienced dysphagia after laparoscopic Nissen fundoplication (Fig. 1). In five patients it was present before surgery (5 [8%] of 60) and in eight it was new onset (8 [8%] of 103). The prevalence of new-onset dysphagia was significantly more common in patients with a competent LES—that is, normal total length, abdominal length, and resting pressure (22%, 5 of 23), than in those with a defective sphincter (4%, 3 of 80; $P = 0.01$) (Fig. 2). Sixty-three percent (5 of 8) of those with new-onset dysphagia had normal preoperative LES pressures and lengths. On univariate analysis, patients with a normal LES were found to have a 5.8 times higher relative risk of newly developed dysphagia than those with an abnormal LES. Preoperative LES competence ($P = 0.02$) and mean LES pressure ($P = 0.04$) were the only preoperative variables associated with the development of postoperative dysphagia (see Table 2). Interestingly, mean preoperative LES pressures increased with the severity of this new-onset dysphagia. This association was not statistically significant, likely because of the small number of patients involved, but showed a strong positive trend ($P = 0.07$) (Fig. 3). It was also observed that preoperative LES pressure correlated significantly with postoperative LES pressure ($r = 0.48$, $P = 0.01$) and with mean residual LES (nadir) pressure ($r = 0.33$, $P = 0.05$), both of which have been associ-

Table 2. Risk factor analysis for postoperative dysphagia (n = 103)*

Risk factors	Significance
Preoperative dysphagia	NS
Sex (female)	NS
Age	NS
Height	NS
Weight	NS
Symptoms	NS
Esophageal manometric length	NS
Esophagitis	NS
Stricture	NS
Barrett's esophagus	NS
Length of Barrett's esophagus	NS
Hiatal hernia	NS
Size hiatal hernia	NS
pH score	NS
LES competence	$P = 0.02$
Mean LES pressure	$P = 0.04$
Total LES length	NS
Abdominal LES length	NS

NS = not significant.
*The 60 patients with preoperative dysphagia have been excluded from this analysis.

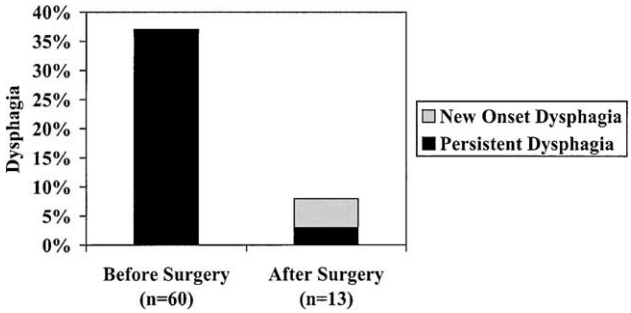

Fig. 1. Incidence of preoperative and postoperative dysphagia (n = 163; $P = 0.0001$).

ated with the development of dysphagia after laparoscopic Nissen fundoplication.

DISCUSSION

Dysphagia is a "typical" symptom of GERD and is present in 20% to 50% of patients referred for surgery.[4–6,15] Our finding of a 37% incidence of preoperative dysphagia among patients undergoing laparoscopic Nissen fundoplication for GERD is consistent with this fact. It was more likely to be present in women and in patients with peptic strictures. We also found that preoperative dysphagia is relieved in the vast majority of patients, and that there is no association between dysphagia present before and after surgery. Others have reported similar findings.[15–17] It has been postulated that antireflux surgery resolves many of the mechanisms responsible for dysphagia in patients with GERD including impaired peristalsis, hiatal hernia, esophageal inflammation, and altered esophageal bolus transport.[18]

In contrast to its presence before surgery, dysphagia that develops after antireflux surgery is uncommon and can be unpredictable. Its reported incidence varies widely, ranging anywhere from 2% to 44%.[10] This disparity is likely the result of differences in the scoring systems used, the time at which dysphagia is measured, and the person recording its presence.[18,19] We attempted to control for these factors by using a standard scoring system and recording dysphagia only in the presence of objective swallowing difficulties, by including patients 6 months or more after surgery, and by using a person other than the surgeon to gather the data.

Some degree of temporary dysphagia is almost universal immediately after fundoplication. Given the fact that a Nissen procedure almost certainly "loosens" with time, and that recurrent reflux may occur, temporary postoperative dysphagia may even be desirable. In most patients it improves rapidly within the first week or two after surgery and has been shown to continue to improve throughout the first year.[4,5,18] Difficulty swallowing will remain, however, in 5% to 10% of patients.[9] The mechanism of this dysphagia has remained poorly understood. The choice of surgical technique, technical errors, and the development of complications such as recurrent herniation, hiatal stenosis, misplacement or slippage, twisting, or an excessively tight fundoplication probably account for a proportion of these.[20] None of the patients experiencing postoperative dysphagia in this study had a mechanical or technical complication, and those with abnormal motility were excluded. All had the same procedure, namely, a 1 to 2 cm fundoplication performed over a 60 F bougie, with full fundic mobilization. Thus mechanisms other than those noted earlier must be present in some patients.

Several investigators have observed that both the magnitude of the postoperative LES resting pressure and the residual (nadir) pressures with swallowing are associated with the development of postoperative dysphagia.[8,21,22] We found that both of these are as-

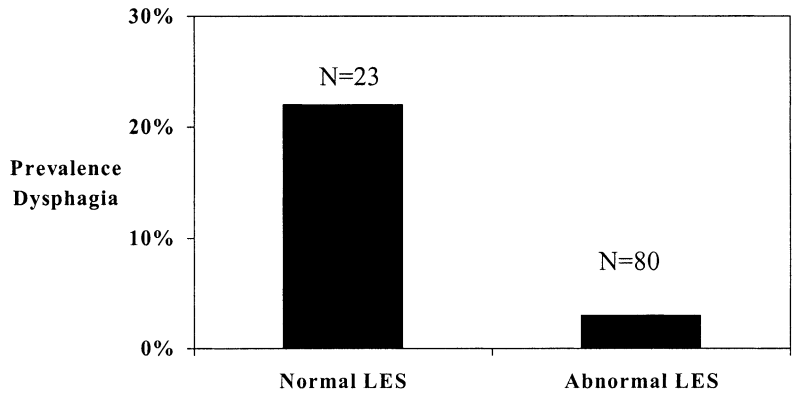

Fig. 2. New-onset dysphagia and LES status (relative risk = 5.8; $P = 0.01$).

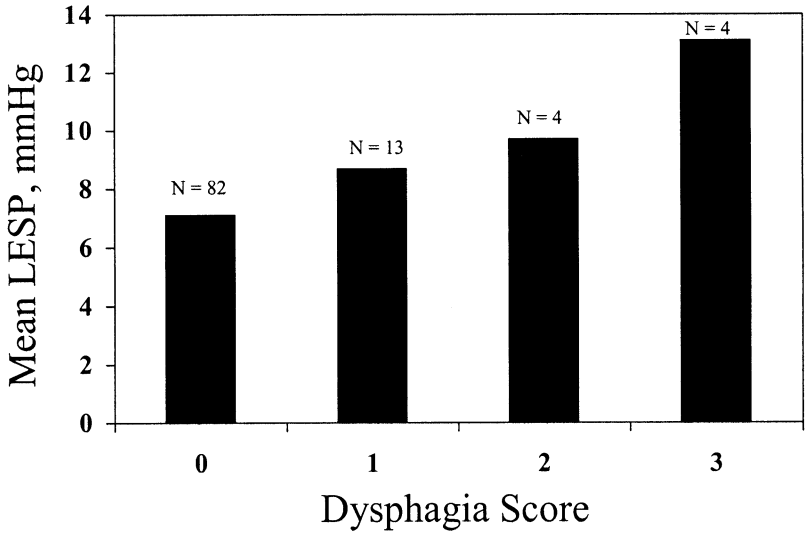

Fig. 3. Dysphagia score and mean LES pressure ($P = 0.07$).

sociated with the mean preoperative sphincter pressure, thus providing insight into the physiologic mechanism of this new-onset dysphagia.

We have previously shown that fundoplication increases the resting mean LES pressure and residual (nadir) pressures and that these pressures are significantly higher in individuals who start with higher presurgical values.[23] This likely occurs because of the additive extrinsic pressure afforded by the hiatal closure and fundoplication. This principle is supported by the observation that high residual (nadir) pressures and a high prevalence of dysphagia have been reported after placement of an Angelchik prosthesis.[24] Studies of the mechanism of fundoplication have shown that as gastric pressure increases, as with a meal, the fundoplication exerts increasing radial forces at the gastrosophageal junction.[25] This increased pressure gradient can compromise antegrade bolus transport in addition to preventing reflux of gastric contents.[26] Kahrilas et al.[26] demonstrated that a fundoplication limits the opening dimensions of the gastroesophageal junction and inhibits the normal axial movement present during bolus transport through the gastroesophageal junction. This leads to increases in the intrabolus pressures and can lead to the failure of esophageal emptying.[26] This idea that incomplete LES opening (i.e., incomplete relaxation) manifested by an increased LES residual (nadir) pressure is the cause of post-Nissen dysphagia is supported by Bais et al.[27] who studied patients with persistent dysphagia after Nissen fundoplication. They concluded that a return to complete LES relaxation and a decrease in LES residual (nadir) pressure were important in resolving persistent dysphagia.

CONCLUSION

This study reports the novel observation that preoperative physiologic parameters may play a role in the development of dysphagia after laparoscopic fundoplication, and that preoperative LES characteristics can be used to predict those at risk. Patients with either a normal sphincter or a high LES resting pressure are at an increased, albeit small, risk of developing postoperative dysphagia. The mechanism appears to be the increased esophageal outflow resistance afforded or manifested by a higher LES residual pressure following fundoplication in patients with normal sphincters before surgery.

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Discussion

Dr. R. Bell (Englewood, Colo.): You have identified a risk factor but you have not answered the question of why these patients have dysphagia postop. Is it because the patients have an extraordinary increase in their resting LES pressure with the fundoplication? Is it because they do not have adequate LES relaxation? What in the postoperative characteristics of the patients tells you why these patients have dysphagia?

Dr. D. Blom: I did not show that here, but we found that the patients with postoperative dysphagia did have both higher mean LES pressures and, more important, higher residual pressures or nadir pressures, and that the preoperative LES pressure does correlate with these higher postoperative residual pressures.

Dr. C. Deveney (Portland, Ore.): Did you look at esophageal body peristaltic pressure and was there any correlation with those pressures?

Dr. Blom: We did, and there was none. Although we excluded patients with named motility disorders, we did not exclude them based purely on esophageal body amplitude. The amplitudes in the two most distal measuring segments did not correlate at all with the development of new-onset dysphagia.

Dr. V. Fink (Chicago, Ill.): I also want to compliment the authors on an excellent paper, and I want to direct a question to Dr. Tom DeMeester. You have here some breakdown on this Nissen operation: you have a 23% pH positive, you have some loss of a protective cough, you have some dysphagia, and you have some achalasia. Where does this fit in with this selection of medical vs. surgical therapy? When you state that approximately 90% achieve good results, does this include all of these so-called complications, which we have discussed today?

Dr. M. Murr (Tampa, Fla.): Dr. DeMeester, you may want to address this in your expert commentary at the end of the session.

Dr. C.D. Smith (Atlanta, Ga.): I have a question similar to one that was asked during the preceding presentation: What is the natural history in these patients? In many ways is this the future patient with "secondary achalasia" that we just heard about from Dr. Rattner? How have you been addressing these patients with dysphagia? Do you take these fundoplications down? Do you perform Heller myotomies?

Dr. Blom: It was interesting to listen to the preceding presentation and it made me think of the same things.

There were only eight patients who developed this new-onset dysphagia out of the 103. Only two experienced improvement, and in both this was after 2 years. So the majority of these patients, who developed this new-onset dysphagia, continue to have the problem, and if they do get better, it takes years. None of the patients in this cohort were operated on for this problem because there were no anatomic or mechanical complications demonstrated on postoperative testing.

Dr. Murr: How are these data going to affect your practice? Are you going to change your selection process? Are you going to do anything different with those patients whom you identify preoperatively?

Dr. Blom: I think these findings just underscore the fact that each patient has to be individualized and we have to tailor our procedures to each patient and on the basis of their preoperative workups. This is very important. I think in patients who have a normal valve and complications of GERD or significant GERD, one can still perform a Nissen fundoplication, as shown by the small numbers and small incidence of this complication, but one should be aware of the problem and take extra steps to ensure that the wrap is not too tight. The common denominator in this problem appears to be a wrap that is too tight, so we need to be careful of that and warn patients appropriately.

Long-Term Survival After Esophagectomy for Barrett's Adenocarcinoma in Endoscopically Surveyed and Nonsurveyed Patients

Mark K. Ferguson, M.D., Amy Durkin, M.S., P.A.-C.

There is growing controversy over the cost-effectiveness of surveillance endoscopy for patients with Barrett's esophagus. A retrospective review was performed of 80 patients who underwent resection for Barrett's adenocarcinoma to assess the influence of endoscopic surveillance on long-term survival. Twelve patients initially were diagnosed with benign Barrett's esophagus and were followed with endoscopic surveillance. The remaining 68 patients had the diagnosis of Barrett's esophagus made at the time of their cancer diagnosis or resection. Patients in surveillance programs were younger (53 vs. 64 years; $P = 0.008$), had better performance status (8.9 vs. 8.2; $P = 0.04$), had less weight loss (0.3 vs. 5.5 kg; $P < 0.001$), had a similar incidence of gastroesophageal reflux disease symptoms (75% vs. 60%), and were less likely to undergo preoperative chemotherapy and/or radiation therapy (8% vs. 28%). Pathologic stage was 0 or I in 9 (75%) of 12 patients in the surveillance group compared to 12 (18%) of 68 of those in the no surveillance group ($P < 0.001$). Median survival for patients in the surveillance group was 107 months compared to 12 months for those in the no surveillance group ($P < 0.001$). Stratifying for stage, surveillance (hazard ratio = 3.05; confidence interval = 1.09 to 8.57; $P = 0.034$) was the only predictor of survival. Surveillance endoscopy permits early diagnosis of adenocarcinoma in patients with Barrett's esophagus and contributes substantially to long-term survival. (J GASTROINTEST SURG 2002;6:29–36.)

KEY WORDS: Surveillance, endoscopic, Barrett's, neoplasm, esophagus, adenocarcinoma, columnar-lined

Barrett's esophagus is a premalignant condition that is associated with a substantial increase in the risk of adenocarcinoma. Its relatively high frequency in Western populations, etiologic relationship to gastroesophageal reflux disease (GERD), and sequential changes from metaplasia through dysplasia to adenocarcinoma make it an ideal model for the study of neoplasia. These features also make patients with Barrett's esophagus good candidates for surveillance to detect high-grade dysplasia or carcinoma in situ to permit intervention before the development of invasive cancer.

Surveillance endoscopy has previously been shown to identify patients with Barrett's adenocarcinoma in earlier stages of disease than in patients who have not undergone surveillance endoscopy, resulting in a substantial improvement in long-term survival in the former group.[1–3] Whether improved survival can be anticipated for all patients with Barrett's adenocarcinoma with the institution of widespread surveillance programs is not yet known.[4] In addition, the overall cost and cost per year of life gained associated with endoscopic surveillance are both high, and whether current surveillance practices can be justified remains open to question.[5,6] These factors suggest that the advantages of surveillance endoscopy are unproved. We undertook a retrospective study of patients with Barrett's adenocarcinoma to analyze the potential benefits of surveillance endoscopy to overall survival and to determine whether other clinical markers might help to identify subsets of patients who are more likely to benefit from surveillance endoscopy.

METHODS

We performed a retrospective review of patients who underwent resection for Barrett's adenocarci-

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noma at The University of Chicago Medical Center from January 1980 through December 2000. The diagnosis was based on typical findings of adenocarcinoma of the distal esophagus or gastroesophageal junction and required that Barrett's esophagus was histologically documented before the development of adenocarcinoma or was adjacent to adenocarcinoma in the resected specimen. Barrett's esophagus was identified by the presence of columnar mucosa more than 3 cm proximal to the esophagogastric junction or by the presence of specialized intestinal epithelium in columnar mucosa within 3 cm of the esophagogastric junction. Barrett's mucosa was classified as demonstrating nondysplastic changes, low-grade dysplasia, high-grade dysplasia, intramucosal carcinoma (of which carcinoma in situ is a subcategory), or invasive adenocarcinoma based on standard nomenclature.[7] Pathologic staging was done according to the TNM system of the American Joint Committee on Cancer.[8] Tumors were classified as well, moderately, or poorly differentiated on the basis of the pathology report. If more than one tumor grade was described, the worst grade was used to classify that patient.

All patients in the study population underwent esophagectomy for locally resectable disease without evidence for distant metastases. Some patients with regionally advanced disease underwent preoperative chemotherapy or combined chemoradiation therapy. Postoperative adjuvant chemotherapy and/or radiation therapy were not routinely used. Techniques used for resection included left thoracotomy with intrathoracic or cervical anastomosis, transhiatal resection with cervical anastomosis, and combined laparotomy, thoracotomy, and cervical anastomosis (modified Ivor Lewis technique). Reconstruction was accomplished with tubularized stomach under most circumstances. The selection among resection and reconstructive techniques was determined by patient age and comorbid conditions, the extent of the Barrett's esophagus, whether neoadjuvant therapy was administered, and the personal preference of the surgeon. Preoperative, perioperative, and postoperative clinical and histopathologic data were collected from patient records and from a prospective database that was begun in 1990. Patients were divided into two groups depending on whether they had a preexisting diagnosis of Barrett's esophagus and were undergoing surveillance endoscopy for 4 months or more at the time of diagnosis of adenocarcinoma (surveillance group) or whether the diagnosis of Barrett's esophagus was made within 3 months of resection for high-grade dysplasia, intramucosal carcinoma, or invasive adenocarcinoma (no surveillance group). Patients were followed until death or until March 2001.

Comparisons between groups were made using the two-sided unpaired *t* test for continuous data and chi-square test or Fisher's exact test where appropriate for categorical data. Survival was estimated by means of the Kaplan-Meier technique, and comparisons between survival curves were performed using the log-rank test. Determinants of operative mortality and survival were identified using multivariate backward stepwise logistic regression analysis after selecting covariates for the regression models by univariate methods.

RESULTS

We identified 80 patients who underwent esophagectomy for Barrett's adenocarcinoma during the stated time period, of whom 12 progressed to high-grade dysplasia or adenocarcinoma during endoscopic surveillance and 68 were not in a surveillance program. The clinical characteristics of the two groups and of the overall population are listed in Table 1. Patients in the surveillance group were younger, had a similar incidence and duration of heartburn symptoms, had a lower incidence of dysphagia, experienced less weight loss, and had a better performance status compared to patients who did not undergo surveillance. The surveillance group included three patients who had undergone previous surgery for GERD and two patients who had undergone attempted mucosal ablation for high-grade dysplasia. Sufficient clinical information was available to permit us to track the progression of dysplasia during surveillance endoscopy in nine patients (Fig. 1). Most patients in the surveillance group had a diagnosis of high-grade dysplasia or carcinoma in situ at the time of operation, whereas most patients in the no surveillance group had a preoperative diagnosis of invasive adenocarcinoma. Three patients had other preoperative diagnoses including extensive low-grade dysplasia in one and squamous cell carcinoma (subsequently determined to be adenocarcinoma) in two.

One patient in the surveillance group underwent preoperative adjuvant therapy, whereas 19 patients in the no surveillance group underwent such treatment (Table 2). The types of operations, the degree of blood loss, the volume of blood transfused, and the duration of postoperative stay were similar between the surveillance and no surveillance groups. Surveillance patients were more likely to undergo colon interposition for reconstruction, had a slightly higher incidence of nonfatal complications, and had a somewhat lower incidence of operative mortality. Univariate analysis identified patient age, performance status, serum albumin, total serum bilirubin,

Table 1. Clinical characteristics of patients undergoing esophagectomy for Barrett's adenocarcinoma

	All patients (80 patients)	Surveillance (12 patients)	No surveillance (68 patients)	*P* values
Age (yr)	62.3 ± 11.5 (range 35 – 84)	53.4 ± 10.9 (range 39 – 73)	63.9 ± 10.9 (range 35 – 84)	0.008
Sex (male/female)	76/4	12/0	64/4	1.0
Race (white/other)	76/4	12/0	64/4	1.0
Performance status*	8.3 ± 1.0	8.9 ± 1.0	8.2 ± 0.9	0.038
Weight loss (kg)	4.7 ± 5.7	0.3 ± 1.0	5.5 ± 5.8	<0.001
Serum albumin (g/dl)	3.9 ± 0.4	4.3 ± 0.3	3.9 ± 0.4	0.014
Serum total bilirubin (mg/dl)	0.6 ± 0.3	0.9 ± 0.3	0.6 ± 0.2	0.038
Serum creatinine (mg/dl)	1.2 ± 1.0	1.1 ± 0.2	1.2 ± 1.0	0.3
Presenting symptoms	72/80	6/12	66/68	<0.001
Dysphagia†	55/79	4/12	51/67	0.007
Pain	13/77	0/12	13/65	0.2
Bleeding	9/77	1/12	8/65	1.0
Other	4/77	0/12	4/65	1.0
History of heartburn	50/80	9/12	41/68	0.5
Duration of heartburn (mo)‡	113 ± 117	121 ± 94	111 ± 123	0.8
Endoscopic Barrett's length (cm)	6.9 ± 3.0	8.2 ± 2.8	6.7 ± 3.0	0.1
Prior antireflux surgery	3	3	0	—
Prior mucosal ablation	2	2	0	—
Preoperative diagnosis				
HGD/CIS	11	7	4	<0.001§
Adenocarcinoma	66	5	61	—
Other	3	0	3	—

Values are mean ± SD. HGD/CIS = high-grade dysplasia/carcinoma in situ.
*Karnofsky performance status; rated on a scale of 1 to 10, with 10 being the most fit.
†Dysphagia grading system: 1 = no dysphagia; 2 = difficulty swallowing solids; able to swallow semisolids; 3 = unable to swallow solids, able to swallow liquids; 4 = difficulty swallowing liquids; 5 = unable to swallow liquids.
‡Duration of heartburn was calculated for nine patients in the surveillance group and 41 patients in the no surveillance group.
§Comparison among HGD/CIS and adenocarcinoma frequencies only.

participation in an endoscopic surveillance program, and pathologic stage (0 to II vs. III or IV) as factors potentially associated with operative mortality. Multivariate analyses demonstrated that only serum albumin (hazard ratio [HR] for a 1 g/dl decrement = 5.5, 95% confidence interval [CI] = 0.98 to 30.81; P = 0.052) and stage (HR for advanced stage = 4.14, 95% CI = 0.88 to 19.4; P = 0.071) approached significance as covariates for operative mortality.

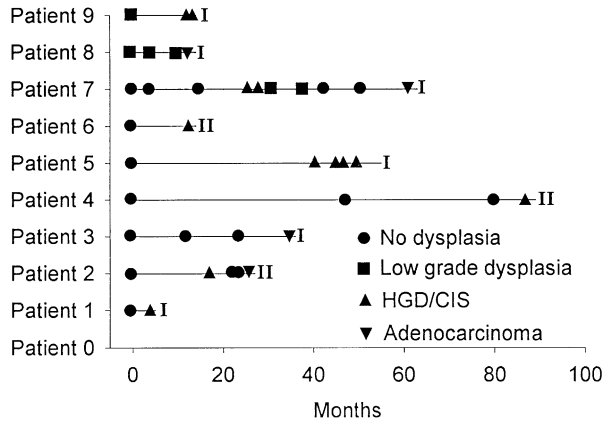

Fig. 1. Time course of progression from dysplasia to adenocarcinoma in nine patients who underwent surveillance endoscopy. Numbers at the conclusion of each time line represent pathologic cancer stage at the time of resection. HGD/CIS = high-grade dysplasia/carcinoma in situ.

Patients in the surveillance group were significantly more likely to have early-stage cancer compared to patients in the no surveillance group (Fig. 2). Stage was unrelated to the endoscopic length of Barrett's esophagus and was not related to the presence or duration of reflux symptoms. Patients in the endoscopic surveillance group were also much more likely to have well-differentiated tumors than those who did not undergo surveillance (Table 2).

At the time of last follow-up, 13 patients were alive, 64 had died, and three were lost to follow-up. Follow-up was thus complete in 77 of 80 patients, or 96%. Overall (not cancer-specific) survival by stage is illustrated in Fig. 3. Long-term overall (not cancer-specific) survival was significantly better in the surveillance group than in the no surveillance group, with median survivals of 107 months vs. 12 months

Table 2. Therapy for patients with Barrett's adenocarcinoma

	All patients (80 patients)	Surveillance (12 patients)	No surveillance (68 patients)	*P* values
Preoperative chemotherapy	20/80	1/12	19/68	0.3
Preoperative radiation therapy	11/80	1/12	10/68	1.0
Type of resection				1.0
Left thoracotomy	46	7	39	
Modified Ivor Lewis	14	2	12	
Transhiatal	20	3	17	
Organ used for reconstruction				0.015
Gastric tube	72	8	64	
Colon interposition	8	4	4	
Intraoperative blood loss (ml)	1214 ± 1470	1171 ± 935	1222 ± 1550	0.9
Units of blood transfused	2.5 ± 4.0	1.7 ± 2.0	2.6 ± 4.2	0.3
Major nonfatal complications	43/69	10/12	33/57	0.12
Operative mortality	11/80	0/12	11/68	0.2
Postoperative length of stay (days)	15.7 ± 11.0	18.0 ± 12.0	15.0 ± 10.8	0.5
Tumor grade				<0.001
Well differentiated	21	9	12	
Moderately differentiated	26	1	25	
Poorly differentiated	33	2	31	

and 5-year survival rates of 84% vs. 16%, respectively ($P < 0.001$; Fig. 4). Univariate analysis of variables associated with survival identified participation in an endoscopic surveillance program, patient age, performance status, serum albumin, dysphagia as a presenting symptom, and tumor grade as potentially important covariates. Serum albumin was not included in the multivariate analysis because more than 22% of the values were missing, and tumor grade was omitted because it was strongly linked to whether or not patients underwent surveillance. Multivariate analyses, stratified by stage, yielded only participation in an endoscopic surveillance program to be a significant covariate (HR = 3.05, 95% CI = 1.09 to 8.57; $P = 0.034$).

Because of the higher operative mortality rate in the patients who did not undergo surveillance, a second analysis of long-term survival was performed after patients suffering operative mortality were excluded from the database. With these patients excluded, patient characteristics and treatments were similar in proportion to those listed for all patients in Tables 1 and 2, with the exception of operative mortality and duration of postoperative hospital stay. Long-term survival was significantly better in the surveillance group than in the no surveillance group, with median survivals of 107 months vs. 13 months

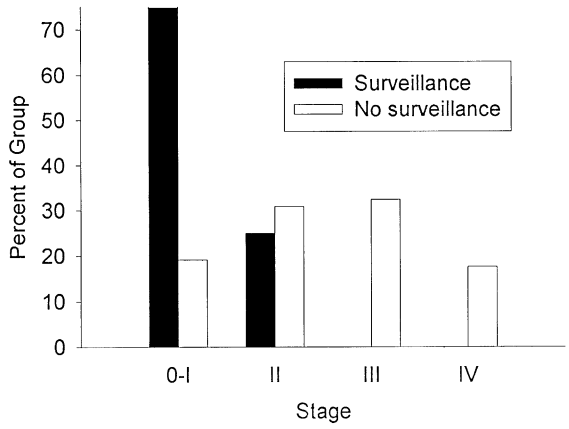

Fig. 2. Distribution of pathologic stages for patients in surveillance and no surveillance groups after esophagectomy for Barrett's adenocarcinoma.

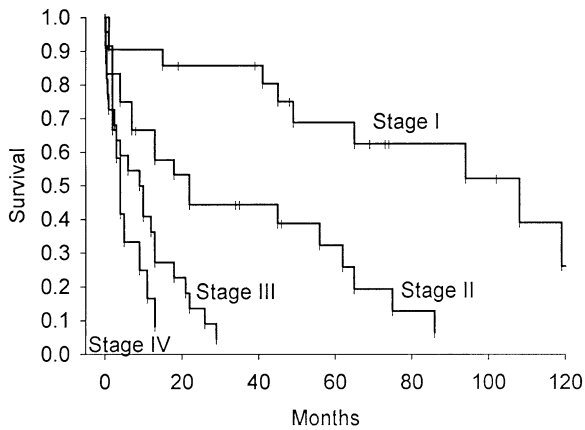

Fig. 3. Overall (not cancer-specific) survival by stage for patients with Barrett's adenocarcinoma.

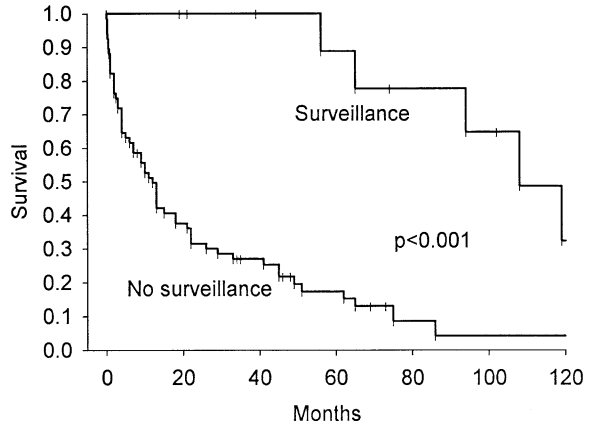

Fig. 4. Overall (not cancer-specific) survival for patients in surveillance and no surveillance groups after esophagectomy for Barrett's adenocarcinoma.

and 5-year survivals of 84% vs. 19%, respectively ($P < 0.001$). When patients suffering operative mortality were excluded, multivariate analysis (using the same variables as above and stratifying by stage) yielded only participation in an endoscopic surveillance program to be a potentially significant covariate (HR = 2.68, 95% CI = 0.93 to 7.72; $P = 0.067$).

DISCUSSION

Since its recognition as a unique pathologic entity in the 1950s and subsequent to the first reports of the increased risk of cancer associated with Barrett's esophagus in the 1970s, the columnar-lined esophagus has steadily grown in importance from both clinical and research perspectives. The fact that it is a premalignant condition that appears to undergo progressive transformation from metaplasia through dysplasia to invasive cancer, and the lack of a suitable animal model for research study, make Barrett's esophagus an ideal entity for the study of cancer development in humans.

The development of both Barrett's esophagus and adenocarcinoma of the distal esophagus and gastroesophageal junction are clearly linked to the presence of gastroesophageal reflux.[9–11] Barrett's esophagus is thought to be a primary factor in the development of such adenocarcinomas, which are increasing in frequency at a rate greater than that for any other solid tumor in Western society.[12] These facts have precipitated considerable discussion regarding the appropriate role of screening endoscopy to identify a population at risk for adenocarcinoma. In the present study, among patients who developed Barrett's adenocarcinoma in the no surveillance group, 60% had a history of GERD symptoms. This percentage is similar to that reported in one recent publication but is much higher than the 20% to 40% incidence quoted in other studies.[10,13,14] In Western populations the prevalence of GERD symptoms is approximately 20%, and approximately 10% of those persons have moderate-to-severe symptoms.[15–17] For a population of 209 million adults in the United States (based on the 2000 census), there are an estimated 20 million persons with GERD symptoms and two million persons with moderate-to-severe symptoms. The large number of patients in this cohort makes the routine use of screening endoscopy untenable. Whether a high-risk group that represents a more appropriate population for screening can be identified among those persons with GERD symptoms will need to be determined by large epidemiologic studies. In addition, there is a cohort of patients without symptoms of GERD who do not have easily identifiable risk factors and for whom no screening is likely to be possible in the near future.

Considerable effort has been expended in attempts to identify markers that will predict the development of malignancy in patients with Barrett's esophagus, but no reliable marker has yet been identified.[18] As a result, histologic recognition of dysplasia remains the "gold standard" for identifying high-risk patients. Recent studies confirm the reproducibility of the diagnosis of dysplasia in Barrett's esophagus and illustrate the utility of dysplasia as a predictive marker for the development of invasive carcinoma.[19–21] These facts have fostered the use of surveillance endoscopy to monitor patients with Barrett's esophagus so that intervention can be offered to those individuals with high-grade dysplasia or intramucosal carcinoma.[22] Our findings echo those of previous reports, in which patients undergoing surveillance had their cancers identified at an earlier stage and enjoyed a longer survival compared to patients who did not undergo routine surveillance endoscopy.[1–3]

There are several important issues surrounding the recommendation for the use of surveillance endoscopy in patients with Barrett's esophagus; these include its cost, whether it identifies pseudodisease rather than a real clinical problem (length bias), and whether it results in improved survival in patients undergoing surveillance, which is in part related to lead-time bias. The cost of surveillance has been estimated at between $25,000 and $98,000 per year of life gained, and calculations suggest that surveillance performed only every 5 years is likely to lead to an optimal balance between expenditures and improved survival.[6,23] In response to this, the cost of surveillance endoscopy for Barrett's esophagus per year of life gained has been shown to be comparable to costs

for screening more common malignancies such as breast and colon cancer and for other accepted practices such as heart transplantation and screening for tuberculosis.[6,24] When viewed in this perspective, surveillance endoscopy for Barrett's esophagus can be justified because its costs and benefits are similar to those for other standard medical procedures. However, whether our society can afford such costs is an issue that must be addressed by those controlling global health care expenditures.

Does surveillance endoscopy really identify many patients who might never develop invasive cancer, thus diagnosing a pseudodisease in many patients with Barrett's esophagus? The effect of length bias is considered operative for conditions such as lung cancer, in which improvements in imaging techniques result in the identification of a large number of radiographic abnormalities that may never create clinical problems for the patient.[25,26] Similar concerns have been expressed for screening studies for prostate cancer and for appropriate management of small, asymptomatic renal cell cancers.[27–29] In contrast, a number of reports track the progression of dysplasia in patients with Barrett's esophagus to invasive cancer.[30–32] Although this progression is not inevitable, the current assumption must be that in most patients high-grade dysplasia will likely progress to cancer, and that surveillance is not identifying a pseudodisease but a real clinical problem.

It might be argued that the improvement in long-term survival afforded by surveillance endoscopy is the result of lead-time bias and is, in fact, not a genuine finding. In the case of Barrett's esophagus, however, the endoscopic findings are neither subtle nor clinically unimportant, and they are not the result of recent technologic improvements. Instead, they represent a change in clinical findings that has occurred over time through the use of standard technology. Our study and others demonstrate that improved survival is not merely the result of a shift in the survival curve leftward (lead-time bias) but is due in large part to a high rate of cure among patients in the surveillance group. In fact, among the 12 patients in the surveillance group in our study, as many as eight can be considered cured of their cancer, having survived more than 5 years from the time of diagnosis.

The disproportionate use of neoadjuvant therapy among patients in the no surveillance group was due to the presence of more advanced stages of disease at the time of diagnosis in those patients. Neoadjuvant therapy has the effect of downstaging tumors in up to 70% of patients, although its effect on overall survival is unknown. In our study there was a significant difference in stage at diagnosis between the surveillance and no surveillance groups. The use of neoadjuvant therapy in patients in the no surveillance group may have resulted in an underestimation of the real stage differences between the two groups.

The implications of our findings and those of others regarding the use of surveillance endoscopy for patients with a diagnosis of Barrett's esophagus are clear. At the present time, surveillance endoscopy can be performed at a cost per year of life gained that is similar to costs for surveillance of other common conditions. The use of surveillance endoscopy results in the identification of a cohort of patients who have an earlier stage of cancer than those patients with Barrett's adenocarcinoma detected as a result of cancer symptoms or discovered serendipitously. This, in turn, results in improved survival of surveillance patients, an effect that does not appear to be due to length or lead-time bias. Participation in an endoscopic surveillance program was the single strongest predictor of long-term survival other than pathologic stage. Our study supports the routine use of surveillance endoscopy in patients with Barrett's esophagus.

Future efforts need to be directed toward several important areas. Appropriate indications and methods for screening for Barrett's mucosa must be identified. For the cohort of patients diagnosed with Barrett's esophagus, techniques must be developed for identifying which patients are at risk for developing dysplasia or, in individuals in whom dysplasia already exists, in which patients dysplasia is likely to progress to invasive cancer. For this high-risk group, methods for reversal of dysplasia or ablation of the Barrett's segment require development. The successful culmination of these efforts will eliminate the need for prophylactic esophagectomy in the majority of patients for whom it is now standard therapy.

CONCLUSION

Endoscopic surveillance identifies patients with Barrett's adenocarcinoma who experience a high rate of cure after resection. Participation in an endoscopic surveillance program was the single strongest predictor, other than stage, of long-term survival in patients with Barrett's adenocarcinoma. The continued use of endoscopic surveillance in patients diagnosed with Barrett's esophagus is appropriate.

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Discussion

Dr. L. Way (San Francisco, Calif.): Is this report based on a special surveillance program? Perhaps it is in the manuscript, but you did not really define surveillance, or perhaps I missed it. I just wondered what the regimen of surveillance consisted of, if there was a specified regimen or whether this was just the result of random practice patterns in the community.

My corollary question is this—in a surveillance program, one would hope that the lesions would be detected before dysphagia develops, so I am wondering what the relationship is between the subgroup with dysphagia in the surveillance group and what the intervals of surveillance endoscopy were?

Dr. M. Ferguson: As you might imagine in an institution such as ours, many of these patients were referred to us for management after the discovery of high-grade dysplasia. As a result, there was an ad hoc surveillance regimen for most of the patients. I could not give you an average interval for the endoscopy. It depended, to some extent, on the findings at the previous endoscopy. I would guess that the patients probably underwent endoscopy on an average of every 9 to 12 months; some of them were diagnosed with cancer within 6 months of their diagnosis of Barrett's esophagus, and some were in a surveillance program for up to 8 years before they needed surgery.

As far as the dysphagia is concerned, we had a very low level of suspicion for dysphagia. So some of the patients who had nonspecific motility abnormalities and reported having dysphagia were recorded as having that even though there was no obstructive lesion. With 75% of the patients in the surveillance cohort having stage I disease, there really were no obstructive problems in the vast majority of them.

Dr. S. Marcus (New York, NY.): In your surveillance group, were there additional patients who underwent esophagectomy for dysplasia and did not have evidence of cancer on final pathologic examination? Are those patients included in your denominator? How did those patients do with regard to morbidity and mortality?

Dr. Ferguson: Yes, we have other patients who were not shown to have cancer on final pathology examination. The last time we reviewed this, the total number of patients with high-grade dysplasia preoperatively was approximately 30, and subsequently we have added approximately six more. At the time we last reported on that, 45% of the patients who had preoperative high-grade dysplasia had invasive cancer on their pathology specimens. Of the last six, only one of these patients had invasive cancer. The overall percentages have shifted downward, so the incidence of invasive cancer is probably about 40%. We still have 0% mortality for resection in those patients undergoing surveillance compared to the other patients.

Dr. C. Pellegrini (Seattle, Wash.): I think the question was, did you include those patients in the calculation of survival?

Dr. Ferguson: The answer is no. Only patients with invasive cancer were included in this group.

Dr. J. Peters (Los Angeles, Calif.): I was struck by two things in your data. One is the 10- to 12-year difference in the ages of the patients in the surveillance vs. the no surveillance group. I cannot believe it takes that long to develop a symptomatic cancer. The second is the falloff in mortality after 5 years in your surveillance group. Did that include noncancer deaths? Can you talk about the age difference and the falloff in mortality?

Dr. Ferguson: The numbers are relatively small, particularly in the surveillance group, so I would not make too much of the age difference. It may be that gastroenterologists are a bit more aggressive about entering younger patients into surveillance programs and excluding some older patients from these programs. The mortality rate includes deaths from all causes. It is not disease-specific mortality. That accounts for the dropoff.

Dr. S. Mattar (Atlanta, Ga.): As a result of the data analysis, were you able to arrive at predictive patient factors that might determine whether a patient is likely to accept and adhere to a surveillance program?

Dr. Ferguson: Unfortunately, no, we do not have any useful information regarding that. It is not a detailed enough database.

Dr. Pellegrini: The important issue here is the one brought up by Dr. Way, I believe. If you look at it from the point of view of when the patient is diagnosed with cancer, and then you backtrack and you question whether surveillance is effective, what you are actually comparing is patients whose cancers were discovered because of a surveillance program as opposed to patients who walked in with an established cancer. I think the real crux of the issue is to be able to state, as you concluded, that surveillance with endoscopy is important and that we must look at patients with Barrett's esophagus, and see what happens if you take the patients with Barrett's esophagus over a number of years and follow just that population.

In the Seattle study that was begun in 1983, by 1998 (i.e., 15 years into a study that included only patients who had Barrett's esophagus), there had been 309 patients entered somewhere between 1983 and 1998, with a median follow-up of 6 years for those patients. Altogether, 74 cancers have appeared; however, 43 of these cancers were in patients whose initial diagnosis was high-grade dysplasia, and only 3.4% of the patients with low-grade dysplasia ended up developing cancer.

So that gives you, I believe, a weight in terms of whether a program is useful or not. And it all depends on how you want to count the economics. It takes a lot of money and a lot of endoscopies to detect a single cancer in a patient who has Barrett's esophagus.

Dr. Ferguson: Exactly, and, unfortunately, we do not have a better technique right now. That is why I think the efforts need to be expanded to identify those patients who are at high risk. The techniques that we have at the present time are clearly inadequate.

Novel Nuclear Shuttle Peptide to Increase Transfection Efficiency in Esophageal Mucosal Cells

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The major barrier to successful transfection appears to be passage of the DNA plasmid from the cytoplasm into the cell nucleus. The M9 nuclear localization peptide, a fragment of the naturally occurring heterogeneous nuclear ribonucleoprotein A1, which serves to shuttle messenger RNA across the nuclear membrane, has been proposed as a tool for enhancing transfection efficiency. We tested three different reporter plasmids to assess the ability of M9 to improve transfection efficiency in esophageal mucosal cells. The effect of M9 on the intracellular movement of plasmid was also assessed using fluorescent microscopy to trace rhodamine-labeled plasmid. The M9 nuclear shuttle peptide consistently increased the transfection efficiency. When transfection was carried out with specific plasmids, β-galactosidase enzyme activity, keratinocyte growth factor–1 growth factor levels, and the number of transfected cells expressing growth factor peptides were progressively increased with increasing M9 to plasmid ratios. Fluorescent microscopy demonstrated that the M9 shuttle allowed rhodamine-tagged plasmid to gain access to the nucleus, while it was located exclusively in the cytoplasm without the peptide. The M9 shuttle peptide increases transfection efficiency in esophageal mucosal cells, and therefore may have a useful role in gene therapy applications involving the esophagus.
(J GASTROINTEST SURG 2002;6:37–42.)

KEY WORDS: Esophagus, DNA transfection, keratinocyte growth factor–1

A variety of peptides, including various growth factors, may be of benefit in treating esophageal diseases. Esophageal disorders that could be addressed include functional motility problems, inflammatory peptic ulceration associated with gastroesophageal reflux disease, as well as treatment of cancer and precancerous conditions such as Barrett's esophagus. Prokinetic peptides, factors to enhance mucosal healing or defense such as growth factors or protective enzymes, and tumor suppressor genes may be of use in improving some of these conditions or preventing their development. Such agents could be given systemically, but local delivery is preferable to maximize efficacy while limiting side effects. However, the esophagus is relatively inaccessible for repeated drug administration and many growth factor peptides have short half-lives. The advantage of a gene therapy approach for esophageal disease is that sustained local production of therapeutic agents may be produced by endoscopically transfecting autologous cells, without the need for frequent repeat dosing.

Nonviral gene therapy is currently limited by the inefficiency of transfection. Evidence suggests that although plasmid enters the cytoplasm relatively easily, the major barrier to gene expression is the nuclear membrane.[1] Liposomal agents currently available allow DNA plasmid to enter the cytoplasm. But typically the DNA is sequestered in the cytoplasm and cannot gain entry to the nucleus where it could initiate the transcription process to produce peptide product. Heterogeneous nuclear ribonucleoprotein–A1 is a nuclear localizing protein complex that shuttles messenger RNA across the nuclear membrane.[2] A 38–amino acid segment of this protein, termed M9, confers its nuclear import[3] and export[4] characteristics. To improve binding of the M9 peptide to DNA plasmid, a scrambled sequence of the cationic SV40 T antigen was complexed to the M9 sequence.[5] We assessed this construct to improve transfection efficiency in an immortalized esophageal mucosal cell line and an esophageal adenocarcinoma cell line. The intracellular location of plasmid was also examined by fluorescent microscopy imaging rhodamine-tagged plasmid DNA.

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MATERIAL AND METHODS

Cell Lines and Plasmids

The immortalized esophageal mucosal cell line HET-1A and esophageal adenocarcinoma SEG-1 cell line were obtained from G. Harris, National Institutes of Health, Bethesda, Md., and Dr. P. Beer, University of Michigan, Ann Arbor, Mich., respectively. Before transfection, cells were grown in Dulbecco's modified Eagle medium plus 10% fetal calf serum in 24-well plates or two-well borosilicate chamber slides for 24 to 48 hours.

β-Galactosidase and keratinocyte growth factor–1 (KGF-1) encoding plasmids were obtained from Invitrogen, Carlsbad, Calif. Plasmids were grown in DH-5α transformed bacteria, and purified using an endotoxin-free plasmid purification kit (Qiagen, Santa Clara, Calif.). Purified plasmids were resuspended in sterile phosphate-buffered saline (PBS) at 2 mg/ml and stored at −70° C until required. Green fluorescent protein and rhodamine-labeled plasmid were obtained from Gene Therapy Systems, San Diego, Calif.

Nuclear Localization Peptide

The M9 peptide and scrambled SV40 T antigen (ScT) were manufactured and supplied by both the Johns Hopkins University Peptide Synthesis Core facility and by the Department of Bioengineering, University of Pennsylvania, Pa. (courtesy of Scott Diamond, Ph.D.).

$$M9 = {}^{268}\text{NQSSNFGPMKGGNFGGRSSG}\ \text{PYGGGGQYFAKPRNQGGY}^{306} \quad (1)$$

$$\text{ScT} = \text{KCRGKVPGKYGKG} \quad (2)$$

The M9 sequence was coupled to the cationic ScT peptide to enhance its DNA binding capability, using a commercial cross-linker SMCC (Pierce, Rockford, Ill.). The 13-residue ScT was incubated with 10 mol/L SMCC in PBS for 2 hours at 22° C. Unbound SMCC was removed by gel filtration using G-25 sephadex spin columns (Worthington Biochemical Corp., Lakewood, N.J.). The M9 peptide was incubated with TCEP-HCl (Pierce) for 30 minutes at 22° C followed by gel filtration using G-25 sephadex spin columns. The two peptides were then incubated together overnight at 4° C. Cross-linking was confirmed by sodium dodecylsulfate–polyacrylamide gel electrophoresis.

Transfection

Plasmid was complexed to the M9-ScT peptide at M9: plasmid weight-to-weight ratios of 0:1, 10:1, 50:1, or 100:1 by incubation for 15 minutes at room temperature. This complex was then combined with 0 to 6 μl Lipofectamine for an additional 15 minutes at room temperature. This solution was made up to 1 ml with Optimem before adding it to the cells. Cells were incubated for 2 hours at 37° C with 300 μl per well of the transfection media. The standard growth medium was then replaced. Assays were carried out at either 24 or 48 hours.

β-Galactosidase

At 24 hours after transfection, the medium was removed, cells were lysed by freeze-thawing, and the quantitative β-galactosidase activity was determined photometrically using a commercial assay (Stratagene, La Jolla, Calif.).

KGF-1

KGF-1 protein expression was measured by enzyme-linked immunosorbent assay. Antibodies were obtained from R & D, Madison, Wis. Microtiter plates were coated with 100 μl/well of mouse monoclonal anti–KGF-1 antibody at 1 mg/ml in PBS, and incubated overnight. Nonspecific sites were blocked with 300 μL blocking buffer (PBS, 1% bovine serum albumin, 5% sucrose, 0.05 NaN_3) per well for 1 hour. Test samples and KGF-1 standard were diluted in 100 μl/well of buffer (PBS-Tween, 1% blotto; Santa Cruz Biotechnologies, Santa Cruz, Calif.). After a 2-hour incubation, plates were washed in PBS-Tween, and incubated with biotinylated rabbit anti–KGF-1 detection antibody (200 ng/ml in Tris-buffered saline, pH = 7.2, 0.1% bovine serum albumin, 0.05% Tween-20). After washing the plate four times with PBS-Tween, a 1:4000 dilution of horseradish peroxidase–conjugated streptavidin was added and incubated for 45 minutes. TMB substrate solution was added and allowed to develop for 30 minutes, stopped with 2 mol/L H_2SO_4, and absorbance was measured at 450 nm using a Dynatech MR4000, 96-well spectrophotometer (Ashford, Middlesex, U.K.).

Fluorescent Microscopy

Growth factor peptide (GFP) transfection was assessed at 24 hours by counting the GFP-positive cells indicated by green cytoplasmic fluorescence using fluorescent microscopy (Nikon Eclipse TE 300, Nikon USA Inc., Melville, N.Y.).

The intracellular location of the rhodamine-labeled plasmid was determined at 24 hours by fluorescent microscopy. Media were aspirated and cells washed with PBS. Nuclei were counterstained with the DNA flu-

orescent stain 4′, 6-diamidino-2-phenylindole dihydrochloride (DAPI) at a concentration of 300 nmol/L for 10 minutes, followed by further washing in PBS. Cells were examined in situ on the chamber slides to determine the relative position of the rhodamine-labeled plasmid with respect to the blue counterstained nuclei.

Statistics

Differences in the mean values of experimental groups were assessed for significance using analysis of variance (ANOVA) or Student's *t* test.

RESULTS

β-Galactosidase

We assessed various combinations of Lipofectamine and M9 to determine their ability to improve transfection efficiency with the β-galactosidase plasmid in SEG-1 cells (Fig. 1). After transfection with plasmid without Lipofectamine, there was no evidence of transfection. Neither M9 alone nor Lipofectamine alone at low concentrations resulted in significant transfection with the β-galactosidase plasmid. With increasing amounts of Lipofectamine there was a progressive modest increase in the level of β-galactosidase activity ($P < 0.001$, ANOVA). The addition of M9 to the transfection media caused a large increase in the transfection efficiency at each concentration of Lipofectamine/plasmid tested, as evidenced by the β-galactosidase activity ($P < 0.001$, *t* test). This effect was most apparent at the lower Lipofectamine concentrations. The combination of M9 and Lipofectamine had a dramatic effect on the transfection efficiency (Fig. 2). At a Lipofectamine concentration of 4 μl/ml, increasing the M9 ratio increased the β-galactosidase activity up to a ratio of 50:1 M9 to plasmid; a higher ratio of M9 tended to reduce the beneficial effect (Fig. 3).

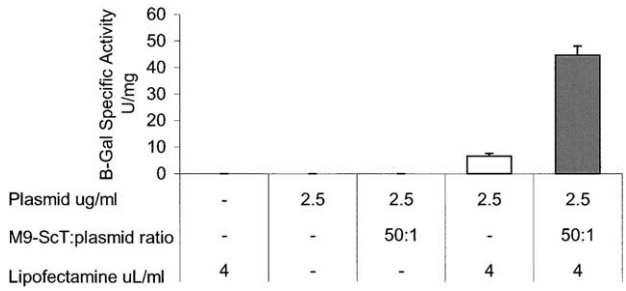

Fig. 2. The effect of combinations of plasmid, Lipofectamine, and M9 on β-galactosidase activity. The M9 and Lipofectamine together, significantly improved transfection efficiency ($P < 0.001$ ANOVA).

KGF-1

A KGF-1 encoding plasmid was used to examine the effect of M9 on the amount of growth factor produced by transfected HET-1A cells. The M9 peptide caused a significant increase in the amount of KGF-1 protein produced at an M9 to plasmid ratio of 50:1 ($P < 0.001$, ANOVA) (Fig. 4).

GFP

The M9 peptide caused a dose-responsive increase in the number of SEG-1 cells expressing the GFP protein, indicated by green cytoplasmic fluorescence ($P < 0.05$ ANOVA) (Fig. 5). The highest rate of transfection seen was approximately 1% of cells in experiments with 100:1 M9 to plasmid ratio.

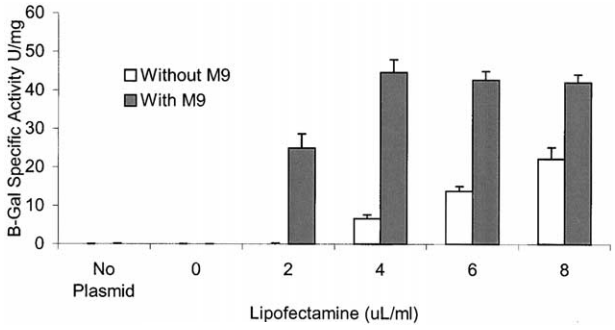

Fig. 1. Transfection efficiency indicated by β-galactosidase activity, with and without the M9-ScT peptide at 50:1 M9 to plasmid ratio, at various concentrations of Lipofectamine. The addition of M9 increased β-galactosidase activity ($P < 0.001$, *t* test).

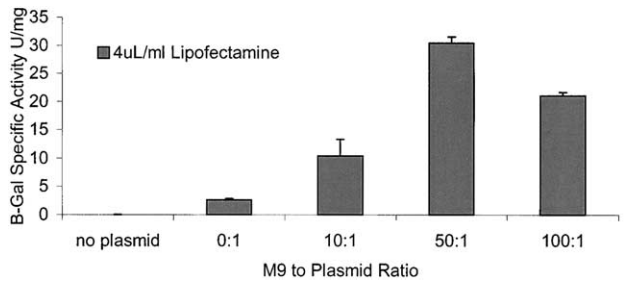

Fig. 3. The effect of increasing the ratio of M9 to plasmid in the presence of 4 μl/ml of Lipofectamine on the β-galactosidase activity. The maximal effect was seen at a ratio of 50:1 M9 to plasmid; higher levels than this caused an attenuated response ($P < 0.001$, ANOVA).

Rhodamine-Labeled Plasmid

After transfection with rhodamine-labeled plasmid without Lipofectamine, either in the presence or absence of M9, there was no evidence of intracellular fluorescence 24 hours after transfection in SEG-1 cells. After Lipofectamine-mediated plasmid transfection, without M9, the plasmid occupied an exclusively cytoplasmic position (Fig. 6). In the presence of both Lipofectamine and M9, the plasmid appeared in the nucleus (Fig. 7).

DISCUSSION

The current work extends the investigation of the M9-ScT construct shuttle to HET-1A and SEG-1 esophageal cells and explores the mechanism of the effect using plasmid expression markers, Lipofectamine dose-response analysis, and fluorescent microscopic tracing of rhodamine-tagged plasmid. The M9-ScT construct has previously been shown to improve transfection efficiency in confluent endothelial cells.[5]

The current experiments show that the M9-ScT construct, acting with Lipofectamine, significantly increases transfection efficiency in the esophageal cell lines. Plasmid alone without a lipid cofactor produced no detectable transfection. The M9-ScT alone was also ineffective at enhancing transfection efficiency as expected, because it targets the nuclear membrane and not the cell membrane. Lipofectamine alone improved transfection in a dose-responsive manner with successful transfection at relatively high levels. Previous reports suggest that if the cytoplasmic concentration of plasmid is high enough, gene expression will occur, presumably by overcoming the nuclear membrane barrier.[6] The combination of the M9-ScT shuttle and Lipofectamine had a dramatic effect increasing β-galactosidase activity at each concentration tested. This result can be explained by the ability of the two agents to facilitate transport across the nuclear and cell membranes, respectively. The effect was particularly dramatic at the lower concentrations of Lipofectamine. These findings were consistent with the rhodamine-labeled plasmid experiments, where Lipofectamine-mediated transfection allowed the plasmid access to the cytoplasm, but not the nucleus, whereas the addition of M9 allowed plasmid to enter the nucleus.

As expected, small differences were seen among the results with the three different plasmids. The KGF, but not the β-galactosidase plasmid, produced some transfection with 2 μl/ml of Lipofectamine, presumably because of differences in the plasmid constructs or differences between the SEG-1 and HET-1A cells. The GFP plasmid results did not show the dramatic effect of the M9 construct, but these experiments were done with 4 μl/ml Lipofectamine, so baseline transfection was relatively high, and the cells may have approached a plateau in the beneficial effect of the combination of liposome and M9.

Gene therapy has the potential to treat a variety of acquired and inherited diseases of the gastrointestinal tract. Currently the major hurdle preventing successful gene therapy is efficient gene delivery into cells for expression. Although viral vectors can achieve a high level of transfection efficiency, both in vitro and in vivo, there are concerns regarding both the immunogencity and safety of this approach. For successful transfection of eukaryotic cells, the plasmid must enter the nucleus where the transcription apparatus exists.

Several lines of evidence suggest that the nuclear membrane is a significant barrier to plasmid transfection. Plasmid gene expression is increased following mitosis during which the nuclear membrane is disrupted.[7] Although liposomal-mediated transfection causes efficient plasmid delivery to the cytoplasm,[6] most is sequestered within cytoplasmic endosomes[1]

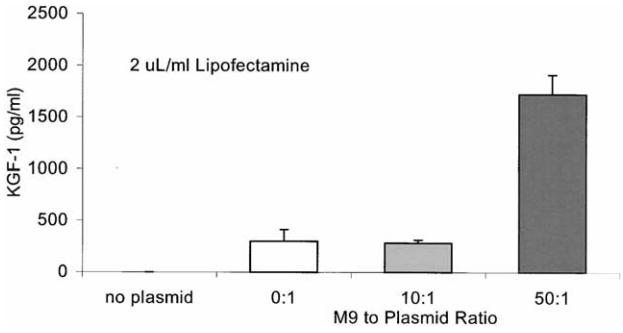

Fig. 4. The amount of KGF-1 produced, as determined by enzyme-linked immunosorbent assay, in the absence and presence of M9. M9 at 50:1 increased KGF-1 production ($P < 0.001$, ANOVA).

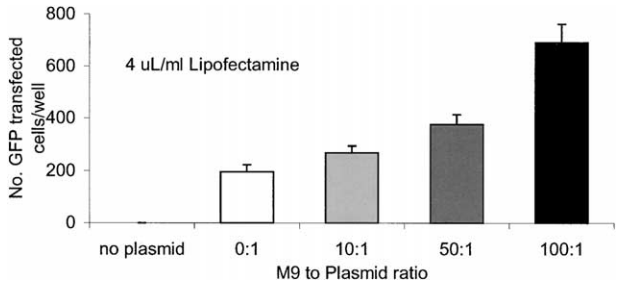

Fig. 5. The number of transfected cells per well as indicated by green fluorescent protein expression was increased with the M9 peptide ($P < 0.05$, ANOVA).

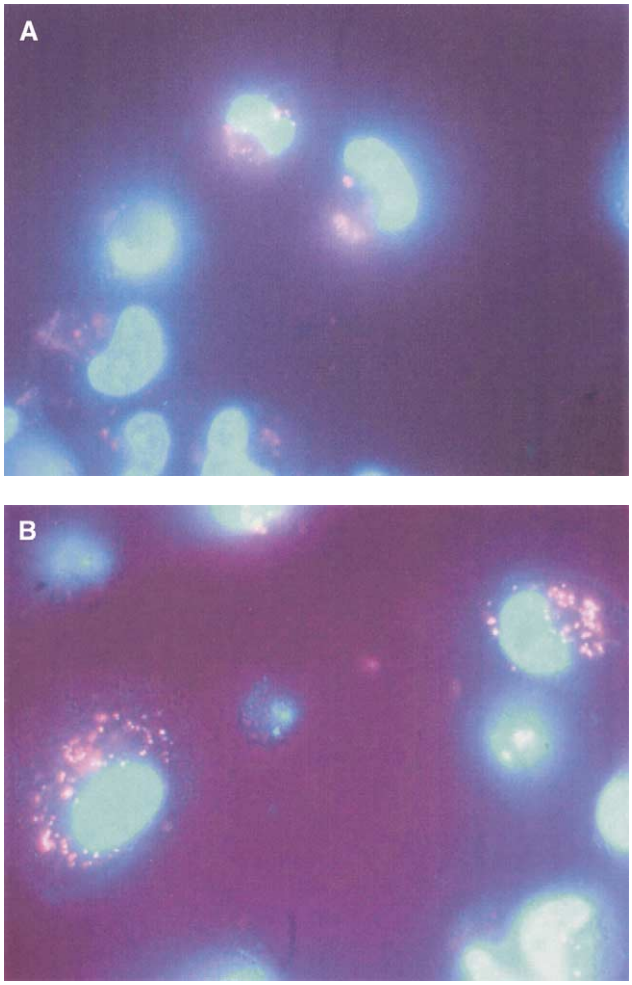

Fig. 6. A, B, Following transfection with rhodamine-labeled plasmid and Lipofectamine, fluorescence is only seen in the cytoplasm.

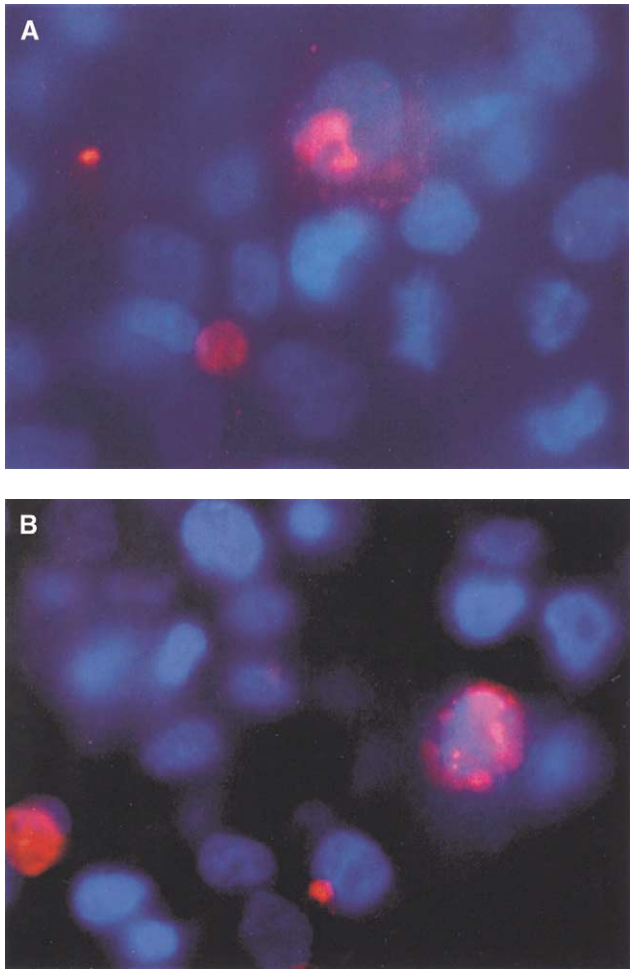

Fig. 7. A, B, After transfection in the presence of Lipofectamine and the M9 nuclear localization peptide, rhodamine-labeled plasmid appears within the nuclei.

and fails to reach the nucleus. After microinjection of plasmid into the cytoplasm, there is modest gene expression after a time delay, whereas with nuclear injection, expression is rapid and at higher levels.[8]

The nuclear membrane contains pores, which only allow free diffusion of molecules up to 30 to 60 kDa in size.[9] Typical plasmids are considerably larger than this. Active transport mechanisms exist that can transport large molecules, such as mRNA and nucleoproteins across the nuclear membrane.[10,11] These processes are mediated by specific nuclear import and export sequences. Heterogeneous nuclear ribonucleoprotein is an mRNA-binding protein complex that shuttles RNA between the nucleus and cytoplasm through the nuclear pore complex.[2] A 38-amino acid component of hnRNP-A1, termed M9, is responsible for both the nuclear import[3] and export[4] characteristics. In the cytoplasm, M9 binds to Transportin-1 (also known as karyopherin-β2) before transport across the nuclear pore complex into the nucleus.[12] M9 has been shown to cause the nuclear accumulation of cytoplasmic proteins.[3]

CONCLUSION

Acting as a nuclear localization signal, directing cytoplasmic plasmid to the nucleus, the M9 peptide may be a useful tool for increasing transfection in vitro, especially with low concentrations of lipofection agents. This approach may be of use for increasing transfection efficiency in vivo for gene therapy applications, where current means of enhancing transfection, such as lipofection, are much less effective. M9 may also have a role in ex vivo transfection applications where cells may be harvested, transfected in vitro, and reimplanted into the host where the desired gene may be expressed.

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Does Mechanical Massage of the Abdominal Wall After Colectomy Reduce Postoperative Pain and Shorten the Duration of Ileus? Results of a Randomized Study

Isabelle Le Blanc-Louvry, M.D., Bruno Costaglioli, M.D., Catherine Boulon, Anne-Marie Leroi, M.D., Ph.D., Philippe Ducrotte, M.D., Ph.D.

The aim of this study was to determine the effectiveness of mechanical abdominal massage on postoperative pain and ileus after colectomy. We hypothesized that parietal abdominal stimulation could counteract induced pain and postoperative ileus, through common spinal-sensitive pathways, with nociceptive visceral messages. After preoperative randomization, 25 patients (age 52 ± 5 years) underwent active mechanical massage by intermittent negative pressure on the abdominal wall resulting in aspiration (Cellu M50 device, LPG, Valence, France), and 25 patients (age 60 ± 6 years) did not receive active mechanical massage (placebo group). Massage sessions began the first day after colectomy and were performed daily until the seventh postoperative day. In the active-massage group, amplitude and frequency were used, which have been shown to be effective in reducing muscular pain, whereas in the placebo group, ineffective parameters were used. Visual analogue scale (VAS) pain scores, doses of analgesics (propacetamol), and delay between surgery and the time to first passage of flatus were assessed. Types and dosages of the anesthetic drugs and the duration of the surgical procedure did not differ between groups. From the second and third postoperative days, respectively, VAS pain scores ($P < 0.001$) and doses of analgesics ($P < 0.05$) were significantly lower in patients receiving active massage compared to the placebo group. Time to first passage of flatus was also significantly shorter in the active-massage group (1.8 ± 0.3 days vs. 3.6 ± 0.4 days, $P < 0.01$). No adverse effects were observed. These results suggest that mechanical massage of the abdominal wall may decrease postoperative pain and ileus after colectomy. (J GASTROINTEST SURG 2002;6:43–49.)

KEY WORDS: Colectomy, postoperative ileus, mechanical massage

Gastrointestinal motility and transit are transiently impaired following abdominal surgery leading to bloating, distention, visceral pain, and emesis. This paralytic state is longer when surgery involves the distal rather than the proximal digestive tract.[1]

The pathogenesis of digestive ileus has not been completely clarified and it appears to be multifactorial. Animal studies have demonstrated that ileus could be related to an inflammatory process—that is, surgical manipulation of the small intestine leads to intense leukocyte infiltration of the intestinal muscularis within 24 hours[2,3] and significant inducible nitric oxide (NO) synthase induction.[4] On the other hand, ileus in the immediate postoperative phase also seems to be the result of an inhibitory nervous reflex facilitating inhibitory autonomic and enteric neural activity, which may lead to inhibition of both small intestine motility and gastrointestinal transit. Sensory input from the gut could promote corticotropin-releasing factor[5] within the paraventricular nucleus of the hypothalamus and the dorsal vagal complex through capsaicin-sensitive afferent reflex pathways.[6] This central neural activity may stimulate an efferent inhibitory motor pathway, thus causing ileus through an increase in adrenergic and nitrergic neuromuscular activity.[7,8]

The modulation of peripheral sensory inputs affects ileus; fedotozine, a kappa-opioid agonist, has been shown to reverse experimental ileus via an action at the peripheral kappa-opioid receptor level.[9,10] Spinal afferent fiber nerve ablation has been reported to reverse postoperative delay of gastrointestinal transit.[11] Immunoneutralization of calcitonin gene-related peptide, a widely distributed neuropeptide in the intrinsic and extrinsic neurons of the gastrointestinal wall involved

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in nociception, has been shown to have a similar effect.[11,12]

Anatomically, digestive primary afferent neurons are connected at the spinal dorsal horn level with somatosensory neurons. This may explain why spinal dorsal horn neuron activity involved in the transmission of nociceptive signals was found to be inhibited by heterotophic noxious conditioning stimuli.[13] Human studies have also demonstrated that painless somatic stimulation can reduce perception of gut distention leading to discomfort without affecting gut tone or reflex gut response.[14] These results were the basis of this study. We hypothesized that somatic stimulation begun in the early postoperative period could interact with digestive sensory input and modify the inhibitory nervous reflex leading to ileus. Abdominal massage could be useful to promote somatic stimulation via nerve stimulation of the skin. Previous studies have shown that massage is effective in relieving somatic pain, that is, cutaneous pain for burn tissues,[15,16] and also lower back pain[17] or premenstrual symptoms.[18]

The aim of this randomized controlled study was to determine if mechanical abdominal massage during the postoperative period after colectomy was effective in reducing postoperative abdominal pain and ileus. To test this hypothesis, two groups of patients were randomized to receive active mechanical massage or sham nonactive mechanical massage (placebo group).

METHODS

Patients

After preoperative randomization on the day before colectomy and after giving informed consent, 25 patients received active mechanical massage of the abdominal wall with a Cellu M50 device (LPG, Valence, France), and 25 patients underwent sham nonactive mechanical massage (placebo group). Patients were excluded from randomization if they were under 18 or over 75 years of age, if they had undergone previous surgery or had to undergo noncurative surgery for their colonic lesions, or if they had had severe neuromuscular, dermatologic, cardiovascular, or psychiatric disease. Obese patients (body mass index >35) were also excluded because effective mechanical massage of the abdomen would be difficult. All types of colectomies (total, right and left) were included. Indications for surgery were colon cancer, diverticular disease, or inflammatory disease (Table 1).

Anesthetic and Surgical Methods

Patients remained in the fasting state for 8 hours before surgery and were premedicated with oral hydroxyzine (1 mg/kg) (UCB Pharma, Nanterre, France) 1 hour before surgery. During general anesthesia, the same drugs were used in all patients including a postsedative inducer (propofol; Diprivan, Zeneca Pharma, Cergy, France) at a dosage of 5 mg/kg/hr after an initial dose of 2 mg/kg; opiates (fentanyl; Fentanyl, Janssen Cilag SA, Issy les Moulineaux, France) by intravenous injection of 2 mg/kg every 20 minutes after an initial dose of 3 mg/kg; and a curaremimetic (Norcuron, Organon-Teknika, Fresnes, France), 0.02 mg/kg every 20 minutes after an initial dose of 0.08 mg/kg. Anesthesia was maintained with isofluorane.

Colectomy was performed through a median laparotomy. After left, right, or total colonic resection, digestive continuity was restored by colocolic, ileocolic, or ileorectal anastomosis, respectively, without ileostomy or colostomy.

Mechanical Massage Device

The massage was performed with a Cellu M50 device (LPG, Valence, France), which powers a computer-driven hand-held massage head that produces intermittent aspiration and induces the formation and mobilization of skin folding. This technique results in the same mechanical massage as a manual massage, but is easier to reproduce.

Massage heads were connected to the vacuum pump by a flexible tube. The vacuum pump creates a

Table 1. Characteristics of patients and features of surgical procedure

	Active massage (n = 25)	Sham massage (n = 25)
Age (yr)	52 ± 5	−60 ± 6
Hamilton test*		
Before surgery	13.6 + 1.1	12.2 + 1.2
7 days after surgery	12.1 + 0.9	12.9 + 1.9
Indications for surgery		
Colon cancer	18	20
Diverticular disease	4	2
Inflammatory bowel disease	3	2
Surgical procedures		
Total colectomy	2	1
Left colectomy	17	19
Right colectomy	6	4
Doses of anesthetic drugs†		
Fentanyl (μg)	1350 ± 132	1210 ± 125
Diprivan (mg)	220 ± 9	232 ± 8
Norcuron (mg)	32 ± 4	29 ± 3
Duration of surgery (min)	145 ± 46	133 ± 14

Values are means ± SEM; no statistical difference was observed between patients receiving active massage and the sham group.
*Determines the anxiety scale by evaluating 14 somatic and psychological items calibrated from 0 (minimal) to 4 (maximal).
†Total preoperative doses of anesthetic drugs.

depression effect, and the level is adjusted and permanently controlled by an electronic regulation system. The smallest massage head was used because there is intermittent suction in the depression chamber resulting in gentler massages. Mechanical stimulation was rhythmic because previous studies have shown that this is less invasive with deeper effects that are not limited to local cutaneous muscular tissue.[19] This device can induce chamber depression ranging from 50 mbar (level 0) to 500 mbar (level 10). The frequency of stimulation varies from 0.08 Hz (depression for 12.2 seconds: level 1) to 12.5 Hz (depression for 0.08 seconds: level 99). Finally, the "on/off" ratio ranged from 1 to 9, with level 5 representing an equal amount of on and off time. The intensity and frequency of stimulation were effective in the active-massage group but were not effective in the placebo group. Efficiency levels were determined according to results obtained during muscular massage to relieve pain. For active massage, the depression intensity was 3 (300 mbar), the frequency was 85 (2.17 Hz), and the on/off ratio was 7. For sham massage, the intensity was 120 mbar (level 1), the frequency was 55 (0.38 Hz), and the on/off ratio was 1. With these parameters there was no suction of the abdominal wall, but patients had a slight sensation of the head rolling on their skin. The device was used according to the manufacturer's instructions throughout the study.

Study Design

Massages were begun on the first day after colectomy and were performed by a single operator (C.B.) once a day until postoperative day 7 with patients in a supine position. The massage head was placed successively along the diaphragm insertions, on the lower abdominal wall along the crural arcades, and finally along the median incision by making concentric ellipses. Each session lasted 15 minutes.

Walking during the postoperative period was standardized, and as of postoperative day 2, patients walked twice a day—once in the morning before the massage session and once in the afternoon.

The level of postoperative pain was assessed by a visual analogue scale (VAS) with scores ranging from 0 (absence of pain) to 10 (significant pain)[20] and by daily doses of chlorhydrate or propacetamol (Pro-dafalgan, UPSA, Rueil Malmaison, France) administered intravenously (2 grams per injection). Pain was assessed on the VAS before mechanical massage, 30 minutes after the end of massage, and then at 2-hour intervals until 12 P.M. On the first two postoperative days, patients routinely received 6 grams of propacetamol per day. When more analgesics were needed to control pain, the total dose could be increased to 8 grams per day. After the second postoperative day, analgesics were only given (2 grams doses) on request by the patient and/or when routine pain evaluation (every 2 hours) showed VAS pain scores above 2. Doses of propacetamol never exceeded 8 grams per day.

The day of the first passage of flatus and/or stool was used to define the duration of postoperative ileus. The duration of postoperative ileus (hours) was defined as the interval between the end of surgery and the first passage of gas or stool through the anus. Eating was allowed once the first gas occurred. No prokinetic drugs were given during the postoperative period.

The following adverse effects of mechanical massage were evaluated: acute painful sensations during or after massage, skin modification, parietal hematomas, and functional digestive symptoms.

Evaluation of outcome was blinded and included assessement of pain scores, daily doses of propacetamol, and the day of first passage of flatus or stool. Evaluations were performed by a clinician (B.C.) who was unaware of the randomization and who did not perform any of the massages (C.B.).

Finally, to determine the patient's degree of anxiety, the Hamilton score was used.[21] This test provides a quantitative evaluation of anxiety based on 14 items (somatic and psychic) scored from 0 (absence) to 4 (maximal intensity) with possible scores ranging from 0 to 60. The Hamilton score was determined in each patient on the day before surgery and at the end of the study on day 7.

Statistical Analysis

No previously published data could be used to accurately calculate the sample size for this trial. In a preliminary study, pain intensity was determined for the first seven postoperative days in 20 colectomized patients. Mean ($\pm$ SEM) VAS pain scores were 8.1 ± 0.9, 7.2 ± 1.1, 7.0 ± 0.8, 5.4 ± 0.6, 5.1 ± 0.3, 4.3 ± 0.2, and 3.1 ± 0, respectively, during the 7 days after surgery. The number of patients in both groups was determined to detect a 25% pain scale difference with 5% alpha and beta error risks.

Data are given as mean $\pm$ SEM. The chi-square test with the Yate's correction was used to analyze qualitative parameters. The Mann-Whitney U test was used to compare quantitative data between the two groups, and the paired Wilcoxon signed-rank test was used to compare quantitative data within each group. One-way analysis of variance was used to assess the influence of postoperative delay on pain intensity and the need for propacetamol, and to investigate significant variations in pain scores and analgesic dosages after each massage session.

RESULTS

The groups did not differ with regard to patient's age, anxiety level before surgery, indications for colectomy and type of colectomy, doses of anesthetic drugs (propofol, fentanyl, curare), and duration of surgery (see Table 1).

The mean VAS pain score was lower from the second to the fifth postoperative day ($P < 0.001$) in the active-massage group compared to in the sham group (Fig. 1). Between the fifth and the seventh day, the pain scores remained lower in the active-massage group, but the difference was not significant. One-way analysis of variance showed that in patients receiving active massage, a significant decrease in the VAS pain score was observed between day 1 and day 4 ($P < 0.04$), whereas in the sham group, the VAS pain score was significantly decreased in comparison to the day after surgery after the fifth postoperative day only ($P < 0.05$).

On each postoperative day, pain intensity varied only slightly with standard errors for interindividual VAS pain scores ranging from 0.7 to 1.3 on day 1 and from 0.2 to 0.3 on day 7. Nevertheless, patients who received active mechanical massage had the lowest daily pain scores 45 minutes after the beginning of massage ($P < 0.05$) (Fig. 2). Moreover, in this group, during the first three postoperative days, the VAS pain score progressively increased in relation to the time (hours) between massage and pain assessment ($P < 0.05$). Pain intensity tended to decrease more slowly in the sham group (see Fig. 2).

Propacetamol doses were lower in the active-massage group than in the placebo group until postoperative day 3 ($P < 0.05$) (Fig. 3). Doses of propacetamol progressively decreased from day 1 to day 4 in patients receiving active massage ($P < 0.03$) (see Fig. 3). In the sham group, doses of analgesic did not decrease significantly during this period.

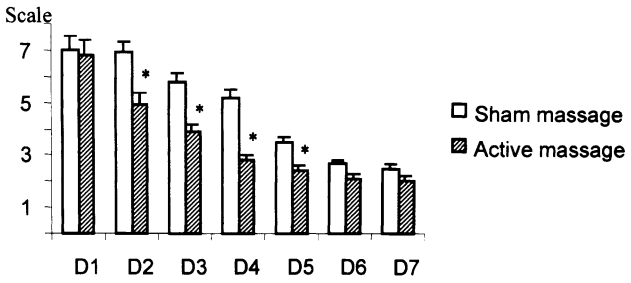

Fig. 1. Pain intensity assessed by visual analogic scale (VAS) during the postoperative period. D = day after surgery. $P < 0.001$ vs. placebo group. By one-way analysis of variance: VAS score decreased when postoperative delay increased; from day 1 to day 4 in the active-massage group ($P < 0.04$), until day 5 in the placebo group ($P < 0.05$).

Flatus preceded the emission of stool in all patients. Time to first passage of flatus was shorter in patients who received active massage than in the placebo group (1.8 ± 0.3 days vs. 3.6 ± 0.3 days, $P < 0.01$). Fig. 4 shows a trend toward a relationship between the early onset of flatus and a low pain score.

Time to discharge from the hospital did not differ between the two groups: 8.1 ± 0.1 days in the active-massage group and 7.6 ± 0.1 days in the placebo group.

No significant changes in the Hamilton anxiety scores were observed between the day before surgery and postoperative day 7 in either group, and at the end of the study anxiety scores did not differ between the two groups.

None of the patients complained of acute abdominal pain during massage, and no adverse effects from massage were observed.

DISCUSSION

This randomized controlled study shows that after colectomy, in comparison to standard management with analgesics alone, mechanical massage of the abdominal wall reduced both the duration of ileus and the intensity of postoperative pain assessed directly by

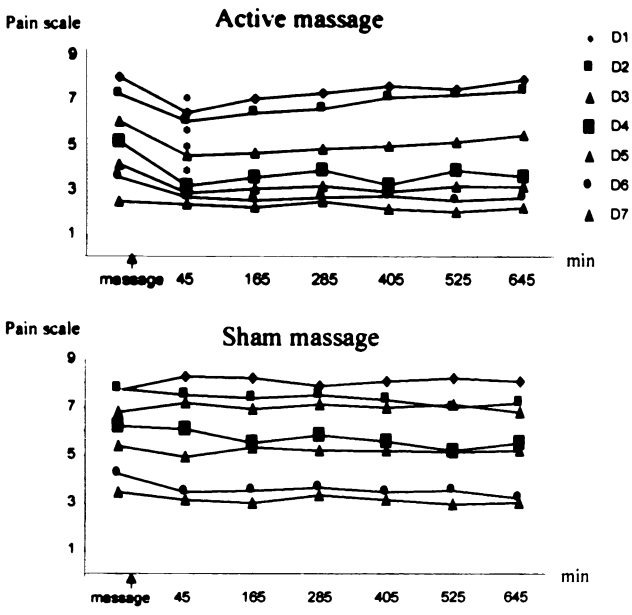

Fig. 2. Daily variations in pain intensity assessed by visual analogic scale (VAS) for each postoperative day in patients receiving active massage and in the sham group. D = day after surgery. $P < 0.05$ vs. VAS pain score before massage. By one-way analysis of variance: In the actives massage group, VAS scores increased as the delay after massage increased ($P < 0.05$).

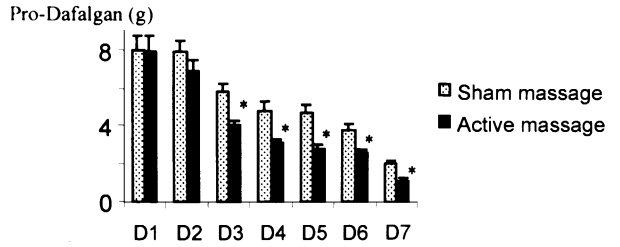

Fig. 3. Propracetamol doses during the postoperative period. D = day after surgery. $P < 0.05$ vs. sham-massage group. By one-way analysis of variance: Doses of propacetamol decreased as the postoperative delay increased (between day 1 and day 4) in the active-massage group ($P < 0.05$).

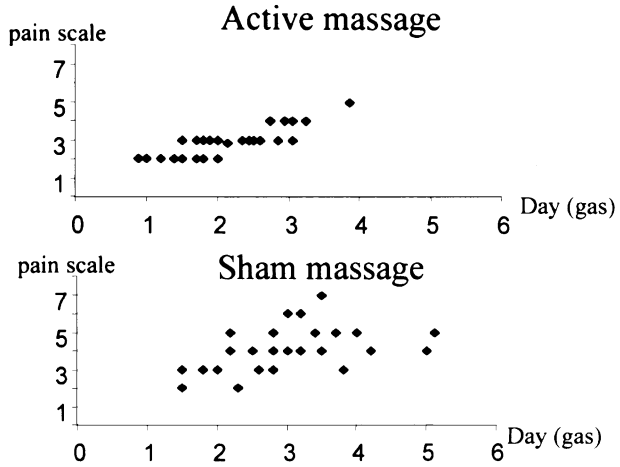

Fig. 4. Relation between duration of ileus and VAS pain scale.

VAS scores and indirectly by the dosages of analgesics required by the patients. These differences were obtained in comparison to a control group in which postoperative pain and the duration of ileus were similar to what was reported in the literature.[1,22] Furthermore, this study emphasizes that, even in the early postoperative period, massage was well tolerated, as evidenced by the fact that none of the patients complained of acute abdominal pain during massage and no adverse effects were observed. The design of this study does not allow us to calculate a cost/benefit ratio or to demonstrate any decrease in time to discharge because the duration of the hospital stay was 7 days for all patients even when, as was the case in several patients, significant improvement in pain and a short duration of ileus would have allowed hospital discharge before the seventh postoperative day.

The trial was performed in patients undergoing curative colectomy only. By chosing a single, well-standardized surgical procedure, we were able to evaluate the effects of massage in a homogeneous group of patients without taking into account possible differences related to various types of surgery. The lack of difference in the duration of the surgical procedure and the dosages of anesthetic received during surgery also facilitate comparisons between the groups. Colonic surgery was selected because we thought it would be the best way to demonstrate the potential benefits of this technique. Indeed, the paralytic state is usually longer when surgery affects the distal rather than the proximal gastrointestinal tract.[1]

This study was performed in patients with severe abdominal pain. Data on the pain scores in our preliminary study were confirmed in this trial by showing that in the early postoperative period, VAS pain scores varied from 7 to 8 on a scale of 0 to 10. Therefore, for ethical reasons, we did not propose massage therapy alone for patients in the active-massage group. Patients systemically received a daily dose of analgesics of 6 grams for the first 2 days of the study. Thus in the early postoperative period, the results obtained were based on a combination of abdominal massage and analgesics.

The duration of daily massage was set at 15 minutes because we believed that prolonged massage might not be well tolerated by patients with a recent laparotomy scar. This duration was chosen in reference to the duration of massage for other pathologic situations such as the treatment of burn scars.[19] A short duration of treatment is also a feature of nonpharmaceutical treatments such as acupuncture.[23,24] This study showed the therapeutic benefit of massage on pain and ileus with this duration of treatment, and changes in the VAS pain score in the first 4 days after surgery suggest that a second session of massage, in the late afternoon, could have been beneficial to avoid the progressive increase in pain when the delay between massage and pain assessment was longer. The parameters selected for the Cellu M50 device (intensity and frequency of vacuum depression, on/off ratio for the use of the device) were also chosen on the basis of parameters to improve muscular pain.[19] In two pilot studies that assessed the efficacy of massage to improve pain in irritable bowel syndrome [25,26] or in the treatment of pelvic pain,[27] patients had global massages involving both the anterior and the posterior abdominal walls. For reasons of tolerance we only performed an anterior abdominal massage in patients in a supine position to avoid moving the patient in the very early postoperative period.

The mechanism involved in the clinical efficacy of massage remains unclear. Several massage studies have shown reduced pain associated with decreased stress and anxiety for painful procedures and conditions including labor pain,[27] debridement procedures (skin brushing) for burn patients,[15,16] and low back

pain.[17] The patients enrolled in this study had low anxiety levels assessed by the Hamilton score on entry in the study. Moreover, if massage really had a beneficial effect on abdominal pain due to the potential for stress reduction, an improvement in the anxiety score should have been observed after active-massage sessions. However, anxiety scores did not change during this study and remained nonsignificantly different between the two groups. This suggests that massage therapy may not only act as a stress reduction tool. These results also suggest that a somatic stimulation in the early phase after surgery might interact with digestive sensory inputs and modify the inhibitory nervous reflex leading to ileus. Indeed, human studies have demonstrated that painless somatic stimulation can reduce an uncomfortable perception of gut distention without affecting gut tone or reflex gut responses.[14] Somatic stimulation was different in the two groups. In the active-massage group, the stimulation parameters led to gut wall aspiration. In contrast, in the sham group the head of the device only induced a slight rolling sensation. Stimulation of the anterior abdominal wall from the epigastrium to the crural area stimulated T6 to T12 dermatomas. In these dermatomas, sensitive fibers are connected in the dorsal horn of the medulla at the same level as sensitive afferences from the small and large intestines. Although our hypothesis on the putative effects of massage on pain are plausible, the design of this study does not allow us to draw definite conclusions. Moreover, we also speculated that the effects of massage on ileus could be related to its effects on pain, but our results do not support this hypothesis as we did not show that ileus ended when the intensity of pain was the lowest. Motor effects could also be due to a somatovisceral reflex induced by the dermatomal stimulation.[28]

CONCLUSION

These results suggest that aspiration massage in the abdominal wall may decrease pain and the duration of ileus after colectomy. Nevertheless, further studies are required to determine the mechanism of action of this promising therapeutic option, to test whether other massage modalities (longer duration, stimulation of another area, particularly dorsal massage) could be beneficial and to determine the cost/benefit ratio of this technique in clinical practice.

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Discussion

Dr. H.C. Sax (Rochester, NY.): The Program Committee should be congratulated for bringing this type of a study to the program as we study mind-body interactions. I have two questions: First, did every patient have a midline incision or were there any instances where a transverse incision was used for the right colon where muscle is cut?

The second question is for those of us who do, for example, bariatric surgery, where a patient may be excited about having surgery, it is really surprising how little analgesia is needed. Were all patients counseled ahead of time that this massage would help postoperative pain, even if they were going to be randomized to the sham group, and among those who did received a sham massage, did they really understand that this was a sham? In other words, could they tell the difference?

Dr. P. Ducrotte: Concerning your first question, the incision was standardized and all patients had a midline incision.

I need to describe what constitutes a sham massage, because patients were unaware of whether they had a sham or active massage. Indeed, during the sham massage, the massaging head of the device rolled on the abdominal wall without creating any depression.

Dr. B.L. Bass (Baltimore, Md.): I am wondering about the logistics of the procedure. How much will this treatment cost and how much time will it take a nurse or therapist to administer? What was the duration of each massage and how long did the effect last? How much does the massage device cost? Is this conceivably a treatment patients could do for themselves as opposed to having someone else do it for them?

Dr. Ducrotte: Concerning the first question, we observed a significant decrease in pain scores in the active-massage group immediately after the massage session. This decrease and the improvement of pain lasted for several hours after the massage session, but we observed each day a trend toward a slow increase in the pain score during the latter part of the day. So we believe that a second session could be beneficial.

Dr. Bass: How long does it take to do the massage?

Dr. Ducrotte: We standardized the duration of the massage to 15 minutes. It is quite empirical because we only considered the usual massage parameters proposed to relieve postoperative pain after burn injuries. Perhaps a longer massage, 20 or 25 minutes, would be more beneficial than a 15-minute massage. This needs to be tested.

Concerning the cost, I do not know what the cost is in the United States. I do not know if this device is distributed in the United States.

Dr. Bass: My third question is whether this could be a self-administered treatment, whether patients can do this massage themselves to avoid having to use nurses or therapists of some sort.

Dr. Ducrotte: I believe it is possible. The technique is quite simple. You have only to roll the massage head on the abdomen and the mechanical massage is automatically delivered by the device.

Dr. M.G. Sarr (Rochester, Minn.): I would be surprised if, in the United States, we would be allowed to give our patients only Tylenol (or paracetamol) for postoperative pain after a celiotomy. My question is, do you think you would achieve the same effect if the patient also had an epidural catheter or was given intravenous morphine. Would the massage have the same beneficial effects?

Dr. Ducrotte: This is a very relevant question, but one that I am unable to answer. I believe it is possible, but we wanted to avoid opiates in this study because we believe that this technique could be an alternative to opiate treatment in the early postoperative period. That is why the patients in our study did not receive opiates.

Should Suspected Early Gallbladder Cancer Be Treated Laparoscopically?

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Early gallbladder cancer (EGC), defined as T1 and T2 disease, is frequently curable when completely excised without bile spillage. The objective of the present study was to determine what effect initial laparoscopic cholecystectomy has on outcome in patients with EGC. Of 89 patients referred to our institution with gallbladder cancer over an 11-year period, 26 had undergone initial laparoscopic cholecystectomy. Sixteen of the 26 patients had T1 or T2 disease and are the subjects of this report. These patients were reviewed retrospectively to assess preoperative diagnosis, intraoperative bile spillage, and outcome (recurrence and survival). In addition, the Western literature was reviewed to determine the impact of initial laparoscopic cholecystectomy on recurrence and survival of patients with EGC. Six patients had a preoperative ultrasound consistent with a mass in the gallbladder wall. Seven (44%) had documented bile spillage during the laparoscopic cholecystectomy. T stage based on the laparoscopic cholecystectomy was T1 (n = 1) and T2 (n = 15). Twelve patients underwent reexploration of whom seven underwent further radical excision (gallbladder liver bed resection and extensive lymphadenectomy). After a mean follow-up of 20.1 months (range 4 to 39 months), 69% of patients have had a recurrence or died. Three patients had a port-site recurrence. Five (71%) of seven patients with bile spillage at laparoscopic cholecystectomy have had a recurrence or died of disease. A review of the Western literature on EGC initially removed by laparoscopic cholecystectomy (including the present series) yielded 21 patients with T1 and 42 patients with T2 disease. One-year Kaplan-Meier survival (T1 = 89%, T2 = 71%) and 3-year Kaplan-Meier survival (T1 = 47%, T2 = 40%) of these patients is worse than prior reports for open cholecystectomy. An initial laparoscopic cholecystectomy with its potential for bile spillage can convert potentially curable EGC to incurable disease. Patients with preoperative findings suspicious for gallbladder cancer should undergo open exploration with intent to perform a radical cancer operation as a primary procedure if the diagnosis is confirmed intraoperatively. (J GASTROINTEST SURG 2002;6:50–57.)

KEY WORDS: Laparoscopic cholecystectomy, gallbladder cancer

In 1970 Nevin et al.[1] published a sentinel review of gallbladder cancer staging and survival following open cholecystectomy. They noted 100% 5-year survival in patients with cancer confined to the gallbladder wall (early gallbladder cancer [EGC]). However, those patients with cancers involving the full thickness of the gallbladder wall or disease outside of the gallbladder had a poor prognosis. Despite improvement in oncologic surgery in the past 40 years, metastatic and advanced regional gallbladder cancer continues to be associated with a dismal prognosis. Recent reports, however, have demonstrated better survival after aggressive radical resection in selected patients with advanced disease.[2–7]

Since its introduction in 1985, laparoscopic cholecystectomy has become the preferred method of gallbladder removal for benign disease.[8] An estimated 700,000 cholecystectomies are done by this approach annually. Approximately 0.35% to 1% of removed gallbladders harbor a focus of cancer.[9–11] Many of these cases are incidentally identified postoperatively on pathologic review of the specimen. However, a significant fraction of these incidentally discovered gallbladder cancers removed laparoscopically may have findings suspicious for carcinoma on preoperative workup.[12]

In many recent series, EGC removed laparoscopically does not seem to have the excellent prognosis

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reported by Nevin et al.[1] Port-site recurrences and recurrences away from the liver bed following laparoscopic removal of T1 and T2 gallbladder cancers have been reported.[9–11] The frequency of abdominal wall recurrence following laparoscopic cholecystectomy for gallbladder cancer has ranged from 11% to 19% as compared to 3% after open cholecystectomy.[9,11,13,14] These recurrences may be secondary to bile spillage, microperforation, or incomplete gallbladder wall resection from the liver bed during the laparoscopic procedure.[15–18] An alternative source of recurrence is nodal disease not detected at laparoscopy, which included 33% of T2 patients in one large series.[7] Regardless of the cause, recurrence nearly always indicates incurable disease.

The objective of the present study was to determine what effect initial laparoscopic cholecystectomy has on recurrence and survival in patients with EGC. This assessment was undertaken in a similar manner to the original study by Nevin et al.[1] First, a retrospective analysis of patients referred to our center with gallbladder cancer following laparoscopic cholecystectomy was done. Second, a review of the Western literature of patients with gallbladder cancer who had undergone laparoscopic cholecystectomy was completed.

METHODS

The study group consists of patients presenting with gallbladder cancer after undergoing laparoscopic cholecystectomy over an 11-year period (12/89–12/00). The University of Wisconsin Cancer Registry and the University of Wisconsin billing record codes were reviewed during this time period to identify the patient population, which was then retrospectively analyzed. Patient records were evaluated for preoperative symptoms, physical examination findings, and radiologic findings. The T stage was determined for each patient from the pathology report using the American Joint Committee on Cancer Staging classification of gallbladder cancer (Table 1). Operative notes were reviewed for evidence of bile spillage during the procedure. Postoperative recurrences and survival were determined from review of records and/or contact of the patients or families by telephone.

The Western literature review was performed by searching the Medline database from 1966 to February 2001. The search was performed using the following key words: gallbladder cancer, laparoscopy, and biliary neoplasm. Only those series reporting cases where the initial procedure was a laparoscopic cholecystectomy were included. Studies were selected when case inclusion was independent of outcome (e.g., port-site recurrence studies were excluded). Only those investigations that reported the gallbladder cancer stage, follow-up time, and outcome on a case-by-case basis were included. When necessary, follow-up times were estimated from published Kaplan-Meier survival curves if censored subjects were plotted. The Kaplan-Meier estimator was used to estimate patient survival. The endpoint event was patient death. A patient was censored if he or she was alive at last follow-up, regardless of disease status. Because of inconsistent reporting of individual times of recurrence, we could not estimate disease-free survival.

RESULTS

Eighty-nine patients referred to our institution with gallbladder cancer over an 11-year period were identified. An initial laparoscopic cholecystectomy was performed in 26 patients who represent the study population (Table 2). T-stage classification included one T1, fifteen T2, eight T3, and two T4 gallbladder cancers. The 16 patients with T1 and T2 tumors were considered to have EGC. The mean follow-up for all patients with EGC was 20.1 months (range 4 to 39 months). The mean follow-up of EGC patients alive with or without disease was 17.7 months. Seventeen patients were women and nine were men. The mean age at the time of diagnosis was 63 years. Twenty-three patients had complained of right upper quadrant abdominal pain. One patient had jaundice at presentation.

Preoperative ultrasound identified a mass within the gallbladder in 6 of the 16 patients with EGC. Of these six patients, three underwent CT, which in all cases confirmed a mass within the gallbladder. One additional patient with T2 disease without prior ultrasound had a CT scan demonstrating a mass involving the gallbladder wall. Preoperative ultrasound in the 10 patients with advanced gallbladder cancer (T3 and T4) identified four patients with mass lesions and three patients with markedly thickened gallbladder walls. Three of these patients were evaluated by follow-up CT, with two scans confirming the abnormal finding identified by ultrasound and the third scan in a patient with a T3 tumor being within normal limits. One T3 patient presenting with diffuse abdominal pain underwent initial evaluation by CT, which showed a thickened gallbladder wall.

Of the 16 patients with EGC, only one case was converted from a laparoscopic cholecystectomy to an open cholecystectomy. Conversion in this patient was secondary to a tear in the gallbladder wall. Of the eight patients with T3 tumors, six cases were completed laparoscopically. One patient in this group of

Table 1. Gallbladder cancer staging

AJCCS	Nevin stage
T1—Mucosa or muscularis invasion	Stage I—Limited to mucosa
T2—Perimuscular tissue not beyond serosa	Stage II—Mucosa and muscularis
T3—Perforated serosa and/or invades liver (<2 cm of liver invasion)	Stage III—Involves all layers of the gallbladder wall
T4—Invades liver >2 cm or into adjacent organs	Stage IV—Cystic duct lymph node involved
	Stage V—Distant spread

AJCCS = American Joint Committee on Cancer Staging.

six suffered a common bile duct injury and subsequent bile leak. The remaining two T3 patients underwent conversion to an open simple cholecystectomy. Conversion to an open procedure was necessary in both patients with T4 tumors. One T4 patient was found on open exploration to have a positive lymph node for adenocarcinoma and underwent a palliative cholecystojejunostomy. The second T4 patient underwent a cholecystectomy and right hepatic lobectomy.

Eleven (46%) of 24 patients had documented bile spillage on review of the initial operative report. Two additional patients (one T2 and oneT3) had intraoperative cholangiograms performed that were a potential cause for bile spillage. Of the 16 patients with EGC, 7 (44%) of 16 patients had documented bile spillage, including the sole T1 patient. This group of seven excludes the T2 patient who underwent intraoperative cholangiography. Bile spillage occurred in three (38%) of eight T3 patients and one (50%) of two T4 patients.

Reexploration was performed in 12 of the 16 patients with EGC (see Table 2). The mean time interval to reexploration for patients with EGC was 54 days (range 17 to 310 days; median 29 days). The factor most responsible for delay was length of time between initial laparoscopic cholecystectomy and referral. Five patients had gross evidence of metastatic disease or positive nodal tissue on frozen-section analyses and were deemed unresectable. Of this group, three patients had peritoneal or omental implants, one patient had a positive celiac axis node, and one patient had a positive inferior hepatoduodenal ligament node. The remaining seven patients underwent a gallbladder liver bed resection with an extensive hepatoduodenal ligament lymphadenectomy. Five of the seven patients undergoing radical resections also had excision of their laparoscopic port sites. Three of the seven patients had no residual cancer found at the time of resection and are alive without evidence of disease at 12, 20, and 34 months, respectively. Four T2 patients did not undergo reexploration. Of this group, one patient refused reoperation (alive at 15 months), two patients were referred in 1994 and not offered reexploration (died at 27 and 34 months, respectively), and the fourth patient had an unresectable recurrence at the liver hilum and abdominal wall identified on CT scan (died at 4 months).

Reexploration was performed in six patients with T3 tumors. One of these patients underwent a combined gallbladder liver bed wedge resection and hepatoduodenal ligament lymphadenectomy. Another underwent an isolated gallbladder liver bed resection. The remaining four T3 patients had metastatic disease, resulting in exploration alone in three patients and a palliative bypass in the remaining patient.

Three patients with EGC (T1 = 1,T2 = 2) developed port-site recurrences. All three patients had bile spillage at their initial laparoscopic procedure and all three subsequently died of their disease (T1 = 27 months, T2 = 4 months, T2 = 32 months). The patient with T1 disease had no other evidence of disease, whereas both T2 patients had a recurrence at the gallbladder/liver bed. Five (71%) of the seven patients with EGC who had bile spillage at the initial laparoscopic operation have had a recurrence or died of their disease. Additionally, the T2 patient who had undergone intraoperative cholangiography developed peritoneal implants and is alive with disease at 8 months. Three of six patients with preoperative imaging demonstrating a gallbladder mass had bile spillage. Of the three patients, one died of recurrence at 4 months, one is alive with disease at 11 months, and the final patient is alive without disease at 19 months.

The Kaplan-Meier survival curve for the patients with EGC in our series is shown in Fig. 1. The lone T1 patient in our series died at 27 months. The 1-year and 3-year survival rates for T2 patients were 67% and 35%, respectively.

In the Western literature review of patients undergoing laparoscopic cholecystectomy with postoperative findings of gallbladder cancer, only six reports met the criteria outlined in the Methods section.[5,10, 19–22] The information from these investigations were combined with the results of the present study to estimate survival rates following laparoscopic cholecystectomy for patients with T1 and T2 stage gallbladder cancer. Twenty-one patients had T1 tumors and 42 patients had T2 tumors. The Kaplan-Meier sur-

Table 2. Clinicopathologica findings in 26 patients with gallbladder cancer treated by laparoscopic cholecystectomy

Patient	Age (yr)	Sex	Preoperative imaging	Bile spillage	Primary tumor	Reexploration (days)	Outcomes (mo)
1	66	F	—	Yes	T1	N0M1 (22)	DEAD (27)
2	29	M	Mass	No	T2	N0M0 (17)	A&W (12)
3	63	M	Stone	Yes	T2	N1M1 (42)	DEAD (31)
4	80	M	—	Yes	T2	N1M0 (24)	DEAD (12)
5	57	F	Mass	Yes	T2	N0M0 (21)	A&W (20)
6	63	F	Mass	Yes	T2	—	DEAD (4)
7	54	F	—	No	T2	N0M1 (310)	DEAD (30)
8	42	F	Polyp	Yes	T2	N1M0 (32)	A&D (11)
9	68	F	—	No	T2	—	DEAD (39)
10	70	M	Stone	No	T2	N1M0 (31)	DEAD (8)
11	75	F	Mass	No	T2	N1M0 (17)	A&W (26)
12	53	F	Stone	No	T2	M1 (54)	DEAD (20)
13	66	F	Stone	Yes	T2	N0M0 (27)	A&W (33)
14	71	F	Stone	No	T2	—	DEAD (27)
15	56	M	Mass	No	T2	—	A&W (14)
16	57	M	Mass	IOC	T2	M1 (47)	A&D (8)
17	71	M	Stone	Yes	T3	—	DEAD (3)
18	88	F	Mass	No	T3	—	DEAD (1)
19	77	F	Stone	No	T3	LB N1M0 (24)	DEAD (18)
20	66	F	TW	Yes	T3	LB M1 (38)	DEAD (3)
21	68	M	Mass	No	T3	LB N0M0 (34)	DEAD (24)
22	71	M	Mass	Yes	T3	—	DEAD (74)
23	62	F	Mass	No	T3	N1M0 (37)	A&D (3)
24	65	F	TW	IOC	T3	N1M0 (19)	DEAD (6)
25	70	F	Stone	Yes	T4	—	DEAD (6)
26	50	F	TW	No	T4	—	DEAD (6)

A&W = alive and well without known disease; A&D = alive with known disease; TW = thickened gallbladder wall; LB = liver bed recurrence; N = nodal disease (0 = none, 1 = positive); M = metastatic disease (0 = none, 1 = disease advanced beyond local-regional, i.e., port-site implants or peritoneal implants); IOC = intraoperative cholangiogram.

vival curves are shown in Fig. 2. One-year and 3-year survival rates for T1 patients were 89% and 47%, respectively. One-year and 3-year survival rates for T2 patients were 71% and 40%, respectively.

DISCUSSION

The most notable finding of our study was the high frequency of recurrence and compromised survival in patients with EGCs who had undergone initial laparoscopic cholecystectomy. The 89% 1-year and 47% 3-year survival rates of patients with T1 tumors is considerably less than the 100% 5-year survival rates for stage I and stage II gallbladder cancers removed by open cholecystectomy reported by Nevin et al.[1] and for T1 gallbladder cancers removed by open cholecystectomy reported by Shirai et al.[2] Likewise, the 71% 1-year and 40% 3-year survival rates for patients with T2 tumors does not compare favorably with the estimated 57% 3-year survival rate following open cholecystectomy reported by Shirai et al.[2]

A close review of the study and classification system of Nevin et al.[1] is required to appropriately compare their survival results to current studies, which use the TNM staging system. Nevin's series included 66 patients from their institution and 399 patients identified in a literature search prior to 1975. Nevin stage I and II tumors involve the mucosa and muscularis, respectively. Their series included 18 stage I and 39 stage II gallbladder cancers with 5-year survival rates for both groups of 100%. In contrast, only 8 of 114 stage III patients survived 5 years. Nevin et al.[1] described stage III tumors as those involving all three layers of the gallbladder wall. Therefore many of these tumors likely penetrate through the gallbladder serosa and may be potentially invading other structures. The remaining patients with Nevin stage IV and V gallbladder cancers (lymph node involvement or metastatic disease) rarely survived more than 1 year.

It is difficult to make a direct comparison between the Nevin and TNM staging systems. The TNM clas-

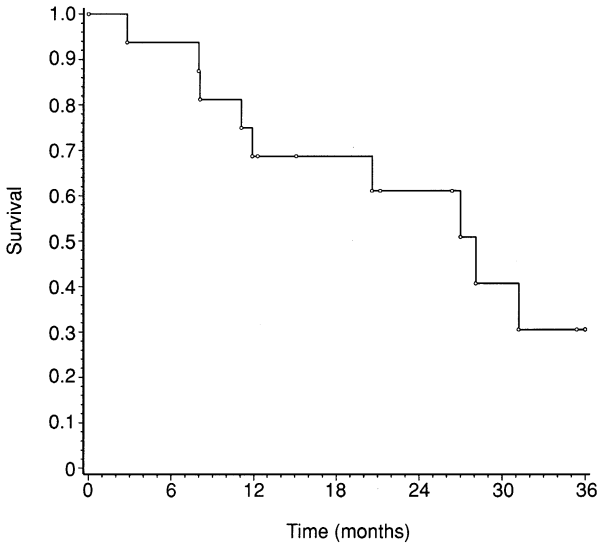

Fig. 1. Kaplan-Meier survival curve for EGC patients withT1 and T2 tumors referred to the University of Wisconsin Hospital following laparoscopic cholecystectomy.

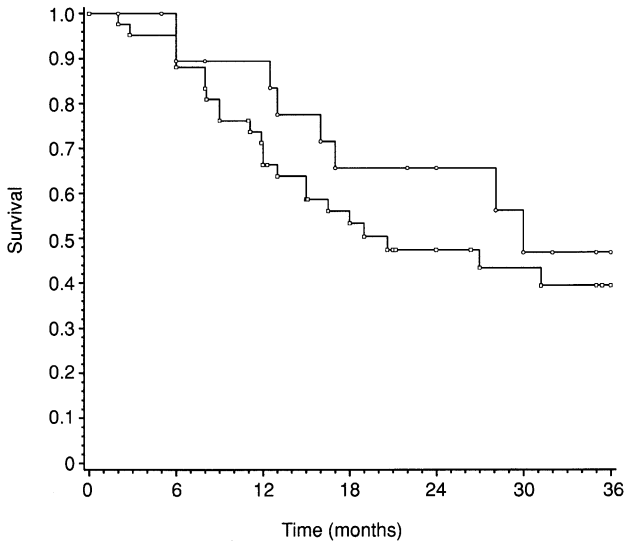

Fig. 2. Kaplan-Meier survival curves for EGC patients with T1 (■) and T2 (○) tumors following laparoscopic cholecystectomy from a combined University of Wisconsin Hospital series and a review of the Western literature.

sification describes T1 tumors as those limited to the muscularis, which correlates with Nevin stage I and II tumors. T2 tumors invade the perimuscular connective tissue but do not go beyond the serosa. These tumors are limited to the gallbladder wall and cannot be compared directly to Nevin stage III tumors, some of which may penetrate the gallbladder serosa.

The 100% 5-year survival rate seen in patients with Nevin stage I and II gallbladder cancer has been achieved in more recent small series of open cholecystectomies in patients with T1 tumors.[2,23] These survival results for T1 tumors have never been equaled in series of significant size where patients initially underwent laparoscopic cholecystectomy. A comparison of survival of patients with laparoscopically excised gallbladder carcinomas, relative to open removal, has been difficult to evaluate because of the common practice of proceeding with subsequent radical resections.[3–7] Shirai et al.[2] reported a 57% 3-year and 40% 5-year survival in T2 patients undergoing a simple open cholecystectomy alone as compared with a 90% 5-year survival in T2 patients undergoing subsequent radical resections. Our series and review found a 40% 3-year survival in T2 patients undergoing initial laparoscopic cholecystectomy, with several patients undergoing further radical resection.

The advent of laparoscopy has markedly altered the field of biliary surgery. This less invasive method for excision of the gallbladder has resulted in an increase in the number of gallbladders removed annually in the United States.[24] The increased number of cholecystectomies has resulted in a larger number of patients in whom EGC is incidentally diagnosed. A possible disadvantage of the laparoscopic approach is the conversion of curable to incurable disease.

Bile spillage is a potential cause of conversion to disseminated disease. Spilled bile from a gallbladder containing cancer cells can contaminate both the intraperitoneal space and the abdominal wall trocar sites. It has been estimated that bile spillage during routine laparoscopic cholecystectomy occurs in 26% to 36% of cases.[25–27] However, the frequency of bile spillage is probably higher in patients with gallbladder cancer. The rate of bile spillage in the present series and a series of gallbladder cancer patients reported by Suzuki et al.[28] is 46% and 50%, respectively.

Bile spillage in patients with EGC almost certainly has an impact on survival. Multiple series and case reports have identified patients with EGC and bile spillage during laparoscopic cholecystectomy who have had unexpected recurrences at trocar sites or in the intraperitoneal space.[9–11] In most cases these recurrences resulted in unresectable disease and compromised survival. Seventy-one percent of the EGC patients with bile spillage in our series have either died or had a recurrence.

Factors other than overt bile spillage may potentially compromise outcome when EGC is treated by laparoscopic cholecystectomy. Microperforation consists of inapparent perforations of the gallbladder wall during laparoscopic manipulation, thus resulting in release of cells from the gallbladder wall and mucosa into the peritoneal cavity.[15,16] Intraoperative cholangiography may contaminate the abdominal cavity by leaking bile

and mucosal cells during the procedure. Pneumoperitonuem may contribute to circulation of these cells throughout the abdomen as has been demonstrated in an animal model of colon cancer.[29,30] A similar animal model has demonstrated increased implantation of gallbladder cancer cells in trocar sites.[31]

The laparoscopic technique hinders the surgeon's sense of touch for both identifying a gallbladder cancer and for determining a safe margin of resection. When a tumor penetrates into the muscularis propria, it is unlikely that an appropriate margin would be obtained following laparoscopic removal. The present series includes multiple patients with positive margins at the resection surface following laparoscopic cholecystectomy. This compromise in oncologic principles can result in local recurrence and/or dissemination of tumor cells.

To manage EGC optimally by open resection, it must be suspected on preoperative imaging studies or during laparoscopic exploration. In the present series, 38% of patients with EGCs had findings suspicious for cancer on preoperative ultrasound. Ultrasonography and CT are both quite sensitive for identifying asymmetric gallbladder wall thickening, mass lesions, and liver infiltration, all of which are suspicious for gallbladder cancer.[32–34] When gallbladder polyps are larger than 10 mm in diameter, cancer should be suspected.[35,36] The finding of a porcelain gallbladder has a strong association with gallbladder cancer.[37,38] Laparoscopic findings consistent with gallbladder cancer include white plaques on the gallbladder wall (present in one third of gallbladder cancers) and identification of metastases in the liver and implants on the peritoneum.[39] Any of these preoperative or intraoperative findings may alert the surgeon to potential gallbladder neoplasm and alter the surgical approach.

This study, like several other reported retrospective gallbladder cancer series, has several shortcomings. First, gallbladder cancer is a relatively rare neoplasm resulting in small study populations. Second, the present series has only one T1 patient. This is most likely the result of a lack of referral of such patients who many physicians believe are adequately treated by cholecystectomy alone. The Western literature review was limited by the relative lack of papers that report specific stage and survival on a per patient basis. Finally, laparoscopic cholecystectomy may understage patients with gallbladder carcinoma because lymph nodes are not generally removed.

CONCLUSION

Laparoscopic cholecystectomy with its risks for bile spillage, microperforation, and incomplete tumor resection may convert potentially curable EGC to incurable disease. The patients most likely to benefit from a nonlaparoscopic approach are those with preoperative findings suspicious for gallbladder cancer. These patients should undergo open exploration with the intent to perform an extensive cancer operation if the diagnosis is confirmed intraoperatively. These patients should be referred to a tertiary center if the primary surgeon is not prepared to perform an extensive cancer operation at the time of initial exploration. Those patients referred following intentional or incidental laparoscopic gallbladder cancer removal should undergo reexploration and a more extensive resection of the gallbladder liver bed and port sites, as well as hepatoduodenal ligament and celiac axis lymphadenectomy in the absence of disseminated disease.

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Discussion

Dr. Weiland: If I can answer your second question first, clearly, if you examine earlier series of open gallbladder cancers, the preoperative assessment radiologically was usually in the magnitude of about 10%, but with the maturation of both CT scanning and ultrasound imaging, it has been found that preoperative gallbladder cancers are diagnosed more at the rate of 75% to 80%. So I think that those numbers are reasonable and will continue to improve as technology continues to advance.

In regard to your first comment, we would agree. Dr. Fong and his colleagues did show in their series presented in *Annals of Surgery* (2001;232:557–569) that 32% of patients who have T2 tumors, which we perceive as disease confined to the gallbladder, have nodal disease as positive, and, as such, other series have reported figures as high as 40%. So we would agree that there is another reason why these patients need to undergo an open procedure to help clear disease, particularly since laparoscopic procedures seldom get any nodes with the specimen taken.

Dr. L.W. Way (San Francisco, Calif.): What was the lymph node status in your patients?

Dr. Weiland: In our series of patients with T1 and T2

disease, none of the patients had positive nodes taken in their initial specimens. When we looked at their pathology reports, there was no nodal tissue reported.

Dr. D.T. Dempsey. (Philadelphia, Pa.): I think maybe what Dr. Way was asking is when you did the radical resection in those seven or eight patients, how many of those patients turned out to have positive nodes?

A second question would be in your patients who underwent reoperation, how much of the disseminated disease do you think was there the first time and missed by the operating surgeon, for instance, a small liver nodule high up that might not have been detected the first time around?

Dr. Weiland: In regard to a combination of the two questions, but specifically the second question, I think that is one of the main reasons why these patients should not be approached laparoscopically, because the chance of missing disease is significant. Clearly, referring to the nodal disease that we discussed earlier, several of these patients, at least one third with T2 tumors, are going to have disease outside of the gallbladder. When assessing patients with findings of tumor on ultrasound, it is impossible to stage them and know whether it is going to be a T1 or a T2 tumor. In those patients, I think the best way to manage them is with early exploratory surgery, opening the gallbladder on the back table, and identifying what type of disease is present.

American Hepato-Pancreato-Biliary Association: Who Are We and Where Are We Going?

Henry A. Pitt, M.D.

The American Hepato-Pancreato-Biliary Association (AHPBA) was initiated in 1994 following the first World Congress of the International Hepato-Pancreato-Biliary Association (IHPBA), which was held in Boston. Presently, the AHPBA has more than 500 dues-paying members whose median age is in the mid-40s. More than 90% of members reside in North America. Approximately 80% of members have completed a fellowship in transplantation, hepato-pancreato-biliary surgery and/or research, surgical oncology, gastroenterology, or laparoscopy. Approximately 90% have a faculty appointment with 80% of these being full-time faculty. More than half of the average AHPBA member's time is spent in patient care, but approximately 45% of time is divided equally among research, teaching, and administration. Approximately 85% of members perform biliary, 75% hepatic, and 45% pancreatic surgery, whereas 25% perform liver and pancreatic transplantation. Nearly 90% are members of the American College of Surgeons, two thirds The Society for Surgery of the Alimentary Tract, 60% the Association for Academic Surgery, and 40% the IHPBA. The AHPBA's vision is to be the leading American association devoted to hepato-pancreato-biliary education, research, surgical training, and patient care and to serve as the American chapter of the IHPBA. The AHPBA mission is as follows: (1) to disseminate knowledge of hepato-pancreato-biliary disease, techniques, and research; (2) to facilitate clinical trials in hepato-pancreato-biliary disease; (3) to coordinate advanced training in hepato-pancreato-biliary surgery; and (4) to foster excellence in the care of patients with hepato-pancreato-biliary disease. The AHPBA has strategic initiatives to increase membership, bring value to a journal affiliation, and enhance its education, research, and training missions through multiple collaborations and better communication. (J GASTROINTEST SURG 2002;6:58–65.)

KEY WORDS: Liver, pancreas, biliary tract

The American Hepato-Pancreato-Biliary Association (AHPBA) was founded in the fall of 1994. The origins of the AHPBA came from the International Biliary Association (IBA), which later became the International Hepato-Biliary-Pancreatic Association (IHBPA), and the World Association of Hepato-Pancreato-Biliary Surgery (WAHPBS). The IHBPA and the WAHPBS merged into the International Hepato-Pancreato-Biliary Association (IHPBA), which met for the first time in June 1994 in Boston. At the same time, William C. Meyers, M.D., was organizing a group of surgeons in the United States with an interest in hepatobiliary and pancreatic surgery.

An organizational meeting was held in Chicago in October 1994 to work on a constitution and bylaws for the AHPBA, which were based on those of the newly organized IHPBA. A month later the first meeting of the AHPBA was held in Chicago at the same time as the American Association for the Study of Liver diseases (AASLD). J. Michael Henderson, M.D. became the first president, William C. Meyers, M.D. was the president-elect, Henry A. Pitt, M.D. was the secretary, and Mark S. Roh, M.D. was the treasurer of the newly formed AHPBA. Over the next 6 years, a closer relationship was developed between the AASLD and the AHPBA. Since 1995, a cosponsored AASLD/AHPBA Hepatobiliary Surgery Forum has been presented. This postgraduate course is designed to attract more surgeons to the liver meetings that are held each fall and has been a primary educational program of the AHPBA.

As the American chapter of the IHPBA, the AHPBA took on the responsibility of conducting a regional Americas Congress in 1997. The IHPBA holds World Congresses in the even-numbered years. The Asian Society of Hepato-Biliary-Pancreatic Surgery (ASHBPS) began holding regional meetings in Asia in the odd years in 1991. The Euro-

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pean chapter of the IHPBA began holding European Congresses in the odd years in 1995. The first Americas Congress was held in Miami, Florida, and the tradition of holding this meeting in south Florida was continued in 1999 and 2001. Goals set for the AHPBA in 1999 by the incoming president, Henry A. Pitt, M.D., were as follows: (1) to have at least 500 dues-paying members; (2) to establish a journal affiliation; (3) to develop, with industry support, a research fellowship; (4) to facilitate clinical trials developed by the American College of Surgeons Oncology Group (ACOSOG); (5) to continue to discuss advanced training fellowships, which were the topic of William C. Meyer's Presidential Address; and (6) to go through a strategic planning process based on data from a membership survey.

MEMBERSHIP SURVEY

In October 1999 the Executive Committee, many of whom were new, met in San Francisco for an initial strategic planning meeting. The history of the AHPBA to that point was reviewed, options with respect to future meeting management were discussed, strategies to achieve the stated goals were developed, initial drafts of the vision and mission statements were created, and a decision was made to develop and distribute an AHPBA Membership Survey. This survey gathered information about (1) the members, (2) their participation in and satisfaction with the APHPA, (3) their association with other societies, (4) their opinions about surgical journals, and (5) their priorities with respect to education, research, training, and relationships with other societies. Surveys were mailed in July and October 2000 and distributed at the Hepatobiliary Surgery Forum in November. A total of 116 responses were received.

MEMBERS' PROFILE

The demographics of the AHPBA members responding to the survey are presented in Table 1. The median age of AHPBA members is the mid-40s, and nearly 70% of members are under 50 years of age. Ninety-eight percent of survey respondents were men and only 2% were women. Eighty-five percent of AHPBA members reside in the United States, and the regional distribution mimics the general population. Ninety-eight percent of the survey respondents had an M.D. degree, whereas 10% also had a Ph.D. or another advanced degree. Approximately one third of AHPBA members completed their residency training within 10 years, 10 to 20 years, or more than 20 years previously.

Table 1. AHPBA membership profile

	% of Members
Age	
30s	23
40s	46
50s	19
60s	12
Sex	
Male	98
Female	2
Country/Continent	
United States	85
Canada	6
South America	6
Central America	2
United States Region	
Northeast	36
Midwest	25
Southwest	22
West	17
Degrees	
M.D.	98
Ph.D.	10
Other	10
Completed Residency	
1–10 yr ago	35
11–20 yr ago	37
>20 yr ago	28

Interestingly, nearly 80% of AHPBA members did fellowship training beyond residency. The most common fellowships were transplantation (34%), hepato-pancreato-biliary surgery (13%), surgical oncology (8%), or gastroenterology (8%) (Fig. 1, *A*). An additional 4% of respondents had done laparoscopy and 3% had done endoscopy fellowships. Ninety percent of AHPBA members hold a medical school faculty appointment with 73% having a full-time academic commitment (Fig. 1, *B*). The average time spent in clinical, administrative, research, and teaching responsibilities was 53%, 17%, 16%, and 14%, respectively (Fig. 1, *C*). Eighty-five percent of AHPBA members perform biliary, 76% hepatic, 43% pancreatic, and 25% liver and/or pancreatic transplant surgery (Fig. 1, *D*).

MEMBERS' SOCIETIES

At the time the membership survey was administered, the AHPBA was only 6 years old. Forty-nine percent of the respondents had been AHPBA members for more than 5 years, whereas 21% had been members for 3 to 4 years, and 30% had been members for only 1 to 2 years. As a result, in the previous

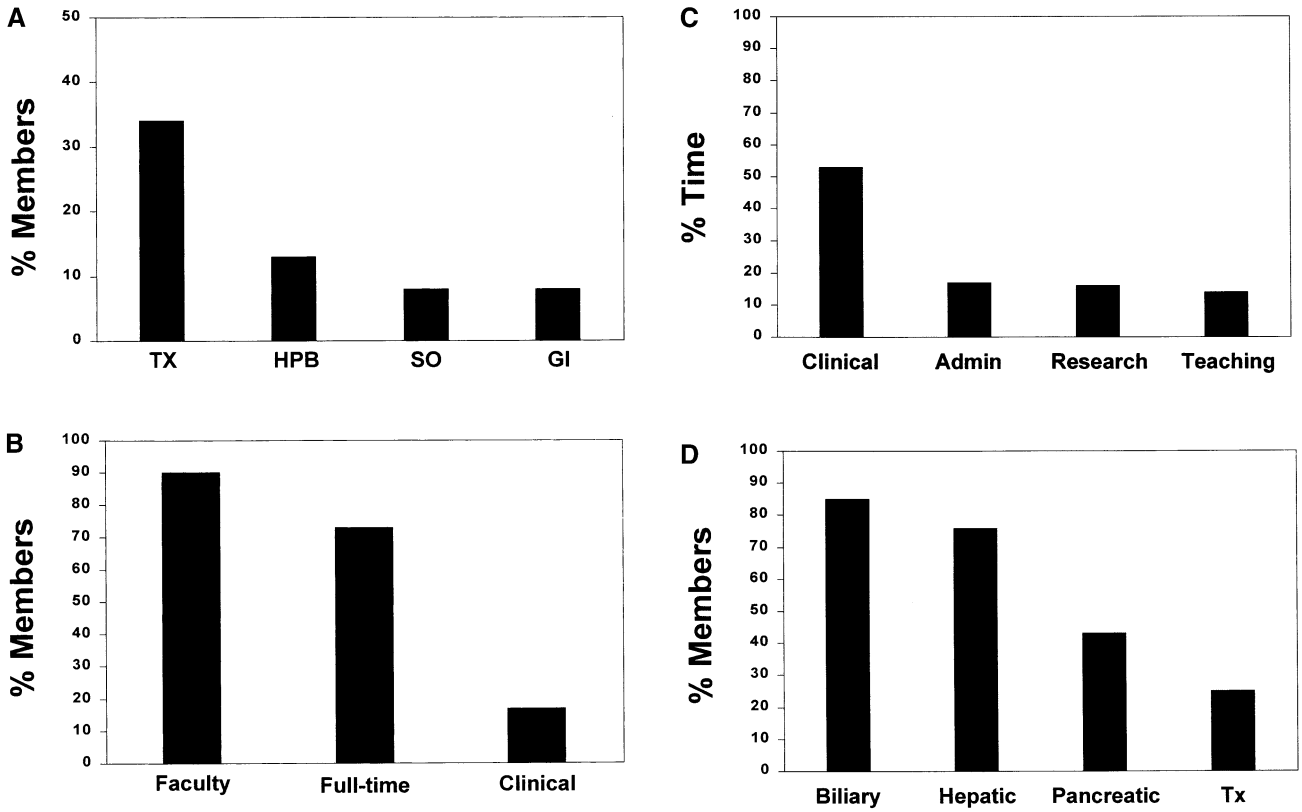

Fig. 1. A, Percentage of AHPBA members completing a transplant (Tx), hepato-pancreato-biliary (HPB) surgery, surgical oncology (SO), or gastroenterology (GI) fellowship. **B**, Percentage of AHPBA members with a faculty appointment, either full-time or clinical. **C**, Percentage of time spent by AHPBA members in clinical, administrative (Admin), research, or teaching activities. **D**, Percentage of AHPBA members doing biliary, hepatic, pancreatic, or liver/pancreas transplant (Tx) surgery.

5 years 35% of respondents had not attended an AHPBA educational program. When asked why they had not been able to attend, the most frequent responses were schedule conflicts (53%) and budget concerns (32%) as opposed to content (7%) or location (5%). Forty-five percent had attended a Hepatobiliary Surgery Forum or Americas Congress once or twice, and 20% had attended three to five of these events. When asked why they had joined the AHPBA, survey respondents rated on a scale of 1 (very important) to 5 (very unimportant) the most important reasons as networking (2.0), committee opportunities (2.1), participation (2.3), and professional recognition (2.3). Less important reasons were policy information (2.5), career development (2.6), the AASLD meeting (2.7), and fellowship opportunities (3.1).

AHPBA members also were asked what other society memberships they held (Table 2). Nearly 90% of AHPBA members are also fellows in the American College of Surgeons (ACS). Two thirds are members of The Society for Surgery of the Alimentary Tract (SSAT). Fifty-seven percent are members of the Association for Academic Surgery (AAS), whereas 42% are also members of the International Hepato-Pancreato-Biliary Association. Approximately one third are members of the Society of American Gastrointestinal Endoscopists (SAGES), the Society of University Surgeons (SUS), or the American Association for the Study of Liver Diseases. About one quarter of AHPBA members are also members of the Society of Transplant Surgeons (STS) or the International Liver Transplant Society (ILTS).

When asked which societies did the "best job" in several areas, the ACS and the SSAT received the highest marks. The ACS was rated highest for advocacy, education and training, teaching, recognition, defining purpose, their journal, and their website. The SSAT was most appreciated for networking and publishing opportunities as well as knowledge exchange.

MEMBERS' SERVICES

Members were asked to rate AHPBA services on a scale of 1 (very important) to 5 (very unimportant). The services receiving the highest ratings were the Americas Congresses (2.0), the Hepatobiliary Sur-

Table 2. AHPBA members' societies

Society	% Members
American College of Surgeons (ACS)	89
The Society for Surgery of the Alimentary Tract (SSAT)	66
Association for Academic Surgery (AAS)	57
International Hepato-Pancreato-Biliary Association (IHPBA)	42
Society of American Gastrointestinal Endoscopists (SAGES)	37
Society of University Surgeons (SUS)	36
American Association for the Study of Liver Diseases (AASLD)	34
Society of Transplant Surgeons (STS)	26
American Gastroenterological Association (AGA)	25
International Society for Digestive Surgery (ISDS)	25
International Liver Transplant Society (ILTS)	23
Pancreas Club, Inc.	20
American Society of Gastrointestinal Endoscopy (ASGE)	17
Society of Surgical Oncology (SSO)	14
American Pancreatic Association (APA)	14
American College of Gastroenterology (ACG)	9

Table 3. AHPBA members' journals

Journal	% Members
Annals of Surgery	76
Journal of the American College of Surgeons	73
American Journal of Surgery	66
Archives of Surgery	60
Surgery	55
Journal of Gastrointestinal Surgery	49
Hepatology	37
Gastroenterology	31
HPB	29
Transplantation	27
Digestive Diseases and Sciences	13
American Journal of Gastroenterology	10
Digestive Surgery	9
GUT	8

gery Forum (2.1), and the AASLD meeting (2.2). Relatively lower on the list were the newsletter (2.5), the research fellowship (2.7), and the website (2.8). When asked about their overall satisfaction with the AHPBA, 77% were very satisfied or satisfied. Members were also asked whether the AHPBA should have its own journal, and a majority (61%) said yes. However, when asked whether the AHPBA should affiliate with an existing journal, 93% of respondents agreed with this approach. When queried as to which journal they would prefer, 57% responded the JOURNAL OF GASTROINTESTINAL SURGERY, the official journal of the SSAT, and 34% responded *HPB*, the official journal of the IHPBA. Only 11% preferred *Liver Transplantation and Surgery*, an official journal of the AASLD and the ILTS.

AHPBA members were also asked which journals they read routinely (Table 3). Approximately three quarters responded that they read *Annals of Surgery* and the *Journal of the American College of Surgeons*, whereas two thirds read the *American Journal of Surgery*. Fifty to sixty percent also routinely read *Archives of Surgery*, *Surgery*, and the JOURNAL OF GASTROINTESTINAL SURGERY. Only 25% to 30% routinely read *HPB* or *Transplantation*. However, when asked which journal they found "most valuable," 35% responded *Annals of Surgery* and 18% chose the JOURNAL OF GASTROINTESTINAL SURGERY. Other journals receiving votes for "most valuable" were *Transplantation* (12%), the *Journal of the American College of Surgeons* (11%), *Hepatology* (9%), the *American Journal of Surgery* (8%), *Surgery* (5%), and *Archives of Surgery* (5%).

AHPBA MISSIONS

A primary mission of the AHPBA is education. To date, the major venues for this mission have been the Hepatobiliary Surgery Forum and the Americas Congresses. AHPBA members who had attended the Hepatobiliary Surgery Forum were asked to rate the programs on a scale of 1 (very valuable) to 5 (not valuable). The programs receiving the highest ratings were hepato-pancreato-biliary techniques (1.7), treatments (1.8), debates (1.9), and the interactive case management sessions (2.0). Basic science presentations were somewhat less well received (2.5). Similarly, the aspects of the Americas Congresses that were rated the highest were the keynote and update lectures (1.7), the plenary free papers (1.7), the other free papers (1.9), the symposia (2.0), and the film festivals (2.2). The live teleconferences (2.5) and the posters (2.5) were less well received.

Members were also asked whether the AHPBA should be involved in research and training. Eighty-six percent of survey respondents thought that a primary mission for the AHPBA should be research, whereas 70% also responded that training was an appropriate mission. Members were asked to prioritize AHPBA research activities (Fig. 2, *A*). On a scale of 1 (high priority) to 5 (low priority), the conduct of ACOSOG and AHPBA clinical trials was rated the highest (1.8). Establishment of liver surgery and pan-

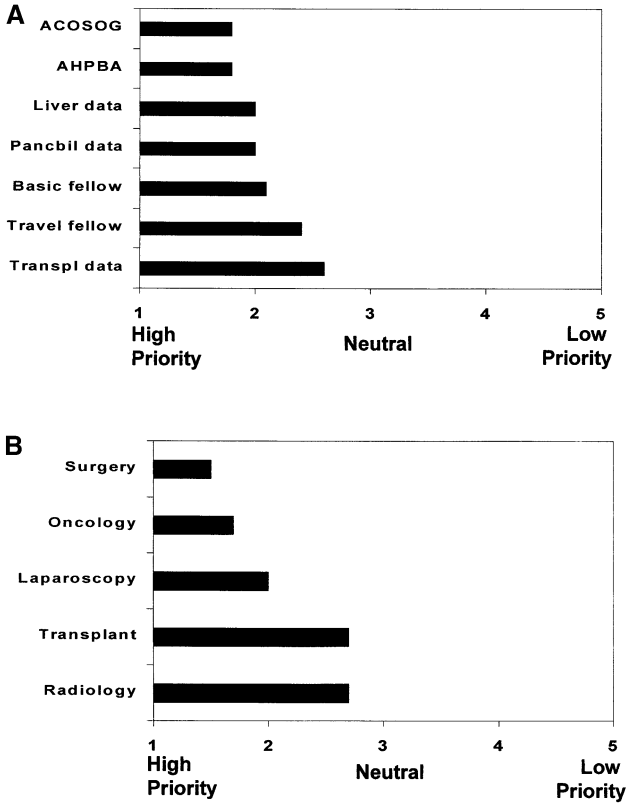

Fig. 2. A, Mean priority of AHPBA members with respect to research. ACOSOG = American College of Surgeons Oncology Group; Pancbil = pancreatobiliary; fellow = fellowship; Transpl = transplant. **B**, Mean priority of AHPBA members with respect to fellowship training activities.

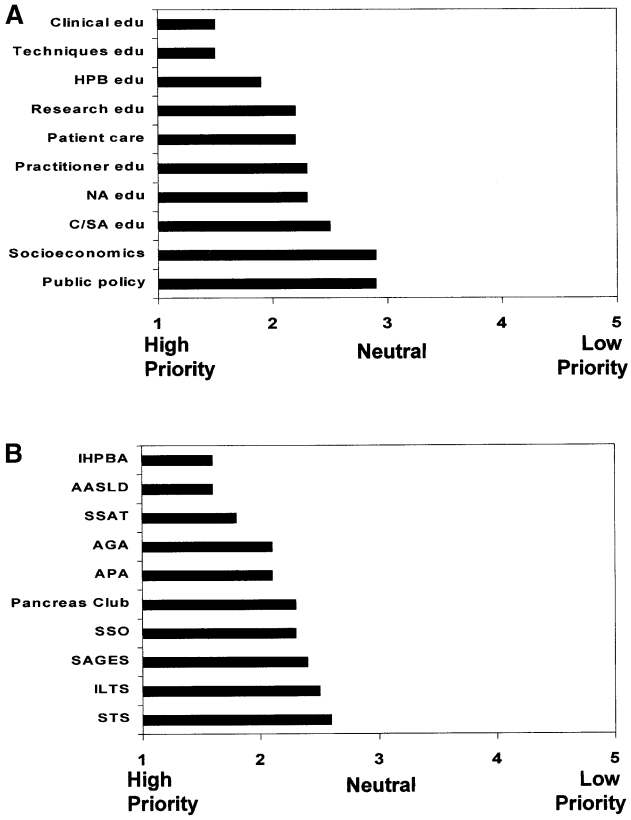

Fig. 3. A, Mean priority of AHPBA members with respect to various educational *(edu)*, socioeconomic, and public policy issues. HBP = hepato-pancreato-biliary; NA = North American; C/SA = Central/South American. **B**, Mean priority of AHPBA members with respect to relationship with other societies (see Table 2 for full names).

creatobiliary databases was rated 2.0, and the basic science research fellowship received a priority of 2.1. Members were also asked to prioritize AHPBA training activities (Fig. 2, *B*). Hepato-pancreato-biliary surgery (1.5), oncology (1.9), and laparoscopy (2.0) received the highest priority. Not surprisingly, establishment of transplant databases and transplant fellowships were not rated as high priorities for the AHPBA.

AHPBA PRIORITIES

Members were further asked to prioritize various educational options as well as patient care, socioeconomic, and public policy issues (Fig. 3, *A*). Again, on a scale of 1 (high priority) to 5 (low priority), clinical and techniques education received the highest priority (1.5). Education of hepato-pancreato-biliary fellows and specialists (1.9) received a higher priority than education of practitioners (2.3). Research education (2.2) and patient care (2.2) also were thought to be high priorities. Interestingly, education of North Americans (2.3) received a slightly higher priority than education of Central or South Americans (2.5). AHPBA members were neutral on both socioeconomic (2.9) and public policy (2.9) issues.

AHPBA members were also asked to prioritize the relationship to other societies (Fig. 3, *B*). The same scale of 1 (high priority) to 5 (low priority) was used for this question. The two societies receiving the highest priority (1.6) were the International Hepato-Pancreato-Biliary Association and the American Association for the Study of Liver Disease. The Society for Surgery of the Alimentary Tract also received a very high rating (1.8). Interestingly, the American Gastroenterological Association, with whom the AHPBA has had minimal contact, as well as the American Pancreatic Association (APA), also received relatively high priorities (2.1). Finally, when asked to prioritize membership development, 52% of respondents thought that hepato-pancreato-biliary surgeons and trainees should be the top priority. Thirty percent responded that gastroenterologists, hepatologists, oncologists, and radiologists should be recruited. Only

18% thought that the AHPBA should broaden its focus to include more practicing general surgeons.

AHPBA FUTURE

During the 20 months between the 1999 Americas Congress and a second strategic planning meeting in November 2000, a number of the stated goals had been accomplished. First, the goal of having 500 dues-paying members had been achieved largely through the work of C. Wright Pinson, M.D., Treasurer; Keith D. Lillemoe, M.D., Secretary; and Charles J. Yeo, M.D., Membership Committee Chairman. Second, a decision had been made to work with the SSAT to establish an affiliation with the *Journal of Gastrointestinal Surgery*. Third, a generous gift had been received from Ethicon to establish the Ethicon/AHPBA Research Fellowship, and the first award of $25,000 had been given by W. Scott Helton, M.D., and the Research and Education Committee to Taylor Sohn, M.D., of Johns Hopkins for her research on pancreatic cancer. Fourth, members of the AHPBA, including Drs. Yuman Fong, Steven Strasberg, John Cameron, Charles Yeo, and Howard Reber have played a large role in the development of hepatobiliary and pancreatic protocols for the ACOSOG. Fifth, an intersociety committee from the SSAT, SAGES, and the AHPBA has been formed to discuss fellowship training in gastrointestinal, hepato-pancreato-biliary, and laparoendoscopic surgery. With accomplishment of these goals and preliminary results of the membership survey available, the Executive Council at its second strategic planning meeting further defined the vision and mission statements and developed 10 strategic initiatives.

Table 4. AHPBA vision and mission

VISION

- The AHPBA will be the leading American association devoted to hepato-pancreato-biliary education, research, surgical training, and patient care
- The AHPBA will serve as the American chapter of the International Hepato-Pancreato-Biliary Association

MISSION

- EDUCATION: To disseminate knowledge of hepato-pancreato-biliary disease, techniques, and research through the annual Hepatobiliary Surgery Forum, the biennial Americas and World Congresses, and publication in an affiliated journal
- RESEARCH: To facilitate clinical trials in hepato-pancreato-biliary disease organized by the American College of Surgeons oncology group, the AHPBA, and industry as well as a basic research fellowship
- TRAINING: To coordinate advanced training in hepato-pancreato-biliary surgery
- PATIENT CARE: To foster excellence in the care of patients with hepato-pancreato-biliary disease

VISION AND MISSION

The vision and mission statements developed by the Executive Council are presented in Table 4. Some might have questioned in 1994 whether a new American society devoted to hepato-pancreato-biliary education, research, surgical training, and patient care was necessary. Nevertheless, the AHPBA had evolved into a group of more than 500 relatively young, American, fellowship-trained faculty who are primarily clinicians but are also involved in teaching, research, and administration. In 2001 the AHPBA clearly does have a niche that is not fulfilled by any other American association. In addition, the unique position as the American chapter of the IHPBA gives the AHPBA the opportunity to play a significant role worldwide in hepato-pancreato-biliary education, research, surgical training, and patient care.

The primary mission of the AHPBA remains education. The annual AASLD/AHPBA Hepatobiliary Surgery Forum and the biennial Americas and World Congresses provide two opportunities each year for postgraduate education for AHPBA members and other physicians with similar interests. The opportunity to publish papers presented at these venues in an affiliated journal is likely to improve the quality of the programs and expand the educational mission. The APHBA also has adopted research as a primary mission. The research infrastructure with respect to funding, data management, and quality control developed by the American College of Surgeons Oncology Group provides a unique opportunity for the AHPBA to facilitate hepatobiliary and pancreatic protocols. As new technologies evolve, the AHPBA will be positioned to develop its own protocols and to partner with industry in clinical research. Support of a basic research fellowship further enhances the research mission of the AHPBA .

At this time advanced training in hepatobiliary and pancreatic surgery is neither organized nor overseen by the Accreditation Council for Graduate Medical Education (ACGME). In conjunction with other societies interested in advanced training in gastrointestinal surgery, the SSAT, and SAGES, the AHPBA will take on a third mission to coordinate advanced training in hepato-pancreato-biliary surgery. Finally, through improved education, research, and training, the AHPBA will strengthen its fourth mission to foster excellence in the care of patients with hepatobiliary and pancreatic disease.

Table 5. AHPBA strategic initiatives

Initiative	Plan
Membership	Increase membership
	Trainees and women
	Americas Committee
Journal affiliation	*Journal of Gastrointestinal Surgery*
	Agreement with SSAT
	One issue per year
Hepatobiliary Surgery Forum	Partner with AASLD
	Continue annual course
Americas Congresses	Postgraduate course with industry
	Improve quality, increase attendance
	Biennial odd years
World Congresses	Support IHPBA
	Host 2004 and 2010 Congresses
	Biennial even years
Research fellowship	Partnership with Ethicon
	One fellow per year
Clinical trials	ACOSOG, AHPBA
	Partnership with industry
Clinical fellowships	Partnership with SSAT and SAGES
Collaboration	IHPBA, AASLD, SSAT, SAGES
	Ethicon Research Fellowship
	ACOSOG clinical trails
	Corporate council
Communication	Biannual newsletter
	Web page, directory
	List serve, e-mail

STRATEGIC INITIATIVES

The 10 strategic initiatives developed by the Executive Council are presented in Table 5. These initiatives are extensions of the previously stated goals and steps to accomplish the AHPBA's mission. To achieve its vision as a leading American association, the AHPBA must further increase its membership. Strategies to accomplish this initiative include recruitment of all trainees and women working in the field. In addition, Steven M. Strasberg, M.D., the incoming president of AHPBA, intends to create an Americas Committee. This committee will work as a subcommittee of the membership comittee and have representatives from North, Central, and South America with a goal to increase membership from outside of the United States.

The next four initiatives are all related to the educational mission. Negotiations have been completed with the SSAT with respect to a 3-year agreement regarding the *Journal of Gastrointestinal Surgery*. This arrangement brings new subscribers to the journal and an increased flow of manuscripts while providing AHPBA members with an additional opportunity to publish. The AHPBA will be responsible for one issue per year from papers presented at their meetings. The Hepatobiliary Surgery Forum in conjunction with the AASLD will be continued as an annual event during the liver meetings held in the fall. The addition of a postgraduate course on ablative techniques in liver surgery organized by Steven M. Strasberg, M.D., and W. Scott Helton, M.D., and strongly supported by industry was a great addition to the 2001 Americas Congress. This model, increased AHPBA membership, and the opportunity to publish in an affiliated journal should all improve future biennial Americas Congresses. A recent discussion by the Executive Committee of the IHPBA to hold their World Congress in the Americas every sixth year will also increase educational opportunities. Thus, the World Congress will be held in Washington, D.C. in 2004 and will return to the Americas in 2010.

Discussions continue with Ethicon to extend the Ethicon/AHPBA Research Fellowship beyond the first 2 years. The AHPBA will document the accomplishments of these research fellows and determine whether a return on investment is achieved as these individuals apply for funding as junior faculty. To date, the partnership with the ACOSOG has led to protocol development. Hopefully, the goal of facilitation of trials will be achieved in the next 2 years as these protocols are implemented. Similarly, the recent discussions about clinical fellowships among the SSAT, SAGES, and the AHPBA are the closest that any of these groups have come to achieving fellowships that are consistent with ACGME guidelines. Through this cooperation, achieving intersociety approval of advanced training in hepatopancreato-biliary surgery in the next few years is a realistic goal.

All of the AHPBA's strategic initiatives require collaboration and enhanced communication. The AHPBA will continue to collaborate most closely with the IHPBA, the AASLD, the SSAT, and SAGES to enhance education and training. Similarly, the AHPBA will continue to collaborate with Ethicon and the ACOSOG to improve research in hepatopancreato-biliary disease. Further partnership with industry through creation of a Corporate Council should help to grow both the educational and research missions of the AHPBA. Finally, communication with other societies has been good because of cross appointments of key individuals on the Executive Committees and other committees of the various societies. This plan should continue and, perhaps, other intersociety committees should be formed. The AHPBA will continue its spring and fall newsletters and its web page (http://www.ahpba.org). However, a further effort will be made to create a web directory with the ability to communicate regularly by e-mail through a list serve mechanism. This enhanced ability to communicate electronically will further im-

prove the AHPBA's opportunity to educate, to facilitate clinical research, to coordinate advanced training and, ultimately, to improve patient care.

The many physicians who have played a key role in the development of the AHPBA are appropriately mentioned in the manuscript. The understanding of my devoted wife, Betty, and wonderful children, Laura, David, and Susan, cannot be adequately acknowledged. The administrative support of Lori Davenport in Baltimore and Kathy Rossi in Milwaukee has been crucial to the success of the AHPBA. The professional management of the first Americas Congress by Wes Harrington, of the Hepatobiliary Surgery Forum, and the second Americas Congress by Pam Ballinger, and the third Americas Congress by Bill Curreri also have been key in the development of this new organization.

Cystic Pancreatic Neuroendocrine Tumors: Is Preoperative Diagnosis Possible?

Steven A. Ahrendt, M.D., Richard A. Komorowski, M.D., Michael J. Demeure, M.D., Stuart D. Wilson, M.D., Henry A. Pitt, M.D.

Pancreatic neuroendocrine tumors rarely undergo cystic degeneration leading to a radiologic appearance, which is often interpreted as a pancreatic mucinous cystadenoma or pseudocyst. We reviewed our experience with 38 neuroendocrine tumors, four of which were cystic, and 24 other cystic pancreatic tumors (mucinous cystadenoma [n = 5], cystadenocarcinoma [n = 6], serous cystadenoma [n = 3], solid/cystic papillary neoplasm [n = 3], intraductal papillary mucinous tumor [n = 6], and mucinous adenocarcinoma [n = 1]) managed operatively between 1990 and 2000. This review was undertaken to identify clinical and pathologic features useful for preoperative diagnosis of cystic neuroendocrine tumors. Two of the four patients with cystic neuroendocrine tumors presented with abdominal pain, one patient was asymptomatic, and one patient had hypoglycemia. Three of the four cystic neuroendocrine tumors were identified by CT scan, and none were biopsied preoperatively. Preoperative diagnoses included mucinous cystadenoma in two patients (n = 2), pancreatic cystic neoplasm in one patient, (n = 1) and insulinoma in one patient (n = 1). All four cystic neuroendocrine tumors were benign and were completely resected (distal pancreatectomy [n = 2], enucleation [n = 2]). Cystic neuroendocrine tumors are difficult to diagnose preoperatively because the majority of these tumors are nonfunctional, and CT does not differentiate these tumors from other cystic neoplasms. Cystic neuroendocrine tumors represent a subgroup of pancreatic cystic and neuroendocrine tumors with malignant potential. Their high resectability rate further supports the role of surgical exploration and resection in the treatment of pancreatic cystic neoplasms. (J GASTROINTEST SURG 2002;6:66-74.)

KEY WORDS: Pancreatic neoplasm, pancreatic cystic neoplasm, pancreatic neuroendocrine tumor, pancreatic islet cell tumor, pancreatic surgery

Pancreatic neuroendocrine tumors rarely manifest cystic changes.[1,2] Cystic pancreatic neuroendocrine tumors are usually confused radiologically with other cystic pancreatic tumors, such as mucinous cystadenoma, mucinous cystadenocarcinoma, serous cystadenoma, and solid and cystic papillary tumors, or with non-neoplastic pseudocysts.[3,4] Most cystic neuroendocrine tumors are nonfunctional.[1,2] However, cystic insulinomas, gastrinomas, and glucagonomas have been reported.[1,2,4-9] In the absence of any signs and symptoms of hormonal excess, cystic neuroendocrine tumors are rarely suspected preoperatively. These lesions have frequently been managed inappropriately with surgical or percutaneous drainage or observation because of the difficulty in establishing the correct diagnosis nonoperatively.[2,4] Therefore we reviewed our experience with cystic and solid pancreatic neuroendocrine tumors and other cystic pancreatic tumors managed over a 10-year period to determine any clinical or pathologic features of cystic neuroendocrine tumors, which might prove useful in establishing a preoperative diagnosis.

MATERIAL AND METHODS

Patient Population

A retrospective review was carried out of all patients undergoing surgical exploration at Froedtert Memorial Lutheran Hospital and the Medical College of Wisconsin who had a pathologic diagnosis of either cystic pancreatic tumor or pancreatic neuroendocrine tumor over a 10-year period from 1990

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to 2000. Sixty-two patients were identified with either a cystic pancreatic neoplasm (n = 28) or a pancreatic neuroendocrine tumor (n = 38), including four patients with a cystic pancreatic neuroendocrine tumor. The 28 cystic pancreatic tumors included three serous cystadenomas, five mucinous cystadenomas, six mucinous cystadenocarcinomas, three solid and cystic papillary tumors, six intraductal papillary mucinous tumors, a single mucin-producing adenocarcinoma, and the four cystic pancreatic neuroendocrine tumors. Clinical presentation, preoperative diagnostic tests, surgical management, tumor characteristics, and clinical outcome were reviewed.

Diagnostic Criteria

Patients presenting with appropriate signs, symptoms, and biochemical evidence of hormonal excess were classified as having a functional neuroendocrine tumor (insulinoma, glucagonoma).[10] Patients presenting without an apparent clinical syndrome or with normal serum hormone levels were classified as having nonfunctional neuroendocrine tumors, regardless of the results of the immunohistochemical evaluation of the tumor.[10] Neuroendocrine tumors were classified as cystic when fluid-filled or empty cavities were present histologically.

Tumor Characteristics

Information concerning tumor size and the presence of tumor at the surgical margins was obtained from the pathology reports. Neuroendocrine tumors were defined as malignant if lymph node or distant metastases were identified.[10] Cystic tumors were classified as previously described.[11]

Statistical Analysis

Data are presented as mean ± standard error of the mean. Comparisons among groups were performed using Student's *t* test or χ^2 analysis.

RESULTS

Case Reports

Case 1. A 50-year-old man presented with a several month history of bloating in the right upper quadrant after meals. His initial evaluation included an ultrasound examination of the gallbladder and an upper gastrointestinal series, both of which were unremarkable. An abdominal CT scan demonstrated a 1 cm cyst in the body of the pancreas suspicious for a mucinous cystadenoma. At exploration, a single 1.5 cm cyst was identified on the anterior surface of the pancreatic tail and enucleated. Histologic sections revealed fragments of a neuroendocrine tumor within a fibrotic cyst wall. No nuclear atypia, mitotic activity, or metastases were present. Immunohistochemical stains for synaptophysin and chromogranin were positive. The postoperative course was prolonged by a peripancreatic fluid collection requiring percutaneous drainage. The patient was doing well 1 year after resection.

Case 2. A 38-year-old woman with Hashimoto's thyroiditis presented with a 7-month history of right

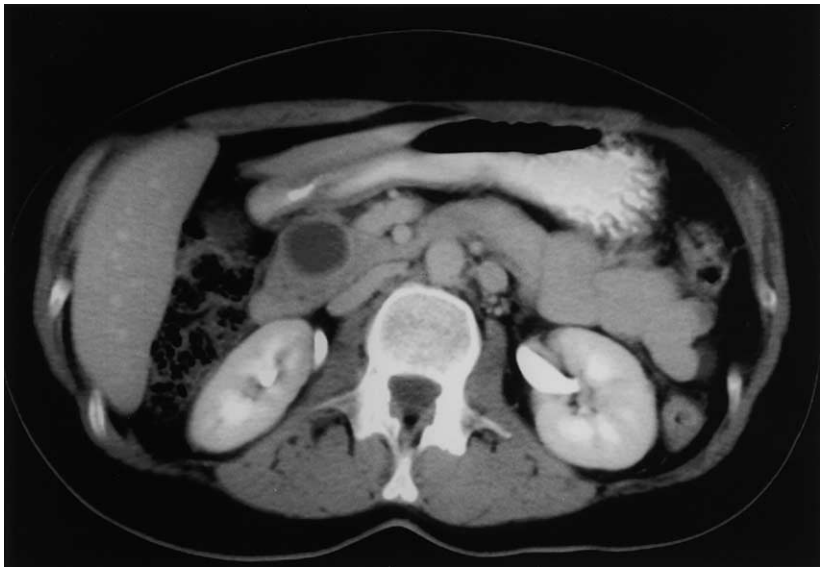

Fig. 1. CT scan from case 2 demonstrating pancreatic cystic neuroendocrine tumor. Image shows a single homogeneous cyst in the head of the pancreas with slight contrast enhancement.

Fig. 2. Pancreatic cystic neuroendocrine tumor following enucleation from the head of the pancreas (case 2).

upper quadrant abdominal pain and mild nausea. An abdominal CT scan showed a 2.5 cm cystic mass in the head of the pancreas (Fig. 1). Endoscopic retrograde cholangiopancreatography revealed normal bile and pancreatic ducts. Laparotomy and intraoperative ultrasonography demonstrated a cystic mass in the head of the pancreas free of the superior mesenteric vessels. The cystic mass was enucleated and contained clear gelatinous fluid (Fig. 2). Histologic sections of the cyst wall revealed fibrous connective tissue containing nests of neoplastic uniform neuroendocrine cells without any cytologic atypia, mitotic figures, or necrosis (Fig. 3). The tumor cells stained positive with immunohistochemical stains for glucagon, pancreatic polypeptide, and vimentin. The postoperative course was complicated by a pancreatic fistula. A follow-up CT scan 1 year after resection showed no evidence of recurrence.

Case 3. A 54-year-old man was seen in the emergency department with diminished mental acuity and an undetectable serum glucose level following a 3-month history of episodic confusion. A diagnosis of insulinoma was made during an inpatient fast from the following serum values: glucose, 43 mg/dl; insulin, 36 μU/ml (normal range 5 to 25); C-peptide, 6.2 ng/ml (normal range 0.8 to 4.0); and proinsulin, 0.99 ng/ml (normal range 0 to 0.2). A CT scan was unremarkable. A selective mesenteric angiogram showed a focal hypervascular lesion in the tail of the pancreas. Intraoperative ultrasonography confirmed a lesion in the pancreatic tail and no other lesions. A distal pancreatectomy was performed. Histologic sections of the 1.0 × 0.9 × 0.8 cm neuroendocrine tumor revealed uniform cells with marked hemorrhage adjacent to large cystlike spaces lined with nests of tumor (Fig. 4). Immunoperoxidase stains were positive for insulin and chromogranin. The patient was discharged on postoperative day 7 and has had no further episodes of hypoglycemia.

Case 4. A 67-year-old man with a history of nephrolithiasis underwent CT scanning to further evaluate an episode of acute flank pain. The CT scan

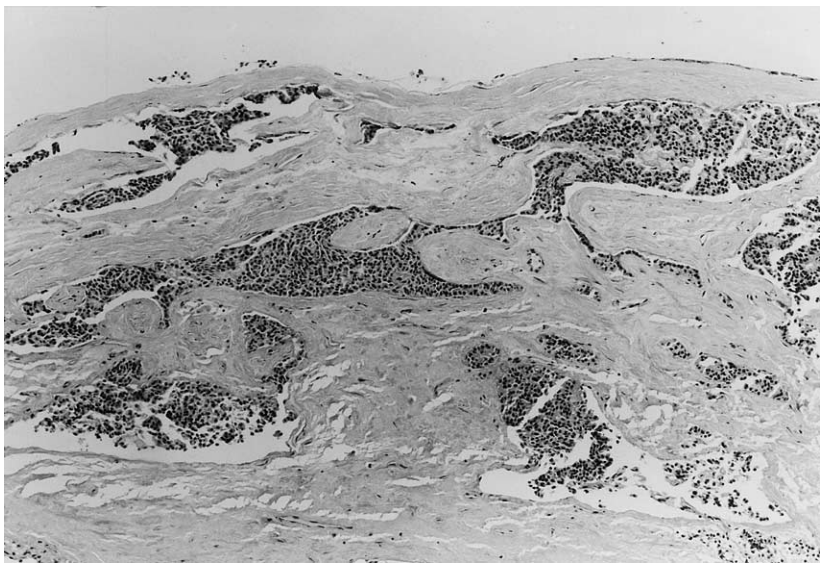

Fig. 3. Representative histologic section from a cystic pancreatic neuroendocrine tumor. Histologic section from the cyst wall demonstrates thick fibrous connective tissue containing nests of neoplastic uniform neuroendocrine cells. No epithelial lining is present surrounding the cyst (*top*).

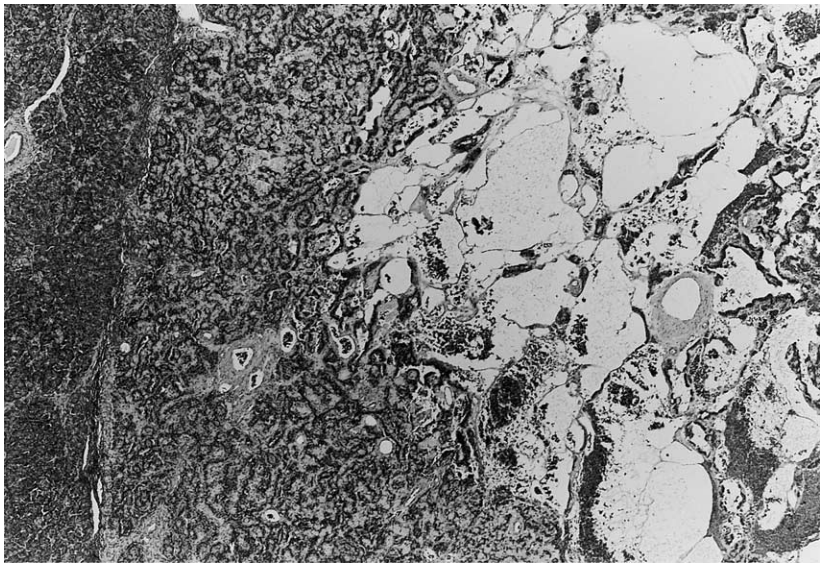

Fig. 4. Cystic insulinoma from case 3. Neoplasm containing uniform cells adjacent to multiple cysts. Hemorrhage is present at the interface between the solid and cystic components. Normal pancreas is present at the left.

demonstrated a large cystic mass involving the body and tail of the pancreas (Fig. 5). The patient denied having any abdominal pain, nausea, or weight loss. At laparotomy an 11.4 × 9.4 × 4.9 cm cystic mass was resected with a distal pancreatectomy. The tumor contained multiple mucus-filled cystic spaces measuring up to 1.6 cm in diameter. Sections of the tumor revealed numerous cystic spaces, extensive hyalinization, and uniform neuroendocrine cells with no vascular invasion or mitotic activity. The tumor cells stained diffusely positive for chromogranin, synaptophysin, and pancreatic polypeptide. The patient's postoperative course was uneventful.

Patient Characteristics

The mean age of the 62 patients with either a pancreatic neuroendocrine or a cystic pancreatic tumor was 53 years (Table 1). Patients with solid neuroendocrine tumors were younger than patients with

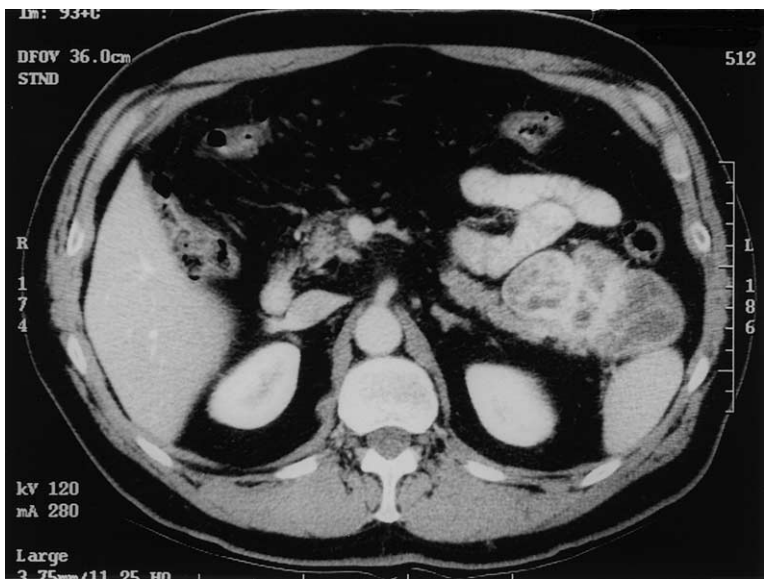

Fig. 5. CT scan from case 4 showing multicystic mass originating from the tail of the pancreas.

Table 1. Patient and tumor characteristics

Group	No. of patients	Age (yr)	% Male	Tumor size (cm)		% Tumors in body and tail	% Malignant
				Median	Mean		
Cystic neuroendocrine tumors	4	52 ± 6	75	1.9	4.0 ± 2.5	75	0
Solid neuroendocrine tumors	34	49 ± 3	56	2.2	3.0 ± 0.4	56	32
Functional	13	47 ± 5	54	1.8	2.3 ± 0.5†	70	23
Nonfunctional	21	50 ± 4	57	2.5	3.4 ± 0.6	40	38
Other cystic tumors*	24	59 ± 4‡	25‡	5.0	5.6 ± 0.7‡	29‡	42

*Includes serous cystadenoma, mucinous cystadenoma, mucinous cystadenocarcinoma, solid and cystic papillary tumors, intraductal papillary mucinous tumor, and mucin-producing adenocarcinoma.
†$P < 0.05$ vs. other cystic tumors.
‡$P < 0.05$ vs. solid neuroendocrine tumors.

non-neuroendocrine cystic pancreatic tumors (49 vs. 59 years, $P = 0.04$). This series included 34 women (55%) and 28 men (45%). The majority of patients with neuroendocrine tumors were men (solid 57%, cystic 75%), whereas 75% of patients with non-neuroendocrine cystic pancreatic tumors were women. In none of the three patients with nonfunctional cystic neuroendocrine tumors was the pathologic diagnosis suspected preoperatively.

Operative Management

Three of the four cystic neuroendocrine tumors were located in the body or tail of the pancreas, and all four tumors were resected with negative margins (distal pancreatectomy [n = 2], enucleation [n = 2]). The solid neuroendocrine tumors were more evenly distributed between the body and head of the pancreas (Table 2). Twenty-eight of the 34 solid neuroendocrine tumors were resected (distal pancreatectomy [n = 13], pancreaticoduodenectomy [n = 9], enucleation [n = 6]). The non-neuroendocrine cystic tumors were significantly ($P < 0.05$) more likely to be located in the head of the pancreas than the pancreatic neuroendocrine tumors (71% vs. 44%). Twenty-one of the 24 cystic tumors were resected (distal pancreatectomy [n = 5], pancreaticoduodenectomy [n = 16]). Among resected patients, pancreaticoduodenectomy was performed in none of the patients with cystic neuroendocrine tumors, 25% with solid neuroendocrine tumors, and 76% with other cystic pancreatic tumors.

Tumor Characteristics

Median and mean diameters of the cystic neuroendocrine tumors were 1.9 and 4.0 cm, respectively, and were similar to their solid counterparts. The solid neuroendocrine tumors were significantly ($P < 0.05$) smaller than the other non-neuroendocrine cystic tumors. None of the cystic neuroendocrine tumors demonstrated lymph node or distant metastases, and all were classified as benign. Thirty-two percent of the solid neuroendocrine tumors and 42% of the non-neuroendocrine cystic tumors were malignant.

DISCUSSION

Cystic pancreatic neuroendocrine tumors represented 10% of the pancreatic neuroendocrine tumors and 14% of the cystic pancreatic tumors managed at our institution over a 10-year period. Similar to solid pancreatic neuroendocrine tumors, cystic pancreatic neuroendocrine tumors were diagnosed most often in men, commonly originated in the body and tail of the pancreas, were smaller than other cystic pancreatic tumors, and were benign.

Before 1990, fewer than 20 cases of cystic pancreatic neuroendocrine tumors were reported as individual case reports.[1,2] More than 20 additional cases have been reported over the past 10 years.[4-9,12-22] Cystic neuroendocrine tumors are rare lesions comprising a small fraction of all neuroendocrine or cystic pancreatic tumors. Approximately 1.5% to 4.5% of pancreatic neuroendocrine tumors reported in large, single-institution series demonstrate cystic changes.[1,4,23,24] Similarly, cystic neuroendocrine tumors represent only 0.7% to 3.4% of all pancreatic cystic neoplasms.[1,3,4,25,26] Most cystic neuroendocrine tumors are nonfunctional. Thirty-four (71%) of 48 tumors in which preoperative symptoms (including this series) have been reported were nonfunctional.[1,2,4-9,12-22] Cystic insulin-, gastrin-, and glucagon-secreting tumors have been reported, including a cystic insulinoma in a patient with multiple endocrine neoplasia.[1,2,4-9]

Several theories have been proposed to explain the evolution of cystic neuroendocrine tumors. Kamisawa et al.[27] suggested that these slow-growing tumors develop a fibrous capsule, which eventually decreases the blood supply to the tumor leading to

Table 2. Cystic pancreatic neuroendocrine tumors: Clinical and pathologic characteristics

Author	Year	Age (yr)	Sex	Symptoms	Functional	Procedure	Site	Size (cm)	Malignant	Follow-up
Before 1992										
Iacono et al.[1] (n = 24)	NA	50 ± 3*	61% F 39% M	Nonfunctional Pain 60% Mass 30% Weight loss 20% Jaundice 5% Asymptomatic 5% Functional Endocrine 100% Pain 50% Weight loss 50%	Nonfunctional 20/24 (83%) Functional 4/24 (17%) Insulinoma (n = 2) Gastrinoma (n = 2)	DP (n = 15) Enucleation (n = 5) PD (n = 1) TP (n = 1) IP (n = 1)	Head (n = 6) Body (n = 13) Tail (n = 4)	6.7 ± 0.7*	Benign (n = 16) Malignant (n = 7)	Variable
After 1992										
Goto et al.[6]	1994	30	M	Whipple's triad	Insulinoma	DP	Tail	4.5	No	Alive 1 mo
Marrano et al.[7]	1994	29	M	Whipple's triad	Insulinoma	DP	Tail	10	No	Alive 5 yr
Weissmann et al.[4]	1994	82	F	Whipple's triad	Insulinoma	DP	Tail	2	No	—
		64	F	Asymptomatic	No	DP	Tail	7	No	Alive 2 yr
Schwartz et al.[12]	1994	51	F	Pain	No	PD	Head	10	No	Alive 3 yr
		40	M	Pain	No	Palliative	Head	6	Yes	Alive 3 yr
		24	F	Jaundice, pain	No	TP	Head	4.5	Yes	Alive 1 yr
Sarui et al.[17]		52	M	MEN 1, asymptomatic	No†	DP	Body	3	No	Alive 18 mo
Taniguchi et al.[14]	1995	68	F	Pain	No	PD	Head	6	No	Alive 2 yr
Tandan et al.[16]	1995	28	F	Pain	No	DP	Tail	5.5	—	—
Brown et al.[8]	1998	37	M	Asymptomatic	No	DP	Body	10	No	Alive 1 mo
		48	M	Polyuria, polydipsia	Glucagonoma	DP	Body	4.5	No	Alive 26 mo
Sohaib et al.[15]	1998	40	F	MEN 1, asymptomatic	No†	NS	Multiple	0.8 − 1.6	No	—
Kotoulas et al.[13]	1998	29	F	Mass, weight loss	No	DP	Tail	18	No	Alive 3 yr
Present study	2001	50	M	Pain	No	Enucleation	Body	1.5	No	Alive 1 yr
		38	F	Pain	No	Enucleation	Head	2.5	No	Alive 1 yr
		54	M	Whipple's triad	Insulinoma	DP	Body	1.0	No	Alive 1 mo
		67	M	Asymptomatic	No	DP	Tail	11	No	Alive 6 mo

(*continued*)

Table 2. (*Continued*)

Author	Year	Age (yr)	Sex	Symptoms	Functional	Procedure	Site	Size (cm)	Malignant	Follow-up
Summary (n = 42)		49 ± 3*	56% F 44% M	Nonfunctional Pain 58% Mass 21% Weight loss 20% Jaundice 6% Asymptomatic 21% Functional Endocrine 100% Pain 15% Weight loss 15%	Nonfunctinal 33/42 (79%) Functional 9/42 (21%) Insulinoma (n = 6) Gastrinoma (n = 2) Glucagonoma (n = 1)	DP (n = 27) Enucleation (n = 7) PD (n = 2) TP (n = 2) Other (n = 3)	Head (n = 11) Body (n = 18) Tail (n = 7) Multiple (n = 1)	6.4 ± 0.7*	Benign (n = 31) (78%) Malignant (n = 9) (22%)	5-yr survival 96%

DP = distal pancreatectomy; IP = intermediate pancreatectomy; MEN 1 = multiple endocrine neoplasia type 1; NA = not applicable; PD = pancreatoduodenectomy; TP = total pancreatectomy.
* Mean ± standard error of the mean.
†No symptoms related to excess circulating hormone.

infarction and liquefaction necrosis. Buetow et al.[28] noted a cystic appearance on CT or magnetic resonance scans in 54% of the cases of nonfunctioning islet cell tumors referred to the Armed Forces Institute of Pathology. The presence of cystic change or necrosis was correlated with large tumor size. However, the mean tumor size in the Armed Forces Institute of Pathology series (8 cm) was markedly greater than that in the current series (3 cm) or in other series of nonfunctioning neuroendocrine pancreatic tumors.[10,24,28] Other investigators have suggested that hemorrhage in these highly vascular tumors is the initial event leading to cyst development.[1,19,27] Hemorrhage was present surrounding the cystic spaces in the small (1 cm diameter) tumor in case 3. Several case reports have documented bloody fluid contained within the cystic spaces of pancreatic neuroendocrine tumors.[14,19] In three of our four cases the tumors were small (≤2.5 cm), and two of these tumors had a well-developed fibrous cyst wall. These findings indicate that the evolution of cysts in pancreatic neuroendocrine tumors can occur in small tumors and suggests that hemorrhage may be the inciting event. Malignant degeneration in a pseudocyst wall has been suggested as a possible etiology.[1,2] However, an antecedent history of pancreatitis was not present in our four patients or in other reports in the literature.

Spiral CT scanning is currently the most widely used modality for imaging pancreatic tumors. Despite advances in imaging techniques over the past decade, CT is unable to reliably differentiate among the different cystic pancreatic tumors. Misinterpretation of a cystic neuroendocrine tumor as a pancreatic pseudocyst is also common.[3,4] Thirty-one percent of patients reviewed by Davtyan et al.[2] had undergone an unsuccessful surgical internal drainage procedure (cystogastrostomy or cystojejunostomy) before pancreatic resection. Fine-needle aspiration with fluid and cytologic analysis has been proposed in the evaluation of pancreatic cysts.[1,4,29] Cyst aspiration in a single case of cystic insulinoma yielded elevated levels of insulin and amylase in the cyst fluid.[4] In addition, the identification of neuroendocrine cells within the cyst fluid has also been used to establish the diagnosis in a single cystic neuroendocrine tumor.[5] However, cyst-fluid hormone levels have not been reported in nonfunctioning tumors in which a preoperative diagnosis of neuroendocrine tumor is more likely to be uncertain. In this setting an elevated amylase level might lead erroneously to a diagnosis of pancreatic pseudocyst.[2,9] Small nests of tumor cells within the fibrous cyst wall and the absence of an epithelial lining (see Fig. 3) in some cystic neuroendocrine tumors would likely lead to consider-

able sampling error with fine-needle aspiration. In fact, open biopsy of the cyst wall has led to the erroneous diagnosis of pseudocyst. Furthermore, the frequent presence of bloody, dark, or necrotic debris-filled fluid within cystic neuroendocrine tumors may also diminish the accuracy of cyst-fluid evaluation.[8,15,20] Low diagnostic accuracy with percutaneous biopsy has been reported in other unusual pancreatic tumors.[30]

The prognosis in patients with cystic neuroendocrine tumors has been good. The majority of these lesions are benign, and 5-year survival has been reported in a patient with liver metastases at the time of pancreatic resection. However, limited or no follow-up are available in the other reported malignant cases.

Cystic neuroendocrine tumors are uncommon pancreatic neoplasms. The correct preoperative diagnosis is rarely made because the majority of these tumors are nonfunctional, and CT does not differentiate between these tumors and other cystic neoplasms. Therefore the preoperative diagnosis of nonfunctioning cystic neuroendocrine tumor is not possible with current diagnostic imaging techniques. The diagnosis of cystic neuroendocrine tumors should be considered especially in men with small cystic mass lesions in the body and tail of the pancreas. Along with most other cystic pancreatic tumors, cystic neuroendocrine tumors have malignant potential. Preoperative biopsy should be avoided. The high resectability rate and excellent prognosis in patients with cystic neuroendocrine tumors further support the role of surgical exploration and resection for the treatment of pancreatic cystic neoplasms.

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Diagnostic Laparoscopy for Periampullary and Pancreatic Cancer: What Is the True Benefit?

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The role of diagnostic laparoscopy in patients with periampullary and pancreatic malignancies is controversial. A retrospective review was performed including all patients (n = 188) with a periampullary or pancreatic malignancy who underwent *both* CT and laparotomy at our institution between January 1997 and December 1999. The overall resectability rate for all periampullary cancers was 67.3% (115 of 171 patients). This compared favorably with the resectability rate for cancers of the pancreatic body and tail (3 of 17 patients, 17.6%; $P < 0.01$ vs. periampullary cancers). Fifty percent of patients with periampullary cancers were unresectable because of metastatic disease, whereas metastatic disease precluded resection in 64.3% of patients with cancers of the pancreatic body and tail. After patients undergoing operative palliation were eliminated, a nontherapeutic laparotomy would have been precluded by the use of diagnostic laparoscopy in only 2.3% of patients with periampullary cancers (4 of 171 patients). In contrast, 6 (35.3%) of 17 patients with cancers of the pancreatic body and tail underwent a nontherapeutic laparotomy ($P < 0.01$ vs. periampullary cancers). One hundred fifty-eight (84%) of the 188 CT reports reviewed could be definitively categorized as either "likely to be resectable" or "likely to be unresectable." The remaining 16% were equivocal. Of the 107 patients categorized as likely to be resectable, 89 were actually resected (83.2%). In contrast, only 10 of the 51 patients categorized as likely to be unresectable could be resected (19.6%). (J GASTROINTEST SURG 2002;6:75–81.)

KEY WORDS: Periampullary cancer, pancreatic cancer, diagnostic laparoscopy

Periampullary carcinomas originate from four different sites: head of the pancreas, distal bile duct, ampulla of Vater, and duodenum. The majority of these cancers are pancreatic adenocarcinoma, which has a yearly incidence in the United States of approximately 29,000 cases per year.[1] Although surgical resection offers a chance for cure, most patients with pancreatic cancer are unresectable at the time of presentation.[2,3] The mean survival in this setting is approximately 6 months.[4-7] Therefore, given the large number of patients with unresectable pancreatic cancer and their poor prognosis, significant effort has focused on developing the most appropriate diagnostic, staging, and treatment methods for this disease.

Traditionally, surgery has been necessary for adequate staging, determination of resectability, and palliation for unresectable periampullary cancer. The development of nonoperative means to palliate periampullary cancer has led to a greater importance for determining resectability without the need for laparotomy. Recently, newer modalities including noninvasive (spiral CT, MRI, and positron emission tomography [PET]) and minimally invasive (endoscopic ultrasonography, diagnostic laparoscopy, laparoscopic ultrasonography, and peritoneal cytology) techni–ques have been championed by groups for the staging of pancreatic and periampullary carcinoma. To adequately evaluate the role of these modalities, however, it is important to identify the overall impact of these studies on both staging and cost-effectiveness.

The role of diagnostic laparoscopy remains controversial. Proponents believe that laparoscopy can identify a substantial number of unresectable patients with more advanced disease and, therefore,

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should be uniformly applied to all patients with potentially resectable periampullary tumors. Opponents believe that the inherent cost of such a practice far outweighs the benefit to the small number of patients in whom diagnostic laparoscopy is useful. The goal of this study was to assess the benefit of diagnostic laparoscopy in patients with potentially resectable periampullary and pancreatic malignancies and to evaluate the accuracy of the CT scan, which has been the mainstay of preoperative staging at this institution.

METHODS

A retrospective review of all patients (n = 188) with a potentially resectable periampullary or pancreatic malignancy who underwent both preoperative CT *and* laparotomy at the Johns Hopkins Hospital between January 1997 and December 1999 was completed. Diagnostic laparoscopy was not performed on any patient. This review consisted of analysis of the radiologic reports, operative notes, and pathologic findings for all patients. The diagnosis of adenocarcinoma was histologically confirmed and included tumors arising in the head, body, and tail of the pancreas, distal common bile duct, ampulla of Vater, and duodenum. The pathologic reports were reviewed to identify the specific organ of origin for all resected tumors. The organ of origin for unresectable tumors was determined based on preoperative evaluation including CT, endoscopy, and cholangiographic appearance and operative findings.

At laparotomy, patients were deemed unresectable if biopsy-proved metastatic disease (hepatic or peritoneal) or local major vessel invasion was identified. The potential role of laparoscopy was then determined based on the number of patients discovered at laparotomy to have either hepatic or peritoneal metastases. The presence of local vascular invasion was not considered detectable by diagnostic laparoscopy. The resectability rate and the potential role for diagnostic laparoscopy were then determined for each site of tumor origin.

Surgical palliation for unresectable patients included biliary-enteric bypass and gastrojejunostomy. The number of patients undergoing each form of palliation was determined. Patients not undergoing any type of palliative procedure were considered to have undergone a nontherapeutic laparotomy.

Finally, the preoperative CT scans for each patient were retrospectively analyzed and placed into one of three categories: (1) likely to be resectable—showing no evidence of visceral vascular involvement or metastatic disease; (2) likely to be unresectable—showing evidence of likely vascular encasement or invasion or lesions highly suspicious for metastases; or (3) equivocal—indeterminate vascular involvement or metastatic lesions. The actual resectability rate for each patient was then correlated with the radiologic findings to determine the value of the preoperative CT studies.

Differences between groups were evaluated using chi-square analysis. A P value of <0.05 was considered statistically significant.

RESULTS

During the 3-year time period, 115 (67.3%) of the 171 patients undergoing laparotomy for periampullary cancer were found to be resectable for potential cure (Table 1). The rate of resectability for the remaining 17 patients with a cancer arising in the body and tail of the pancreas was significantly lower at 17.6% (3 of 17 patients, $P < 0.01$). The resectability rate for patients with periampullary malignancy was then determined based on the site of origin of the cancer. The resectability rate was 59.7% for tumors of the head of the pancreas (71 of 119), 76.0% for distal bile duct tumors (19 of 25), 100% for tumors of the ampulla of Vater (14 of 14), and 84.6% for cancers of the duodenum (11 of 13). The resectability rate for cancers of the head of the pancreas was significantly lower than for tumors of all other sites of origin ($P < 0.01$).

The reason for unresectability in patients with periampullary carcinoma (n = 56) was equally divided between metastatic disease (28 patients, 50%) and

Table 1. Resectability rate and percentage of unresectable patients with metastatic disease for each site of tumor origin

	% Resectable	% Metastatic disease
Periampullary (total)	115/171 (67.3%)	28/56 (50%)
Head of pancreas	71/119 (59.7%)*	23/48 (47.9%)
Distal bile duct	19/25 (76.0%)	3/6 (50%)
Ampulla	14/14 (100%)	0/0 (0%)
Duodenum	11/13 (84.6%)	2/2 (100%)
Pancreatic body and tail	3/17 (17.6%)†	9/14 (64.3%)

*$P < 0.01$ vs. all other periampullary tumors.
†$P < 0.01$ vs. all periampullary tumors.

local vascular invasion (28 patients, 50%) (see Table 1). Patients with unresectable tumors arising in the body or tail of the pancreas (n = 14) were unresectable because of metastatic disease in 64.3% (n = 9), whereas 35.7% (n = 5) had local invasion.

The number of patients identified at laparotomy to have metastatic disease (histologically confirmed liver metastasis or serosal implants) was then used to determine the potential benefit of diagnostic laparoscopy for the entire patient population. Metastatic disease was ultimately discovered in 28 (16.4%) of 171 patients with periampullary carcinoma (Table 2). The specific incidence of metastatic disease was also determined based on site of origin of the tumor (see Table 2). Diagnostic laparoscopy might have been useful in 19.3% of patients with a cancer in the head of the pancreas (23 of 119), 12% of patients with a distal bile duct tumor (3 of 25), and 15.4% of patients with duodenal cancers (2 of 13), but in none of the 14 patients with ampullary cancers. In contrast, 52.9% of patients with a cancer of the pancreatic body or tail (9 of 17) were discovered to have distant metastases intraoperatively. The incidence of metastases potentially detectable by laparoscopy was significantly higher in patients with cancers of the pancreatic body and tail than all other sites ($P < 0.01$).

To further define the role of diagnostic laparoscopy in avoiding a nontherapeutic laparotomy, we next determined the need for surgical palliation. Twenty-four of 28 patients (85.7%) with unresectable periampullary cancer due to distant metastasis required some type of palliative procedure. This included a combined biliary bypass and gastrojejunostomy in 17 patients (60.7%), a biliary bypass alone in three patients (10.7%), or a gastrojejunostomy alone in four patients (14.3%). The remaining four patients received no palliative bypass procedure (14.3%). Only three (33%) of nine patients with an unresectable pancreatic body or tail cancer due to distant metastases underwent some form of surgical palliation. The other six patients (66.7%) received no surgical palliation and therefore were also considered to have undergone an unnecessary laparotomy. The need for surgical palliation was significantly less frequent ($P < 0.01$) in patients with body and tail cancers as compared to those with periampullary tumors. Based on analysis of all patients undergoing laparotomy for periampullary carcinoma, only 4 (2.3%) of 171 patients underwent a nontherapeutic laparotomy because of the presence of metastatic disease (see Table 2). Among those patients with periampullary pancreatic carcinoma, 3 (2.5%) of 119 underwent a nontherapeutic laparotomy. In contrast, 6 (35.3%) of 17 of all patients with cancers arising in the pancreatic body or tail underwent a nontherapeutic laparotomy. This difference was statistically significant ($P < 0.01$).

One hundred fifty-eight of the 188 CT reports reviewed were categorized as either likely to be resectable (107 of 188, 56.9%) or likely to be unresectable (51 of 188, 27.1%). The remaining 16.0% were considered equivocal. For patients with periampullary cancers and a CT report categorized as being resectable, 87 (84.5%) of 103 were actually resected (Table 3). There was no difference in the predictive value based on the site of origin of the tumor. Only 50% of patients with tumors in the body or tail of the pan-

Table 2. Potential benefit of diagnostic laparoscopy for each site of tumor origin

	% Potentially detectable by laparoscopy	% of laparotomies potentially avoided by laparoscopy
Periampullary (total)	28/171 (16.4%)	4/171 (2.3%)
Head of pancreas	23/119 (19.3%)	3/119 (2.5%)
Distal bile duct	3/25 (12%)	1/25 (4.0%)
Ampulla	0/14 (0%)	0/14 (0%)
Duodenum	2/13 (15.4%)	0/13 (0%)
Pancreatic body and tail	9/17 (52.9%)*	6/17 (35.3%)*

*$P < 0.01$ vs. periampullary tumors.

Table 3. Actual surgical resectability rate for each radiologic category

	Likely to be resectable	Equivocal	Likely to be unresectable*
Periampullary (total)	87/103 (84.5%)	19/28 (67.9%)	9/40 (22.5%)
Head of pancreas	49/60 (81.7%)	16/25 (64.0%)	6/34 (17.6%)
Distal bile duct	16/20 (80.0%)	2/2 (100%)	1/3 (33.3%)
Ampulla	13/13 (100%)	1/1 (100%)	0/0 (0%)
Duodenum	9/10 (90.0%)	0/0 (0%)	2/3 (66.6%)
Pancreatic body and tail	2/4 (50.0%)	0/2 (0%)	1/11 (9.1%)

*$P < 0.01$ for likely to be resectable (total) vs. likely to be unresectable (total).

creas who were thought to be resectable based on radiographic evidence (2 of 4 patients) could actually be resected. In contrast, for those patients with a periampullary cancer, whose CT was categorized as likely to be unresectable, only 22.5% (9 of 40) were resected. In patients with a pancreatic cancer of the body or tail thought likely to be unresectable on CT, only 9.1% (1 of 11 patients) were resectable. These results correlate with an overall positive predictive value of 83.2% and a negative predictive value of 78.4% for CT.

DISCUSSION

Over the past two decades, significant progress has been made in the management of periampullary cancer. Pancreaticoduodenectomy is now performed routinely with a perioperative mortality rate of less than 5%[5,7] and with improved long-term survival.[4,5] Furthermore, excellent short- and long-term outcomes following surgical palliation of unresectable disease can be expected.[3] In addition, nonoperative means of palliation now exist, which can provide long-term relief of biliary obstruction.[8-12] Despite these advances, the majority of patients with pancreatic cancer are unresectable with a limited life expectancy at the time of presentation.[2-7] Therefore, establishing the diagnosis, determining the potential for resection, and choosing how to best utilize the available treatment options for each individual patient are of key importance.

A multitude of techniques are now available for the preoperative staging of patients with pancreatic and periampullary cancer. Most of these techniques have been championed as decreasing the need for "unnecessary laparotomies" in patients with unresectable disease. Examples of the techniques now available include dynamic contrast–enhanced spiral CT, transcutaneous or endoscopic ultrasonography, MRI with vascular or cholangiographic techniques, and PET. Diagnostic laparoscopy with or without ultrasound offers an advantage over other staging techniques in that it allows histologic confirmation of unresectability. Diagnostic laparoscopy, however, is an invasive surgical procedure, which requires general anesthesia and can be associated with significant cost and some potential for morbidity. These final points have led many surgeons to avoid routine diagnostic laparoscopy and has led to the significant controversy concerning its use.

Diagnostic laparoscopy has been consistently shown to be useful for detecting small (<1 cm) hepatic or peritoneal metastases, which may be missed on routine CT imaging. Yet careful analysis of the results can still lead to questions with respect to the overall value of the procedure in patients with periampullary cancer. The technique of diagnostic laparoscopy was first popularized by Warshaw et al.[13] at Massachusetts General Hospital. In their initial report in 1986, diagnostic laparoscopy was performed in 40 patients. Seventeen (42%) were found to have metastatic disease with 14 (35%) detected by laparoscopy and three by laparotomy. A recent update of their experience included 125 consecutive patients with pancreatic cancer undergoing staging laparoscopy between 1994 and 1998.[14] In that series 39 patients (31.2%) had unsuspected metastasis found at laparoscopy despite a normal preoperative CT scan. Yet, of the 31 patients considered resectable by laparoscopy, only 74% were actually resected. It should be noted that only 62% of tumors in this series were located in the head of the pancreas. Although specific data are not provided, the authors acknowledge that metastases detected by laparoscopy were more common for tumors of the pancreatic body and tail.

In a series reported from the Memorial Sloan-Kettering Cancer Center, 115 patients with radiologically resectable (by CT scan) pancreatic cancer underwent laparoscopic staging.[15] Because of a prior surgical procedure, only 108 patients were able to undergo a complete examination. Of those 108 patients, 41 were found to be unresectable. Hepatic metastases were found in 20 patients, mesenteric vascular encasement in 14, extrapancreatic/peritoneal involvement in 16, and celiac or portal lymphatic metastases in eight patients. Yet laparoscopy failed to identify hepatic metastasis in five patients (20% of those patients were ultimately found to have liver metastases). There was no perioperative morbidity or mortality associated with the laparoscopic procedure; however, the length of stay for 25 patients undergoing the laparoscopic procedure alone was 3.6 days (median 2 days, range 1 to 13 days). Furthermore, of those patients who did not undergo resection because of laparoscopic findings, 32% still required a further surgical procedure. Finally, it should again be noted that in only 64% of the patients was the pancreatic cancer located in the head of the gland.

More recently, the group in Amsterdam performed laparoscopic staging in 203 patients with periampullary carcinoma.[16] In that series diagnostic laparoscopy detected metastasis in 15% of patients, but another 9% of patients had metastasis missed at laparoscopy but detected at laparotomy. The sensitivity for detection of metastasis was only 60%. Furthermore, 37 patients were considered unresectable because of tumor ingrowth, but histologic diagnosis could not be obtained. In this situation patients may be denied a potentially curative procedure. In five patients the laparoscopic

findings were not confirmed at laparotomy, giving a false positive rate of 14%. Finally, because of the need for palliation, the authors conclude that only 15% of patients were spared an unnecessary laparotomy.

A number of investigators have, as in the present series, retrospectively analyzed the potential benefit of laparoscopy based on findings at laparotomy. Holzman et al.[17] analyzed their findings in 23 patients undergoing laparotomy based on CT criteria and found only one patient (4.4%) with peritoneal metastases, which could have been detected by laparoscopy. In a prospective analysis from M.D. Anderson Cancer Center, thin-section CT scans were obtained from 145 patients suspected of having resectable periampullary cancers.[18] Forty-two patients fulfilled the radiologic criteria for resectability. Of these 42, only two (5%) had peritoneal or superficial liver metastases that potentially could have been detected by laparoscopic examination. Finally, the group from Mannheim, Germany analyzed 398 patients who underwent a laparotomy for pancreatic cancer between 1990 and 1995.[19] Although positive findings of hepatic or peritoneal metastases were present in 107 patients (26.9%), after those patients in whom a palliative procedure was necessary were eliminated, laparotomy would have been avoided in only 29 patients (7.3%). Furthermore, if one focuses only on patients with tumors of the periampullary region, the number of unnecessary laparotomies fell to 5.5%. The results of these series are similar to the findings in the current report. In our series, diagnostic laparoscopy would have potentially detected findings precluding resection in only 16.4% of patients with periampullary cancer. Laparoscopy would have been potentially more useful in patients with cancer of the pancreatic body or tail, proving unresectability in more than 50% of patients.

Laparoscopic ultrasound and analysis of peritoneal cytology have been offered as additional measures to improve the ability of laparoscopic staging. In a recent series reported from Memorial Sloan–Kettering Cancer Center, 303 patients underwent extended laparoscopic staging for "radiologically resectable" pancreatic cancer.[20] One hundred ninety-nine were considered to have resectable disease following laparoscopic staging and subsequently underwent open exploration with 181 (91%) resectable. In another series, 67 patients underwent diagnostic laparoscopy and ultrasound examination.[21] Advanced disease, precluding curative resection, was found in 30 patients. Laparoscopic ultrasound was considered to have revealed additional information beyond simple laparoscopy, precluding resection in 22 of these patients. Of the 33 patients thought to be resectable, 29 (94%) were actually resected. The sensitivity of the study was 100%, the specificity was 88%, the positive predictive value was 89%, and the negative predictive value was 100%.

The role of peritoneal cytology was first reported by surgeons at Massachusetts General Hospital.[22] In their initial report these authors found that 33% of patients were found to have positive peritoneal cytology for malignant disease at the time of staging laparoscopy. In a recent update from that group the incidence of positive cytology had fallen to 18%, and only 9.6% of patients had cytologic evidence of disease without visible metastases.[23] However, survival of patients with positive cytology and no visible metastases was poor, and was no different from survival of patients with visible disease. Positive findings on cytologic examination were more frequent in tumors of the body or tail of the pancreas (36%) versus the head of the pancreas (9%). Other groups have found that positive peritoneal cytology without microscopic metastasis at laparoscopy is rare. Investigators from Amsterdam found that in only 2 (0.84%) of 236 cases did this occur.[24] Another important drawback of peritoneal cytologic analysis is that using the technique requires that diagnostic laparoscopy and cytologic sampling be performed as a separate procedure with the patient under general anesthesia.

Although it can be accepted that laparoscopy alone or including ultrasonography and peritoneal cytology may detect patients with unsuspected distant metastases, the role of laparoscopy in avoiding laparotomy is less clear. Many authors cite four prospective randomized studies completed in the 1980s comparing nonoperative versus operative palliation.[25-28] These studies consistently show that nonoperative palliation was associated with lower procedure-related morbidity and mortality and decreased length of stay as compared to the operative technique. Critics of these studies, however, point out that the incidence of late complications of recurrent jaundice, cholangitis, and duodenal obstruction was significantly greater in the nonoperative palliation group. Furthermore, the perioperative morbidity and mortality in the surgical arms of these series are considered unacceptable by today's standards.

The question of recurrent jaundice and cholangitis in patients undergoing nonoperative palliation may be decreased with the development of self-expanding metal stents (Wallstents) with improved long-term patency. The question of late duodenal obstruction, however, has not been adequately addressed. In the prospective randomized trials of nonoperative palliation, late gastric outlet obstruction occurred in 14% in the nonoperative arms. Three meta-analyses of more than 10,000 reported cases have shown that

13%, 21%, and 17% of patients not undergoing gastric bypass at initial laparotomy required a gastrojejunostomy before death.[29-31] Finally, in a prospective randomized trial recently completed at the Johns Hopkins Hospital, 19% of patients undergoing laparotomy without a gastrojejunostomy required a gastric bypass before they died.[32] No patient who received a prophylactic gastrojejunostomy developed late gastric outlet obstruction ($P < 0.01$), despite the fact that patients were randomized only after assessment of preoperative symptoms, endoscopic and radiologic studies, and operative findings, all of which suggested a low probability of duodenal obstruction. Other authors, however, argue that the need for surgical palliation is overexaggerated. A prospective experience from Memorial Sloan-Kettering Cancer Center by Espat et al.[33] followed 155 patients with adenocarcinoma of the pancreas who underwent laparoscopic staging alone. In this series only 2% required an operation at any time to provide palliation.

It is the ability to provide long-term palliation of all symptoms of periampullary cancer—jaundice, duodenal obstruction, and pain (via chemical splanchnicectomy)—with a single procedure that many surgeons find advantageous for operative palliation. Current results suggest that operative palliation can be accomplished with acceptable perioperative mortality (<5%) and morbidity (<25%).[3] This bias is clearly reflected in the results of the current study where only 2.3% of patients with periampullary cancer were found to have unresectable disease that did not require any form of surgical palliation. In contrast, cancers of the pancreatic body and tail would appear less likely (35%) to achieve any palliative benefit. Whether similar results can be obtained with laparoscopic palliation is yet to be seen.

The final aspect of our study was the analysis of CT scan results. To allow scans of similar quality, we focused only on spiral CT scans obtained at our own institution in the period immediately prior to laparotomy. These studies were retrospectively analyzed for evidence of metastatic disease or local vascular invasion. Among those patients found not to have evidence suggesting either finding, patients were resectable in 84.5% of cases of periampullary carcinoma. With CT scans thought to show evidence that the cancer was unresectable, the resectability rate was significantly lower. Yet, despite the worrisome CT appearance, more than 20% of these patients were still resectable, offering the potential chance for long-term survival. The rapidly improving quality and accuracy of imaging technology including thin sections (1 to 2 mm) and three-dimensional vascular reconstruction may further improve these results.

CONCLUSION

In this study in which findings at laparotomy were used to predict the potential benefit of laparoscopy, we have determined that diagnostic laparoscopy would have been useful in 16.4% of periampullary cancers. Furthermore, a laparotomy would have been potentially avoided in only 2.3% of patients. In contrast, for tumors of the body and tail of the pancreas, 52.9% of patients would have benefited by laparoscopy with 35.3% of patients avoiding an unnecessary laparotomy. These findings support our opinion that routine use of diagnostic laparoscopy is not indicated for patients with periampullary carcinoma. The technique may be of use in patients with tumors of the body and tail of the pancreas because of the relatively high yield of laparoscopy and low need for palliative procedures. These opinions obviously reflect the institutional bias favoring operative palliation at our institution. It is recognized that other institutions do not share similar views and that this paper will add to and not resolve the controversy concerning the role of diagnostic laparoscopy. It is our opinion that these issues will only be resolved by a properly designed prospective randomized study to address not only the short-term benefits but also the long-term outcomes and cost-effectiveness of diagnostic laparoscopy in patients with potentially resectable pancreatic cancer.

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Pancreas-Preserving Duodenectomy in the Management of Duodenal Familial Adenomatous Polyposis

Matthew F. Kalady, M.D., Bryan M. Clary, M.D., Douglas S. Tyler, M.D., Theodore N. Pappas, M.D.

Most patients with familial adenomatous polyposis (FAP) develop disease in the duodenum. The duodenal lesions mostly occur in the periampullary region, but some patients develop diffuse polyposis involving all parts of the duodenum. These neoplastic polpys have malignant potential, and thus warrant surveillance and timely intervention. We reviewed our experience with management of FAP over a 10-year period, focusing on patients who had diffuse polyposis of the duodenum and their subsequent management. Three patients with FAP had diffuse duodenal involvement, documented by upper gastrointestinal endoscopy. Neoplasia was confirmed by endoscopic biopsy, but no patients had histologic evidence of carcinoma. The patients underwent resection of the entire duodenum from the pylorus to the ligament of Treitz with preservation of the pancreas. Our surgical technique is described. One patient had a postoperative wound infection and one patient had a biliary leak that resolved with closed suction drainage for 5 days. Long-term follow-up in these patients revealed excellent functional status. One patient had polyp recurrence in the jejunum at 5-year follow-up, but no patients have developed adenocarcinoma. We conclude that patients with duodenal polyps associated with FAP may be safely and effectively treated by pancreas-preserving duodenectomy. (J GASTROINTEST SURG 2002;6:82–87.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Pancreas-preserving duodenectomy, familial adenomatous polyposis, duodenal polyps

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome characterized by hundreds of premalignant adenomas in the gastrointestinal tract. All patients with this disease manifest colonic lesions that progress to colon cancer if not treated. Most patients also develop duodenal adenomas,[1,2] which have malignant potential.[3] For those patients with FAP who have been treated by proctocolectomy, duodenal adenocarcinoma is a leading cause of death.[4,5] Therefore early detection of premalignant and malignant change followed by appropriate intervention is critical. Treatment of duodenal adenomas in FAP varies from endoscopic polypectomy to complete duodenal resection, depending on the severity and distribution of disease. This paper describes our technique and results of pancreas-preserving duodenectomy for three patients with duodenal polyposis associated with FAP, and proposes a clinical algorithm for treatment of duodenal polyposis.

PATIENTS AND METHODS

Patients

We reviewed our experience with the management of duodenal polyps in patients with FAP over a period of 10 years (1990 to 2000), with particular focus on patients with diffuse duodenal polyposis. Three patients with FAP who had prior proctocolectomy were noted to have diffuse polyps involving the first, second, and third portions of the duodenum by surveillance endoscopy. Neoplasia was confirmed by multiple endoscopic biopsies. All patients agreed to

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undergo complete duodenectomy with preservation of the pancreas.

Surgical Technique

The operation is performed through a right subcostal or generous midline incision. After wide Kocherization of the duodenum, the gallbladder is removed and the gastrointestinal tract is divided at the pylorus, with the pylorus included in the resected specimen. A safe dissection plane is created between the duodenum and the pancreas in the supra-ampullary region. The small vessels that provide the common blood supply between these two organs are identified and divided with small clips and ties. This varies from the technique described by others that employs intramural duodenal dissection to separate the pancreas from the duodenum.[6,7]

Preoperative endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography is essential to exclude pancreas divisum. In the absence of pancreas divisum, the minor pancreatic duct may simply be ligated. It has been the experience of one of us (T.N.P.) that in the setting of a patent main pancreatic duct, ligation of the accessory duct may be performed safely. This experience correlates with reports of main pancreatic duct ligation or obliteration following pancreaticoduodenectomy for cancer. When comparing duct ligation or obliteration to anastomosis during pancreaticoduodenectomy, morbidity and mortality were similar.[8,9] Rates of fistula formation after duct ligation[10] or obliteration[11] are as low as 4% to 16%. Therefore similar or better results can be expected when a lesser operation is being performed, such as ligating the minor duct in the setting of a normal main duct.

The duodenum is then excised from the orifice of the pancreatic duct/bile duct confluence, leaving the cut ends of both ducts for later reconstruction. The remainder of the resection is completed to the fourth portion of the duodenum and the ligament of Treitz is divided with a stapling device. Planes of dissection are shown graphically in Fig. 1. The jejunum is advanced into the duodenal position, and the bile duct and main pancreatic duct are anastomosed to the jejunum. This anastomosis is facilitated if the two ducts are sutured together so a single anastomosis around both ducts can be accomplished (Fig. 2). Patients with pancreas divisum require two separate anastomoses for the minor pancreatic duct and the bile duct/main pancreatic duct. The gastrointestinal tract is reconstructed as a loop gastrojejunostomy, which allows future endoscopic surveillance. Closed suction drains are placed around the anastomoses. Completed reconstruction is shown in Fig. 3.

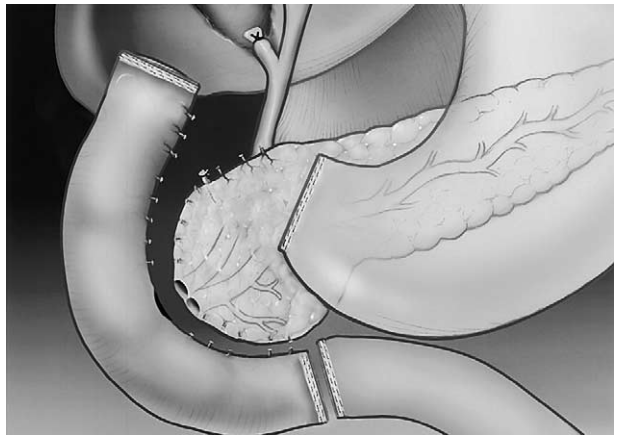

Fig. 1. Planes of dissection between the pancreas and duodenum, and boundaries of resection.

RESULTS

Three patients with FAP who had prior proctocolectomy underwent pancreas-preserving duodenectomy for diffuse adenomas. The polyps were primarily clustered around the ampulla of Vater, but extended from the first through fourth portions of the duodenum. None of the patients had jejunal polyps. One patient had symptomatic ulcerated polyps. Patient demographics and clinical results are presented in Table 1.

One patient was male and two patients were female. The mean age was 38 years. There were no intraoperative complications and the mean operative time was 4 hours 39 minutes. No patients required

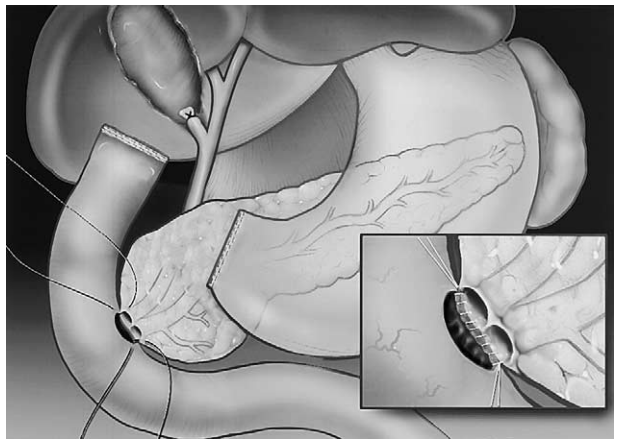

Fig. 2. The distal common bile duct and main pancreatic duct are sutured together and reimplanted as a single anastomosis to the jejunum.

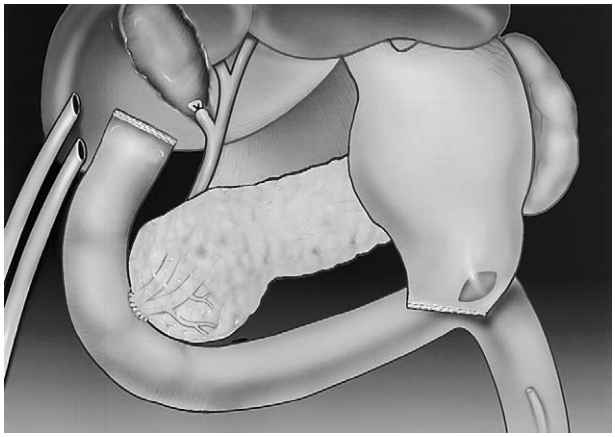

Fig. 3. Completed resection with ductal anastomosis, loop gastrojejunostomy, and drains.

blood transfusion or postoperative intensive care. One patient developed a wound infection that healed secondarily, and one patient developed a biliary leak that healed spontaneously with controlled catheter drainage for 5 days. No patient had postoperative pancreatitis. Two patients were discharged 8 days postoperatively, whereas a wound infection prolonged the hospital treatment to 17 days for one patient. The final pathology report in all patients showed tubulovillous adenoma with and without dysplasia, but there was no evidence of carcinoma in any of the three specimens.

There were no deaths in this series. Patients have been followed for a mean of 2.2 years (range 6 months to 5 years). All patients have normal gastrointestinal function and maintain a normal weight. None of the patients have dumping syndrome. The patient who has been followed for 5 years has developed jejunal polyps.

DISCUSSION

As many as 90% of patients with FAP have duodenal involvement.[1,2,12,13] Like their colonic counterparts, duodenal polyps have malignant potential[3] and approximately 2% to 5% of patients with FAP will develop adenocarcinoma in the duodenum over their lifetime.[12,14–16] Among patients with FAP who have been treated by proctocolectomy, adenocarcinoma of the duodenum is a leading cause of death.[4,5] The only effective means of prevention of duodenal carcinoma currently is prophylactic resection.

Although the association between duodenal polyps and cancer has been well defined,[3,17] predicting which polyps will progress to carcinoma and at what rate remains challenging. Spigelman et al.[2] have defined stages of duodenal disease in FAP based on the number, size, histologic type, and degree of dysplasia in the polyps. These staging criteria are listed in Table 2. Using these criteria, by endoscopic appearance and pathology, Kashiwagi et al.[18] categorized 76 patients with FAP to have either minor or major ampullary polyposis. At a mean follow-up of 44 months, 41% of patients with major ampullary polyposis showed evidence of progression compared to progression of only 7% of patients with minor disease ($P < 0.01$). Although no patients developed ampullary cancer during this observation period, patients with advanced polyposis clearly are at increased risk for early disease progression. Based on these criteria, Wallace and Phillips[19] proposed that patients with stage I or II disease may be safely evaluated every 3 years, whereas patients with stage III or IV disease should undergo endoscopy and biopsy annually.

Findings on screening endoscopy that necessitate treatment include enlarging lesions (>1 cm), severe dysplasia, villous histology, and carcinoma. In addition, polyps causing symptomatic disease such as pancreatitis, or pain or bleeding from ulceration, warrants intervention. Endoscopic ultrasonography is essential in evaluating patients with lesions suspicious for invasive adenocarcinoma, since invasion changes management. Patients must be fully informed of all treatment options, including required follow-up, before deciding on a plan of care.

Endoscopic intervention is a reasonable initial treatment for patients with few polyps, noncancer-

Table 1. Patient demographics and clinical results

	Patient 1	Patient 2	Patient 3
Age	33 yr	43 yr	38 yr
Sex	Male	Female	Female
Intensive care stay	None	None	None
Blood transfusion	None	None	None
Complications	Wound infection	None	Biliary leak
Hospital stay	17 days	8 days	8 days
Final pathology	Tubulovillous adenoma with high-grade dysplasia	Tubulovillous adenoma	Adenoma with hyperplasia
Follow-up	5 yr	1 yr	6 mo

Table 2. Duodenal polyposis staging system as proposed by Spigelman et al.[2]

Characteristic	Points assigned		
	1	2	3
Number of polyps	1 to 4	5 to 20	>20
Polyp size	1 to 4	5 to 10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Scoring system: stage 0 = 0 points; stage I = 1 to 4 points; stage II = 5 to 6 points; stage III = 7 to 8 points; stage IV = 9 to 12 points.

ous histologically advanced lesions, or patients who are not operative candidates because of medical comorbidities. Polypectomy by endoscopic snare or electrocaurtery is often accomplished. These techniques are challenging and particularly problematic for duodenal polyps in FAP because of the morphology and periampullary location of most duodenal polyps in this disease. Sessile polyps are not amenable to endoscopic snaring and attempts may lead to intestinal perforation. Electrocoagulation for periampullary lesions may lead to pancreatitis and bile duct scarring and stricture. In addition, these lesions recur in most patients and therapy often involves multiple treatment sessions. Alarcon et al.[15] reviewed recurrence in patients with advanced disease who were treated by endoscopic therapy. Six patients were treated endoscopically with a mean of 9.6 treatment sessions. Four patients failed therapy or developed a recurrence; three of them required surgery.

Complete duodenectomy is the only definitive means of preventing duodenal cancer. For patients

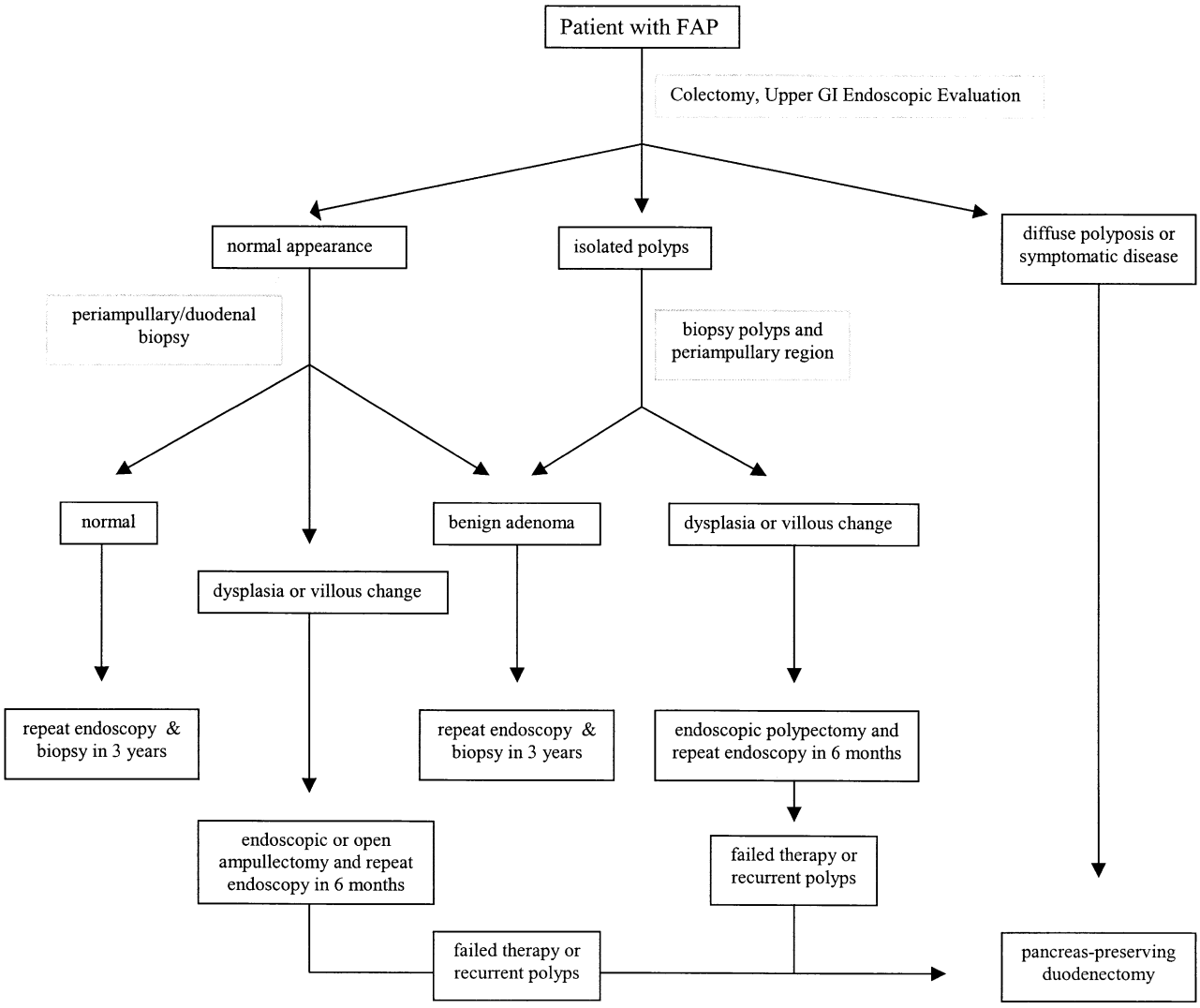

Fig. 4. Proposed clinical algorithm for treatment of duodenal polyps associated with familial adenomatous polyposis (FAP).

who have dysplasia, adenocarcinoma, or diffuse disease for which endoscopic therapy is impractical, surgical intervention is warranted. Pancreaticoduodenectomy is established and well described for malignant pancreatic and duodenal disease and also has traditionally been the surgical procedure of choice for diffuse polyposis.[20] In an effort to reduce the extent of resection in focal periampullary disease, several surgeons employed local resection or ampullectomy.[21] Local duodenal polyp resection has been well described in FAP, but is also associated with a high recurrence rate and significant morbidity.[15,22]

Chung et al.[6] first described pancreas-sparing duodenectomy in 1995 for four patients with FAP and one patient with duodenal trauma and no pancreatic pathology. This technique allows complete removal of disease without the morbidity of pancreas resection. These investigators report a 60% complication rate and no mortality with patients doing clinically well at follow-up of 6 months to 7 years. Our experience supports these results.

Given the small number of patients in our series and others, it is difficult to draw broad conclusions about the relative safety of pancreas-preserving duodenectomy compared to pancreaticoduodenectomy. Theoretically there are both technical and functional advantages to the pancreas-preserving procedure. First, performing a pancreaticojejunostomy in a nondiseased pancreatic duct is technically challenging because of small size and friable tissue. The periductal tissue in the head of the pancreas is more fibrous than that in the body of the pancreas, and the combined-duct anastomosis performed in the head with pancreas-preserving duodenectomy is larger and easier to sew. Second, preservation of the entire pancreas provides the advantages of uncompromised long-term endocrine and exocrine function.

Our clinical algorithm is summarized in Fig. 4. We suggest that patients with FAP undergo endoscopic evaluation of the upper gastrointestinal tract at the time of diagnosis with biopsy of any visually abnormal tissue as well as a normal-appearing periampullary region. If results are normal or the patient is determined to have stage I or II disease (see Table 2), endoscopic surveillance with biopsy should be repeated in 3 years. If a patient has visible polyps, several representative biopsies of the polyps as well as biopsies of the periampullary region should be performed. Benign adenomas may be watched for 3-year intervals without intervention. If a patient is found to have stage III or IV disease, yet does not have dysplasia or any other indication for intervention, the screening interval is 1 year. If polyps are larger than 10 mm or tissue biopsy reveals villous histology or dysplasia, intervention is indicated for premalignant change. Endoscopic ultrasound is used to evaluate for invasive disease. A small number of polyps may be amenable to endoscopic therapy with follow-up in 6 months. If endoscopic therapy fails or polyps recur, pancreas-preserving duodenectomy is recommended. Duodenectomy is also recommended, as for all patients in our series, for patients with diffuse polyposis in which local control is not feasible, or for patients with symptomatic disease. The timing of jejunal evaluation for polyps following pancreas-preserving duodenectomy is yet to be determined by longer follow-up.

In summary, the majority of patients with FAP develop duodenal polyposis with malignant potential. Although screening and intervention strategies continue to be debated, only total duodenectomy prevents duodenal adenocarcinoma. Pancreas-preserving duodenectomy is a safe, effective procedure with excellent functional outcome, but development of polyps in the jejunum may be expected. These results in comparison to those of standard pancreaticoduodenectomy for benign duodenal disease remain to be determined.

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Diabetes Is Associated With Increased Perioperative Mortality but Equivalent Long-Term Outcome After Hepatic Resection for Colorectal Cancer

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Diabetes is associated with alterations in liver metabolism and immune response that may influence postoperative recovery and long-term survival after hepatectomy for cancer. Patients with type I or type II diabetes mellitus submitted to a potentially curative hepatic resection for metastatic colorectal cancer were identified from the prospective database, and compared with patients with hepatic colorectal metastases submitted to resection during the same time interval, but without diabetes mellitus. Data on operative morbidity and mortality and long-term survival were analyzed. Between December 1990 and July 1999, a total of 727 patients underwent hepatic resection, 61 of whom (8.1%) had type I and type II diabetes mellitus. Operative mortality in the diabetic patients was significantly greater than in nondiabetic patients (8% vs. 2%, $P < 0.02$). Among patients with diabetes mellitus, four of the five perioperative deaths were due to liver failure after major hepatic resection (lobectomy or greater). All four of these patients had significant parenchymal abnormality (three with steatosis). Long-term survival was identical to that in nondiabetic control subjects. We conclude that the presence of diabetes is associated with a higher incidence of perioperative mortality. In patients with diabetes mellitus and parenchymal steatosis, major hepatic resection should be undertaken with caution. (J GASTROINTEST SURG 2002;6:88–94.)

KEY WORDS: Diabetes mellitus, steatosis, hepatic resection, chemotherapy

It is known that diabetes mellitus is associated with alterations in liver metabolism, which in experimental models compromise the ability of the liver to regenerate after major hepatic resection. Immune function is also altered in patients with diabetes, such that they theoretically may have compromised immune surveillance and thus may be predisposed to disease recurrence after resection of primary or secondary tumors. Previous reports examining the results of major hepatic resections have documented an increased level of postoperative morbidity in diabetic patients after elective resection for primary liver carcinoma,[1] a condition also associated with hepatitis and cirrhosis.[2,3] However, there is little information available about the effect of diabetes mellitus after elective hepatic resection for metastatic disease, both on perioperative outcome and long-term survival. The purpose of this study is to clarify the effect of diabetes mellitus on morbidity and mortality after elective hepatic resection in a population without hepatitis to determine whether acute perioperative outcome is affected by diabetes mellitus and to establish any adverse effect on long-term survival.

MATERIAL AND METHODS

Patients evaluated for colorectal cancer metastatic to the liver and treated by hepatic resection at Memorial Sloan–Kettering Cancer Center between December 1990 and July 1997 were identified from a prospective database. Medical records of all such patients were retrospectively reviewed. Admission notes, consultations, laboratory reports, radiologic imaging

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reports, operative reports, and pathology reports, as well as discharge summaries and follow-up records, were appraised. Variables measured at admission included patient demographics and comorbidity. The type of operation, transfusion requirements, histologic findings in the uninvolved liver, and complications were recorded. Patients with diabetes mellitus were identified at preoperative admission by the requirement for insulin or oral hypoglycemic drugs to control serum glucose. Patients with hepatic colorectal metastases submitted to resection during the same time interval, but without diabetes mellitus, served as the control group. The main outcome measures were the development of perioperative complications, particularly hepatic failure, and long-term survival.

Definitions

The nomenclature for defining hepatic resections is that of Goldsmith and Woodburne.[4] A right lobectomy refers to resection of Couinaud's[5] segments 5 through 8; a left lobectomy refers to resection of segments 2 through 4. An extended right hepatectomy refers to resection of segments 4 through 8; an extended left hepatectomy refers to resection of segments 2, 3, 4, 5, and 8. Diabetes mellitus was defined as a fasting serum glucose level above 7.8 mmol/L, abnormal results of a 75 g oral glucose tolerance test, or the need for oral hypoglycemic drugs or insulin for control of serum glucose. Perioperative morbidity and mortality were defined as any complication or death occurring within 30 days of operation. Hepatic decompensation was defined as the development of encephalopathy, hyperbilirubinemia (serum bilirubin > 3 mg/dl), and coagulopathy (prothrombin time > 18 seconds).[6]

Statistics

The chi-square test or Fisher's exact test, where appropriate, was used for univariate comparisons. Differences were considered significant at $P = 0.05$.[7] Patient long-term survival was calculated using the Kaplan-Meier method[8] and included all hospital deaths. The log-rank test was used to compare differences in survival distributions observed in subsets of patients.[9] All statistical analyses were carried out using SPSS 10.0 for Windows (SPSS, Chicago, Il.).

RESULTS

Patient Demographics and Follow-Up

Between December 1990 and July 1997, a total of 727 patients with colorectal carcinoma metastatic to the liver underwent a potentially curative hepatic resection. There were 417 men (57.4%) and 310 women (42.6%). Median age was 62 years (range 23 to 85 years). Diabetes mellitus was identified in 61 patients (8.1%). Median follow-up in all patients was 24 months (range 1 to 112 months). The extent of hepatic resection was trisegmentectomy in 212 (29.2%), lobectomy in 243 (33.4%), multiple segmentectomy in 126 (17.3%), segmentectomy in 68 (9.4%), and subsegmentectomy in 78 (10.7%).

Perioperative Results

Table 1 provides a summary of all primary and secondary procedures performed; there was no significant

Table 1. Procedures performed

	Nondiabetics		Diabetics	
	Primary liver procedure (n)	Secondary* procedure (n)	Primary liver procedure (n)	Secondary procedure (n)
Wedge or atypical resection	73	84	5	8
Segmental resection	58	30	5	
Bisegmentectomies				
Right posterior sectorectomy	31	6	2	2
Left lateral segmentectomy	39	2	7	1
Other bisegmentectomy	44	0	3	0
Left lobectomy (3 segments)	38	0	5	0
Right lobectomy (4 segments)	178	0	22	0
Extended left lobectomy (5 segments)	41	0	2	0
Extended right lobectomy (5 segments)	159	0	10	0
Caudate resection	5	0	0	4
Hemicolectomy	—	5	—	0
Arterial infusion pump	—	78	—	8
Total	666	205	61	23

*Other procedures including hepatic resections performed in addition to primary hepatic resections.

Table 2. Overall perioperative results

	Non-DM lobectomy n (%)	DM lobectomy n (%)	*P*	Non-DM lobectomy n (%)	DM lobectomy n (%)	*P*	All DM patients n (%)	All Non-DM patients n (%)	*P*
Total number	243 (36.5)	22 (36.1)	NS	423 (63.5)	39 (63.9)	NS	61 (8.4)	666 (91.6)	—
Blood loss									
<2 liters	231 (95.1)	19 (86.4)	NS	382 (90.3)	38 (97.4)	NS	57 (93.4)	613 (92.0)	NS
≥2 liters	12 (4.9)	3 (13.6)		41 (9.7)	1 (2.6)		4 (6.7)	53 (8.0)	
Complications	87 (35.8)	6 (27.2)	NS	175 (41.4)	18 (46.1)	NS	24 (39.3)	262 (39.3)	NS
Median hospital stay in days (range)	8 (0–46)	8 (4–23)	NS	8 (0–67)	8 (1–26)	NS	8 (1–26)	8 (0–67)	NS
30-Day mortality	2 (0.8)	0	NS	14 (3.3)	5 (12.8)	0.02	5 (8.0)	16 (2.4)	0.02

DM = diabetes mellitus; NS = not significant.

difference between the types of hepatic resection performed, with right lobectomy and extended right lobectomy being the most commonly performed procedures in both cohorts. Table 2 shows the overall perioperative outcomes for both diabetic and nondiabetic patients, based on the magnitude of liver resection (greater or lesser than a lobectomy), the proportion of which was similar in both groups. There were no significant differences in volume of blood loss, length of hospital stay, or postoperative complication rate between patients with and without diabetes mellitus for either size of resection. There was no significant difference in postoperative mortality in all patients with hepatic resections of less than a lobectomy. However, there was a significant difference in mortality between diabetic and nondiabetic patients (8.0% vs. 2.4%, $P = 0.02$). In patients who were subjected to resections of a lobectomy or greater, the difference in mortality rates was even more marked (12.8% vs. 3.3%, $P = 0.02$). Table 3 provides a summary of the causes of postoperative death in the five diabetic patients who constitute this subgroup. In four of these patients, death was the result of hepatic failure. All five patients underwent resection of a hepatic lobectomy or greater, and all had underlying parenchymal steatosis. Table 4 illustrates the various types of postoperative complications that occurred. Of note, there was no significant increase in infective complications in the diabetic cohort. However, diabetic patients did have a higher incidence of postoperative hepatic decompensation (21.2% vs. 2.5%).

The incidence of hepatic steatosis was similar in diabetic and nondiabetic patients (n = 22 [36%] and n = 200 [30%], respectively). Six patients (0.9%) in the nondiabetic group had cirrhosis of the liver and 18 (2.7%) had fibrosis. None of the livers of the diabetic patients were cirrhotic. Table 5, *A* illustrates the relationship between the presence of hepatic steatosis and the incidence of postoperative complications. There was no significant difference in complication rates in patients with hepatic steatosis. However, mortality rates were significantly increased in patients with parenchymal steatosis and

Table 3. Summary of perioperative deaths in patients with diabetes mellitus

Patient	Sex	Age (yr)	Primary operation	Complication	Liver parenchyma	Preoperative chemotherapy	Setting	Duration
1	M	53	RL, Ch	Intraoperative hemorrhage	Unknown	5-fluorouracil plus levamisole	A	Unknown
2	M	72	RT	Hepatorenal failure	Steatosis, bridging fibrosis	5-fluorouracil plus leucovorin	A	14 mo
3	M	72	RL	Hepatorenal failure	Focal scarring, cholesterolosis	5-fluorouracil plus levamisole	A	12 mo
4	M	71	RH, PV, C, Ch	Hepatorenal failure, abdominal sepsis	Steatosis	5-fluorouracil	N	1 mo
5	M	75	RL, W	Hepatorenal failure, polymicrobial sepsis, gastrointestinal hemorrhage	Steatosis, portal chronic inflammation	5-fluorouracil	A	Unknown

A = chemotherapy given adjuvant to bowel resection; C = repair of common hepatic duct; Ch = cholecystectomy; L = lobectomy; N = chemotherapy given neoadjuvant to liver resection; PV = excision and repair of portal vein; R = Right; T = extended hepatectomy; W = wedge resection.

Table 4. Complications after liver resection

	Nondiabetics (n = 262)		Diabetics (n = 24)	
	n	%	n	%
Infections				
Wound	15	5.4	3	9.1
Urinary tract	8	2.9	0	0
Intraperitoneal	17	6.2	4	12.1
Total infective complications	40	15.3	7	29.2
Hepatic decompensation	7	2.5	7	29.2
Bile leak	31	11.2	5	15.2
Hemorrhage				
Gastrointestinal	3	1.1	2	6.1
Intraperitoneal	7	2.5	1	3.0
Cardiac	28	10.1	2	6.1
Respiratory	27	9.8	6	18.2
Other	133	48.2	3	9.1
Total number of complications	276	—	33	—
Overall complication rate	262	39.3	24	39.3
Overall postoperative mortality rate	16	2.4	5	8.2

diabetes compared to nondiabetic patients (13.6% vs. 3.5%, $P = 0.01$). This is further explored in Table 5, *B*, which examines how resection size influences perioperative mortality. In diabetic patients with hepatic steatosis, resection of a lobe or more was associated with a 20% perioperative mortality rate, compared to no deaths in the group treated by a resection of less than a lobectomy. There is a similar pattern in patients who received preoperative chemotherapy (i.e., chemotherapy given in an adjuvant setting after resection of the primary colorectal tumor or as neoadjuvant therapy before liver resection) (Table 5, *C*). All diabetic patients who died after surgery had been given chemotherapy before hepatectomy. In diabetic patients who received chemotherapy, hepatic lobectomy or greater was associated with a 20% mortality rate, compared to no deaths in the group who underwent resection of less than a lobectomy.

Long-Term Survival

Fig. 1 illustrates long-term survival after hepatic resection for both cohorts. There was no significant difference between diabetic and nondiabetic patients, with median survival being 42 months and 43 months, respectively. The 1-year, 3-year, and 5-year survival rates for diabetic and nondiabetic patients, respectively, were 89%, 55%, and 30% and 91%, 59% and 35%.

DISCUSSION

Over the past decade, advances in surgical technique, anesthesia, and perioperative management have resulted in improved postoperative outcome after partial hepatectomy for metastatic colorectal disease such that the mortality rate at major centers is now less than 5%.[10] Despite these improvements, the level of postoperative morbidity is still significant, and postoperative liver failure remains an important cause of early death in these patients. This study identifies a subgroup of patients who may be at increased risk for postoperative death resulting from hepatic decompensation. Patients with diabetes mellitus who undergo elective hepatic resection for metastatic disease may have a significantly higher perioperative mortality rate, particularly if they have underlying hepatic steatosis. This difference is even more pronounced in diabetic patients who receive preoperative chemotherapy.

Diabetes mellitus is associated with an increased level of cardiovascular and renal dysfunction that may be expected to result in higher levels of overall postoperative morbidity. The effect of diabetes mellitus on major gastrointestinal resections remains controversial.[11,12] Previous studies have shown that the presence of diabetes mellitus is an independent predictor of morbidity after elective hepatic resection for hepatocellular carcinoma.[13] In the current study of hepatic resections for metastatic colorectal cancer, the incidence of overall postoperative morbidity was comparable in diabetic and nondiabetic patients. In particular, there was no significance difference in the incidence of infective complications (5.4% vs. 9.1%) or cardiac events (6.1% vs. 10.1%). This may, in part, reflect careful patient selection and current cardiovascular support for patients at high risk. However, the incidence of hepatic decompensation was significantly higher in the diabetic group (29.2% vs. 2.5%). This was despite the fact that the magnitude of hepatic resections was comparable in both groups, with approximately 63% of patients undergoing resection of lobectomy or greater (see Table 2). The increased incidence of hepatic failure may be the result of the inability of the diabetic liver to withstand major hepatic resection and for the remnant liver to provide adequate hepatic metabolic and synthetic function while regeneration takes place. In support of this, Shirabe et al.[1] reported in 1999 that in patients with a liver remnant volume of less than 250 ml/m^2, the presence of diabetes was an independent risk factor for postoperative liver failure. Additionally, it is known that hepatic regeneration requires significant metabolic effort, and it may be that, as a result of altered glucose metabolism, the liver parenchyma of diabetic patients is un-

Table 5. Influence of hepatic steatosis or chemotherapy on postoperative complications and mortality

A. Influence of steatosis

	Nondiabetics		Diabetics			Total	
	n	%	n	%	*P*	n	%
Complications							
Steatosis present	88 of 20	44.0	11 of 22	50.0	0.8	99	44.6
Steatosis absent	174 of 466	37.3	13 of 39	33.3	0.7	187	37.0
Post operative deaths							
Steatosis present	7 of 200	3.5	3 of 22	13.6	0.01	11	4.9
Steatosis absent	9 of 466	1.9	1 of 39	2.6	0.4	10	2.0

B. Influence of steatosis and resection size on mortality

	Nondiabetics with steatosis (n = 202)		Diabetics with steatosis (n = 22)	
	≥ Lobectomy	< Lobectomy	≥ Lobectomy	< Lobectomy
Total number (%)	124 (61.4)	78 (38.6)	15 (68.2)	7 (31.8)
Perioperative death (n)	5	2	3	0
Perioperative death (%)	4.0	2.6	20.0	0

C. Influence of chemotherapy and resection size on mortality

		Perioperative death	
	Total number	n	%
Diabetics with preoperative chemotherapy (n = 38)			
≥ Lobectomy	25	5	20
< Lobectomy	13	0	0
Diabetics with no preoperative chemotherapy (n = 23)			
≥ Lobectomy	14	0	0
< Lobectomy	9	0	0
Nondiabetics with preoperative chemotherapy (n = 304)			
≥ Lobectomy	194	4	2.1
< Lobectomy	110	0	0
Nondiabetics with no preoperative chemotherapy (n = 362)			
≥ Lobectomy	229	10	4.4
< Lobectomy	133	2	1.5

able to generate sufficient energy to allow the regenerative process to occur adequately in the immediate postoperative period.

Further evidence comes from histologic examination of the parenchyma of the uninvolved liver after resection. Steatosis was common in the diabetic patients (36% incidence). The incidence of fibrosis and inflammation was comparable in the two groups. When the actual cause of death is examined in each of the five diabetic patients who died postoperatively (see Table 2), it can be seen that hepatic failure (with or without subsequent hepatorenal syndrome) was the cause of death in four of five cases. It is significant that all four patients had some degree of hepatic parenchymal abnormality and all four underwent a resection of greater than a lobectomy. Several factors have been associated with an increased level of hepatic failure and mortality after liver resection. These include intraoperative blood loss and the volume and function of the remaining liver.[10,14–16] Studies in animal models have shown that the ability of parenchymal regeneration is impaired in steatotic livers,[17] and work by Behrns et al.[18] in 1998 indicated that hepatic steatosis is a major risk factor for death following hepatic resection, with a reported mortality rate greater than 14%.

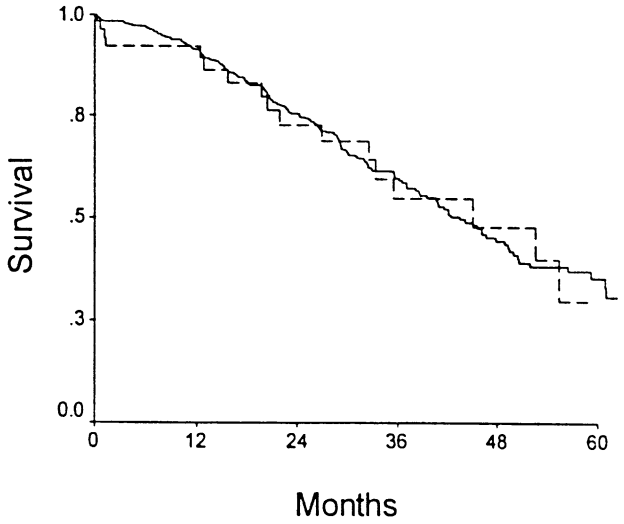

Fig. 1. Kaplan-Meier curve for long-term survival in diabetic (*broken line*) and nondiabetic patients (*solid line*).

The incidence of steatosis in the livers of diabetic patients may partly explain the inability of some diabetic patients to withstand major hepatic resection. Of note, nondiabetic patients with steatosis did not exhibit the high mortality seen in diabetic patients. This suggests differences in hepatic metabolism and repair between the two groups that warrant future studies.

Portal vein embolization has emerged in recent years as a preoperative protective strategy for patients at risk for postresection hepatic failure. The purpose is to initiate compensatory hypertrophy in the intended liver remnant and thus provide greater residual hepatic function and minimize postoperative hepatic failure.[19] Whether this or other techniques may be appropriate to improve outcome of major hepatic resection in the diabetic patient with steatosis also warrants investigation.

Long-term survival was slightly lower in diabetic patients, although this did not reach statistical significance, with comparable 5-year survival rates of 30% for diabetic and 35% for nondiabetic patients. This small difference can be explained by the difference in initial perioperative mortality. There have been several reports linking diabetes mellitus to an increased risk of primary liver cancer.[3,20,21] However, little information exists regarding the effect that immune dysfunction related to altered glucose metabolism may have on tumor recurrence and the ability of the immune system to deal with micrometastases. Based on the survival data from our study, there did not appear to be an increased level of tumor recurrence, and so this would appear not to be a clinically significant factor in metastatic colorectal cancers.

CONCLUSION

Hepatic resection of a lobectomy or greater was poorly tolerated by a subset of diabetic patients (i.e., those with coexisting hepatic steatosis and/or prior chemotherapy). The implications of this are that when contemplating major hepatic resection in patients with diabetes mellitus, surgeons should be aware that the presence of diabetes mellitus may portend a higher incidence of hepatic failure postoperatively. Further studies in this area should focus on possible protective strategies for the steatotic liver.

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Cryosurgery After Chemoembolization for Hepatocellular Carcinoma in Patients With Cirrhosis

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Most cirrhotic patients with hepatocellular carcinoma (HCC) are not candidates for resection. Transarterial chemoembolization (TACE) may ablate a significant portion of the tumor but has a high rate of recurrence. Cryosurgery may permit successful ablation of hepatic tumors but can be complicated by postoperative hemorrhage and is also associated with a significant risk of recurrence. The combination of the two techniques might be beneficial. We evaluated in a prospective study the safety and efficacy of this combination in cirrhotic patients with unresectable HCC. Fifteen patients were included in this study. All but one patient underwent one or several sessions of TACE before cryosurgery. Cryoablation was successfully performed in each patient. The patient who did not undergo preoperative TACE required reoperation for hemorrhage. Another patient with Child-Pugh class B cirrhosis died postoperatively of hepatic and multiorgan failure. At a mean follow-up of 2.5 years, three patients had recurrence of disease, and 13 of 15 patients were alive with the longest survival time being 5 years. The actuarial survival rate at 5 years was 79%. Cryosurgery after TACE is feasible in cirrhotic livers with HCC and can increase the cure rate in large tumors. TACE may reduce the risk of hemorrhage after cryosurgery but can increase the risk of hepatic failure in patients with poor hepatic function. (J GASTROINTEST SURG 2002;6:95-101.)

KEY WORDS: Cryosurgery, transarterial chemoembolization, hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a major cause of death worldwide and is increasing in incidence in the United States and Europe as a result of hepatitis B– and C–induced cirrhosis.[1] Hepatectomy is considered the best option for the treatment of HCC but is not feasible in many patients with cirrhosis. Resection rates range from 12% to 45%,[2,3] and morbidity and mortality rates reach 26% to 46%[3–5] and 7% to 23%,[2,4–9] respectively. The 5-year survival rate after resection of HCC in patients with cirrhosis ranges from 21% to 41%.[2,4,5,9]

An alternative or adjunct to resection is transarterial chemoembolization (TACE), but this approach has a high risk of leaving residual disease. In one study, neoplastic cells were found in 47% of patients within the capsule or in the pericapsular tissue from specimens obtained after TACE.[10] This suggests that TACE should be followed by another procedure to achieve additional tumor ablation, if feasible. In the same study, patients who underwent TACE followed by resection had a higher survival rate than those who underwent TACE alone.[10] In another study, TACE followed by percutaneous ethanol injection yielded an improvement in survival compared to TACE alone, although it was not statistically significant.[11]

Another therapeutic option is cryosurgery.[12] In 1979 Dutta et al.[13] demonstrated the feasibility of cryoablation of large volumes of liver tissue in canine experimental models. The cryoablated tissue was left in situ and was shown to be gradually absorbed. Initially, hepatic cryotherapy was performed by direct application of liquid nitrogen to surface lesions. Lesions located deeper in the liver required the development of insulated probes that carried recirculating liquid nitrogen. When used in conjunction with intraoperative ultrasound, these probes have enabled the safe application of cryoablation to most locations within the liver.

Although this technique is used in a number of centers, the indications and results remain unclear.[1]

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Promising results were reported in studies that used cryoablative surgery alone and cryoablative surgery plus ethanol injection for HCC in patients with cirrhosis.[14,15] Because cryosurgery alone is associated with high recurrence rates and may be complicated by postoperative hemorrhage, we reasoned that preoperative TACE might improve outcome. In 1995 we initiated a prospective study in a selected group of patients with unresectable HCC to evaluate the safety and efficacy of TACE combined with cryosurgery.

MATERIAL AND METHODS

We prospectively evaluated cirrhotic patients with HCC treated with TACE followed by cryosurgery at Duke University Medical Center between June 1994 and December 1999. Patients were considered candidates for the procedure if they had biopsy-proved HCC or a suspicious mass on imaging studies associated with major elevation of the serum alpha-fetoprotein (α-FP) level of more than 1000 U/ml in the setting of cirrhosis. In all cases, the tumor was considered to be unresectable or surgical resection was not thought to be feasible because of tumor location or size, or patient comorbidity. Patients who had Child-Pugh class B cirrhosis with ascites or Child-Pugh class C cirrhosis were excluded from this protocol. Postoperative changes in platelet count, hepatic enzymes, bilirubin levels, and serum α-FP levels were evaluated preoperatively and at 3, 6, 12, and 18 months, and yearly thereafter. Preoperative status of the disease, tumor characteristics, and survival rates were analyzed. Statistical analysis for the survival rate was performed by the Kaplan-Meier method.

Transarterial Chemoembolization

TACE was performed in the interventional radiology suite after cross-sectional images were reviewed. Coagulation abnormalities were corrected and platelets were administered if the platelet count was <100,000. Ceftriaxone, 1 g, was administered intravenously. The right groin was prepped and draped in sterile fashion. A 6 French vascular sheath was placed into the femoral artery, and a 0.035 inch diameter Mickaelson catheter was advanced into the celiac and superior mesenteric arteries. Contrast was injected into the arteries during rapid-sequence radiographic imaging. Arterial branches supplying the tumor were noted. The venous phase was carefully examined for patency of the portal veins. The vessels were analyzed for the presence of anatomic variation. A 0.018 inch diameter Tracker catheter was advanced through the Mickaelson catheter to the arterial branches that supply the tumor. Doxorubicin, 50 mg, and Mitomycin, 10 mg, were mixed with Ivalon particles (150 to 250 micron diameter), and the mixture was injected into the arterial branches until hemostasis was achieved. If the tumor had a multivessel arterial supply, TACE was performed in two stages, 2 weeks apart.

Cryosurgery

Cryoablation was performed 2 to 4 weeks after TACE during an open surgical procedure in all but one patient using the LCS 3000 Cryosurgical System (Candela Corp., Boston, Mass.). The period of 2 to 4 weeks was to offer sufficient time for patients to recover after the TACE procedure, and the belief that necrosis would be maximal after 2 weeks. This system has the advantage of flow control, which provides control of the size of the ice ball forming around the cryoprobe. Our cryoablation protocol[16] began with an extensive preoperative workup that included a spiral CT scan, evaluation of tumor markers (α-FP, CEA, and CA19.9), and in selected patients, positron emission tomography (PET) using the glucose analogue fluoro-2-deoxy-D-glucose to screen for extrahepatic disease. We routinely began the operative procedure with a laparoscopic examination before celiotomy to detect extrahepatic or diffuse intrahepatic disease. Intraoperative ultrasound imaging with the use of 5.0 and 7.5 MHz probes was then performed to determine the number of lesions, their sizes and locations, and their proximity to bile ducts or major vessels. The liver was mobilized and isolated from surrounding tissues, and needle biopsies were performed if this had not been done preoperatively. Smaller lesions were ablated with a 5 mm probe, which produces a 4 to 5 cm freeze zone. For larger lesions a 10 mm probe was used. These probes were introduced into the lesion by a modified Seldinger technique under real-time ultrasound guidance with special care to avoid major bile ducts and vessels. Once the probe was positioned, freezing was initiated by circulating liquid nitrogen. Each cycle consisted of a freeze phase of 15 minutes once the maximum ice ball size was reached followed by thawing at −20° C (Fig. 1), at which point the probes were no longer adherent to the tissues and could be safely removed. The intention is to create a freeze zone of at least 1 cm beyond the margins of the tumor. Once the probe was removed, the tract was filled with Gelfoam strips soaked in thrombin. The peritoneal cavity should not be washed until the liver is completely thawed. No abdominal drains were left, and precautions were taken to avoid hypothermia by use of warm blankets and warm intravenous fluids.

Fig. 1. A 10 mm cryoprobe (LCS 3000) in the process of freezing a large (7 cm) HCC previously subjected to chemoembolization.

Patient Follow-Up

Patients were evaluated postoperatively for recurrence or residual disease by measuring serial α-FP levels and by reviewing abdominal CT scans at 3, 6, 12, 18, and 24 months, and every year after surgery. Overall survival was measured from the time of surgery until the time of death or last follow-up. The Kaplan-Meier method was used to derive survival curves.

RESULTS

From June 1994 to December 1999, fifteen patients (11 men and 4 women) underwent cryoablation for HCC (Table 1). During the same time period, we performed a palliative cryosurgical procedure on an additional patient with recurrent fibrolamellar HCC, but because of the palliative aim and the different natural history of this tumor subtype, we did not include this patient in the present data analysis. The median age was 63 years (range 25 to 79 years). All patients had cirrhosis. Eleven patients were Child-Pugh class A, and four were class B without ascites. The diagnosis was established histologically in 12 cases by percutaneous biopsy, and in three cases by the presence of a suspicious hepatic mass associated with major elevation in α-FP levels (1400, 2500, and 9000 U/ml).

Table 1. Patients, tumor characteristics, and outcome

Patient	Age (yr)	Underlying cause of cirrhosis	Child class	No. of lesions	Size of lesion (cm)	Location segment	Reason for unresectability	Postoperative morbidity	Hospital stay (days)	Survival
1	74	Hemochromatosis	A	1	3	8	Comorbidity*	Skin freezing injury†	6	Alive 5 yr
2	56	Hepatitis C	B	1	5	8	Location and size	N	6	Alive 5 yr
3	76	Methotrexate toxicity	A	1	9	4	Comorbidities, location, and size	Biloma	9	R 14 mo Died 17 mo
4	39	Alcohol	B	1	6	5	Location, size, and liver disease	Liver failure	5	Died 21 days
5	73	Cryptogenic	A	1	3	1	Comorbidity*	N	7	R 33 mo Alive 41 mo
6	48	Alcohol	A	1	7.5	5 - 6	Comorbidity,* location and size	N	4	Alive 28 days
7	61	Cryptogenic	B	1	5.5	8 - 4a	Location and size	N	8	R 21 mo Alive 30 mo
8	67	Hepatitis C	A	1	6	4a + b	Location and size	N	4	Alive 20 mo
9	56	Cryptogenic	A	1	6	8	Location and size	N	3	Alive 28 mo
10	79	Cryptogenic	A	1	8	8	Comorbidities, location and size	N	5	Alive 2 yr
11	76	Cryptogenic	A	1	12	8	Location and size	N	4	Alive 21 mo
12	57	Hepatitis B	A	1	3	6	Comorbidity*	N	5	Alive 1 yr
13	60	Cryptogenic	A	1	6	4	Location and size	N	5	Alive 27 mo
14	60	Alcohol	A	1	5	6 - 7	Location and size	N	4	Alive 15 mo
15†	68	Alcohol	B	2	6	7 - 8	Comorbidity	Bleeding	7	Alive 1 yr

HepB = hepatitis B; Seg = segment; N = no complications; R = recurrent tumor.

*Refers to severe cardiac or pulmonary conditions thought to significantly affect the surgical risk.

†A laparoscopic approach was used in this patient. Freezing injury of the skin occurred during the procedure, which required local treatment for 6 months.

‡This patient had no transarterial chemoembolization before cryosurgery and was reexplored for the bleeding on postoperative day 1.

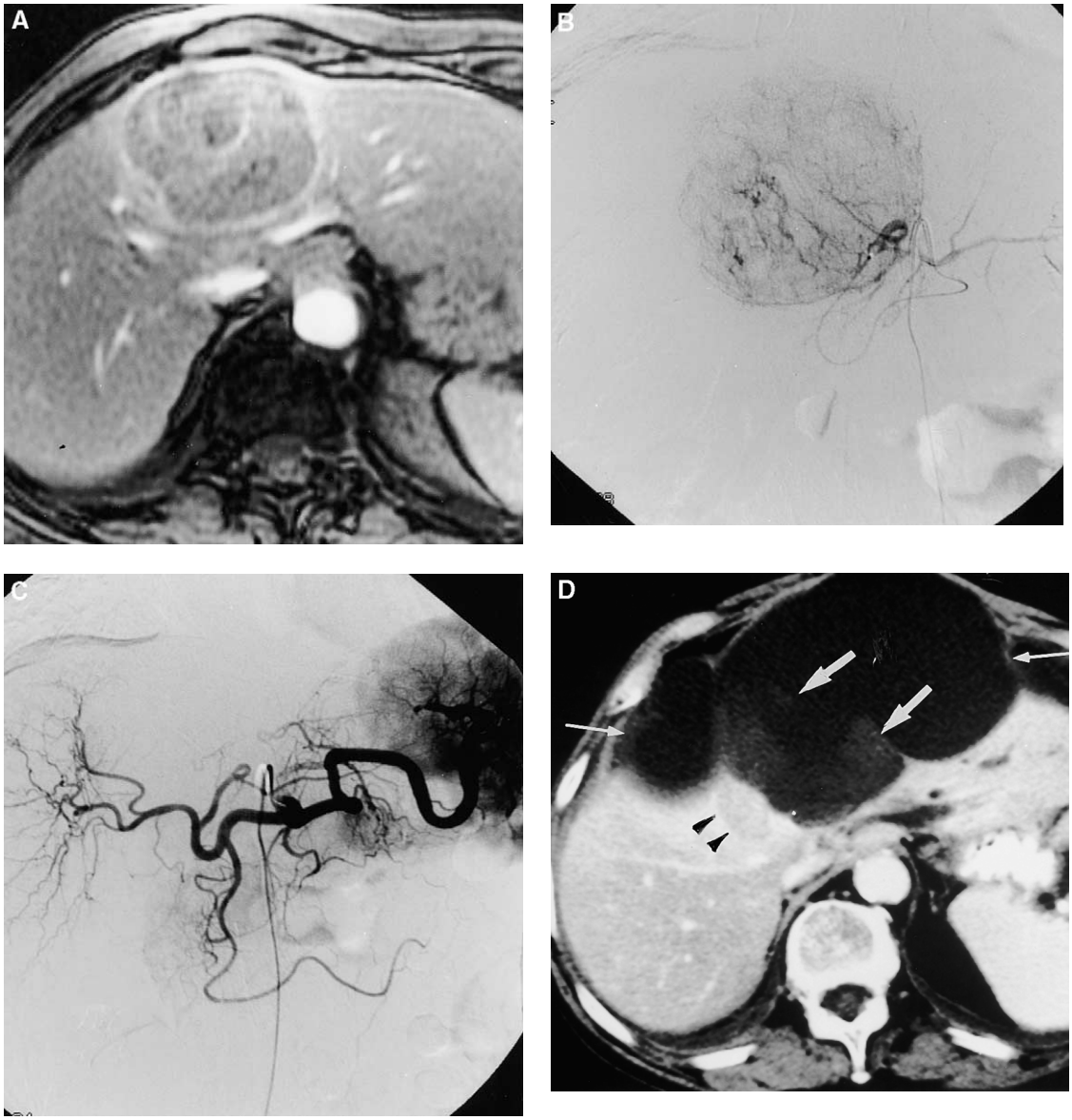

Fig. 2. A, Dynamic T1-weighted MRI from a 76-year-old woman (patient 3) shows a large heterogeneous mass with an enhancing capsule in segment IV of the liver. **B**, This patient had cirrhosis related to long-term methotrexate treatment for psoriasis. She underwent chemoembolization with selective catheterization of the left hepatic artery. **C**, Control celiac arteriogram after chemoembolization demonstrates abrogation of the vascularity of the mass. This patient underwent cryoablation of the tumor 4 weeks later. **D**, Dynamic contrast-enhanced CT of the liver 14 months after cryosurgery shows infarcted tissue (*wide arrow*), adjacent fluid collections (*narrow arrows*), and residual tumor (*arrowheads*).

Fourteen patients were treated with TACE 1 to 4 weeks before cryosurgery, which was well tolerated in each patient who required hospitalization for 1 to 4 days to receive intravenous analgesics and antiemetics. Thirteen patients had one session and two patients had two sessions 2 weeks apart because of multiple arterial supply to large (>7 cm) tumors. One patient had cryosurgery alone because of the failure of TACE. Fourteen patients had a single tumor confined to one lobe, 12 in the right lobe and two in the left lobe, and only one patient had bilobar disease. The median diameter of the tumor was 6.5 ± 2.8 cm (range 3.5 to 12 cm). Cryoablation was well tolerated. For example, the preoperative and postoperative imaging studies of patient 3 are shown in Fig. 2. Laboratory studies detected a decrease in platelet counts with a nadir of 100,900 ± 60,700/mm^3 occurring on the fifth to seventh postoperative day (Fig. 3). Only two patients required intraoperative or postoperative blood transfusions (1 and 4 units of packed

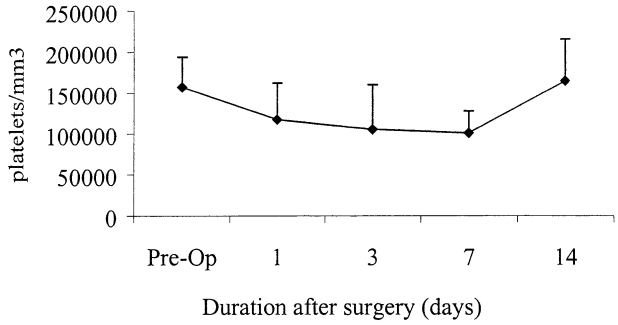

Fig. 3. Platelet count was the lowest on postoperative day 7 (100,900 ± 60,700/mm^3). Levels normalized within 2 weeks of surgery.

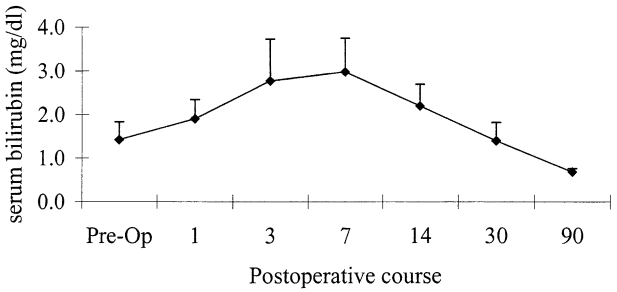

Fig. 5. Serum bilirubin levels after cryosurgery peaked at postoperative day 7 and progressively normalized by 3 months.

red cells, respectively). The one patient who did not undergo preoperative embolization underwent surgical reexploration on the first postoperative day for intra-abdominal bleeding. In each patient, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated during the immediate postoperative period but recovered quickly (Fig. 4). Bilirubin levels peaked on the seventh postoperative day and normalized progressively by 1 month (Fig. 5). The median duration of hospitalization was 5 days (range 3 to 9 days). In a patient who was Child-Pugh class B, hepatic and renal failure occurred postoperatively and resulted in death on the twenty-first day.

Postoperatively we evaluated patients for recurrence based on α-FP levels and abdominal CT scans at 3, 6, 12, 18, and 24 months, and every year after surgery. During this study period we observed three recurrences (20%). One of these patients had a recurrence at 14 months and died at 17 months; one had a recurrence at 21 months (Fig. 6) and was alive at 2.5 years, and one had a recurrence at 33 months after cryosurgery and was alive at 3.5 years. In these three patients the recurrence was located in the vicinity of the area of cryoablation (see Fig. 2, *D*), suggesting that the "failures to cure" were related to residual cancer cells after cryosurgery. The first two patients had elevated α-FP levels (2450 U/ml and 1800 U/ml) before they were enrolled in the study, which normalized within 3 months after cryosurgery. α-FP levels were in the normal range at 6 and 18 months, respectively, but increased to 900 U/ml after 13 months in the first patient and to 350 U/ml after 18 months in the second. The third patient had normal α-FP levels before and after treatment. Among the 11 other patients, 10 had abnormally elevated α-FP levels before surgery (range 80 to 9000 U/ml), which returned to normal within 6 months of surgery in each case.

At a median follow-up of 2.5 years (range 1 to 5 years), 13 of 15 patients were alive for actuarial 3- and 5-year survival rates of 79% (Fig. 7).

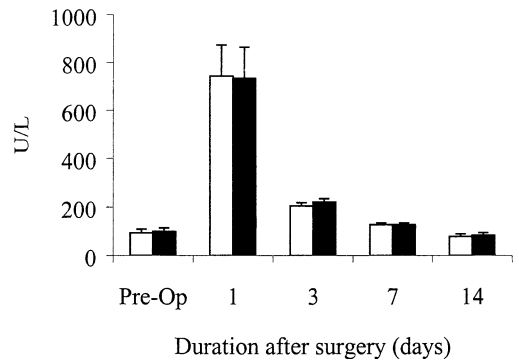

Fig. 4. Serum transaminase levels after cryoablation. AST (□) and ALT (■) peaks occurred on postoperative day 1, and dramatically decreased until 2 weeks after cryosurgery. AST = aspartate aminotransferase; ALT = serum alanine aminotransferase.

DISCUSSION

We report the clinical results of TACE followed by cryosurgical ablation of unresectable HCC in patients with cirrhosis. The combined procedures were well tolerated with one death due to hepatorenal failure in a Child-Pugh class B patient. The most consistent postoperative biochemical changes were transient thrombocytopenia, hyperbilirubinemia, and elevation of the serum hepatic enzymes AST and ALT, which recovered within 2 weeks in most of the patients. During this study period we observed two recurrences and a 5-year actuarial survival of 79% in this selected group.

There are few reports of cryosurgery for HCC in the English literature. Most reports of hepatic cryosurgery describe its use in the palliative treatment of metastatic tumors such as colon cancer. Two recent reports of cryosurgery for HCC suggested that cryosurgery with curative intent is feasible and safe, but palliative cryosurgery in advanced disease yields poor results.[14,17] Some authors have suggested that alcohol ablation after cryosurgery is an important adjunct in treating residual tumor and controlling recurrences.[17]

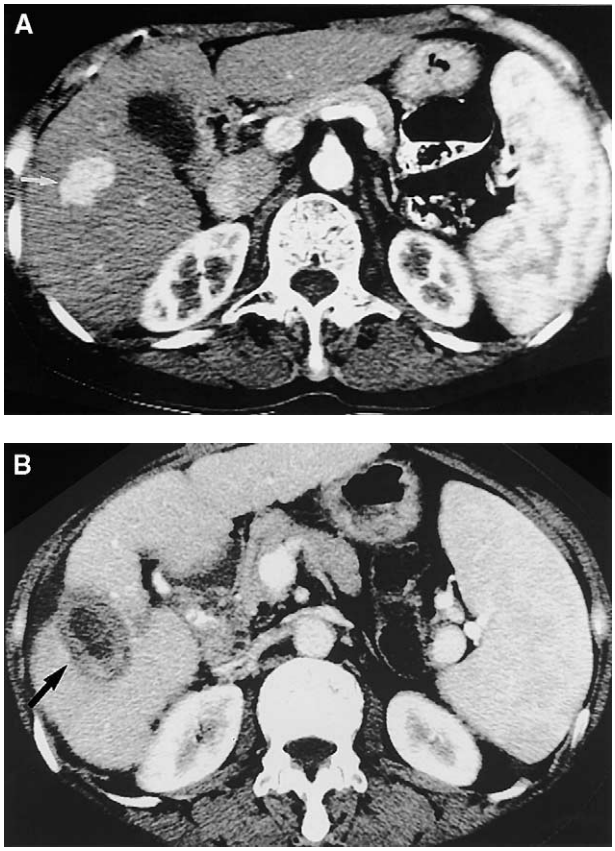

Fig. 6. Dynamic contrast-enhanced CT scan of the liver in a 61-old-man (patient 7) with cryptogenic cirrhosis revealed a mass in the right hepatic lobe at the hepatic arterial phase (**A**) and at the portal venous phase (**B**) 21 months after cryosurgery for a large mass in segment VIII. There is a necrotic focus in the right hepatic lobe with a thick rim of granulation tissue.

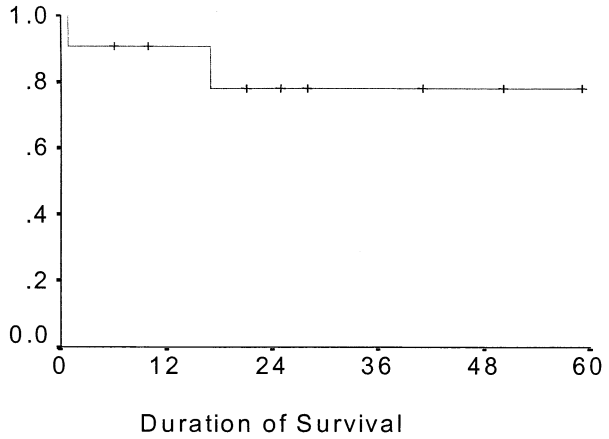

Fig. 7. Actuarial survival curve after cryosurgery for hepatocellular carcinoma in cirrhotic liver (Kaplan-Meier method).

Our study differs from previous reports in terms of disease stage, tumor characteristics, and survival of the patients. Our technique of cryoablation, incorporating two freeze-thaw cycles per lesion with an ice ball of 1 cm around the lesion, was similar to that used by a number of other groups.[18,19] Intraoperative ultrasonography is essential because it not only defines the extent of the disease but also guides the decision of whether to use resection or cryoablation. Most patients in the prior reports had stage III or IV HCC with multiple masses and poor survival. In our series, most of the patients had only one lesion and had well-compensated cirrhosis. Although long-term follow-up is needed, our results demonstrate lower recurrence rates and longer survival. If the tumor recurs, reablation of the tumor by means of cryosurgery or radiofrequency ablation (RFA) remains possible.

The major complications of cryosurgery in our highly selected group of patients were postoperative hemorrhage in a patient who did not undergo TACE and one death after liver failure in a patient with Child-Pugh class B cirrhosis. Patients with ascites or class C cirrhosis were not included. We further suggest that patients who have Child-Pugh class B cirrhosis undergo additional preoperative testing of hepatic functional reserve such as indocyanine green excretion and/or the galactose elimination test.

The beneficial role of TACE in our study is speculative. TACE alone is associated with a 47% rate of residual viable tumor within the capsule.[10] The survival rates for 41 patients treated with TACE were 82%, 53%, and 28% at 1, 2, and 3 years, respectively.[20] A similar result was shown in other studies.[21,22] TACE followed by percutaneous ethanol injection is associated with a nonsignificant increase in survival compared with TACE alone.

One advantage of performing TACE before cryosurgery is a possible reduction in postoperative bleeding, as well as an increase in the rate of tumor ablation. We performed cryosurgery without prior TACE in one patient who required reexploration for postoperative bleeding. In contrast, the risk of hepatic failure may increase in those who undergo TACE first.[11] One patient with Child-Pugh class B cirrhosis developed liver and renal failure 3 weeks after cryosurgery. The period of 2 to 4 weeks between TACE and the cryosurgery procedure remains speculative. The rationale was to give the patient an opportunity to recover from the TACE and the belief that necrosis could be maximal after 2 weeks. However, we cannot exclude the possibility that a shorter period could be more effective because of the possibility of rapid recanalization or collateralization after chemoembolization.

A recent question is whether RFA, which can be performed percutaneously, could replace cryosurgery. A recent consecutive prospective nonrandomized study comparing these two modalities showed that cryosurgery caused a significantly higher rate of complications (41% vs. 3%, $P > 0.001$), and was associ-

ated with a higher rate of recurrence (14% vs. 2%, $P > 0.01$).[23] This study has been criticized because of its higher rate of complications from cryosurgery compared to other reports. Furthermore, cryosurgery is able to ablate larger and more difficult to reach tumors than RFA. Because RFA is usually performed percutaneously, the probe cannot be placed as accurately as the cryoprobe during the open cryosurgery procedure. Also, with the RFA probes previously available, the largest tumors that could be ablated were 3 cm in diameter. If 3 cm is used as the upper limit of tumor size treatable by RFA, eight of the lesions in our study would not have been amenable to RFA because of their size and/or location. However, a prospective randomized study between cryosurgery and RFA will ultimately be necessary to determine the role of each modality in the treatment of HCC. Finally, a study comparing resection and cryosurgery in patients with cirrhosis is warranted. For cirrhotic patients with compromised hepatic reserve and the potential to develop multiple hepatomas, cryosurgery may be better tolerated and more feasible.[24]

CONCLUSION

Cryosurgery after TACE is an effective, well-tolerated modality for ablating hepatic tumors in selected patients with cirrhosis who are not candidates for tumor resection.

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Hepatocellular Carcinoma: A Prime Indication for Living Donor Liver Transplantation

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Cadaveric liver transplantation for hepatocellular carcinoma (HCC) is limited by donor organ availability. This report reviews our initial experience with living donor liver transplantation (LDLT) for HCC. Since August 1998, a total of 71 adults have undergone LDLT; 27 (38%) for HCC. Underlying diagnoses included hepatitis C in 17, hepatitis B in eight, cryptogenic cirrhosis in one, and primary biliary cirrhosis in one. Four patients had recurrent HCC after resection. Patients with tumors measuring 5 cm or larger received a single dose of intravenous doxorubicin intraoperatively and six cycles of doxorubicin at 3-week intervals beginning 6 weeks postoperatively. All HCC patients are followed with CT scans and alpha-fetoprotein measurements every 3 months during the first 2 years after transplant. Mean waiting time to transplant for patients with HCC was 83 days, compared to 414 ($P = 0.001$) days for 50 patients with HCC who were transplanted with cadaveric organs during this period. At median follow-up of 236 days, there have been four deaths due to non–tumor-related causes and one death from recurrence; recurrence has been observed in one other patient. LDLT permits expeditious transplantation in patients with early HCC, and provides access to transplantation for patients with HCC exceeding the United Network of Organ Sharing criteria for prioritization who are, in effect, barred from receiving cadaveric organs. (J GASTROINTEST SURG 2002;6:102–107.)

KEY WORDS: HCC, transplantation, living donor

Hepatocellular carcinoma (HCC) is the seventh most common cause of cancer-related death worldwide.[1] In more than 90% of cases, HCC develops in the setting of underlying liver disease, most commonly chronic hepatitis B or C. The incidence of HCC rose in North America by 71% over the 20-year period between 1976 and 1995, from 1.4/100,000 to 2.4/100,000,[2,3] primarily because of the rising incidence of hepatitis C; HCC-related mortality increased 41% during the same period.[4,5]

Physical removal or destruction of HCC prior to metastasis is the only hope for cure, but cirrhosis and multicentricity preclude resection in most patients.[6,7] Transplantation is a logical approach in such cases, as it can potentially cure both the cirrhosis and the HCC.[8] The limited availability of cadaveric donor organs, however, has restricted the applicability of liver transplantation in HCC. The recent development of adult living donor liver transplantation (LDLT) provides an alternative source of donor livers for transplantation. We report herein our initial experience with adult LDLT for HCC.

PATIENTS AND METHODS

Candidates for LDLT must meet United Network of Organ Sharing (UNOS) minimal listing criteria. Only patients with HCC recognized preoperatively were included in this study; three additional patients with HCC discovered incidentally at pathologic examination were not included. Tumor evaluation included dual-phase helical CT scan or MRI with gadolinium of the abdomen, chest CT scan, and bone scan. Patients with evidence of extrahepatic tumor spread, including invasion of the main portal vein, were excluded. The number and size of tumors and the presence of intrahepatic vascular invasion were not considered contraindications to LDLT. Patients with tumors measuring

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5 cm or larger received a single dose of doxorubicin, 10 mg/m^2 intravenously intraoperatively, followed by six cycles of doxorubicin at three-week intervals beginning 1 month postoperatively.[9] Donor selection was according to previously published criteria.[10] Patients with tumors 5 cm or larger underwent preliminary exploration on the planned day of surgery to rule out the presence of extrahepatic disease before the donor operation was begun. Careful pathologic study (1 cm slices) of all livers removed at transplantation was performed routinely. Tacrolimus-based immunosuppression was employed in all cases. Follow-up studies included CT scans of the abdomen and chest and measurement of alpha-fetoprotein levels every 3 months during the first 2 years after transplantation, every 6 months during the third year, and yearly thereafter.

Variables recorded included the following:

1. Demographics (recipient and donor age and sex, underlying liver disease, Child-Pugh score, UNOS status at the time of transplant, and waiting time measured as the number of days between completion of recipient evaluation and the date of transplant.
2. Surgical aspects [previous treatments, graft type (right vs. left lobe), graft-recipient weight ratio, and number of transfusions]1.
3. Pathology (number, size, and location of tumors, vascular invasion [none, microscopic, or macroscopic], and histologic grade).
4. Follow-up (patient and graft survival, and freedom from recurrence).

Statistical Analysis

Descriptive statistics were expressed as mean ± standard deviation (SD) and median. Relationships between categorical variables were tested by means of chi-square analysis; $P < 0.05$ was considered significant. Survival was estimated by the Kaplan-Meier method.

RESULTS

Between August 1998 and February 2001, a total of 71 adults underwent LDLT at our institution; of these, 27 (38%) had recognized HCC. Mean follow-up was 276 ± 213 days, with a median follow-up of 236 days. Demographics, pathologic findings, pretransplant treatment, follow-up, and recurrence are presented in Table 1; surgical data are presented in Table 2. The mean waiting time for LDLT was 83 days.

There were no donor deaths and no major donor complications; minor complications included bile leakage from the cut surface managed by percutaneous drainage in two patients, wound infection in one, and small bowel obstruction treated laparoscopically in one. Recipient complications included bile leakage in nine patients, biliary stricture in two, mycotic aneurysm in two, hepatic artery thrombosis in one, venoocclusive disease requiring retransplant in one, colonic perforation in one, distal Roux-en-Y anastomotic leak in one, retrocaval bleeding in one, and "small-for-size" syndrome in two. Reoperation was required in 13 patients, including two who were retransplanted.

There were five deaths (18.5%). Three occurred perioperatively due to transplant-related complications (sepsis related to bile leak, sepsis after mycotic aneurysm rupture, and sepsis following retransplantation for massive graft necrosis due to venoocclusive disease). One patient died 555 days after transplantation with no tumor recurrence. One patient, who underwent transplantation for recurrent HCC after hepatic resection, died at 159 days of a tumor recurrence that was first detected at 134 days. Recurrence has been noted in one additional patient at 332 days after transplantation. This patient also underwent transplantation for recurrent HCC after resection. He is currently well after resection and radiofrequency ablation of three tumor nodules in the transplanted liver.

When we compared rates of reoperation, retransplant, and hospital mortality between patients in this study and LDLT recipients without HCC, there were no significant differences. When the same factors were compared in LDLT recipients and cadaveric recipients, the only significant difference between the two groups was in the reoperation rate ($P < 0.001$).

One-year patient and graft survival rates are 81.5% and 77.5%, respectively (Fig. 1). Freedom from recurrence at 1 year is 83%.

During the period of this study, 575 patients with known or suspected HCC were seen at our institution, 280 of whom were initially considered to be potential transplant candidates. The outcome in this overall population is presented in Fig. 2.

DISCUSSION

Liver transplantation is now acknowledged as the treatment of choice for patients with early, unresectable HCC.[11–15] This is reflected in the assignment by UNOS of priority status 2B to patients with early HCC (1 tumor ≤5 cm; 2 to 3 tumors all ≤3 cm), equivalent to that assigned patients with Child-Pugh class C cirrhosis. Despite this priority, these patients must wait a long time for a cadaveric donor; the median waiting time in the United States in 1999 for patients listed as status 2B was 206 days, and the mean

Table 1. Recipients demographics, pathologic findings, pre-transplant treatment, follow-up, and recurrence

Diagnosis	Age (yr)	Sex	Child class	No. of tumors	Size (cm)	Location	Grade	Vascular invasion	Pre-Tx Treatment	Follow-up (days)	Recurrence
Hepatitis C	62	F	C	5	6	L	Mod	Macro	CE	704	No
PBC	60	F	B	1	7	L	Mod	Macro	No	663	No
Hepatitis C	56	M	B	NA	7	B	Mod	Micro	No	601	No
Hepatitis C	55	M	A	1	3	R	Mod	Macro	No	591	No
Hepatitis C	54	M	A	NA	1	R	Mod	N	Rsx	556	No
Hepatitis B	47	M	C	1	9	R	P	Micro	No	555	No
Hepatitis C	60	M	B	1	4	R	Mod	N	PEI	358	No
Hepatitis B	72	M	B	1	4	R	P	Micro	No	352	No
Hepatitis C	61	M	B	NA	7	B	P	Macro	Rsx/CE	332	Yes
Hepatitis C	47	M	B	1	7	R	Mod	Micro	CE	330	No
Hepatitis C	51	F	A	1	4	L	Mod	Macro	No	248	No
Hepatitis C	50	M	B	2	3	B	W	N	No	243	No
Cryptogenic	66	M	C	5	3	R	W	N	No	236	No
Hepatitis C	68	M	B	2	4	B	W	NA	No	201	No
Hepatitis C	47	M	C	7	8	R	P	Micro	PEI	152	No
Hepatitis B	64	M	C	4	6	R	P	Micro	Rsx	132	Yes
Hepatitis B	59	M	B	2	6	R	W	N	CE	131	No
Hepatitis B	51	M	A	3	8	R	Mod	N	PEI	118	No
Hepatitis C	49	M	B	1	12	L	W	Macro	No	105	No
Hepatitis B	43	M	C	1	4	R	W	Micro	No	78	No
Hepatitis C	58	F	C	1	2	R	W	N	No	69	No
Hepatitis C	62	M	B	2	2	R	W	N	PEI	64	No
Hepatitis C	57	F	A	3	3	R	W	N	No	62	No
Hepatitis C	51	M	B	5	3	B	W	Macro	No	37	No
Hepatitis B	64	M	A	2	4	R	W	N	No	36	No
Hepatitis B	46	M	B	1	10	R	P	Macro	No	27	No
Hepatitis C	60	M	C	3	4	R	W	Micro	Rsx/CE	21	No
Mean	56.30			2	5.1						
SD	7.50			1.71	2.66						

NA = not available; L = left; R = right; B = bilateral; P = poorly; Mod = moderately; W = well differentiated; N = NO; Micro = microvascular; Macro = macrovascular; Rsx = Resection; PEI = percutaneous ethanol injection; CE = chemoembolization.

wait for the 37 patients transplanted with cadaveric donor livers at Mount Sinai during the period of this study was 414 days. Because of this long waiting time, attempts are routinely made to treat identified HCC in transplant candidates in order to prevent disease progression while they are waiting. Despite these efforts, many patients have disease progression that rules out transplantation. For example, in a recent study from Barcelona, where the mean waiting time was 162 days, 23% of patients with early HCC dropped out because of tumor progression.[8]

Table 2. Surgical details

Graft	Left	4
	Right	23
Bile	1	19
	2	6
	>2	2
Biliary reconstruction	Roux-	20
	Duct-	7
GRWR	Mean	1.08 ± 0.21%
V-V	Yes	12
	No	15

GRWR = graft-recipient weight ratio; V-V = veno-venous bypass.

The UNOS criteria for assigning waiting list priority to patients with early HCC were adopted from the 1996 paper by Mazzaferro et al.,[16] which showed that patients with HCC transplanted according to the preceding criteria had a 4-year survival of 75%, which is not significantly different from patients transplanted for a variety of nontumor diagnoses. A number of studies that examined risk factors for HCC recurrence after transplantation support the 5 cm criterion established by Mazzaferro et al.,[16] tumor size has repeatedly been shown to correlate with recurrence, with the likelihood of recurrence beginning to rise significantly as tumor diameter approaches 5 cm. Apart from lymph node metastasis (which should be identified at exploration and should

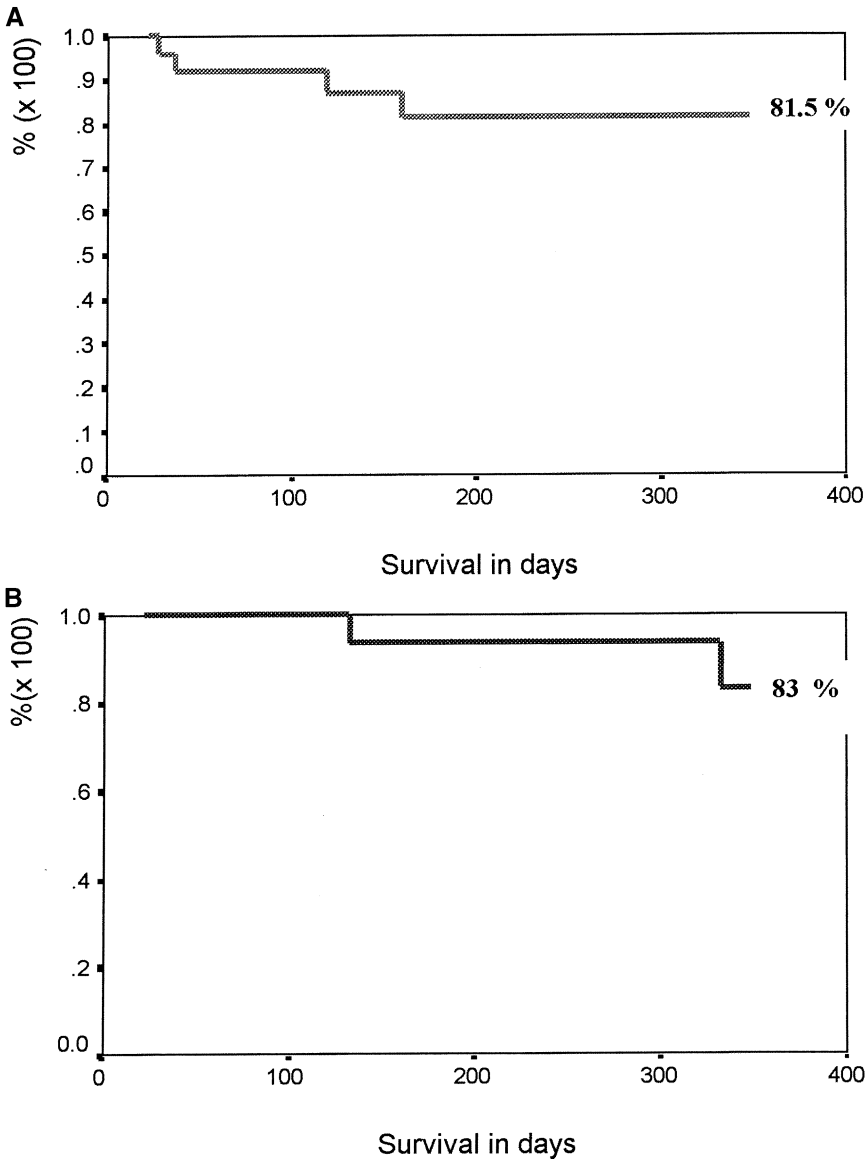

Fig. 1. A, LDLT in HCC, patient survival (n = 27). **B**, LDLT in HCC, disease-free survival (n = 27).

preclude transplantation), vascular invasion is the finding that correlates most strongly with recurrence.[11,14,15] The fact that vascular invasion commonly begins as tumor diameter approaches 5 cm likely explains the correlation of diameter with recurrence; indeed, when larger tumors are found not to have vascular invasion (as is commonly observed in the setting of hepatitis B), post-transplant recurrence is relatively unlikely.[17]

The origin of the three-lesion criterion is obscure. HCC is often multicentric by its nature. Advances in liver imaging now allow for the identification of HCCs as small as 1 cm in diameter, revealing many more tumors than could have been detected when this criterion was developed.[18] Many patients with innocuous small tumors are thus ruled out for UNOS waiting list priority.

Although it is true that patients with larger tumors and/or vascular invasion have an increased likelihood of post-transplant tumor recurrence, the fact remains that many patients with unresectable HCCs larger than 5 cm in whom a careful search reveals no evidence of extrahepatic tumor are curable with liver transplantation. In our series of 43 patients transplanted for HCCs 5 cm or larger, 48% were free of recurrence at 4 years with a mean follow-up of 55 months (unpublished data). These patients, because they do not meet the UNOS criteria for waiting list prioritization, are effectively barred from receiving a cadaveric donor liver.

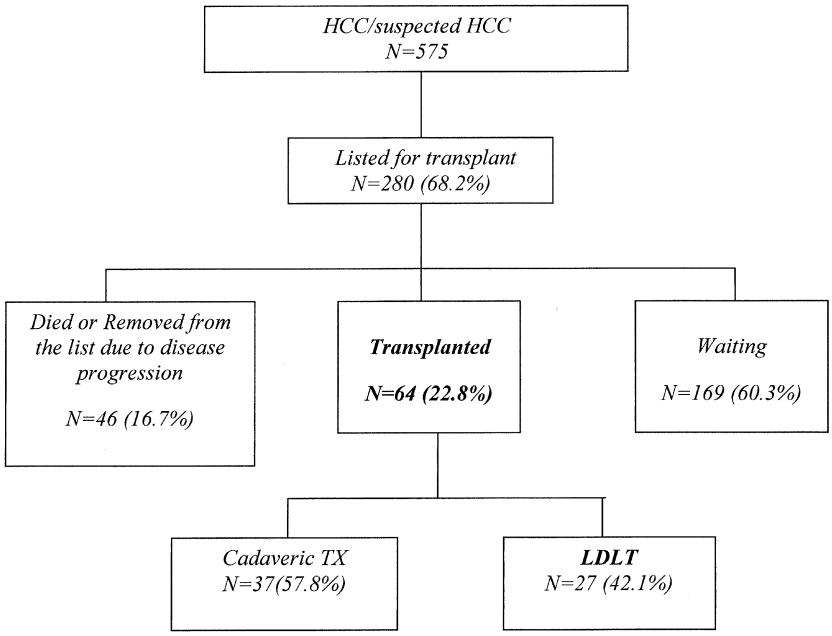

Fig. 2. Applicability of the transplant as HCC treatment in the LDLT era.

Adult LDLT became a clinical reality 7 years ago.[19,20] Close to 2000 procedures have now been performed worldwide, with centers actively pursuing this approach in Asia, Europe, and America. Despite significant technical and logistical hurdles, the procedure has proved workable.[21,22] In 2000, a total of 43 adult LDLT procedures took place at Mount Sinai Hospital, and we are currently performing between one and two procedures a week.[10] HCC has been the leading indication for adult LDLT, with 27 (38.0%) of 71 patients undergoing transplantation for HCC.

From a technical standpoint, HCC is an ideal indication for adult LDLT. The size of the donor liver graft required for safe transplantation has been shown to correlate with the degree of liver failure and portal hypertension in the recipient, rendering critically ill patients with end-stage liver disease relatively poor candidates for LDLT. By contrast, transplant candidates with HCC generally have preserved liver function and are thus better able to tolerate implantation of a relatively undersized liver graft.

By allowing expeditious transplantation (the mean waiting time for LDLT was 83 days in our series, compared to 414 days in HCC patients who received cadaveric grafts over the same period) ($P = 0.001$), LDLT obviates pretransplant tumor treatment. (Although some investigators have argued that pretransplant treatment, e.g., chemoembolization, will reduce post-transplant tumor recurrence,[23] this is entirely unproven; there are, in fact, studies that suggest that such treatment may increase the risk of metastasis.[24])

The reason why patients with HCC exceeding the UNOS criteria are denied waiting list priority is because the risk of tumor recurrence decreases the likelihood of long-term patient survival; transplanting these patients is thus considered a relatively poor use for a scarce resource. From the standpoint of the patient, however, transplantation is by far the best treatment option, if a careful search reveals no extrahepatic disease. For the patient who has a living donor, a donor organ is not a scarce resource, and the UNOS criteria are not necessarily relevant.

Clearly the justification for subjecting a healthy donor to the risk of surgery is the possibility that the recipient will benefit from the procedure. There is thus room for debate as to the level of risk of tumor recurrence that is reasonable. Based on our own historical data demonstrating that approximately half of the patients with HCCs larger than 5 cm who have undergone transplantation at Mount Sinai Hospital since 1992 were cured by the procedure, we have decided to consider these patients for LDLT. The shorter waiting time for LDLT as compared with that in our historical series, and the possibility of avoiding pretransplant interventions that may increase morbidity, offer hope that results may, in fact, improve with LDLT.

CONCLUSION

LDLT permits expeditious transplantation of patients with early HCC and provides access to trans-

plantation for patients with HCC exceeding UNOS criteria for prioritization who are, in effect, barred from receiving cadaveric organs.

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Effects of Hepatitis C Virus Infection and Its Recurrence After Liver Transplantation on Functional Performance and Health-Related Quality of Life

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Our aim was to examine the effects of hepatitis C virus (HCV) infection, a leading cause of end-stage liver disease, and its recurrence after liver transplantation on functional performance and health-related quality of life. Functional performance, liver function, and HCV recurrence were assessed longitudinally in 75 adult transplant recipients (28 with HCV). Quality of life was reported once after transplantation. Functional performance improved through year 2 ($P < 0.001$) and then declined in those with HCV, whereas the others remained stable ($P = 0.05$). Time had a positive effect ($\beta = 0.22$, $P = 0.05$) and HCV infection had a negative effect ($\beta = -0.28$, $P = 0.01$) on post-transplant functional performance. Educational level ($\beta = 0.24$, $P < 0.05$) and recent functional performance ($\beta = 0.31$, $P = 0.01$) had positive effects on quality of life. HCV recurrence was associated with relatively poorer pretransplant functional performance, a greater rate of improvement through month 3 ($P < 0.05$), and abnormal transaminase values between years 1 and 2 ($P < 0.001$). Rehospitalization for recurrent HCV was associated with reduced functional performance ($P < 0.05$). Functional performance improves with time following liver transplantation, but HCV infection exerts an opposing and comparably strong effect. Post-transplant functional performance, in turn, directly affects post-transplant quality of life. Severe, recurrent HCV illness is associated with reduced functional performance. (J GASTROINTEST SURG 2002;6:108–115.)

KEY WORDS: Liver transplantation, quality of life, hepatitis C virus, Karnofsky performance

Cirrhosis from chronic hepatitis C virus (HCV) infection is a predominant cause of progressive liver disease leading to liver transplantation.[1] Although persistent viremia is universal following liver replacement for HCV, only 30% to 40% of liver transplant recipients develop recurrent acute viral hepatitis C and 10% progress to recurrent cirrhosis.[2,3] Despite the risk of hepatitis recurrence, transplantation for HCV has been shown to result in patient and graft survival outcomes that are equivalent to those of other causes of end-stage liver disease.[4]

Although there is a growing body of outcomes literature demonstrating improved health-related quality of life (HRQOL) and functional performance following liver transplantation for a variety of etiologies, controversy exists as to what degree HRQOL and functional performance are affected by HCV and its potential recurrence.[5–7] Parameters of psychological and social well-being, in addition to physical functioning, affect overall HRQOL. Each of these components can be measured by objective criteria assessed by clinical caregivers, and by subjective perceptions of HRQOL assessed by patients and family members.[8]

In this study we applied three well-accepted measurement scales to liver transplant patients at our institution to further define the relationship of HCV and its recurrence on HRQOL and functional performance.

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PATIENTS AND METHODS

Patients and Data Acquisition

The sample included 75 adult patients who had undergone liver transplantation at the Vanderbilt University Transplant Center between 1991 and 1999. Clinical and demographic data were accumulated concurrently and abstracted retrospectively from patient medical records and from Vanderbilt University Hospital administrative and transplantation outcomes databases. Subjective HRQOL was reported by the patients via assessment instruments that were either mailed or hand delivered at clinic visits, with a response rate of 86%.

Demographic and Clinical Measures

Pretransplant demographic measures included age, sex, race, and education. Pretransplant clinical measures included primary diagnosis, serum creatinine, and the presence of hypertension or diabetes. Longitudinal clinical data included serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and immunosuppressive therapy. HCV recurrence was monitored in the 28 patients whose primary liver disease was HCV related.

Functional Performance and Health-Related Quality of Life

Objective Karnofsy functional performance status was evaluated by transplant nurse coordinators before and after transplantation at 3 months, 6 months, and annually thereafter (through 7 years, maximum). The Karnofsky scale ranges from 0 to 100. Scores from 80 to 100 represent ability to carry out normal work and activity, scores from 50 to 70 represent inability to work but ability to care for most personal needs with varying amounts of assistance, and scores from 0 to 40 represent inability to care for one's self and the need for chronic hospitalization.[8,9]

Subjective HRQOL was assessed once, at some point after transplantation, via two self-report instruments. These cross-sectional data were grouped as nominal 1, 2, and 3 years after transplantation for descriptive purposes. The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess physical, functional, emotional, and social dimensions. The standard scoring system is to weigh the eight individual domains to form the physical and mental component summary scales, which are standardized to the general population and centered with a mean of 50 and a standard deviation of 10. Higher scores represent better functioning.[10]

The Psychosocial Adjustment to Illness Scale (PAIS) was used to assess additional functional, emotional, and social dimensions of HRQOL. Scores were computed for each of seven psychosocial domains and were totaled to form a global PAIS score. Higher scores represent poorer functioning and adjustment to illness.[11,12]

Statistical Methods

Summary data are presented throughout as the mean ± standard error of the mean. Longitudinal functional performance was analyzed via mixed-model repeated-measures analysis of variance to test the main effect of time after transplantation and the interaction effect of time after transplantation and HCV on functional performance. The main effect of time reflects overall change in functional performance after liver transplantation. The interaction effect tests whether patients with HCV infection (HCV+) have different overall trajectories in functional performance than those without HCV infection (HCV−). Repeated contrasts and interaction contrasts were used to test overall differences between adjacent time points, and whether HCV+ patients differed from HCV− patients with regard to these comparisons. Comparable analyses were performed in the HCV+ subsample to examine the effects of time and postoperative HCV recurrence on functional performance, with HCV recurrence being documented by biopsy. Analysis of variance and covariance methods were used to evaluate the effects of HCV infection and its recurrence on HRQOL and postoperative clinical measures. Time after transplantation was held as a covariate to statistically control for individual differences in the point at which cross-sectional HRQOL data were collected.

Principal component factor analysis was used to derive a weighted HRQOL composite comprising all 15 SF-36 and PAIS domains.[13] This composite, which represents each patient's overall HRQOL, was used as the criterion in multiple regression-based path analyses. These analyses modeled the effects of education, preoperative functional performance, HCV status (HCV+ or HCV−), time after transplantation, and the postoperative functional performance score most contemporaneous with the HRQOL data point on the HRQOL composite (referred to as the saturated model). The size of the sample (n = 75) limited the total number of variables that could be included in the saturated model, so variables were selected on the basis of earlier research[14] and to examine the effect of pretransplant HCV infection on post-transplant HRQOL. Predictors and paths that did not contribute significantly to

the model were deleted and path coefficients were recomputed as the simplified model.

RESULTS

Preoperative demographic and clinical measures for the entire sample (n = 75) are outlined in Table 1. In 28 patients the primary liver disease was related to HCV. The HCV− group (n = 47) included patients with alcoholic liver disease (n = 11), cryptogenic cirrhosis (n = 9), primary biliary sclerosis (n = 7), fulminant failure (n = 4), autoimmune disease (n = 2), Wilson's disease (n = 2), and miscellaneous causes of liver failure (n = 12). Data from patients with HCV only (n = 22) and HCV plus alcohol-related disease (n = 6) were pooled after ruling out effects in this sample on functional performance and HRQOL due to alcohol as a second cause of liver failure ($P = 0.28$ and $P = 0.59$, respectively). With the exception of sex (proportion male, chi-square $P = 0.04$), measures summarized in Table 1 (mean values or distributions of patients) did not differ on the basis of HCV status.

Effect of HCV Recurrence on Transaminase and Alkaline Phosphatase Values

Ten of the 28 patients with HCV-related liver failure had documented HCV recurrence after transplantation. HCV recurrence was identified in the first post-transplant year in eight patients and in the second year in two patients.

HCV+ and HCV− patients demonstrated statistically significant (repeated contrast $P < 0.05$) and comparable (interaction contrast $P = 0.39$) reductions in ALT from pretransplant to post-transplant year 1. However, HCV+ patients showed a statistically significant and sustained increase in ALT between post-transplant years 1 and 2, whereas those who were HCV− sustained a normal ALT (interaction contrast $P < 0.05$). Fig. 1 depicts ALT through year 2 in the three patient groups (HCV−, HCV+ with recurrence, and HCV+ without recurrence) and demonstrates that this hepatic injury profile was confined to the HCV+ patients who had documented HCV recurrence (interaction contrast $P < 0.001$). The analysis of AST data reveals the same findings (data not shown). The change in alkaline phosphatase values over time did not differ among the three groups (interaction $P = 0.50$).

Effect of HCV on Functional Performance and Health-Related Quality of Life

Fig. 2 depicts Karnofsky functional performance through year 3 for HCV+ and HCV− patients. Overall functional performance improved after liver transplantation ($P < 0.001$) from 54 ± 4 before transplantation to 73 ± 3, 84 ± 2, 94 ±, 1, 97 ± 1, and 95 ± 2 at 3 months, 6 months, and 1, 2, and 3 years, respectively. The HCV+ and HCV− patients did not differ in their overall trajectory over time (interaction $P = 0.41$). Improvement for each time point versus the preceding point was statistically significant through year 2 (all repeated contrasts $P \leq 0.001$). In addition, both groups demonstrated the same pattern of improvement from point to point through year 2 (all interaction contrasts $P \geq 0.5$). However, the HCV+ group demonstrated a decline in functional performance between years 2 and 3 (from 97 ± 1 to 91 ± 4) that was not present in the HCV− group, which remained stable at 96 ± 1 to 97 ± 1 (interaction contrast $P = 0.05$).

Table 1. Demographic and clinical measures before liver transplantation by preoperative HCV status

	Total (n = 75)	HCV+ (n = 28)	HCV− (n = 47)	HCV+ vs. HCV− (*P*)
Age at transplant (yr)	49.7 ± 1.1	48.1 ± 1.6	50.7 ± 1.5	NS
Age at HRQOL (yr)	52.2 ± 1.2	50.5 ± 1.7	53.2 ± 1.5	NS
Sex (male) (%)	64	79	55	0.04
Race (white) (%)	96	93	98	NS
High school graduate (%)	89	86	92	NS
College graduate (%)	29	30	29	NS
Serum creatinine (mg/dl)	1.3 ± 0.1	1.2 ± 0.1	1.4 ± 0.1	NS
IDDM (%)	3	4	2	NS
NIDDM (%)	11	18	6	NS
Hypertension (%)	4	0	6	NS

HCV+ = hepatitis C virus positive at time of transplant; HCV− = hepatitis C virus negative at time of transplant; IDDM = insulin-dependent diabetes mellitus; NIDDM = non–insulin-dependent diabetes mellitus; NS = not statistically significant.

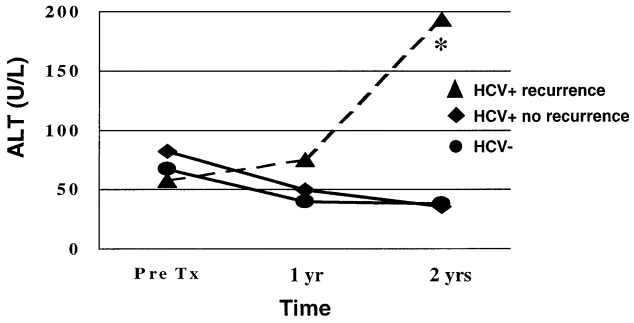

Fig. 1. HCV+ patients who experienced a recurrence showed an elevation in ALT between post-transplant (*Tx*) years 1 and 2 that was not present in HCV+ patients without recurrence or in HCV− patients (* = interaction contrast $P < 0.001$). Although not shown, AST was elevated in a similar fashion at year 2 in HCV+ patients with recurrence.

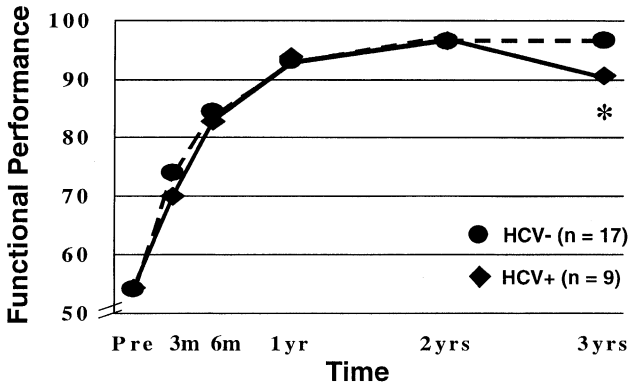

Fig. 2. Overall functional performance improved after liver transplantation ($P < 0.001$). However, HCV+ patients showed a reduction in functional performance between years 2 and 3 that was not present in the HCV− patients (* = interaction contrast 3 years vs. 2 years, $P = 0.05$).

The overall HRQOL data are presented in Table 2. After controlling for the number of months after transplantation at which HRQOL data were collected, a trend toward diminished SF-36 physical scores was demonstrated in the HCV+ vs. HCV− patients ($P = 0.09$). No statistically significant differences were observed between those with and without documented HCV recurrence on the HRQOL measures. Cross-sectional HRQOL data, grouped as nominal 1, 2, and 3 or more years after transplantation, are presented in Table 3. Although HRQOL scores appear relatively better at year 3 in comparison to year 1, differences were not statistically significant and our sample did not permit analysis of an early post-transplant stratum (e.g., within the first 6 months after transplantation). However, a trend toward a poorer PAIS global score is observed among the HCV+ vs. HCV− patients by the third follow-up year ($P = 0.10$). Our sample did not permit further analysis of these cross-sectional HRQOL data on the basis of HCV recurrence.

Principal component factor analysis of the 15 individual PAIS and SF-36 subscales was used to compute a single composite score representing HRQOL. The saturated model (Fig. 3, *A*) tests the effects of HCV status, baseline functional performance, educational level, and months after transplantation on post-transplant HRQOL and a contemporaneous determination of functional performance. The statistically significant effects of HCV status and time after transplantation on post-transplant functional performance, and of post-transplant functional performance and education, on HRQOL are indicated by solid arrows. All other effects were not significant, and thus were deleted from the saturated model to produce the simplified model (Fig. 3, *B*). The simplified model demonstrates that time after transplantation had a positive effect on the functional performance score most contemporaneous with HRQOL ($\beta = 0.22$, $P = 0.05$) and that HCV-related liver failure had a negative effect ($\beta = -0.28$, $P = 0.01$) on functional performance. Education ($\beta = 0.24$, $P < 0.05$) and recent post-transplant functional performance ($\beta = 0.31$, $P = 0.01$) both had significant direct effects on post-transplant HRQOL.

Table 2. Overall post-transplant health-related quality of life by preoperative HCV status and recurrence

	All patients				HCV+ patients		
	Total	HCV+	HCV−	ANCOVA *P*	Recurrence	No recurrence	ANCOVA *P*
SF-36 physical component summary	38 ± 1	35 ± 2	40 ± 2	0.09	37 ± 4	35 ± 3	0.23
SF-36 mental component summary	49 ± 1	48 ± 2	49 ± 2	0.70	52 ± 3	45 ± 3	0.16
PAIS global score*	31 ± 2	35 ± 3	29 ± 3	0.21	31 ± 4	38 ± 5	0.29

HCV+ = hepatitis C virus positive at time of transplant; HCV− = hepatitis C virus negative at time of transplant; ANCOVA *P* = *P* value via analysis of covariance (HCV+ vs. HCV− and Recurrence vs. No recurrence) after controlling for the number of months after transplantation.
*Lower PAIS scores represent better functioning.

Table 3. Overall health-related quality of life by time after transplant and preoperative HCV status

	Total	HCV+	HCV−	HCV+ vs. HCV− (*P* value)
SF-36 physical component summary				
One year	35 ± 3	34 ± 4	37 ± 4	
Two years	37 ± 2	33 ± 4	39 ± 3	
≥ Three years	40 ± 2	39 ± 4	41 ± 3	NS
SF-36 mental component summary				
One year	47 ± 4	46 ± 5	49 ± 5	
Two years	47 ± 2	47 ± 4	47 ± 3	
≥ Three years	50 ± 2	50 ± 4	50 ± 3	NS
PAIS global score*				
One year	34 ± 5	38 ± 7	29 ± 7	
Two years	36 ± 5	37 ± 7	35 ± 5	
≥ Three years	28 ± 3	34 ± 6	25 ± 5	0.10

HCV+ = hepatitis C virus positive at time of transplant; HCV− = hepatitis C virus negative at time of transplant; NS = not statistically significant.
*Lower PAIS scores represent better functioning.

Effect of HCV Recurrence After Transplantation on Functional Performance

The comparison of longitudinal functional performance through post-transplant year 2 in HCV+ patients who had documented recurrence of the virus after transplantation versus those who did not is depicted in Fig. 4. Both groups improved after transplantation ($P < 0.001$). Those whose HCV recurred

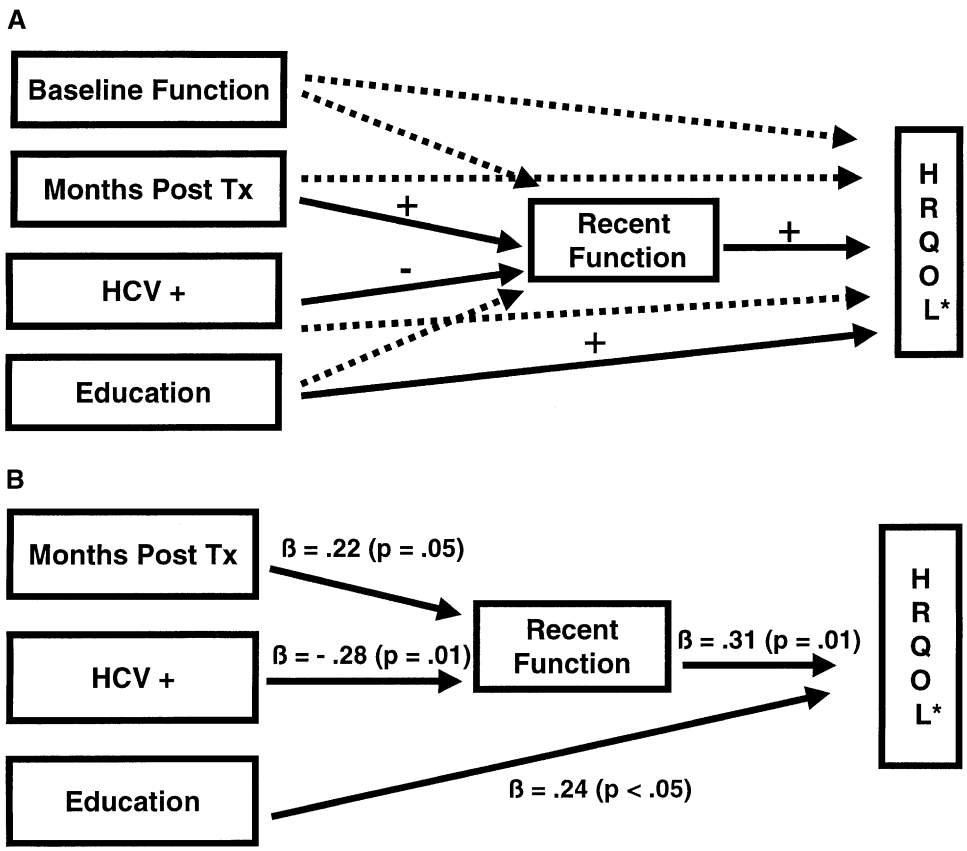

Fig. 3. **A,** Saturated model depicting potential paths between pretransplant (baseline) functional performance and HCV infection status (+ or −), education, and time after transplantation (*Tx*) on post-transplant (recent) functional performance and a composite HRQOL measure (*) derived from the SF-36 and PAIS. Statistically significant paths are indicated by the solid arrows. **B,** Simplified model depicting the negative direct effect of HCV infection on post-transplant functional performance and the positive effect of time after transplantation on this measure. Post-transplant functional performance has a direct effect on HRQOL, as does educational level.

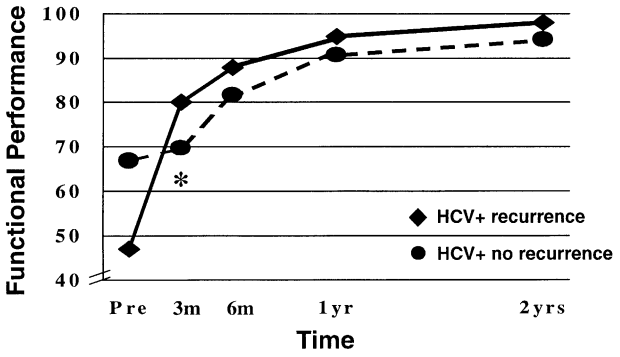

Fig. 4. On average, all HCV+ patients showed significantly improved functional performance after liver transplantation ($P < 0.001$) through year 2. Those whose HCV recurred after transplantation had a significantly higher rate of improvement over the first 3 months because of a relatively lower pretransplant functional performance compared to those whose HCV did not recur (* = interaction contrast 3 months vs. before transplantation, $P < 0.05$).

after transplantation had a significantly higher rate of improvement over the first 3 months because of a relatively lower pretransplant functional performance compared to those whose HCV did not recur (interaction contrast $P < 0.05$). Improvement in functional performance did not differ between the two groups between 3 months and 2 years (all $P > 0.3$). After controlling for time after transplantation, rehospitalization for HCV-related illness was associated with decreased functional performance (rehospitalized for HCV, mean = 77 ± 4; not rehospitalized for HCV, mean = 91 ± 2; $P < 0.05$).

DISCUSSION

Outcomes analysis after liver transplantation regularly includes measures of patient and graft survival, complications, and cost. Increasing emphasis has been recently placed on assessment of the impact of transplantation on recipients' quality of life and residual disability. As noted in previous reports, liver transplantation for unspecified end-stage liver disease leads to early and dramatic improvements in HRQOL and functional performance.[14–17] HCV represents the largest single cause of liver disease leading to cirrhosis and the need for organ replacement. Although operative outcome and early patient/graft survival are equivalent for HCV+ and HCV− recipients, HCV recurrence can occur and lead to graft hepatitis and graft cirrhosis, a potential chronic illness that HCV− transplant recipients do not experience.[3,4] In this study 36% (10 of 28) of the HCV+ patients undergoing liver transplantation developed recurrent allograft hepatitis within the first 2 years after liver replacement, and the remainder had no evidence of clinical recurrent hepatitis.

Investigations of quality of life in HCV+ liver transplant patients have thus far been limited. Dickson et al.[6] followed patients for more than 2 years to compare the quality of life of patients transplanted for HCV to patients transplanted for hepatitis B virus (HBV) who were treated with an effective hepatitis B immunoglobulin immunoprophylaxis protocol. Although the HBV patients had better functional status and psychosocial function relative to the HCV group, no data were presented regarding clinically active HCV recurrence or its potential role in this difference. Singh et al.[7] compared liver transplant recipients with recurrent HCV to a heterogeneous group that included patients with HBV, nonrecurrent HCV, alcohol-related liver disease, and hepatocellular carcinoma. Six months after transplantation, both groups had significantly improved Karnofsky functional performance scores, with improvement being less in patients with recurrent HCV. The overall perceived quality of life, depression, mood disturbance, and coping scores also improved during this period, with no between-group differences on these measures. By 12 months, persistently lower functional performance scores, perceived quality of life, and psychosocial well-being (increased depression and mood disturbance scores) were observed in the patients with HCV in comparison to all other patients combined.

In our current report the Karnofsky functional performance score improved over the first 2 years after liver transplantation for both HCV− and HCV+ recipients. Furthermore, maximal functional recovery was not predicted by pretransplant functional performance. Patients who before their liver transplants were either ICU bound or minimally disabled from cirrhosis had equivalent functional performance at 2 years after liver transplantation (data not shown). This finding mirrors results that have been presented by our group in other reports.[15,16] With longer follow-up, however, our HCV+ patients showed a decline in functional performance when compared to the stable functional performance seen in HCV− recipients. Between the second and third years after transplantation, Karnofsky scores declined in the HCV+ group from 97 ± 1 to 91 ± 4, whereas HCV− recipients maintained functional performance scores of 96 ± 1 to 97 ± 1. Eighty percent of HCV recurrence was identified in the first year after liver transplantation, yet recurrence of clinically active HCV did not alter the maximal functional performance at 2 years. Fig. 4, which compared HCV+ patients with recurrence to HCV+ patients without recurrence, demonstrated

that, even during the time frame in which recurrence was noted, improvement in functional performance was not impaired despite a lower pretransplant functional performance score (possibly because of their underlying HCV). If HCV+ patients who developed recurrent hepatitis are compared to HCV+ patients without hepatitis recurrence, only hepatitis severe enough to require hospitalization affected functional performance to a measurable degree.

Overall, HCV+ liver transplant recipients demonstrated no significant differences in HRQOL measures when compared to the HCV− group, perhaps because of the limited sample or possibly due to unaccounted effects on HRQOL (e.g., education). Similarly, HCV recurrence showed no effect on SF-36 physical or mental component scores or on the PAIS global score. Furthermore, although there was a trend toward an impaired PAIS global score among HCV+ patients who were at least 3 years post liver transplantation, this was not statistically significant and was not mirrored by SF-36 scores.

In an effort to further elucidate the effects of HCV status on functional performance and HRQOL, principal component analysis was performed to generate a composite measure of HRQOL that could be used in path analysis modeling. Path analysis is a multiple regression–based method for modeling hypothesized relationships among variables.[18] A "single-step" path between two variables (e.g., the path from HCV to post-transplant functional performance) depicts the direct effect of one variable on another after controlling for the effect(s) caused by any other variable(s) having an influence on the measure (e.g., after controlling for the effect of time after transplantation on post-transplant functional performance). An effect between two variables that requires two or more steps, and passes through one or more variables, represents an indirect effect (e.g., the effect of HCV infection on HRQOL). Reported path coefficients are the standardized regression coefficients (i.e., "beta weights"), which represent a unit change in one variable that can be expected on the basis of a unit change in another if both variables are scaled on a common metric (the z score). These standardized path coefficients may be tested for statistical significance and are also interpreted on the basis of their absolute value, with coefficients < 0.10 generally considered to be trivial and those ≥ 0.20 being substantive.[19]

These path analyses evaluated the effect of demographic factors (education), time after transplantation, and pre- and post-transplant functional performance on the HRQOL measure. We did not include pretransplant diabetes, hypertension, renal failure, or age in the path analyses because the HCV+ and HCV− groups did not differ on these measures, and the overall variability was limited. This modeling showed that pretransplant HCV infection and recovery time from transplant directly influence post-transplant functional performance. Likewise, post-transplant functional performance and educational status directly influence HRQOL. Although HCV infection has an indirect negative impact on HRQOL (via post post-transplant functional performance), its effect seems to be abrogated by the much-improved functional ability of the patients recovering from liver transplantation.

As with all studies, there are limitations to this review. Because HRQOL was not assessed longitudinally, we were able to model the effects of education, time after transplantation, and a contemporaneous measurement of post-transplant functional performance on post-transplant HRQOL, but we could not directly examine the effect of these measures on changes in HRQOL over time. Recurrent HCV after liver transplantation has been demonstrated in longer term follow-up to be associated with fibrosing cholestatic hepatitis and recurrent cirrhosis in 8% to 10% of patients by year 5.[2,20] With HCV recurrence risk, there is often a major change in the medication profiles of the liver transplant recipients, reflecting a reduction in overall immunosuppression and consideration of antiviral therapy. Fundamental questions about antiviral therapy for risk of HCV recurrence after liver transplantation remain. Treatment protocols with interferon and ribavirin, individually or in combination, have been studied for both prophylactic and postrecurrence administration. Although early treatment with combined therapy seems most effective for control of HCV, application can be limited by serious side effects and symptoms.[20] The potential beneficial and detrimental effects of these drugs could be evaluated by the methods used in this study, in addition to the other accepted outcome variables, to provide more extensive and sensitive analysis.

CONCLUSION

We have shown that patients undergoing liver transplantation for HCV have overall maximal functional recovery that is comparable to that which is seen in HCV− patients and that, during the first 2 years after transplantation, recurrent HCV does not impair functional performance. However, there is a pattern of deteriorating functional performance after 2 years in HCV+ recipients, and this reduction is a function of the severity of recurrent HCV illness. HCV cirrhosis leading to liver transplantation exerts its negative effect on post-transplant functional per-

formance directly. Better post-transplant HRQOL is a direct effect of improved post-transplant functional performance. However, a negative effect on HRQOL resulting from HCV infection was demonstrated to be mediated by recent post-transplant functional performance. This is a preliminary report and longer term longitudinal studies with larger samples will be required to further determine the nature and extent of the effects of HCV infection on HRQOL in liver transplant recipients.

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Repair of Bile Duct Injuries With Gore-Tex Vascular Grafts: Experimental Study in Dogs

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Bile duct injury is the most feared complication related to biliary tract operations. The goal of this investigation was to offer an alternative treatment that might prevent this complication. Twelve mongrel dogs, thin-walled FEP-ringed Gore-Tex vascular grafts, and Gore-Tex sutures were used in this study. The dogs were randomized into three groups of four according to the length of time of graft implantation: group 1 = 1 month; group 2 = 2 months; and group 3 = 3 months. During the first part of the study, a biliary injury was induced by ligating the middle choledocus after performing a conventional cholecystectomy. During the second part of the study, biliodigestive and biliobiliary anastomosis were performed using Gore-Tex vascular grafts prior to resection of the stenotic area. Initially, an increase in serum bilirubin and alkaline phosphatase levels was noted. Two weeks later, after implantation of the grafts, these values returned to normal. Thin-walled FEP-ringed Gore-Tex vascular grafts were found to be useful in the repair of bile duct injuries, especially in complete transections of the common bile duct. The ductility and flexibility of the material allows any type of anastomosis to be performed, especially when bile duct–gut anastomosis is technically difficult. (J GASTROINTEST SURG 2002;6:116–120.)

KEY WORDS: Bile duct injuries, vascular grafts, bilioenteric anastomosis

The most feared complication related to biliary surgery, either open cholecystectomy or laparoscopic cholecystectomy, is bile duct injury.[1,2] It is estimated that 1500 to 2000 lesions may appear each year in the United States alone. The incidence of injuries resulting from this surgical intervention is 0.3% to 0.6% for laparoscopic cholecystectomy in comparison to 0.125% for the open cholecystectomy.[3,4] Both of these operations have the potential to produce future harmful effects in the patient undergoing these procedures.[5,6] The main goal of this investigation was to offer an alternative treatment in hopes of preventing this type of injury.

MATERIALS AND METHODS

Twelve mongrel dogs (mean weight 9 kg) were used for this study. A 4 mm thin-walled FEP-ringed Gore-Tex vascular graft and CV-7 Gore-Tex sutures (W.L. Gore & Associates, Inc., Flagstaff, Ariz.) were used in each of them. The first part of the study involved intentionally creating an obstruction of the common bile duct by a ligature on the choledocus. The dogs were anesthetized by intravenous injection of ketamine (10 mg/kg), and acepromazine (2.5 mg). A conventional cholecystectomy was performed, followed by ligation of the middle choledocus with the use of 3/0 silk sutures.

Seven days after the ligation, as the second part of the experimental study, a celiotomy was performed with resection of the stenotic segment and placement of a Gore-Tex vascular graft between the common bile duct and the duodenum. In all instances except one, the technique used was a choledochoduodenal anastomosis with interrupted sutures; in the one exception an end-to-end choledochal anastomosis was performed with interrupted sutures on both sides of the graft. The experiments were carried out as follows: in group 1 (n = 4) the dogs were observed for 1

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Table 1. Type of anastomosis and postoperative findings

Animal	Type of anastomosis	Time of graft evaluation	Weight (kg)		Autopsy evaluation
			Before	After	
Group 1					
1	End-to-side (C-D)	1	7	6.5	Bile in cavity
2	End-to-side (H-D)	1	10	10	Satisfactory
3	End-to-side (C-D)	1	11	11	Satisfactory
4	End-to-side (C-D)	1	10	11	Satisfactory
Group 2					
5	End-to-side (C-D)	2	7	7.5	Satisfactory
6	End-to-side (C-D)	2	6	6	Satisfacotry
7	End-to-side (C-D)	2	6	6	Satisfactory
8	End-to-side (C-D)	2	5	5.5	Satisfactory
Group 3					
9	End-to-end (C-D)	3	10	12	Satisfactory
10	End-to-side (C-D)	3	16	18	Satisfactory
11	End-to-side (C-D)	3	11	11	Satisfactory
12	End-to-side (H-D)	3	9	9.5	Satisfactory

C-D = choledochoduodenal; H-D = hepaticoduodenal.

month after graft fixation; dogs in group 2 (n = 4) were observed 2 months after fixation; and group 3 (n = 4) was observed 3 months after fixation. A 3-month observation period was selected to accomplish our objectives based on previous experiments, which had shown an increase or decrease in hepatic enzymes and bilirubin after graft implantation.

During the operation, the grafts were implanted as outlined in Table 1. All dogs received intravenous fluids containing Hartmann solution and antibiotic therapy with cephalexine (Erocetin, 0.5 g/day intravenously for 5 days), after which they progressed to a regular diet. Blood samples were obtained during the preoperative and postoperative phases of the study for measurement of bilirubin and alkaline phosphatase levels. These measurements were repeated 15 and 30 days after placement of the protheses.

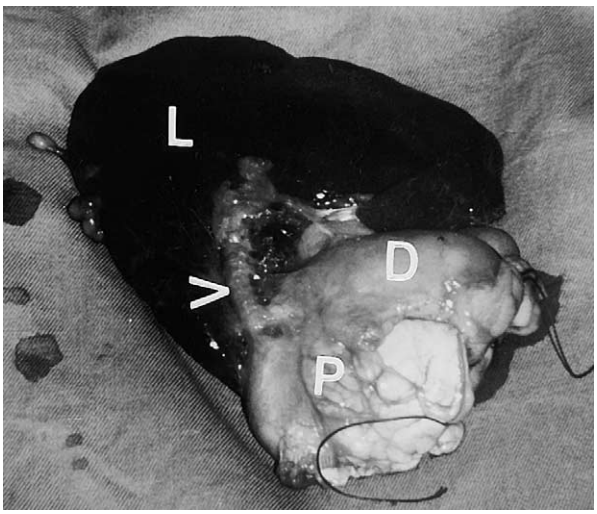

Fig. 1. Liver (*L*), duodenum (*D*), and pancreas (*P*) tissue and the Gore-Tex graft *(arrow)* from a study dog.

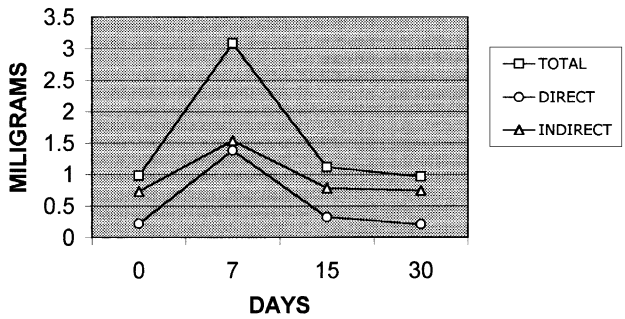

Fig. 2. Changes in serum bilirubin levels throughout the study.

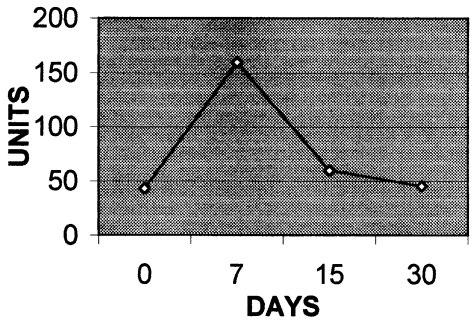

Fig. 3. Changes in serum alkaline phosphatase levels throughout the study

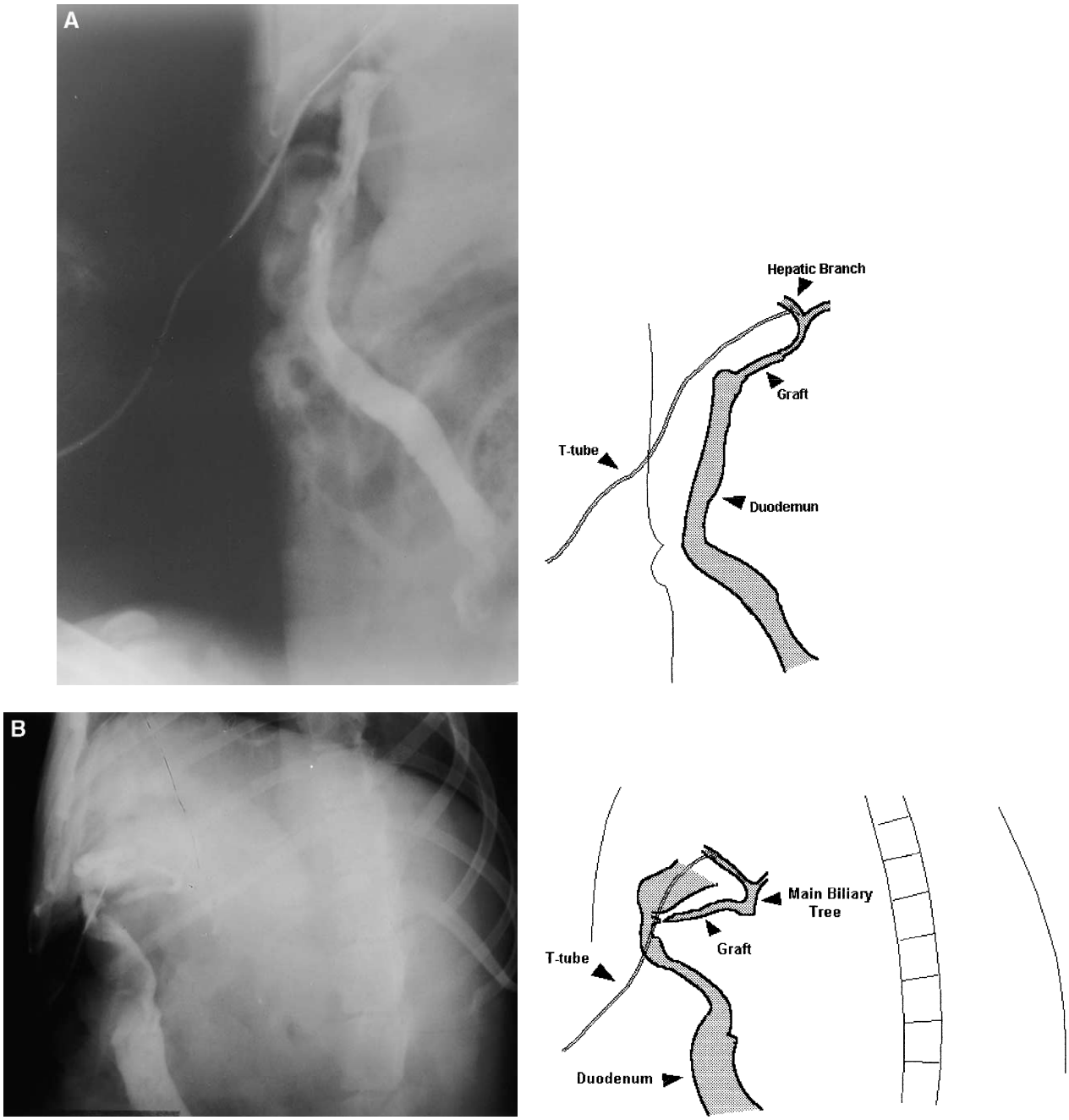

Fig. 4. Cholangiograms with their respective diagramatic representations. **A**, After 60 days. **B**, After 90 days.

A second celiotomy was performed in each animal after their respective observation periods followed by intraoperative cholangiography for a total revision of the biliary tree. The dogs were then killed in order to obtain the samples for pathologic examination (Fig. 1). All experiments were conducted in accordance with the recommendations of the Declaration of Helsinki and the International Guiding Principles for Biomedical Research Involving Animals.

RESULTS

In the first part of our study, 1 week after the bile duct injury, there was an increase in serum bilirubin and alkaline phosphatase levels. One week after graft implantation, these values decreased to almost-normal levels and they were still normal 15 days later (Figs. 2 and 3). All three groups showed the same patterns in their laboratory results during the first 4 weeks after

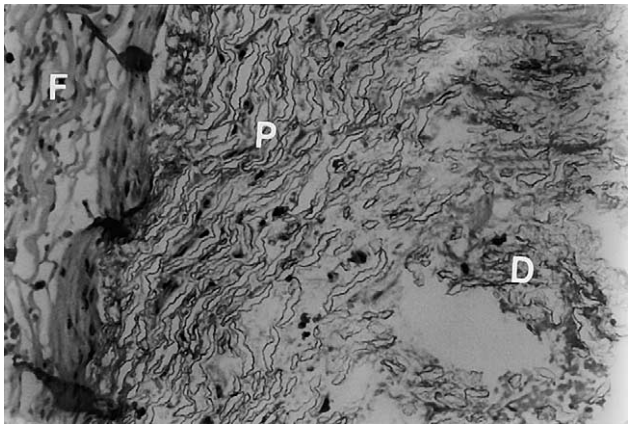

Fig. 5. Photomicrograph showing duodenum (*D*), fibrous tissue (*F*), and the prosthesis (*P*).

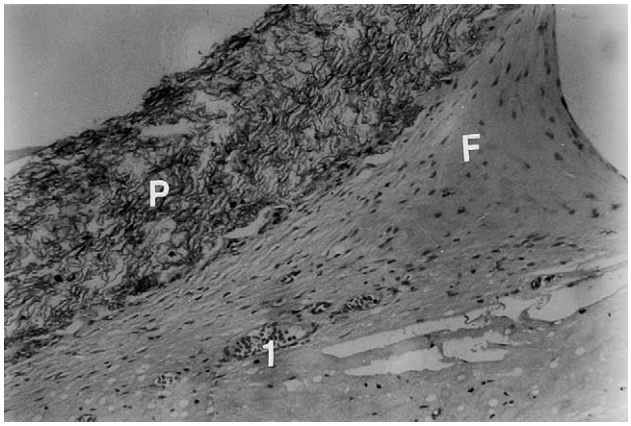

Fig. 6. Photomicrograph showing the prosthesis (*P*), fibrous tissue (*F*), and capillary congestion (*1*).

implantation, with no significant statistical differences among them ($P \geq 0.05$). None of the dogs in any of the groups lost weight or had any other complications, except for one animal in group 1 in which a small biloma located at the right upper quadrant was found.

The cholangiograms demonstrated normal passage of contrast medium into the duodenum (Fig. 4). All grafts were found to be surrounded by dense fibrous tissue and adhesions from the liver to the duodenum. There was no evidence of anastomotic dehiscence in any of the grafts. Pathology reports showed no signs of acute graft rejection. The grafts were surrounded by fibrous tissue with capillary congestion and scarce lymphocyte infiltration. The hepatic tissue did not show any changes. These results indicate an acceptable inflammatory response on the part of the host (Figs. 5 and 6).

DISCUSSION

This experimental study was designed to demonstrate that thin-walled FEP-ringed Gore-Tex vascular grafts can be considered as an option for bile duct injury repair. Previous studies have shown that nonreinforced expanded polytetrafluoroethylene (ePTFE) grafts produce unsatisfactory results—that is, they gradually become compressed or dislodged—whereas ePTFE rigid ring-reinforced grafts provide satisfactory bile drainage for several months but also show a certain degree of bile stasis because of the rigidity of the graft.[7,8]

In our study the thin-walled FEP-ringed Gore-Tex vascular grafts provided satisfactory bile drainage without becoming compressed by proliferating fibrous tissue or dislodged by liver respiratory movements or intestinal peristalsis. Reinforcement of the graft wall with FEP rings made it resistant to compression and allowed the anastomosis to be performed more easily, especially in fixation to the duodenum.

Treatment of bile duct injuries represents a serious challenge, even for the most experienced biliary surgeons. The majority of lesions are the result of surgical trauma during cholecystectomy, either intraoperative or laparoscopic cholecystectomy. They can also be present in other types of abdominal operations, such as gastrectomy, hepatectomy, trauma surgery, or portocaval shunt. The standard management of major bile duct injuries is Roux-en-Y hepaticojejunostomy,[9–11] and endoscopic[12–15] or percutaneous[16,17] techniques. Nonsurgical treatment options can be used in patients who are poor operative candidates or in less complicated cases. Although biliary sludge is a long-term complication that depends on the lithogenic predisposition of bile and its drainage flow, long-term results are needed to exclude any correlation between fixation of biliary tree–gut anastomosis with FEP-ringed vascular graft and biliary sludge or any other long-term complication.

Moreover, based on these results, thin-walled FEP-ringed Gore-Tex vascular grafts can be useful in the repair of major bile duct injuries, especially in complete transections of the common bile duct. The ductility and flexibility of the material allows any type of required anastomosis to be performed, especially when bile duct–gut anastomosis is technically difficult.[7] The grafts did not produce any obliterations, obstructions, dislodgment, or biochemical alterations.

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A Time of Change

Keith A. Kelly, M.D., John L. Cameron, M.D., Co-Editors

The first issue of the JOURNAL OF GASTROINTESTINAL SURGERY appeared 5 years ago in an atmosphere of cautious optimism. There were some who believed there were already too many surgical journals, and that one dedicated entirely to gastrointestinal surgery would not prosper. The JOURNAL, however, had the great advantage of having The Society for Surgery of the Alimentary Tract (SSAT) as its owner and sponsor. This Society had become, since its founding in 1960, the voice of gastrointestinal surgery in the United States and had established itself as an integral part of Digestive Disease Week (DDW), the consortium of concurrent meetings of the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the American Society for Gastrointestinal Endoscopy, and the SSAT. The SSAT put its strength behind the JOURNAL and directed its papers, addresses, symposia, and other material from the Annual Meeting to the JOURNAL for publication. The Society struggled over a name for the JOURNAL, but settled on the JOURNAL OF GASTROINTESTINAL SURGERY, recognizing that gastrointestinal surgery includes the surgical treatment of diseases not only of the gastrointestinal tract, but also those of the esophagus, the liver and biliary tree, the pancreas, the spleen, and the abdominal wall.

The JOURNAL aspired to be the voice for surgical gastroenterology in the United States and abroad, recognizing that the diseases we treat transcend national boundaries and involve surgeons in this type of work throughout the world. We sought to appeal to gastrointestinal surgeons, gastroenterologists, radiologists, pathologists, basic scientists, and others who deal with diseases of the gastrointestinal tract, and to their fellows, residents, and students. A policy of careful peer review of all papers, including those from the Annual Meeting of the SSAT, was established and a distinguished, hard-working Editorial Board was appointed to help the Co-Editors accomplish this purpose.

We were fortunate to engage as our publisher, Quality Medical Publishing, Inc. (QMP). QMP is a company that concentrates on the quality of their publications, as their name implies. They had the reputation of producing an outstanding product. We were not disappointed. The early issues and those subsequently published have been attractive, expertly done, and on time. The Co-Editors have not had a single author complain that a paragraph of a paper was omitted, a table mislabeled, or a figure published upside down, or that any other publishing mishap marred the final printout. For this superb effort, the Co-Editors and the SSAT are extremely grateful to QMP and express our admiration, gratitude, and deep thanks.

Our young enterprise having been launched, the reputation of the JOURNAL for excellence grew rapidly during its early years. The quality of the JOURNAL was quickly recognized by the National Library of Medicine, and it was added to *Index Medicus* after its first year in print. A poll of SSAT members taken 3 years after the JOURNAL had been established recognized the JOURNAL as being a strong asset to the Society and to the field of gastrointestinal surgery, and a first-rate publication.

During our first 5 years, the JOURNAL has grown, reflecting the growth in the membership of the SSAT and the growth in size of its Annual Meeting. The SSAT membership has expanded from approximately 1400 members in 1996 to more than 2500 members today. All members receive the JOURNAL. Another 2000 copies of the JOURNAL were sent to senior residents in surgery, thanks to the generous support of U.S. Surgical Corporation and Ethicon, Inc. Moreover, the program presented by the SSAT during DDW has expanded, partly because of greater participation by international surgeons. Manuscripts from countries other than the United States now represent 37% of the total number of manuscripts submitted to the JOURNAL. Not only have international surgeons presented frequently at the SSAT meetings and published many papers in the JOURNAL, they also now hold leadership positions in the SSAT.

The SSAT and the JOURNAL have grown in another important way. In 2001 the SSAT signed an agreement with the American Hepato-Pancreato-Biliary Association (AHPBA), naming the JOURNAL OF GASTROINTESTINAL SURGERY as the official journal of the AHPBA. The designation appears for the first time on the cover of this issue. This issue also contains, for the

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first time, the Presidential Address and papers presented at the Annual Meeting of the AHPBA.

As a reflection of the growth of the SSAT and its new journal, the increase in international participation, and our new association with the AHPBA, a time for change has arrived. We begin our second 5 years with a new publisher, Elsevier Science Inc. Elsevier is one of the oldest and largest publishers of medical journals in the world and one with a global perspective. The company's record as a publisher of scientific material dates back at least to the early seventeenth century, when Louis Elzevir published Galileo's scientific work, "Two New Sciences," in 1638. Publication of the work in Italy was not possible at that time because of the censure against Galileo by the Roman Inquisition, but publication was possible in Holland. Today, Elsevier's home base in the Netherlands and its branch offices abroad put the company in an ideal position to bring the JOURNAL to a large national and international audience. Moreover, Elsevier is adding to its superb reputation by employing the latest in computer and Internet-based technology, modalities so important in today's publishing world.

Under our new relationship with Elsevier, we expect to see an immediate increase in the size of each issue of the JOURNAL and a gradual increase in the number of issues published each year. We hope to reach our long-term goal of 12 issues per year in the near future. The electronic publishing capabilities of Elsevier will disseminate the JOURNAL quickly to readers around the world. Moreover, all issues of the JOURNAL from Volume 1, Issue 1 to the present issue, and continuing with future issues, will shortly be available on the Internet to all paid subscribers of the JOURNAL. The table of contents and the abstracts of the articles published in the JOURNAL will continue to be accessible to the general public through the SSAT web site (www.ssat.com). We are excited about these changes and look forward to working with our new publisher.

With change and growth there likely will be "growing pains." We ask our readers to be in touch with us during this transition period and let us know what they like and what they do not like. Your feedback will be appreciated. Perhaps in the future, the JOURNAL will become solely an electronic medical publication, but we hope not. We still have a personal preference for the printed page, bound in attractive single issues that can rest comfortably on the library shelf. No doubt this sentiment reflects yet another example of age. Nonetheless, the printed page has stood the test of time—not a bad thing in a time of change.

To the Editors:

I read with great interest the excellent article by Bammer et al.[1] concerning late results of laparoscopic Nissen fundoplication. I have some questions and comments for the authors:

1. Of the 291 patients operated, only 171 (58.7%) were available for this study. What happened to the other 41% of the patients? I usually evaluate at least 80% of patients in a late follow-up, to achieve an accurate statistical evaluation.
2. What were the results of manometric and 24-hour pH studies in these patients late after surgery?
3. I notice that the results of the endoscopic evaluation are missing. It is well known that there are some patients who have persistent esophagitis without symptoms.
4. I am also wondering about the results of the biopsy specimens taken late after surgery. Did you determine how many patients had Barrett's esophagus, before the surgery and how many patients developed intestinal metaplasia or even dysplasia in the late control period?

I believe these are very important points that must be addressed to establish the true late objective results of antireflux surgery.

Prof. Dr. Attila Csendes, F.A.C.S.
Department of Surgery,
Clinical Hospital
University of Chile
Santiago, Chile

REFERENCES

1. Bammer T, Hinder RA, Klaus A, Klingler PJ. Five to eight-year outcome of the first laparoscopic Nissen fundoplications. J GASTROINTEST SURG 2001;5:42–48.

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Reply

Patients in our practice came from a wide area, making comprehensive follow-up difficult. The patients had returned to the care of their primary physicians, and so it was not possible to carry out routine 24-hour esophageal pH manometry and endoscopy as suggested by Prof. Csendes. The scope of this investigation did not include a protocol for the retesting of esophageal function and endoscopy. The purpose of the study was to identify the patients' perception of the outcome and to elicit information on their current symptoms and medical management.

Ronald A. Hinder, M.D., Ph.D.
Department of Surgery
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Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery Mini Fellowship Program, January 20–25, 2002; March 24–29, 2002; August 25–30, 2002; November 3–8, 2002; The University of Texas Southwestern Medical Center at Dallas. Fees: $10,000 (team of 2 physicians and 1 nurse); $5000 (physician); $1000 (nurse). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

American Society for Gastrointestinal Endoscopy (ASGE) Advanced ERCP Training Course: The 2002 ASGE Hands-On Series, February 8–9, 2002, Endo-Surgery Institute, Cincinnati, Ohio. Course Directors: Bret T. Peterson, M.D., Mayo Clinic; and Kenneth Binmoeller, Pacific Medical Center. For further information and to register, contact: The Endo-Surgery Institute. Toll free at 1-877-477-6333; e-mail: contactesi@eesus.jnj.com

Surgery of the Foregut, February 11–12, 2002, Marriott Harbor Beach Resort and Spa, Ft. Lauderdale, Florida. For further information contact: Cleveland Clinic Florida, Continuing Medical Education. Phone: 954-659-5490; toll free: 1-800-359-5101; fax: 954-659-5491; e-mail: cme@ccf.org; website: www.cmeccf.com

Medical and Surgical Aspects of Esophageal and Foregut Disorders: Pathophysiology and Treatment, February 14–19, 2002, Hyatt Regency Maui Hotel, Maui, Hawaii. For further information contact: Continuing Medical Education. Phone: 800-USC-1119 or 323-442-2555; fax: 888-665-8650 or 323-442-2152; e-mail: usccme@hsc.usc.edu; website: www.usc.edu/schools/medicine/cme

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery, February 15–16, 2002; June 21–22, 2002; September 27–28, 2002; The University of Texas Southwestern Medical Center at Dallas. Fees: physicians $300 (lecture only), $1050 (lecture and lab); UTSW and SCMIS Alumni $250 (lecture only), $950 (lecture and lab); nurse $175 (lecture only); $375 (lecture and lab). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Live Advanced Endoscopic Techniques: American Society for Gastrointestinal Endoscopy 18th Interim Postgraduate Course, March 22–23, 2002, Fairmont Copley Plaza Hotel, Boston, Massachusetts. Course Directors: William R. Brugge, M.D., Massachusetts General Hospital; and David L. Carr-Locke, M.D., Brigham & Women's Hospital. For further information contact: American Society for Gastrointestinal Endoscopy. Phone: 978-526-8330; fax: 978-526-7521; e-mail: asge@shore.net

American Society for Gastrointestinal Endoscopy Hands-On Endoscopy Series: 2002 EUS Training Course, April 5–6, 2002, Endo-Surgery Institute, Cincinnati, Ohio. Course Directors: Irving Waxman, M.D., University of Chicago; and Maurits J. Wiersema, M.D., Mayo Medical School and Clinic. For further information contact: Endo-Surgery Institute. Toll free: 1-877-477-6333; e-mail: contactesi@ eesus.jnj.com

Society for Surgery of the Alimentary Tract 35th Annual Meeting & Postgraduate Course, May 19–22, 2002, San Francisco, California. Includes the postgraduate course, guest speakers, Poster Session, SSAT/ASCR Symposium, SSAT/SAGES Symposium, Consensus Conference, SSAT Public Policy Committee Panel, and plenary sessions. For more information, contact: SSAT Meetings Department, 13 Elm Street, Manchester, Massachusetts 01944. Phone: 978-526-8330; fax: 978-526-7521; e-mail: ssat @prri.com

American Society for Gastrointestinal Endoscopy (ASGE) Annual Postgraduate Course Endoscopic Oncology: Gastrointestinal Endoscopy and Cancer Management, May 22–23, 2002, San Francisco, California. Course Directors: Gary W. Falk, M.D., and Douglas O. Faigel, M.D. Fees: $450, ASGE members; $550, nonmembers; reduced fees for fellows and assistants. For further information contact: American Society for Gastrointestinal Endoscopy. Phone: 978-526-8330; fax: 978-526-7521; e-mail: asge@ shore.net