J Gastrointest Surg (2007) 11:1579–1588
DOI 10.1007/s11605-007-0318-5

Laparoscopic Nissen Fundoplication Effectively Relieves Symptoms in Patients with Laryngopharyngeal Reflux

Robert A. Catania · Stephen M. Kavic · J. Scott Roth · Tommy H. Lee · Tanya Meyer · George T. Fantry · Paul F. Castellanos · Adrian Park

Received: 21 May 2007 / Accepted: 27 August 2007 / Published online: 12 October 2007

Abstract
Introduction The utility of laparoscopic Nissen fundoplication in the treatment of laryngopharyngeal reflux symptoms remains controversial. We hypothesized that a carefully selected population with these symptoms would benefit from antireflux surgery.
Materials and Methods Sixty-one consecutive patients have undergone antireflux surgery for laryngopharyngeal reflux at a single institution. Preoperative evaluation including upper endoscopy, laryngoscopy, and 24-h ambulatory pharyngeal pH probe monitoring confirmed the diagnosis. Patients completed two validated symptom assessment instruments preoperatively and at multiple time points postoperatively.
Results Patients were followed for up to 3 years with a mean follow-up of 15.2 months. A significant improvement in reflux symptom index score (preoperative=31.5±7.4 vs 3 years=12.4±10.9, $p<0.01$), laryngopharyngeal reflux health-related quality of life overall score (preoperative=55.0±26.0 vs 3 years=11.3±13.9, $p<0.01$), and symptom domain scores (voice, cough, throat clearing, and swallowing) occured within 1 month of surgery and remained improved over the course of the study.
Conclusion Laparoscopic Nissen fundoplication is effective in relieving the symptoms of laryngopharyngeal reflux in a carefully selected patient population. Benefits are seen within 1 month of surgery and persist for at least 3 years.

Keywords Laryngopharyngeal reflux · Laparoscopic Nissen fundoplication · Quality of life · Antireflux surgery · Outcomes

Presented at the Digestive Disease Week 2007, May 22, 2007, Washington, DC.

R. A. Catania · S. M. Kavic · J. S. Roth · T. H. Lee · A. Park (✉)
Division of General Surgery,
University of Maryland Medical Center,
22 South Greene Street, Room S4B14,
Baltimore, MD 21201-1595, USA
e-mail: apark@smail.umaryland.edu

T. Meyer
Department of Otolaryngology,
University of Maryland Medical Center,
Baltimore, MD, USA

G. T. Fantry
Department of Gastroenterology,
University of Maryland Medical Center,
Baltimore, MD, USA

P. F. Castellanos
Division of Otolaryngology,
University of Alabama at Birmingham,
Birmingham, AL, USA

Introduction

Gastroesophageal reflux disease (GERD) is a common condition in the American population, with up to 40% of adults experiencing symptoms of this disease at least monthly. Laparoscopic Nissen fundoplication (LNF) is a well established and highly efficacious treatment for GERD and has been shown to provide durable relief from the typical symptoms of heartburn, regurgitation, and water brash.[1,2] Laryngopharyngeal reflux (LPR), in contrast, is a much less familiar condition characterized by symptoms of sore throat, cough and choking, hoarseness, globus, or dysphagia.[3] Other extraesophageal manifestations of reflux have also been described, including asthma,[4] bronchitis, vocal cord granulomas, sinusitis, chest pain, dental ero-

sions, sleep apnea, and laryngeal cancer.[5] We refer to this broad group of conditions related to reflux as laryngeal extraesophageal reflux disease or LERD (coined by Castellanos, one of the senior authors).

Although uncommon in the clinical practice of surgeons and gastroenterologists, it has been estimated that up to 10% of patients presenting to an otolaryngologist have symptoms related to LPR.[6] Prior studies have demonstrated that gastric acid suppression with a proton pump inhibitor (PPI) can diminish both the pulmonary and ear, nose, and throat disorders thought to be associated with LPR.[7] The existing literature is less clear about the benefit of antireflux surgery for patients with LPR, with some studies showing benefits,[8–10] while others show little improvement.[11,12]

It has been postulated that careful patient selection is essential to see benefits in LPR symptoms after antireflux surgery.[8] We choose to study a highly selected group of patients with clear evidence of LPR to determine if antireflux surgery would diminish their symptoms and improve their overall disease-related quality of life.

Materials and Methods

Patients referred to the University of Maryland Aerodigestive Center with symptoms consistent with LPR were asked to participate in this study. The study protocol was reviewed and approved by the Human Research Protections Office at The University of Maryland Medical Center before initiation.

Patients referred for surgical evaluation were suspected to have LPR based on history and documented evidence of reflux-associated laryngeal injury as demonstrated by laryngoscopy. Preoperative evaluation of patients with LPR consisted of dual-probe 24-h pH testing with the distal probe placed 5 cm above the lower esophageal sphincter and the upper probe placed 1–2 cm above the upper esophageal sphincter. An elevated Johnson–DeMeester score or evidence of 3 or more reflux episodes at the pharyngeal probe in addition to laryngoscopically proven laryngeal injury was considered sufficient to confirm the diagnosis of LPR. Esophageal manometry was performed to evaluate for evidence of esophageal motility disorders. Upper endoscopy was performed by the primary surgeon to assess for evidence of reflux, hiatal hernia, or neoplasia.

Patients were admitted to the study if the primary aim of antireflux surgery was control of LPR symptoms. Patients were excluded from analysis if they had not yet undergone an antireflux procedure, if no follow-up data were available, or if they had a history of prior antireflux surgery, paraesophageal hernia, achalasia, or irreversible upper airway injury. The patients excluded for irreversible airway injury had all required prolonged tracheostomy for management of laryngeal disease, including tracheal stenosis and laryngeal cancer, and although these patients did undergo antireflux surgery, it was not performed with the expectation that they would show symptomatic improvement but rather to prevent further deterioration in their airway disease. The majority of our patients had undergone previous airway instrumentation for laryngeal biopsy or excision of polyps or granulation tissue. Data were obtained prospectively using two validated LPR survey instruments administered before initial consultation, then again 1 month, 6 months, 1 year, 2 years, and 3 years after surgery.

The first instrument, the Reflux Symptom Index (RSI) is a self-administered, nine-item, 45-point survey designed to quantify symptoms of LPR.[13] The instrument has been validated, and a RSI score greater than 13 is considered abnormal. Patients with a score greater than 19 were considered to have LPR, and a postoperative decrease in RSI of 5 or more points was considered evidence of improvement.[14] The second instrument, the Laryngopharyngeal Reflux-Health-related Quality of Life (LPR-HRQL) Instrument, is a self-administered 43-item questionnaire that uses Likert response scales to assess symptom distress and the effects of LPR on social and occupational functioning, vitality, well-being, and perceived health.[6] Four predominant LPR symptom clusters (voice/hoarse, cough, clear throat, swallow) and overall well being are assessed by this validated instrument, allowing us to quantify changes in symptoms and quality of life after surgery. Comparisons were made between preoperative scores and the scores obtained postoperatively. Not every patient completed the survey at every time point.

Surgical intervention consisted of LNF for all patients participating in the study. Hiatal closure was performed as deemed necessary by the operating surgeon (senior author Park or Roth). All patients were seen by a dietitian and placed on an 8-week graduated diet after surgery. Patients were observed overnight after the operation and discharged from the hospital within 12–72 h.

Data are expressed as mean plus or minus standard deviation in Table 1. Paired t test analysis was used for statistical analysis of score data, with a p value less than 0.01 being considered significant to allow for the effect of multiple comparisons. Pearson chi-squared analysis was used to assess differences in outcome between patients who presented with LPR and those who presented with LPR/GERD, with a p value of less than 0.05 being considered significant. Statistical analysis was performed using commercially available software (SPSS 12.0 for Windows). Box plot data are presented in standard fashion, with the boundary of the box closest to zero indicating the 25th percentile and the boundary of the box farthest from zero indicating the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles. The solid

Table 1 Results of the Reflux Symptom Index (RSI) and Laryngopharyngeal Reflux-Health-related Quality of Life (LPR-HRQL) Instruments Administered Pre- and Postoperatively to Patients Surgically Treated for LPR

	Preoperative (n=58)	1 Month (n=30)	6 Months (n=28)	1 Year (n=35)	2 Years (n=19)	3 Years (n=7)
RSI	31.5±7.4	10.1±6.8*	11.9±8.9*	11.4±9.5*	10.5±7.8*	12.4±10.9*
Voice	26.7±20.7	10.8±16.3*	7.0±9.8*	8.9±13.0*	8.5±9.1*	11.1±11.8**
Cough	15.1±11.0	2.9±4.8*	4.2±6.4*	2.8±4.0*	3.8±5.9*	5.1±7.8*
Throat	14.9±9.7	4.7±6.2*	4.9±6.9*	3.6±5.4*	3.1±3.7*	5.7±8.7*
Swallow	15.1±8.7	3.7±4.9*	3.3±4.5*	3.2±5.0*	2.4±2.8*	2.4±3.9*
Overall	55.0±26.0	13.2±17.2*	13.3±18.5*	11.4±18.1*	13.1±14.7*	11.3±13.9*

Overall health-related quality of life and symptoms from the four prominent symptom domains (voice/hoarseness, cough, throat clearing, and swallowing) are addressed by the LPR-HRQL.
*p<0.01, **p<0.05 by paired Student's t test

line within the box represents the median, and the dashed line represents the mean.

Results

Since January 2004, 106 consecutive patients with complaints consistent with LPR were evaluated. Of these patients, three had end-stage laryngeal disease (one with a tracheostomy, one with severe laryngeal stenosis, and one following laryngectomy for laryngeal/pharyngeal cancer), 28 had another indication for foregut surgery (paraesophageal hernia, achalasia, or failed prior antireflux surgery), and 14 have not yet had surgery. Eliminating the above patients resulted in a population of 61 patients who underwent LNF for the primary presenting complaint of LPR.

Follow-up data were available for 58 patients (95%). The average length of follow-up was 15.2 months, with 21 patients being followed for 2 or more years. This series consisted of 19 male and 42 female patients averaging 58 years of age (range 18–72). Symptomatically, 41% of patients had only complaints of LPR, while 59% of patients had some degree of heartburn (GERD symptoms) in addition to those of LPR. Patients had the presence of laryngeal reflux confirmed by findings at laryngoscopy or by evidence of acid reflux above the upper esophageal sphincter on 24-h ambulatory pH probe monitoring. All patients in this series underwent LNF; there were no conversions, no major complications requiring repeat surgery, and no deaths in the study group. Three patients required postoperative balloon dilatation for complaints of persistent dysphagia, and symptoms improved/resolved in all cases. Average length of hospital stay after surgery was 1.7 days.

After surgery, there was a significant decline in RSI as early as 1 month postoperatively, and this reduction in RSI score was evident throughout the entire study period (Fig. 1). Improvement was seen in 97% of patients (as defined by a decrease in the postoperative RSI score of 5 or greater points at the time of last follow-up), and 86% of patients no longer had symptomatic LPR as defined by an RSI score less than 19 at the time of last follow-up (Fig. 2). The response to surgery for individual patients can be seen in Fig. 3. Thirty-eight patients (65%) had a normal RSI (<13) after surgery. An additional 12 patients (21%) had a reduction in their RSI score to below the diagnostic threshold score of 19. Of these 12 patients, six presented with symptoms of LPR, while six presented with mixed symptoms (LPR/GERD). Six patients (11%) had a notable decline in their LPR symptoms (as defined by a decrease in the RPI of over 5 points) yet still met the RSI criteria of LPR. Of these six, two presented with LPR only, while four presented with LPR/GERD. No decline in the postoperative RSI score was noted in two patients, and they are considered nonresponders. Both of these patients initial complaint was of LPR. There was no difference in response

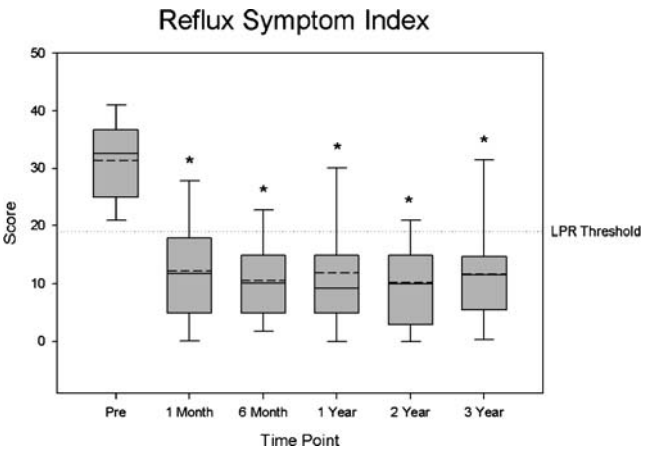


Fig. 1 Reflux Symptom Index (RSI)—The RSI was calculated for patients presenting with LPR preoperatively, and then again at 1 month, 6 months, 1 year, 2 years, and 3 years after laparoscopic Nissen fundoplication (LNF). An RSI above the threshold score of 19 defines the presence of LPR. The *shaded box* bounds the 25–75% confidence interval, the *error bars* bound the 10–90% confidence interval, the *solid line within the box* represents the median, and the *dashed line* represents the mean. *Asterisk*, p<0.01 vs the preoperative RSI score.

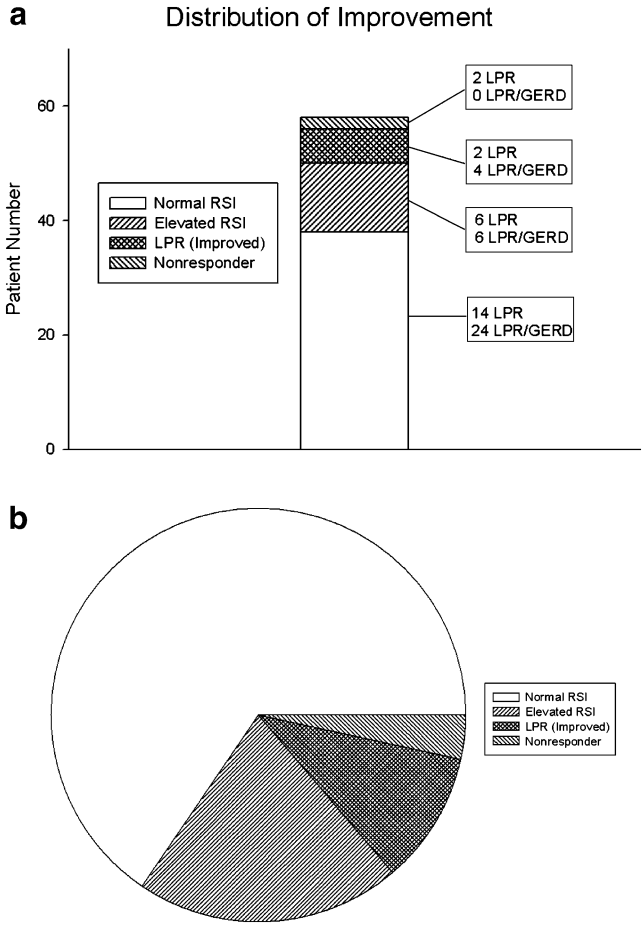


Fig. 2 Distribution of improvement/response to surgery—after LNF, the RSI was calculated for patients at the time of their last follow-up. **a** In 38 patients, the RSI had normalized (decreased below 13, the mean score in the general population), 12 patients had an elevated RSI that was above normal but below the RSI diagnostic threshold of 19, six patients had improvement in the RSI (a 5 or greater point decrease, which, by definition, demonstrates a benefit from surgery) but continued to have LPR, while two patients were nonresponders. The number of patients with presenting complaints of either LPR or LPR/GERD is shown in the *box along side* of the graph. **b** Pie chart demonstrating proportion of patients with a response to surgery.

to surgery between patients who presented with LPR and those who presented with LPR/GERD (Pearson χ^2=3.226, p=0.199)

There was a significant improvement in disease-related quality of life after surgery, as defined by a decline in the LPR-HRQL overall score, and this improvement was evident as soon as 1 month postoperatively and persisted throughout the study period (Fig. 4). Significant improvement in LPR-HRQL domain scores were seen in voice, cough, throat clearing, and swallowing symptoms. Again, the benefit was evident as early as 1 month after surgery. Improvements in cough, throat clearing, and swallowing persisted throughout the study period. The improvement in voice symptoms evident at the 1-month, 6-month, 1-year, and 2-year follow-up did not achieve statistical significance

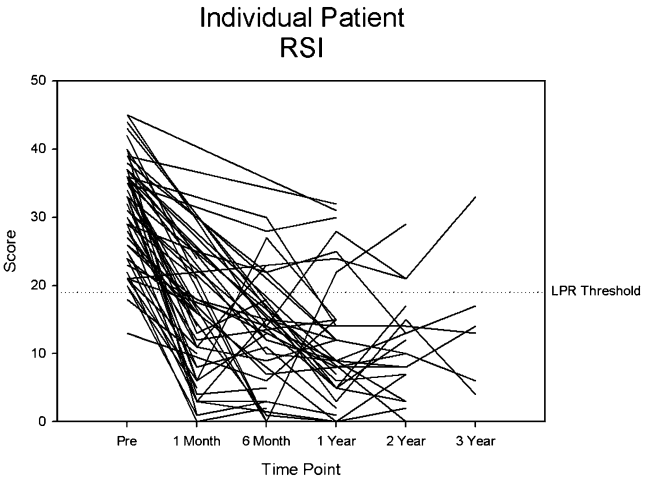


Fig. 3 Reflux Symptom Index (RSI) score by individual patient. Each line represents the RSI score at each time point. Eighty-six percent of patents had an RSI below the threshold score of 19 at the time of last evaluation.

at the 3-year time point (Fig. 5). The individual patient response to surgery for the symptom domains are seen in Fig. 6. The results of the data are summarized in Table 1.

Discussion

There is a broad differential diagnosis that must be considered when patients present for evaluation of chronic upper airway symptoms (including sore throat, cough,

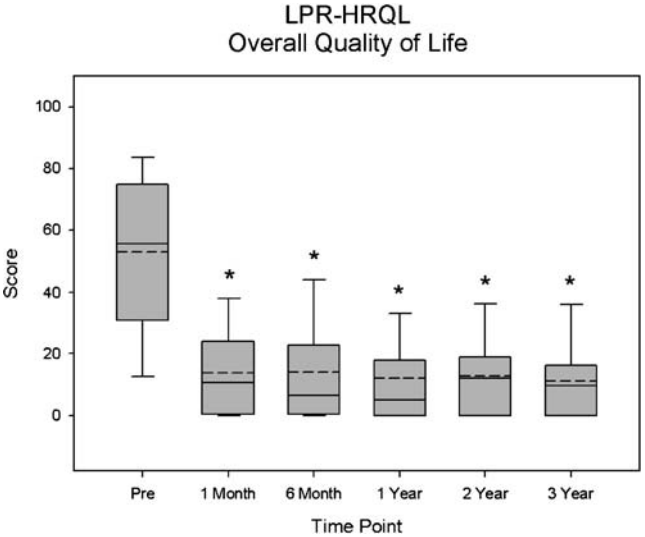


Fig. 4 Laryngopharyngeal Reflux-Health-related Quality of Life score (LPR-HRQL)—The overall health-related quality of life score was calculated for patients presenting with LPR preoperatively and then again at 1 month, 6 months, 1 year, 2 years, and 3 years after laparoscopic Nissen fundoplication. The *shaded box* bounds the 25–75% confidence interval, the *error bars* bound the 10–90% confidence interval, the *solid line* within the box represents the median, and the *dashed line* represents the mean. *Asterisk*, p<0.01 vs preoperative LPR-HRQL overall score.

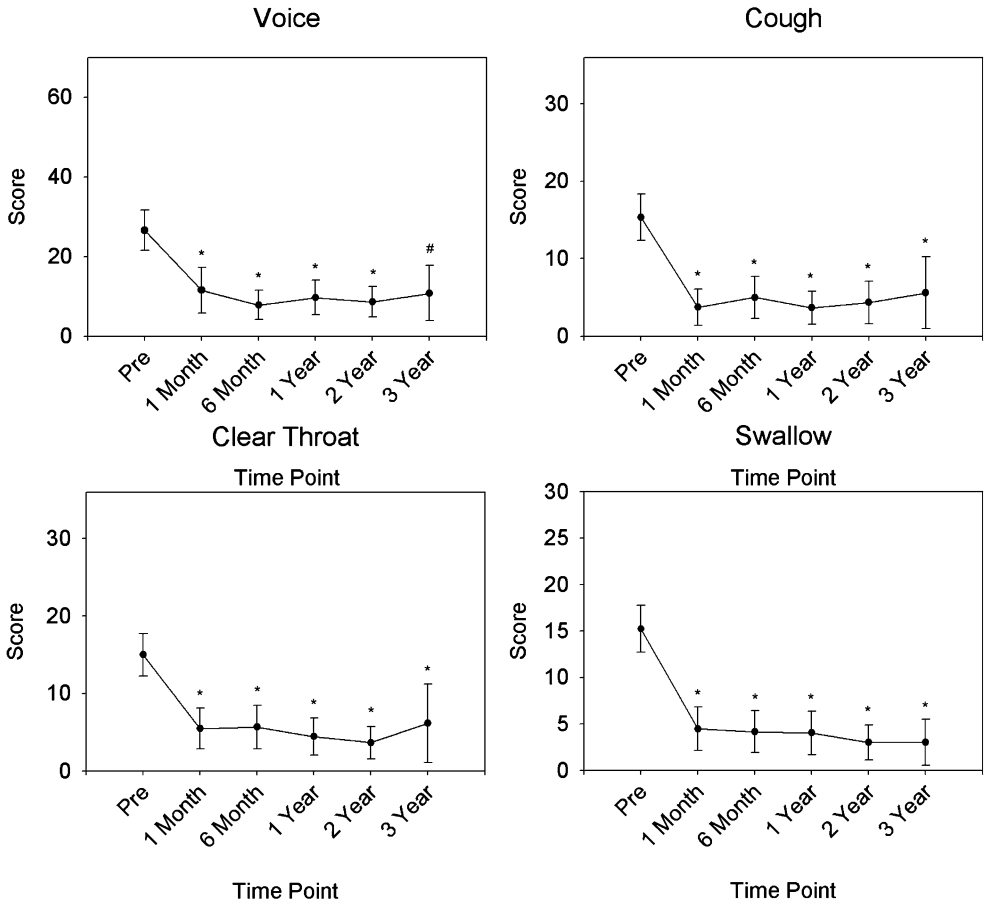


Fig. 5 Laryngopharyngeal Reflux-Health-related Quality of Life score (LPR-HRQL) symptom domain scores—The aggregate LPR-HRQL domain score for voice, cough, throat clearing, and swallowing are shown. Data are reported as mean±standard error, *asterisk*, $p<0.01$ vs the preoperative score.

hoarseness, globus, dysphagia, or asthma) that includes LPR. Even when these patients present with concomitant heartburn, reflux is not necessarily the cause of their upper airway symptoms.[15] In patients with suspected LPR, correctly making the diagnosis is especially important before selecting the appropriate therapy. When considering LPR as the etiology of upper airway symptoms, an appropriate workup includes both laryngoscopy and pharyngeal pH probe monitoring, as neither test alone is sufficiently sensitive or specific to definitively establish reflux as the cause.[16] LPR should also be suspected when patient's upper airway symptoms exhibit a therapeutic response to a PPI trial,[17] and it has been suggested that symptomatic improvement on PPI therapy is associated with improved outcome after antireflux surgery.[18] However, PPI therapy does not eliminate laryngeal reflux but merely renders the pH of the refluxate neutral, thus it cannot be expected to be fully efficacious.

In our center, we see a diverse complex of pharyngeal and upper airway symptoms caused by gastroesophageal reflux. We refer to the broad spectrum of airway diseases secondary to reflux as LERD. In this study, we analyzed the effect of LNF on the symptoms of a well-characterized subset of LERD patients, those with LPR. We chose to do this as there are several validated symptom scores that directly measure the degree of patient discomfort secondary to gastroesophageal reflux into the upper airway. Despite limiting the current study to LPR symptoms, we believe that antireflux surgery has a role in the treatment of the other pathology seen in LERD, such as asthma, chronic bronchitis, dental erosions, and sleep apnea as well.

The laryngeal injury caused by LPR is believed to be the result of repeated exposure of the delicate upper airway tissues to gastric contents. Chronic reflux above the upper esophageal sphincter produces a constellation of findings in the larynx, including laryngeal edema, vocal fold granulations, interarytenoid or posterior glottic inflammation or erythema, and hypertrophy of the posterior commissure, with the "classic finding" being posterior laryngitis. A reflux finding score (RFS) was developed to encompass all of the varied findings of LPR and quantify the degree of injury sustained by the larynx in response to these repeated insults.[19] Ultimately, patients may develop tracheal stenosis or laryngeal/pharyngeal cancer requiring tumor extirpation and/or reconstructive surgery. Dental injuries are also known to result from chronic oral acid exposure. The finding of dental erosions (the superficial loss of the hard tissues of the teeth by a chemical process) is distinct from dental carries and is associated with both reflux and bulimia.[20]

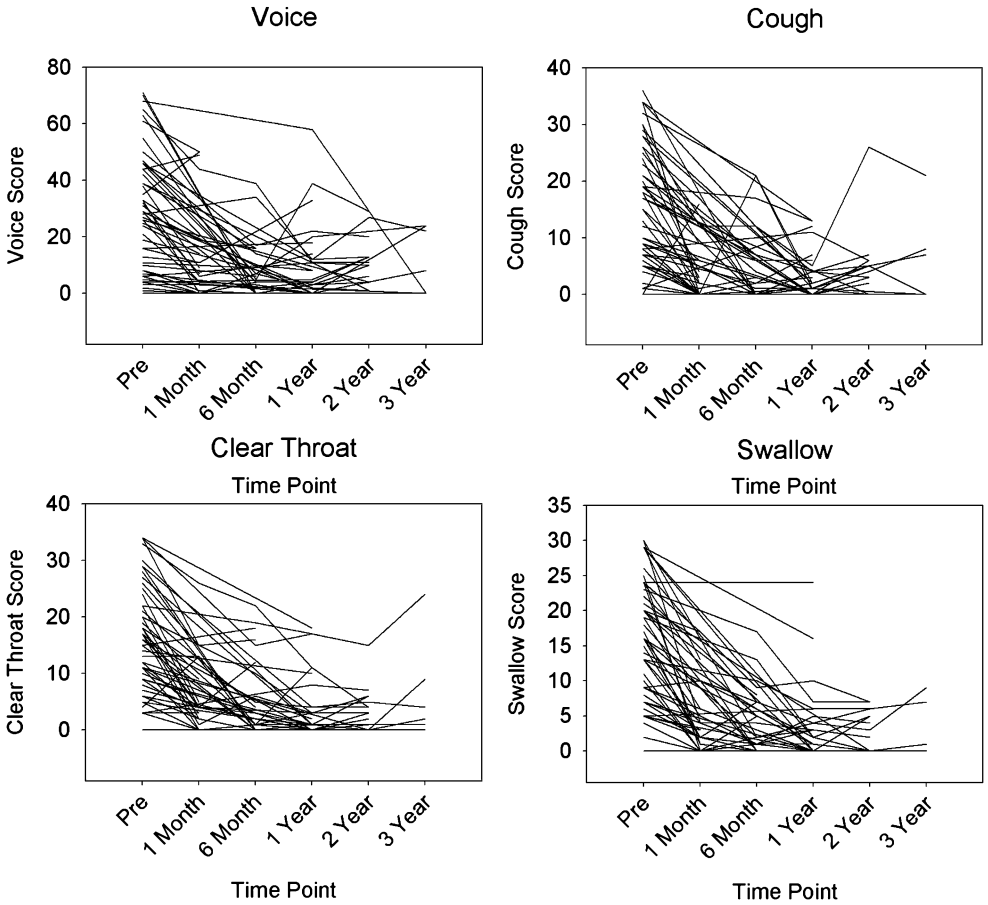


Fig. 6 Laryngopharyngeal Reflux-Health-related Quality of Life score (LPR-HRQL) symptom domain scores—The LPR-HRQL domain score for voice, cough, throat clearing, and swallowing by individual patient. Each *line* represents the domain score for a single patient at each time point measured.

It is now well accepted that antireflux surgery is extremely efficacious in eliminating regurgitation of gastric contents above the gastroesophageal junction. The protection afforded by antireflux surgery is sufficient to allow the majority of patients suffering from GERD to discontinue acid suppression therapy, achieve resolution of associated esophagitis, and arrest or perhaps even reverse the metaplasia induced by frequent exposure of the esophageal mucosa to gastric contents.[21] Despite the impressive results achieved in the surgical treatment of GERD, antireflux surgery does not completely eliminate reflux of gastric contents above the gastroesophageal junction. It has been postulated that the number, volume, and total exposure time of the aspiration events associated with LPR is so small relative to those seen in GERD that even the trivial amount of reflux present after a well-performed antireflux procedure could be sufficient to perpetuate the laryngeal damage and thus render surgery an ineffective treatment for this disease. Prior studies have demonstrated an efficacy as low as 54% for resolution of laryngeal symptoms after antireflux for LPR.[12] It seems reasonable to hypothesize, however, that by reducing reflux by 85–95% (as is typical after Nissen fundoplication), some degree of benefit will be achieved.

Our results suggest that LNF in a carefully selected patient population can result in improvement in symptoms of LPR in up to 97% of patients, with complete resolution of symptoms achieved in 65% of patients. The symptomatic improvement can be seen as early as 1 month after surgery, and the benefits of surgery appear to persist throughout medium-term follow-up (2–3 years), although our mean follow-up period of 15.2 months makes long-term conclusions premature. The benefit of surgery can be seen in all four major symptom clusters, including voice changes/hoarseness, cough, throat clearing, and swallowing. The improvement seen in cough, throat clearing, and swallowing were durable over the entire course of the study, whereas a small increase in the voice score at the 3-year time period made the improvement seen at this time point not statistically significant. This may be due to the small sample size at the 3-year time point (n=7), and further follow-up of this sample population may ultimately prove that the benefit of surgery on voice symptoms is durable. Beyond improvement in symptom clusters, patients exhibited an overall improvement in their disease-specific quality of life. There was a greater than fourfold improvement in overall quality of life scores after antireflux surgery, and this benefit was also evident within a month of surgery and persisted for the duration of the follow-up. The long-term durability of these improvements remains to be demonstrated. Planned annual follow-up of our patient cohort should allow us to address this issue in the future.

It is interesting to note that our results show a dramatic improvement in symptom scores as early as 1 month after surgery. It had previously been suggested that 3 months of therapy was required to demonstrate improvement in reflux-related airway symptoms.[13] This conclusion is based on results obtained with PPI therapy for the treatment of LPR. Thus, it may be possible that the more rapid improvement seen after antireflux surgery is due to the elimination of most pH neutral refluxate after surgery. Alternatively, the referral pattern at our institution stressing the early treatment of LPR with antireflux surgery may account for the rapidity of the improvement seen in our population.

Chen and Thomas[12] presented a case series of 90 patients who underwent antireflux surgery for heartburn and found that 56% of their patients also exhibited atypical symptoms (defined as cough, chest pain, indigestion, vomiting, choking, and belching). They found that after surgery, heartburn improved in 95% of their patients, while atypical symptoms improved in only 54%. It was not specified if any particular cluster of atypical symptoms responded more favorably to surgery nor if reflux above the upper esophageal sphincter was present in any of their patients. Primary indications for surgery were symptoms and evidence of either esophagitis or abnormal 24-h pH monitoring. Farrell et al.[11] evaluated the efficacy of surgery on the treatment of atypical GERD symptoms (defined as asthma, chest pain, cough, and hoarseness) by stratifying patients by presence of symptoms into three groups: severe heartburn/mild atypical symptoms, severe heartburn/severe atypical symptoms, or mild heartburn/severe atypical symptoms. They found that whereas 99% of patients with predominantly GERD improved and 87% had complete resolution of symptoms after surgery, only 93% of patients with predominantly atypical symptoms improved, and 48% had complete resolution of symptoms after surgery. Again, the patients underwent a typical evaluation for GERD including esophagoscopy, manometry, and standard pH testing. So et al.[18] reported a response rate for laryngeal symptoms of 78%, pulmonary symptoms of 58%, and chest pain of 48% after antireflux surgery. It is interesting to note in patients who had documented reflux above the upper esophageal sphincter, the response rate for laryngeal symptoms was 86%. It has been shown that 90% of normal (asymptomatic) subjects experience one or fewer episodes of pharyngeal reflux daily,[22] with three or greater episodes generally considered pathologic.[16,23] In this analysis, we did not correlate specific preoperative findings/test results with outcome, but further evaluation of our data may allow us to better define preoperative predictors of success.

The studies cited above suggest that there is a wide range of nonheartburn symptoms associated with GERD that are not necessarily responsive to antireflux procedures. This is in agreement with a body of literature advanced by Oelschlager et al.[8,15,16] that suggests that not all "atypical" symptoms associated with GERD can be taken as evidence of LPR and that the presence of GERD is not sufficient to make the diagnosis of LPR in patients with atypical symptoms. They posit that the use of pharyngeal pH monitoring, particularly when combined with findings of reflux-related injury at laryngoscopy, is the most accurate method of making this diagnosis. Westcott et al.[23], utilizing pharyngeal pH monitoring to establish the diagnosis of LPR, selected a series of 41 patients who underwent fundoplication and then followed these patients symptomatically for 14 months with two disease-specific validated survey instruments and the RFS, a laryngoscopic-based airway injury score. They found that after LNF, there was improvement in patient symptom scores at 4 and 14 months and that RFI scores continued to improve over time. Thus, carefully selected patients with LPR can expect a benefit in both symptomatic relief and resolution of airway injury after antireflux surgery. Despite these findings, 16% of their patients failed to show improvement in their RSI score after surgery. This may be partially explained by patient selection, with five of the seven unimproved patients exhibiting structural changes in their airways at the time of surgery. In our study, we excluded patients with significant structural changes, which may account for our 97% RSI improvement rate. This is not to say that patients with structural changes are not candidates for antireflux surgery. Many of our otolaryngologists now recognize the benefit of eliminating reflux and insist that antireflux surgery be performed on their patients before performing laryngeal reconstructive surgery.

A number of previous studies have demonstrated improvement in airway-related and laryngeal symptoms after antireflux surgery. Spivak et al.[4] demonstrated reduction in asthma symptom scores and the need for systemic corticosteroids to control asthma symptoms in patients in whom reflux-related asthma had been diagnosed. In that series, seven of nine patients (78%) who had been steroid dependent preoperatively were able to wean off of steroids completely after surgery. Novitsky et al.[24] studied the effects of antireflux surgery on patients with chronic cough symptoms that correlated with esophageal reflux by 24-h pH probe monitoring. They found that 62% of patients had complete resolution of symptoms, and 86% had some improvement in symptoms after Nissen fundoplication. Similarly, Greason et al.[25] in a series of 65 patients documented improvement in symptoms including pneumonia, cough, hoarseness, steroid and theophylline use as well as regurgitation, choking episodes, and antacid usage in patients who had undergone a variety of antireflux procedures over a 12-year period. Wright and Rhodes[10] presented a series of 145 patients who underwent laparos-

copic Hill hiatal hernia repair, with roughly one third of the patients reporting symptoms of LPR. Symptomatic improvement in voice, cough, globus, and sore throat symptoms was 89–92%. Duffy et al.[9] demonstrated that after LNF, quality of life scores improved in both patients with typical GERD as well as LPR symptoms.

Our study corroborates previous findings demonstrating that antireflux surgery is efficacious in the treatment of LPR. Our complete response rate of 65% and improvement rate of 97% are consistent with or exceed previously published series. This may be due to the stringent preoperative testing regiment designed to identify patients whose laryngeal symptoms were, in fact, due to LPR. We also selected patients who had not yet developed "end-stage" upper airway pathology, as our methodology relied upon symptomatic improvement to define success. It is our belief that while patients with more severe upper airway pathology (e.g., tracheal stenosis, laryngeal cancer, etc.) are candidates for and do benefit from antireflux surgery, it was not reasonable to expect that there would be evidence of symptomatic improvement in the scores measured by our survey instruments. Additionally, each patient at our institution undergoes extensive pre- and postoperative counseling by the operating surgeon, program nurse, and program dietitian. A graduated diet is introduced over an 8-week postoperative period, and education regarding postoperative eating habits is provided. We believe the patient bears the responsibility to "take care of the wrap" after surgery to ensure the best possible long-term functional outcome. Finally, we have shown that the majority of patients can expect relief from a wide array of atypical symptoms including voice changes/hoarseness, chronic cough, throat clearing, and dysphagia/odynophagia. Overall patient quality of life is also likely to improve after surgery, the benefits of which are evident as early as 1 month after the procedure and are durable over a medium-term follow-up period.

Despite an aggressive selection process designed to identify patients who were most likely to respond to surgical therapy, there were still two nonresponders and six patients who had only mild symptomatic relief. There was no correlation between presenting complaints and symptom resolution after surgery. This suggests that not even thorough preoperative testing is uniformly sufficient to predict successful resolution of LPR symptoms, although it does appear to improve the likelihood that patients will see a significant benefit after surgery. Although our study did not evaluate the issue, it would be helpful to determine the etiology of failure, particularly in patients who had an initial good response followed by symptomatic relapse. It is likely that a percentage of these patients continue to experience infrequent reflux episodes after surgery, which may be responsible for perpetuating symptoms. Oelschlager et al.[8] studied patients postoperatively with 24-h pH monitoring and noted that even after antireflux surgery, LPR patients experienced 1.6 episodes per day of pharyngeal reflux and esophageal acid exposure times of 2.1%. It is plausible that these physiologic events may be sufficient to perpetuate symptoms; alternatively, other causes of laryngeal symptoms not related to reflux may remain to be elucidated.

Conclusion

LNF is an effective treatment for LPR and can be expected to improve both patient symptoms and overall quality of life. With appropriate patient selection, pre- and postoperative patient education, compliance with perioperative instruction, and adequate follow-up, surgeons can confidently predict symptomatic improvement in more than 95% of patients. Fully, 65% of patients who are treated before the onset of end-stage laryngeal injury can expect complete resolution of their complaints. The results of fundoplication are durable over a medium-term follow-up period, and continued surveillance of our population will allow us to extend these findings to the long term.

References

1. Papasavas PK, Keenan RJ, Yeaney WW, Caushaj PF, Gagné DJ, Landreneau RJ. Effectiveness of laparoscopic fundoplication in relieving the symptoms of gastroesophageal reflux disease (GERD) and eliminating antireflux medical therapy. Surg Endosc 2003;17:1200–1205.
2. Desai KM, Soper NJ. Laparoscopic Nissen fundoplication. In: In Soper NJ, Swanstrom LL, Eubanks WS, editors. Mastery of Endoscopic and Laparoscopic Surgery. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 193–203.
3. Ahmad I, Batch AJG. Acid reflux management: ENT perspective. J Laryngology & Otology 2004;118:25–30.
4. Spivak H, Smith CD, Phichith A, Galloway K, Waring JP, Hunter JG. Asthma and gastroesophageal reflux: Fundoplication decreases need for systemic corticosteriods. J Gastrointest Surg 1999;3:477–482.
5. Copper MP, Smit CF, Stanojcic LD, Devriese PP, Schouwenburg PF, Mathus-Vliegen LMH. High incidence of laryngopharyngeal reflux in patients with head and neck cancer. Laryngoscope 2000;110:1007–1011.
6. Carrau RL, Khidr A, Gold KF, Crawley JA, Hillson EM, Koufman JA, Pashos CL. Validation of a quality-of-life instrument for laryngopharyngeal reflux. Arch Otolaryngol Head Neck Surg 2005;131:315–320.
7. Nord JH. Extraesophageal symptoms: What role for the proton pump inhibitors? Am J Med 2004;117:56S–62S.
8. Oelschlager BK, Eubanks TR, Oleynikov D, Pope C, Pellegrini CA. Symptomatic and physiologic outcomes after operative treatment for extraesophageal reflux. Surg Endosc. 2002;16:1032–1036.
9. Duffy JP, Maggard M, Hiyama DT, Atkinson JB, McFadden DW, Ko CY, Hines OJ. Laparoscopic Nissen fundoplication improves quality of life in patients with atypical symptoms of gastroesophageal reflux. Am Surgeon 2003;69:833–838.

10. Wright RC, Rhodes KP. Improvement of laryngopharyngeal reflux symptoms after laparoscopic Hill repair. Am J Surg. 2003;185: 455–461.
11. Farrell TM, Richardson WS, Trus TL, Smith CD, Hunter JG. Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery. Br J Surg 2001;88:1649–1652.
12. Chen RYM, Thomas RJS. Results of laparoscopic fundoplication where atypical symptoms coexist with oesophageal reflux. ANZ J Surg 2000;70:840–842.
13. Belafsky PC, Postma GN, Koufman JA. Laryngopharyngeal reflux symptoms improve before changes in physical findings. Laryngoscope 2001;111:979–981.
14. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the Reflux Symptom Index (RSI). J Voice 2002;16:274–277.
15. Oelschlager BK, Chang L, Pope CE, Pellegrini CA. Typical GERD symptoms and esophageal pH monitoring are not enough to diagnose pharyngeal reflux. J Surg Res 2005;128:55–60.
16. Oelschlager BK, Eubanks TR, Maronian N, Hillel A, Oleynikov D, Pope CE, Pellegrini CA. Laryngoscopy and pharyngeal pH are complementary in the diagnosis of gastroesophageal–laryngeal reflux. J Gastrointest Surg 2002;6:189–194.
17. Dore MP, Pedroni A, Pes GM, Maragkoudakis E, Tadeu V, Pirina P, Realdi G, Delitala G, Malaty HM. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. Dig Dis Sci 2007;52:463–468.
18. So JBY, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. Surgery 1998;124:28–32.
19. Belafsky PC, Postma GN, Amin MR, Koufman JA. Symptoms and findings of laryngopharyngeal reflux. Ear Nose Throat J 2002;81(S2):10–13.
20. Munoz JV, Herreros B, Sanchiz V, Amoros C, Hernandez V, Pascual I, Mora F, Minguez M, Bagan JV, Benages A. Dental and periodontal lesions in patients with gastro-oesophageal reflux disease. Dig Liver Dis 2003;35:461–467.
21. Oelschlager BK, Barreca M, Chang L, Oleynikov D, Pellegrini CA. Clinical and pathologic response of Barrett's esophagus to laparoscopic antireflux surgery. Ann Surg 2003;238:458–466.
22. Maldonado A, Diederich L, Castell DO, Gideon RM, Katz PO. Laryngopharyngeal reflux identified using a new catheter design: Defining normal values and excluding artifacts. Laryngoscope 2003;113:349–355.
23. Westcott CJ, Hopkins MB, Bach K, Postma GN, Belafsky PC, Koufman JA. Fundoplication for laryngopharyngeal reflux disease. J Am Coll Surg 2004;199:23–30.
24. Novitsky YW, Zawacki JK, Irwin RS, Hussey VM, Callery MP. Chronic cough due to gastroesophageal reflux disease: Efficacy of antireflux surgery. Surg Endosc 2002;16:567–571.
25. Greason KL, Miller DL, Deschamps C, Allen MS, Nichols FC, Trastek VF, Pairolero PC. Effects of antireflux procedures on respiratory symptoms. Ann Thorac Surg 2002;73:381–385.

Discussion

C. Daniel Smith, M.D. (Jacksonville, FL): I want to thank the authors for inviting me to comment on this work and providing the manuscript in advance and also congratulate you. This is a difficult patient population; it is a very difficult diagnosis, and probably the hardest of all is drilling down on the outcomes and making sense of outcomes. You have done a good job at trying to achieve that. However, I am going to challenge you on a couple of things, and I have four questions for you.

First relates to the definition of your patient population. Sixty percent of your patients had both LPR and GERD symptoms, which are typical GERD symptoms. My question is, did you look at the outcomes of those with LPR only? You have stated that LPR was the primary indication for surgery, but did you actually isolate out those patients who had only LPR and look at their outcomes, and if not, why not?

The second question is how do you explain or at least offer some comments about the significant improvement at 1 month, because that is surprising. Most of us caution these patients that it is going to take months and months before they are going to achieve any significant change in their symptoms because of the chronic inflammatory changes associated with the larynx and the vocal cords. I was really struck that you had such dramatic and sustained improvement starting as early as 1 month.

Third, are there any data or any thoughts on PPIs? They were sort of absent from your whole talk, and most of us will use response to PPIs as a predictor of outcome, at least for typical GERD symptoms. In addition, what about continued use of PPIs postoperatively. You did not tell us anything about how many of these patients still needed any PPIs at all and if none of them are needing PPIs, which is a pretty remarkable outcome, that should be included.

And finally, what is your definition of success? QoL, quality of life, is a great outcome, but it is very difficult to interpret quality of life without a control group, and you did not provide us a control. Therefore, I am not sure we can rely simply on quality of life. There is another way to interpret your data, and that is that 35% of patients failed to normalize their LPR. They had improvement, but they failed to normalize. This, without any objective data on pH postoperatively or PPI use postoperatively could lead to a completely different conclusion; these patients are not doing as well as you would like with 35% of patients failing this approach and perhaps not such a favorable outcome.

I look forward to your comments, and again, thanks for the chance to comment on this paper.

Robert A. Catania, M.D. (Baltimore, MD): Thank you very much, Dr. Smith. To answer the questions, separation of the pure LPR versus the mixed population, did we perform a statistical analysis of the LPR only group? It could have been done very quickly, but we did not analyze the data that way. To drill down on differences between the two groups, what we did instead was a chi-squared analysis. We did expect that there would be a difference, as it has been suggested in the past that there is a difference. In our study, we found that both groups responded equally well to surgery.

The demonstrated improvement at the 1 month time point, I agree, was also somewhat surprising, particularly with vocal symptoms. Some symptom clusters have been shown

in the past to respond quickly, particularly things like coughing and choking episodes, and you would expect that when you stop the reflux that is causing the coughing and choking, the symptoms would similarly stop. Previously, it has been shown that it takes a couple of months for the vocal changes to improve, but we found in our population that that was not the case.

Now, our results may be partially due to a selection bias in that when we designed the study, we wanted to see if this was an intervention that was going to help people early in the diagnosis of LPR to answer the question should we treat them with antireflux surgery early in the course of the disease. We specifically excluded people who had structural damage to their larynx, as we were using symptom scores to quantify success. We excluded people who had previous tracheostomies and people who had previous reconstructive surgery. There were a few people who had had polyps or granulation tissue removed from their vocal cords. I cannot give you a specific number on that. I think that may be why we saw an improvement so much faster than previously reported, because in earlier studies they did not exclude those patients with structural changes. Our thought was if there are already significant structural changes of the larynx, we would not expect them to symptomatically improve, which is why we excluded them from our population.

In terms of PPIs, we have added questions about PPI therapy to our questionnaire that goes out now, but for the first year of collection, we did not have any of that data. It may be a reasonable thing to go back and retrospectively try to collect that, but I do not have that information for the entire population, and therefore I did not include it in the analysis.

Finally, I present the definition of success. I agree that 35% failed to normalize, but the RSI is a dynamic index, and when you look at it, control patients in the early studies do not have a definite score of 0 or 5. Their scores covered a range between 8 and 15. A score below 13 was chosen to be the definition of normal because that score included 75% of normal patients. Some of the patients in our study that fall into the 13 to 19 range I think are probably normal. We just are bound by the definition reported by previous authors.

J Gastrointest Surg (2007) 11:1589–1597
DOI 10.1007/s11605-007-0330-9

Esophagectomy for High Grade Dysplasia is Safe, Curative, and Results in Good Alimentary Outcome

Valerie A. Williams · Thomas J. Watson · Fernando A. Herbella · Oliver Gellersen · Daniel Raymond · Carolyn Jones · Jeffrey H. Peters

Received: 21 May 2007 / Accepted: 5 September 2007 / Published online: 2 October 2007

Abstract
Background The increasing adoption of endoscopic therapies and expectant surveillance for patients with high grade dysplasia (HGD) in Barrett's esophagus has created considerable controversy regarding the ideal treatment choice. Confusion may be due, in part, to a limited understanding of the outcomes associated with surgical resection for HGD and extrapolation of data derived from patients undergoing an esophagectomy for invasive cancer. The purpose of our study was to document the perioperative and symptomatic outcomes and long-term survival after esophagectomy for HGD of the esophagus.
Material and Methods The study population consisted of 38 patients who underwent esophagectomy for biopsy-proven HGD between 10/1999 and 6/2005. Three patients were excluded from analysis due to obvious tumor on upper endoscopy. Patients were evaluated regarding ten different foregut symptoms and administered a ten-question appraisal of eating and bowel habits. Outcome measures included postoperative morbidity and mortality, the prevalence of invasive cancer in the esophagectomy specimens, symptomatic and functional alimentary results, patient satisfaction, and long-term survival. Median follow-up was 32 months (range, 7–83).
Results Thirty-day postoperative and in-hospital mortality was zero. Complications occurred in 37% (13/35), and median length of stay was 10 days. Occult adenocarcinoma was found in 29% (10/35) of surgical specimens (intramucosal in four; submucosal in five; and intramuscular in one with a single positive lymph node.) Patients consumed a median of three meals per day, most (76%, 26/34) had no dietary restrictions, and two-thirds (23/34) considered their eating pattern to be normal or only mildly impacted. Meal size, however, was reported to be smaller in the majority (79%, 27/34) of patients. Median body mass index (BMI) decreased slightly after surgery (28.6 vs 26.6, $p>0.05$), but no patient's BMI went below normal. The number of bowel movements/day was unchanged or less in a majority (82%) of patients after surgery. Fifteen of 34 (44%) patients reported loose bowel movements, which occurred less often than once per week in 10 of the 15. One patient had symptoms of dumping. Mean symptom severity scores improved for all symptoms except dysphagia and choking. Four patients developed foregut symptoms that occurred daily. Most patients (82%) required at least one postoperative dilation for dysphagia. Almost all (97%) patients were satisfied. Disease-free survival was 100%, and overall survival was 97% (34/35) at a median of 32 months.
Conclusion Esophagectomy is an effective and curative treatment for HGD and can be performed with no mortality, acceptable morbidity, and good alimentary outcome. These data provide a gold standard for comparison to alternative therapies.

Poster presented at the 48th Annual Meeting of the Society for Surgery of the Alimentary Tract, Washington, DC, USA, May 21, 2007.

V. A. Williams · T. J. Watson · F. A. Herbella · O. Gellersen · D. Raymond · C. Jones · J. H. Peters
Division of Thoracic and Foregut Surgery, Department of Surgery, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

V. A. Williams
e-mail: Valerie_Williams@urmc.rochester.edu

V. A. Williams · T. J. Watson (✉)
Division of Thoracic and Foregut Surgery, Department of Surgery, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, USA
e-mail: Thomas_Watson@urmc.rochester.edu

Keywords Esophagectomy · High-grade dysplasia · Esophageal cancer

Introduction

The incidence of esophageal adenocarcinoma continues to increase in Western countries.[1] National Cancer Institute data predict that approximately 15,560 cases of esophageal carcinoma will occur in the USA in 2007, of which approximately 8,000 will be adenocarcinoma.[2] Barrett's esophagus, characterized by the replacement of normal esophageal squamous mucosa with metaplastic columnar mucosa resembling intestinal epithelium, has long been recognized to be a precursor of esophageal adenocarcinoma.[3,4] Current thought holds that Barrett's esophagus may progress through the intermediate steps of low-grade and high-grade dysplasia before developing into invasive carcinoma.

High-grade dysplasia (HGD) is a neoplastic process with disease still confined to the epithelium, and its natural history is not well understood. Some cases of HGD progress to invasive malignancy,[3,4] whereas others may not, although the ability to predict whether and when progression might occur is limited at present. The distinction of HGD from intramucosal carcinoma can be difficult, even by experienced gastrointestinal pathologists.[5,6] In addition, when patients have undergone esophagectomy for the preoperative diagnosis of HGD, occult carcinoma has been detected in a significant percentage of the resected specimens.[7–33] The presence of Barrett's esophagus with HGD, therefore, has been representative of an unstable esophageal epithelium in transition to carcinoma and a marker of existing carcinoma. For these reasons, HGD has traditionally been an indication for esophagectomy in patients physiologically fit enough to tolerate the operation, as resection is both a prophylactic and potentially curative therapy for esophageal adenocarcinoma.

Esophagectomy has been challenged, however, as the most appropriate therapy for HGD. Critics of this approach cite the magnitude of the procedure, the potential for postoperative morbidity and mortality, and the negative impact on quality of life that foregut reconstruction can impose. Other treatment strategies, including rigorous endoscopic surveillance or a variety of endoscopic mucosal therapies, have arisen as alternatives to esophagectomy for HGD, particularly in patients who are deemed as being at high risk for surgery. Although such modalities hold promise, each less invasive alternative has its own potential risks and limitations that must be weighed against perceived advantages. To make informed comparisons between each of the treatment alternatives for HGD, accurate data regarding the outcomes of esophagectomy for HGD are essential. Toward this end, the purpose of our study was to document the perioperative complications, symptomatic outcomes, patient satisfaction, and long-term survival after esophagectomy for HGD.

Material and Methods

Study Population

Approval from our institutional review board was obtained before the start of this study. Thirty-eight patients who underwent esophagectomy for biopsy-proven HGD during the years 1999 to 2005 were retrospectively evaluated. Three patients were excluded from evaluation due to obvious malignancy on preoperative upper endoscopy. Of the remaining 35 patients, 5 had small mucosal nodules or irregularities. All patients underwent a mapping biopsy protocol with four-quadrant biopsies taken every 1 cm and additional biopsies taken at the site of any visible mucosal nodularity. Biopsies were examined by two separate pathologists, one typically an expert in the pathology of gastrointestinal dysplasia, to confirm the presence of HGD.

Thirty-three patients (94.3%) underwent an esophagectomy via a transhiatal approach and two (5.7%) through a combined laparotomy and right thoracotomy. Of those patients undergoing transhiatal esophagectomy, 4 (12.1%) were completed using a vagal-sparing technique. All but one patient underwent a cervical incision with cervical esophagogastric anastomosis, regardless of approach. A single patient underwent esophagogastric anastomosis performed in the high intra-thoracic position. All patients, except those undergoing vagal-sparing esophagectomy, underwent either pyloromyotomy or pyloroplasty for gastric drainage.

Outcome Assessment

Outcome was assessed by four primary measures: (1) postoperative morbidity and mortality; (2) alimentary function; (3) patient satisfaction; and (4) long-term survival. Preoperative evaluation, perioperative data, and surgical pathology were collected through retrospective review of both inpatient and outpatient charts. Patients were contacted after esophagectomy via telephone and interviewed regarding current symptoms and changes in symptom frequency. Patients were queried regarding ten different foregut symptoms, which included heartburn, regurgitation, dysphagia, odynophagia, chest pain, epigastric pain, cough, choking, nausea, and vomiting. Symptoms were assigned a standardized symptom severity score (Table 1). Patients were also administered a ten-question appraisal of eating and bowel habits. Specifically, patients were questioned regarding diet quality and meal size, frequency, and pattern. In addition, the number and quality of daily bowel movements were documented. Patients were asked to give an

Table 1 Symptom Severity Score

Score	Description
4	Symptom occurs daily.
3	Symptom occurs less than once per day.
2	Symptom occurs less than once per week.
1	Symptom occurs less than once per month.
0	Asymptomatic.

overall subjective assessment of their outcome. Specifically, they were asked whether they were satisfied with the result of their surgery and whether they would undergo the operation again if given the choice.

Median follow-up after esophagectomy was 32 months (range, 7–83). Follow-up was obtained in 100% of patients. One patient died secondary to a non-cancer related cause before the time of the follow-up questionnaire.

Statistics

The Student's *t* test was used to compare continuous data between individual groups. Chi-square or Fischer exact test was used to compare proportions between individual groups. The Wilcoxon or Mann–Whitney *U* test was used for paired and unpaired, independent, nonparametric data. A p value of less than 0.05 defined statistical significance.

Results

Clinical Characteristics and Perioperative Outcome

Thirty-three males and two females with a median age of 64 (range, 41–89) underwent esophagectomy for biopsy-proven HGD. HGD was multi-leveled, defined as positive biopsies taken more than 1 cm apart, in 37% (13/35). All patients had pathologically confirmed Barrett's mucosa. Barrett's was long-segment (≥3 cm) in 11% (4/35) and short-segment (<3 cm) in 89% (31/35).

Thirty-day perioperative and in-hospital mortality was zero. Complications occurred in 13 of 35 patients (37%; Table 2). Three patients (8.5%) developed anastomotic leaks that were self-contained and treated medically with antibiotics and nothing per os. A single patient developed a chyle leak that resolved without surgical intervention. Median length of stay was 10 days (range, 7–74).

Occult adenocarcinoma was found in 29% (10/35) of surgical specimens. Tumor depth was intramucosal in 4 (40%), submucosal in 5 (50%), and intramuscular in 1 (10%). The single patient with intramuscular tumor had one lymph node positive for cancer. Of those patients without cancer, HGD was found in 21 (84%) and LGD (low grade dysplasia) in 4 (16%). Of those patients with mucosal irregularity noted on preoperative endoscopy, 60% (3/5) had invasive cancer in their surgical specimen. As importantly, of patients without mucosal irregularity, 23% (7/30) were found to have an occult carcinoma (Table 3).

Symptomatic and Functional Outcome

Mean symptom severity scores improved for all symptoms except dysphagia and choking (Fig. 1). Dysphagia and choking, however, were mild, occurring less often than once per month in 83% (10/12) of these patients. Three patients developed symptoms that occurred daily. Of these patients, one had chest pain and one had epigastric pain. Both described these symptoms as short lasting and occurring at meals. One patient experienced daily dysphagia. Two-thirds (23/34) of patients were taking antacid medications for symptoms of heartburn or regurgitation, all with good relief. Most patients (82%) required at least one postoperative dilation for dysphagia.

Patients consumed a median of three (range, two to eight) meals per day. Two-thirds (23/34) of patients considered their eating pattern to be normal or only mildly impacted (Fig. 2). Most (76%) were able to eat an unrestricted diet. Meal size, however, was reported to be smaller after surgery than before surgery in the majority (79%, 27/34) of patients. Despite this fact, 56% considered their postoperative meal size to be normal, suggesting they were overeating before surgery. Of those who did not consider their meal size to be normal, 11(73%) described their meals as being one-half the size of a TV dinner and 4 (27%) one-fourth the size of a TV dinner. Importantly, those patients consuming meals comparable to one-fourth the size of a TV dinner ate more frequent meals per day (median 4.5, 3–8) compared to the others. Of those patients consuming restricted diets, spicy foods were avoided in two and meats such as steak were avoided in six. Median body mass index (BMI) decreased slightly after surgery (28.6 vs 26.6, $p>0.05$), but no patient's BMI went below normal.

Patients experienced a median of two (range, one to five) bowel movements per day after esophagectomy. Impor-

Table 2 Early Postoperative Complications

Complication (13/35, 37%)	
Pneumonia	3
Anastomotic leak	3
Wound infection	2
ARDS	1
Atrial fibrillation	1
Thoracic duct leak	1
Alcohol withdrawal	1
Acute renal failure	1
Ileus	1

Table 3 Occult Carcinoma Found in Those With or Without Endoscopically Detected Esophageal Mucosal Irregularity Within Barrett's Esophagus

	Endoscopic Finding	Pre-operative Biopsy: HGD	Postoperative Pathology: (+) Adenocarcinoma	Tumor Depth/Stage
Visible mucosal irregularity (n=5)	Ulcer (n=1) Nodule (n=4)	100%	60% (n=3)	66% (2/3) Submucosal/I 33% (1/3) Intramuscular and node (+)/ IIb
No visible mucosal irregularity (n=30)	Barrett's only; No ulcer or nodule	100%	23% (n=7)	57% (4/7) Intramucosal/I 43% (3/7) Submucosal/I

tantly, this number was unchanged or less than preoperatively in the majority (82%) of patients. Fifteen of 34 (44%) reported loose bowel movements, which occurred less often than once per week in 10 of the 15 (67%). One patient described symptoms consistent with dumping easily controlled with smaller and more frequent meals.

Almost all (97%, 33/34) patients were satisfied with the results of their operation. Similarly, 97% stated they would undergo the same operation again. One patient was not satisfied because of his inability to eat larger meals, and one patient stated he would choose a less invasive option if given the choice again.

Survival

Disease-free survival was 100% at a median follow-up of 32 months (range, 7–83). One patient, with comorbid heart disease, died 7 months after esophagectomy secondary to a myocardial infarction. This patient had stage IIb esophageal adenocarcinoma, due to involvement of a single lymph node by cancer, but had no evidence of recurrent disease at the time of his death. Overall survival was 97% (34/35).

Discussion

Our data show that esophagectomy can be performed for HGD with no mortality and with acceptable morbidity. Occult carcinoma was detected in 29% of esophagectomy specimens. Symptomatic and functional outcomes were good, with mean symptom scores improving after surgery for all symptoms other than dysphagia or choking. The majority considered their eating habits to be normal or only mildly impacted by surgery. Patient satisfaction was high (97%), with almost all patients stating they would choose surgery again if given the choice. Medium-term survival was excellent, approaching 100% at nearly 3 years follow-up.

Operative Mortality

Critical to the acceptance of esophagectomy as the treatment of choice for HGD is evidence that resection can be performed with a low rate of mortality and major perioperative complications. If high, mortality and morbidity from surgical intervention can negate any benefit derived from prevention or cure of cancer. Esophagectomy for esophageal carcinoma historically was associated with a high rate of early postoperative mortality.[35] Recent results derived from large administrative databases demonstrate operative mortality after esophagectomy far less than what had been previously reported. In a publication regarding outcomes from Veterans Administration hospitals covering 1,777 esophagectomies in 109 facilities from the years 1991–2000,[36] 30-day operative mortality was 9.8%. The vast majority (85%) of these procedures, however, were for esophageal carcinoma. In addition, many of the procedures were performed in hospitals with a small institutional or surgeon experience in performing esophagectomy, as the average institution performed only 1.6 esophagectomies per year. The importance of institutional volume was also demonstrated in a report derived from a Medicare database that analyzed esophagectomy outcomes during the time period 1994–1999.[37] Mortality after esophagectomy was 20.3% in hospitals where fewer than 2 esophagectomies were performed, compared to 8.4% in hospitals performing more than 19 esophagectomies per year. In fact, of all operations assessed, esophagectomy was found to be

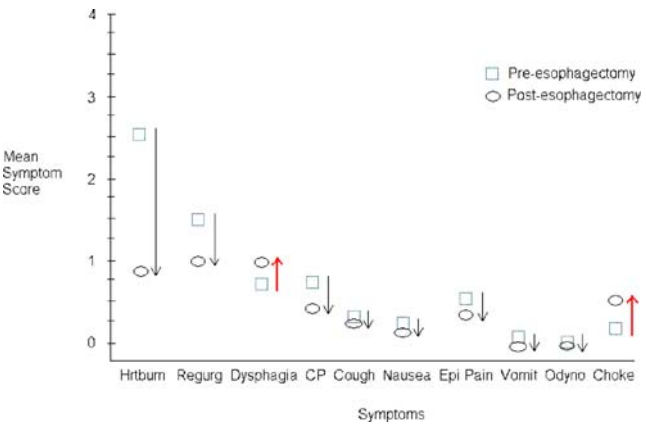


Figure 1 Pre- to postesophagectomy mean symptom scores. An improvement in mean scores was seen for all symptoms except dysphagia and choking.

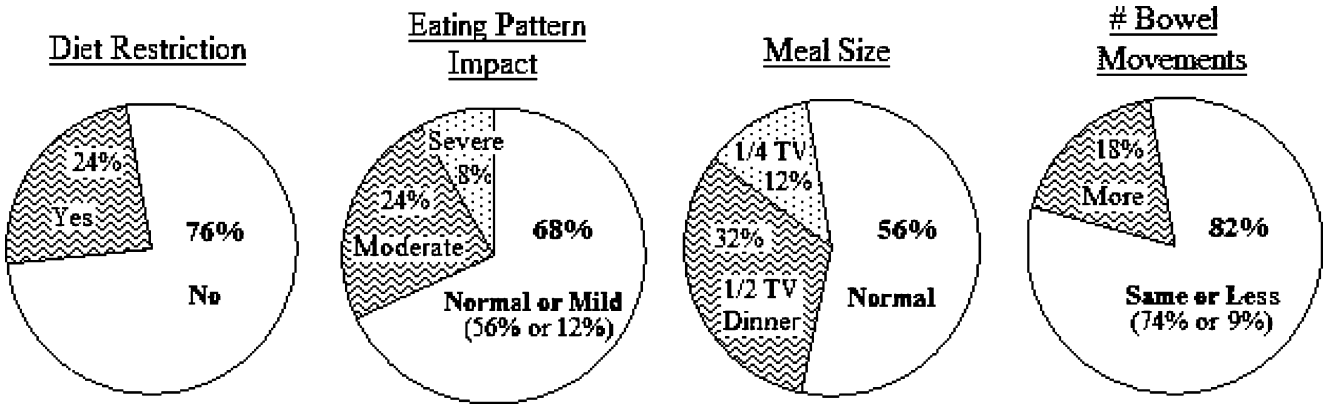


Figure 2 Functional alimentary outcomes after esophagectomy.

among the most sensitive to the influence of institutional procedural volume on operative mortality.

While operative mortality statistics for esophageal cancer have improved over recent decades, the rates of mortality stated above are still unacceptable when considering esophagectomy as prophylaxis for a pre-malignant condition or as potentially curative therapy for early cancer. Recent data from high-volume centers in the USA specializing in esophageal surgery reveal mortality statistics in the 3.5–5% range or lower after esophagectomy for carcinoma (Table 4). Of importance, however, are the numerous reports specifically addressing mortality after esophagectomy for the preoperative diagnosis of HGD (Table 5). Similar to our experience, most centers report an extremely low mortality rate after esophagectomy for HGD, such that the cumulative mortality from all series approximates 1%.

A number of plausible explanations exist for the improved outcomes in patients with the preoperative diagnosis of HGD compared to those undergoing esophagectomy for known invasive esophageal carcinoma. Patients with HGD most assuredly represent a different, and perhaps healthier, patient population than those presenting with esophageal squamous cell carcinoma, for instance, given the divergent risk factors for the two diseases. Lacking cancer and its potential to cause dysphagia and weight loss, patients with HGD typically do not present in a malnourished or immunologically compromised state. Likewise, patients without cancer generally can and should be optimized for surgical intervention, addressing such issues as cardiopulmonary comorbidities, smoking or alcohol cessation, or general deconditioning, without the time-pressure imposed by a malignancy and its potential physiological and psychological consequences. Neoadjuvant treatment consisting of chemotherapy or combined chemo-radiation, with its associated risks and potential for contributing to perioperative complications, is not a consideration in patients lacking proof of invasive cancer.

In some centers, a less aggressive operation may be offered for resection of HGD than what is performed for invasive cancer with its potential for nodal metastasis. For instance, we and others generally perform a transhiatal resection for HGD, sometimes with a vagal-sparing technique. For known or suspected invasive carcinoma, on the other hand, we often consider a more aggressive en bloc esophagectomy that requires the addition of a right thoracotomy with its associated morbidity, particularly the potential for respiratory complications.[41]

Of most significance, perhaps, is the ability to optimize patient selection for esophagectomy in the setting of HGD. Given the presence of non-operative management options for HGD, such as mucosal resection/ablation or endoscopic surveillance, esophagectomy can only be justified in patients judged to be at low risk for operative intervention. High-risk patients commonly are managed by less invasive means, as the benefit of surgery may not justify the risk in such

Table 4 Mortality After Esophagectomy for Cancer at US Specialty Centers

Author	Resection Type	Year	Number of cases	Mortality (%)
Swanson et al.[38]	TTE	2001	250	3.6
Altorki et al.[39]	3-field en bloc	2002	80	5
Portale et al.[40]	THE/TTE/en bloc	2004	263	4.5
University of Rochester[a]	THE/TTE	2007	244	4.1

THE Transhiatal esophagectomy; *TTE* transthoracic esophagectomy; *MIE* minimally invasive esophagectomy
[a] Unpublished data

Table 5 Mortality After Esophagectomy for HGD

Author	Year	Number of Cases	Mortality (%)
Hamilton and Smith[10]	1987	5	0
Altorki et al.[13]	1991	8	0
Pera et al.[15]	1992	18	0
Levine et al.[16]	1993	7	14
Streitz et al.[17]	1993	9	0
Peters et al.[19]	1994	9	0
Edwards et al.[20]	1996	11	0
Ferguson and Naunheim[21]	1997	15	0
Cameron and Carpenter[22]	1997	19	0
Patti et al.[23]	1999	11	0
Nigro et al.[24]	1999	14	7
Nguyen et al.[25]	2000	12	0
Zaninotto et al.[26]	2000	13	0
Headrick et al.[27]	2002	54	1.8
Romagnoli et al.[28]	2003	21	0
Tseng et al.[29]	2003	60	1.7
Reed et al.[30]	2005	49	2
Sujendran et al.[31]	2005	17	0
Moraca and Low[32]	2006	23	0
Rice et al.[33]	2006	111	0
Chang et al.[34]	2006	9	0
Williams et al.[a]	2007	35	0
Total	1987–2007	530	0.94%

[a] Current study

situations. A low-risk management option typically does not exist for patients diagnosed with potentially operable esophageal carcinoma, as curative endoscopic therapies commonly are not suitable or available and surveillance is not an option. While combined chemoradiation without surgery may be an option in the high-risk patient, whether the risk/benefit ratio of such therapy is better compared to esophagectomy, and whether the patient and his treating oncologists will consider and be able to complete such therapy may be questionable. Esophagectomy may be chosen by the patient and physician as the best treatment option, despite the presence of comorbidities and the risks of intervention.

Functional Outcomes

As esophagectomy for carcinoma historically was associated with low rates of cure, operation was commonly undertaken for short-term palliation of symptoms.[34] Traditional outcomes assessment, therefore, focused on cure rates and operative mortality. Esophagectomy for HGD or early invasive carcinoma, on the other hand, is performed with the expectation of long-term survival. As a result, additional outcome measures such as quality of life after esophagectomy have assumed increasing importance.

Little data exist in the literature regarding functional outcomes specifically in patients undergoing esophagectomy for HGD. Headrick et al.[27] evaluated the quality of life of 54 patients who underwent esophagectomy for HGD and found that these patients scored better than national norms in role-physical and role-emotional categories with no differences in the categories of bodily pain, health perception, energy/fatigue, physical and social functioning, and mental health. The authors reported reflux in 68%, although symptoms were minimal on medical therapy. Furthermore, while 51% of patients required at least one postoperative dilation for presumed esophagogastric anastomotic stricture, only 38% (18/38) complained of dysphagia. Dysphagia was mild in the majority (83%).

These data are quite similar to what we report in that two-thirds of our patients were taking acid suppressive medications for symptoms of heartburn or regurgitation. Over 80% of our patients, however, required at least one postoperative dilation for presumed esophagogastric anastomotic stricture, although only approximately one-third experienced dysphagia at the time of follow-up assessment and 83% of such individuals had episodes of dysphagia less than once per month.

Chang, et al.[34] reported on quality of life in 34 patients undergoing esophagectomy for HGD or adenocarcinoma detected during the course of surveillance for Barrett's esophagus. At a mean follow-up of 46 months, SF-36 (version 2) scores were equal to or better than those of healthy individuals, based on national averages reported in 1998, in all seven areas tested. The most frequently reported postoperative symptoms were reflux (59%), diarrhea (55%), and bloating (45%). The frequency and severity of these symptoms, however, were mild.

We found that patients ate an average of three meals per day after esophagectomy and were able to eat an unrestricted diet in a quantity that, although generally less that what was consumed before surgery, was still deemed to be normal by most. In addition, while there was a trend toward weight loss after surgery (median BMI decreasing from 28.6 to 26.6), the postoperative median BMI was still in the "overweight" category and no patient's BMI diminished below the normal range.

Moraca and Low[32] reported on outcomes after esophagectomy for HGD and intramucosal carcinoma. Seventy-nine percent of their patients after esophagectomy reported "normal or insignificantly impacted eating." Similar to our experience, mean BMI decreased from 28.9 to 25.6 ($p=0.003$) as a result of surgery, and no patient was found to be underweight at the time of follow-up. Of those patients completing postoperative SF-36 questionnaires, health-related quality of life (HRQL) scores equaled or exceeded age- and sex-matched norm-based values in seven of eight domains.

While esophagectomy has been associated with the potential for postoperative dumping and diarrhea, an interesting finding in our patient population was that the median number of bowel movements per day after esophagectomy was only two and that 82% of patients reported that this number was equal to or less than the number they experienced before surgery. In addition, in the minority of patients experiencing intermittent loose stools, the frequency was less than once per week in the majority. Only one patient in our cohort experienced symptoms consistent with dumping and was managed with dietary modifications with good results.

Occult Carcinoma

Of the 35 patients who underwent esophagectomy for the preoperative diagnosis of HGD, 29% were found to have occult carcinoma in their surgical specimen. This percentage is consistent with other reports in the literature (Table 6). Our analysis of the available studies dating back to 1983 reveals a 37% incidence of occult carcinoma in the setting of known HGD, without a significant trend toward diminution in recent years. The presence of a visible mucosal nodule in association with HGD was a particularly worrisome finding in that 60% (three out of five patients) had an invasive carcinoma detected in the operative specimen, also consistent with prior reports.[42–45]

Of particular concern is the fact that 60% of the invasive cancers extended beyond the mucosa, for a prevalence of 17% in all patients undergoing resection for HGD. These data are extremely important when a strategy other than esophagectomy is contemplated for the management of HGD. Tumors limited to the mucosa are associated with only an approximately 5–10% risk of nodal metastasis.[44] When the tumor invades into the submucosa, however, the risk of nodal metastasis increases substantially to the 30–50% range. Currently available esophageal mucosal resective or ablative procedures, such as endoscopic mucosal resection, photodynamic therapy, or radiofrequency ablation, are best suited for disease limited to the mucosa. Any such therapies are potentially inadequate once tumor has invaded into the submucosa or beyond, not only due to the extent of intramural disease but also because of the potential for lymphatic spread.

Despite the cancer risk, our data demonstrate that esophagectomy for HGD is generally a curative treatment. Disease-free survival at a median of 32 months follow-up in our study was 100%. Limitations of the current data are that follow-up is not available beyond 5 years on average, and we do not know the potential for recurrent intestinal metaplasia, dysplasia, or frank carcinoma in the esophageal remnant over the long term.

Table 6 Prevalence of Occult Cancer After Esophagectomy for HGD

Author	Year	Number of Cases	% Cancer in Resected Specimens
Skinner et al.[7]	1983	3	67
Schmidt et al.[8]	1985	2	100
Lee[9]	1985	2	50
Hamilton and Smith[10]	1987	5	60
Reid et al.[11]	1988	4	0
DeMeester et al.[12]	1990	2	50
Altorki et al.[13]	1991	8	50
McArdle et al.[14]	1992	3	67
Pera et al.[15]	1992	18	50
Levine et al.[16]	1993	7	0
Streitz et al.[17]	1993	9	22
Ortiz et al.[18]	1996	2	0
Peters et al.[19]	1994	9	55
Edwards et al.[20]	1996	11	73
Ferguson and Naunheim[21]	1997	15	53
Cameron and Carpenter[22]	1997	19	10
Patti et al.[23]	1999	11	36
Nigro et al.[24]	1999	14	43
Nguyen et al.[25]	2000	12	42
Zaninotto et al.[26]	2000	13	23
Headrick et al.[27]	2002	54	35
Romagnoli et al.[28]	2003	21	38
Tseng et al.[29]	2003	60	30
Reed et al.[30]	2005	49	37
Sujendran et al.[31]	2005	17	65
Moraca and Low[32]	2006	23	26
Rice[33]	2006	111	45
Chang et al.[34]	2006	9	11
Williams et al.[a]	2007	35	29
Total	1983–2007	548	37.4%

[a] Current study

Conclusions

Esophagectomy remains the standard of care for most patients with HGD, once the diagnosis has been established and independently confirmed, although the decision must be individualized. Esophagectomy should be performed only in high-volume centers with a proven track record in terms of operative mortality, morbidity, and functional outcomes. In such settings and with proper patient selection, operative mortality approximates 1% or less, functional outcomes are good with high patient satisfaction, and cure rates are excellent. The benefits of operative intervention appear to justify the risks in such situations.

Esophagectomy is a highly reliable curative therapy for HGD. Alternative treatment options, including emerging technologies, will have to be judged against this modern day standard.

References

1. Pohl H, Welch HG. J Natl Cancer Inst. 2005;97:142–146.
2. American Cancer Society. Cancer Facts and Figures 2007. Atlanta, GA: American Cancer Society, 2007. http://www.cancer.org Last accessed March 31, 2007.
3. Hameeteman W, Tytgat GNJ, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology. 1989;96:1249–1256.
4. Spechler SJ. The natural history of dysplasia and cancer in esophagitis and Barrett esophagus. J Clin Gastroenterol. 2003;36 (5 Suppl):S2–S5. (discussion S26–S28).
5. Ormsby AH, Petras RE, Henricks WH, Rice TW, Rybicki LA, Richter JE, Goldblum JR. Observer variation in the diagnosis of superficial oesophageal adenocarcinoma. Gut. 2002;51:671–676.
6. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol.. 2001;32(4):368–378.
7. Skinner DB, Walther BC, Riddell RH, et al. Barrett's esophagus: Comparison of benign and malignant cases. Ann Surg. 1983;198: 554–566.
8. Schmidt HG, Riddell RD, Walther B, et al. Dysplasia in Barrett's esophagus. J Cancer Res Clin Oncol. 1985;110:145–152.
9. Lee RG. Dysplasia in Barrett's esophagus: A clinicopathologic study of six patients. Am J Surg Pathol. 1985. 845–852.
10. Hamilton SR, Smith RL. The relationship between columnar epithelial dysplasia and invasive carcinoma arising in Barrett's esophagus. Am J Clin Pathol. 1987;87:301–312.
11. Reid BJ, Weinstein WM, Lewin KJ, et al. Endoscopic biopsy can detect high-grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. Gastroenterology. 1998;94:81–90.
12. DeMeester TR, Attwood SE, Smyrk TC, Therkildsen DH, Hinder RA. Surgical therapy in Barrett's esophagus. Ann Surg. 1990;212 (4):528–540.
13. Altorki NK, Sunagaawa M, Little AG, et al. High-grade dysplasia in the columnar-lined esophagus. Am J Surg. 1991;161:97–100.
14. McArdle JE, Lewin KJ, Randall G, et al. Distribution of dysplasia and early invasive carcinoma in Barrett's esophagus. Hum Pathol. 1992;23:479–482.
15. Pera M, Trastek VF, Carpenter HA, et al. Barrett's esophagus with high-grade dysplasia: An indication for esophagectomy. Ann Thorac Surg. 1999;54:204.
16. Levine DS, Haggett RC, Blout PL, et al. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. Gastroenterology. 1993;105: 40–50.
17. Streitz JM, Andrews CW, Ellis FH. Endoscopic surveillance of Barrett's esophagus: does it help? J Thorac Cardiovasc Surg. 1993;105(3):383–388.
18. Ortiz A, Martinez de Haro LF, Parrilla P, et al. Conservative treatment versus antireflux surgery in Barrett's esophagus: Long-term results of a prospective study. Br J Surg. 1996;83:274–227.
19. Peters JH, Clark GWB, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. J Thorac Cardiovasc Surg. 1994;108(5):813–822.
20. Edwards MJ, Gable DR, Lentsch AB, et al. The rationale for esophagectomy as the optimal therapy for Barrett's esophagus with high-grade dysplasia. Ann Surg. 1996;223:585–591.
21. Ferguson MK, Naunheim KS. Resection for Barrett's mucosa with high-grade dysplasia: Implications for prophylactic photodynamic therapy. J Thorac Cardiovasc Surg. 1997;114:824–829.
22. Cameron AJ, Carpenter HA. Barrett's esophagus, high-grade dysplasia, and early adenocarcinoma: A pathological study. Am J Gastroenterol. 1997;92:586–591.
23. Patti MG, Arcerito M, Feo CV, Worth S, De Pinto M, Gibbs VC, Gantert VC, Tyrrell D, Ferrell LF, Way LW. Barrett's esophagus: a surgical disease. J Gastrointest Surg. 1999;3(4):397–403.
24. Nigro JJ, Hagen JA, DeMeester TR, et al. Occult esophageal adenocarcinoma: Extent of disease and implications for effective therapy. Ann Surg. 1990;230:433–444.
25. Nguyen NT, Schauer P, Luketich JD. Minimally invasive esophagectomy for Barrett's esophagus with high-grade dysplasia. Surgery. 2000;127:284–290.
26. Zaninotto G, Parenti AR, Ruol A, et al. Oesophageal resection for high-grade dysplasia in Barrett's oesophagus. Br J Surg. 2000;87: 1102–1105.
27. Headrick JR, Nichols FC, Miller DL, Allen MS, Trastek VF, Deschamps C, Schleck CD, Thompson AM, Pairolero PC. High-grade esophageal dysplasia: long-term survival and quality of life after esophagectomy. Ann Thorac Surg. 2002;73(6): 1697–1703.
28. Romagnoli R, Collard JM, Gutschow C, Yamusah N, Salizzoni M. Outcomes of dysplasia arising in Barrett's esophagus: a dynamic view. J Am Coll Surg. 2003;197:365–371.
29. Tseng EE, Wu TT, Yeo CJ, Heitmiller RF. Barrett's esophagus with high grade dysplasia: surgical results and long-term outcome - an update. J Gastrointest Surg. 2003;7(2):164–170.
30. Reed MF, Tolis G, Edil BH, Allan JS, Donahue DM, Gaissert HA, Moncure AC, Wain JC, Wright CD, Mathisen DJ. Surgical treatment of esophageal high-grade dysplasia. Ann Thorac Surg. 2005;79:1110–1115.
31. Sujendran V, Sica G, Warren B, Maynard N. Oesophagectomy remains the gold standard for treatment of high-grade dysplasia in Barrett's oesophagus. Eur J Cardiothorac Surg. 2005;28: 763–766.
32. Moraca RJ, Low DE. Outcomes and health-related quality of life after esophagectomy for high-grade dysplasia and intramucosal cancer. Arch Surg. 2006;141:545–551.
33. Rice TW. Esophagectomy is the treatment of choice for high-grade dysplasia in Barrett's esophagus. Am J Gastroenterol. 2006;101:2177–2184.
34. Chang LC, Oelschlager BK, Quiroga E, Parra JD, Mulligan M, Wood DE, Pellegrini CA. Long-term outcome for high-grade dysplasia or cancer found during surveillance for Barrett's esophagus. J Gastrointest Surg. 2006;10:341–346.
35. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. Br J Surg. 1980;67: 381–390.
36. Bailey SH, Bull DA, Harpole DH, et al. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg. 2003;75:217–222.
37. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Eng J Med. 2002; 346(15):1128–1137.
38. Swanson SJ, Batirel HF, Bueno R, Jaklitsch MT, Lukanich JM, Allred E, Mentzer SJ, Sugarbaker DJ. Transthoracic esophagectomy with radical mediastinal and abdominal lymph node dissection and cervical esophagogastrostomy for esophageal carcinoma. Ann Thorac Surg. 2001;72:1918–1925.
39. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236(2):177–183.
40. Portale G, Hagen JA, Peters JH, Chan LS, DeMeester SR, Gandamihardja TA, DeMeeser TR. Modern 5-year survival of resectable esophageal adenocarcinoma: single institution experience with 263 patients. J Am Coll Surg. 2006;202(4):588–596.
41. Hulscher JBF, van Sandick JW, de Boer AGEM, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;3477: 1662–1669.

42. Schnell TG, Sontag SL, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology. 2001;120(7):1607–1619.
43. Weston AP, Sharma P, Mathur S, et al. Risk stratification of Barrett's esophagus: updated prospective multivariate analysis. Am J Gastroenterol. 2004;99(9):1657–1666.
44. Oh DS, Hagen JA, Chandrasoma PT, et al. Clinical biology and surgical therapy of intramucosal adenocarcinoma of the esophagus. J Am Coll Surg. 2006;203:152–161.
45. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology. 2001;120(7):1630–1639.

J Gastrointest Surg (2007) 11:1598–1606
DOI 10.1007/s11605-007-0283-z

Detection of Micrometastases in Peritoneal Washings of Pancreatic Cancer Patients by the Reverse Transcriptase Polymerase Chain Reaction

Kimberly Moore Dalal · Yanghee Woo · Charles Galanis · Mithat Gonen · Laura Tang · Peter Allen · Ronald DeMatteo · Yuman Fong · Daniel G. Coit

Received: 20 May 2007 / Accepted: 29 July 2007 / Published online: 19 September 2007

Abstract
Objective Pancreatic cancer patients with positive (+) peritoneal cytology have a prognosis similar to stage IV patients. We studied the ability of quantitative real time-polymerase chain reaction (RT-PCR) to detect micrometastases in patients undergoing staging laparoscopy.
Methods Peritoneal washes were obtained prospectively from 35 consecutive patients with pancreatic adenocarcinoma undergoing staging laparoscopy and 16 patients undergoing laparoscopy for benign disease. Each sample was assessed by cytologic examination and RT-PCR analysis for tumor markers: CEA, CK7, Kras2, and MUC1. Markers and their combinations were evaluated on the basis of their deviance from the ideal marker.
Results Pathologic stages for pancreatic cancer patients were: 1A-1 (3%), IB-1 (3%), IIA-5 (15%), IIB-13 (38%), III-5 (15%), IV-9 (26%). Eight patients were cytology (+) and stages IIA-1, IIB-2, IV-5. Twenty-five patients were RT-PCR (+). The optimal threshold for cycle amplification was 35 based on a receiver operating characteristic curve. CEA had the best profile of sensitivity, specificity, PPV, NPV, and the smallest deviance.
Conclusion RT-PCR using a panel of tumor markers, including CEA, was comparable in sensitivity, specificity, PPV, and NPV to cytology. RT-PCR could represent a more sensitive method for detection of subclinical peritoneal tumor dissemination; this may be useful in patient selection for operative management and clinical trials.

Keywords Pancreatic cancer · Peritoneal washings · Cytology · Micrometastases · RT-PCR

Introduction

The prognosis of pancreatic cancer is poor with an overall 5-year survival rate of 2–13%.[1] Even in patients who undergo an R0 resection, 70–80% will suffer an incurable local relapse, distant metastases, or peritoneal carcinomatosis,[2] the latter of which results from dissemination of

Presented at the Society for Surgery of the Alimentary Tract Annual Meeting, May 21, 2007, Washington, D.C.

Sources of support: none

Y. Woo · C. Galanis · P. Allen · R. DeMatteo · Y. Fong · D. G. Coit (✉)
Department of Surgery, Memorial-Sloan Kettering Cancer Center,
1275 York Avenue,
New York, NY 10021, USA
e-mail: coitd@mskcc.org

K. M. Dalal
Department of Surgery,
David Grant U.S. Air Force Medical Center,
Travis AFB, CA, USA

M. Gonen
Department of Epidemiology and Biostatistics,
Memorial Sloan-Kettering Cancer Center,
New York, NY, USA

L. Tang
Department of Pathology,
Memorial Sloan-Kettering Cancer Center,
New York, NY, USA

malignant cells. Warshaw[3] reported a 30% incidence of positive peritoneal cytology (PPC) in "early" pancreatic cancer and suggested that peritoneal cytology may add to preoperative staging evaluation. Patients with PPC have significantly lower resection rates[4] and decreased 5-year survival rates.[4,5] These cancer cells, however, may not be detectable in the peritoneum with conventional diagnostic tools. Immunocytologic methods may yield residual disease in 29% of R0 resected patients leading to death within 15–18 months compared with a 5-year survival of 30% in patients with negative cytology.[6] From a clinical perspective, cytology-positive patients have an extremely poor prognosis and are unlikely to benefit from a radical surgical approach unless effective systemic adjuvant chemotherapy can be identified.

Real time-polymerase chain reaction (RT-PCR) of peritoneal fluid in patients with pancreatic cancer has not been studied as extensively as that of gastric cancer patients.[7–10] Detection of Kras mRNA by PCR has been shown to have a sensitivity of 89% in ascites supernatants of patients with pancreatic carcinoma.[11] Carcinoembryonic antigen (CEA) and CK20 have been detected by immunohistochemistry in patients with metastatic pancreatic adenocarcinoma at a sensitivity rate of 92 and 78%, respectively.[12] Likewise, MUC1 and cytokeratin 7 (CK7) have been shown to be positive in 89 and 91% of patients with pancreatic cancer, respectively.[13,14] As these proteins are detectable in patients with pancreatic adenocarcinoma by immunohistochemistry, detection of the antecedent mRNA transcripts by RT-PCR may have a clinically relevant role in the staging of these patients. Moreover, the use of multiple markers may optimize the ability to detect metastatic disease with a high degree of sensitivity and specificity.[9]

The purpose of this study was to investigate the ability of a quantitative RT-PCR assay to detect cancer cells in peritoneal washings of patients undergoing laparoscopy for pancreatic cancer, to define the parameters to optimize RT-PCR, and to estimate the sensitivity, specificity, false positive, and false negative rate of peritoneal cancer cell detection by quantitative RT-PCR when compared to cytology as the gold standard.

Material and Methods

Patients

From March to August 2006, peritoneal washes were obtained prospectively from 35 consecutive patients with pancreatic adenocarcinoma undergoing diagnostic laparoscopy for staging at Memorial Sloan-Kettering Cancer Center (MSKCC). Patients eligible for this pilot study were >18 years of age and presented to the Surgical Services at MSKCC with pancreatic cancer based on dynamic, contrast-enhanced computed tomography (CT) scan or pathologic examination. If found to be potential candidates for surgical treatment, patients were scheduled for laparoscopy. Patients were identified preoperatively, offered participation, and required to provide informed consent. Only patients who had histologically confirmed pancreatic adenocarcinoma either after resection or during laparoscopic staging were included in the study.

In addition, peritoneal washes were obtained from 16 patients undergoing laparoscopy for benign conditions (e.g., gallstones, hernia, and prophylactic risk-reducing bilateral salpinoophorectomy). These negative control research subjects were identified preoperatively by a member of the patient's treatment team at MSKCC. This study was conducted after MSKCC Institutional Review Board approval.

Cancer Cell Lines

Established pancreatic cell lines (MIA PaCa-2, BxPC3, and CAPAN2) were obtained from the American Type Culture Collection (ATCC; Manassas, VA). Gastric cell line OCUM was generously donated by Osaka City University Graduate School of Medicine (Osaka, Japan). Cells were cultured as recommended. Histologic gradings of CAPAN2, BxPC3, and MIA PaCa-2 are well-differentiated, moderately differentiated, and poorly differentiated, respectively. CAPAN2 strongly expresses the marker genes for ductal differentiation, CK7 and MUC1. BxPC3 is also known to express these marker genes and CEA. MIA PaCa-2 expresses MUC1.[15] These cell lines were used as positive cancer controls for the RT-PCR assay. Cells were incubated at 37°C with 5% CO_2. RNA was isolated using the RNeasy Mini-Kit (Qiagen; Valencia, CA) as described by the manufacturer using cells harvested at 70–80% confluence. A 20-gauge needle was used to homogenize the cells during lysis. RT-PCR was performed with available RNA ≤ 2 μg in a 100-μL reaction using random hexamer priming and TaqMan® Reverse Transcription Reagents (Applied Biosystems; Foster City, CA) on a Thermo Hybrid thermocycler (Waltham, MA).

Laparoscopic Evaluation

Patients underwent diagnostic laparoscopy in the standard fashion under general anesthesia. An open technique was used for creation of pneumoperitoneum in all cases. A 30° telescope was placed through the umbilical port. Trocars were placed in the right and left upper quadrants. A systemic examination of the peritoneal cavity was performed. Normal saline was introduced into the right upper abdomen, left upper abdomen, and pelvis and aspirated after gentle agitation but before manipulation of the primary or metastatic tumor. In all, three samples—from the right upper abdomen, left upper abdomen, and pelvis—were

collected and divided into two parts: 30 mL from each sample was sent to the pathology department for cytologic examination with conventional Papanicolaou staining. In addition, 50 mL was collected into a specimen cup and transported on ice to the laboratory for RNA isolation. During the laparoscopic examination, any suspicious lesions were biopsied and sent for frozen section. A schema of the protocol is illustrated in Fig. 1.

Cytologic Evaluation

After retrieval, cytologic specimens were placed in Cytolyte fixative (Cytyc Corp; Marlborough, MA) and submitted to the cytology laboratory for evaluation. After centrifugation for 10 min, the resulting cellular pellet underwent PreservCyte (Cytyc Corp) fixation. Using the Thin Prep procedure, two slide preparations were made. The first was stained with a modified hematoxylin and eosin preparation, and the second using the Papanicolaou method.

RNA Isolation

Each of three peritoneal wash samples per patient was centrifuged at 800 rpm for 5 min at 4°C. From each sample, 10 mL of supernatant was removed for storage. The remaining specimens were centrifuged again at 800 rpm for 5 min at 4°C. The three remaining pellets were combined and resuspended in 1 mL of supernatant and centrifuged at 8,000×*g* for 5 min at 4°C. The pellet was processed according to he RNeasy Mini-Kit as described by the manufacturer. In brief, the pellet was disrupted by addition of 350 μL of buffer RLT with mercaptoethanol and homogenized through a 20-gauge needle, rinsed with 70% ethanol, transferred to the RNeasy mini column, washed with buffer RW1, and eluted in a 50-μL volume of RNase-free water. The samples were stored at −80°C.

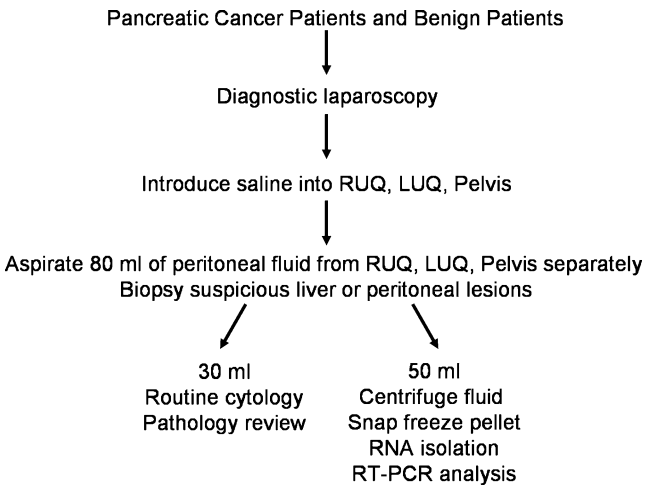


Figure 1 Schema of protocol. Patients underwent staging laparoscopy for pancreatic cancer or laparoscopy for benign disease (negative controls). Normal saline was introduced into the right upper abdomen, left upper abdomen, and pelvis and aspirated after gentle agitation. In all, three samples—from the right upper quadrant (RUQ), left upper quadrant (LUQ), and pelvis—were collected and divided into two parts: 30 mL from each sample underwent cytologic examination with conventional Papanicolaou staining. In addition, 50 mL underwent RNA isolation and RT-PCR analysis for tumor markers: CEA, CK7, Kras2, and MUC1.

RT-PCR

Reverse transcription was performed using the TaqMan® Universal Reverse Transcriptase Master Mix (Applied Biosystems). First, the amount of RNA isolated from the washings was assessed using spectrophotometry. While each reverse transcriptase reaction requires 1.5 to 2 μg of RNA for optimal cDNA creation, most of the specimens had <0.1 μg/μL of RNA. Therefore, we used the maximum volume of 38.5 μL of RNA from each peritoneal wash sample which was amplified in a 100-μL reaction containing 1 uM of each primer, 20 μL of deoxynucleotide triphosphate, 25 mM $MgCl_2$, 10× Taq Buffer, random hexamers, RNAse inhibitor, and 2.5 μL Multiscribe Reverse Transcriptase. The samples were transferred to the Thermo Hybrid thermocycler at 25°C for 10 min, 48°C for 30 min, and 95°C for 5 min. The cDNA samples were stored at −20°C.

TaqMan® Assays-on-Demand Gene Expression Assay primers for carcinoembryonic antigen (CEA) mRNA, cytokeratin 7 (CK7) mRNA, kras2 mRNA, MUC1 mRNA, and 18s rRNA were purchased from Applied Biosystems. Real-time quantitative RT-PCR was performed using the ABI-PRISM 7900 HT Sequence Detection System (Applied Biosystems). DNA was amplified in a 20-μL reaction containing 1 μM of the appropriate primer, 2 μL cDNA, and TaqMan® Gene Expression Master Mix including AmpliTaq Gold Polymerase. Each PCR reaction was subjected to initial setup of 30 min at 48°C, 10 min at 95°C, followed by 40 cycles at 95°C for 15 s and 60°C for 60 s. Each sample was assayed in triplicate with positive PCR controls, which were the cell lines that over-expressed these tumor markers. The endogenous control gene, 18s rRNA, was used to confirm the presence of mRNA in the peritoneal wash samples.

Statistical Analysis

Patient data, including clinical characteristics and pathologic findings, were recorded and entered into a prospective database. Data for analysis included patient demographics, tumor pathologic characteristics, status of peritoneal cytology, and status of peritoneal tumor markers. The optimal threshold for cycle amplification was chosen using a receiver operating characteristic (ROC) curve.[16] The

ROC curve was used to distinguish between the patients positive and negative for intraperitoneal metastases. The ROC curve is constructed by plotting sensitivity and specificity pairs for tumor marker amplification cycles, resulting from varying the cutoff values over the range of results. Sensitivity on the *y*-axis was plotted against the false-positive fraction (1-specificity) on the *x*-axis for various cutoff values of cycle amplification to construct the ROC curve. The sensitivity and specificity of the tumor markers were estimated by using cytology as the gold standard, incorporating the information from negative controls and patients with malignancies. The "true positives" were defined as the patients who were found to have peritoneal metastases based on positive cytology. Positive predictive value (PPV) and negative predictive value (NPV) of each marker were also computed. In addition, markers and their combinations were evaluated on the basis of their distance, or deviance, from the ideal marker (i.e., an ideal marker is 100% sensitive and specific).

Results

Patient Demographics

From March through August 2006, 51 patients underwent laparoscopy and were entered into this pilot study; 35 patients had pancreatic cancer, and 16 had benign pathology. Patient demographic and clinicopathologic factors are shown in Table 1. Median age of the entire cohort was 67 years (range, 44–85). Median age of the cancer patients (72 years; range, 45–85) was older compared with that of the benign patients (58; range, 44–68) (Table 1). A total of 34 patients (68%) were female; these comprised 60 and 81% of the pancreatic cancer and benign patient groups, respectively. Within the pancreatic cancer group, 29% of patients (n=10) underwent laparoscopy with biopsy, while 57% underwent resection (pancreaticoduodenectomy, n=17; distal pancreatectomy, n=3). Another five patients underwent bypass surgery with a gastrojejunostomy or choledochojejunostomy. Within the benign group, 75% of patients (n=12) underwent risk-reducing bilateral salpingoophorectomy, while the others underwent laparoscopic cholecystectomy or laparoscopic ventral hernia repair.

Table 1 Patient Demographics

	Cancer Patients (N=35)	Benign Patients (N=16)
Median age, range	72 (45–85)	58 (44–68)
Female gender	21 (60%)	13 (81%)
Procedure	Laparoscopy and biopsy 9	Laparoscopy 1
	Laparoscopy, celiac plexus nerve block 1	Laparoscopic RRSO 12
	Pancreaticoduodenectomy 17	Laparoscopic cholecystectomy 2
	Distal pancreatectomy 3	Laparoscopic ventral hernia repair 1
	Choledochojejunostomy 2	
	Gastrojejunostomy 3	

A tumor was located in the head of the pancreas in 72% (n=25) of pancreatic cancer patients (Table 2). Moderately differentiated adenocarcinoma occurred in 43% of patients, while 31% had a moderately poor to poorly differentiated cancer. A well-differentiated lesion was found in one patient. A T3 tumor was found in 56% (n=19) of pancreatic cancer patients, while 9% of patients had either a T2 or a T4 tumor. T1 cancer was found in one patient. Another nine patients (26%) presented with an unknown T stage.

Pathologic stages for pancreatic cancer patients were the following: stage 1A-1 (3%), stage IB-1 (3%), stage IIA-5 (15%), stage IIB-13 (38%), stage III-5 (15%), and stage IV-9 (26%) (Table 3). Positive cytology was identified in eight patients. Stages of their disease included stage IIA (n=1), stage IIB (n=2), and stage IV (n=5). Three patients had peritoneal metastases; all had positive cytology. Six patients had liver metastases; two of these had positive cytology.

Cytology

The sensitivity and specificity of cytology to detect any metastatic disease in this cohort was 56 and 95%, respectively. The PPV was 0.71 and NPV 0.91. The sensitivity and specificity of cytology to detect peritoneal metastatic disease was 100 and 90%, respectively. The PPV was 38%, and NPV was 100%. There were no cytology-positive patients in the benign patient group.

Primer Optimization and Positive Controls

A total of four genes, CEA, kras2, MUC1, and CK7 were tested for expression in pancreatic and gastric cancer cell lines (Table 4). CEA and kras2 mRNA transcripts amplified at PCR cycle 22 in the OCUM and MIA PaCa-2 cell lines, respectively. MUC1 amplified in the BxPC3 pancreatic cancer cell line at cycle 28 while CK7 amplified in the CAPAN2 cell line at cycle 24. For each primer and cell line combination, the slopes of the PCR amplification ranged from −3.2 to −3.87.

Expression of mRNA Transcripts

All 51 patients had amplifiable RNA, as detected by the amplification of the ribosomal 18s subunit. ROC curve

Table 2 Pathologic Variables

Variable	Values (*N*=35)
Location	
Head	25 (72%)
Body/Tail	10 (28%)
Differentiation	
Well to moderately well	1 (3%)
Moderate	15 (43%)
Moderately poor to poor	11 (31%)
Not stated	8 (23%)
T Stage	
Tx	9 (26%)
T1	1 (3%)
T2	3 (9%)
T3	19 (56%)
T4	3 (9%)

analysis was performed for tumor marker mRNA expression using data from all patients evaluated. Sensitivities and specificities were calculated based on the diagnosis of positive cytology made at laparoscopy. The point on the ROC curve that was closest to the best possible threshold was 35 cycles (Fig. 2). Therefore, a tumor marker was deemed positive if 18s rRNA was amplified and if there was tumor marker cycle amplification within 35 cycles. Each potential tumor marker was evaluated separately.

Real-time RT-PCR using the TaqMan® Assays-on-Demand Gene Expression Assay allowed detection of CEA mRNA transcripts in 11 patients within 35 cycles of amplification. Six of the eight with positive cytology had detectable levels of CEA. In addition, CEA mRNA was detected in five other patients. The integrity of the extracted mRNA was confirmed by the presence of amplification of the 18s ribosomal subunit within 20 cycles of amplification. Of the four tumor markers, CEA had the best profile of sensitivity (75%), specificity (88%), PPV (55%), and NPV 95% (Table 5). The deviance from the "ideal marker" was 0.08.

Kras2 mRNA transcripts were expressed in 30 patients within 35 cycles of RT-PCR with a sensitivity of 63% and specificity of only 42%. The deviance of kras2 from the ideal marker was 0.48.

CK7 mRNA transcripts were expressed in 20 patients within 35 cycles of RT-PCR with a sensitivity and specificity of 67 and 62%, respectively. The deviance of CK7 from the ideal marker was 0.26.

MUC1 mRNA transcripts were expressed in 26 patients within 35 cycles of RT-PCR with a sensitivity of 67% and specificity of 48%. The deviance of MUC1 from the ideal marker was 0.39.

After each tumor marker was assessed individually, combinations of mRNA expression were analyzed for sensitivity, specificity, PPV, NPV, and deviance (Table 5). Combinations of CEA and CK7, CEA plus Kras2 with CK7, and CEA and CK7 with MUC1, and CEA plus kras2, CK7, and MUC1 had specificity and NPV rates of 90 and 93%, respectively; deviances were 0.26.

Overall, 25 patients had at least one marker positive by RT-PCR (Table 3). Seventeen patients from stages IA through IV were cytology negative but RT-PCR positive, and they comprise the group of "false positives" with regard to RT-PCR when compared to the gold standard of cytology (Table 5). For the pancreatic cancer patients, four patients expressed CEA mRNA transcripts. Thirteen patients were Kras2 positive. CK7 and MUC1 mRNA transcripts were expressed in 12 and 18 of the "false positive" pancreatic cancer patients, respectively.

From the benign group which served as our negative controls, eight patients had at least one marker positive by RT-PCR; all eight patients expressed Kras2 mRNA transcripts. One patient was CEA positive. Four patients expressed both CK7 and MUC1 mRNA transcripts.

Discussion

We have demonstrated that real-time RT-PCR can detect cancer cells in peritoneal washings of patients undergoing laparoscopy for pancreatic cancer. After selecting possible primers of genes expressed in pancreatic cancers by PCR or immunohistochemistry, primers for CEA, kras2, CK7, and MUC1 were amplified and optimized within gastric (OCUM) or pancreatic (MIA PaCa-2, BxPC3, CAPAN2) cells, respectively. These positive controls were used to make standards employed in the RT-PCR reactions. Moreover, this pilot study defined the sensitivity, specificity, false positive, and false negative rates of RT-PCR for the four tumor markers when compared to the gold standard, cytology. These four tumor markers were evaluated separately and in combination to detect free cancer cells in the peritoneal fluid of patients with pancreatic cancer. CEA, with a sensitivity of 75%, a specificity of 88%

Table 3 Stage and Cytology

Stage	All Cancer Patients (*N*=35)	Positive Cytology (*N*=8)	Any Positive RT-PCR (*N*=25)	Negative Cytology /Positive RT-PCR (*N*=17)
IA	1 (3%)		1	1
IB	1 (3%)		1	1
IIA	5 (15%)	1	4	3
IIB	13 (38%)	2	9	7
III	5 (15%)		2	2
IV	9 (26%)	5	8	3
Liver	6 (17%)	2	5	3
Peritoneum	3 (9%)	3	3	0

Table 4 Optimization of Pancreatic RT-PCR Primers

Primer	Cell Line	Cycle	Slope
CEA	OCUM	22	−3.20
Kras2	MIA PaCa-2	22	−3.87
CK7	CAPAN2	24	−3.74
MUC1	BxPC3	28	−3.61

and a deviance of 0.08 from the ideal tumor marker, was comparable to conventional cytology, which had sensitivity and specificity rates of 100 and 98%, respectively. As CEA alone had the smallest deviance, detection of kras2, CK7, and MUC1 in combination with CEA did not appear to provide additional benefit.

As 70–80% of patients who undergo an R0 resection will suffer an incurable recurrence that may include peritoneal carcinomatosis, [2] laparoscopy with peritoneal cytology has become part of preoperative evaluation of patients with pancreatic adenocarcinoma in many institutions. At MSKCC, Merchant et al. [4] previously demonstrated in a cohort of 228 patients who underwent laparoscopic staging between 1993 and 1996 that pancreatic resection was significantly lower in patients with positive peritoneal cytology (PPC). Moreover, overall survival was significantly higher in patients with negative peritoneal cytology (NPC) compared with PPC although PPC was not an independent prognostic variable for survival on multivariate analysis. More recently, Ferrone et al. [5] reviewed 462 patients from MSKCC between 1995 and 2005 who had radiologically resectable pancreatic cancer. In a review of a subset of 217 patients who underwent resection for pancreatic cancer, resected patients with positive cytology experienced a significantly decreased 5-year survival rate ($p<0.001$). Therefore, detection of peritoneal disease before R0 resection is important for optimal treatment planning.

Immunocytologic methods can enhance detection of clinically occult peritoneal disease. In a single study, 29% of R0 resected patients had positive peritoneal cytology found with immunostaining, including CA 19-9. Patients with positive peritoneal cytology died within 15–18 months, whereas patients who were negative had a 5-year survival rate of 30% ($p<0.0001$).[6] From a clinical perspective, patients who are immunocytologically negative might benefit from a more aggressive surgical approach, which is not currently recommended in most stage III patients. Moreover, those cytology positive patients who have an extremely poor prognosis are unlikely to benefit from a radical surgical approach unless effective systemic adjuvant chemotherapy can be identified.

With regard to pancreatic cancer, RT-PCR of peritoneal fluid has not been studied extensively to date. Kras mRNA was found by RT-PCR in 89% of ascites supernatants of patients with pancreatic carcinoma.[11] Our study successfully detected mRNA of tumor markers overly expressed in peritoneal washes of pancreatic cancer patients. The level at which to cut off cycle amplification was determined by using a receiver operating characteristic (ROC) curve. An ROC curve is a plot of sensitivity vs specificity at each possible threshold and shows the spectrum of attainable operating characteristics (i.e., sensitivity and specificity) by dichotomizing the marker at each possible value. The point on the ROC curve that was closest to the best possible threshold was 35 cycles. Moreover, the sensitivity and specificity rates of each tumor marker at 35 cycles were compared to those at 30 cycles of RT-PCR amplification. While lowering the number of cycles increased the specificity of each tumor marker, it likewise decreased each marker's sensitivity and did not appear to improve the tumor markers' overall profiles. Finally, as the PCR evaluation of peritoneal washings was performed after definitive surgery, and as the prognostic significance of RT-PCR positivity is unknown, no therapeutic decisions were made based on these molecular test results.

While CEA had high sensitivity and specificity rates, kras2, CK7, and MUC1 RT-PCR positive groups had large

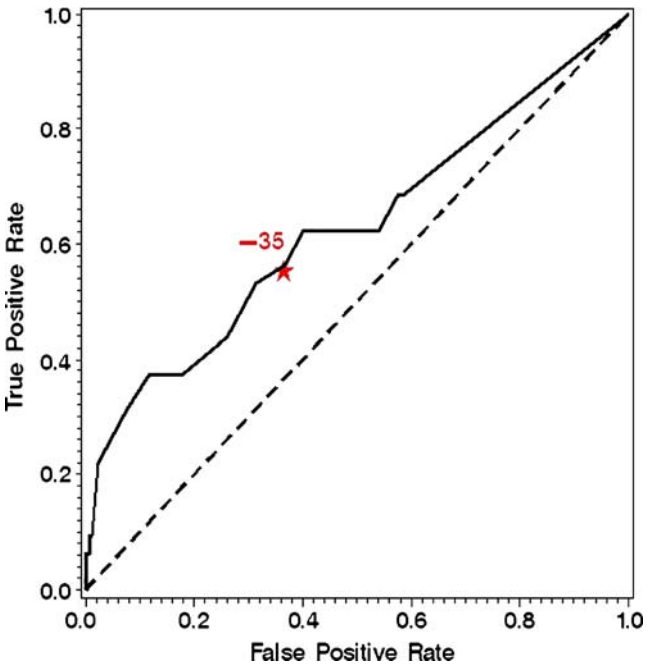


Figure 2 Receiver operating characteristic (ROC) curve for tumor marker expression in peritoneal washes of patients with pancreatic carcinoma. The curve is constructed by plotting sensitivity and specificity pairs for tumor marker amplification, resulting from varying the cutoff values over the range of results. Sensitivity on the *y*-axis was plotted against the false-positive fraction (1-specificity) on the *x*-axis for various cutoff values of cycle amplification. The point on the ROC curve that was closest to the best possible threshold was 35 cycles. Therefore, a tumor marker was deemed positive if 18s rRNA was amplified and if there was tumor marker cycle amplification within 35 cycles.

Table 5 Expression of Tumor Markers, Separately and in Combination, Defined by Amplification within 35 Cycles of RT-PCR

Tumor Marker mRNA	True Positive	True Negative	False Positive	False Negative	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Deviance
CEA (n=51)	6	38	5	2	0.75	0.88	0.55	0.95	0.08
Kras2 (n=51)	5	18	25	3	0.63	0.42	0.17	0.86	0.48
CK7 (n=48)	4	26	16	2	0.67	0.62	0.20	0.93	0.26
MUC1 (n=48)	4	20	22	2	0.67	0.48	0.15	0.91	0.39
CEA +Kras2	4	38	5	4	0.50	0.99	0.44	0.90	0.26
CEA+CK7	3	38	4	3	0.50	0.90	0.43	0.93	0.26
CEA+MUC1	3	37	5	3	0.60	0.88	0.38	0.93	0.26
Kras2+CK7	4	26	16	2	0.67	0.62	0.20	0.93	0.26
Kras2+MUC1	4	21	21	2	0.67	0.50	0.16	0.91	0.26
CK7+MUC1	4	26	16	2	0.67	0.62	0.20	0.93	0.26
CEA+Kras2+CK7	3	38	4	3	0.50	0.90	0.43	0.93	0.26
CEA+Kras2+MUC1	3	37	5	3	0.50	0.88	0.38	0.93	0.26
CEA+CK7+MUC1	3	38	4	3	0.50	0.90	0.43	0.93	0.26
Kras2+CK7+MUC1	4	26	16	2	0.67	0.62	0.20	0.93	0.26
CEA+Kras2+CK7+MUC1	3	38	4	3	0.90	0.90	0.43	0.93	0.26

numbers of false positive patients. Out of the 35 patients with pancreatic cancer, 8 patients were cytology (+)/RT-PCR (+). Overall, 25 patients had at least one marker positive by RT-PCR resulting in ten patients who were cytology (−)/RT-PCR (−). When we look at the stages of disease, cytology status, and RT-PCR results, we have identified 17 patients from all stages who can be considered to be false positives. Therefore, RT-PCR potentially triples the number of cytology (+) patients among all pancreatic cancer patients. Moreover, when we look at stages I through III patients, three patients were cytology (+)/RT-PCR (+) and nine patients were cytology (−)/RT-PCR (−). Therefore, we identified a yield of 14 patients who would be considered operative candidates who are "false positives". This underscores the potential importance of this technique in resectable patients. This was the primary reason for our attempt to develop these tumor markers as more sensitive diagnostic tools in detecting free cancer cells in the peritoneal cavity. In addition to displaying high sensitivity and specificity rates with positive and negative controls, we expect a marker to show some discordance with negative cytology results. This may be an indication that the marker in question may increase the sensitivity of detection of cancer cells in the peritoneal cavity. This group that is negative by cytology but positive for RT-PCR may represent an important population for study, as it may denote the yield of RT-PCR over cytology. The clinical significance of these "false positives" will only be elucidated by long-term follow-up and analysis of recurrence and survival.

Limitations of this pilot study included the small sample size and the logistical challenges of transporting the specimen from the patient to the laboratory within one hour. Transport time was minimized by regular and detailed communication with the operating room staff and laboratory fellows. Another important limitation was the inability to quantify the RNA before converting it to cDNA. After RNA was isolated from the peritoneal washes, two different spectrophotometers were used in an effort to assess the concentration of mRNA. For fear of losing much of the limited samples, repeated measurements were not pursued as they were not reproducible. From specimens that did undergo spectrophotometry, the concentrations of mRNA were roughly <0.1 μg/μL. Instead, of using 2 μg of RNA for reverse transcription, 2 μL of the RNA were used. The assumption was if RNA was present, the transcript would amplify; this was the main aim of this pilot study. Moreover, 2 μL of the cDNA template were used in the PCR reaction. The presence of mRNA was confirmed by amplification of the 18s ribosomal subunit. In addition, the presence of tumor marker RNA was assessed by amplification of signal within 35 cycles of the PCR reaction. Although specimens may have amplified mRNA at various cycles of the PCR reaction, we could not determine that a specific specimen had higher or lower levels of a tumor marker mRNA, as each sample did not begin with equal concentrations of mRNA. With the conclusion of this pilot study, we have begun to quantify mRNA with the use of a Nanodrop ND-1000 spectrophotometer (Wilmington, DE).

As this pilot study demonstrated that real-time RT-PCR can detect cancer cells in peritoneal washings of patients undergoing laparoscopy for pancreatic cancer, and defined the sensitivity, specificity, false positive, and false negative rates of RT-PCR for tumor markers compared to conventional cytology, our group is planning to conduct a prospective, longitudinal study with a larger cohort to define the predictors and clinical significance of a positive

RT-PCR result. An answer of clinical significance may not be fully available until the patients are enrolled and adequate follow-up of at least 2 years is obtained. Of interest will be the RT-PCR positive/cytology negative patient undergoing curative resection. If a positive RT-PCR assay can identify a patient population at very high risk for early recurrence and death, this will clearly improve our therapeutic approach to patients with pancreatic cancer. Those patients may be unlikely to derive any meaningful benefit from resection, and their treatment plan could be altered to include preoperative or definitive chemotherapy. Moreover, the cost of conducting RT-PCR in these patients, even at a separate anesthetic, may provide the benefit of preventing the potential morbidity, operative mortality, subsequent decrease in quality of life, and additional costs that may result from an operation that will not result in a curative resection. Ultimately, this would then result in improved selection of patients for operative management, reduction in operative resection and morbidity in patients who will have poor survival, and establishment of the routine use of laparoscopy, cytology, and mRNA of tumor markers as part of the preoperative workup.

Conclusion

RT-PCR using a panel of tumor markers, including CEA, was comparable in sensitivity, specificity, PPV, and NPV to cytology. The clinical significance of "false positive" over-expression of CEA, Kras2, CK7, or MUC1 remains to be defined. RT-PCR could represent a more sensitive method for detection of subclinical peritoneal tumor dissemination; this may be useful in improving selection of patients for operative management and clinical trials.

Acknowledgments We would like to acknowledge members of the Fong Laboratory, Yun Shin Chun, MD, and David Eisenberg, MD, as well as research study assistants Judy Fong and Maria Janakos.

References

1. Conlon KC, Klimstra D, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. Ann Surg 1996;223:273–279.
2. Henne-Bruns D, Vogel I, Luttges J, Kloppel G, Kremer B. Ductal adenocarcinoma of the pancreas head: survival after regional versus extended lymphadenectomy. Hepatogastroenterology 1998; 45:855–866.
3. Warshaw AL. Implications of malignant-cell DNA content for treatment of patients with pancreatic cancer. Ann Surg 1991; 214:645–647.
4. Merchant NB, Conlon K, Saigo P, Dougherty E, Brennan MF. Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. J Am Coll Surg 1999;188:421–426.
5. Ferrone CR, Haas B, Tang L, Coit DG, Fong Y, Brennan MF, Allen PJ. The influence of positive peritoneal cytology on survival in patients with pancreatic adenocarcinoma. J Gastrointest Surg 2006;10:1347–53.
6. Vogel I, Kruger U, Marxsen J, Soeth E, Kalthoff H, Henne-Bruns D, Kremer B, Juhl H. Disseminated tumor cells in pancreatic cancer patients detected by immunocytology: a new prognostic factor. Clin Cancer Res 1991;5:593–599.
7. Kodera Y, Nakanishi H, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T, Kito T, Tatematsu M. Prognostic value and clinical implications of disseminated cancer cells in the peritoneal cavity detected by reverse transcriptase-polymerase chain reaction and cytology. Int J Cancer 1998;79:429–433.
8. Kodera Y, Nakanishi H, Ito S, Yamamura Y, Kanemitsu Y, Shimizu Y, Hirai T, Yasui K, Kato T, Tatematsu M. Quantitative detection of disseminated free cancer cells in peritoneal washes with real-time reverse transcriptase-polymerase chain reaction: a sensitive predictor of outcome for patients with gastric carcinoma. Ann Surg 2002;235:499–506.
9. Kodera Y, Nakanishi H, Ito S, Yamamura Y, Fujiwara M, Koike M, Hibi K, Ito K, Tatematsu M, Nakao A. Prognostic significance of intraperitoneal cancer cells in gastric carcinoma: detection of cytokeratin 20 mRNA in peritoneal washes, in addition to detection of carcinoembryonic antigen. Gastric Cancer 2005;8:142–148.
10. Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T. Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. J Surg Oncol 1999;72:60–64.
11. Yamashita K, KidaY, Shinoda H, Kida M, Okayasu I. K-ras point mutations in the supernatants of pancreatic juice and bile are reliable for diagnosis of pancreas and biliary tract carcinomas complementary to cytologic examination. Jpn J Cancer Res 1999;90:240–248.
12. Hornick JL, Lauwers G, Odze RD. Immunohistochemistry can help distinguish metastatic pancreatic adenocarcinomas from bile duct adenomas and hamartomas of the liver. Am J Surg Pathol 2005;29:381–389.
13. Chu PG, Schwarz R, Lau SK, Yen Y, Weiss LM. Immunohistochemical staining in the diagnosis of pancreatobiliary and ampulla of Vater adenocarcinoma: application of CDX2, CK17, MUC1, and MUC2. Am J Surg Pathol 2005;29:359–367.
14. Goldstein NS, Bassi D. Cytokeratins 7, 17, and 20 reactivity in pancreatic and ampulla of Vater adenocarcinomas. Percentage of positivity and distribution is affected by the cut-point threshold. Am J Clin Pathol 2001;115:695–702.
15. Sipos B, Moser S, Kalthoff H, Torok V, Lohr M, Kloppel G. A comprehensive characterization of pancreatic ductal carcinoma cell lines: towards the establishment of an in vitro research platform. Virchows Arch 2003;442(5):444–445.
16. Zweigh MH, Campbell G. Receiver-operating characteristics (ROC) plots, a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561–577.

DISCUSSION

Keith D. Lillemoe, M.D. (Indianapolis, IN): Kim, that was a very nice presentation. Seeing you up there in uniform reminds me that I think both myself and immediate Past President Dr. Bass had our first SSAT presentations in

uniform too. So I think your future looks bright in this organization, as we all knew it would be.

I have a few questions. I guess the first thing is, really, what value is this? If I am not correct, you do your laparoscopic staging at the time that you plan to explore the patients for resection. In other words, you are really not using this information at all for clinical decision-making. So I guess the first question is, when are you going to believe your cytology data to start doing it as a planned procedure, a day, a week or whatever it takes, before you can plan exploration for resection? A lot of groups talk about the value of peritoneal cytology, but when the rubber hits the road, in their clinical practice, they do not really practice the use of it that much.

Let us just assume that this analysis was of value. What is the cost associated with this analysis? In the end, we will be adding not only this, but a separate laparoscopic procedure with general anesthesia, some time in the hospital, or at least in the recovery room. Is this really going to have a cost/benefit ratio in helping the small number of patients where it is going to be of benefit?

Obviously you alluded to it, but we obviously want to see a second paper showing the follow-up of these people with a "false positive" RT-PCR positivity to see if indeed their survival is affected.

Finally, where I think this analysis might be of value are those patients who we see in follow-up after pancreatic resection who develop ascites. Many times we do not know the cause of that ascites. If we could tap the ascites and find out definitely if they have malignant disease, it may help us better direct their therapy.

It is a beautiful study. I am not sure if it is quite ready for prime time application to all those people who are doing pancreatic surgery, but I think it adds to our knowledge of the disease. Nice presentation.

Kimberly M. Dalal, M.D. (Travis AFB, CA): Thank you for your comments and for your support. When will we believe the data and actually apply them to our patients? Well, that is probably not for at least 5 years. Now that this pilot study has established the feasibility and optimized the primers and parameters for RT-PCR, Drs. Fong and Coit and a couple of current surgical oncology fellows have taken on a prospective study looking at 200 patients with pancreatic adenocarcinoma. To accrue 200 patients and to obtain 2 years of follow-up will take about 5 years. I agree; actually using this information to make treatment decisions is not something we can do immediately.

With regard to your second question about the cost benefit of RT-PCR, I will say that to perform laparoscopy under general anesthesia at a separate setting and to process the peritoneal wash samples for RNA isolation and RT-PCR for the panel of tumor markers will cost several hundred to a thousand dollars. However, if we could identify patients who would not benefit from surgery, this would provide a tremendous benefit that may outweigh that initial cost by preventing the potential morbidity that can be associated with pancreatic resections, decrease in quality of life, and additional costs that may result from an operation that ultimately would not lead to a curative resection. This procedure may, in fact, come out to have a definite cost benefit. But again, we will not know this for at least 5 years.

Craig P. Fischer, M.D. (Houston, TX): How about the use for malignant ascites, do you think that that has some utility?

Dr. Dalal: I think it does. We have not pursued that ourselves, but I think that it is definitely something to consider investigating in future studies.

J Gastrointest Surg (2007) 11:1607–1622
DOI 10.1007/s11605-007-0266-0

Curative Laparoscopic Resection for Pancreatic Neoplasms: A Critical Analysis from a Single Institution

Laureano Fernández-Cruz · Rebeca Cosa · Laia Blanco · Sammy Levi · Miguel-Angel López-Boado · Salvador Navarro

Received: 16 May 2007 / Accepted: 19 July 2007 / Published online: 25 September 2007

Abstract Laparoscopic pancreatic surgery (LPS) has seen significant development but much of the knowledge refers to small and benign pancreatic tumors. This study aims to evaluate the feasibility, safety, and long-term outcome of the laparoscopic approach in patients with benign, premalignant, and overt malignant lesions of the pancreas. This study, currently, is the largest single center experience worldwide. One hundred twenty-three consecutive patients underwent laparoscopic pancreatic surgery from April 1998 to April 2007, 20 patients with cysts or pseudocysts for acute and chronic pancreatitis, laparoscopic pancreatic drainage was performed, and were excluded from the analysis. The 103 patients were divided based on preoperative diagnosis: group I, inflammatory tumors for chronic pancreatitis (eight patients); group II, cystic pancreatic neoplasms (29 patients); group III, intraductal papillary mucinous neoplasms (10 patients); group IV, neuroendocrine pancreatic tumors (NETs) (43 patients); and group V ductal adenocarcinoma (13 patients). The median tumor size was 5.3 cm. Pathologic data include R_0 or R_1 resection (transection margins on the specimen were inked). Perioperative data, postoperative complications, and resection modalities were compared using statistical analysis. Long-term outcomes were analysed by tumor recurrence and patient survival. The overall conversion rate was 7%. Laparoscopic distal pancreatic resection was performed in 82 patients (79.6%). Laparoscopic spleen-preserving distal pancreatectomy (Lap SPDP) was performed in 52 patients (63.7%), but with splenic vessels preservation in 22% and without splenic vessels preservation in 41.5%. Laparoscopic en-bloc splenopancreatectomy (Lap SxDP) was performed in 30 patients (36.6%) and laparoscopic enucleation (Lap En) in 20 patients (19.4%). There was no mortality. The overall complication rate was 25.2, 16.7, and 40% after Lap SPDP, Lap SxDP, and Lap En, respectively. The overall morbidity rate was significantly higher ($p>0.05$) in the group of Lap SPDP without splenic vessels preservation comparing with Lap SPDP with splenic vessels preservation because of the occurrence of splenic complications (20.6%). The overall pancreatic fistulas was 7.7, 10, and 35% after Lap SPDP, Lap SxDP, and Lap En, respectively; the severity of fistula was significantly higher in the Lap En group ($p>0.05$). The mean hospital stay was within 1 week in all groups, except in the

L. Fernández-Cruz · R. Cosa · L. Blanco · S. Levi · M.-A. López-Boado
Surgical Department, ICMD Hospital Clínic de Barcelona, Villarroel, 170, 08036 Barcelona, Spain

S. Navarro
Gastroenterology Department, ICMD Hospital Clínic de Barcelona, Villarroel, 170, 08036 Barcelona, Spain

L. Fernández-Cruz (✉)
Department of Surgery, University of Barcelona, Hospital Clínic, Villarroel 170, Escalera 6, 4th Floor, E-08036 Barcelona, Spain
e-mail: lfcruz@clinic.ub.es

group of ductal adenocarcinoma, which is 8 days. In this series, 27 patients (26.2%) had malignant disease. R_0 resection was achieved in 90% of ductal adenocarcinoma and 100% for other malignant tumors. The median survival for ductal adenocarcinoma patients was 14 months. This series demonstrates that LPS is feasible and safe in benign-appearing and malignant lesions of the pancreas.

Keywords Laparoscopic pancreatic surgery · Laparoscopic pancreatic malignancies · Laparoscopic neuroendocrine tumors · Laparoscopic cystic neoplasms · Laparoscopic pancreatic techniques · Laparoscopic pancreatic complications

Introduction

Laparoscopic pancreatic resection was first introduced in 1994 by Gagner and Pomp[1] and Cushieri.[2] The procedure, however, has not been widely accepted because it is regarded as a complicated procedure with a steep learning curve.

Using the criteria of Cushieri and Jakimowicz[3], the probable benefit of minimally invasive surgery over conventional open surgery depends on the ratio of access trauma to procedural trauma. In pancreatoduodenectomy, the access trauma forms only a small component of the total operative insult to the patient. Therefore, this operation through the laparoscopic approach is valid only when the postoperative course of the patient promises a better outcome than with the current open approach. However, favorable postoperative results in terms of less pain, less analgesia requirement, early return of bowel function, and shorter hospital stay, in patients who underwent laparoscopic pancreatic resection for left-sided pancreatic lesions have been consistently reported.[4–10] Also, laparoscopic pancreatic enucleation may be performed in selected patients with pancreatic tumors with obvious advantages over open laparotomy in terms of parietal damage to the abdomen.[11–17] The majority of reports on laparoscopic pancreatic surgery are often based on limited experience with short-term outcome. Recently, a multi-institutional European study (25 European Centers), including 127 patients, demonstrated that laparoscopic pancreatic resection is feasible and safe in selected groups of presumed benign pancreatic lesions requiring enucleation procedures or left-sided pancreatic resections.[18] A point of criticism of this study was that only four centers (16%) reported more than 10 patients.

Some authors have suggested that malignant pancreatic neoplasms are a contraindication to laparoscopic resection because of concerns on the radicality of the resection and the oncological outcomes.[5]

The aim of this study is to evaluate the feasibility, safety, and long-term outcome of the laparoscopic approach in patients with benign, premalignant, and overt malignant lesions of the pancreas. To our knowledge, this is the largest single-institution series on this subject to date.

Materials and Methods

Laparoscopic pancreatic surgery was carried out in 123 consecutive patients between April 1998 and April 2007. Laparoscopic drainage was performed in 20 patients with cysts and pseudocysts for acute and chronic pancreatitis and were excluded from the analysis. The 103 patients were divided based on preoperative diagnosis (Table 1):

Group I: Inflammatory mass for chronic pancreatitis (eight patients), group II: cystic pancreatic neoplasms [CyN] (29 patients), group III: intraductal papillary mucinous neoplasms [IPMN] (10 patients), group IV: neuroendocrine pancreatic tumors [NPTs] (43 patients), and group V: ductal adenocarcinoma [DA] (13 patients).

Group I: Inflammatory mass for chronic pancreatitis (eight patients): There were five men and three women; mean age was 40 years (range 23–52). The aetiology was obstructive pancreatitis. Abdominal pain for 6 months or more was the main complaint in all patients. Multiple hospital readmissions because of exacerbation of abdominal pain, with increased serum amylase >1,000 UI/l (normal value, 10–200) was observed in six patients. Computed tomography (CT scan), showed an enlargement of the body and tail of the pancreas in five patients; a pseudocyst in the tail of the pancreas in two patients (3 and 5 cm, respectively). Endoscopic retrograde cholangioancreatography (ERCP) showed a complete blockage in the duct of Wirsung in one patient. In all patients, the duct of Wirsung in the head of the pancreas had a normal size (3–4 mm). Serum glucose was normal in all patients.

Group II: CyN: 29 patients were included, 27 women and 2 men, with a mean age of 55 years (range 26–70). Abdominal

Table 1 Laparoscopic Pancreatic Surgery

Type of Tumor	Number (%)	Mean Age Years (Range)	Sex
Inflammatory: Chronic Pancreatitis	8 (7.7)	40 (23–42)	5 M/3 F
Cystic Neoplasms	29 (28.1)	55 (26–70)	2 M/27 F
Intraductal Papillary Mucinous Neoplasm	10 (9.7)	68 (51–83)	10 M/–
Neuroendocrine	43 (41.7)	60 (22–83)	5 M/38 F
Ductal adenocarcinoma	13 (12.6)	63 (44–76)	6 M/7 F
Total	103 (100%)	57 (22–83)	28 M/75 F

and back pain were the most common complaint. The average size was 5.2 cm (range 4–8) and they were located in the body–tail of the pancreas. The lesions were characterized by CT scan: 4 serous and 25 mucinous tumors.

Group III: IPMN: 10 men were included with a mean age 68±4 (range 51–83). All patients were symptomatic with chronic abdominal pain (four patients) and recurrent pancreatitis (six patients). Magnetic resonance cholangiopancreatography (MRCP) outlined the gross appearance and communication with the pancreatic duct: 8 cm cystic tumor and dilatation (10 mm) of the duct of Wirsung (one patient); 6 cm cystic tumor in the body of the pancreas (one patient); branch-duct cyst 3 cm in the body of the pancreas (one patient); branch-duct cyst 4 cm in the tail of the pancreas (one patient); multifocal branch-duct IPMN with dominant lesions >2 cm in the body–tail of the pancreas (six patients).

Group IV: NETs (43 patients): 28 patients had functioning tumors. Three patients, 22, 56, and 61 years old, respectively, had symptoms compatible with Zollinger-Ellison syndrome. Basal and stimulated (with secretin) gastrin levels were markedly elevated. CT scan showed an 0.8-mm hypervascular lesion in one patient in the area between the duodenum and vena cava and in another MEN-1 patient, two lesions (2 and 1.5 cm) in the body–tail of the pancreas; these lesions were confirmed by Octreoscan imaging. In another patient, an 80-mm duodenal gastrinoma was diagnosed by endoscopic ultrasonography (EUS). Two women (69 and 72 years old, respectively) had profuse watery diarrhea, hypokalemia, and hypotension for more than 6 months. The diagnosis was based on elevated vasoactive intestinal polypeptide (VIP) levels; CT scan showed 3- and 3.5-cm tumor, respectively, in the body of the pancreas. One woman, 66 years old had abdominal pain and elevated glucagon levels; CT scan showed a 4-cm tumor in the body of the pancreas. There were 20 patients (18 women and 2 men) with organic hyperinsulinism, (11 patients with sporadic insulinoma and two MEN-1 patients were previously reported[15]; the mean age of all patients was 43 years (range 16–83). CT scan was performed in all patients and the results correctly diagnosed the tumor in 11 patients. EUS was performed in 19 patients and detected the tumor in 18 patients. The 17 presumed benign sporadic insulinoma were localized to the head of the pancreas (3), the neck of the pancreas (5), the body of the pancreas (6), and in the tail of the pancreas (3). In one 83-year-old woman, CT scan showed a 13×9-cm tumor in the body–tail of the pancreas with multiple bilobar liver metastases. Two women aged 64 and 73 years had abdominal pain and diarrhea. CT scan showed 3.5 and 7 cm tumor in the body and tail of the pancreas, respectively; in addition, two metastatic lesions were shown in the right lobe of the liver in one patient and two bilobar liver lesions (two right and one left) in another patient. EUS and fine needle aspiration cytology (FNA) were suspicious for carcinoid tumors. 5-HT in the urine was markedly elevated in both patients. Octreoscan imaging showed positive spots in the pancreas and in the liver in both patients. Fifteen patients (14 women and 1 man) had nonfunctioning tumors. The mean age of all patients was 58±9 (range 44–78). Eleven patients had abdominal pain but four others were asymptomatic. Abdominal ultrasonography and CT scan showed well-defined tumors; mean size 5 cm (range 2.5–11 cm). EUS and FNA were used in four asymptomatic patients to confirm the diagnosis of neuroendocrine tumor.

Group V: DA included 13 patients (six men and seven women). The mean age was 63 years old (range 44–76). The most common symptoms were abdominal pain (13/13) and weight loss (10/13). CT scan showed a tumor mass; mean size 5 cm (range 3–6). Two patients had splenic vein thrombosis and one patient signs of invasion of the splenic–mesenteric vein junction. CA-19.9 was elevated in 10 patients but was normal in three patients. Tumors were staged according to the TNM classification: IA (one patient), IB (two patients), IIA (three patients), IIB (four patients), and III (three patients).

Techniques of Laparoscopic Surgery

Laparoscopic distal pancreatectomy (Lap DP) was performed with or without spleen preservation. When performing spleen-preserving distal pancreatectomy (Lap SPDP), this operation was performed with or without splenic vessels preservation (Warshaw's technique). We have previously published the technical details of these operations.[19,20] These techniques were performed in patients with presumed benign pancreatic lesions.

En-bloc laparoscopic distal pancreatectomy with splenectomy (Lap SxDP) was performed in patients with suspected pancreatic malignancy and in patients with ductal adenocarcinoma of the body–tail of the pancreas. The principles of this operation follow the technique described by Strasberg et al.[21] in 2003, called radical antegrade modular pancreatosplenectomy (RAMPS). The technical details of this operation performed laparoscopically are as follows: The patient is placed in the Lloyd Davis position with the table tilted head up. The operating surgeon stands between the patient's legs, and two assistants stand on both sides of the patient. Four ports are placed: a 10-mm port in the midline above the umbilicus for the laparoscope, a 10-mm port in the left midclavicular line, 1–3 cm below the costal margin, and 11-mm port in the left mid-axillary line below the costal margin, and 11-mm port in the right midclavicular line. The first step is to divide the lienorenal ligament and dissect the adjacent fascia lateral to the spleen. The splenocolic ligament is

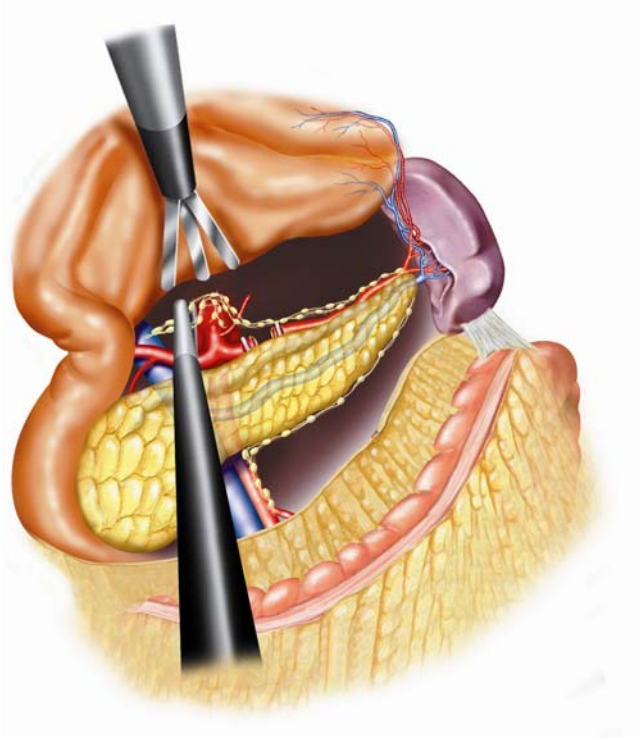


Figure 1 Laparoscopic surgery for malignant pancreatic tumors. Step 1, identification of celiac trunk and its branches. Step 2, lymphadenectomy in the area of common hepatic artery, celiac artery and left gastric artery. Step 3, the splenic artery is clipped at the origin.

divided using the harmonic scalpel. The splenic flexure of the colon is mobilized downward. The gastrocolic omentum is widely opened up to the level of the mesenteric vessels, and the body–tail of the pancreas is then visualized. The anterior aspect of the pancreas is exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. The omentum is opened to facilitate identification of the coeliac trunk and its branches to perform regional lymphadenectomy. Careful placement of a liver retractor creates a substantial working space. A grasping forceps is then passed behind the stomach from left to right to facilitate anterior and lateral retraction of the stomach. A large lymph node is usually present in the hepatoduodenal ligament and the hepatic artery can usually be found just cephalic to this. The common hepatic artery is then identified proximal and distal to the gastroduodenal artery; at this point, the lymph nodes are mobilized. A complete dissection of the superior border of the pancreas in front of the common hepatic artery allows identification of the anterior surface of the portal vein. This maneuver is usually bloodless and the dissection is continued along the coeliac trunk to identify the left gastric artery and the splenic artery. Once the lymphadenectomy is completed around these vessels, the splenic artery is clipped (7 mm titanium clips) and divided 1–2 mm from its origin of the coeliac trunk (Fig. 1). The inferior border of the pancreas is dissected and the body and tail of the pancreas are completely detached from the retroperitoneum. This mobilization of the left pancreas allows visualization of the posterior wall of the gland, where the splenic vein is easily identified. At this point, the splenic vein is divided between 7-mm clips. The pancreas is then transected with a 30-mm endoscopic linear stapler; usually, two stapler applications are necessary. The left pancreas is then lifted up and mobilized posteriorly with the splenic artery and vein. The lymph nodes along the superior border of the body and tail are mobilized. The dissection now proceeds to expose the anterior surface of the superior mesenteric artery; in this area, the lymph nodes, fat, and fibrous tissue are taken. The dissection is continued posteriorly and the inferior attachments of the pancreas are divided. The inferior border of the pancreas is dissected including Gerota's fascia on the superior surface of the kidney. This dissection is continued anterior to the adrenal gland which is resected if invaded by tumor (Fig. 2). When pancreatosplenectomy is indicated, division of the lienorenal ligament and division of the short gastric vessels are the last step in the procedure (Fig. 3). Table 2 describes the surgical steps using the laparoscopic approach for presumed benign lesions and for suspected or overt malignant lesions.

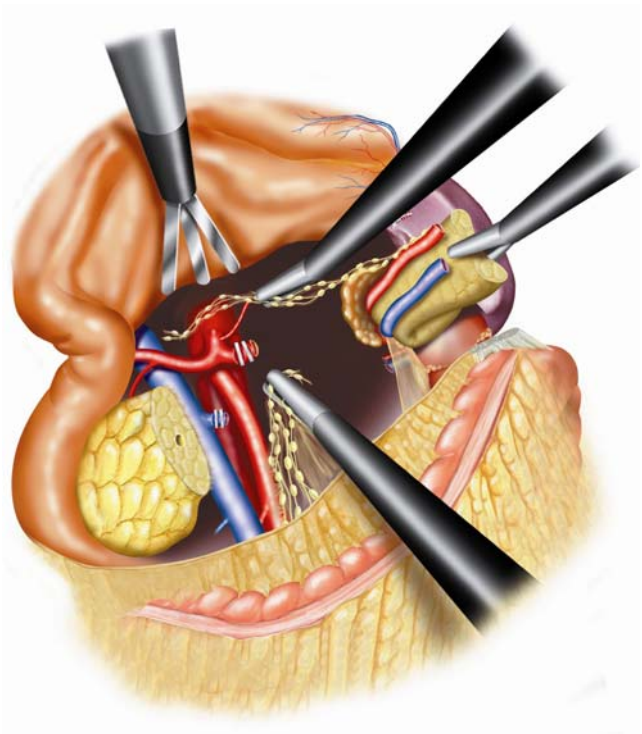


Figure 2 Laparoscopic surgery for malignant pancreatic tumors. Lymphadenectomy on the superior border of the pancreas and along the superior mesenteric artery. Fatty tissue, lymph nodes, and nerves are removed between the posterior wall of the pancreas and the adrenal gland and left kidney. Adrenalectomy when adrenal invasion.

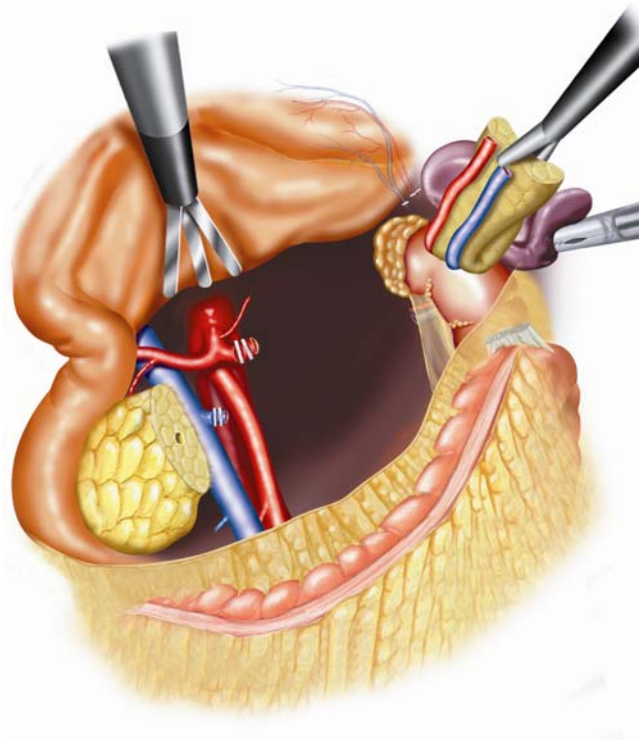


Figure 3 Modified laparoscopic radical antegrade modular pancreatosplenectomy is completed.

Laparoscopic Enucleation

Laparoscopic tumor enucleation [Lap En] was performed, when indicated, for small neuroendocrine tumors (mainly insulinomas) and in selected cases of nonfunctioning tumors. We have previously published the technical details of this operation.[22]

Clinical Data Analysis

Data on operative, intraoperative, and postoperative care were prospectively collected. Preoperative parameters included patient demographics (age, gender); intraoperative parameters include total operative time, blood loss, and blood transfusion. Postoperative events were recorded according with the following definitions.

1. Pancreatic fistula, according to the International Study Group on Pancreatic fistula (ISGPF)[23] was defined as any measurable drainage from an operatively placed drain on or after postoperative day 3, with amylase content greater than three times the upper limit of normal serum amylase levels. All patients below this threshold were considered to have no biochemical evidence of fistula. Those

Table 2 Laparoscopic Pancreatic Resection: Technical Options

	Presumed Benign Lesions	Suspected or Malignant Lesions
Position of the patient	Half-lateral with the left side up	Lloyd Davis
Surgeon	On the left side of the patient	Between the patient's leg
Surgical Steps		
1	Division of splenocolic ligament Splenic flexure of the colon is mobilized downward Gastrocolic omentum is widely opened	
2	Inferior border of the pancreas dissected Body and tail of the pancreas completely detached from the retroperitoneum	
3	The splenic vein is visualized and clipped	Identification of celiac trunk and its branches
4	The pancreas is transected. The left pancreas is retracted anteriorly and traction is applied to expose the splenic artery	Lymphadenectomy in the areas of common hepatic artery, celiac artery and left gastric artery
5	The splenic artery is clipped at its origin	The splenic artery is clipped at the origin
6	Preservation of the short gastric vessels	The neck of the pancreas is transected
7	Transection in the area between the tail of the pancreas and the hilum of the spleen	The splenic vein is clipped at its junction with the mesenteric vein
8	Preservation of the spleen	Lymphadenectomy on the superior border of the pancreas
9		Lymphadenectomy along the superior mesenteric artery
10		Fatty tissue, lymph nodes and nerves are removed between the posterior wall of the pancreas and the adrenal gland and left kidney. Adrenalectomy when adrenal invasion
11		The Gerota's fascia attached to the lateral border of the pancreas is removed
12		The short gastric vessels are coagulated and divided
13		Pancreatosplenectomy

patients with fistula were then classified into three grades of severity according to ISGPF. Grade A fistulas are a transient asymptomatic fistulas, evident only by elevated drain amylase levels. Drains are removed within 3 weeks, almost always within the first 7 days after the operation. Grade B fistulas are symptomatic, clinically apparent fistulas that require diagnostic evaluation and therapeutic management. Operatively placed drains may remain in situ at the time of discharge, and are frequently required for management longer than 3 weeks. Grade C fistulas are severe, clinically significant fistulas that require major interventions in clinical management.

2. Splenic complications: splenic infarct, focal, or massive, detected by color Doppler ultrasound (CD-US); perisplenic fluid collection with pain in the left upper quadrant of the abdomen.
3. Abscess: culture-positive purulent drainage from intra-abdominal fluid collection obtained percutaneously or operatively, and/or radiographically confirmed fluid collection with systemic or localized signs of infection.
4. Pneumonia: presence of new infiltrate on chest radiograph, and the following: body temperature >38°C, abnormal elevation of white blood count, or positive symptoms Gramm stain or culture, and requiring intravenous antibiotic treatment.
5. Delayed gastric emptying: failure to resume oral liquid intake by postoperative day 10, and/or emesis over 500 ml on or after postoperative day 5, and/or continued nasogastric drainage >500 ml on or after postoperative day 5.
6. Length of stay (LHS): days from the initial operation to hospital discharge.
7. Conversion was defined as the necessity for an abdominal incision to deal with any intraoperative complication. The need for prematurely making an abdominal incision when safe dissection is not possible, an oncological grounds was also considered conversion.
8. Completeness of resection was assessed by reviewing the operative and pathological reports. The pancreatic transection margin and all tangential margins on the specimen were inked. An R_o resection was considered to have been performed if the primary tumor was removed with negative margins. Patients with microscopically positive margins or grossly positive margins were classified as having a R_1 or R_2 resection, respectively.
9. Recovery was measured by questioning the patient's time to return to activities of daily living.

Statistical Analysis

Perioperative data, postoperative complications, and resection modalities were compared using the chi-square statistics, analysis of variance, and the Student's *t* tests. Statistical significance was accepted at a P value<0.05. All statistical computations were performed using the SPSS 11.5 program for Windows.

Follow-up

All patients underwent regular follow-up examination postoperatively every 6 months and annually thereafter.

Results

Group I: Inflammatory tumor for chronic pancreatitis (eight patients): One patient was converted to open surgery because of firm adhesions of the inferior border of the pancreas to the transverse colon. Laparoscopic distal pancreatectomy was performed in seven patients; Lap SPDP with splenic vessel preservation was achieved in six patients. One patient underwent Lap SxDP. Overall, the mean operative time was 210 min (range 180–300). The mean blood loss was 470 ml (range 300–800). One patient had reoperation 4 days after surgery for a perforated duodenal ulcer through a midline laparotomy. The mean LHS was 6 days (range 5–14). At a mean follow-up of 40 months (range 6–85), two patients became insulin-dependent diabetics and five patients (62.5%) are completely pain-free.

Group II: Laparoscopic distal pancreatectomy was performed in 29 patients, Lap SPDP in 26 patients; splenic vessel-preservation was attempted in 11 patients but was converted to Warshaw's technique in five patients. In three patients, LSxDP was performed: in one because the tumor was densely adherent to the splenic hilum and in two others because of suspected malignancy. Overall, the mean operative time was 198±26 (range 150–270) and the mean blood loss 370±50 ml (range 200–880). Only one patient required blood transfusion.

Pancreatic fistula was observed in three patients and all were grade A fistulae. The drain was discontinued within 3 weeks after surgery. Splenic complications occurred in four patients with Lap SPDP without splenic vessels preservation. Three patients CD-US showed a focal splenic infarct of 3, 3.5, and 4 cm, respectively; one patient was asymptomatic but two others had pain in the left upper quadrant of the abdomen. Another patient was discharged 5 days after surgery; however, 2 days later, the patient represented with fever and clinical sepsis. This patient was rehospitalized and splenectomy was performed for massive necrosis of the spleen. The overall mean LHS was 5.7 days (range 5–8).

The final pathological report showed serous cystoadenoma in three patients, mucinous cystoadenoma in 22 patients, borderline mucinous cystic tumor in one patient, and mucinous cystoadenocarcinoma in three patients

(Table 3). The mean follow-up was 38 months (range 2–88). No tumor recurrences were observed; three patients with invasive mucinous tumors are still alive 4 months, 2, and 4 years, respectively.

Group III: IPMN (10 patients): Lap SPDP was performed in six patients and en-bloc Lap SxDP in four patients. Overall, the mean operative time was 200±30 (range 160±260) and the mean blood loss 550±20 ml (range 250±750). A grade A pancreatic fistula was observed in one patient. One patient had an asymptomatic focal splenic infarct, which is 4 cm in diameter. The overall mean LHS was 7 days (range 5–8). All patients with branch-duct type cysts between 3 and 4 cm and all patients with multifocal branch-duct type had benign lesions; however, two patients with 6 and 8 cm cystic tumors had invasive IPMN (Table 3). At follow-up at 22 months (range 2–40), no patient had a pancreatic remnant recurrence. Two patients with invasive IPMN are still alive, 1.5 and 3 years, respectively.

Group IV: NETs (43 patients): Lap SPDP was performed in one patient with multiple gastrinoma in the body–tail of the pancreas (MEN-1), one patient had a malignant glucagonoma, one patient a vipoma and five patients had hyperinsulinism (three sporadic insulinoma and two MEN-1 patients), and six patients had nonfunctioning tumors. Lap SPDP was performed in six patients with splenic vessels preservation and in eight patients was performed the Warshaw's technique. The mean operative time in patients was 195±40 min (range 125–270). One patient developed a grade A pancreatic fistula. A focal splenic infarct 3 and 4 cm in size was observed in two patients, respectively; both patients had pain in the left upper quadrant of the abdomen, but one patient developed a splenic abscess successfully treated with radiological intervention. The mean LHS was 5.9 days (range 5–14).

En-bloc Lap SxDP was performed in one malignant vipoma, two malignant pancreatic carcinoid, one malignant insulinoma, and in four nonfunctioning tumors (Table 3). In all these patients with malignant or suspected malignant tumors, a lymph node dissection was performed. The mean operative time was 280±20 min (range 190–310). At primary operation, localized liver metastases were present in two malignant pancreatic carcinoids and in one nonfunctioning pancreatic tumor. In two patients, a concomitant extended right hemihepatectomy was carried out through a separate right J abdominal incision. In one patient, a right hepatectomy was performed 8 weeks after primary tumor resection using open right J abdominal incision. The presence of bilobar hepatic spread was a contraindication for hepatic resection in the patient with malignant insulinoma. One patient had a grade A pancreatic fistula. The mean LHS was 7.5 days (range 5–12).

Enucleation was performed in 20 patients (46.5%). The group of patients that benefited from this organ preserving procedure were: one patient with a gastrinoma localized to the medial posterior aspect of the duodenum under the ampulla of Vater (0,80 mm in size), 14 patients with sporadic insulinoma (mean size 15.8 mm), and five patients with nonfunctioning tumors (mean size 3.2 cm). Laparoscopic ultrasound was used in all patients and confirmed the localization of the tumor except in one patient. This particular patient had a pedunculated insulinoma 15 mm in diameter at the inferior border of the pancreas resected by open surgery. The mean operative time was 120 min (range 60–150). One insulinoma patient had reoperation 36 h after surgery for bleeding from a gastroepiploic vessel. Pancreatic fistula occurred in seven patients (35%): grade A in four (20%) and grade B in three (15%) patients. One patient with a grade B pancreatic fistula was rehospitalized for abdominal pain 6 weeks after surgery and was discharged 48 h later. The mean LHS was 5.5 days (range 5–7).

A nodule 0.8 mm, localized between the common bile duct and the vena cava, was excised and it turned out to be a lymph node primary gastrinoma.

The mean follow-up was 37 months (range 2–89). All patients with gastrinomas are clinically and biochemically cured. One of the vipoma patients is still alive 6 years after surgery. The patient with malignant vipoma, by the presence of lymph node metastases at primary presentation, developed liver metastases after 3 years of observation and subsequently was lost to follow-up. The patient with a glucagonoma after 2 years was free of disease, developed lymph node local recurrence by CT scan and somatostatin receptor scintigraphy (SRS); during reoperation lymph node metastases found in the area of coeliac artery were successfully removed. However, 1 year later, SRS showed diffuse liver metastases despite the patient being asymptomatic. Two patients with malignant pancreatic carcinoid are clinically and biochemically cured 2 and 6 months after surgery. The patient with malignant insulinomas is free of

Table 3 Laparoscopic Pancreatic Surgery

Type of Tumor	Number	Conversion to Open Surgery	Malignancy (%)
Inflammatory: Chronic Pancreatitis	8	1 (12.5)	–
Cystic Neoplasms	29	–	3 (10.3%)
Intraductal Papillary Mucinous Neoplasm	10	–	2 (20%)
Neuroendocrine	43	3 (7%)	9 (20.9%)
Ductal Adenocarcinoma	13	3 (23%)	13 (100%)
Total	103 (100%)	7 (7%)	27 (26.2%)

Table 4 Laparoscopic Pancreatic Surgery (103 Patients)

Techniques	Number	Percentage (%)
Excision	1	0.9
Enucleation	20	19.4
Distal Pancreatectomy	82	79.6

clinical symptoms 1 year after surgery despite the patient having bilobar diffuse liver metastases. One patient with nonfunctioning pancreatic tumor who had concomitant primary tumor and liver resection for metastatic involvement developed metachronous hepatic metastases 2.5 years after surgery. Two patients with nonfunctioning pancreatic tumors and lymph node involvement at primary presentation are free of disease 3 and 5 years after surgery. One patient with a 6 cm nonfunctioning pancreatic tumor developed metachronous hepatic metastases in the left lobe of the liver, 2 years after primary surgery and developed diffuse liver metastases 2 years after successful left hepatic resection. This patient is still alive. In all patients with sporadic hyperinsulinism and MEN-1 the tumors were benign; laparoscopic tumor enucleation and laparoscopic pancreatic resection achieved a cure in all patients at the mean follow-up of 36 months (range 1–54 months).

Group V: Ductal adenocarcinoma (13 patients). Lap SxDP was planned in all patients but conversion was necessary in three patients at the initial of the laparoscopic procedure for difficulties in anatomical dissection (firm adhesions to the left diaphragmatic crura (one patient) and invasion of the transverse colon (two patients). In 10 cases, a modified laparoscopic RAMPS was performed. In this operation performed laparoscopically, the superior mesenteric artery was not skeletonized and the left renal vessels were not dissected. The mean operative time after Lap SxDP was 310±20 min (280–330). The mean blood loss was 720 ml± 450 ml (range 300–1,300 ml). Pancreatic fistula grade A occurred in one patient. Delayed gastric emptying was observed in one patient and another patient developed pneumonia. The mean LHS was 8 days (range 7–11). In three patients who had conversion to open surgery, other intraabdominal structures were resected en block with the distal pancreas: a portion of diaphragm (one patient) and partial colectomy (two patients) (Table 3). Histopathological studies showed ductal adenocarcinoma, three well differentiated, six moderately differentiated, and four poorly differentiated. The mean number of nodes was 14.5±3 (range 6–20) and five patients had between 1–4 lymph nodes positive for malignancy. Three patients had positive tangential margins in the group Lap SxDP 1/10 (10%) and in 2/3 (67%) of patients who needed conversion to open surgery. Chemotherapy with 5-FU was given to all patients. The median survival time was 14 months. Three patients died within 1 year with local recurrence and liver metastases.

Overall Analysis of the Perioperative Data

Operative time, blood loss, length of hospital stay, medical, and surgical complications were compared with respect to the laparoscopic technique used: enucleation, distal pancreatic resection with splenic-salvage (with and without splenic vessel preservation), and en-bloc splenopancreatectomy (Tables 4 and 5).

The operative time and blood loss were significantly lower in the enucleation group (mean 120 min and less than 220 ml), compared with the others laparoscopic techniques ($P<0.01$). The group of patients with ductal adenocarcinoma undergoing Lap SxDP had a longer operative time and greater blood loss (mean 310 min; mean 720 ml), compared with the other techniques of distal pancreatectomy performed in the other groups included in this study ($P<0.05$).

The mean LHS was within 1 week in all groups of the study except the group of patients with ductal adenocarcinoma (8 days) (NS).

Overall postoperative complications were significantly higher in the groups of laparoscopic enucleation compared with the other groups undergoing laparoscopic pancreatic resection ($P<0.01$). These complications were mainly pancreatic fistula: 7.7% after Lap SPDP, 10% after Lap SxDP, and 35% after Lap En; the severity of fistula was also significantly higher in the Lap En group ($P<0.05$). Perioperative somatostatin analogs were not used in this study. The overall morbidity rate was significantly higher ($P<0.05$) in the group of Lap SPDP without splenic vessel preservation comparing with Lap DP with splenic vessels preservation because of the occurrence of splenic complications 7/34 (20.6%) (Table 6).

Table 5 Laparoscopic Distal Pancreatectomy

Tumors (*n*)	Spleen Preserving		
	Splenic Vessels Preservation	Warshaw's Technique	En-bloc Splenectomy
Inflammatory Tumor (8)	6	–	2
Cystic Neoplasm (29)	6	20	3
Intraductal Papillary Mucinous Tumor (10)	–	6	4
Neuroendocrine Tumor (22)	6	8	8
Ductal Adenocarcinoma (13)	–	–	13
Total	18 (22%)	34 (41.5%)	30 (36.6%)

Table 6 Laparoscopic Pancreatic Surgery: Complications

	Spleen-Preserving Distal Pancreatectomy (n=52)	En-bloc Splenopancreatectomy (n=30)	Enucleation (n=20)	Excision (n=1)
Pancreas related				
Overall Pancreatic Fistula	4 (7.7%)	3 (10%)	7 (35%)	–
ISGPF Grade A	2 (3.8%)	2 (6.7%)	4 (20%)	–
ISGPF Grade B	2 (3.8%)	1 (3.3%)	3 (15%)	–
ISGPF Grade C	–	–	–	–
Spleen related				
Overall splenic infarct	7 (13.5%)[a]	–	–	–
Asymptomatic	2 (3.8%)			
Symptomatic	5 (9.6%)			
Abscess	1	–	–	–
Pneumonia	–	1	–	–
Delayed Gastric Emptying	–	1	–	–
Perforation duodenal ulcer	1	–	–	–
Postoperative bleeding	–	–	1	–
Total[b]	13 (25.2%)	5 (16.7%)	8 (40%)	0 (0%)

[a] This complication was only observed in the group of Lap SPDP without splenic vessels preservation, 7/34 (20%).
[b] Lap SPDP vs Lap SxDP $p<0.05$; Lap En vs Lap SPDP $p<0.01$; Lap En vs Lap SxDP $p<0.01$.

The mean time for patients undergoing laparoscopic pancreatic resection and Lap En to resume previous activities was 3 weeks. There were no postoperative (30 days) or hospital deaths.

Discussion

The most common indications for laparoscopic pancreatic surgery were benign-appearing pancreatic tumors, such as neuroendocrine neoplasms (41.7% in the present series). Other indications were cystic neoplasms of the pancreas, mainly mucinous cystic neoplasms (28.1%) and IPMN (9.7%) with premalignant or an overtly malignant tendency. Ductal adenocarcinoma represented 12.6% of the indications in this series and less common indications were left-sided chronic pancreatitis with inflammatory tumors (7.7%).

Laparoscopic pancreatic surgery was feasible in 93% of the patients. Indications for conversion included technical problems, anatomical (occult tumor) or oncological features that precluded a safe laparoscopic approach. The most frequent technique used in this series was laparoscopic distal pancreatic resection (79.6%) but with splenic salvage in 63.5% of cases.

The question of splenic-preserving distal pancreatectomy is controversial. Talamini et al.[24] reported that 74% of patients with mucinous cystoadenomas undergoing open distal pancreatic resection (DPR) had splenectomy. One late septic death occurred in this group. Recently, Lillemoe et al.[25] reported the largest single institution experience with open DPR (235 patients) for a variety of pancreatic disorders including chronic pancreatitis and benign and malignant pancreatic tumors, and only 16% of patients had splenic preservation. In another series of 71 patients reported by Fernández Del Castillo et al.[26], the incidence of splenic preservation was 20%. Published data from two retrospective reviews comparing patients who had surgery mainly for trauma or pancreatitis, undergoing open DPR with and without splenectomy have shown no differences in complication rates between groups, indicating that splenectomy should not be a routine part of DPR. However, in a retrospective study by Benoist et al.[27], pancreatic complications such as fistula or subphrenic abscess occurred more frequently in patients after spleen-conserving surgery. More recently, Shoup et al.[28] reported the series from Memorial Sloan-Kettering Cancer Center including 211 patients undergoing open DPR. Splenectomy was performed in 79 patients (63%) and splenic preservation in 46 (37%). Perioperative complications occurred in 49% of patients after splenectomy and in 39% after splenic preservation. Perioperative infectious complications and other severe complications were significantly higher in the splenectomy group (28 and 11%, respectively), compared with the splenic preservation group (9 and 2%, respectively). Length of hospital stay was 9 days after splenectomy and 7 days after splenic preservation.

In our current series, there were statistically significant differences in the overall postoperative complications between Lap SxDP (16.7%) and Lap SPDP (25.2%). The latter group included patients without splenic vessels preservation with spleen-related complications [splenic infarct in 7/34 (20.6%)].

We recommend Lap SPDP in patients with benign-appearing tumors to prevent the potential long-and short-

term complications associated with splenectomy. The question is whether it should be performed with[29] or without splenic vessels preservation. The latter technique, in which the short gastric and gastroepiploic vessels are the only blood supply to the spleen, was described by Warshaw[30] in open surgery. Splenomegaly is a contraindication for this method of spleen conservation because the increased mass is insufficiently nourished by the short gastric vessels. There is no doubt that by preserving the splenic artery and vein, the blood supply to the spleen is well maintained and the danger of splenic necrosis and abscess formation is reduced. On the other hand, distal pancreatectomy with conservation of the splenic artery and vein is both time and labor consuming. Dissecting the splenic vessels from the pancreas may be difficult in the presence of tumors distorting and compressing the course of the vessels. We have reported a prospective study including patients with SCN and MCN of the pancreas to evaluate the feasibility and outcome of Lap SPDP with and without splenic vessel preservation. Our results indicate that preservation of the splenic vessels is not always possible when dealing with large tumors.[19] Furthermore, comparison between groups undergoing splenic vessel preservation and Warshaw's technique demonstrated a statistically significant difference in operative time and intraoperative blood loss in favor of division of the splenic vessels.[31] In all circumstances, we advocate Lap SPDP that preserves the short gastric and gastroepiploic vessels, and thus where it is necessary to remove the splenic artery and vein, splenic vascularization will be maintained. We believe that Warshaw's technique is less demanding than the dissection and conservation of the splenic artery and vein. Regarding conservation of the splenic vessels, we agree with Warshaw[31], "if the goal is to save the spleen, having options allows the surgeons to match the tactics to the terrain".

In our current series, Lap SPDP was performed in 41.5% according with Warshaw's technique and with preservation of both the artery and the splenic vein in 22%. The overall complication rates were higher in the group of Lap SPDP without splenic vessel preservation because of the occurrence of splenic complications in seven patients (20.6%). These complications may occur in asymptomatic patients (2/7 patients) or may be suspected clinically by the presence of fever and left upper abdominal pain (5/7 patients). CD-US will show the area of focal infarct. The mean size of focal splenic infarct in our patients was 3.4 cm (range 3.4–4 cm). One patient developed splenic abscess requiring drainage by radiological intervention. A more serious complication is massive splenic necrosis with local infection requiring splenectomy. Shein et al.[32] reported that splenectomy had to be performed 24 h after Warshaw's technique because of splenic necrosis. However, the reduction of blood supply leading to splenic necrosis may take days, as happened in one of our patients. This particular patient was discharged home 5 days after surgery, however, 2 days later represented with fever and clinical sepsis; he was rehospitalized and splenectomy was performed for massive necrosis of the spleen. It might be that the splenic complications after Warshaw's technique are not a result of failure of the technique but a failure to properly perform the procedure as it was originally described, i.e., preservation of all vascular collaterals nourishing the spleen. We believe that CD-US should be performed routinely in all patients undergoing Lap SPDP without splenic vessel preservation to diagnose promptly areas of infarct and to prevent abscess formation with antibiotic administration.

One of the most serious complications of distal pancreatic resection (DPR) is the development of a postoperative pancreatic fistula, which may lead to a subphrenic abscess, sepsis, or lethal arterial bleeding. In the recent literature (based on more than 100 patients), the incidence of pancreatic fistula after pancreatic left resection is highly variable, ranging from 3 to 34%.[33] These differences might be related to the variability of definitions of pancreatic fistula. Factors that have been implicated as potentially important in the development of pancreatic leak include the method of pancreatic stump closure, the underlying disease process (chronic pancreatitis, benign tumors, malignant tumors, trauma, etc...), and concomitant splenectomy.

In open DPR, the optimal method of pancreatic stump closure is still controversial. Conventional ligation of the main pancreatic duct with closure of the resected margin with sutures may leave small branches open and allow them to leak. The staple method has the advantage of simplicity and speed. In some series, pancreatic leaks occurred more often after a sutured closure of the pancreatic stump compared with those that were stapled. However, Bilimoria et al.[34] have shown that failure to identify and selectively closing the pancreatic duct was the only factor associated with an increased risk of pancreatic leak after open DPR. Balzano et al.[33] have recently reported analysis of a retrospective study of 123 patients undergoing left pancreatectomy, comparing the fistula rate after different methods of closure of the pancreatic remmant. There was no surgical difference in the leakage rate between different groups: 38% after suture closure, 34% after stapled closure alone, and 31% with the combined technique.

Automatic stapling is often used in laparoscopic distal pancreatectomy for transection of the pancreas.[35] The device is simple to use and ligation of the duct of Wirsung is not necessary. In the Multicenter European Study, pancreas-related complications occurred in 35% with laparoscopic linear stapling.[18] In the current series, after laparoscopic distal pancreatic resection with stapled closure, the overall pancreatic fistula rate was 8.5% (7/82): 4.9% (4/82) biochemical grade A fistula (no impact in the

clinical outcome) and 3.6% (3/82) grade B fistula (requiring drain in situ more than three weeks). Somatostatin or its analogs were not used in the perioperative period.

Recently, a meta-analysis of technique for closure of the pancreatic remmant after distal pancreatectomy indicated a statistically nonsignificant, but possibly clinically relevant, trend towards superiority of staple closure.[36] However, even this favored technique resulted in a fistula rate of 22.9% in the meta-analysis. This percentage is higher than the 8.5% observed in the current laparoscopic series. It may be that the site of stapler transection may play a role in the occurrence of pancreatic fistula. We believe that, whenever possible, the site of the stapler transection should be at the neck of pancreas as the narrowest part of the gland (performed in the majority of our patients) avoiding the bulky area of the body of the pancreas. In any case, we and others[36] believe that stapler transection and closure of the pancreatic remmant should probably be regarded as the current state-of-the-art technique of distal pancreatectomy minimizing the occurrence of pancreatic fistula.

In this report, the mean hospital stay after laparoscopic surgery was 1 week. This is a notable reduction of the postoperative length of stay in comparison with the largest single institution experience with open DPR, reporting a mean of 15 days. In a report from The Massachusetts General Hospital, it was demonstrated that after open DPR, patients had a decreased length of stay from 9 to 7 days.[37]

Lap En was performed in 20/102 patients (19.4%). Enucleation offers the possibility of complete tumor removal without splenectomy or the loss of pancreatic parenchyma and possible diabetes. In this report, Lap En was indicated in patients with neuroendocrine tumors. This technique was associated with a higher incidence of overall postoperative complications in 40% compared with patients undergoing Lap SPDP and Lap SxDP, mainly because of the rate of pancreatic fistulae (35%). However, only 15% were clinically relevant pancreatic fistula (grade B).

Other surgeons have used enucleation in open surgery, to manage patients with CyN.[24] In one series the incidence of pancreatic fistula after tumor enucleation was reported to be 30 to 50%, leading to a long hospital stay (19.5 days); other morbidity includes pseudocyst formation and pancreatitis in up to 35% of patients. Recently, Kiely et al.[38] have introduced several modifications to reduce the complications after tumor enucleation in open surgery: in 11 patients with CyNP, enucleation was performed but in eight (73%) closure was performed with one or two "figure-of-eight" 3-0 absorbable sutures. This group was compared with 19 patients who underwent resection with 11 having a distal pancreatectomy (64% with splenic preservation). The incidence of pancreatic fistula was 27% in the enucleation group and 26% in the resection group. The mean hospital stay was 12.6+2.8 days in the enucleation group and 15.7+2.5 days in the resection group. The surgical refinements introduced by these authors[38], did not avoid the high fistula rate and prolonged hospital stay associated to tumor enucleation.

We believe that laparoscopic tumor enucleation performed with the assistance of Laparoscopic Ultrasound (Lap US) allows identification of the duct of Wirsung to avoid duct injury. Pancreatic fistula, in the current series, probably occurred as a result of small pancreatic ducts left open in the cavity after tumor enucleation: these usually closed in few days with no impact on the clinical outcome.

Regarding the indications for laparoscopic surgery, this report provides evidence for the benefit of this minimally invasive approach in patients with left-sided chronic pancreatitis in achieving long-term pain control and minimal endocrine dysfunction.

Surgery remains the only curative modality currently available for resectable NETs. With the exception of gastrinomas and somatostinomas which are found in the pancreatic head in 60–70% of cases, other NPTs are located predominantly in the body and tail of the pancreas. This localization makes NETs suitable for the laparoscopic approach. Surgical management varies with tumor type, location, and size. Small NETs may be treated with enucleation. In this report, 14/17 (82.3%) of patients with sporadic insulinoma and 5/15 (33.3%) of patients with nonfunctioning NETs not exceeding 3 cm in diameter, were treated with laparoscopic enucleation. Other functioning and nonfunctioning NETs should be managed with extended pancreatic resection including peripancreatic lymph node dissection. In our series of 43 NETs, excluding 19 patients with hyperinsulinism (17 sporadic and 2 MEN 1), 9/24 (36.6%) were malignant NETs. Laparoscopic pancreatic resection achieved R_o resection in all malignant NETs. In addition, some patients presented at the time of diagnosis with liver metastases and were treated with concomitant primary tumor and liver resection. Other patients some years after laparoscopic pancreatic surgery presented with liver metastasis that were treated with liver resection. In a recent publication[39], we reported a detailed analysis of the surgical strategies that should be undertaken in benign and malignant functioning and nonfunctioning NETs. In this report, the group of patients with NETs was included with other pancreatic neoplasms to emphasize the feasibility, safety, and outcome of the laparoscopic approach in the management of patients with pancreatic tumors.

Some authors have recommended resection for all CyN, serous, and mucinous tumors, whereas others advocate a more selective approach. The management of patients with CyN should be based on the appropriate histopathologic classification of CyN: tumor size, anatomical location within the pancreas, clinical symptoms, and age of the patients. In general, with the exception of the scanty reports of well-documented cases of malignant serous cystadeno-

carcinoma of the pancreas, serous CyN should be considered benign and approached therapeutically as such.[40] There is no question that resection is indicated in the presence of mass related symptoms or in patients in whom a mucinous tumor or side-branch IPMN cannot be comfortably excluded. Controversy exists regarding asymptomatic lesions.[40] For some surgeons, serous CyN have little malignant potential and may be observed with clinical follow-up and serial imaging. For other surgeons, when serous CyN involves the body or tail of the pancreas, resection is indicated. There is no controversy in the management of mucinous CyN. Surgical excision is the treatment of choice as these tumors are either premalignant or frankly malignant.[41,42] Serous cystadenomas and mucinous cystic neoplasms are suitable for the laparoscopic approach based on the frequent location of these tumors in the body or tail of the pancreas. We encourage Lap SPDP for the majority of CyN, but Lap SxDP should be performed with suspected malignancy (large tumor). In this report, 3/29 (10%) of tumors over 6 cm in diameter were found to be invasive mucinous tumors. Long-term surveillance in this group of patients has shown no tumor recurrence in either noninvasive proliferative mucinous CyN or invasive mucinous cystoadenocarcinoma.

According to Sakorafas and Sarr[43], the aim of resection in the management of IPMN is to remove all the adenomatous or malignant mucosa and to minimize the chance of recurrence in the pancreatic remnant. Pancreatoduodenectomy or distal pancreatic resection is recommended when IPMN is localized or in cases of branch-duct disease. When dilatation of the main pancreatic duct involves the whole pancreas (main-duct IPMN) most surgeons will proceed with total pancreatectomy.[44] The appropriate candidates who could benefit from minimally invasive surgery are 15% IPMN patients, with the disease involving the body–tail of the pancreas requiring distal pancreatectomy. Is there any place for nonanatomical resections for IPMN? These techniques are contraindicated because of the 20–60% incidence of invasive cancer. In addition, tumor enucleation is considered inappropriate in the majority of patients, based on the presence of communication between the tumor and the duct of Wirsung. Preoperative and peroperative pathological distinction between benign and malignant IPMN is, in most cases, impossible.[45] In the current series, invasive IPMN was found in 20% of patients. The frequency of lymph node metastases in invasive IPMN range from 29 to 46%.[44] Therefore, when surgery is indicated, an oncological procedure should be performed including regional lymphadenectomy.

This report is, to our knowledge, the first to present data on the short- and long-term outcome of laparoscopic pancreatic resection in patients with ductal adenocarcinoma.

Malignant tumors in the body and tail of the pancreas are typically present in a more advanced stage than those of the proximal gland.[46] Operative dissection to achieve a negative margin is often difficult because of local inflammatory response or by malignant infiltration of the neighboring tissues or organs. In the literature, there are few reports in which margin clearance and survival rates are reported.

Howard et al.[47] reports that in 226 patients with pancreatic adenocarcinoma operated on between 1990 and 2002, tumors were located overwhelmingly (94%) in the pancreatic head resulting in the vast majority of resections being either pancreatoduodenectomy (90%) or total pancreatectomy (4%); distal pancreatectomy was performed in 13 patients (6%). In this analysis using multivariate analysis, tumor size, tumor differentiation, a margin-negative R_o resection and completing the operation without major postoperative complications were identified as covariates affecting long-term survival. In the distal pancreatectomy group, there were more poorly differentiated tumors and a margin-negative R_o resection was achieved with this operation in only 31%; 10 out of 13 patients did not survive for 3 years. In this report, the technique used for distal pancreatic resection is not stated. In 2003, Strasberg et al.[21] described a novel approach for resection of adenocarcinoma of the body and tail of the pancreas, called radical antegrade modular pancreatosplenectomy (RAMPS). This procedure is modular in that the plane of the posterior dissection may be directly on the left adrenal gland and Gerota's fascia (anterior RAMPS) or may be posterior to the adrenal and Gerota's fascia (posterior RAMPS). The dissection commences from right-to-left with early division of the neck of the pancreas and the splenic vessels, as well as coeliac node dissection. From there, the plane of dissection runs posteriorly in a sagittal plane along the superior mesenteric and coeliac arteries to the level of the aorta and then laterally either anterior or posterior to the adrenal. Strasberg et al.[21] reported negative tangential margins in 90% of patients. This procedure offers advantages over the standard left-to-right procedure. The latter may result in failure to remove N_1 nodes, late control of blood supply, and poor visibility of the planes of dissection. Shoup et al.[48] reported 57 patients who had resection of adenocarcinoma of the pancreas over 17 years (1983–2000); 41/57 (72%) of patients had negative margins and 16/57 (28%) had positive margins. The number of nodes in resected specimens was not stated. Margin positivity was not significantly associated with poorer survival but lymph node positivity present in 48% of patients was. Overall survival, reported as disease-specific survival, was 16 months and the 5-year survival was about 15%. Christein et al.[49] reported 93 patients treated over a 16-year period (1986–2003), 27 of whom had carcinoma arising in cystic disease of the pancreas and 66 had ductal adenocarcinoma. Eighty-three percent had negative margins, but according to the authors, tangential (radial) margins were reported in only 62% of the specimens. No lymph

nodes were identified in 15% of specimen, and the number of nodes resected in the other patients is not stated. Thirty percent had positive nodes. The median survival in 66 patients with ductal adenocarcinoma was 16 months and the 5-year survival about 5%. Shimada[50] reported 88 patients with ductal adenocarcinoma treated over 15 years (1990–2004). Approximately 66/88 (75%) of patients had negative margins and 22/88 (25%) had positive margins. The number of nodes resected is not given but 78% of patients had positive nodes. Node positivity was significantly related to reduced survival. The median survival was 22 months and the 5-year overall survival was 19%. It is not possible to compare the different series to allow meaningful conclusions. In the majority of reports, the technique of distal pancreatectomy is not described, the surgical morbidity not stated, the number of nodes resected is not given, and inking is not described nor is the site of margin positivity.

If long-term survival is entirely dependent on tumor stage, differentiation, or on the presence of occult systemic disease at the time of diagnosis, then progress in long-term survival will require improvements in chemotherapeutic agents or identification of specific molecular tumor targets that can be utilized in adjuvant or neoadjuvant treatment strategies.[51,52] According to Howard et al.[47], "the surgeon's role is currently to provide adequate margin-negative R_o resection with a minimum of postoperative complications to remove macroscopic tumor burden and preserve the patient's physiologic function to ensure they are capable of receiving timely and appropriate adjuvant therapy". Our technique of modified laparoscopic RAMPS achieved negative tangential margins in 90% of patients and N_1 dissection in resectable carcinoma of the body and tail of the pancreas. The overall complication rate was 23% with a mean LHS of 8 days. These results made it possible to refer all patients for chemotherapy 2–3 weeks after surgery.

Conclusions

The open DPR has a long, proven track record of providing a cure for pancreatic diseases with acceptable morbidity and mortality after surgery. Laparoscopic DPR is a complex advanced laparoscopic operation that accomplishes the same objectives as open DPR but avoids large upper midline or subcostal abdominal incisions. The differences between laparoscopic and open DPR are the method of access and exposure; the surgical insult should be less after laparoscopic compared with open pancreatic surgery.

Laparoscopic spleen-preserving distal pancreatectomy with or without splenic vessels preservation is feasible and can be achieved in most cases. Laparoscopic en-bloc splenopancreatectomy using a modified RAMPS procedure can achieve negative tangential margins in a high percent of patients with resectable malignant tumors of the body and tail of the pancreas.

The reduced incidence of wound infection after Lap DPR is one of the recognized advantages of the laparoscopic approach. Furthermore, another clinical advantage of the Lap DPR is the reduced incidence of a late incisional hernia. Recovery is a very important outcome and can be measured by the patients' time to return to activities of daily living. In the current series, the mean time for the patients undergoing laparoscopic distal pancreatectomy or Lap En to return to previous activities was 3 weeks.

Laparoscopic En was indicated in patients with solitary benign neuroendocrine pancreatic tumors not exceeding 3 cm in diameter. The use of Lap US is an integrant part of the laparoscopic procedure, and the information achieved is valuable for both confirming localization and decision making concerning the most appropriate surgical procedure. The main morbidity continues to be the occurrence of pancreatic fistula, but the clinical course is without clinical impact in most instances.

In summary, the results of this prospective study indicate that laparoscopic pancreatic surgery performed in patients with a variety of pancreatic disorders, benign, premalignant, and malignant lesions provides no mortality, morbidity rates lower than reported in open surgery, and all the advantages of a minimally invasive approach with reference to pain, cosmetic results, reduced hospital stay, and faster postoperative recovery. Laparoscopic pancreatic surgery achieved in patients with chronic pancreatitis, long-term pain control; in patients with benign mucinous neoplasms and NETs, long-term cure with no recurrence; in patients with malignant neoplasms, acceptable long-term survival. We agree that without a randomized controlled study, it is not possible to confirm, at the present time, the superiority of the laparoscopic approach over traditional open surgery. However, the promising results presented in this report makes laparoscopic surgery a valid option, in selected patients with pancreatic disorders.

Acknowledgement We thank Tom Gorey Professor of Surgery in Dublin (Ireland) for the article preparation.

References

1. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. Surg Endosc 1994;8:408–410.
2. Cushieri A. Laparoscopic surgery of the pancreas. JR Coll Surg Edinb 1994;39:187–194.
3. Cuschieri A, Jakimowicz J. Laparoscopic pancreatic resections. Semin Laparosc Surg 1998;5:168–179.
4. Fabre JM, Dulucq JL, Vacher C, Lemoine MC, Wintringer P, Nocca D. Is laparoscopic left pancreatic resection justified? Surg Endosc 2002;19:507–510.

5. Patterson EJ, Gagner M, Salky B, Inabnet WB, Brower S, Edye M, Gurland B, Reiner M, Pertsemlides D. Laparoscopic pancreatic resection: Single-institution experience with 19 patients. J Am Coll Surg 2001;193:281–287.
6. Shimizu S, Tanaka M, Mizumoto K, Yamaguchi K. Laparoscopic pancreatic surgery: Current indications and surgical results. Surg Endosc 2004;18:402–406.
7. Fernández-Cruz L, Sáenz A, Astudillo E, Martinez I, Hoyos S, Pantoja JP, Navarro S. Outcome of laparoscopic pancreatic surgery: Endocrine and nonendocrine tumors. World J Surg 2002;26: 1057–1065.
8. Edwin B, Mala T, Mathisen O, Gladhayg I, Buanes T, Lunde OC, Soreide O, Bergan A, Fosse E. Laparoscopic resection of the pancreas: A feasibility study of the short-term outcome. Surg Endosc 2004;18:407–411.
9. Velanovich V. Case-control comparison of laparoscopic versus open distal pancreatectomy. J Gastrointest Surg 2006;10:95–98.
10. Park AE, Heniford BT. Therapeutic laparoscopy of the pancreas. Ann Surg 2002;236:149–158.
11. Berends FJ, Cuesta MA, Kazemier G, van Eijck CH, de Herder WW, van Muiswinkel JM, Bruining HA, Bonjer HJ. Laparoscopic detection and resection of insulinomas. Surgery 2000;128:386–390.
12. Gramatica L, Herrera MF, Mercado-Luna A, Sierra M, Verasay G, Brunner N. Videolaparoscopic resection of insulinomas: Experience in two institutions. World J Surg 2002;26:1297–1300.
13. Ihiara M, Obara T. Minimaly invasive endocrine surgery: Laparoscopic resection of insulinomas. Biomed Pharmacother 2002;56:227–230.
14. Ayav A, Bresler L, Brunand L, Boissel P. Laparoscopic approach for insulinoma: A multicenter study. Langenbecks Arch Surg 2005;390:134–140.
15. Fernández-Cruz L, Martinez I, Cesar-Borges G, Astudillo E, Orduña D, Halperin I, Semilo G, Puig M. Laparoscopic surgery in patients with sporadic and multiple insulinomas associated with multiple endocrine neoplasia type 1. J Gastrointest Surg 2005;9:381–388.
16. Assalia A, Gagner M. Laparoscopic pancreatic surgery for islet cell tumors of the pancreas. World J Surg 2004;28:1239–1247.
17. Sa Cunha A, Beau C, Rault A, Catargi B, Collet D, Masson B. Laparoscopic versus open approach for solitary insulinoma. Surg Endosc 2007;21:103–108.
18. Mabrut JY, Fernández-Cruz L, Azagra JS, Bassi C, Delvaux G, Weerts J, Fabre JM, Boulez J, Baulieux Peix JL, Gigot JF. Laparoscopic pancreatic resection: Results of a multicenter European study of 127 patients. Surgery 2005;137:597–605.
19. Fernández-Cruz L, Martinez I, Gilabert R, Cesar-Borges G, Astudillo E, Navarro S. Laparoscopic distal pancreatectomy combined with preservation of the spleen for cystic neoplasms of the pancreas. J Gastrointestl Surg 2004;8:493–501.
20. Fernández-Cruz L. Distal pancreatic resection: Technical differences between open and laparoscopic approaches. HPB 2006;8:49–56.
21. Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreatosplenectomy. Surgery 2003;133:521–527.
22. Fernández-Cruz L, César-Borges G. Laparoscopic strategies for resection of insulinoma. J Gastrointest Surg 2006;10:752–760.
23. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: An international study group (ISGPF) definition. Surgery 2005;138:8–13.
24. Talamini MA, Moesinger R, Yeo CJ, Poulose B, Hruban RH, Cameron JL, Pitt HA. Cystadenomas of the pancreas: Is enucleation an adequate operation? Ann Surg 1998;227:896–903.
25. Lillemoe KD, Kaushal S, Cameron JL, Sohn TA, Pitt HA, Yeo CJ. Distal pancreatectomy: Indications and outcomes in 235 patients. Ann Surg 1999;229–693.
26. Fernández del Castillo C, Rattner DW, Washaw I. Standards for pancreatic resection in the 1990s. Arch Surg 1995;130:295–300.
27. Benoist S, Dugue L, Sauvanet A, Valverde A, Mauvais F, Paye F, Farges O, Belghiti J. Is there a role of preservation of the spleen in distal pancreatectomy? J Am Coll Surg 1999;188: 255–260.
28. Shoup M, Brennan MF, Mc White K, Leung DH, Klimstra D, Conlon KC. The value of splenic preservation with distal pancreatectomy. Arch Surg 2002;137:164–168.
29. Kimura W, Inone T, Futawake N, Shiukai H, Hau I, Muto T. Spleen preserving distal pancreatectomy with conservation of the splenic artery and vein. Surgery 1996;120:885–890.
30. Warshaw L. Conservation of the spleen with distal pancreatectomy. Arch Surg 1998;123:550–553.
31. Warshaw A. Letter to the editor. Techniques of preserving the spleen with distal pancreatectomy. Surgery 1997;121:974.
32. Shein M, Freinkel W, D'Egidio A. Splenic conservation in distal pancreatic injury: Stay away from the hilium! J Trauma 1991;31 (3):letter.
33. Balzano G, Zerbi A, Cristallo M, Di Carlo V. The unsolved problem of fistula after pancreatectomy: The benefit of cautions drain management. J Gastrointest Surg 2005;9:837–842.
34. Bilimoria MM, Cormier JN, Mun Y, Lee JE, Evans DB, Pisters PWT. Pancreatic leak after pancreatectomy is reduced following main pancreatic duct ligation. Br J Surg 2003;90:190–196.
35. Takenchi K, Tsuzuki Y, Ando T, Sekihara M, Hara T, Kori T, Nakajima H, Kuwano H. Distal pancreatectomy: Is staple closure beneficial? Aust N Z J Surg 2003;73:922–925.
36. Knaebel HP, Diener MK, Wente MN, Buchler MW, Seiler CM. Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. Br J Surg 2005;92:539–546.
37. Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y, Fernández del Castillo C. Ten-years experience with 733 pancreatic resections: Changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391–398.
38. Kiely JM, Nakeeb A, Komorowski RA, Wilson SD, Pitt HA. Cystic pancreatic neoplasms: Enucleate or resect? J Gastrointest Surg 2003;7:890–897.
39. Fernández-Cruz L, Blanco L, Cosa R, Rendón H, Astudillo E. Is laparoscopic approach an adequate procedure in patients with bening-appearing and overt malignant neuroendocrine pancreàtic tumors? World J Surg (in press).
40. Tseng JF, Warshaw AL, Sahani D, Lauwers GL, Rattner DW, Fernández-del Castillo C. Serous cystadenoma of the pancreas. Tumor growth rates and recommendation for treatment. Ann Surg 2005;242:413–421.
41. Sarr MG, Carpenter, HA, Prabhakar LP, Orchard TF, Hughes S, van Heerden JA, DiMagno EP. Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas: Can one reliably differentiate benign from malignant (or premalignant) neoplasms? Ann Surg 2000;231:205–212.
42. Sarr MG, Murr M, Smyrk C, Yeo CJ, Fernandez del Castillo C, Hawes RH, Freeny PC. Primary cystic neoplasms of the pancreas. Neoplastic disorders of emerging importance-current state-of-the-art and unanswered questions. J Gastrointest Surg 2003;7:417–428.
43. Sakorafas GH, Sarr MG. Cystic neoplasms of the pancreas: What a clinician should know. Cancer Treat Rev 2005;31:507–535.
44. Lai ECH, Lau WY. Intraductal papillary mucinous neoplasms of the pancreas. Surgeon 2005;5:317–324.
45. Jiménez RE, Warshaw AL, Z'graggen K, Hartwig W, Taylor D, Compton C, Fernández del Castillo C. Sequential accumulation of K-ras mutations and p53 overexpression in the progression of pancreatic mucinous cystic neoplasms to malignancy. Ann Surg 1999;230:501–511.
46. Fabre JM, Houry S, Manderscheid JC, Huguier M, Baumel H. Surgery for left-sided pancreatic cancer. Br J Surg 1996;83:1065–1070.

47. Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LF, Madura JA, Wiebke EA, Lillemoe KD. A margin negative Ro resection accomplished with minimal postoperative complications. Is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg 2006;10:1338–1346.
48. Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extendet resection for adenocarcinoma of the body or tail of the pancreas justified? J Gastrointest Surg 2003;7:946–952.
49. Christein JD, Kendrick ML, Iqbal CW, Nagorney DM, Farneil MB. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. J Gastrointest Surg 2005;9:922–927.
50. Shimada K, Sakamoto Y, Sano T, Kosuge T. Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail. Surgery 2006;139:288–295.
51. Z'graggen K, Centeno BA, Fernández-del-castillo C, Jimenez AE, Werner J, Warshaw AL. Biological implication of tumor cells in blood and bone marrow of pancreatic cancer patients. Surgery 2001;129:537–546.
52. Traverso LW. Pancreatic cancer: Surgery alone is not sufficient. Surg Endosc 2006;S446–S449.

Discussion

Michel Gagner, M.D. (New York, NY): Thank you for the privilege of the floor. First of all, I want to congratulate Professor Fernández-Cruz for this nice series, 103 patients with tumors over a time span of 10 years. That is about one patient per month and it really demonstrates that using oncologic principles, you can operate on malignancy in about a quarter of those patients.

Another testament to his skills is that there is no mortality in this series. In fact, if you look at the almost 15 years report of lap distal pancreatectomy, the mortality is extremely low; you really have to find and look in the series to find it. Mortality of lap distal pancreatectomy is in fact lower than hip replacement. So I congratulate him for making these statements.

I had two questions, one that is philosophical and one that relates to techniques. Regarding the philosophy of all your indications, I agree with everything, with perhaps the exception of patients with IPMN tumors that have major duct disease. There it is recommended to do perhaps a total pancreatectomy or a duodenum-preserving total pancreatectomy. Perhaps this can be done laparoscopically, but this is going to be a bit difficult and will require excellent advanced technical skills.

The other area regards all the malignant islet cell tumors, for example, gastrinoma, vipoma, and carcinoid. What we found in 1996 when we presented our findings at this meeting is that gastrinoma was very difficult to surgically treat laparoscopically because they had metastatic nodes, they had metastasis to the liver, and you may need to have a laparotomy to really deal with the multicentricity of this disease. So, perhaps you can tell us what are your lists of indications where you would rather do a laparotomy instead of a laparoscopy?

Regarding the technical questions, first there is the 35% fistula rate with enucleation. That is probably twice as high a fistula rate as in a resection. Is it perhaps better to do a resection and avoid this fistula rate, or is the enucleation too close to the pancreatic duct and it is unavoidable in one-third of cases? Did the fistulae result in a prolonged hospital stay? If so, could you have avoided that by just doing a distal pancreatectomy? Finally, what was the length of the incision you used to resect a splenopancreatectomy specimen? In these cases, you could consider doing a hand-assisted procedure and maybe save half the operative time with mobilization using the hand, because if you make an 8- or 10-cm incision, then you could have your hand at the beginning of the operation.

I enjoyed the manuscript very much. Thank you.

Laureano Fernández-Cruz, M.D. (Barcelona, Spain): Thank you, Michel, for your questions. Regarding the indications of IPMN, all these patients did not have duct-dilated disease. For those patients, they do require, for most of them, a total pancreatectomy. And those patients that did have a branch duct type or a dominant branch duct type in the left side of the pancreas, we did perform a distal pancreatectomy. I think we should not do this operation in a dilated Wirsung duct from the head to the tail of the pancreas. I think, in this particular situation, a distal pancreatectomy is not indicated, open or laparoscopically.

Regarding malignant tumors, we applied this technique in our series for malignant glucagonoma, malignant carcinoids, and also patients with gastrinoma. I think we can explore the lymph node area and to do lymphadenectomy as well as we do in open surgery, and there is no contraindication to use the laparoscopic approach for these tumors, either benign or malignant. Gastrinomas are very difficult ones because the tumors are located mainly in the duodenum, and in some patients it is difficult to localize the tumor, but if you have already localized the tumor, I think we can do the excision of the tumor using the laparoscopic approach.

Regarding the fistula rate after laparoscopic enucleation, the mean hospital stay in this group of 20 patients after laparoscopic enucleation was 5 days. And although in some patients they had grade B fistula, they were discharged home with the drain in situ. And the reason why we classified those patients as grade B is because some of the patients needed the drain to be removed more than 3 weeks after the operation. But the postoperative course was very smooth and no patient needed to be reoperated or the need of radiological intervention for fluid collection.

The fistula, after laparoscopic enucleation, in some patients, is because of the small ducts remains temporarily open. But in our series, we do believe we did not damage any pancreatic duct, by using laparoscopic ultrasound.

We enlarged the incision and it depends how big is the tumor. We enlarged the incision between the trocars to remove the big tumors.

Andrew L. Warshaw, M.D. (Boston, MA): Laureano, I congratulate you on the largest single series of laparoscopic resections of pancreatic neoplasms, and I comment from the point of view of the smallest single series because I have never done one. I tried once and I could not do it.

My questions relate to the significance of your accomplishment. The postoperative length-of-stay of your patients was a week; your operative time was somewhat longer than an open procedure would be; and you must make an incision to remove the specimen. One of my teachers a long time ago said that incisions heal from side to side, not end to end, so maybe a little bit shorter does not make that much difference. What is the advantage of this procedure when all is said and done? That is question number one.

Second, you encountered a significant number of splenic infarcts, perhaps a bit more in this series than in some others, but my question regards the clinical significance of those splenic infarcts. In our experience, only once or twice in more than 70 patients has it been clinically important or led to reoperations to remove the infarcted spleen. Most are small geographic lesions that usually have no significance. What has been your experience?

Dr. Fernández-Cruz: I will start with your last question. I think a spleen-related complication is not frequent, but it occurs, and it depends how careful you check your patients. After a spleen-preserving distal pancreatectomy without splenic preservation, you can pick up patients with a focal splenic infarct and without clinical symptoms. However, some patients have abdominal pain in the left quadrant of the abdomen and even sometimes patients develop fever, and if you checked these patients you found a focal splenic infarct. Most of them are not clinically relevant, but some are, and I think it is important to look for these possible complications and to treat with antibiotics those patients before they do develop a splenic abscess.

J Gastrointest Surg (2007) 11:1623–1627
DOI 10.1007/s11605-007-0329-2

Acute Pancreatitis and Pregnancy: A 10-Year Single Center Experience

Alejandro Hernandez · Maxim S. Petrov · David C. Brooks · Peter A. Banks · Stanley W. Ashley · Ali Tavakkolizadeh

Received: 23 May 2007 / Accepted: 5 September 2007 / Published online: 2 October 2007

Abstract
Background Acute pancreatitis in pregnancy is rare. We report our institutional therapeutic approaches to this disease and its effect on maternal and fetal outcomes.
Methods A retrospective review of medical records of pregnant women admitted to Brigham and Women's Hospital between 1996 and 2006.
Results Twenty-one patients, presenting with 34 episodes of acute pancreatitis were identified. Most attacks (56%) occurred in the second trimester. Twelve patients had biliary pancreatitis. Three had pancreatitis secondary to other causes and six had "undetermined" etiologies. Of those with biliary pancreatitis, six underwent cholecystectomy; in a third of these cases, initial conservative therapy had failed. The other six patients underwent endoscopic sphincterotomy (n=2) or conservative therapy (n=4). Fifty percent of the patients with biliary pancreatitis managed conservatively had a recurrent episode of pancreatitis vs none in the cholecystectomy group. There was no significant difference in length of hospital stay between the three treatment groups (cholecystectomy, sphincterotomy, and conservative therapy). No maternal deaths were observed; there were four preterm labors and one fetal loss.
Conclusion If treated conservatively, pregnant patients with biliary pancreatitis appear to have a high recurrence rate. Early surgical intervention is appropriate, safe, and does not increase the length of hospital stay.

Keywords Acute pancreatitis · Pregnancy · Cholecystectomy · Gallstones

Introduction

Pregnancy is associated with physiological changes that alter the presenting symptoms and signs of many disease processes. It also influences the diagnostic accuracy of many tests and alters the disease prognosis and outcome. The impact of the disease process on the outcome of pregnancy also adds to the challenges that physicians face when dealing with this patient population. Acute pancreatitis (AP) during pregnancy is a rare disease with a reported incidence of 1 case per 1,000–4,000 pregnancies.[1–4] Pancreatitis has generally been regarded as extremely dangerous to the mother and fetus with a few reports from the 1990s documenting some improvements in both maternal and fetal outcomes.[4–6] There are, however, no contemporary reports documenting the outcome of this disease process in pregnancy, during a period when the management of AP has undergone substantial changes. The introduction of laparoscopic cholecystectomy has reduced

This study was presented in part at the Digestive Disease Week 2007, Washington, DC.

A. Hernandez · M. S. Petrov · D. C. Brooks · S. W. Ashley · A. Tavakkolizadeh (✉)
Department of Surgery, Brigham and Women's Hospital,
Harvard Medical School,
75 Francis Street,
Boston, MA 02115, USA
e-mail: atavakkoli@partners.org

P. A. Banks
Department of Medicine, Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA, USA

the morbidity of surgical intervention in those with biliary pancreatitis, even in high-risk patients such as those pregnant. In addition, there have also been reports of the safe application of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) in pregnant patients.[7–10]

There are no contemporary reports of the overall impact of these procedures on the management of AP in the pregnant patient. The aim of the present study is to provide a current and comprehensive analysis of a single center's experience with AP in the setting of pregnancy.

Methods

The study was approved by the Brigham and Women's Hospital Committee for the Protection of Human Subjects. Hospital charts and computerized medical records were reviewed for every pregnant woman with AP consecutively admitted to Brigham and Women's Hospital (Boston, MA) from January 1, 1996 through January 1, 2006. The search was confined to patients with the International Classification of Disease-9 (ICD-9) code for AP (ICD:577.0) while pregnant, using a computerized patient database. Those patients with AP in their puerperium period were excluded. Trimester categorization was defined based on the weeks of gestational age, as first (1–12 weeks), second (13–28 weeks), and third (29 weeks to delivery).

Records were reviewed for patient's age, gestational age, obstetrical risks factors, etiology of AP, diagnostic procedures, management, length of stay (LOS), and maternal outcomes. Available birth records were evaluated for fetal outcomes together with birth weights. Severity of AP was categorized as defined by the Atlanta criteria.[11]

The data analysis was performed using the SPSS® 13.0 software package (SPSS, Chicago, IL, USA). Data are expressed as the mean±SD. Comparisons were made between groups using the ANOVA with post hoc analysis. A p value of <0.05 was taken as significant.

Results

Demographics

A total of 21 pregnant patients were identified that met the inclusion criteria, representing a total of 34 episodes of AP. The total number of deliveries in our hospital during the study period was 93,440, which estimates the incidence of AP in pregnancy at 0.02%, or 1 in 4,449 pregnancies.

The age ranged from 18 to 40 years with a mean of 27.6±5.6 years. The mean gestational age was 26.3±7.8 weeks with most of the episodes occurring in the second trimester (Table 1). Seven patients (33%) experienced two to five recurrences during the same pregnancy. All patients had mild AP with no patient scoring greater than eight points on the APACHE score.

Table 1 Trimester Distribution of Episodes of Acute Pancreatitis

Trimester (*N*; %)	Age, years (mean±SD)	GA, weeks (mean±SD)	LOS, days (mean±SD)
1st (2; 6)	30±1.4	6±1.4	6±1.4
2nd (19; 56)	28.1±5.3	23.5±4.1	5.9±4.9
3rd (13; 38)	26.5±6.3	33.4±2.4	4.3±2.4
Total (34; 100)	27.6±5.6	26.3±7.8	5.3±4.0

GA: gestational age, *LOS*: length of stay, *N*: episodes

Etiology

Abdominal ultrasonography (US) was done in 20 of the patients (95%). Biliary AP (B-AP), defined as the presence of gallstones or sludge in the biliary tree or the gallbladder, was the most common etiology, and identified in 12 subjects (57%) (Table 2). Three patients presented with AP secondary to other causes: alcoholic, cystic fibrosis, and pancreatic divisum. The remaining six patients fell in the "undetermined" group. These patients had negative US and no other etiological reasons for AP. In this group, one patient had a total of seven episodes of AP during two separate pregnancies. This patient had a cholecystectomy after her initial episode of AP, as her abdominal ultrasound findings were consistent with biliary disease and chronic cholecystitis; nevertheless, she was placed in our "undetermined" group, as cholecystectomy did not resolve her symptoms and a subsequent ERCP did not identify any abnormalities. She experienced five episodes during her first pregnancy and, 8 years later, presented with two more episodes during a second pregnancy.

Management

Several patients underwent additional diagnostic imaging. Two patients had CT scans, one had a magnetic resonance cholangiopancreatography (MRCP), and five patients underwent an ERCP under fluoroscopy including two therapeutic sphincterotomies. During the ERCP examinations, the pelvis of all patients was lead-shielded to reduce radiation to the fetus. Indications for ERCP included US findings of a dilated pancreatic duct, atypical common bile duct (CBD) stones, and the possibility of a secondary process (a tumor or ecstasies), as well as increases in total bilirubin and CBD size suggesting the possibility of obstructing CBD stones. No procedure-related complications were seen during or after the procedure.

Table 2 Etiology of Acute Pancreatitis

Etiology	Age, years (mean±SD)	Patients, *n* (%)	Episodes, *N* (%)	Trimester (*N*)		
				First	Second	Third
B-AP	25.4±4.3	12 (57)	16 (47)	–	10	6
Undetermined	29.8±6.3	6 (29)	14 (41)	2	8	4
Others	28.5±5.1	3 (14)	4 (12)	–	1	3

B-AP: biliary acute pancreatitis, *N*: episodes

All patients with AP of unknown etiology and those with nonbiliary etiology (n=9, 43%) underwent conservative management (CM) that consisted of bowel rest, intravenous fluid hydration, and analgesia. The mean LOS in this group was 5.3±3.4 days and the mean nil per os (NPO) duration was 3±1.9 days with one patient requiring total parenteral nutrition (TPN).

Management in the B-AP group included cholecystectomy (CCY) in six patients, ERCP with endoscopic sphincterotomy (ES) in two patients, or CM in four patients (Table 3). All CCY were performed laparoscopically, except in one patient. There were no postoperative complications. The recurrence rate in patients with B-AP who underwent CCY was 0%, whereas in the CM group, there was a 50% recurrence rate, all requiring readmission. In a third of the cases that had CCY, conservative management was pursued first but failed. The mean LOS in the B-AP group was 5.3±4.7 days with no significant difference between the CCY, ERCP+ES, and CM groups (7.8±6.9 vs 3.6±2 vs 5.0±1.4 days, respectively, p>0.05) (Table 3). One patient required TPN, however, the remaining patients were restarted on oral feeds after 3.8±3.2 days of NPO. Of note, the mean LOS in the CCY was increased mainly because of two patients who were in the hospital for 10 and 21 days. Neither had surgical complications, but were kept in the hospital because of obstetric issues.

Fetal and Maternal Outcomes

There were no maternal deaths. Six patients with AP had high risk pregnancies because of advanced age (older than 35 years, n=2), diabetes mellitus (n=1), gestational diabetes (n=1), multiple gestation (n=2), and chronic hypertension (n=1). Four preterm labors were identified; two were twin pregnancies that presented with AP at 28 and 33 weeks of gestation and were delivered at 36 and 34 weeks, respectively. The other two women with preterm labor experienced AP at 28 and 32 weeks and were delivered at 28 and 35 weeks, respectively. All these four patients had been treated conservatively. One fetal loss was found. This patient belonged to the B-AP group and was treated conservatively. Severe oligohydramnios and placental insufficiency was reported as the cause.

Available perinatal records of patients with B-AP were reviewed (n=8), showing no significant difference in birth weights between patients in the various treatment groups (CCY vs ES vs CM).

Discussion

The present study confirms that AP remains a rare disease in pregnancy. Of the 93,440 deliveries performed at our institution during the study period, we identified only 21 patients with AP (1 in 4,449 pregnancies) giving it an incidence of 0.02%, which is in accordance with previous series.[1–4] In our experience, more than a half of the events (56%) presented in the second trimester, contrary to previous studies, which have shown an increased incidence with increasing gestational age.[2,4,12]

Only a few groups have studied AP in this patient population. The first description of the disease is attributed

Table 3 Management of Biliary Acute Pancreatitis

Management	Patients, *n* (%)	Trimester (patients)			Recurrence rate	LOS (mean±SD)
		First	Second	Third		
CCY	6 (50)	–	5	1	0%[a]	7.8±6.9
CM	4 (33)	–	2	2	50%	3.6±2
ERCP+ES	2 (17)	–	1	1	–[b]	5.0±1.4

CCY: cholecystectomy, *CM*: conservative management, *ERCP+ES*: endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy, *LOS*: length of stay

[a] Follow-up rate 67%.

[b] Patients in this group were lost to follow-up.

to Schmitt and Wien in 1818 and later,[12] several old literature reviews collated the outcome of this disease in pregnancy.[5,12–14] Most of these studies, however, included patients with AP during pregnancy as well as the first 6 postpartum weeks. The inclusion of the time after delivery reflects an initial hypothesis for an etiological relationship between physiological changes of pregnancy and AP. However, the Mayo Clinic study suggested that in most cases it is not pregnancy per se,[15] but the presence of gallstones that is directly related to pregnancy-associated pancreatitis. It is now believed that the passing of biliary sludge (microscopic crystals) through the ampulla of Vater can cause a mechanical obstruction in a similar way as gallstones that may lead to an episode of AP. Biliary sludge and gallstones form in up to 31% and 3% of pregnant women, respectively, with the sludge frequently resolving postpartum.[16–18] In our study, 57% of the patients had B-AP, which is in line with the rate of 70% reported by Ramin et al.[4] Sex steroid hormones, increased during pregnancy, are thought to be the cause for bile lithogenicity and predisposition to gallstones. These hormonal changes begin with an increase in estradiol after conception, followed by a rise in progesterone around the tenth week of gestation. These changes result in smooth muscle relaxation, bile stasis and reduced gallbladder motility.[19] In our study, there were no cases of B-AP in the first trimester, a reflection of the time required for the described physiological changes to occur, and possibly in part because of the relatively small number of patients in our study.

Initial reviews of AP in pregnancy reported maternal and fetal mortality rates as high as 20% and 50%, respectively.[2,4,5,12,14,20] These studies are dated and their relevance to current practice are unknown. We observed no maternal mortality and only one fetal loss (4.7%), compatible with more recent publications. These improvements likely reflect the development of rapid enzyme assays leading to earlier diagnosis, as well as improvements in both supportive and intensive care. High perinatal mortality rates described in earlier series reflect neonatal deaths after preterm delivery. The marked reduction in perinatal mortality described in more recent series reveal improvements in neonatal intensive care.[2,4,6]

Identification of a biliary etiology for AP is important because recurrent episodes will occur in one-third to two-thirds of these patients, unless gallstones are removed.[21–23] In our B-AP group, 50% of those with conservative management had a recurrent episode of AP during the same pregnancy. This is similar to Swisher et al.[6] who noted a relapse rate of 70% in pregnant patients with gallstone-induced AP. These numbers are in line with other symptoms of gallstones, as identified by Dixon et al.[24] who found that 58% of all pregnant women with biliary colic relapsed before delivery.

Despite initial concerns, pregnancy is not a contraindication to laparoscopic surgery,[25–27] and it has been associated with good maternal and fetal outcomes. The occurrence of premature labor or fetal death appears to be related to the underlying pathology, and independent of the laparoscopic intervention.[28] Our data would suggest that laparoscopic cholecystectomy during the second and third trimesters of pregnancy is safe and that this therapeutic approach for patients with B-AP prevents recurrent attacks without increasing morbidity.

Another area of discussion is the safety of ERCP in pregnancy. Tham et al.[29] reported their experience with ERCP in pregnancy (15 patients over 5 years) with fetal radiation dose measurement. The authors showed that the fetal radiation dose could be reduced to a level less than that considered to be teratogenic. By limiting fluoroscopy time, shielding the pelvis and fetus with lead, and avoiding direct x-ray films, the fetal radiation dose can be reduced to far below the maximum permissible doses. In our study, only patients in the second or third trimester had an ERCP with no cases in the first trimester, when the fetus has maximal sensitivity to radiation and hence carcinogenic and teratogenic effects. Because of ongoing concerns for radiation in pregnancy, alternative methods for evaluating the biliary tree such as MRCP and endoscopic ultrasonography (EUS) should be first line choices for diagnostic evaluations.[30] A recent trial comparing EUS with ERCP included 140 nonpregnant patients with AP. In this study, Liu et al.[31] showed that EUS could safely replace diagnostic ERCP in patients with B-AP.

The role of therapeutic ES in the management of pregnant patients with B-AP continues to be controversial. This approach would prophylactically prevent AP attacks by facilitating the passage of potential stones from the gallbladder through the papilla in patients without bile duct stones. In a small series, Barthel et al.[9] reported three pregnant patients with B-AP where ES was performed without demonstrated choledocholithiasis and found that there was no recurrence of pancreatitis in any of the patients. Furthermore, Tham et al.[29] considered ES as an alternative to CCY in pregnancy to prevent recurrent pancreatitis. Further studies are needed to define the role and efficacy of prophylactic and therapeutic ES in preventing recurrent episodes of B-AP in pregnancy and to compare the outcomes with those of laparoscopic CCY. In our series, both patients who underwent ES were lost to follow-up.

Cost of treatment is an important issue when considering therapeutic options. Although we were unable to do an accurate cost analysis, it has been documented that two-thirds of the cost of medical treatment is attributable to hospitalization.[32] Early interventions are preferable if they reduce the length of hospitalization. Therefore, in pregnant

patients with B-AP, based on the lack of significant difference in the initial length of stay, but the reduction in recurrence rates, early surgical intervention should reduce the overall hospitalization needs and costs.

One of the limitations of our study is the small size of patients used for analysis, and the loss to follow-up of patients treated with ERCP+ES. The small number is, however, a reflection of the low incidence of this disease, and the series presented is one of the largest patient cohorts with this diagnosis. Thus, based on our data, we can conclude that pregnant patients with B-AP appear to have a high recurrence rate. Early intervention in the form of laparoscopic CCY is appropriate and safe. This approach is likely to prevent recurrences and may be cost-effective.

References

1. McKay AJ, O'Neill J, Imrie CW. Pancreatitis, pregnancy and gallstones. Br J Obstet Gynaecol 1980;87:47–50.
2. Ramin KD, Ramin SM, Richey SD, Cunningham FG. Acute pancreatitis in pregnancy. Am J Obstet Gynecol 1995;173:187–191.
3. Dreiling DA, Bordalo O, Rosenberg V, Rudick J. Pregnancy and pancreatitis. Am J Gastroenterol 1975;64:23–25.
4. Ramin KD, Ramsey PS. Disease of the gallbladder and pancreas in pregnancy. Obstet Gynecol Clin North Am 2001;28:571–580.
5. Corlett RC, Mishell DR. Pancreatitis in pregnancy. Am J Obstet Gynecol 1972;113:281–290.
6. Swisher SG, Hunt KK, Schmit PJ, Hiyama DT, Bennion RS, Thompson JE. Management of pancreatitis complicating pregnancy. Am Surg 1994;60:759–762.
7. Jamidar PA, Beck GJ, Hoffman BJ, Lehman GA, Hawes RH, Agrawal RM, Ashok PS, Ravi TJ, Cunningham JT, Troiano F, Sherman S, Brodmerkel GJ. Endoscopic retrograde cholangiopancreatography in pregnancy. Am J Gastroenterol 1995;90:1263–1267.
8. May GR, Shaffer EH. Should elective endoscopic sphincterotomy replace cholecystectomy for the treatment of high-risk patients with gallstone pancreatitis? J Clin Gastroenterol 1991;13:125–128.
9. Barthel JS, Chowdhury T, Miedema BW. Endoscopic sphincterotomy for the treatment of gallstone pancreatitis during pregnancy. Surg Endosc 1998;12:394–399.
10. Kahaleh M, Hartwell GD, Arseneau KO, Pajewski TN, Mullick T, Isin G, Agarwal S, Yeaton P. Safety and efficacy of ERCP in pregnancy. Gastrointest Endosc 2004;60:287–292.
11. Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11–13, 1992. Arch Surg 1993;128:586–590.
12. Wilkinson EJ. Acute pancreatitis in pregnancy: A review of 98 cases and a report of 8 new cases. Obstet Gynecol Surv 1973;28:281–303.
13. Langmade CF, Edmondson HA. Acute pancreatitis during pregnancy and the postpartum period; a report of nine cases. Surg Gynecol Obstet 1951;92:43–52.
14. Montgomery WH, Miller FC. Pancreatitis and pregnancy. Obstet Gynecol 1970;35:658–664.
15. Maringhini A, Lankisch MR, Zinsmeister AR, Melton LJ 3rd, DiMagno EP. Acute pancreatitis in the postpartum period: A population-based case-control study. Mayo Clin Proc 2000;75:361–364.
16. Ko CW. Risk factors for gallstone-related hospitalization during pregnancy and the postpartum. Am J Gastroenterol 2006;101:2263–2268.
17. Maringhini A, Ciambra M, Baccelliere P, Raimondo M, Orlando A, Tine F, Grasso R, Randazzo MA, Barresi L, Gullo D, Musico M, Pagliaro L. Biliary sludge and gallstones in pregnancy: Incidence, risk factors, and natural history. Ann Intern Med 1993;119:116–120.
18. Valdivieso V, Covarrubias C, Siegel F, Cruz F. Pregnancy and cholelithiasis: Pathogenesis and natural course of gallstones diagnosed in early puerperium. Hepatology 1993;17:1–4.
19. Menees S, Elta G. Endoscopic retrograde cholangiopancreatography during pregnancy. Gastrointest Endosc Clin N Am 2006;16:41–57.
20. Scott LD. Gallstone disease and pancreatitis in pregnancy. Gastroenterol Clin North Am 1992;21:803–815.
21. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–2400.
22. Mayer AD, McMahon MJ, Benson EA, Axon AT. Operations upon the biliary tract in patients with acute pancreatitis: Aims, indications and timing. Ann R Coll Surg Engl 1984;66:179–183.
23. Paloyan D, Simonowitz D, Skinner DB. The timing of biliary tract operations in patients with pancreatitis associated with gallstones. Surg Gynecol Obstet 1975;141:737–739.
24. Dixon NP, Faddis DM, Silberman H. Aggressive management of cholecystitis during pregnancy. Am J Surg 1987;154:292–294.
25. Gurbuz AT, Peetz ME. The acute abdomen in the pregnant patient. Is there a role for laparoscopy? Surg Endosc 1997;11:98–102.
26. Cohen-Kerem R, Railton C, Oren D, Lishner M, Koren G. Pregnancy outcome following non-obstetric surgical intervention. Am J Surg 2005;190:467–473.
27. Rollins MD, Chan KJ, Price RR. Laparoscopy for appendicitis and cholelithiasis during pregnancy: A new standard of care. Surg Endosc 2004;18:237–241.
28. Bisharah M, Tulandi T. Laparoscopic surgery in pregnancy. Clin Obstet Gynecol 2003;46:92–97.
29. Tham TC, Vandervoort J, Wong RC, Montes H, Roston AD, Slivka A, Ferrari AP, Lichtenstein DR, Van Dam J, Nawfel RD, Soetikno R, Carr-Locke DL. Safety of ERCP during pregnancy. Am J Gastroenterol 2003;98:308–311.
30. Makary MA, Duncan MD, Harmon JW, Freeswick PD, Bender JS, Bohlman M, Magnuson TH. The role of magnetic resonance cholangiography in the management of patients with gallstone pancreatitis. Ann Surg 2005;241:119–124.
31. Liu CL, Fan ST, Lo CM, Tso WK, Wong Y, Poon RT, Lam CM, Wong BC, Wong J. Comparison of early endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in the management of acute biliary pancreatitis: A prospective randomized study. Clin Gastroenterol Hepatol 2005;3:1238–1244.
32. Neoptolemos JP, Raraty M, Finch M, Sutton R. Acute pancreatitis: The substantial human and financial costs. Gut 1998;42:886–891.

J Gastrointest Surg (2007) 11:1628–1635
DOI 10.1007/s11605-007-0322-9

Is Autotaxin (ENPP2) the Link between Hepatitis C and Hepatocellular Cancer?

Amanda B. Cooper · Jianmin Wu · Debao Lu · Mary A. Maluccio

Received: 22 May 2007 / Accepted: 3 September 2007 / Published online: 25 September 2007

Abstract
Introduction Hepatitis C is the most significant risk factor for development of hepatocellular carcinoma. Inflammation, fibrosis, and liver cell proliferation may contribute to cancer development either through malignant hepatocyte transformation or extracellular matrix remodeling within the tumor microenvironment. The study objective was to investigate differences in gene expression between patients with Hepatitis C (± cancer) and normal that might explain the increased cancer risk.
Methods Liver tissue was collected from three patient groups: 1) healthy patients, 2) Hepatitis C patients without cancer, 3) patients with Hepatitis C and hepatocellular carcinoma. Microarray analysis was performed on samples from each group. Western blot and real-time polymerase chain reaction (PCR) analyses corroborated the microarray data. A p value of 0.05 was set as significant.
Results Microarray analysis showed overexpression of autotaxin in patients with cancer versus hepatitis patients or normal patients. Rho GTPase binding proteins (Cdc42s) associated with lysophosphatidic acid signaling were also overexpressed in cancer patients. Real-time polymerase chain reaction showed overexpression of several factors associated with autotaxin in patients with Hepatitis C (± cancer) versus normal patients.
Conclusions Patients with Hepatitis C and hepatocellular carcinoma show differential expression of various components of the autotaxin pathway versus normal patients. This merits further investigation in the context of early diagnosis.

Keywords Hepatitis C · Hepatocellular carcinoma · Autotaxin · ENPP2 · RhoA

Introduction

Autotaxin (ENPP2 or ATX) was initially characterized as an autocrine motility factor from A2058 melanoma cell-conditioned medium.[1] Since that time, ATX has been shown to be an important mediator in cancer cell growth and metastasis.[2–4] It is one of several members of the ecto-nucleotide pyrophosphatases/phosphodiesterases (E-NPPs) family. Current evidence suggests that E-NPPs have multiple related physiological purposes, including nucleotide recycling, modulation of purinergic receptor signaling, and stimulation of cell motility.[5] Aberrant expression of E-NNPs has been demonstrated in several pathologic processes including angiogenesis and tumor cell invasion and migration.

ATX displays intrinsic lysophospholipase activity through which it hydrolyzes lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA). LPA acts through

This work was presented as a plenary session at the SSAT annual meeting, May 22, 2007, Washington, DC.

A. B. Cooper · J. Wu · D. Lu · M. A. Maluccio
Department of General Surgery,
Indiana University School of Medicine,
Indianapolis, IN, USA

M. A. Maluccio (✉)
OPW 425, Indiana University School of Medicine,
1001 W 10th St,
Indianapolis, IN 46202, USA
e-mail: mmalucci@iupui.edu

the G-protein coupled EDG (endothelial differentiation gene) receptors to modulate cell motility (Fig. 1). EDG (aka LPA) receptor signal transduction is associated with a number of physiologic and pathophysiologic effects. In the context of cancer, the pathophysiologic effects of LPA include stress fiber formation, membrane ruffling, and lamellipodia formation,[4] which have been linked to the malignant phenotype. The combination of ATX expression with *ras* transformation has been shown to produce cells with greatly amplified tumorigenesis and metastatic potential compared to *ras*-transformed control cells.[6] Thus, ATX appears to augment cellular characteristics necessary for tumor aggressiveness.

The liver changes associated with chronic Hepatitis C infection progress in stages. Stage 0 is observed in patients with positive Hepatitis C serology, but no evidence of fibrosis within the liver. Stage 4 patients have clinical evidence of cirrhosis. When hepatocellular carcinoma (HCC) develops, it usually does so in the background of histological evidence of cirrhosis or stage 4 fibrosis. With this in mind, one would predict that there are measurable changes within the hepatitis-infected liver as the disease progresses from stage 0 to stage 4 fibrosis, and that these changes may account for the increase in cancer risk. Unfortunately, the mechanism behind hepatitis-associated cancer remains elusive.

Pathways in oxidative stress and DNA damage are a recurring theme in hepatitis-associated fibrosis, highlighting the central role the liver plays in nucleic acid metabolism. In light of this, purinergic pathways represent a target for investigation of potential biomarkers in hepatitis and hepatocellular carcinoma.

The objective of this study was to investigate differences in gene expression profiles between patients with Hepatitis C (with and without cancer) and normal patients that might explain the increased risk of developing HCC seen in patients with Hepatitis C.

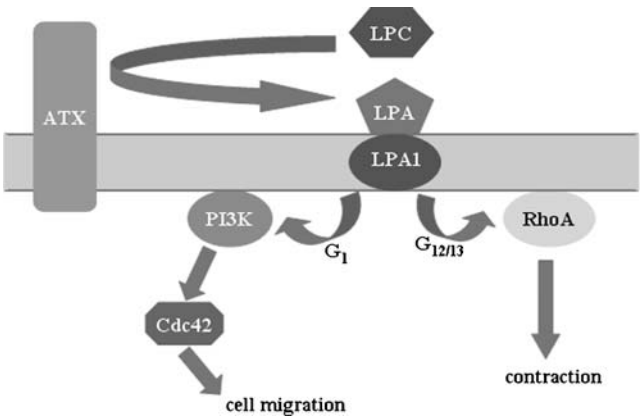


Figure 1 Simplified schematic of the Autotaxin signaling pathway.

Material and Methods

Human Tissue Resources Liver tissue was collected from Hepatitis C patients undergoing resection or liver transplantation. Normal control liver tissue was obtained from patients undergoing liver resection for non-hepatitis related diseases. The protocol for this tissue collection was approved by the Indiana University IRB. All samples were either flash-frozen in liquid nitrogen or placed in ribonucleic acid (RNA) stabilization fluid and stored at −80°C. Additional tissue was obtained from an established tissue bank. IRB authorization was obtained to analyze and present these data.

Microarray Studies Total RNA from liver samples was extracted using the Trizol method and the RNeasy kit (Qiagen, Valencia, CA). RNA integrity was evaluated using the Agilent system. Affymetrix human gene chip, HG-U133 microarray analysis was carried out using 20 μg of total RNA and focusing on purine metabolic pathways. Samples (six normal, six Hepatitis C without cancer, six Hepatitis C with HCC) were run in triplicate to assure accuracy. Only probe sets called "present" by MAS5 in at least half of the arrays were analyzed.

Real-Time PCR Total RNA was isolated from snap frozen human liver tissue using the RNeasy kit (Qiagen). RNA integrity and concentration were measured using the Nanodrop ND-1000 Spectrophotometer (Wilmington, DE). Total RNA from each sample (1 μg) was reverse transcribed for 10 min at 25°C, for 120 min at 37°C, for 30 sec at 85°C, and for 10 min at 4°C. Real-time PCR was performed starting with cDNA derived from 100 ng of total RNA, a 500-nM concentration of both forward and reverse primer, and a 200-nM concentration of probe in a final volume of 50 μL using TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA). Real-time PCR was run for 2 min at 50°C, for 10 min at 95°C, for 45 cycles of 15 sec at 95°C, and for 1 min at 60°C. Analysis of 18s ribosomal RNA was performed simultaneously using the TaqMan ribosomal RNA control kit (Applied Biosystems) to normalize gene expression. Table 1 shows the oligonucleotides used. The cycle threshold number (C_T) at which amplification entered the exponential phase was determined using Applied Biosystems' 7500 Sequence Detection System Software (v1.4, Applied Biosystems). Each sample (nine normal samples, nine Hepatitis C samples, and eight Hepatitis C with HCC samples) was run on a plate with corresponding 18s ribosomal RNA as the constitutively expressed gene. Expression of the target gene was calculated as the average of either duplicate or triplicate values with each sample normalized to its 18s rRNA internal control. Gene expression for each sample was

Table 1 Oligonucleotides Used for Real-Time PCR

Gene	Forward Primer (5′ to 3′)	Reverse Primer (5′ to 3′)	Probe (5′ to 3′)
ATX	TGCCGACAAGTGTGACGG	CCGGTGAGGCAGGATGAA	CCTCTCTCTGTGTCCTC
RhoA	GGCTGGACTCGGATTCGTT	CCATCACCAACAATCACCAGTT	CCTGAGCAATGGCTGCCATCCG
Cdc42	GTGGAGAACCATATACTCT TGGACTTT	TGTGGATAACTCAGCGGTCGTA	TGATACTGCAGGGCAAGAGGAT TATGACAGA
LPA1	CCCAATACTCGGAGACTGACTGT	CCGTCAGGCTGGTGTCAAT	CACATGGCTCCTTCGTCAGGGCC
LPA2	TGCCAGCATCGCATCAT	GGTAGCTAAAGGGTGGAGTCCAT	CTTCCCGAGAACGGCCACCCAC
LPA3	CTTGACTGCTTCCCTCACCAA	CGCATCCTCATGATTGACATG	TTGCTGGTTATCGCCGTGGAGAGG

compared relative to one normal sample and RQ values were calculated and displayed as fold change relative to normal.

Western Blot Analysis Total protein was isolated from snap-frozen human liver tissue using Tissue Extraction Reagent I (Biosource, Camarillo, CA) and a protease inhibitor cocktail (Sigma, St. Louis, MO). Fifty micrograms of total protein was loaded and separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) on a 5/10% gel. The proteins were then transferred to a 0.45-μm nitrocellulose membrane (Bio-Rad, Hercules, CA). EDG2 (LPA1) was detected with anti-EDG2 antibody (Orbigen, San Diego, CA) at a 1:1,000 concentration. Goat anti-rabbit HRP (Pierce, Rockford, IL) at a concentration of 1:1,000 was used as the secondary antibody. β-actin (Sigma) at 1:1,000 concentration was used to normalize the amount of protein loaded per well. Goat anti-mouse HRP (Pierce, Rockford, IL) at a concentration of 1:7,000 was used as the secondary antibody for β-actin. Protein bands were visualized using a peroxide/luminol kit (Pierce).

Statistical Analysis Statistical analyses were performed with GraphPad Prism 5 (San Diego, CA). Differences between groups were analyzed using ANOVA. Significance was set at a p value <0.05.

Results

Microarray Analysis of Liver Tissue

To identify gene expression differences between normal liver and hepatitis-infected liver, we compared mRNA samples prepared from the three clinical groups: normal, Hepatitis C patients without cancer, and Hepatitis C patients with hepatocellular carcinoma. We looked for genes that were differentially expressed more than 1.5-fold higher in hepatitis-infected liver compared to normal. The data values from the triplicate arrays were merged and analyzed using Genesifter software (VizX Labs, Seattle, WA). There were 4,686/5,4675 genes that were differentially expressed between the three clinical groups. KEGG pathways analysis showed that three genes within the purinergic pathway were upregulated in hepatitis patients compared to normal. Autotaxin was significantly upregulated in patients with hepatitis and HCC compared to normal (12,081 vs. 12,881 vs. 4,595 copies/μg total RNA respectively, p=0.01).

To evaluate molecular interactions associated with ATX expression, we analyzed the microarray data in the context of several associated genes, including RhoA, and Cdc42EP1, EP3, EP5 (Rho GTPase binding proteins), and Cdc42SE1 and SE2 peptides.

The guanosine triphosphatase Rho regulates remodeling of the actin cytoskeleton during cell morphogenesis and motility.[7] Activation of RhoA contributes to endothelial cell contraction, cell shape change, and increased endothelial permeability. Accumulating evidence suggests that RhoA overexpression contributes to human cancer development.[8,9] ATX exerts its effect through RhoA activation and therefore, we predicted that expression of RhoA within our tissue samples would parallel ATX. RhoA was highly expressed in liver tissue (21,500 copies/μg total RNA in normal samples) and was overexpressed in hepatitis-infected liver, both with and without HCC, compared to normal (p=0.009), similar to the pattern that we observed for ATX expression.

The Rho GTPase, Cdc42, regulates a wide variety of cellular activities, including the regulation and organization of the actin cytoskeleton, by its interaction with several downstream effector proteins (Cdc42EP1, EP3, and EP5), which have been shown to be responsible for pseudopodia formation.[9] In the context of cancer cell migration, the association between ATX, RhoA, and Cdc42 may represent the method by which cancer cells gain motility.[10] The Cdc42 binding proteins SPEC1 and SPEC 2 (Cdc42SE1 and SE2) modulate these regulatory activities and should parallel the expression of ATX. Comparing the three clinical groups, Cdc42EP1, EP3, and EP5 expression were all higher in patients with hepatitis, both with and without HCC, compared to normal (p=0.01, 0.009, and 0.001, respectively). In addition, Cdc42SE1 and SE2 were also

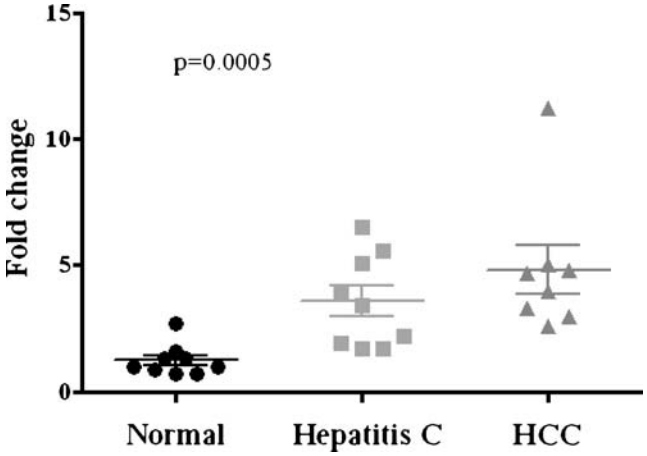


Figure 2 Fold change in Autotaxin mRNA expression for normal patients, patients with Hepatitis C, and patients with HCC as measured by real-time PCR. Data points represent individual samples. Lines represent median values for each group. Error bars represent the SEM.

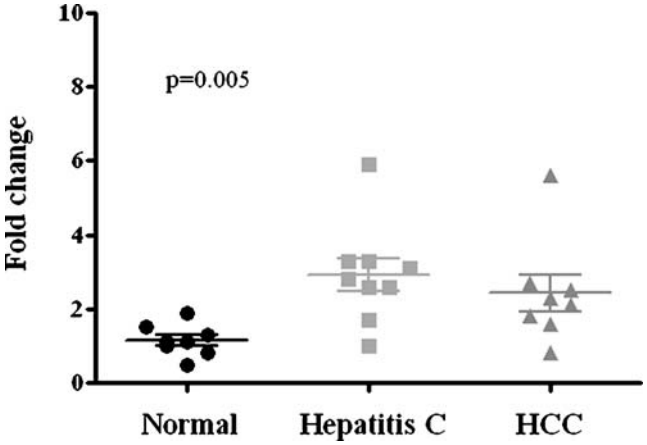


Figure 4 Fold change in Cdc42 mRNA expression for normal patients, patients with Hepatitis C, and patients with HCC as measured by real-time PCR. Data points represent individual samples. Lines represent median values for each group. Error bars represent the SEM.

overexpressed in patients with hepatitis and in patients with HCC (p=0.009, by analysis of variance [ANOVA]).

Real-time PCR Analysis of Liver Tissue

ATX

ATX expression within hepatitis-infected liver may provide an additional mechanism whereby the hepatocellular carcinoma cells are able to take advantage of the unique microenvironment induced by chronic inflammation. Real-time PCR analysis was performed on tissue from the three clinical groups: normal liver, Hepatitis C, and Hepatitis C with hepatocellular carcinoma (HCC). ATX was moderately expressed in normal liver tissue (average Ct value=24± 0.29). ATX was uniformally overexpressed in patients with Hepatitis C and patients with HCC, with an average 3.5-fold increase seen in patients with Hepatitis C and 4.8-fold increase in patients with hepatocellular carcinoma (p= 0.0005 by ANOVA Fig. 2).

RhoA

Locomotion in cellular migration involves reorganization of the actin cytoskeleton. The molecular control of actin filament assembly is dependent on the Rho family of small GTPases, particularly RhoA and Cdc42.[10] RhoA expression within liver cancer may provide the mechanism whereby tumor cells gain motility within the tumor microenvironment. RhoA was uniformally overexpressed in patients with HCC, with a 2.6-fold increase in RhoA expression compared to normal (p=0.003 ANOVA, Fig. 3). In general, elevated levels of RhoA expression correlated with elevated levels of ATX expression within each sample. For example, samples

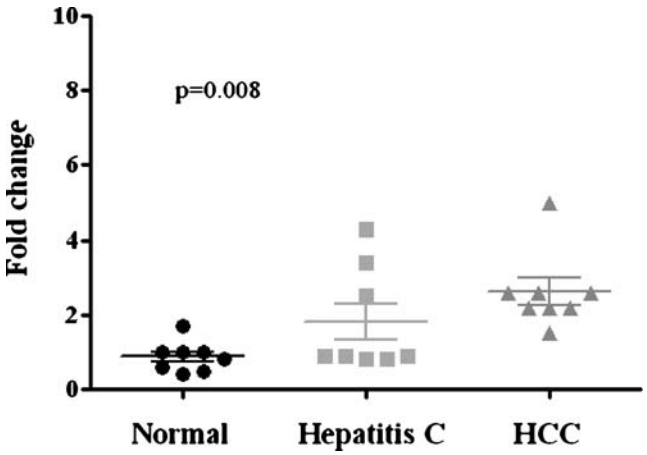


Figure 3 Fold change in RhoA mRNA expression for normal patients, patients with Hepatitis C, and patients with HCC as measured by real-time PCR. Data points represent individual samples. Lines represent median values for each group. Error bars represent the SEM.

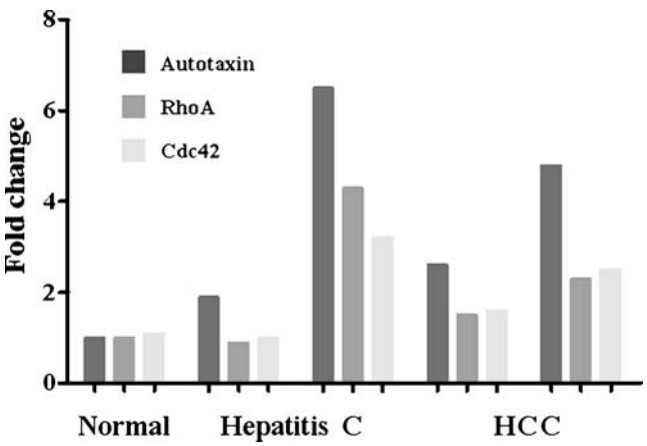


Figure 5 Correlation of expression of Autotaxin, RhoA, and Cdc42 expression for normal patients, patients with Hepatitis C, and patients with HCC. Levels of expression are expressed as fold-change in mRNA expression for each molecule.

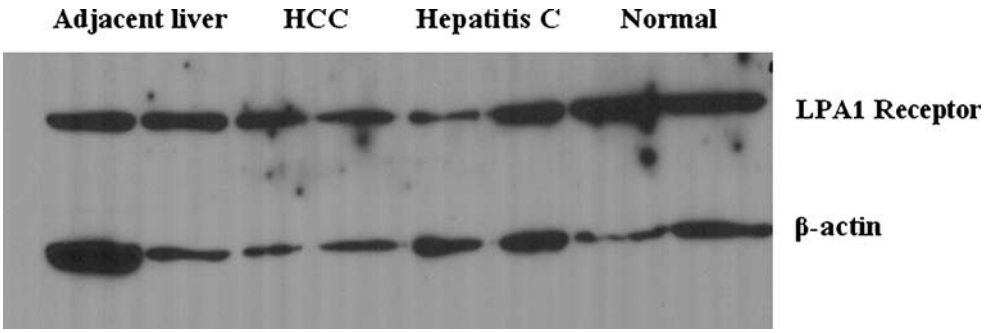


Figure 6 Western blot showing LPA_1 Receptor expression (with β-actin control) in normal patients, patients with Hepatitis C, and patients with HCC. Fifty micrograms of total protein was loaded per well.

with the highest level of ATX expression had the highest level of RhoA expression among the group.

Cdc42

As with ATX and RhoA, the downstream effector molecule Cdc42 was also overexpressed in patients with Hepatitis C and in patients with HCC, with an average 2.9-fold increase in Cdc42 expression in patients with Hepatitis C and 2.6-fold increase in expression in patients with HCC compared to normal (p=0.006, Fig. 4).

Although consistent overexpression of autotaxin, RhoA, and Cdc42 was not seen in all patients, overexpression of RhoA and Cdc42 did tend to correlate with overexpression of ATX (Fig. 5). In general, samples from patients with Hepatitis C or HCC which demonstrated at least a two-fold increase in expression of autotaxin mRNA expression also demonstrated at least a 1.5-fold increase in both RhoA and Cdc42.

Expression of LPA Receptors

Autotaxin exerts its effect through the production of lysophosphatidic acid (LPA). LPA interacts with at least three G-protein coupled transmembrane receptors, namely, LPA_1 (Edg2), LPA_2 (Edg4), and LPA_3 (Edg7). Expression of LPA receptors in tumors has not been fully characterized. Previous studies have found that malignant transformation results in aberrant expression of LPA receptors in ovarian cancer[11] and diffuse type gastric cancer,[12] suggesting that LPA receptor expression might also be an important event in the development of cancer within the high-risk liver. Western blot analysis was performed to evaluate the degree to which LPA_1 is expressed in representative samples from each clinical group. LPA_1 protein expression was observed in both normal and diseased liver, with variable expression in Hepatitis C patients, and in patients with hepatocellular carcinoma (Fig. 6).

Corroborative real-time PCR analysis of LPA_1, LPA_2, and LPA_3 expression confirmed the presence of LPA_1 in human liver with a 2.5-fold increase seen in patients with cancer compared to normal. This was not significantly different (p= 0.7, Fig. 7), which can be explained by the large amount of variability in expression within each group. Elevated levels of LPA_1 were observed in select samples from each clinical group, with the highest levels of LPA_1 expression observed in a patient with a poorly differentiated stage IIIb tumor

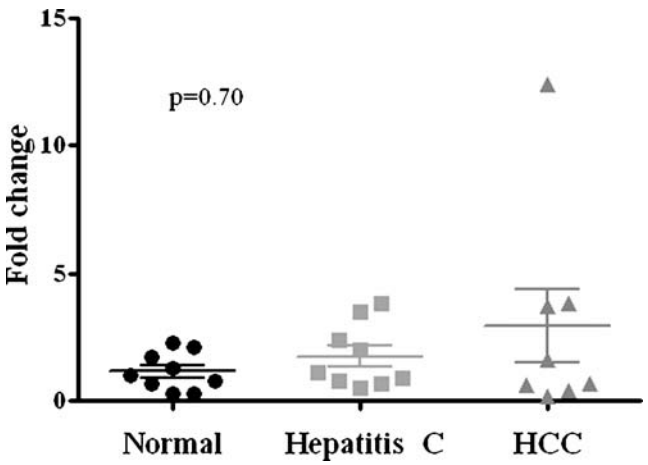


Figure 7 Fold change in LPA_1 mRNA expression for normal patients, patients with Hepatitis C and patients with HCC as measured by real-time PCR. Data points represent individual samples. Lines represent mean values for each group. Error bars represent the SEM.

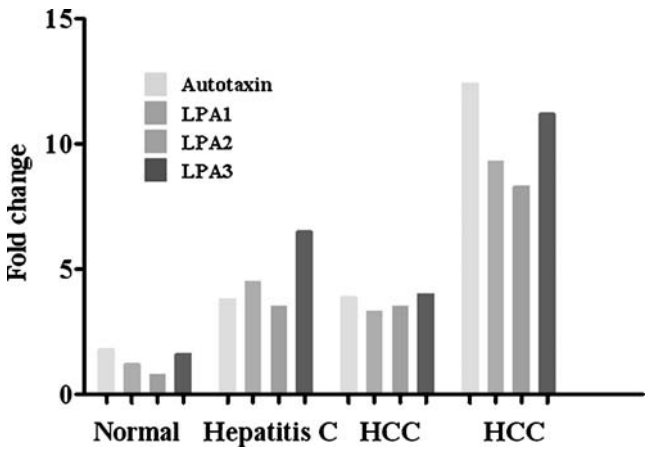


Figure 8 Correlation of expression of Autotaxin, LPA_1, LPA_2, and LPA_3 expression for normal patients, patients with Hepatitis C, and patients with HCC. Levels of expression are expressed as fold-change in mRNA expression for each molecule.

(12.4-fold higher than normal). There was no significant difference in LPA_2 or LPA_3 mRNA expression among the groups (data not shown). As with LPA_1 expression, elevated levels of LPA_2 and LPA_3 were observed in select samples from each clinical group, with the highest expression seen in samples with elevated LPA_1 levels.

Although levels of mRNA expression for the various LPA receptors correlated with one another, high ATX expression did not necessarily translate into enhanced LPA receptor expression. For example, several Hepatitis C patients had elevated ATX expression, but no significant increase in LPA receptor expression relative to control. However, essentially all the samples that demonstrated elevated levels of LPA receptor expression also had elevated levels of ATX expression (Fig. 8).

Discussion

Chronic inflammation in a disease like Hepatitis C is associated with disruption of the extracellular matrix within the liver environment and exposure of occult tumor cells to components in circulating plasma that might affect cell growth and invasion.

Contemporary series would suggest that 20% of patients with Hepatitis C will develop a clinically significant cancer with a 3% per year incidence of cancer seen in all Hepatitis C patients.[13] Why some patients with Hepatitis C develop cancer while others are somehow spared remains unknown.

The microarray analysis in this study confirmed that there are extraordinary differences in the genetic profiles of patients with hepatitis compared to a "normal" cohort. With an interest in evaluating pathways that are known to link inflammation to cancer, we were able to hone our analysis on more subtle differences between patients with and without cancer. ATX was one of very few genes that showed enhanced expression in cancer patients over their non-cancer bearing counterparts. In addition, ATX has been linked to cancer invasion and metastasis in other cancers, which made it an ideal candidate for further evaluation.

The real-time PCR analysis clarified the expression of not only ATX in Hepatitis-C-infected liver, but also highlighted the expression of other key elements involved in ATX-induced cell motility, namely, RhoA and Cdc42. We were able to show that there was a correlation between ATX expression and both RhoA and Cdc42 expression, such that anything higher than a twofold increase in ATX expression was associated with upregulation of other members of the pathway. This may suggest that a twofold increase in ATX expression represents a significant threshold for activation of the pathway and triggering of clinically significant changes; however, this will need further validation in prospective studies.

Although the results of the real-time PCR analyses for LPA receptors were not significantly higher for patients with either Hepatitis C or HCC, dramatic elevations were seen in select samples. All samples from either group that demonstrated notable elevations in expression of mRNA for the LPA_1, LPA_2, and LPA_3 receptors came from patients who also demonstrated at least twofold elevations in ATX expression. These dramatic elevations in LPA receptor expression were seen in relatively few samples, but did occur in samples from patients with more advanced tumors (T4 stage IIIb or N1 disease). This may suggest that the upregulation of LPA receptors either occurs later in the course of hepatocellular tumorigenesis or represents a more aggressive cancer phenotype. Data from a much larger sample of patients will be needed to confirm or refute this hypothesis.

There are certain limitations to this study: 1) The microarray data were based on highly selected samples to allow for comparison of homogeneous groups. Human tissue and human liver in particular is very heterogeneous and affected by both tissue-and patient-specific differences (i.e., smoking, alcohol, ischemic time). For the pathways we were particularly interested in, the microarray profiles for the samples within each group were all consistent. The real-time PCR data were performed on more heterogeneous samples because we wanted to determine if the measurement of this particular target, namely, autotaxin, would be applicable to a more diverse group of Hepatitis C patients. This explains the variability in gene expression levels within each group, although the significance of the observation remained. 2) The sample size is too small to draw broad conclusions about patient surveillance. The goal of this project was to identify potential biomarkers in high-risk patients. Although these findings suggest that this pathway may ultimately prove useful for patient surveillance, further validation with prospective studies is necessary to determine the utility of ATX as a biomarker for cancer risk.

The clinical group that seemed to be most variable was the one that included patients with Hepatitis C and no cancer. There are several possible explanations for this: 1) There is less correlation between ATX and the development of cancer than we would hope; 2) patients with elevated levels of ATX (1.5- to twofold) may have been censored (i.e., undergone resection or transplantation) before the development of a clinically detectable cancer in a liver that would have developed a cancer over time without intervention; or 3) patients with elevated ATX levels may have had occult cancer that was not recognized on pathology because of sampling error within such a large specimen. Only prospective analysis of patients under surveillance will help clarify these issues. What was clear from our data was that the handful of patients with very high ATX levels

had either large tumors (T4, stage IIIb) or evidence of vascular invasion/nodal involvement, which would be consistent with previously published data in patients with HCC.[14]

Conclusions

Patients with Hepatitis C and hepatocellular carcinoma show differential expression of various components of the autotaxin pathway versus normal patients. Gene expression was most variable in patients with Hepatitis C and no cancer. With established surveillance programs, the significance of low vs. high ATX in these patients may allow us to stratify patients into low vs. high cancer risk.

Conflicts of Interest/Disclosures There are no conflicts of interest or financial disclosures relevant to this paper for any of the authors.

Grant Support This project was supported by a grant from the NIH (K22-CA111393).

References

1. Stracke ML, Krutzsch HC, Unsworth EJ, Arestad A, Cioce V, Schiffmann E, Liotta LA. Identification, purification, and partial sequence analysis of autotaxin, a novel motility-stimulating protein. J Biol Chem 1992;267(4):2524–2529.
2. Kishi Y, Okudaira S, Tanaka M, Hama K, Shida D, Kitayama J, Yamori T, Aoki J, Fujimaki T, Arai H. Autotaxin is overexpressed in glioblastoma multiform and contributes to cell motility of glioblastoma by converting lysophosphatidylcholine to lysophosphatidic acid. J Biol Chem 2006;281(25):17492–17500.
3. Black EJ, Clair T, Delrow J, Neiman P, Gillespie DAF. Microarray analysis identifies Autotaxin, a tumour cell motility and angiogenic factor with lysophospholipase D activity, as a specific target of cell transformation by c-Jun. Oncogene 2004;23(13):2357–2366.
4. Hama KAJ, Fukaya M, Kishi Y, Sakai T, Suzuki R, Ohta H, Yamori T, Watanabe M, Chun J, Arai H. Lysophosphatidic acid and autotaxin stimulate cell motility of neoplastic and non-neoplastic cells through LPA1. J Biol Chem 2004;279(17):17634–17639.
5. Goding JW, Grobben B, Slegers H. Physiological and pathophysiological functions of the ecto-nucleotide pyrophosphatase/phosphodiesterase family. Biochim Biophys Acta 2003;1638(1):1–19.
6. Nam SWCT, Campo CK, Lee HY, Liotta LA, Stracke ML. Autotaxin (ATX), a potent tumor motogen, augments invasive and metastatic potential of *ras*-transformed cells. Oncogene 2000;19:241–247.
7. Moolenaar WH. Bioactive lysophospholipids and their G protein-coupled receptors. Exp Cell Res 1999;253(1):230–238.
8. Fukui K, Tamura S, Wada A, Kamada Y, Sawai Y, Imanaka K, Kudara T, Shimomura I, Hayashi N. Expression and prognostic role of RhoA GTPases in hepatocellular carcinoma. J Cancer Res Clin Oncol 2006;132(10):627–633.
9. Stam JC, Michiels F, van der Kammen RA, Moolenaar WH, Collard JG. Invasion of T-lymphoma cells: Cooperation between Rho family GTPases and lysophospholipid receptor signaling. EMBO J 1998;17(14):4066–4074.
10. Moolenaar WH, van Meeteren LA, Giepmans BNG. The ins and outs of lysophosphatidic acid signaling. Bioessays 2004;26(8):870–881.
11. Xu YSZ, Wiper DW, Wu M, Morton RE, Elson P, Kennedy AW, Belinson J, Markman M, Casey G. Lysophosphatidic Acid as a Potential Biomarker for Ovarian and Other Gynecologic Cancers. JAMA 1998;280(8):719–723.
12. Yamashita H, Kitayama J, Shida D, Ishikawa M, Hama K, Aoki J, Arai H, Nagawa H. Differential expression of lysophosphatidic acid receptor-2 in intestinal and diffuse type gastric cancer. J Surg Oncol 2006;93(1):30–35.
13. Di Bisceglie AM, Simpson LH, Lotze MT, Hoofnagle JH, Di Bisceglie AM, Simpson LH, Lotze MT, Hoofnagle JH. Development of hepatocellular carcinoma among patients with chronic liver disease due to hepatitis C viral infection. J Clin Gastroenterol 1994;19(3):222–226.
14. Zhang G, Zhao Z, Xu S, Ni L, Wang X. Expression of autotaxin mRNA in human hepatocellular carcinoma. Chin Med J 1999;112(4):330–332.

DISCUSSION

Paul Kwo, M.D. (Indianapolis, IN): Congratulations, Dr. Cooper and Dr. Maluccio. The relationship of hepatitis C and hepatocellular carcinoma, those of you who are practicing know, is one of the largest clinical conundrums we face, with a half million people in the United States with hepatitis C-related cirrhosis. Alpha fetoprotein, which is the one tumor marker that we historically have used (yet frustrates us), is no longer recommended as a screening test. Whereas many of us still use it to some degree in practice, your work here with autotaxin, if confirmed in larger studies, I think would be a major advance in the ability to have serum markers to screen for hepatoma.

One of the issues is that with hepatitis C, there is a diverse range of disease, ranging from little fibrosis to a large amount of fibrosis or cirrhosis, and indeed I think this may explain why you had so much variability in the hepatitis C group compared to the hepatocellular carcinoma group, where I think the fibrosis distribution is relatively uniform, that is, they are all stage 3 or stage 4 fibrosis, at least advanced fibrosis. My questions are the following.

As you move forward with your future studies, how do you think are you going to need to stratify for not only fibrosis but perhaps for other diseases? For instance, hepatitis C patients drink, they are heavy, they smoke, and all of these factors I think are going to have to be differentiated as you try and differentiate the role of autotoxin in hepatoma screening. And lastly, if you can sort this out and find a role for this, do you plan on pursuing the role of autotaxin in other diseases? For instance, hepatitis C therapies will probably be largely

refined in the next 10 years. Steatosis and cirrhosis caused by obesity is the next big epidemic that we are all going to be dealing with, and I would think if the role of autotoxin be defined in one disease such as hepatitis C, it would be nice to determine its role in other chronic liver diseases.

Amanda Cooper, M.D. (Indianapolis, IN): I agree. I think definitely things that we know to be significant predictors of future development of hepatocellular carcinoma such as degree of fibrosis are certainly things that we would like to stratify in future studies with larger sample sizes. In addition, we do hope in future studies to be able to look at patients with NASH and see if we see these same changes in levels of expression. Hepatitis C happened to be the most convenient large sample size that we had readily available.

Dr. Kwo: Fatty liver is rapidly catching up.

Dr. Cooper: Yes.

J Gastrointest Surg (2007) 11:1636–1646
DOI 10.1007/s11605-007-0315-8

Racial and Geographic Disparities in the Utilization of Surgical Therapy for Hepatocellular Carcinoma

Christopher J. Sonnenday · Justin B. Dimick · Richard D. Schulick · Michael A. Choti

Received: 20 May 2007 / Accepted: 24 August 2007 / Published online: 3 October 2007

Abstract The incidence of hepatocellular carcinoma (HCC) continues to increase, a trend that will likely continue because of the rising prevalence of chronic hepatitis C infection. This study sought to determine the recent patterns of utilization of surgical therapy (hepatectomy, ablation, or liver transplantation) for HCC from the Surveillance, Epidemiology, and End Results national cancer registry. Data were extracted for 16,121 patients with HCC diagnosed between 1998 and 2004. Twenty-three percent of patients underwent surgical therapy (9.5% resection, 7.8% ablation, 6% transplant); the proportion of patients treated with surgical therapy increased ~9% over the study period. On multivariate analysis, female sex, younger age, and smaller solitary tumors were associated with increased utilization of surgical therapy. Blacks and Hispanics were 24–27% less likely to receive surgical therapy than white individuals ($P<0.001$). Racial and geographic disparities persisted despite the adjustment for Health Service Area and limitation of the cohort to small localized HCC. Blacks were especially disadvantaged in the utilization of liver transplant for small HCC (OR=0.42, $P<0.001$). Further investigation to understand the etiology of these profound racial and geographic disparities is essential to ensure equitable provision of surgical therapies, which provide the only potentially curative treatments for HCC.

Keywords Hepatocellular cancer · Racial disparity · Geographic disparity · Liver transplantation · Surgery

Presented at the 48th Annual Meeting of the Society of Surgery of the Alimentary Tract, Digestive Disease Week 2007, Washington, DC.

C. J. Sonnenday · J. B. Dimick
The Department of Surgery,
The University of Michigan,
Ann Arbor, MI, USA

R. D. Schulick · M. A. Choti
The Department of Surgery,
The Johns Hopkins University School of Medicine,
Baltimore, MD, USA

C. J. Sonnenday (✉)
The University of Michigan Medical Center,
1500 East Medical Center Dr., TC 2926,
Ann Arbor, MI 48109, USA
e-mail: csonnend@umich.edu

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents one of the most prevalent forms of cancer worldwide, with greater than 500,000 incident cases estimated for each of the last 7 years.[1] In the USA, the incidence of HCC has been noted to be increasing rapidly,[2] as the age-adjusted incidence has increased from 2.6 per 100,000 in 1975 to 6.1 per 100,000 in 2004.[3] The increase in incident cases is likely contributed to in part by improved diagnostic techniques, increased recognition of HCC as a public health problem, and HCC screening protocols for patients with chronic liver disease. However, certainly, the most commonly assigned reason for the increased incidence of HCC is the associated rise in the prevalence of chronic hepatitis C infection, a pronounced risk factor for hepatocellular carcinogenesis.[4,5]

The past decade has seen a significant expansion in the therapies available for HCC.[6] No curative systemic chemotherapy or radiotherapy exists for HCC. Surgical resection remains a primary mode of therapy for eligible patients, although it is offered to a minority of patients because of

advanced disease or associated chronic liver disease.[7,8] Ablative therapies, including percutaneous injection of alcohol or acetic acid, cryotherapy, and radiofrequency ablation (RFA), have become more available and can provide good results in patients with relatively small volume disease.[9–11] Most notably, orthotopic liver transplantation (OLT) has gained acceptance in recent years as the preferred therapy for small HCC, particularly in patients with chronic liver disease.[12,13] Mazzaferro et al. demonstrated that patients with solitary HCC less than 5 cm or no more than three tumors each less than 3 cm had long-term survival similar to patients with nonmalignant indications for OLT, establishing the Milan criteria for transplantation of HCC.[14] These criteria have been adopted by the United Network for Organ Sharing and currently serve to give patients with HCC that meet these criteria additional points in the US liver allocation system such that they can be transplanted more efficiently.

Despite this expansion of therapies for HCC, little published data exist on the application of these therapies on a national basis. To better understand the utilization of surgical therapy for HCC, a retrospective cohort study was performed using data from the Surveillance, Epidemiology, and End Results (SEER) national cancer registry as maintained by the National Cancer Institute. The SEER registry is a collection of local and regional cancer registries selected to create a representative sampling of the USA, designed to include rural and urban areas with diverse populations based upon race and socioeconomic profile. This data source allows analysis of the interaction of demographic, geographic, socioeconomic, and tumor factors that influence the utilization of therapy for HCC.

Materials and Methods

Primary Data Source

A retrospective cohort study was performed by extracting data from the SEER Program (www.seer.cancer.gov) Limited-Use Data (1973–2004), National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based upon the November 2006 submission. All patients age 18 or older with a diagnosis of HCC (SEER site recode 220) were included in the study cohort. To establish a database reflecting recent patterns of therapy, only patients diagnosed between 1998 and 2004 were included in the study. Individual patients with missing data for age, race, tumor characteristics, or the use of surgical therapy were excluded from the study. Patients recorded as having metastatic disease were also excluded.

The study was deemed by the Johns Hopkins Medicine Institutional Review Board as appropriate for exception from Institutional Review Board oversight, as no personal identifiers were used among the registry data.

The SEER database is linked to information about an individual subject's county of residence as derived from the 2000 Census data. County attribute variables are calculated using the Census 2000 SF files (technical documentation available at www.census.gov/main/www/cen2000.html). In the 2007 release, SEER data are also linked to the health service area (HSA) of residence for each individual. HSAs are individual counties or grouped adjacent counties as delineated by the National Center for Health Statistics, Centers for Disease Control.[15] Each HSA is defined as a confined region in which Medicare patients seek inpatient hospital care, i.e., they are more likely to stay in that area for hospital care rather than travel to another area.[16] These areas are considered to be representative of where patients seek the majority of their medical care, with more accuracy than county- or state-level analysis.[17] Individual HSAs were not identified in reporting the results of this study as the intention of the study was to investigate the degree of variation in treatment of HCC among relatively confined geographic units, rather than to single out individual communities. The relatively low number of cases in some HSAs also created the possibility of identifying individuals by their associated demographics or treatment, which was intentionally avoided.

Race and ethnicity were defined according to SEER coding. Individuals who reported their ethnicity as Hispanic were not included as either white or black for the purposes of this analysis. County attributes tested for association with the primary outcome were as defined by SEER according to the linked 2000 Census data and included percent of population under age 18, percent over age 65, percent with less than a ninth-grade education, percent with less than a high school education, percent with bachelor's degree, percent in white-collar professions, percent living in residences with more than one person per room, percent foreign born, percent unemployed, percent minority, percent Hispanic, median household and family income, percent of persons and families below poverty level, percent of persons below 150% of poverty level, and percent urban. The urban and rural continuum designation as defined by the US Census Bureau was also included. The covariates reported in the results are those covariates that demonstrated a statistically significant association ($P<0.05$) with the primary outcome as determined by the methods described below.

Primary Outcome—Surgical Therapy

Surgical therapy was defined as including hepatectomy, ablation, or liver transplantation. Hepatectomy was defined as segmental or wedge liver resection performed with the

intention of removing all known cancer in the liver. Excisional biopsy and debulking procedures were not included as surgical therapy. Ablation included all methods of local tumor destruction including RFA, cryosurgery, and percutaneous ethanol or acetic acid injection. It is not possible using current SEER data to distinguish between ablative procedures performed percutaneously or operatively. For the purpose of this analysis, all ablative procedures were included as surgical therapy.

Statistical Analysis

Univariate and multivariate analyses were performed to investigate the association of independent covariates with the utilization of surgical therapy. Categorical variables were tested using χ^2 analysis and univariate logistic regression. Continuous variables were tested using the Student's t test and univariate logistic regression. Continuous variables were evaluated for normality using the Shapiro–Wilks test. None of the continuous covariates used in this study had a normal distribution. Thus, locally weighted scatterplot smoothing was used to aid in conversion to appropriate categorical values. Categorical groupings of continuous variables were tested for their association with the primary outcome by χ^2 analysis and univariate logistic regression. Among those covariates that had a significant association with the primary outcome on univariate analysis, defined by a P value less than 0.05, categorical groupings were compared to binary groupings grouped according to the median value of the continuous covariate. In the case of each county attribute (percent of population with less than a ninth-grade education, median household income, proportion of persons living under 150% of the poverty level, unemployment rate, percent Hispanic population, and percent of population living in residences with more than one person per room) included in the final logistic regression analysis, the binary categorical representation of less than or greater than the median value for the continuous variable demonstrated as strong an association as any other categorical grouping. In the case of patient age at diagnosis, a division into tertiles best reflected the trends in association between age and the use of surgical therapy.

The final multivariate logistic regression model was composed by including all covariates that demonstrated a statistically significant association with the primary outcome by univariate analysis ($P<0.05$). The final model included year of diagnosis as well to adjust for the significant increase in therapy over the course of the study period. Forward and backward stepwise logistic regression was used to select covariates for the final model. A Hosmer–Lemeshow goodness-of-fit test was performed to confirm the final model. Interaction between covariates was tested; none of the interactions were significant and were not included in the final model.

The final regression model was composed to include initially the SEER registry for each individual. The entire model was then redone to include the HSA as the geographic location for each individual. These results are reported separately, although the association of race, age, and tumor factors was not significantly different in either model.

An additional logistic regression model was then performed among the subset of patients with solitary HCC less than or equal to 5 cm in size, with no extrahepatic extension. The results of this model are reported as an independent analysis, and all steps in the creation of the final logistic regression model were repeated as described above. This subset was also analyzed with liver transplant only as the primary outcome, and those results are reported separately.

Adjusted analyses were represented graphically by the calculation of adjusted probabilities based upon the final logistic regression models. Probabilities were calculated for the covariate of interest using the base case for all other independent covariates (using the reference group for categorical variables and the median value for continuous variables). A 95% confidence interval was calculated for each probability estimate.

All statistical calculations were performed using Stata 9 SE (College Station, TX).

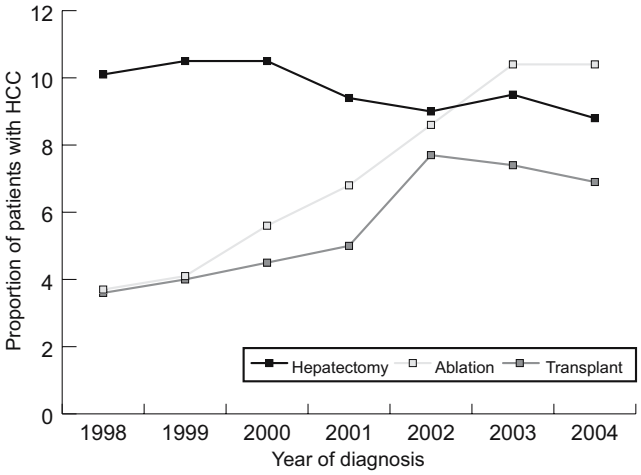
Results

Utilization of Surgical Therapy During the Study Period

A total of 16,121 patients with HCC diagnosed between 1998 and 2004 were included in the study cohort. A total of 3,760 individuals or 23.3% of the entire cohort received surgical therapy during the study period (9.5% hepatectomy, 7.9% ablation, and 6% transplant). The rate of surgical therapy increased notably over the study period, from 17.2% in 1998 to 26% in 2003. The increase in the utilization of surgical therapy was explained by an increase in the use of ablation and transplant, while the rate of hepatectomy remained relatively stable (Fig. 1).

Univariate Analysis

The unadjusted association of patient demographics, geographic location, tumor characteristics, and county attributes with the utilization of surgical therapy is as listed in Table 1. The majority of the patients in the cohort were male (74%), and the median age at diagnosis was 64 years (range 18–104). The racial and ethnic distribution included



Year of diagnosis	1998	1999	2000	2001	2002	2003	2004
% surgical therapy	17.4	18.7	20.5	21.2	25.3	27.3	26.1

Figure 1 Utilization of surgical therapy for HCC, by year of diagnosis, 1998–2004. The rate of surgical therapy by year is displayed in the data table, with the relative proportion of individuals treated with hepatectomy, ablation, and transplant displayed graphically by year.

49% whites, 11% blacks, 22% Asian/Pacific Islander, 1% American Indian/Alaskan Native, and 17% Hispanic. There was a broad distribution of incident cases among the SEER registries, from 14 cases in rural Georgia to 3,452 cases in California. The mean tumor size was 6.4 cm among the cohort, 61% of tumors were solitary, and extrahepatic extension was present in 9% of tumors.

Individuals treated with surgical therapy were significantly more likely to be younger, married, and have smaller, solitary tumors without extrahepatic extension. Women had a higher rate of surgical therapy than men (25 vs 22%, $P<0.001$). A larger proportion of whites and Asians underwent surgical therapy than blacks, American Indians/Alaskan Natives, or Hispanics. Rates of surgical therapy ranged from 12.7% in New Mexico to nearly 35% in Hawaii. Individuals undergoing surgical therapy for HCC tended to live in counties with a lower proportion of less educated residents, fewer persons below 150% of poverty level, lower unemployment rates, less persons living in residences with more than one person per room, and a lower proportion of Hispanic residents. A higher median household income by county of residence was associated with an increased likelihood of surgical therapy.

Multivariate Analysis

The results of a multivariate logistic regression analysis are displayed in Table 2. Female sex remained significantly associated with surgical therapy on adjusted analysis, as women were 42% more likely to be treated than men ($P<0.001$). The utilization of surgical therapy decreased with increasing age, as individuals more than age 71 were 57% less likely to be treated surgically ($P<0.001$). Tumors more than 5 cm were 73% less likely to be treated surgically ($P<0.001$), as were lesions with extrahepatic extension (odds ratio, 0.71, $P<0.001$). Income was the only county attribute that remained significantly associated with surgical therapy on adjusted analysis, as individuals residing in counties with a median household income greater than $45,510 (the median value for the entire cohort) were 23% more likely to undergo surgical therapy ($P=0.002$).

Race remained an important predictor of surgical therapy on multivariate analysis. The adjusted probability of surgical therapy by race is displayed graphically in Fig. 2. Blacks and Hispanics were 24 and 27% less likely to be treated, respectively, when compared to white individuals ($P\leq0.001$ for both). American Indian/Alaskan Natives, although a small proportion (164 individuals) of the total cohort, also seemed to undergo surgical therapy 45% less often than whites ($P=0.02$). In contrast, Asians and Pacific Islanders were 22% more likely to be treated surgically on adjusted analysis ($P=0.001$).

When submitted to multivariate analysis, the variation in rates of surgical therapy by SEER registry became somewhat less prominent, as displayed by the adjusted probability histogram in Fig. 3. Individuals in Atlanta (39% less likely to receive surgical therapy), California (33%), Los Angeles (35%), New Mexico (56%), San Francisco/Oakland (49%), and San Jose (66%) were all significantly less likely to receive surgical therapy for HCC (all $P<0.001$). There were no SEER registry areas where the utilization of surgical therapy was significantly higher than the cohort as a whole.

Multivariate Analysis Adjusted for Health Service Area

To better analyze the apparent geographic disparities in the utilization of surgical therapy on the larger SEER registry level, the multivariate analysis was repeated adjusting for HSA. A total of 171 HSAs are included in the SEER catchment area, and individuals from 124 HSAs were identified during the study period. The adjusted probability of surgical therapy by HSA is displayed in Fig. 4. While there was again noted to be a broad variation in the rate of surgical therapy by HSA, the majority of regions were close to the cohort rate of 22%. However, 11 HSAs were found to have rates of surgical therapy that were significantly higher than the cohort rate, while three HSAs had significantly lower rates of treatment ($P<0.05$). It is interesting to note that the racial disparity in the utilization of surgical therapy did not change when the more refined geographic adjustment by HSA was included in the multivariate analysis (Table 3).

Table 1 Univariate Analysis—Full Cohort

		Surgical Therapy Frequency (%) or Mean (SD)	No Surgical Therapy	*P* Value
N=16,121				
Any surgical therapy		3,760 (23.3%)	12,361 (76.7%)	<0.001
Hepatectomy		1,523 (9.5)		
Ablation		1,274 (7.9)		
Transplantation		963 (6.0)		
Patient characteristics				
Age at diagnosis		60.5 (12.0)	64.7 (12.8)	<0.001
Age by tertile	18–57	1,546 (28.9)	3,809 (71.1)	<0.001
	57–71	1,392 (25.7)	4,016 (74.3)	
	>71	822 (15.3)	4,536 (84.7)	
Sex	Male	2,715 (22.7)	9,252 (77.3)	<0.001
	Female	1,045 (25.2)	3,109 (74.8)	
Race/ethnicity	White	1,907 (24.2)	5,966 (75.8)	<0.001
	Black	351 (19.3)	1,466 (80.7)	
	Asian	974 (27.8)	2,529 (72.2)	
	AI/AN*	26 (15.8)	138 (84.2)	
	Hispanic	502 (18.2)	2,262 (81.8)	
Marital status	Married	2,502 (26.9)	6,811 (73.1)	<0.001
	Single/divorced/widow	1,162 (18.7)	5,054 (81.3)	
Registry	Alaska	8 (30.7)	18 (69.2)	<0.001
	Atlanta	83 (19.5)	342 (80.5)	
	California	773 (22.4)	2,679 (77.6)	
	Connecticut	153 (20.3)	601 (79.7)	
	Detroit	239 (24.5)	735 (75.5)	
	Hawaii	173 (34.9)	323 (65.1)	
	Iowa	99 (23)	332 (77)	
	Kentucky	113 (27)	305 (73)	
	Los Angeles	553 (19.2)	2,330 (80.8)	
	Louisiana	210 (25.7)	606 (74.3)	
	New Jersey	495 (33.7)	974 (66.3)	
	New Mexico	56 (12.7)	384 (87.3)	
	Rural Georgia	3 (21.4)	11 (78.6)	
	San Francisco–Oakland	335 (21.5)	1,227 (78.5)	
	San Jose–Monterey	123 (17.2)	594 (82.8)	
	Seattle	278 (27.1)	749 (72.9)	
	Utah	66 (30.4)	151 (69.6)	
Attributes by county of residence				
Percent population less than ninth-grade education		8.7 (4.7)	9.4 (4.9)	<0.001
Median household income, dollars		48,998 (10,688)	47,782 (10,920)	<0.001
Percent persons <150% poverty level		20.4 (7.8)	21.9 (8.0)	<0.001
Percent unemployment by county		6.3 (2.1)	6.6 (2.2)	<0.001
Percent households with greater than one person/room		10.2 (7.0)	11.2 (7.3)	<0.001
Percent Hispanic		19.2 (15.9)	22.0 (16.8)	<0.001
Tumor characteristics				
Size (cm)		5.2 (4.4)	7.0 (4.3)	<0.001
Extrahepatic extension	Yes	232 (19.6%)	948 (80.3%)	<0.001
	No	3,402 (28%)	8,762 (72%)	
Number of tumors	1	2,527 (31.3%)	5,548 (68.7)	<0.001
	>1	1,107 (21%)	4,162 (79%)	

AI/AN American Indian/Alaskan Native

Table 2 Multivariate Logistic Regression Analysis—Full Cohort

		Odds Ratio	95% CI	*P* Value
Female sex		1.42	1.29–1.58	<0.001
Age at diagnosis	18–57	1.0		
	57–71	0.80	0.73–0.89	<0.001
	>71	0.44	0.25–0.30	<0.001
Race/ethnicity	White	1.0		
	Black	0.76	0.66–0.89	<0.001
	Asian	1.22	1.08–1.37	<0.001
	AI/AN*	0.56	0.34–0.93	0.03
	Hispanic	0.73	0.64–0.83	<0.001
Marital status—married		1.63	1.49–1.79	<0.001
Tumor >5 cm		0.27	0.25–0.29	<0.001
Solitary tumor		1.66	1.52–1.82	<0.001
Extrahepatic extension		0.71	0.6–0.83	<0.001
Median household income >$45,510		1.23	1.08–1.4	0.002
SEER Registry	Atlanta	0.58	0.44–0.76	<0.001
	California	0.67	0.56–0.80	<0.001
	Los Angeles	0.67	0.53–0.84	0.001
	New Mexico	0.45	0.31–0.65	<0.001
	San Francisco	0.51	0.42–0.62	<0.001
	San Jose	0.33	0.25–0.44	<0.001

*AI/AN = American Indian/Alaskan Native

Surgical Therapy Among Solitary HCC Under 5 cm

In an effort to limit confounding factors contributing to the measured racial and geographic disparity in the utilization of surgical therapy in the multivariate analysis, the study cohort was limited to individuals with solitary HCC under 5 cm without extrahepatic extension (N=3,313 or 21% of the study cohort). The rate of surgical therapy among this group was 46% (14% hepatectomy, 17% ablation, 15% transplant). On multivariate analysis, age at diagnosis and tumor size remained significant predictors of surgical therapy (data not shown). No county attributes, including income, remained statistically significant. The effect of race seemed to be less prominent within this restricted cohort, as blacks, Asians, and American Indian/Alaska Natives all had adjusted rates of surgical therapy equivalent to white individuals. However, Hispanics remained 22% less likely to undergo surgical therapy for small solitary HCC (P=0.03). Furthermore, the geographic disparity in the utilization surgical therapy by HSA persisted in the small HCC cohort, with 10 of the 98 HSAs in the analysis having odds ratios of surgical therapy significantly different than the cohort as a whole (P<0.05; Fig. 5).

OLT for Solitary HCC Under 5 cm

The utilization of OLT among the cohort of patients with solitary HCC under 5 cm without extrahepatic extension was analyzed separately by multivariate analysis. A total of 479 patients in the cohort underwent OLT during the study period, with a relative 7% increase per year in the utilization of OLT. On adjusted analysis, age at diagnosis and tumor size remained strongly inversely correlated with the probability of OLT. The probability of OLT by HSA varied widely, with odds ratios of OLT ranging from 0.19 to 9.69 among those HSAs with statistically significant differences from the cohort as a whole (data not shown). Blacks were 58% less likely to be treated with OLT for small HCC when compared to white individuals (P<0.001; Fig. 6).

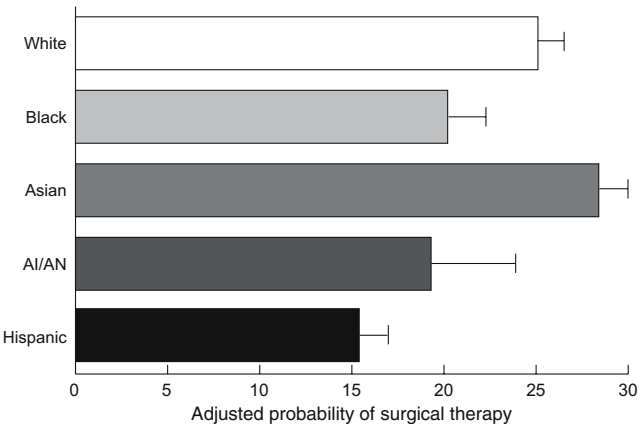


Figure 2 Adjusted probability of surgical therapy by race, full cohort, 1998–2004 (n=16,121). Model adjusted for year of diagnosis, age at diagnosis, race, gender, marital status, tumor size and extent, median household income, unemployment rate, and education level. The adjusted probability of surgical therapy for each race/ethnicity was significantly different from whites (P<0.05).

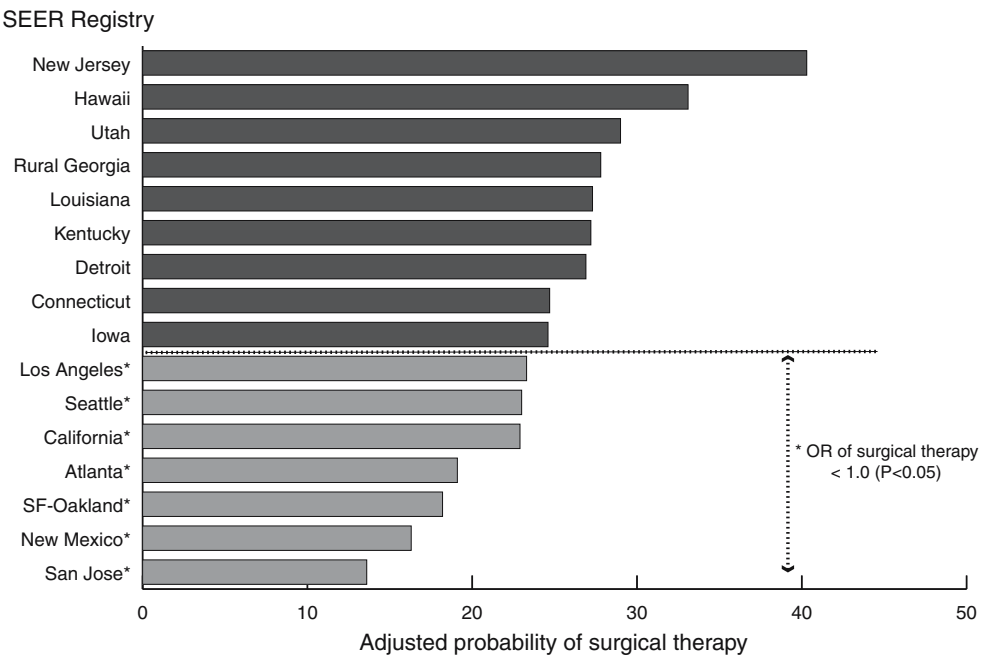


Figure 3 Adjusted probability of surgical therapy by SEER registry, full cohort, 1998–2004. Model adjusted for year of diagnosis, age at diagnosis, race, gender, marital status, tumor size and extent, median household income, unemployment rate, and education level. The SEER registries marked with an *asterisk* had adjusted probabilities of surgical therapy significantly different from the full cohort ($P<0.05$).

Discussion

This study provides information on the utilization of surgical therapy for HCC in the USA from 1998 to 2004 from the nationally representative SEER cancer registry. The findings of this study document that an increasing proportion of individuals with HCC are receiving surgical therapy, driven primarily by the notable rise in the use of ablative therapies and OLT. However, significant racial and geographic disparities exist in the application of surgical therapy. These differences persist despite the adjustment for tumor characteristics, patient demographics, socioeconomic attributes, and geographic location by HSA. Blacks, American Indians/Alaskan Natives, and Hispanics appear particularly affected by these disparities, with treatment rates 25–45% less than comparable white individuals. Among patients with small solitary tumors, geographic disparities appear to persist, while differences in therapy by race appear to lessen. However, the utilization of OLT, which offers the most definitive therapy for HCC in eligible patients, appears to occur two times more frequently in white compared to black individuals.

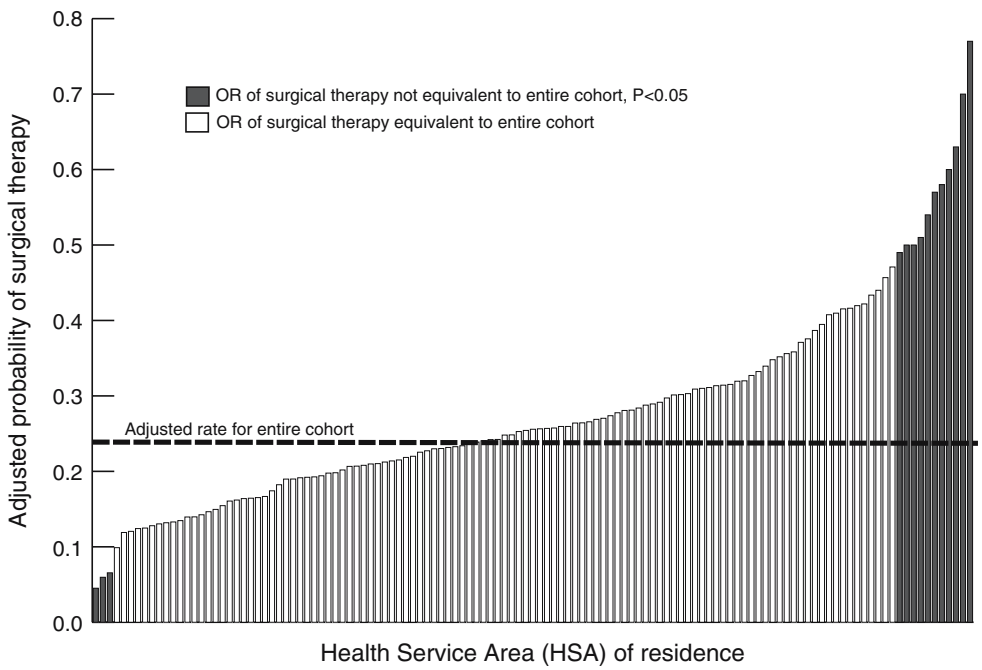


Figure 4 Adjusted probability of surgical therapy by HSA, full cohort, 1998–2004. HSAs are ordered according to increasing adjusted probability of surgical therapy over the study period. Model adjusted for year of diagnosis, age at diagnosis, race, gender, marital status, tumor size and extent, median household income, unemployment rate, and education level. Of the 124 HSAs that contained patients with HCC during the study period, 14 had probabilities of surgical therapy that were statistically significantly different from the full cohort (*dark shaded*, $P<0.05$).

Table 3 Multivariate Logistic Regression Analysis –Adjusted for HSA[a]

		Odds Ratio	95% CI	P value
Age of diagnosis	18–57	1.0		
	57–71	0.78	0.71–0.87	<0.001
	>71	0.42	0.38–0.47	<0.001
Female sex		1.42	1.29–1.58	<0.001
Race/ethnicity	White	1.0		
	Black	0.73	0.63–0.85	<0.001
	Asian	1.17	1.04–1.32	<0.01
	AI/AN[b]	0.55	0.31–0.97	<0.04
	Hispanic	0.70	0.61–0.81	<0.001
Marital status		1.64	1.49–1.80	<0.001
Median household income		0.98	0.75–1.27	<0.89
Tumor size over 5 cm		0.26	0.24–0.29	<0.001
Solitary lesion		1.67	1.52–1.83	<0.001
Extrahepatic extension		0.72	0.61–0.86	<0.001

[a] The model included adjustment for year of diagnosis and for HSA of residence.
[b] *AI/AN* American Indian/Alaskan Native

HCC represents a major world health problem and an emerging source of cancer-related death in the USA.[1,2] The fatality ratio of HCC worldwide is estimated as close to unity, indicating that the vast majority of patients with HCC succumb to their disease.[1] The lack of any effective systemic therapies compounds this problem. The application of any therapy for HCC may be additionally challenging because of the frequent association of HCC with chronic liver disease and cirrhosis. Surgical therapies, defined as including partial hepatectomy, ablative therapies, and OLT, provide the only definitive treatment in select patients. This study reports how these therapies are applied on a national level, across diverse patients and communities.

The encouraging rise in the utilization of surgical therapy for HCC is likely due to improved outcomes among select patients treated by such means. Hepatectomy remains a definitive therapy for resectable HCC, with 5-year survival rates up to 60% in reported series.[18,19] Perioperative mortality of less than 5% has become expected in experienced centers, even in Child's class A cirrhotics.[19] The expansion of ablative therapies, especially RFA, over the last decade has provided similar good outcomes in patients with small tumors.[10] Ablative therapies also allow the extension of treatment to more advanced cirrhotics with less morbidity than hepatic resection. Perhaps most significantly, the establishment of criteria to allow successful liver transplantation for patients with small HCC has provided a definitive oncologic therapy that also remedies associated chronic liver disease.[14] As more is learned about the biology of HCC that allows selection of individuals with favorable tumor biology, the current Milan criteria will likely be expanded to make more patients eligible for OLT.[20,21] Protocols aimed at downsizing select patients with ablative therapies to within acceptable criteria for OLT are currently under investigation.[22]

The unique position of surgical therapy as the only potentially curative option for HCC makes its provision on an equitable basis of paramount importance. Disparities in access and utilization of surgical therapy for HCC likely translate into disparities in survival, as documented by other investigators using SEER data.[23–25] Blacks and Hispanics particularly have been demonstrated to have poorer survival than whites, even among individuals with localized HCC.[23,24]

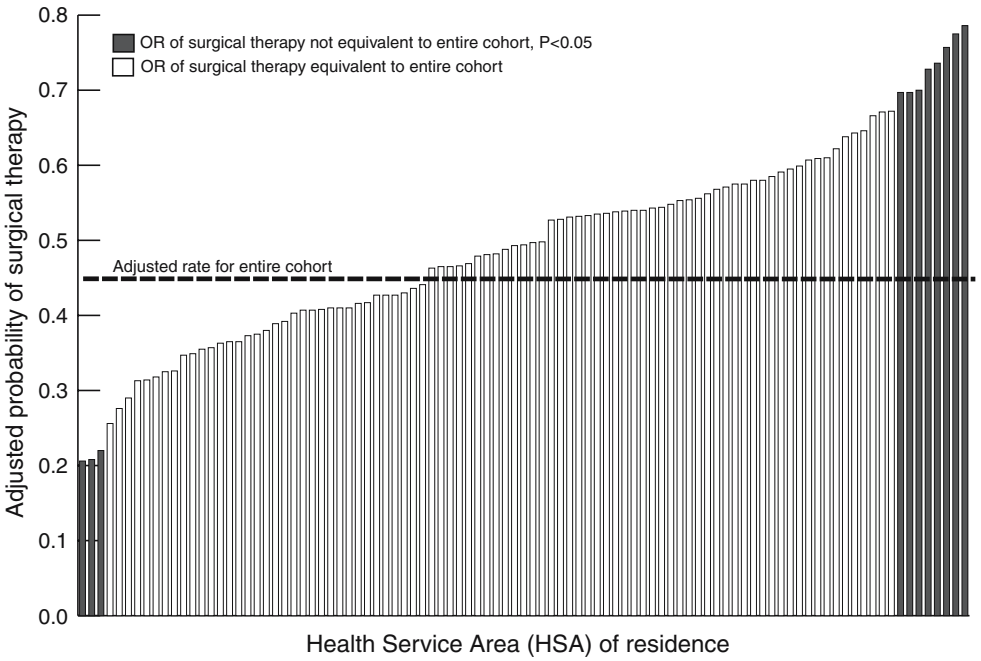


Figure 5 Adjusted probability of surgical therapy by HSA, solitary tumors less than 5 cm, 1998–2004. HSAs are ordered according to increasing probability of surgical therapy over the study period for solitary HCC under 5 cm without extrahepatic extension (N=3,313). Model adjusted for year of diagnosis, age at diagnosis, race, gender, marital status, and tumor size. Of the 98 HSAs that contained patients with small HCC during the study period, ten had probabilities of surgical therapy that were statistically significantly different from the restricted cohort (*dark shaded*, P<0.05).

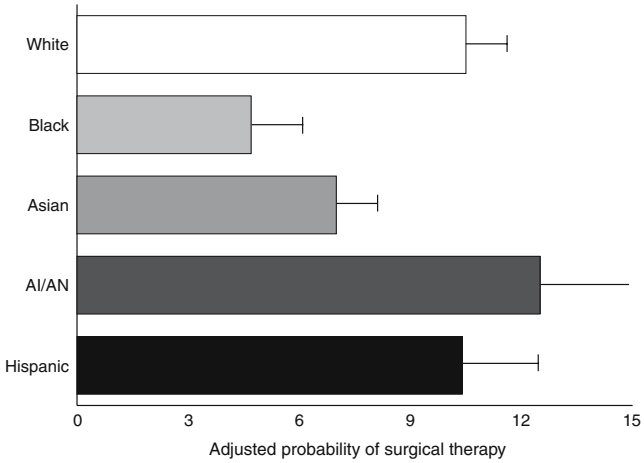


Figure 6 Adjusted probability of transplant, solitary tumors less than 5 cm, 1998–2004. Model adjusted for year of diagnosis, age at diagnosis, race, gender, marital status, and tumor size. Blacks had a significantly lower probability of transplant in comparison to white individuals (odds ratio=0.42, $P<0.001$).

Racial disparities in the surgical therapy for cancer in the USA have been well documented. While some of these differences may be explained by more advanced stages of disease at presentation, other processes of care that take place after diagnosis appear to affect outcome among minority populations as well. A recent analysis by Morris et al. documented that African-Americans with rectal cancer were more likely to be treated by lower-volume surgeons and hospitals and were less likely to receive adjuvant therapy than Caucasians.[26] Similar findings of disparities in treatment and outcomes for African-Americans have been reported for pancreatic and esophageal cancer as well.[27,28] These data correlate with the broader evidence that African-Americans and other minority populations receive medical and surgical care of lesser quality, with poorer outcomes.[29]

Geographic differences in the application of surgical care have also been well studied and described.[30] Utilization of surgical procedures appears to vary widely by region as revealed by multiple studies, despite adjustment for indications and case mix.[31–33] A previous analysis of SEER–Medicare-linked data documented significant variation in treatment and mortality for HCC, despite adjustment for tumor and demographic factors, as in the present study.[25] The etiology of these marked geographic disparities in medical and surgical care is multifactorial, reflecting regional differences in practice and referral patterns, patient compliance and engagement in medical care, provider availability, and processes of care. Efforts to consolidate complex surgical care in high-volume centers likely falls far short of adequately addressing the issue of geographic variation in surgical care, as many regions have no accessible high volume centers,[34] and patients often prefer not to travel even to receive better-quality care.[35] Geographic variation appears to be tightly linked to disparities according to race and ethnicity,[31,36] and it is likely that efforts to address these shortcomings in the health care system will require an integrated approach to these issues.

Racial and geographic variation in the application of transplantation is particularly troublesome and has been well documented in both kidney and liver transplantation.[37,38] OLT remains a relatively exclusive medical procedure, with just more than 6,000 procedures performed in 2005, while the waiting list for OLT currently contains more than 16,000 individuals.[39] The procedure requires surgical expertise that is not available at the majority of medical centers, carries high risk of perioperative morbidity and mortality, and requires extensive responsibility and psychosocial support on the part of the recipient. Thus, this procedure may magnify disparities in access and utilization of medical care and broaden racial and geographic differences, as implied by the present study. Furthermore, now that OLT has an established and potentially increasing role in the therapy of HCC, individuals may not have access to the appropriate spectrum of care for their cancer unless they are treated by a provider and/or center that is familiar with the benefits and responsibilities of OLT. Efforts to broaden the application of OLT racially and geographically will therefore require extensive patient and provider education, as well as establishment of efficient referral networks to transplant centers.

The present study has several limitations that may limit its interpretation. First, as the study is based upon cancer registry data, there is little information to allow adjustment for case mix, specifically comorbid conditions. In the specific case of HCC, information on the degree and primary cause of associated liver disease may aid in adjustment among individuals. For example, one might hypothesize that the higher rates of surgical therapy experienced by Asian/Pacific Islanders in this study are related to the high prevalence of hepatitis B infection in this population, which is associated with the occurrence of HCC in the setting of relatively normal liver function. It is possible that blacks and Hispanics present with HCC in the setting of more advanced associated liver disease, with more contraindications to surgical therapy. However, it is unlikely that this factor explains the degree of disparity in treatment experience by these minority groups, and it does not explain the marked disparity in the utilization of OLT.

Another related limitation of the registry data utilized in this study is the relative lack of provider or hospital covariates available in the database. This limits the ability of the study to identify patterns or processes of care that might be targets for interventions aimed at limiting racial and geographic disparities in the treatment of HCC. In addition, the SEER limited-use data poorly captures the use of transarterial chemoembolization (TACE) for HCC, a

therapy that has been demonstrated to prolong survival in select patients.[40,41] However, TACE is not generally regarded as a definitive therapy, and thus this study likely reflects the current state of therapy for HCC with an intention for cure. Finally, this study does not address those patients listed for transplantation who did not receive an organ before death or progression of disease. Thus, it is impossible to tell what proportion of individuals were offered OLT but did not have the opportunity to be treated because of the lack of an available organ in their region. This likely is a relative minority of study patients, as patients with HCC are given priority in the current allocation system such that they are typically transplanted in 3 to 6 months.[39] Furthermore, the study reflects the reality of the current treatment of HCC in the USA rather than a formal intention-to-treat analysis.

In summary, the present study describes the recent use of surgical therapy for HCC in the USA. While larger numbers of patients are being treated with potentially curative surgical therapies, including OLT, marked racial and geographic disparities exist that likely limit the further expansion of these definitive therapies across all populations. This study provides a means to identify specific populations and HSAs that are significant outliers in the utilization of surgical therapies from the majority of the health care system. Further investigation of the practice and referral patterns, community health initiatives, treatment strategies, and processes of care at work in these unique areas may allow the identification of initiatives that may be more broadly applied in an effort to extend definitive therapy for the emerging health problem of HCC.

Acknowledgment Christopher J. Sonnenday was supported in this work by NIH Grant #T32 DK07713, Basic Scientific Training for GI Surgeons Training Grant.

References

1. Bosch FX, et al. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004;127(5 supp 1):S5–16.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340(10):745–750.
3. Ries LAG, et al. SEER Cancer Statistics Review, 1975–2004. Bethesda, MD: National Cancer Insititute; 2007.
4. El-Serag HB. Epidemiology of hepatocellular carcinoma. Clin Liver Dis. 2001;5(1):87–107. vi.
5. Davila JA, et al. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology. 2004;127(5):1372–1380.
6. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol. 2005;40(3):225–235.
7. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 2005;25(2):181–200.
8. Cha CH, et al. Resection of hepatocellular carcinoma in patients otherwise eligible for transplantation. Ann Surg. 2003;238 (3):315–321. discussion 321–323.
9. Shiina S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology. 2005;129(1):122–130.
10. Lin SM, et al. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or = 4 cm. Gastroenterology. 2004;127(6):1714–1723.
11. Livraghi T, et al. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology. 1999;210(3):655–661.
12. Marrero JA, Pelletier S. Hepatocellular carcinoma. Clin Liver Dis. 2006;10(2):339–51. ix.
13. Hemming AW, et al. Liver transplantation for hepatocellular carcinoma. Ann Surg. 2001;233(5):652–659.
14. Mazzaferro V, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–699.
15. National Center for Health Statistics (US). Atlas of United States Mortality NCHS Atlas CD-ROM No.1. Hyattsville, MD: Dept. of Health and Human Services; 1997.
16. Makuc DM, et al. Health service areas for the United States. Vital Health Stat. 1991;2(112):1–102.
17. Makuc DM, et al. The use of health service areas for measuring provider availability. J Rural Health. 1991;7(4 supp):347–356.
18. Cha C, et al. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg. 2003;197(5):753–758.
19. Fong Y, et al. An analysis of 412 cases of hepatocellular carcinoma at a Western center. Ann Surg. 1999;229(6):790–799. discussion 799–800.
20. Yao FY, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl. 2002;8 (9):765–774.
21. Yao FY, Roberts JP. Applying expanded criteria to liver transplantation for hepatocellular carcinoma: too much too soon, or is now the time? Liver Transpl. 2004;10(7):919–921.
22. Yao FY, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl. 2005;11(12):1505–1514.
23. Sloane D, Chen H, Howell C. Racial disparity in primary hepatocellular carcinoma: tumor stage at presentation, surgical treatment and survival. J Natl Med Assoc. 2006;98(12):1934–1939.
24. Davila JA, El-Serag HB. Racial differences in survival of hepatocellular carcinoma in the United States: a population-based study. Clin Gastroenterol Hepatol. 2006;4(1):104–110. quiz 4–5.
25. El-Serag HB, et al. Treatment and outcomes of treating of hepatocellular carcinoma among Medicare recipients in the United States: a population-based study. J Hepatol. 2006;44(1):158–166.
26. Morris AM, et al. Racial disparities in late survival after rectal cancer surgery. J Am Coll Surg. 2006;203(6):787–794.
27. Dominitz JA, et al. Race, treatment, and survival of veterans with cancer of the distal esophagus and gastric cardia. Med Care. 2002;40(1 supp):I14–I26.
28. Eloubeidi MA, et al. Prognostic factors for survival in pancreatic cancer: a population-based study. Am J Surg. 2006;192(3):322–329.
29. Smedley BD, et al. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care, vol xvi. Washington, DC: National Academies; 2003. p. 764.
30. Dartmouth Medical School. Center for the Evaluative Clinical Sciences. The Dartmouth Atlas of Health Care 1998, 1 Atlas. Chicago, IL: American Hospital; 1998. 305 pp.

31. Skinner J, et al. Racial, ethnic, and geographic disparities in rates of knee arthroplasty among Medicare patients. N Engl J Med. 2003;349(14):1350–1359.
32. Weinstein JN, et al. United States' trends and regional variations in lumbar spine surgery: 1992–2003. Spine. 2006;31(23):2707–2714.
33. Pope GD, Birkmeyer JD, Finlayson SR. National trends in utilization and in-hospital outcomes of bariatric surgery. J Gastrointest Surg. 2002;6(6):855–860. discussion 861.
34. Dimick JB, Finlayson SR, Birkmeyer JD. Regional availability of high-volume hospitals for major surgery. Health Aff (Millwood) 2004;Suppl Web Exclusives:VAR45–VAR53.
35. Finlayson SR, et al. Patient preferences for location of care: implications for regionalization. Med Care. 1999;37(2):204–209.
36. Baicker K, Chandra A, Skinner JS. Geographic variation in health care and the problem of measuring racial disparities. Perspect Biol Med. 2005;48(1 supp):S42–53.
37. Reid AE, et al. Disparity in use of orthotopic liver transplantation among blacks and whites. Liver Transpl. 2004;10(7):834–841.
38. Powe NR, Boulware LE. The uneven distribution of kidney transplants: getting at the root causes and improving care. Am J Kidney Dis. 2002;40(4):861–863.
39. Pomfret EA, et al. Liver and intestine transplantation in the United States, 1996–2005. Am J Transplant. 2007;7(supp 1):1376–1389.
40. Bruix J, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology. 1998;27(6):1578–1583.
41. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37(2):429–442.

Discussion

Layton F. Rikkers, M.D. (Madison, WI): First, I would like to congratulate you, Dr. Sonnenday, on an excellent presentation and also thank you for providing me a copy of the manuscript. This report is another in a long line of studies that clearly show that despite investing more than 15% of our gross national product in health care, an amount far greater than any other country, a significant fraction of Americans do not have adequate access to it. This should be an embarrassment to the wealthiest nation on earth and to each of us as providers of surgical care in what appears to be a broken health care system.

Using the SEER database, Dr. Sonnenday analyzed the likelihood that patients with HCC received one of three surgical therapies in the years 1998 to 2004. The results are not pretty. The only positive is an overall 9% increase in the use of surgery during the time course of the study. The negatives abound. When considering the entire cohort, there are marked geographic and racial disparities regarding who receives surgical treatment, the only known effective therapy for this malignancy. Not surprisingly, racial minorities and geographic areas with a disproportionate percentage from the lower socioeconomic strata were disadvantaged.

Particularly interesting is the subgroup of patients with a solitary tumor less than 5 cm in diameter and with no extrahepatic disease. Although the effect of race was less prominent here, only 46% of this potentially curable group had surgery. I would appreciate Dr. Sonnenday's thoughts regarding this apparent undertreatment presumably for all classes of patients.

Finally, regarding my own health care, I would seem to be fortunate in that I am Caucasian, I have some financial resources, and I live in close proximity to hepatobiliary and transplant surgeons. However, because I am not a member of the female sex, I am less likely to receive surgical therapy should I develop a hepatoma. Does Dr. Sonnenday have any explanation for this apparent gender bias?

I very much enjoyed your presentation.

Christopher J. Sonnenday, M.D. (Ann Arbor, MI): Thank you again for commenting on my paper.

Your first question regarded the 46% rate of surgical therapy for those patients with relatively localized and what should be treatable disease. That pattern is seen for a variety of pancreatic or biliary malignancies; it is true of pancreatic cancer, and it is true of cholangiocarcinoma. I think there are a myriad of factors that contribute to that, some of which were revealed in this study. However, I think it probably reflects an overall bias in the medical community that these are mortal cancers and that patients are referred late, they are treated late, and patients themselves think that there is little to be done. A broader point of this entire work is that education, both on the part of providers and patients, is a key toward addressing this issue.

As for the discrepancies between the rate of females being treated vs males, that is a truth that has been borne out in multiple studies looking at disparities not only in surgical diseases but in cardiovascular diseases, for example. The most commonly assigned reason for that is that women are more vigilant about their health care, they present earlier, they follow through on therapy, and they are more compliant. That is typically the proposed reason for that, and there are actually some prospective health services studies that have confirmed that.

J Gastrointest Surg (2007) 11:1647–1653
DOI 10.1007/s11605-007-0321-x

Preservation of the Anal Transition Zone in Ulcerative Colitis. Long-Term Effects on Defecatory Function

Alessandro Fichera · Laura Ragauskaite · Mark T. Silvestri · Nicholas M. Elisseou · Michele A. Rubin · Roger D. Hurst · Fabrizio Michelassi

Received: 22 May 2007 / Accepted: 3 September 2007 / Published online: 29 September 2007

Abstract
Introduction The anal transition zone (ATZ) after ileal pouch anal anastomosis (IPAA) for ulcerative colitis is considered at risk for dysplasia and persistent or recurrent disease activity. The long-term fate of the ATZ and the effects of histologic changes on defecatory function are not well-known.
Methods To evaluate the inflammatory and preneoplastic changes of the ATZ in patients without preoperative dysplasia, yearly biopsies of the ATZ were obtained and functional results recorded on a questionnaire/diary. Histologic changes were correlated with simultaneous assessment of defecatory function.
Results Between 1992 and 2006, 225 patients underwent a stapled IPAA. A total of 238 successful biopsies of the ATZ were performed. There was no dysplasia found. Acute inflammation was noted in 4.6%, chronic inflammation in 84.9%, and normal mucosa in 10.5% of cases. Patients with chronic inflammation reported an average of 6.2±1.7 bowel movements/day and 93.2% of them were able to delay a bowel movement for at least 30 min. The presence of chronic ATZ inflammation did not seem to have a negative impact on function, with 96.1% of patients reporting perfect continence, and only 5.3% using protective pads.
Conclusions Preservation of the ATZ in selected patients is safe and offers excellent long-term functional results. New onset dysplasia was not noted. Chronic inflammation had limited clinical impact. Presence of ATZ inflammation in a total of 89.5% of patients warrants life-long surveillance with biopsies.

Keywords Ulcerative colitis · Colon and rectal neoplasm · Cancer prevention · Quality of life · Surgical outcome

This paper was presented at the 48th annual meeting of The Society for Surgery of The Alimentary Tract, May 23, 2007, Washington, DC.

A. Fichera · L. Ragauskaite · M. T. Silvestri · N. M. Elisseou · M. A. Rubin · R. D. Hurst
Department of Surgery, University of Chicago, Chicago, IL, USA

F. Michelassi
Department of Surgery, Weill Medical College of Cornell University, New York, NY, USA

A. Fichera (✉)
Department of Surgery, MC 5031, University of Chicago Hospitals, 5841 S. Maryland Avenue, Chicago, IL 60637, USA
e-mail: afichera@surgery.bsd.uchicago.edu

Abbreviations

ATZ	Anal transition zone
IPAA	Ileal pouch anal anastomosis
RPC	Restorative proctocolectomy
UC	Ulcerative colitis

Introduction

Restorative Proctocolectomy (RPC) with Ileal Pouch Anal Anastomosis (IPAA) is currently the most commonly performed operation for the treatment of Ulcerative Colitis (UC). With increasing experience, this procedure has been offered to pediatric and older patients with excellent functional results.[1–4] Originally described to be performed in association with a full mucosectomy, subsequently it was modified to allow retention of a short cuff of anorectum.

However, debate still persists about preservation of the Anal Transition Zone (ATZ), its long-term fate and its impact on functional results. Authors in favor of preserving the ATZ report fewer complications, a faster and easier operation and better defecatory function after stapled IPAA in part because of the ability of the patient to discriminate between gas and stool along with decreased surgical trauma to the sphincter complex.[5–9] On the other hand, the retained ATZ is theoretically at risk for recurrent or persistent disease and has the potential for malignant transformation.[10–13] There is agreement that the retained ATZ should be periodically surveyed endoscopically and biopsied.[14] Prospective randomized studies carried out to compare stapled and hand-sewn IPAA and to assess the fate of the ATZ in terms of disease activity and neoplastic progression have failed to show a difference caused in part by the small sample size and short follow-up.[15–17]

The anatomy of the ATZ is poorly characterized.[18,19] The concept of an ATZ was introduced by Fenger who defined it as "the zone interposed between uninterrupted crypt bearing colorectal type mucosa above and uninterrupted squamous epithelium below".[18] Fenger also described the Alcian blue technique for staining the ATZ macroscopically, based on the fact that columnar epithelium stains dark blue, the squamous epithelium does not stain, and the ATZ stains pale blue because of occasional mucin-producing cells.[18] The location and length of the ATZ are also variable. It has been reported to extend from 6 mm below to 20 mm above the dentate line[18] and to measure between 7 and 23 mm.[19] The ATZ is thought to play a role in maintaining continence by sampling rectal contents and discriminating between gas, liquid, and solid stool.[20,21]

Large studies assessing the oncologic fate and the incidence and long-term functional implications of recurrent or persistent disease activity in the retained ATZ are lacking. Thus, in general the choice of surgical approach is still based on institutional experience, surgeon preference, skills and training and not on solid data. In our practice, we have adopted a selective approach based primarily on the presence of dysplasia, irrespective of the location, but also on patient characteristics and baseline continence status. We have been performing transanal mucosectomy and hand-sewn IPAA for UC patients with preoperative biopsy-proven adenocarcinoma or dysplasia, irrespective of the degree and location. A stapled IPAA with preservation of the ATZ is offered only after adenocarcinoma or dysplasia of any grade has been ruled out with multiple preoperative colonoscopic biopsies.

Hence, the aims of this study were to determine the oncologic risk of the retained ATZ in this selected group of patients over time, asses the ATZ inflammatory changes during follow-up, and evaluate their impact on long-term functional outcome measures.

Materials and Methods

Patients and Operative Technique

Consecutive UC patients who underwent RPC with stapled IPAA between June 1992 and December 2006 were included in the study. A stapled IPAA with preservation of the ATZ was performed only after dysplasia of any grade and or cancer was ruled out on multiple preoperative biopsies. The majority of patients underwent the procedure under elective circumstances according to the technique previously described.[22,23] The stapled anastomosis was performed according to the double staple line technique with perianal insertion of the circular EEA stapling device after closure of the anorectal tract with a linear TA stapler. Perioperative data were accrued in a prospective database approved by the Institutional Review Board of the Division of Biologic Sciences of the University of Chicago (Protocol #11767). Since August of 2002 laparoscopic stapled IPAA patients have also been included in the study.

Surveillance Biopsy of the ATZ

A rigid anoscopy with four quadrant biopsies of the ATZ was scheduled to be performed annually to evaluate patients for new-onset dysplasia. Any inflammatory component was graded as acute, chronic, or absent by an expert gastrointestinal pathologist. Biopsies were excluded from the analysis if they contained small intestinal mucosa or squamous epithelium. Only biopsies with a concurrent detailed questionnaire analysis were included in the analysis of defecatory function and quality of life. The degree of inflammation was correlated with the information concurrently obtained using our previously validated questionnaire.[8]

Questionnaire

The questionnaire consisted of two parts and was mailed to patients at 3, 6, 9, 12, 18, and 24 months after the surgical procedure and yearly thereafter. Part I had two components. The first one consisted of a complete analysis of defecatory functional parameters (use of pharmacological aids and diet restrictions to reduce bowel movement frequency, quality of continence, ability to distinguish flatus from stool and to defer a bowel movement, use of protective pads, incidence of perineal rash, and pruritus). The second component contained questions aimed at assessing patient's quality of life.

Part II consisted of seven daily sheets to record oral intake, sleep pattern, bowel activity, including consistency of bowel movements, and daily continence. The questionnaire was evaluated in our outpatient clinic. Answers that appeared to be unclear or inconsistent with previous answers were clarified, although not changed; bowel

activities and episodes of incontinence were averaged over 7 days and expressed with daytime, nighttime, and 24-h mean values. Diet and medications were reviewed; suggestions were made to improve functional results. A complete physical examination was then performed with anoscopy and biopsies as indicated.

Statistical Analysis

For the analysis of baseline and demographic variables, two sample *t* tests were used for comparison of continuous variables and the Pearson χ^2 test for categorical variables. The Fisher exact test was used when only few observations were available. The continuous variables are presented as either the mean or the median with the standard deviation and the range between brackets. Categorical variables are presented as absolute numbers and by percentages. Measures with more than two categories on the questionnaire were dichotomized according to specified rules. For example, an indicator of continence function such as the ability to defer a bowel movement, which had four categories (never, sometimes, often, and always), was dichotomized into rarely (never and sometimes) and frequently (often and always). For all analyses, the *p* values were two-tailed, and a *p* value of less than 0.05 was considered to indicate statistical significance. The statistical software program SPSS 14.0 (SPSS Inc. Chicago, IL) was employed for the analysis.

Results

Patient Demographics

Between June 1992 and December 2006, 225 consecutive UC patients with no evidence of cancer or dysplasia, as ruled out by multiple preoperative endoscopic biopsies, underwent RPC with stapled IPAA at the University of Chicago Medical Center and were prospectively enrolled in this IRB-approved study. No patients were found to have unexpected cancer or dysplasia on the final pathology review of the surgical specimen after stapled IPAA. Patients' data were prospectively collected in the IBD database. There were 99 females (44%) and 126 males (56%), with mean age at the operation 34.7±11.5 years (range 13–66 years). Their median follow-up was 36 months (range 3–132 months).

ATZ Biopsy Results

During the study period, 238 successful biopsies of the ATZ were performed. Biopsies of the ileal mucosa or squamous epithelium were excluded. The distribution of these biopsies over time is shown in Fig. 1. There was no evidence of dysplasia or cancer in any of the biopsies performed. Furthermore, no patients developed cancer in the pouch, retained ATZ or pelvic floor during follow-up.

Eleven biopsies showed evidence of acute inflammation (4.6%), 202 chronic inflammation (84.9%), and 25 (10.5%) were read as normal. Of the 11 patients with acute inflammatory changes, nine were asymptomatic and two had symptoms suggestive of "cuffitis". They received medical treatment with complete resolution of the symptoms. No surgical treatment was needed for acute inflammation of the ATZ during the study period.

A significant reduction of the available questionnaires over time is noted, compared to the more consistent biopsy rate shown in Fig. 1. Although patients continue to present to the scheduled follow-up visits, their compliance with the long and detailed questionnaire declines over time.

Defecatory Function

Seventy-two successful biopsies had a concurrent questionnaire available for the analysis of defecatory function and quality of life. Of these, five biopsies showed evidence of acute inflammation (7%), 59 showed chronic inflammation (82%), and eight were read as normal (11%). The distribution of these biopsies over time is shown in Fig. 2. As a result of the limited number of patients with normal mucosa or acute inflammation, no significant differences were noted between groups for frequency and consistency of bowel movements. In the chronic inflammation group (CI), the average number of bowel movements/day was 6.2±1.7/day (range 2–10) versus 8.1±3.9/day (range 3–15) in patients with normal biopsies and 6.4±1.8/day (range 4–9) in patients with acute inflammation. The consistency of bowel movements was solid or pasty 92% of the time in the CI group, 87.5% of the time in patients with normal

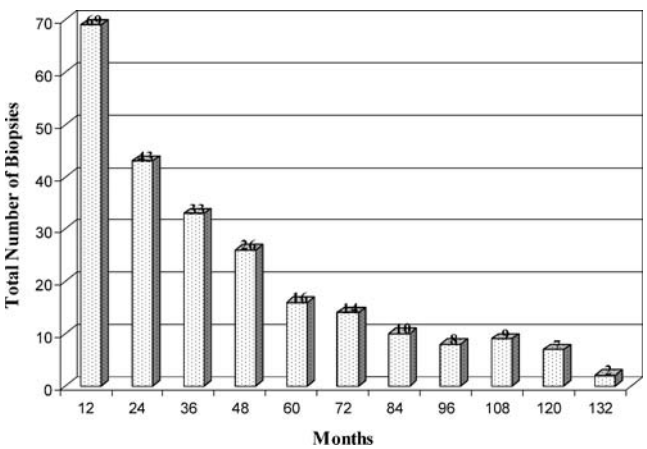


Figure 1 Number of biopsies during follow-up. Biopsies were excluded from the study if they contained small intestinal mucosa or squamous epithelium.

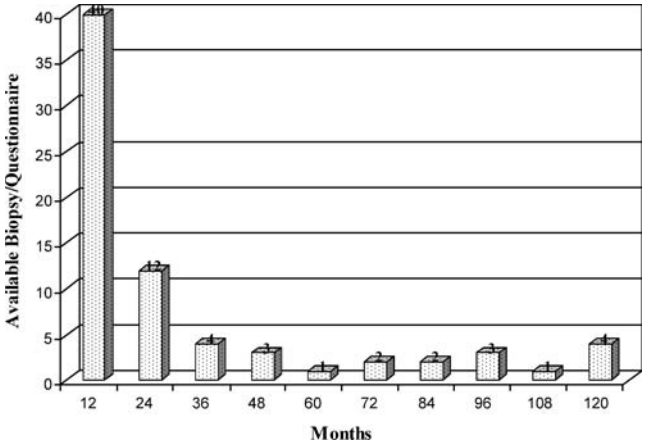


Figure 2 Number of questionnaires available for correlation with degree of inflammation during follow-up.

biopsies, and 100% of the time in patients with acute inflammation (p=0.585). There were no patients with major incontinence episodes and only 3.9% of CI patients reported minor leakage episodes, compared to 12.5% of patients with normal biopsies (p=0.495). Other indicators of stooling function, such as ability to delay a bowel movement, dietary modification, and the use of antidiarrheal medication to control bowel frequency, the ability to discriminate between flatus and stool, the use of protective pads, and the presence of rectal itching or rash, did not differ between groups (Table 1). In the CI group, 96.1% of patients reported perfect continence, 93.2% was able to defer a bowel movement as needed and only 5.3% was using protective pads.

Quality of Life

Patients' subjective assessment of their quality of life did not differ between groups. The CI patients showed overall satisfaction and adjustment with the lifestyle changes imposed by the procedure. CI patients rated their quality of life as much better or better in 96.6% of cases and overall satisfaction and adjustment as excellent or good in 94.7% of cases. Their entire cohort (100%) would recommend the operation to others (Table 2).

Discussion

The retained ATZ after IPAA in highly selected UC patients without preoperative cancer or dysplasia shows persistence of predominantly chronic inflammatory changes. Chronic inflammation was shown to have minimal impact on defecatory function and quality of life in our study. These patients continue to be free of dysplasia in our series at a median follow-up of 36 months.

The presence of dysplasia in UC is thought to be a marker of diffuse "mucosal instability". Gorfine *et al*. have shown that in the presence of dysplasia of any grade, surgical specimens were 36 times more likely to harbor invasive carcinoma than specimens without dysplasia.[24] That study and others suggest that when dysplasia of any grade is present and confirmed by at least two independent observers the risk of cancer present at the time is relatively high, and documented dysplasia should be considered an

Table 1 Defecatory Function

		Chronic inflammation n=59	Acute inflammation n=5	Normal mucosa n=8	p value
Ability to delay BM	Sometimes/Never	6.8	0	0	
	Always/Often	93.2	100	100	0.627
Changes in eating schedules	Yes	28.8	80	25	
	No	71.2	20	75	0.056
Changes in eating habits	Yes	35.6	60	28.6	
	No	64.4	40	71.4	0.497
Use of antidiarrheal medications	Yes	37.3	40	50	
	No	62.7	60	50	0.786
Discriminate flatus/stool	Sometimes/Never	47.5	0	50	
	Always/Often	52.5	100	50	0.116
Protective pads day	Yes	5.2	0	12.5	
	No	94.8	100	87.5	0.597
Protective pads night	Yes	5.2	0	25	
	No	94.8	100	75	0.104
Rectal itching	Always/Often	50	40	62.5	
	Rare/None	50	60	37.5	0.710
Perineal rash	Always/Often	27.1	20	25	
	Rare/None	72.9	80	75	0.937

Values are expressed in percentage.

Table 2 Quality of Life

		Chronic inflammation $n=59$	Acute inflammation $n=5$	Normal mucosa $n=8$	p value
Quality of life	Same/Worse	3.4	0	12.5	
	Much better/Better	96.6	100	87.5	0.442
Overall satisfaction	Fair/Poor	5.3	0	14.3	
	Good/Excellent	94.7	100	85.7	0.554
Overall adjustment	Fair/Poor	5.3	0	14.3	
	Good/Excellent	94.7	100	85.7	0.554
Recommend surgery	No	0	0	14.3	
	Yes	100	100	85.7	

Values are expressed in percentage.

indication for surgery.[24,25] Furthermore, the concept of "mucosal instability" supports the surgical practice of complete transanal mucosectomy and hand-sewn anastomosis to completely eradicate the risk of potential malignant transformation. In fact, the vast majority of reports of cancer in the retained ATZ have been in patients with preoperative evidence of dysplasia or cancer,[26,27] raising concern about leaving residual columnar epithelium in patients with dysplasia or a colorectal cancer.[10] Evidence of postoperative ATZ dysplasia in larger controlled series with adequate follow-up is a rare occurrence.[12,28] In a recent study from the Cleveland Clinic, Remzi *et al.* reported eight cases out of 178 patients (4.5%) of postoperative dysplasia.[28] In two cases, the dysplasia was high grade.[28] In these studies, the occurrence of dysplasia in the postoperative period correlated with the presence of preoperative dysplasia. In our series, limiting stapled IPAA only to patients who had no evidence of preoperative dysplasia appears to effectively minimize the risk of developing postoperative dysplasia. None of our patients developed dysplasia or cancer in the retained ATZ, pouch or pelvic floor.

The number of questionnaires available for comparison with the biopsy results decreased significantly during follow-up. Although patients continue to present to the schedule follow-up visits, their compliance to the detailed questionnaire declines over time. We recognize this to be a limitation of the study, we have previously shown, however, that defecatory function and quality of life plateau at 1 year and remain stable over time with a median follow-up of 33.6 months in that series.[8] Furthermore, in large, controlled series postoperative dysplasia has been identified at a median of 9 to 11 months.[12,28] Although our patients continue to follow-up either in person or through phone interviews when they relocate, they continue to undergo biopsy of the ATZ, but often do not complete the questionnaire. This is true especially if their overall function and quality of life are excellent.

Chronic inflammatory changes are noted in the vast majority of our patients during follow-up and overall function and quality of life results are excellent. Only 7.8% of patients developed acute inflammation of the ATZ and only two of them were symptomatic during follow-up. Our rate of acute inflammation seems to be lower than previously reported.[11,13] It is our goal in surgery to leave a short ATZ. In this study, the ATZ measured a mean of 1.25 cm, as estimated by the operating surgeon after completion of the anastomosis (data not shown). It is clear from the literature that longer rectal stumps are prone to recurrent inflammation, have a significant impact on quality of defecatory function and often require revision.[29] We believe that leaving a short rectal stump decreases the risk of acute "cuffitis" and preserves overall defecatory function in the presence of chronic inflammation. Furthermore, "cuffitis" involving a short ATZ remnant is more likely to respond to medical management as shown in our series where both symptomatic patients promptly responded to topical medical management. In this study, pouch loss has not occurred as a consequence of recurrent or chronic cuffitis.

Our study further emphasizes the need for proper selection to achieve excellent surgical results in the management of UC. Based on the evidence currently available,[10,12,24,28] we believe that UC patients with preoperative cancer or dysplasia, irrespective of grade and location, should not be offered a stapled IPAA, but rather have a complete transanal mucosectomy with hand-sewn anastomosis to truly minimize the oncologic risk. Furthermore, preoperative patient-related factors, such as obesity, nutrition, and medical regimen should be optimized before embarking on the definitive operation to achieve superior functional results and restore quality of life.

Conclusions

In properly selected patients, preservation of the ATZ is oncologically safe and offers excellent defecatory function and quality of life. We believe that to achieve these results, being able to leave a short ATZ is critical. Proper patient selection is essential to achieve these results. After stapled IPAA, because of the presence of inflammatory changes in

a high percentage of patients, life-long surveillance with biopsies of the ATZ is mandatory for early detection and treatment of potential neoplastic degeneration.

Acknowledgment This study was funded in part by the University of Chicago Cancer Research Foundation (UCCRF) Auxiliary Board Research Support Grant (A.F.).

References

1. Bauer JJ, Gorfine SR, Gelernt IM, Harris MT, Kreel I. Restorative proctocolectomy in patients older than fifty years. Dis Colon Rectum 1997;40(5):562–565.
2. Durno C, Sherman P, Harris K, et al. Outcome after ileoanal anastomosis in pediatric patients with ulcerative colitis. J Pediatr Gastroenterol Nutr 1998;27(5):501–507.
3. Lewis WG, Sagar PM, Holdsworth PJ, Axon AT, Johnston D. Restorative proctocolectomy with end to end pouch-anal anastomosis in patients over the age of fifty. Gut 1993;34(7):948–952.
4. Tilney HS, Constantinides V, Ioannides AS, Tekkis PP, Darzi AW, Haddad MJ. Pouch-anal anastomosis vs straight ileoanal anastomosis in pediatric patients: A meta-analysis. J Pediatr Surg 2006;41(11): 1799–1808.
5. Gemlo BT, Belmonte C, Wiltz O, Madoff RD. Functional assessment of ileal pouch-anal anastomotic techniques. Am J Surg 1995;169(1):137–141.
6. Gullberg K, Lindquist K, Lijeqvist L. Pelvic pouch-anal anastomoses: Pros and cons about omission of mucosectomy and loop ileostomy. A study of 60 patients. Ann Chir 1995;49(6):527–533.
7. Lewis WG, Williamson ME, Miller AS, Sagar PM, Holdsworth PJ, Johnston D. Preservation of complete anal sphincteric proprioception in restorative proctocolectomy: the inhibitory reflex and fine control of continence need not be impaired. Gut 1995;36(6):902–906.
8. Michelassi F, Lee J, Rubin M, et al. Long-term functional results after ileal pouch anal restorative proctocolectomy for ulcerative colitis: A prospective observational study. Ann Surg 2003;238 (3):433–441; discussion 42–45.
9. Miller R, Bartolo DC, Orrom WJ, Mortensen NJ, Roe AM, Cervero F. Improvement of anal sensation with preservation of the anal transition zone after ileoanal anastomosis for ulcerative colitis. Dis Colon Rectum 1990;33(5):414–418.
10. Hyman N. Rectal cancer as a complication of stapled IPAA. Inflamm Bowel Dis 2002;8(1):43–45.
11. Lavery IC, Sirimarco MT, Ziv Y, Fazio VW. Anal canal inflammation after ileal pouch-anal anastomosis. The need for treatment. Dis Colon Rectum 1995;38(8):803–806.
12. O'Riordain MG, Fazio VW, Lavery IC, et al. Incidence and natural history of dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of a five-year to ten- year follow-up. Dis Colon Rectum 2000;43(12):1660-1665.
13. Thompson-Fawcett MW, Mortensen NJ, Warren BF. "Cuffitis" and inflammatory changes in the columnar cuff, anal transitional zone, and ileal reservoir after stapled pouch-anal anastomosis. Dis Colon Rectum 1999;42(3):348–355.
14. Schmitt SL, Wexner SD, Lucas FV, James K, Nogueras JJ, Jagelman DG. Retained mucosa after double-stapled ileal reservoir and ileoanal anastomosis. Dis Colon Rectum 1992;35(11): 1051–1056.
15. Luukkonen P, Jarvinen H. Stapled vs hand-sutured ileoanal anastomosis in restorative proctocolectomy. A prospective, randomized study. Arch Surg 1993;128(4):437–440.
16. McIntyre PB, Pemberton JH, Beart RW, Jr., Devine RM, Nivatvongs S. Double-stapled vs. handsewn ileal pouch-anal anastomosis in patients with chronic ulcerative colitis. Dis Colon Rectum 1994;37(5):430–433.
17. Reilly WT, Pemberton JH, Wolff BG, et al. Randomized prospective trial comparing ileal pouch-anal anastomosis performed by excising the anal mucosa to ileal pouch-anal anastomosis performed by preserving the anal mucosa. Ann Surg 1997;225(6): 666–676.
18. Fenger C. The anal transitional zone. Location and extent. Acta Pathol Microbiol Scand 1979;87(5):379–386.
19. Thompson-Fawcett MW, Warren BF, Mortensen NJ. A new look at the anal transitional zone with reference to restorative proctocolectomy and the columnar cuff. Br J Surg 1998;85(11):1517–1521.
20. Miller R, Bartolo DC, Cervero F, Mortensen NJ. Anorectal temperature sensation: A comparison of normal and incontinent patients. Br J Surg 1987;74(6):511–515.
21. Miller R, Lewis GT, Bartolo DC, Cervero F, Mortensen NJ. Sensory discrimination and dynamic activity in the anorectum: Evidence using a new ambulatory technique. Br J Surg 1988;75(10): 1003–1007.
22. Michelassi F, Block GE. A simplified technique for ileal J-pouch construction. Surg Gynecol Obstet 1993;176(3):290–294.
23. Michelassi F, Hurst R. Restorative proctocolectomy with J-pouch ileoanal anastomosis. Arch Surg 2000;135(3):347–353.
24. Gorfine SR, Bauer JJ, Harris MT, Kreel I. Dysplasia complicating chronic ulcerative colitis: Is immediate colectomy warranted? Dis Colon Rectum 2000;43(11):1575–1581.
25. Ullman TA, Loftus EV, Jr., Kakar S, Burgart LJ, Sandborn WJ, Tremaine WJ. The fate of low grade dysplasia in ulcerative colitis. Am J Gastroenterol 2002;97(4):922–927.
26. Sequens R. Cancer in the anal canal (transitional zone) after restorative proctocolectomy with stapled ileal pouch-anal anastomosis. Int J Colorectal Dis 1997;12(4):254–255.
27. Stern H, Walfisch S, Mullen B, McLeod R, Cohen Z. Cancer in an ileoanal reservoir: a new late complication? Gut 1990;31(4): 473–475.
28. Remzi FH, Fazio VW, Delaney CP, et al. Dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of prospective evaluation after a minimum of ten years. Dis Colon Rectum 2003;46(1):6–13.
29. Tulchinsky H, McCourtney JS, Rao KV, et al. Salvage abdominal surgery in patients with a retained rectal stump after restorative proctocolectomy and stapled anastomosis. Br J Surg 2001;88 (12):1602–1606.

Discussion

Thomas Ullman, M.D. (New York, NY): Thank you to my surgical colleagues out here. As a gastroenterologist, it is always a bit intimidating to be in a room with surgeons, but I am happy to be here this morning.

Dr. Fichera's report here really I think puts the nail in the coffin of using hand-sewn anastomoses for patients who are dysplasia-free. He reports really excellent functional results, with about 5% of patients with episodes of leakage at night and the requirement of wearing pads. I think that quite clearly the functional outcomes are so outstanding in this group that it really almost dogmatically now is the operation of choice when it is available for these patients.

The dysplasia and neoplasia story in general really does require even greater follow-up than we have here. These patients were followed for a median of 33 months, and it will be curious to see, as I hope Dr. Fichera will be doing by following these patients into the future, what the true neoplastic potential is. With that in mind and with my 1-minute limitation, I had a couple of brief questions for Dr. Fichera.

The first question is, among these patients who had regularly scheduled anoscopies, how many of them in the intervals in between went on to develop episodes of cuffitis or even pouchitis? And I will leave these here in note form for you when we get to them all.

And then secondly, I wanted to know how many of these patients were truly at risk for the development of neoplasia over time? Specifically, how many patients had colitis for more than 8 years or sclerosing cholangitis or a family history of colorectal cancer?

Finally, what would you speculate ought to be the appropriate interval for dysplasia surveillance in this group?

Alessandro Fichera, M.D. (Chicago, IL): Thank you, Tom, for your comments and questions. The incidence of cuffitis has been reported by us in the past, and it is slightly lower than what has been reported in another series from the Cleveland Clinic. As I speculate in the manuscript, the fact that we do strive to keep a very short anal transition zone probably is responsible for our findings. A series from 1995 collecting patients going back to the 1970s is clearly different that a series from the late 1990s and forward. Our incidence overall of cuffitis including patients that had cuffitis in between the biopsies is approximately 10%. To answer your second question regarding patients at risk of developing cancer or dysplasia in the anal transition zone, in our previously reported experience the main indication for surgery was failure of medical management. Patients with dysplasia or long-standing disease, per se, were approximately 30 to 33% of the entire group.

Now, based on these findings, we changed our follow-up protocol. Obviously, patients will be followed forever, but rather than having them come back every year for a biopsy, and that was a big deterrent for them to come and have a biopsy, we are moving to a 3-year interval: Baseline of 1 year, if obviously we find no dysplasia, we wait 3 years from that, making this into a big event every 3 years rather than an every-year occurrence that really was not very appealing to our patient population.

Susan Galandiuk, M.D. (Louisville, KY): The reading of dysplasia, especially in the field of chronic inflammation, can be very difficult. Did you for purposes of this study have several pathologists review all your specimens for uniformity?

Dr. Fichera: Often patients relocate and we have often biopsies sent to us from outside institutions. Those biopsies were all reviewed by our dedicated pathologists. Furthermore, every biopsy is reviewed as a group at our inflammatory bowel disease conference every other week. So they were reviewed by two or three pathologists.

Bryan M. Clary, M.D. (Durham, NC): Using the same questionnaire, have you compared these results with your patients who underwent a hand-sewn anastomosis?

Dr. Fichera: That is exactly what we are going to do next. In a previous report, you noticed that the hand-sewn patients obviously have a longer follow-up. The series now is shifting more toward more stapled patients. So the comparison will be not totally fair, but that is the next step now that we have identified that the majority of stapled patients indeed have chronic inflammation. And another point is a lot of these normal mucosa patients eventually shift to chronic inflammation over time. So there is clearly a big group of patients with chronic inflammation. Those are the ones, as you are suggesting, that should be compared with the hand-sewn patients.

J Gastrointest Surg (2007) 11:1654–1661
DOI 10.1007/s11605-007-0259-z

Stapled Hemorrhoidectomy versus Conventional Excision Hemorrhoidectomy for Acute Hemorrhoidal Crisis

Huang-Jen Lai · Shu-Wen Jao · Chin-Cheng Su · Ming-Che Lee · Jung-Cheng Kang

Received: 31 May 2007 / Accepted: 19 July 2007 / Published online: 2 October 2007

Abstract We compared the safety and clinical outcomes of stapled hemorrhoidectomy and conventional excision hemorrhoidectomy in the treatment of acute hemorrhoidal crisis, and analyzed various factors associated with complications in stapled hemorrhoidectomy. Forty patients underwent stapled hemorrhoidectomy and forty underwent conventional excision hemorrhoidectomy. All had the operation under local anesthesia with conscious sedation within 24 h of admission. The length of surgery, hospital stay, disability, postoperative pain, and the use of analgesics were significantly less for patients in the stapled hemorrhoidectomy group. Stapled hemorrhoidectomy did not significantly increase the rate of complications. Five patients in the stapled group (12.5%) required further surgical intervention: three with thrombosed hemorrhoids and two with recurrent prolapse. No serious complications were reported in either group. Patient satisfaction was similar in the two groups. Increased age was identified as a factor that significantly elevated the risk of complications in the stapled group (OR, 1.06; 95% CI, 1.01–1.13). Anemia and time between the onset of prolapsed hemorrhoids and hospital admission were also risk factors for complications, although they were not significant. Stapled hemorrhoidectomy is a feasible treatment for selected patients with an acute hemorrhoidal crisis and has a similar complication rate to that of conventional excision hemorrhoidectomy. Stapled hemorrhoidectomy is superior in less-postoperative pain, shorter operation time, shorter hospital stay, and earlier return to normal activity. However, we suggest that older patients with anemia or a prolonged hemorrhoidal crisis are unsuitable for stapled hemorrhoidectomy.

Keywords Procedure for prolapse and hemorrhoids · Stapled hemorrhoidectomy · Hemorrhoids · Crisis

Introduction

The acute stage of hemorrhoidal disease, termed hemorrhoidal crisis, occurs when patients present with severely disabling, irreducible, circumferentially prolapsed or gangrenous hemorrhoids.[1] The crisis is characterized by acute pain, bleeding, inflammation, a foul-smelling discharge, and circumferentially irreducible hemorrhoids. It occurs because the anal sphincter squeezes and strangles the prolapsed internal hemorrhoids. The resulting sphincter spasm and the blockade of venous return cause edema and, occasionally, thrombosis of the external hemorrhoids. The resulting pain, swelling, and disability are dramatic and very severe.[2]

Although hemorrhoidal crisis is infrequent, it usually requires emergency medical treatment. Nonoperative treatments (e.g., warm sitz baths, analgesics, stool softeners, local ointments, suppositories, and manual reduction) had been considered as a safety option. However, these may prolong the disability and cause financial hardship. Moreover, most such patients may require subsequent rehospitalization for surgery.[3] Many investigators have suggested that emergency hemorrhoidectomy for these patients is safe and effective and has a similar complication rate to that of the elective operation for chronic hemorrhoids.[4–6]

Presented at the 48th Annual Meeting of The Society for Surgery of the Alimentary Tract, Washington, DC, May 19–23, 2007 (poster presentation).

S.-W. Jao · J.-C. Kang (✉)
Division of Colorectal Surgery, Department of Surgery,
Tri-Service General Hospital,
325, Section 2, Cheng Kong Road, Nei-Hu Dis.114,
Taipei, Taiwan
e-mail: surgeon.lai@msa.hinet.net

H.-J. Lai · C.-C. Su · M.-C. Lee · J.-C. Kang
Division of Colorectal Surgery, Department of Surgery,
Buddhist Tzu Chi General Hospital, Tzu Chi University,
Hualien, Taiwan

In 1998, Longo[7] first described the use of a circular stapling technique for treating prolapsed hemorrhoids. The essential mechanism of the technique involves pulling up the enlarged sagging hemorrhoidal tissue, reducing the redundant mucosa, and interrupting the branches of the superior hemorrhoidal artery, without dissection or excision of the perianal skin. It therefore avoids a painful cutaneous wound. In recent years, randomized and nonrandomized studies have found that stapled hemorrhoidectomy has potential benefits, including less postoperative pain and faster return to normal activity, than are experienced after conventional hemorrhoidectomy, with a similar complication rate.[8–12] However, stapled hemorrhoidectomy has only rarely been reported for the treatment of hemorrhoidal crisis.[13] We have reported our preliminary results previously.[14] This clinical trial was prospectively designed to compare stapled hemorrhoidectomy with conventional excision in patients with hemorrhoidal crisis, with particular attention to postoperative pain, the time taken to return to normal activity, early and late complications, patient satisfaction, and the analysis of various factors associated with complications in stapled hemorrhoidectomy.

Materials and Methods

Between January 2003 and January 2006, we recruited 80 consecutive patients presenting with acute hemorrhoidal crises (Fig. 1). The exclusion criteria included previous anal surgery, other anorectal disorders, pregnancy, and severe medical problems. This clinical trial was approved by the ethics committee of our institution. A detailed written informed consent was obtained from all patients. Stapled hemorrhoidectomy was performed in 40 patients, and all were operated on by the same surgeon, J. C. Kang, who is familiar with this technique and has previously applied it in more than 100 patients. The other 40 patients underwent conventional excision hemorrhoidectomy and were operated on by senior surgeons of the Colorectal Section. The demographic and clinical characteristics of the two groups are given in Table 1. All patients underwent operation within 24 h of admission. Routine laboratory tests were performed preoperatively in all patients, and complete medical and surgical histories were taken. Patients were requested to complete preoperative and postoperative subjective pain surveys using a visual analogue scale (VAS) ranging from 0 cm (no pain) to 10 cm (the worst pain ever experienced), during the perioperative period. All the data were collected and recorded by a surgical nurse on a prepared information sheet.

All patients received two warm water enemas before the operation. Preoperative antibiotics were routinely administered to each patient. All patients received local anesthesia with conscious sedation and were placed on the operating table in the prone jackknife position during surgery.

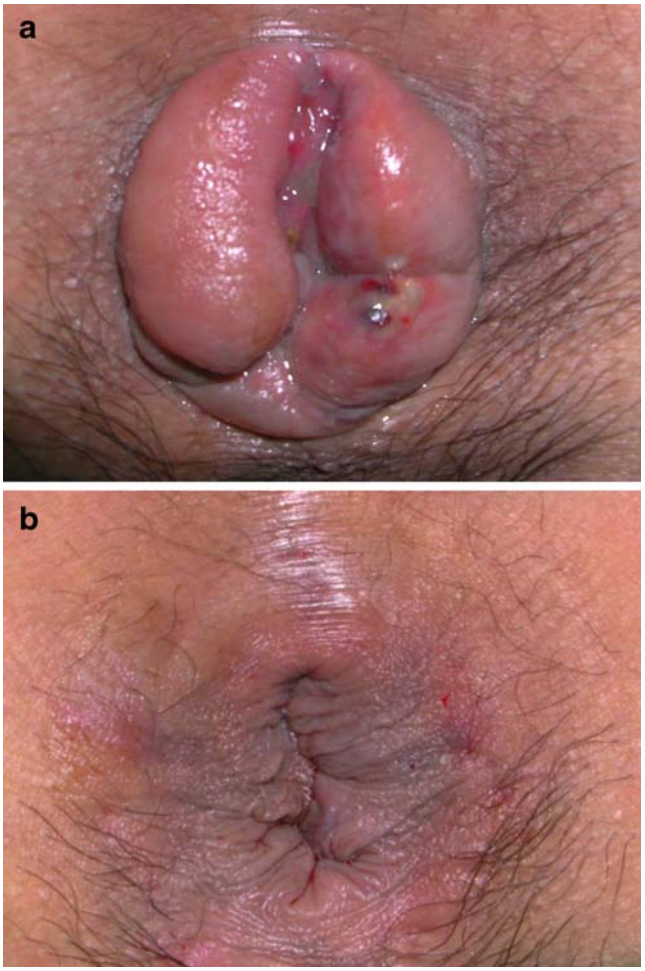


Figure 1 **a** Swelling, prolapsed, and thrombosed hemrrhoids. These are circumferentially irreducible and have some ulceration. **b** After stapled hemorrhoidectomy.

Operative Technique

Stapled hemorrhoidectomy was performed with a PPH™ set (Ethicon, Endo-Surgery, Cincinnati, OH, USA), using a modification of the standard method reported by Longo.[7] After the anal sphincter had been completely relaxed, direct massaging pressure was applied with a sterile pad to reduce the fixed prolapsed hemorrhoids, allowing an adequate and safe operation to be performed. After dilatation of the anal verge, a circular anal dilator and an obturator were inserted into the rectum. A pursestring suture anoscope was inserted and a 2-0 Prolene® (Ethicon, Endo–Surgery, Inc) pursestring suture was placed submucosally about 2–3 cm proximal to the dentate line. Once the pursestring suture had been checked and was complete, the fully opened stapler was inserted through the pursestring into the rectum. With the pursestring secured between its anvil and shoulder, the stapler was fired to excise the excess hemorrhoidal tissue

Table 1 Demographic Data and Clinical Characteristics

Variable	Stapled hemorrhoidectomy (n=40)	Conventional hemorrhoidectomy (n=40)	P value
Age in years[a]	51.78±18.69 (22–82)	40.25±14.67 (21–76)	<0.01[c]
Gender[b]			
Female	14 (35.0)	11 (27.5)	0.47
Male	26 (65.0)	29 (72.5)	
Preoperative hemorrhoidal disease, grade[b]			
None	3 (7.5)	2 (5.0)	0.61
I–II	10 (25.0)	7 (17.5)	
III–IV	27 (67.5)	31 (77.5)	
Putative predisposing factors[b]			
Constipation	24 (60.0)	21 (52.5)	0.72
Diarrhea	7 (17.5)	6 (15.0)	
Barium enema	2 (5.0)	1 (2.5)	
Defecography	1 (2.5)	1 (2.5)	
Long-term sitting inactive	6 (15.0)	11 (27.5)	
Anemia[b]			
No	30 (75.0)	27 (67.5)	0.46
Yes	10 (25.0)	13 (32.5)	
Time between onset of prolapsed hemorrhoids and hospital admission, in hours[a]	42.30±34.79 (12–144)	34.43±24.50 (3–96)	0.47
Operation time, in minutes[a]	29.75±3.39 (25–35)	49.00±18.37 (25–95)	<0.01[c]
Duration of postoperative hospital stay, in days[a]	1.33±0.53 (1–3)	2.80±0.94 (2–5)	<0.01[c]
Normal activity resumed postoperatively, in days[a]	7.53±1.41 (4–10)	10.60±4.98 (4–28)	<0.01[c]

Results expressed as means±SD (ranges) or numbers (percentages)
[a] Mann-Whitney U test
[b] Chi-square test
[c] Statistically significant

and was held tightly for 1 min to facilitate hemostasis. Hemostasis was achieved with suture ligation of any bleeding points. The excised specimen was retrieved from the stapler and inspected to verify that a complete doughnut of tissue had been excised, and a histopathological examination was made. We recorded the mean distance from the line of staples to the dentate line. Finally, a small roll of Gelfoam® (Pharmacia and Upjohn, Kalamazoo, MI, USA) coated with tetracycline ointment was placed into the anal canal.

Conventional excision hemorrhoidectomy was performed with a semiclosed hemorrhoidectomy. At the end of the operation, a pack of Gelfoam was placed using the same protocol as used with the stapling procedure, and several pieces of gauze were applied to the perianal skin. We removed the gauze and Gelfoam on the evening of the operation or the next morning.

Postoperative Care

Postoperatively, all patients were administered regular ketorolac tablets (10 mg four times daily by mouth). Intramuscular meperidine (1 mg/kg body weight per dose) was administered as rescue analgesia. Patients were discharged from the hospital when free from severe pain that required intramuscular analgesia, regardless of whether evacuation had occurred. At the time of discharge, oral analgesia (ketorolac tablets), stool softening agents, and oral antibiotics were prescribed until the next clinic visit. Patients were advised to return to work or return to normal activity as soon as they felt able. A clinical evaluation was performed by the operative surgeon after 7 days, 14 days, 1 month, and 6 months. Patient satisfaction with the surgery was assessed using a seven-point scale ranging from extremely dissatisfied (score −3) to extremely satisfied (score +3) at the last follow-up.[15] Postoperative pain, analgesic requirements, and the time taken to return to normal activity were also recorded by a surgical nurse.

Statistical Analysis

A statistical analysis was performed using the SPSS version 13.0 (SPSS Inc, Chicago, Ill). To describe the basic characteristics of the study subjects in the two groups, their demographic data and specific clinical features were analyzed with descriptive statistics and basic comparisons. These were expressed as means±standard deviations (SD)

for continuous variables, and numbers (percentages) for categorical factors. Because the skewed data distributions and limited sample sizes were concerns, nonparametric methods were used for comparisons. Similar approaches were taken for prognosis-related factors. Possible determinants of complications in the stapled group, including age, sex, anemia, time between onset of prolapsed hemorrhoids and hospital admission, and postoperative pain scores were analyzed using logistic regression (univariate and multivariate analyses) to estimate each variable's individual influence on the occurrence of complications. The odds ratio (OR) with 95% confidence interval (CI) for each variable were used to estimate the relative risks. Statistical significance was set at $P<0.05$.

Results

The demographic and clinical data for the patients are shown in Table 1. There were no differences in sex, grade of preoperative hemorrhoidal disease, putative predisposing factors, anemia, or time between the onset of prolapsed hemorrhoids and hospital admission in the two groups. The mean age of the stapled group was higher than that of the conventional group. The patients were predominantly men ($n=55$, 69%). The most common cause of hemorrhoidal crisis was constipation ($n=45$, 56%).

The operation time was significantly shorter in the stapled group. All patients in this group required a hemostatic suture after the stapler had been fired. The mean distance between the line of staples and the dentate line was 16.6±3.3 mm (range, 10–25 mm). The mean hospital stay and the mean interval to resume normal activity were significantly lower in patients who had undergone stapled hemorrhoidectomy than in those who had undergone conventional hemorrhoidectomy.

The mean duration of follow-up was 12.1 months (range, 6–18 months) in the stapled group and 15.0 months (range, 6–24 months) in the conventional group.

Complications

The operative and postoperative complications are listed in Table 2. An intraoperative complication was noted in one young woman in the stapled hemorrhoidectomy group, who suffered vasovagal syncope when the stapler was fired and was treated with intravenous fluid hydration. We resumed and completed the operation. Other intraoperative events in the stapled hemorrhoidectomy group included flap dehiscence in four patients and incomplete doughnuts in four patients. No intraoperative events or complications were observed in the conventional excision hemorrhoidectomy group.

Urinary retention and fever were the most common early complications (within 7 days of the operation). There were no significant differences between the two groups. The eight patients in the two groups who had urinary retention were treated with temporary catheterization. Two patients from the stapled group and seven patients from the conventional excision group had fever after the operation, and this symptom subsided spontaneously. Postoperative bleeding occurred in two patients in the conventional excision group and in one patient in the

Table 2 Complications

Complication	Stapled hemorrhoidectomy ($n=40$)	Conventional hemorrhoidectomy ($n=40$)	P
Immediate (during operation)			
Flap dehiscence	4 (10.0)	0 (0.0)	
Vasovagal reflex	1 (2.5)	0 (0.0)	
Incomplete doughnut	4 (10.0)	0 (0.0)	
Early (<7 days postoperatively)			
Bleeding	1 (2.5)	2 (5.0)	1.00
Urinary retention	4 (10.0)	4 (10.0)	1.00
Fever	2 (5.0)	7 (17.5)	0.15
Thrombosed hemorrhoids	3 (7.5)	0 (0.0)	0.24
Fecal urgency	3 (7.5)	0 (0.0)	0.24
Late (>7 days postoperatively)			
Recurrent prolapsed hemorrhoids	2 (5.0)	0 (0.0)	0.49
Hypertrophy papillae	2 (5.0)	0 (0.0)	0.49
Fecal impaction	0 (0.0)	2 (5.0)	0.49
Residual skin tag	3 (7.5)	1 (2.5)	0.62
Anal stenosis	1 (2.5)	2 (5.0)	1.00
Anorectal abscess	0 (0.0)	1 (2.5)	1.00

Results are expressed as numbers (percentages)
Statistical method: Fisher's exact probability test

stapled group. All three required check bleeding under local anesthesia in the operating room. Thrombosed hemorrhoids were observed in three patients in the stapled group and in none in the conventional excision group. They were managed with topical ointment and sitz baths for about 1 week. However, these treatments were ineffective and all of these patients required subsequent surgical excision. Fecal urgency occurred in three patients in the stapled group and in none in the conventional excision group. None of these patients had additional treatment, and the symptom subsided within 2 weeks of the operation. In the conventional excision group, two patients experienced two complications each. One had bleeding and urinary retention; the other had bleeding and fever.

Regarding late complications (more than 7 days after the operation), recurrent prolapsed hemorrhoids occurred in two patients in the stapled group and in none in the conventional excision group. Both of these patients failed to respond to rubber band ligation and required further excision hemorrhoidectomy. Two patients in the stapled group had hypertrophy papillae with discomfort and perianal itching, but neither required further treatment. Two patients in the conventional excision group experienced fecal impaction, which was managed with enemas. Three patients in the stapled group and one patient in the conventional excision group had residual skin tags, which were managed with conservative treatments. Anal stenosis developed in three patients: one in the stapled group and two in the conventional excision group. One of the two patients in the conventional excision group required further surgery with anoplasty, and the other two patients underwent anal dilation. One patient in the conventional excision group developed an anorectal abscess, which was managed with incision and drainage.

Stapled hemorrhoidectomy did not significantly increase the risk of complications (early and late) compared with conventional hemorrhoidectomy, according to multivariate analyses (OR, 1.09; 95% CI, 0.38–3.16; P=0.88).

As shown in Table 3, increased age was identified as a factor with a significantly elevated risk of complications among patients with stapled hemorrhoidectomy (OR, 1.05; 95% CI, 1.01–1.10). It is worth noting that the time between the onset of prolapsed hemorrhoids and hospital admission correlated with an elevated risk of complications with borderline significance. Anemia entailed a relative risk of more than threefold, although this risk was not statistically significant. Table 4 shows the multivariate analysis results. Age remained a significant risk factor (OR, 1.06; 95% CI, 1.01–1.13). After we adjusted for the other independent risk factors, the relative risk attributable to anemia increased to 6.79 (95% CI, 0.74–62.22), but it did not reach statistical significance.

Table 3 Univariate Analysis of the Effects of Demographic and Clinical Features on the Occurrence of Early/Late Complications in Patients with Stapled Hemorrhoidectomy (n=40)

Variables	Early/late complications		Odds ratio (95% CI)	P value
	No (n=25)	Yes (n=15)		
Age	46.16± 16.80	61.13± 18.43	1.05 (1.01–1.10)	<0.05*
Gender				
Female	8	6	Reference	0.61
Male	17	9	0.71 (0.19–2.67)	0.61
Time between onset of prolapsed hemorrhoids and hospital admission	33.60± 31.21	56.80± 36.63	1.02 (1.00–1.04)	0.05
Anemia				
No	21	9	Reference	0.10
Yes	4	6	3.50 (0.79–15.48)	0.10
Postoperative VAS score (Day 1)	3.56± 0.58	3.57± 0.52	0.73 (0.22–2.39)	0.60

*Statistically significant

Pain Scores

There was no difference in the preoperative pain scores of both groups. Figure 2 demonstrates that the mean pain score was less in the stapled group than in the conventional group on postoperative days 1, 7, and 14. Intramuscular analgesia requirements in the hospital, the duration of oral analgesia usage, and the postoperative pain scores were

Table 4 Multivariate Analysis of the Effects of Demographic and Clinical Features on the Occurrence of Early/Late Complications in Patients with Stapled Hemorrhoidectomy (n=40)

Variables	Odds Ratio	95% Confidence Interval	P
Age	1.06	1.01–1.13	<0.05*
Gender			
Female	Reference		
Male	1.13	0.21–6.20	0.89
Time between onset of prolapsed hemorrhoids and hospital admission	1.00	0.97–1.02	0.87
Anemia			
No	Reference		
Yes	6.79	0.74–62.22	0.09

*Statistically significant

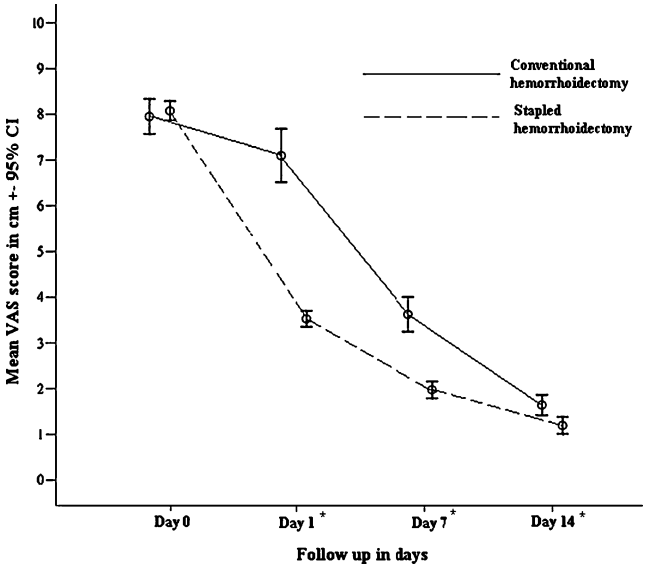


Figure 2 The trend in subjective pain based on VAS scores in cm among patients with hemorrhoidal crisis who underwent stapled hemorrhoidectomy or conventional hemorrhoidectomy (n=80). *Asterisk*, P<0.01 when the two groups are compared with the Mann-Whitney U test.

significantly lower in patients who had undergone stapled hemorrhoidectomy (Table 5).

Patient Satisfaction

The mean satisfaction score at the final follow-up was 1.3± 1.5 (range, −3 to +3) in the stapled group and 1.0±1.6 (range, −3 to +3) in the conventional excision group. It was not significantly different between the two groups (P=0.39).

Discussion

Although circular stapled hemorrhoidectomy has been widely adopted for the treatment of hemorrhoids and mucosal prolapses, this new technique has not been completely accepted by some surgeons, who have raised legitimate concerns regarding major complications such as pelvic sepsis, rectal perforation, rectovaginal fistula, and Fournier's gangrene.[16–18] Theoretically, the use of the stapling technique in the treatment of patients experiencing a hemorrhoidal crisis, who already have ulcerated, thrombosed, or gangrenous hemorrhoids, is unwise because of the potential risk of hemorrhage, pyelophlebitis, and septic complications. However, in our study, no mortality or serious complications were observed. Furthermore, the stapling technique did not increase the complication rate compared with that of conventional excision hemorrhoidectomy.

To the best of our knowledge, only one study has compared stapled mucosectomy with conventional hemorrhoidectomy for acute thrombosed circumferential piles within a follow-up of 6 weeks.[13] That study demonstrated that stapled hemorrhoidectomy is feasible, and that it may result in less pain, a more rapid resolution of symptoms, an earlier return to work, and lower morbidity compared with a conventional procedure. Our study confirmed these advantages.

The purpose of stapled hemorrhoidectomy is the excision of the redundant rectal mucosa and hemorrhoids, and no attempt is made to excise the external component of the hemorrhoids. Regarding this approach to the treatment of thrombosed hemorrhoids, Brown et al.[13] postulated that the thrombosed area does not require excision or decompression, and that the thromboses may resolve with conservative treatment. However, three patients in the stapled group developed persistent thrombosed hemorrhoids after the operation and required further surgical excision because of the failure of the conservative treatment.

Ravo et al.[19] reviewed 1,107 patients treated with stapled hemorrhoidectomy in 12 Italian coloproctological centers. They found that recurrent hemorrhoids were the most common late complication (2.3%), and that 40% of those patients could be successfully treated with rubber band ligation. Singer et al.[12] obtained similar results at two colorectal surgery centers in the USA, where prolapsed

Table 5 Pain Scores (1–10) and Use of Analgesics

	Stapled hemorrhoidectomy (n=40)	Conventional hemorrhoidectomy (n=40)	P value
Preoperative VAS score (day 0)	8.08±0.66 (7–9)	7.90±1.19 (6–10)	0.40
Postoperative VAS score (day 1)	3.53±0.55 (3–5)	7.18±1.82 (4–10)	<0.01*
Postoperative VAS score (day 7)	1.98±0.58 (1–4)	3.68±1.19 (0–6)	<0.01*
Postoperative VAS score (day 14)	1.33±0.57 (1–3)	1.85±0.70 (1–4)	<0.01*
Extra meperidine requirements (mg/kg body weight)	0.33±0.47 (0–1)	2.65±2.14 (0–9)	<0.01*
Days taking ketorolac (10 mg tablets)	3.08±1.02 (1–5)	9.13±3.08 (3–14)	<0.01*

Results expressed as means±SD (ranges)
Statistical method: Mann-Whitney U test
*Statistically significant

hemorrhoids were the most common late complication (7.4%). In our study, two patients (5%) in the stapled group experienced recurrent prolapsed hemorrhoids, which required further surgical excision. Rubber band ligation was attempted to treat the recurrent symptoms, but failed. Because the average distance of the stapled line to the dentate line in these patients was only about 2 cm, there was insufficient space to apply the rubber band. The severe swelling and fibrosis of the rectal mucosa also made it more difficult to stretch the redundant rectal mucosa.

The intraoperative problems were minor. Four patients in the stapled hemorrhoidectomy group (10%) were found to have incomplete doughnuts of resected tissue. The significance of this is not entirely clear. We think this may result from the improper placement of the pursestring suture. Most of our patients with hemorrhoidal crises have massive circumferential piles, and these large prolapsing piles make accurate placement of the pursestring especially difficult. Ideally, the pursestring suture should be in the same plane. And the plane of the pursestring suture and anal canal should be vertical. Otherwise, the stapler incompletely excises the mucosa, resulting in an incomplete doughnut. In our initial experiences, we sometimes had to remove a pursestring suture that we considered improper or unsatisfactory, and reapply it. We also observed flap dehiscence in four patients (10%) in the stapled group. The causes may have been multiple, including such factors as the pursestring suture, improper tension on the suture drawing the bulky prolapsed tissue into the stapler, or the swollen mucosa resulting in an incompletely constructed anastomosis. In the stapled group, one patient developed the rare complication of vasovagal syncope. This is characterized by bradycardia and hypotension, which may be triggered by pain or discomfort.[20] Operative pain and distension of the rectum may have caused vasodilatation of the gastrointestinal vasculature and reduced the blood flow to the brain in this patient. Vasovagal symptoms may also occur during the procedure of rubber band ligation of hemorrhoids.[21]

Unlike the Longo approach,[7] we placed the pursestring suture close to the dentate line (about 2–3 cm) in an attempt to resect a greater amount of prolapsed mucosa. This is perhaps why we observed good results in patients with large circumferential prolapsed hemorrhoids. This did not increase the rate of anal stricture complications in our patients.

Urinary retention remains a problem, and occurred in both the stapled and conventional groups. It was the most common early complication in our study, as in other studies.[4,12] Although we had limited the patients' oral fluids to less than 400 ml and provided adequate postoperative analgesia, four patients (10%) in the stapled group and four patients (10%) in the conventional group developed this problem.

The high rate of postoperative fever (11%) noted in our patients was surprising. This was also reported 30 years ago by Tinckler and Baratham[22] and Mazier.[6] No recent study has reported this, perhaps because the phenomenon has been ignored or has not been recorded. All fevers in our patients were low grade, occurred on the night of the hemorrhoidectomy, and subsided the following day. As Lal and Levitan have pointed out, hemorrhoidectomy may be followed by transitory bacteremia and low-grade fever as a result of the relatively constant release of bacteria into the bloodstream from a feeding focus.[23] LeFrock et al.[24] also reported an 8.5% rate of bacteremia after the proctoscopic examination of patients with no evidence of lower-intestinal disease. Our patients all had thrombosis or gangrene of their prolapsed hemorrhoids, in which local inflammation is more severe than in common prolapsed hemorrhoids. This may account for the high rate of transient low-grade fever in our patients.

Cheetham et al.[11] reported that 5 of 16 patients receiving stapled hemorrhoidectomy developed persistent post defecatory anal pain and fecal urgency for up to 15 months. No patient in our study experienced persistent pain, but three in the stapled group experienced temporary fecal urgency, the causes of which were not clear. Some authors have suggested that the low location of the pursestring suture and the presence of a resected specimen containing muscle fibers may be associated with persistent pain and fecal urgency.[11,19,25] However, in our previous study, we found that the presence of muscle fiber was not associated with perioperative pain, although it was associated with a significantly higher incidence of temporary fecal urgency.[14]

Our logistic regression analysis showed that increased age was associated with a significantly elevated risk of complications (early and late) in the stapled group. Although the number of patients in our study was small, the outcome is still meaningful. Therefore, we should pay particular attention to older patients when they have stapled hemorrhoidectomy for hemorrhoidal crisis. More frequent follow-ups in an outpatient department are advisable. Although not statistically significant, we also found that the risk of complications was higher in patients with anemia or prolonged hemorrhoidal crisis in the stapled group. It is understandable that patients with anemia may experience the symptoms of hemorrhoids for a longer time and anemia may also reduce the blood flow to the anoderm. Furthermore, a prolonged hemorrhoidal crisis entails a greater likelihood of developing inflammation, bleeding, gangrene, and fibrosis of the anoderm. All these factors will influence the surgical result. Based on these analyses, we suggest that older patients with anemia or prolonged hemorrhoidal crisis are not suitable for this surgical approach.

Our results are encouraging, in that the use of stapled hemorrhoidectomy significantly reduced postoperative pain

and was associated with a faster return to normal activity, without increasing the complication rate. Patients with hemorrhoidal crisis have symptoms for a period of time. They delay seeking medical attention because of a fear of postoperative pain or because they are busy with work. So this approach provides an alternative to conventional hemorrhoidectomy.

Despite the clinical responses, there was no difference in patient satisfaction between the two groups. Although stapled hemorrhoidectomy can reduce postoperative pain and disability, satisfaction was not significantly higher in that group than in the conventional excision group. Poor satisfaction within the stapled group was reported among those patients with recurrent symptoms or requiring reoperation.

Conclusions

Our results show that both stapled and conventional excision hemorrhoidectomy are safe and feasible methods for the treatment of acute hemorrhoidal crisis, with only minor and temporary complications. Their clinical advantages are different. Stapled hemorrhoidectomy was superior in producing less postoperative pain, a shorter operative time, shorter hospital stay, and earlier return to normal activity, but was associated with more recurrent and thrombosed hemorrhoids than the conventional excision procedure. We suggest that stapled hemorrhoidectomy is not suitable for older patients with anemia or prolonged hemorrhoidal crisis.

References

1. Nieves PM, Perez J, Suarez JA. Hemorrhoidectomy—how I do it: experience with the St. Mark's Hospital technique for emergency hemorrhoidectomy. Dis Colon Rectum 1977;20:197–201.
2. Eisenstat T, Salvati EP, Rubin RJ. The outpatient management of acute hemorrhoidal disease. Dis Colon Rectum 1979;22:315–317.
3. Grace RH, Creed A. Prolapsing thrombosed haemorrhoids: outcome of conservative management. Br Med J 1975;3:354.
4. Ceulemans R, Creve U, Van Hee R, Martens C, Wuyts FL. Benefit of emergency haemorrhoidectomy: a comparison with results after elective operations. Eur J Surg 2000;166:808–812.
5. Eu KW, Seow-Choen F, Goh HS. Comparison of emergency and elective haemorrhoidectomy. Br J Surg 1994;81:308–310.
6. Mazier WP. Emergency hemorrhoidectomy—a worthwhile procedure. Dis Colon Rectum 1973;16:200–205.
7. Longo A. Treatment of haemorrhoidal disease by reduction of mucosa and haemorrhoidal prolapse with a circular stapling device: a new procedure. 6th World Congress of Endoscopic Surgery. Mundozzi Editore 1998;777–784.
8. Rowsell M, Bello M, Hemingway DM. Circumferential mucosectomy (stapled haemorrhoidectomy) versus conventional haemorrhoidectomy: randomized controlled trial. Lancet 2000;355:779–781.
9. Ganio E, Altomare DF, Gabrielli F, Milito G, Canuti S. Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy. Br J Surg 2001;88:669–674.
10. Wilson MS, Pope V, Doran HE, Fearn SJ, Brough WA. Objective comparison of stapled anopexy and open hemorrhoidectomy: a randomized, controlled trial. Dis Colon Rectum 2002;45:1437–1444.
11. Cheetham MJ, Cohen CR, Kamm MA, Phillips RK. A randomized, controlled trial of diathermy hemorrhoidectomy vs. stapled hemorrhoidectomy in an intended day-care setting with longer-term follow-up. Dis Colon Rectum 2003;46:491–497.
12. Singer MA, Cintron JR, Fleshman JW, Chaudhry V, Birnbaum EH, Read TE, Spitz JS, Abcarian H. Early experience with stapled hemorrhoidectomy in the United States. Dis Colon Rectum 2002;45:360–367.
13. Brown SR, Ballan K, Ho E, Fams YH, Seow-Choen F. Stapled mucosectomy for acute thrombosed circumferentially prolapsed piles: a prospective randomized comparison with conventional haemorrhoidectomy. Colorectal Dis 2001;3:175–178.
14. Kang JC, Chung MN, Chao PC, Lee CC, Hsiao CW, Jao SW. Emergency stapled haemorrhoidectomy for haemorrhoidal crisis. Br J Surg 2005;92:1014–1016.
15. Carapeti EA, Kamm MA, McDonald PJ, Phillips RK. Double-blind randomized controlled trial of effect of metronidazole on pain after day-case hemorrhoidectomy. Lancet 1998;351:169–172.
16. Wong LY, Jiang JK, Chang SC, Lin JK. Rectal perforation: a life-threatening complication of stapled hemorrhoidectomy: report of a case. Dis Colon Rectum 2003;46:116–117.
17. Maw A, Eu KW, Seow-Choen F. Retroperitoneal sepsis complicating stapled hemorrhoidectomy: report of a case and review of the literature. Dis Colon Rectum 2002;45:826–828.
18. Bonner C, Prohm P, Storkel S. Fournier gangrene as a rare complication after stapler hemorrhoidectomy. Case report and review of the literature. Chirurg 2001;72:1464–1466.
19. Ravo B, Amato A, Bianco V, Boccasanta P, Bottini C, Carriero A, Milito G, Dodi G, Mascagni D, Orsini S, Pietroletti R, Ripetti V, Tagariello GB. Complications after stapled hemorrhoidectomy: can they be prevented? Tech Coloproctol 2002;6:83–88.
20. Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. Br J Anaesth 2001;86:859–868.
21. Kumar N, Paulvannan S, Billings PJ. Rubber band ligation of haemorrhoids in the out-patient clinic. Ann R Coll Surg Engl 2002;84:172–174.
22. Tinckler LF, Baratham G. Immediate haemorrhoidectomy for prolapsed piles. Lancet 1964;14:1145–1146.
23. Lal D, Levitan R. Bacteremia following proctoscopic biopsy of a rectal polyp. Arch Intern Med 1972;130:127–128.
24. LeFrock JL, Ellis CA, Turchik JB, Weinstein L. Transient bacteremia associated with sigmoidoscopy. N Engl J Med 1973;289:467–469.
25. Correa-Rovelo JM, Tellez O, Obregon L, Miranda-Gomez A, Moran S. Stapled rectal mucosectomy vs. closed hemorrhoidectomy: a randomized, clinical trial. Dis Colon Rectum 2002;45:1367–1374.

J Gastrointest Surg (2007) 11:1662–1668
DOI 10.1007/s11605-007-0328-3

Stapled Hemorrhoidopexy: A Prospective Study From Pathology to Clinical Outcome

Pierpaolo Sileri · Vito Maria Stolfi · Giampiero Palmieri · Alessandra Mele · Alessandro Falchetti · Sara Di Carlo · Achille Lucio Gaspari

Received: 1 June 2007 / Accepted: 5 September 2007 / Published online: 5 October 2007

Abstract Stapled hemorrhoidopexy is widely accepted to treat hemorrhoids, but serious complications have been reported. In this prospective audit, we correlated clinical outcome with pathological findings. From January 2003 to April 2007, 94 patients underwent hemorrhoidopexy. Macroscopic appearance of the specimen (shape, size, and depth) was recorded. Microscopically, the presence of columnar, transitional, and squamous epithelium, the involvement of circular/longitudinal smooth muscle, and features of mucosal prolapse were assessed. Clinical outcome was evaluated by a validated questionnaire. Postoperative pain, secretion, and bleeding durations were 12.7+/−10.6, 5.6+/−9.6, and 6.3+/−8.4 days. Patient's return to work averaged 16.7+/−10.7 days. Fissure, skin tags, and anal strictures were observed in 23.4%. Seven patients experienced pain for a significantly longer period of time. All specimens contained columnar mucosa, but 29.8% contained columnar and transitional epithelium and 12.8% contained columnar, anal transitional, and stratified squamous epithelium. Smooth muscle was observed in 62.7%. Pain was significantly increased if transitional epithelium was present in the specimen. No correlation or differences were observed if smooth muscle was present, although postoperative bleeding was more frequent. Hemorrhoidopexy is safe and effective. The specimen should always be sent for pathology examination. Only columnar epithelium should be present and, although the presence of smooth muscle does not influence the outcome in terms of functional results, its presence may play a role in postoperative bleeding.

Keywords Hemorrhoidopexy · Hemorrhoids · Outcome

Introduction

Conventional hemorrhoidectomy by open or closed excision is widely used for the treatment of prolapsed third- or fourth-degree hemorrhoids, but the postoperative period is accompanied by considerable pain and delayed return to normal activities.[1,2] Over the last decade, stapled hemorrhoidopexy (SH) gained wide acceptance as an effective, safe, and less painful technique to treat hemorrhoids. It can be performed in a day-surgery setting, and some authors suggested that this could reduce the overall cost of the procedure, but further data are needed.[3] Based on existing literature, over 50,000 patients have been treated in Europe, and this technique seems to be indicated for all hemorrhoid degrees.[4] However, this enthusiasm has recently been tempered by increasing reports of specific technique-related complications, including life-threatening pelvis sepsis and deaths.[5] In this prospective audit, we report our experience with this technique and correlate pathological findings to short- and long-term clinical outcomes.

Presented as poster at the Digestive Disease Week, May 2007, Washington, USA.

P. Sileri · V. M. Stolfi · A. Mele · A. Falchetti · S. Di Carlo · A. L. Gaspari
Department of Surgery, University of Rome Tor Vergata, Rome, Italy

G. Palmieri
Department of Pathology, University of Rome Tor Vergata, Rome, Italy

P. Sileri (✉)
Policlinico Tor Vergata,
6B, Viale Oxford 81,
00133 Rome, Italy
e-mail: piersileri@yahoo.com

Table 1 Patients' Characteristics

Characteristic	Value
Gender (M/F)	56/38
Median age [years +/− SD (range)]	46.9+/−13.6 (21–75)
Hemorrhoids (3rd/4th degree *n*/*n*)	54/40
Previous ambulatory procedures[a] (*n*/%)	8/8.5%

[a] Rubber band ligation and/or sclerotherapy

Patients and Methods

Between January 2003 and April 2007, 94 symptomatic patients underwent hemorrhoidopexy in a day-surgery setting. All procedures were performed by two colorectal surgeons (PS and VMS). Cases performed as emergency procedures or performed by residents as part of the teaching program were excluded from this study. Patients with inflammatory bowel disease, coexisting anorectal disease, or previous anal surgery were excluded as well. Mean follow-up was 20.3+/−14 months ranging from 1 to 52 months.

Patients' demographic data and characteristics are shown in Table 1. Before surgery, all patients underwent digital rectal examination and proctoscopy. Preoperative Wexner continence score was evaluated for all patients. Anorectal manometry and/or ultrasonography (US) were performed if required. All patients received a phosphate enema 2 h before the operation. All surgeries were performed in lithotomy position under local anesthesia, and when required, general anesthesia was provided.

Antibiotic prophylaxis was administered using intravenous cephalosporin (1 g) and metronidazole (500 mg) immediately before surgery. Starting May 2006, our protocol was revised and a single-antibiotic regimen replaced the previous one using intravenous cefotaxime (2 g).

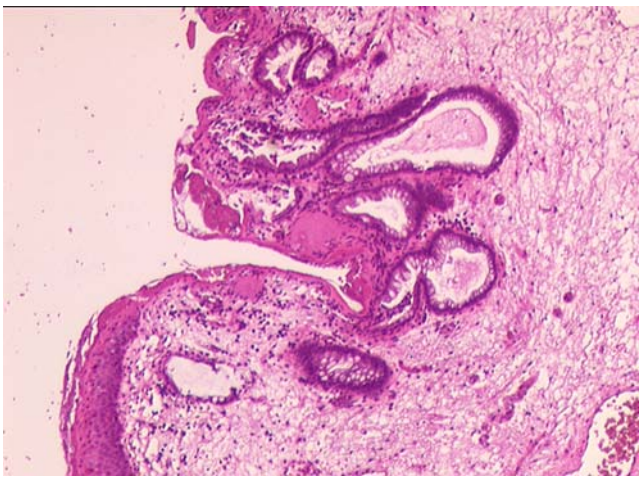


Figure 1 Resected specimen histology: transitional epithelium, diamond-shape crypts, ulcers.

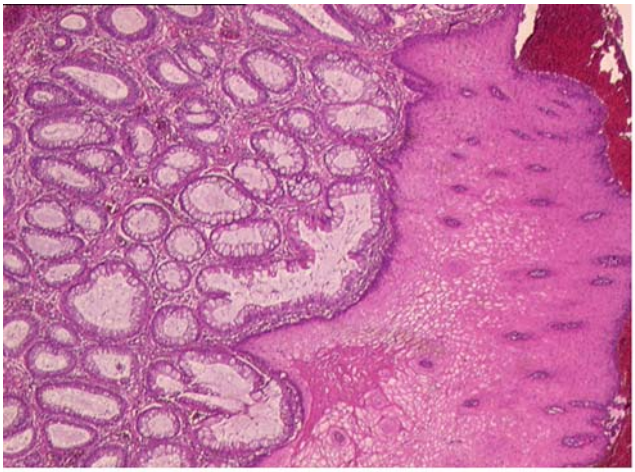


Figure 2 Resected specimen histology: transitional and squamous epithelium above smooth circular muscle (internal sphincter).

The procedure was performed according to the technique described by Longo[6] using the PPH01 kit (Ethicon Endo-Surgery) with no modifications or additional procedures. Mucosal doughnuts retrieved from the stapler were orientated and sent for pathology examination in 10% neutral buffered formalin. All specimens were reviewed by a single consultant pathologist (GP). The macroscopic appearance of each resected specimen, including shape, size, and depth, was recorded.

Microscopically, the presence of columnar, transitional, and squamous epithelium, as well as involvement of circular and longitudinal smooth muscle, was assessed. Smooth muscle beneath the squamous epithelium was considered to represent internal anal sphincter. Features of mucosal prolapse, such as muscularization of the lamina propria, thickening/disruption of the muscularis mucosa,

Table 2 Histology of the Resected Specimens Divided by Gender and Statistical Significance

Pathology findings		Male	Female	*P* value
Epithelium *n* (%)				
Columnar only	54 (57.4%)	32 (59.3%)	22 (68.7%)	NS
+ Transitional	28 (29.8%)	14 (50.0%)	14 (50.0%)	NS
+ Transitional and squamous	12 (12.8%)	8 (66.7%)	4 (33.3%)	0.05
Smooth muscle				
Circular only	48 (51.1%)	26 (54.2%)	22 (45.8%)	NS
+ Longitudinal	11 (11.7%)	7 (63.6%)	4 (36.4%)	0.05
Total	59 (62.7%)	33 (55.9%)	26 (44.1%)	NS

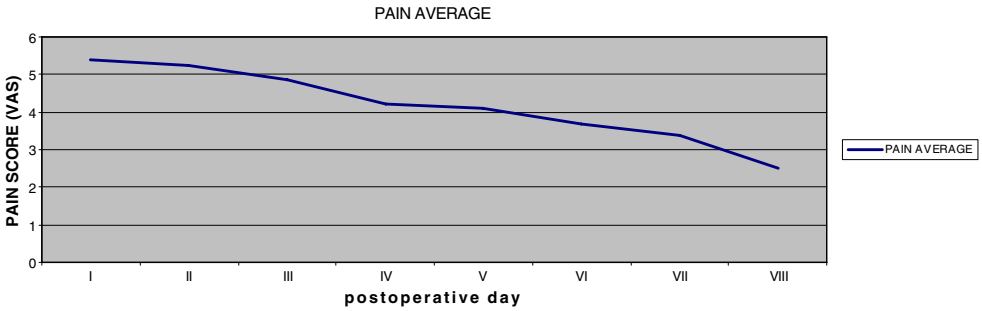


Figure 3 Pain score according to VAS during the first week (expressed as pain VAS score between 1 and 10).

diamond-shaped crypts, surface hyperplasia, and thrombosed vessels, were also assessed as previously described.[7]

Patients were discharged from the day-surgery unit from 4 to 8 h after the procedure. They received oral and written instructions for postoperative care, including painkillers (nonsteroidal anti-inflammatory per os), antibiotics (quinolones twice a day for 5 days), and stool softeners for 7 days. Warm sitz baths were suggested.

Patients were seen after 1 week and pain was assessed using a 10-centimeters (cm) linear visual analogue scale (VAS). Further controls were scheduled at 1, 3, 6, and 12 months or if required. All patients were contacted annually thereafter.

Clinical outcome was assessed by a validated questionnaire on postoperative symptoms and satisfaction supplemented by the Wexner incontinence score. Data on bleeding, body temperature, pain after defecation, prolapse, incontinence, and fecal urgency were recorded and prospectively entered in a database. Patients with delayed healing, chronic pain, or complicated outcome underwent anorectal manometry and/or US

Data were analysed using Fisher exact and Mann–Whitney tests. We evaluated the association between considered variables using odds ratio estimate with 95% confidence limits.

Results

The procedure was carried out under general anesthesia in 75 patients (79.8%), whereas 19 received only local anesthesia. The mean duration of surgery was 21+/−9 min, ranging from 12 to 54 min.

Ninety-one operations were carried out as planned day-case surgery, whereas three patients were admitted to the hospital (3.2%). Indications for hospitalization were severe pain urinary retention and the need for longer patient observation as recommended by the anesthesiologist when surgery was performed later in the day. The median hospital stay for these patients was 1.3 days, ranging from 1 to 4 days. None required further surgical intervention.

Two patients visited the Emergency Department overnight because of urinary retention. Both required urinary catheterization and one was readmitted after 2 days and required the placement of a Foley catheter that was removed 3 days later in an outpatient clinic.

Four patients visited the Emergency Department 2, 5, 5, and 20 days after surgery because of bleeding. These patients had undergone surgery for third- (two) and fourth- (two) degree hemorrhoids, and in all cases, pathology revealed a full thickness resection. Three were admitted,

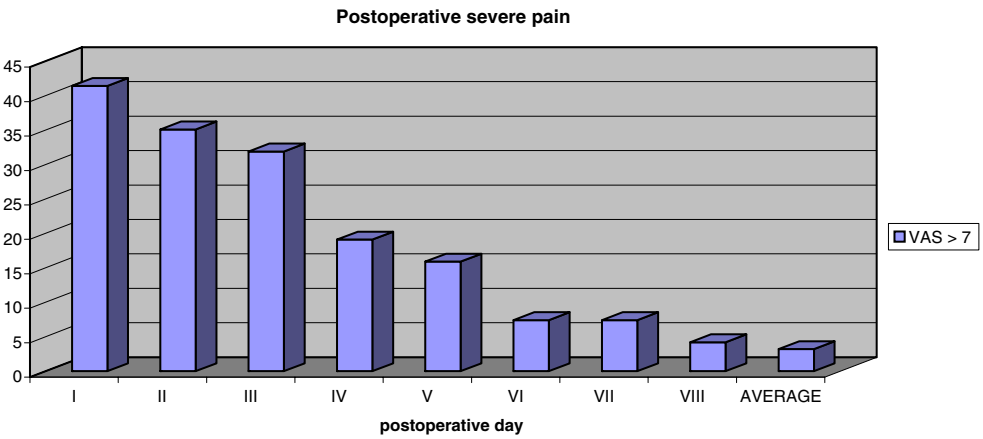


Figure 4 Daily percentages of total patients with severe pain (expressed as VAS score greater than 7) during the first postoperative week.

Table 3 Postoperative Pain, Bleeding, Soiling, and Urgency During the Follow-Up (Expressed as Number of Affected Patient *n*/Total Patients *N*)

	1 week (*n*/*N*)	1 month (*n*/*N*)	3 months (*n*/*N*)	1 year (*n*/*N*)
Pain	48/94	20/94	11/78	3/66
Bleeding	26/94	9/94	7/78	0/66
Soiling	23/94	4/94	0/78	0/66
Urgency	12/94	13/94	3/78	0/66

and a Foley catheter was inserted into the anorectal canal to compress the bleeding vessels. This procedure was effective in all cases but one, which required surgical revision. None of the patients required blood transfusions.

Overall median hospital stay for readmitted patients was 3 days, ranging from 2 to 5 days. Macroscopic appearance of specimens was rectangular with a median size of 4.01+/−1.48 by 2.05+/−0.8 cm. Median depth was 1.03+/−0.31 cm, ranging from 0.1 to 2 cm.

Pathology revealed that 100% of the specimens contained columnar mucosa: 57.4% contained only columnar epithelium; 29.8% contained columnar and transitional epithelium; and 12.8% contained columnar, anal transitional, and stratified squamous epithelium (Fig. 1). Smooth muscle was observed in 62.7% of the specimens (Fig. 2). Circular smooth muscle was present in 51.1%, whereas longitudinal smooth muscle was present in 11.7%. All samples contained at least one feature of prolapse.

Table 2 shows the distribution of squamous epithelium and smooth muscle between genders. Our findings showed significant differences between males and females regarding the presence of squamous epithelium and longitudinal smooth muscle in the resected specimen.

Figure 3 shows average pain experienced recorded by a VAS administered during the first week of follow up. Figure 4 shows the percentages of patients with pain scores greater than 7 for each day during the first week of follow-up. Four patients (4.2%) experienced severe pain, expressed as average VAS score >7. Postoperative pain duration averaged 12.7+/−10.6 days, ranging from 1 to 120 days. Five patients (5.3%) experienced postoperative fever (>38°C) without clinical signs of local or systemic infection. Table 3 shows postoperative pain, pruritus, prolapse, and bleeding at 1 week, 1 month, 3 months, and 12 months follow-up.

Secretion and bleeding durations averaged 5.6+/−9.6 days (range 0–45 days) and 6.3+/−8.4 days (range 1–30 days), respectively. Patient's return-to-work time averaged 16.7+/−10.7 days, ranging from 2 to 60 days. Transient urgency was reported in 12 patients (12.8%). Five patients (5.3%) experienced longer-term urgency (2 to 6 months). Transitory flatus incontinence was observed in two (2.1%) of the patients. No permanent flatus or fecal incontinence was observed during the entire follow-up. Three patients (3.2%) developed tenesmus that lasted up to 3 months.

Six patients (6.3%) developed fissure and were initially treated medically. Two did not respond to medical treatment and underwent lateral internal sphincterotomy after performing anorectal manometry that showed increased tone of the internal anal sphincter.

Three patients experienced severe chronic pain that lasted over 1 year. All underwent anal manometry that did not show significant abnormalities (only one patient was found to have mild internal anal sphincter hypertonia), as well as endorectal ultrasound that showed normal anatomy in all patients. All were treated medically with calcium channel blocker ointment (twice a day for 8 weeks). This treatment was effective in all but one patient, who required anorectal exploration under anesthesia. Removal of retained staples completely resolved the pain. Two patients developed symptomatic anorectal stenosis with urgency and frequency and responded to anal dilatation with anal dilators.

Seven patients (7.4%) suffered from hemorrhoidal recurrence. One patient experienced hemorrhoidal thrombosis 12 days after surgery and was treated medically. Of the remaining patients, 6 developed recurrence after 16+/−5 months from surgery (range 9–26 months). All recurrences were observed in patients who underwent surgery for fourth-degree hemorrhoids. Four symptomatic patients underwent further conventional hemorrhoidectomy (two closed and two open excisions). Skin tags were observed in 14 patients (14.8%).

Table 4 Correlation Between Pathology Findings and Postoperative Pain (*n*=Number of Patients with Specific Pathology Finding and Pain; *N*=Total Number of Patients with Specific Pathology Finding)

Pathology findings/pain	1 week *n*/*N*	1 month *n*/*N*	3 months *n*/*N*	1 year *n*/*N*
Epithelium				
Columnar only	3/54 (NA)	6/54 (NA)	2/54 (NA)	1/54 (NA)
+ Transitional	0/28 (NA)	12/28 (OR=4.5; CL=1.55 & 12.93)	7/28 (OR_1=9; CL=1.7 & 47)	2/28 (NA)
+ Transitional, and squamous	1/12 (NA)	0/12 (NA)	2/12 (OR_2=6, NS)	0 (NA)
Smooth muscle				
Yes	0/59 (NA)	9/59 (OR=0.4, NS)	7/59 (OR=1.0, NS)	2/59 (NA)

A significant association between longer-term pain and the presence of transitional epithelium in the specimen was observed (Table 4). Although a trend in increased postoperative pain if squamous epithelium was also present was observed, this was not significant. No correlation or differences were observed if smooth muscle was present. Squamous epithelium and smooth muscle were both present (indicating the presence of internal sphincter fibers) in six patients (five males and one female). Of those, two experienced longer-term pain and one experienced incontinence. The presence of squamous and/or transitional epithelium and circular or longitudinal smooth muscle in the specimen was not associated with the clinical findings of fecal urgency, tenesmus, or soiling.

Complete satisfaction at 4 weeks follow up was 69.1%, increasing to 77.2% for patients with 1 year follow-up.

Discussion

Stapled hemorrhoidopexy allows removal of a circular section of prolapsed rectal mucosa with immediate mucoso–mucosal anastomosis, achieving a lifting effect for hemorrhoidal cushions and restoring their physiological position.[6] The interruption of the arteriovenous communications may also reduce engorgement of the hemorrhoidal vascular cushions. Moreover, the succeeding deep fibrosis of the stapled line may play a role in maintaining the reduction.[8] Because the suture line is located between 3 and 5 cm from the dentate line, sensory nerve endings are not compromised with significant reduction of postoperative pain when compared to conventional hemorrhoidectomy (either open or closed). Thus, by resecting the rectal mucosa only, the anal canal sensation is unaffected.

Several reports have shown that this innovative approach is safe, effective, and advantageous in terms of reduced pain and faster return to normal activities. As a consequence, over the last decade, we have contributed to an impressive widespread use of this technique.

Recently, this enthusiasm has been tempered by longer-term results and increasing reports of severe septic complications and deaths. Complication rates of SH range from 6.4 to 31%.[9,10] Some complications, such as bleeding, urinary retention, incontinence, and stenosis, are similar to conventional hemorrhoidectomy. Others are specifically related to the technique, such as pelvic sepsis, tenesmus, severe chronic anal pain, rectovaginal fistula, and damage to sphincterial mechanism.[5,11]

Accurate placement of the staple line is mandatory to avoid internal anal sphincter and anodermal tissue involvement.[12] Ideally, as indicated by Shanmugam et al., the resected doughnut should only contain columnar epithelium.[13] If the purse-string suture is performed too low, close to the dentate line, the specimen will contain transitional and/or squamous epithelium with possible increase in postoperative pain. Nevertheless, if the purse string includes the smooth muscle layer that encircles the anal canal, damage to the sphincterial apparatus may occur with continence impairment. On the other hand, if the stapled line is placed too high, the procedure will be ineffective. Rectovaginal fistula may occur if the posterior vaginal wall is incorporated into the staple line.[11] Yet, the anal dilator and obturator used to perform the purse-string suture may also contribute to the development of incontinence through the stretching of the muscular fibers that constitute the anal sphincterial apparatus.[14]

Despite the fact that only columnar epithelium and no smooth muscle should be present in the specimen, in our series, squamous epithelium was present in 12.8% of cases and full-thickness rectal wall in 11.7% of cases. George et al. observed the presence of internal anal sphincter muscle fibers in 38% of the doughnuts and full thickness rectal wall in 42%.[7] In a pathology audit of 106 SHs, Shanmugam et al. reported the inclusion of squamous epithelium in 18% of the cases and smooth muscle in 74.5%, while an involvement of the internal sphincter occurred in 5.6% of the cases.[13] If the smooth muscle layer beneath the squamous epithelium is considered to be part of the internal anal sphincter, in our series it was retrieved in six cases, mostly in male patients (five out of six).

The most dangerous complication reported after SH is pelvic sepsis, usually due to rectal perforation or anastomotic leak. In a recent systematic review of life-threatening sepsis following SH, McCloud et al. described several cases of severe sepsis including retroperitoneal sepsis and rectal perforations, as well as pneumomediastinum and pneumoretroperitoneum and deaths.[5] We did not observe any severe septic complication. However, in our unit, a Hartman's procedure has been performed in a patient with rectal perforation secondary to hemorrhoidopexy performed elsewhere (unpublished data). We did not observe any secondary infection of the stapled line, likely because of the longer antibiotic prophylaxis (extended for 5 days after surgery) compared to other case series in which infection of the staple line has been reported.

The most common complication is postoperative bleeding, which is reported between 2 and 28%.[2,10,15] We observed a 4.2% rate of bleeding requiring admission. A second operation was needed in 25% of cases. According to existing literature, bleeding is rarely life-threatening and can be successfully managed by the insertion of a Foley catheter in the anorectal canal. The need of reintervention is rare.[10] Our bleeding incidence is low if compared to the incidence reported in existing literature. Careful inspection of the staple line at the end of the operation should be mandatory, and any bleeding vessel should be coagulated with diathermy or

oversewn with absorbable stitches. Bleeding events in our series occurred late after surgery, up to 20 days after. Although several authors have shown an increased risk of postoperative bleeding after SH for fourth-degree hemorrhoids, in our experience, the incidence of bleeding in third- and fourth-degree hemorrhoids did not differ significantly.[4,16] On the other hand, the incidence of bleeding was significantly higher if a full-thickness resection was accidentally performed, as demonstrated by pathology.

As previously demonstrated, our experience confirms that SH is associated with reduced postoperative pain and faster return to normal activity when compared to open and closed hemorrhoidectomy. Severe pain (VAS score greater that 7) can be observed only in 4% of patients, an incidence similar to that observed by other authors.[15] Severe chronic postoperative pain can also be a consequence of hemorrhoidal thrombosis, troublesome retained staples, and anal fissure and represents the most common cause of reintervention (up to 45% of cases).[9,10,15–17] Thrombosis is reported as high as 4%.[15–17] Two of our patients experienced thrombosis and responded to standard medical therapy. Fissures were observed in 6.3% of cases. Four patients responded to medical conservative treatment, whereas two required surgery. One patient with severe chronic pain underwent anorectal exploration under anesthesia, and the removal of retained staples completely resolved the pain. Other authors have reported that patients who have had retained staples or stitches removed surgically had complete resolution of the pain.[18] It can be speculated that the metallic staples may act as an irritant stimulus, inducing long-term pain.

Despite the fact that tenesmus is reported in up to 40% of cases, we observed a 3.1% incidence.[19] Correlation between pathology and postoperative pain showed that it was increased if squamous and transitional epithelium were present in the specimen. The presence of smooth muscle seems to be irrelevant with respect to postoperative pain, but if squamous epithelium and smooth muscle are both present (indicating the presence of internal sphincter fibers), longer-term pain (two patients) and incontinence (one patient) can be observed.

Our incidence of urinary retention was 3.2%, similar to that reported in literature (1.5 to 8%).[15,16] Theoretically, the lower postoperative pain should make urethral sphincter spasm unlikely, but, in fact, the incidence of urinary retention is as high as it is in conventional hemorrhoidectomy. The causes of postoperative urinary retention are unclear.

Transient self-limiting fecal urgency with incontinence is reported between 5 and 31%. These symptoms were observed in about 13% of our patients. Along with other authors, we believe that fecal urgency and incontinence may be due to tissue oedema and thrombosis, as well as disruption of the anatomy and function of the normal anal cushions. Follow-up examination is usually negative for abnormalities such as low placement of the staple line or damage to the dentate line. Furthermore, these symptoms are usually transitory.[4,20] The presence of transitional or squamous epithelium or the presence of circular or longitudinal smooth muscle in the specimen does not correlate to the clinical findings of fecal urgency, tenesmus, or postoperative soiling.

We observed a high rate of residual and recurrent hemorrhoids compared to data obtained from existing literature.[15] Shalaby and Desoky reported a 1% incidence of recurrent prolapse, but this study also included patients with second-degree hemorrhoids.[21] Ganio et al. reported a 20% recurrent prolapse rate after a telephone follow-up on 50 patients who underwent SH.[8] In our case series, all recurrences occurred in patients with fourth-degree hemorrhoids. Similarly, Ortiz et al. reported more frequent recurrences in patients with fourth-degree hemorrhoids compared to those with third-degree ones.[2,22] Along with these authors, we believe that fourth-degree hemorrhoids may not represent an appropriate indication for SH, as the success of the operation depends entirely on the resection and reduction of the prolapse by the stapler.[23] Since May 2006, we have reserved SH to third-degree hemorrhoids only and, despite a shorter follow-up compared to the entire group, we did not observe any recurrence to date.

Our experience confirms that this technique is feasible and safe when performed as a day-surgery procedure for third-degree hemorrhoids. Because of the potential for specific technique-related complications, it should not be used for second-degree hemorrhoids, whereas for fourth-degree hemorrhoids, conventional excision might be more effective, reducing the incidence of longer-term recurrence. The correct placement of the purse-string suture is mandatory to avoid postoperative pain, and pathological examination of the resected specimen should always be performed. Only columnar epithelium should be present in the specimen and, although the presence of smooth muscle does not influence the outcome in terms of functional results, it may play a role in postoperative bleeding.

References

1. Roswell M, Bello M, Hemingway DM. Circumferential mucosectomy versus conventional haemorrhoidectomy: randomised controlled trial. Lancet 2000;355:779–781.
2. Ganio E, Altomare DF, Gabrielli F, Milito G, Canuti S. Prospective randomized multicentre trial comparing stapled and open haemorrhoidectomy. Br J Surg 2002;88:669–674.
3. Slawik S, Kenefick N, Greenslade L, Dixon AR. A prospective evaluation of stapled haemorrhoidopexy/rectal mucosectomy in the management of 3rd and 4th degree haemorrhoids. Colorectal Dis 2006;9:352–356.

4. Finco C, Sarzo G, Savastano S, Degregori S, Merigliano S. Stapled haemorrhoidopexy in fourth degree haemorrhoidal prolapse: is it worthwhile? Colorectal Dis 2005;8:130–134.
5. McCloud JM, Jameson JS, Scott ND. Life-threating sepsis following treatment for haemorrhoids: a systematic review. Colorectal Dis 2006;8:748–755.
6. Longo A. Treatment of haemorrhoids disease by reduction of mucosa and haemorrhoidal prolapse with a circular suturing device: a new procedure. In: Proceedings of the 6th World Congress of Endoscopic Surgery, Rome, 1998, pp 777–784.
7. George BD, Shetty D, Lindsey I, Mortensen NJ, Warren BF. Histopathology of stapled haemorrhoidectomy specimens: a cautionary note. Colorectal Dis 2001;4:473–476.
8. Beattie GC, McAdam TK, McIntosh SA, Loudon MA. Day case stapled haemorrhoidopexy for prolapsing haemorrhoids. Colorectal Dis 2005;8:56–61.
9. Kanellos I, Zacharakis E, Kanellos D, Pramateftakis MG, Tsachalis T, Betsis D. Long-term results after stapled haemorrhoidopexy for third-degree haemorrhoids. Tech Coloproctol 2006;10:47–49.
10. Mlakar B, Kosorok P. Complications and results after stapled haemorrhoidopexy as a day surgical procedure. Tech Coloproctol 2003;7:164–168.
11. McDonald PJ, Bona R, Cohen CRG. Rectovaginal fistula after stapled haemorrhoidopexy (letter). Colorectal Dis 2004;6:64–65.
12. Corman ML, Graviè JF, Hager T, Loudon MA, Mascagni D, et al. Stapled haemorrhoidopexy: a consensus position paper by an international working party-indications, contra-indications and technique. Colorectal Dis 2003;5:304–310.
13. Shanmugam V, Watson AJM, Chapman AD, Binnie NR, Loudon A. Pathological audit of stapled haemorrhoidopexy. Colorectal Dis 2004;7:172–175.
14. Ho Y-H, Seow-Cohen F, Tsang C, Eu K-W. Randomized trial assessing anal sphincter injuries after stapled haemorrhoidectomy. Br J Surg 2001;88:1449–1455.
15. Oughriss M, Yver R, Faucheron JL. Complications of stapled haemorrhoidectomy: a French multicentric study. Gastroenterol Clin Biol 2005;29:429–433.
16. Ravo B, Amato A, Bianco V et al. Complications after stapled haemorrhoidectomy: can they be prevented? Tech Coloproctol 2003;6:83–88.
17. Cheetham MJ, Cohen CR, Kamm MA, Philips RKS. A randomised, controlled trial of diathermy haemorrhoidectomy in an intended day-care setting with longer-term follow-up. Dis Colon Rectum 2003;46:491–497.
18. Filingeri V, Gravante G. Stapled haemorrhoidopexy followed by fecal urgency and tenesmus: methodological complication or surgeon's mistake? Tech Coloproctol 2006;10:149–153.
19. Brusciano L, Ayabaca SM, Pescatori M et al. Reinterventions after complicated or failed stapled haemorrhoidopexy. Dis Colon Rectum 2004;47:1846–1851.
20. Cheetham MJ, Mortensen NJ, Nystrom PO, Kamm MA, Philips RKS. Persistent pain and fecal urgency after stapled haemorroidectomy. Lancet 2000;26:730–733.
21. Shalaby R, Desoky A. Randomized clinical trial of stapled versus Milligan–Morgan haemorrhoidectomy. Br J Surg 2001;88:1049–1053.
22. Ortiz H, Marzo J, Armendariz P. Randomised clinical trial of stapled haemorrhoidopexy versus conventional diathermy haemorrhoidectomy. Br J Surg 2002;89:1376–1381.
23. Goulimaris I, Kanellos I, Christoforidis E, Mantzoros I, Odisseos CD. Stapled haemorrhoidectomy compared with Milligan–Morgan excision for treatment of prolapsing haemorrhoids: a prospective study. Eur J Surg 2002;168:621–625.

J Gastrointest Surg (2007) 11:1669–1672
DOI 10.1007/s11605-007-0331-8

Refractory Gastroparesis After Roux-en-Y Gastric Bypass: Surgical Treatment with Implantable Pacemaker

J. R. Salameh · Robert E. Schmieg Jr. · J. Matt Runnels · Thomas L. Abell

Received: 19 May 2007 / Accepted: 5 September 2007 / Published online: 29 September 2007

Abstract

Background Gastroparesis is a rare complication of Roux-en-Y gastric bypass. We evaluate the role of gastric electrical stimulation in medically refractory gastroparesis.

Methods Patients with refractory gastroparesis after gastric bypass for morbid obesity were studied. After behavioral and anatomic problems were ruled out, the diagnosis of disordered gastric emptying was confirmed by radionuclide gastric emptying. Temporary endoscopic stimulation was used first to assess response before implanting a permanent device.

Results Six patients, all women with mean age of 42 years, were identified. Two patients ultimately had reversal of their surgery with gastro-gastrostomy, while another had a total gastrectomy with persistence of symptoms in all three. Five of the patients evaluated had insertion of a permanent gastric pacemaker, with pacing lead implanted on the gastric pouch (2), the antrum of the reconstructed stomach (1), or the proximal Roux limb (2). Nausea and emesis improved significantly postoperatively; mean total symptom score decreased from 15 to 11 out of 20. There was also a persistent improvement in gastric emptying postoperatively based on radionuclide testing.

Conclusion If medical therapy fails, electrical stimulation is a viable option in selected patients with gastroparesis symptoms complicating gastric bypass and should be considered in lieu of reversal surgery or gastrectomy.

Keywords Gastroparesis · Bariatric surgery · Pacemaker

Introduction

Nausea and vomiting are the most common complaints after Roux-en-Y gastric bypass. When these symptoms persist, patients should be investigated to rule out a variety of possible etiologies, including anatomic problems such as anastomotic stricture and small bowel obstruction or behavioral problems such as disordered eating. Gastroparesis is a motility disorder of the stomach, defined by delayed gastric emptying of a solid meal in the absence of mechanical obstruction and is a diagnosis of exclusion. It can occasionally be responsible for severe, persisting nausea, and vomiting symptoms in some of these patients, which can be difficult to treat and is often refractory to medical therapy. Gastric electrical stimulation (GES) has received FDA Humanitarian Use Device approval in 2000 and has been shown to be an effective treatment alternative in patients with medically refractory diabetic or idiopathic gastroparesis.[1] We have used GES in postsurgical or surgery-associated gastroparesis with significant clinical improvements at long term follow-up.[2] In this study, we evaluate the role of electric stimulation therapy in patients with severe gastroparesis complicating Roux-en-Y gastric bypass for morbid obesity.

Presented at SSAT meeting, Washington, DC, May 2007.

J. R. Salameh · R. E. Schmieg Jr.
Department of Surgery, University of Mississippi Medical Center, Jackson, MS, USA

J. M. Runnels · T. L. Abell
Department of Medicine,
University of Mississippi Medical Center,
Jackson, MS, USA

J. R. Salameh (✉)
2500 North State Street,
Jackson, MS 39216, USA
e-mail: Jsalameh@laparo-surgery.com

Material and Methods

All patients with refractory gastroparesis after Roux-en-Y gastric bypass surgery for morbid obesity were identified. Chart review was conducted including records from the referring institution.

Behavioral problems are ruled out by careful nutritional assessments and structured psychiatric interviews. Anatomic problems are ruled out using numerous diagnostic studies including upper gastrointestinal contrast studies, computed tomography (CT) scan of the abdomen and pelvis and upper endoscopy. Diagnosis of disordered gastric emptying was confirmed by radionuclide gastric emptying showing either significant gastric retention at 4 h or rapid emptying of the stomach at 1 h, and this test was repeated after the institution of GES therapy.

GES uses low energy stimuli administered at a frequency higher than the intrinsic slow-wave frequency of the normal stomach. Temporary endoscopically placed stimulation is used first to assess response to stimulation before surgically implanting a permanent device. Permanent GES is implanted surgically via laparotomy: two stimulating electrodes (Medtronic Model 4351 or 4300, Medtronic, Minneapolis, MN) are inserted into the muscularis propria 1 cm apart in the gastric pouch or in the gastric antrum, 10 cm proximal to the pylorus, in cases of reversal of the gastric bypass. When a total gastrectomy with esophago-jejunostomy was performed, electrodes are inserted in the proximal Roux limb. Intraoperative endoscopy is used in all cases to verify that the electrodes placed in the stomach or small bowel wall have not penetrated the mucosa. The electrodes are tunneled through the fascia and connected to a battery-powered neurostimulator (Medtronic ITREL 3 Model 7425G or Enterra, Medtronic, Minneapolis, MN) placed in a subcutaneous pocket. The neurostimulator is programmed and turned on after verifying adequate impedance.

GES implantation follows a study protocol approved by our institutional review board. All patients were assessed sequentially during regularly scheduled office visits and as needed. Symptoms of nausea, vomiting, bloating/distension, early satiety, and abdominal pain are assessed at all stages of treatment and follow-up and are each scored on a scale from 1 to 4 based on severity, 4 being most severe. The sum of all five symptom scores constitutes the total symptom score (TSS), 20 being the highest and worst score possible. Quality of life was assessed on a −3 to +3, worse to best, scale for the temporary GES and by an investigator-derived independent outcome score on a 0 to 30 scale, best to worse, for the permanent GES and compared by *t* tests.[3]

Results

Six patients were referred to our institution for refractory gastroparesis after prior Roux-en-Y gastric bypass (Table 1). Two patients had a concomitant hiatal hernia repair and truncal vagotomy at the time of their bariatric surgery. All six patients were women with mean age of 42 years. Mean total symptom score at presentation was 15. The onset of symptoms varied among the patients, from immediately postoperatively to 16 years after the surgery. All of these patients lost a various amount of weight after their bariatric surgery. Preoperative weights were not available to us, but body mass indexes upon presentation to our institution ranged from 20 to 39 with a mean of 31.

In addition to the many diagnostic studies to rule out anatomic problems, most patients had a surgical reexploration that was normal. All patients did not respond to various prokinetic and antiemetic agents. Two patients ultimately had reversal of their surgery with gastro-gastrostomy, while another had a total gastrectomy with persistence of the symptoms in all three of them.

All patients had markedly abnormal radionuclide gastric emptying with four of six patients showing slow gastric emptying with mean gastric retention of 78% at 4 h and two of six patients with rapid gastric emptying with mean gastric retention of 27% at 1 h. Temporary endoscopic pacing was performed on all six patients with improvement in their total symptom scores to a mean of 8; in addition, gastric emptying improved to 35% at 4 h in the delayed group and to 30% at 1 h in the rapid group.

Five of the patients evaluated had insertion of a permanent gastric pacemaker, with implantation of the pacing leads on the gastric pouch (two patients), the

Table 1 Patient Demographics, Prior Procedures Performed, and Location of Implanted Leads

Patient	Age/gender	Procedure(s)	Lead location
1	44 F	Roux-en-Y gastric bypass, followed by total gastrectomy	Roux limb
2	52 F	Roux-en-Y gastric bypass	Gastric pouch
3	35 F	Roux-en-Y gastric bypass, followed by reversal	–
4	50 F	Roux-en-Y gastric bypass and hiatal hernia repair/truncal vagotomy followed by reversal	Gastric Antrum
5	23 F	Roux-en-Y gastric bypass and hiatal hernia repair/truncal vagotomy	Gastric pouch
6	48 F	Roux-en-Y gastric bypass	Roux limb

antrum of the reconstructed stomach (one), or the proximal Roux limb (two patients). Mean follow-up for these patients was 16 months. Symptoms improved significantly postoperatively with mean nausea score of 1.8/4, mean emesis score of 2.2/4, and mean total symptom score of 11/20. There was also a persistent improvement in gastric emptying postoperatively based on radionuclide testing; the delayed emptying group improved to 28% at 4 h and the rapid emptying group improved to 57% at 1 h. Quality of life changed from mean −3.0 to mean +1.2 after temporary GES ($p<0.05$ by paired t test) and from mean 17.0 to mean 10.0 after the permanent device ($p<0.01$ by paired t test).

Discussion

Delayed-return gastric emptying is a known complication of any gastrojejunostomy; in particular, it has been shown to be increased in patients with nonresection gastric bypass and Roux-en-Y reconstruction.[4] Gastroparesis after partial gastrectomy has been reported in many previous studies, with an incidence of approximately 0.4–5.0%.[5]

Although symptoms of gastroparesis are common after Roux-en-Y gastric bypass for morbid obesity in the immediate postoperative period due to an element of ileus and anastomotic edema, they usually resolve spontaneously. Persistent refractory gastroparesis after Roux-en-Y gastric bypass is rare. Occasionally, it is due to an undiagnosed preoperative diabetic or idiopathic gastroparesis. If a planned or inadvertent truncal vagotomy is performed, the gastroparesis is secondary to the denervation of the gastric pouch. It may occasionally be the consequence of a tight stricture at the gastrojejunostomy with subsequent dilation and aperistalsis of the gastric pouch; this however was not noted in any of our patients. It may also be due to a very wide gastrojejunal anastomosis leading to rapid emptying. Otherwise, the etiology of postsurgical gastroparesis is unclear and probably multifactorial. The contribution of some elements of dumping syndrome and Roux syndrome to the symptomatology is also ill defined.

Post-gastric bypass gastroparesis can have disabling symptoms, frequently leading to malnutrition requiring hospitalization and prolonged parenteral nutrition. Symptoms often fail to be alleviated by drug therapy such as metoclopramide, erythromycin, or tegaserod (5-HT4 antagonist), alone or in combination. Gastric reoperations attempting to correct postsurgical gastroparesis are frequent and usually unsuccessful.[6] Completion or near-completion gastrectomy has been suggested as therapy of choice for refractory postsurgical gastroparesis with good long-term results[6,7]; however, published results are variable and sometimes unsatisfactory. In one study of completion gastrectomy for severe postgastrectomy gastric stasis in 62 patients with prior vagotomy and a median of four previous gastric operations, 57% of patients remained significantly symptomatic (Visick grade III or IV); chronic pain, diarrhea, and dumping syndrome were not significantly affected.[8] In the patient in our series who ultimately had a total gastrectomy, symptoms remained significant.

The reversal of the Roux-en-Y gastric bypass will not resolve the symptoms of chronic gastroparesis as was the case in two of our patients, as these patients have an underlying gastric motility impairment; in addition, the innervation of the gastric remnant may have been divided, either intentionally by dividing the gastrohepatic ligament at the level of the gastric transaction, or inadvertently.

Gastrointestinal neural stimulation has been successfully used for refractory diabetic and idiopathic gastroparesis with significant long-term improvement in symptoms and nutritional parameters.[1,9,10,11] We have expanded our indications for gastric electrical stimulation to include postsurgical gastroparesis with noted improvements in gastrointestinal symptoms, health-related quality of life, and solid and liquid gastric emptying at long term follow-up.[2] We have noted similar results in our current series of postgastric bypass gastroparesis, at least at short term follow-up. Electric stimulation appears beneficial in improving symptoms in this challenging subgroup of patients and seems to normalize gastric emptying. Quality of life also improved with both the temporary and permanent GES devices, consistent with previous work on GES.[3] It should probably be considered the first line of surgical therapy when medical options fail. It is less invasive and less radical than total gastrectomy, which can still be performed as an option of last resort if GES is unsuccessful. Long term follow-up is still needed to see if these promising early results are sustainable.

Conclusion

Gastroparesis is a rare complication of Roux-en-Y gastric bypass, especially in the setting of concomitant vagotomy, and should be considered when no anatomic or behavioral problems are identified. If medical therapy fails, electrical stimulation is a good option in selected patients and should be considered in lieu of reversal surgery or total gastrectomy.

References

1. Abell TL, Van Cutsem E, Abrahamsson H, Huizinga JD, Konturek JW, Galmiche JP, Voelker G, Filez L, Everts B, Waterfall WE, Domschke W, Bruley des Varannes S, Familoni BO, Bourgeois IM, Janssens J, Tougas G. Gastric electrical stimulation

in intractable symptomatic gastroparesis. Digestion 2002;66 (4):204–212.
2. Oubre B, Luo J, Al-Juburi A, Voeller G, Familoni B, Abell TL. Pilot study on gastric electrical stimulation on surgery-associated gastroparesis: long-term outcome. South Med J 2005;98(7):693–697.
3. Cutts TF, Luo J, Starkebaum W, Rashed H, Abell TL. Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term health care benefits? Neurogastroenterol Motil 2005;17 (1):35–43.
4. Kung SP, Lui WY, P'eng FK. An analysis of the possible factors contributing to the delayed return of gastric emptying after gastrojejunostomy. Surg Today 1995;25(10):911–915.
5. Dong K, Yu XJ, Li B, Wen EG, Xiong W, Guan QL. Advances in mechanisms of postsurgical gastroparesis syndrome and its diagnosis and treatment. Chin J Dig Dis 2006;7(2):76–82.
6. Eckhauser FE, Conrad M, Knol JA, Mulholland MW, Colletti LM. Safety and long-term durability of completion gastrectomy in 81 patients with postsurgical gastroparesis syndrome. Am Surg 1998;64(8):711–716.
7. McCallum RW, Polepalle SC, Schirmer B. Completion gastrectomy for refractory gastroparesis following surgery for peptic ulcer disease. Long-term follow-up with subjective and objective parameters. Dig Dis Sci 1991;36(11):1556–1561.
8. Forstner-Barthell AW, Murr MM, Nitecki S, Camilleri M, Prather CM, Kelly KA, Sarr MG. Near-total completion gastrectomy for severe postvagotomy gastric stasis: analysis of early and long-term results in 62 patients. J Gastrointest Surg 1999;3(1):15–21.
9. Familoni BO, Abell TL, Voeller G, Salem A, Gaber O. Electrical stimulation at a frequency higher than basal rate in human stomach. Dig Dis Sci 1997;42:885–891.
10. Abell T, McCallum R, Hocking M, Koch K, Abrahamsson H, Leblanc I, Lindberg G, Konturek J, Nowak T, Quigley EM, Tougas G, Starkebaum W. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 2003;125 (2):421–428.
11. Abell T, Lou J, Tabbaa M, Batista O, Malinowski S, Al-Juburi A. Gastric electrical stimulation for gastroparesis improves nutritional parameters at short, intermediate, and long-term follow-up. JPEN 2003;27:277–281.

J Gastrointest Surg (2007) 11:1673–1679
DOI 10.1007/s11605-007-0341-6

Surgical Management of Gastro–Gastric Fistula After Divided Laparoscopic Roux-en-Y Gastric Bypass for Morbid Obesity

O. N. Tucker · S. Szomstein · R. J. Rosenthal

Received: 23 July 2007 / Accepted: 11 September 2007 / Published online: 3 October 2007

Abstract
Background Gastro–gastric fistula (GGF) formation is uncommon after divided laparoscopic Roux-en-Y gastric bypass (LRYGB) for morbid obesity. Optimal surgical management remains controversial.
Methods A retrospective review was performed of a prospectively maintained database of patients undergoing LRYGB from January 2001 to October 2006.
Results Of 1,763 primary procedures, 27 patients (1.5%) developed a GGF and 10 (37%) resolved with medical management, whereas 17 (63%) required surgical intervention. An additional seven patients requiring surgical intervention for GGF after RYGB were referred from another institution. Indications for surgery included weight regain, recurrent, or non-healing gastrojejunal anastomotic (GJA) ulceration with persistent abdominal pain and/or hemorrhage, and/or recurrent GJA stricture. Remnant gastrectomy with GGF excision or exclusion was performed in 23 patients (96%) with an average in-hospital stay of 7.5 days (range, 3–27). Morbidity in six patients (25%) was caused by pneumonia, $n=2$; wound infection, $n=2$; staple-line bleed, $n=1$; and subcapsular splenic hematoma, $n=1$. There were no mortalities. Complete resolution of symptoms and associated ulceration was seen in the majority of patients.
Conclusion Although uncommon, GGF formation can complicate divided LRYGB. Laparoscopic remnant gastrectomy with fistula excision or exclusion can be used to effectively manage symptomatic patients who fail to respond to conservative measures.

Keywords Complications · Roux-en-Y gastric bypass · Morbid obesity · Fistula · Remnant gastrectomy

Abbreviations

AA	antecolic antegastric
BMI	body mass index
CT	computed tomography
GE	gastroesophageal
GUGI	gastrograffin upper gastrointestinal study
GGF	gastro–gastric fistula
EGD	Esophagogastroduodenoscopy
LRG	laparoscopic remnant gastrectomy
LRYGB	laparoscopic Roux-en-Y gastric bypass
POD	postoperative day
PPI	proton pump inhibitor
RG	remnant gastrectomy
RR	retrocolic retrogastric
RYGB	Roux-en-Y gastric bypass

This paper was presented at the SSAT Poster Presentation session on May 21st 2007 at the SSAT Annual Meeting at Digestive Disease Week, Washington (poster ID M1590).

O. N. Tucker · S. Szomstein · R. J. Rosenthal (✉)
The Bariatric Institute and Division of Minimally Invasive Surgery, Cleveland Clinic Florida,
2950 Cleveland Clinic Blvd.,
Weston, FL 33331, USA
e-mail: rosentr@ccf.org

Introduction

Surgery is the preferred technique to achieve weight loss and resolution of comorbidity in the morbidly obese.[1] However, surgery is not without its complications, and a

wide variety of approaches have been developed over the last three decades in an attempt to reduce morbidity and improve outcome. Laparoscopic Roux-en-Y gastric bypass (LRYGB) is currently the most commonly performed bariatric procedure worldwide.[2–6] Despite advances in technology and improvements in surgical technique, adverse events contributing to serious morbidity and mortality are seen after LRYGB. Fistula formation is an uncommon but potentially significant complication. The most common type encountered is a gastro–gastric fistula (GGF) with an abnormal communication between the gastric pouch and the excluded stomach, which can result in failure of weight loss, weight regain, intractable marginal ulceration with recurrent upper gastrointestinal hemorrhage, pain, and stricture formation.

Historically, the technique of gastroplasty, its subsequent modification to the vertical banded gastroplasty, and the early open RYGB procedures involved the creation of a non-divided or partially divided gastric pouch.[7–9] GGF rates of 49% were reported after primary RYGB when the pouch and stomach were stapled in continuity or partially divided.[10] Following complete transection of the gastric segments, Capella and Capella[10] reported a significant reduction in the incidence of GGF to 2.6%, with further reduction with the use of jejunal limb interposition.[11] These surgical techniques minimize the incidence of GGF formation but do not eliminate it. GGF continue to occur with a reported incidence of up to 6%.[10,12,13] We have previously reported a 1.2% incidence of GGF in our series of patients after divided LRYGB.[14]

The optimal management of GGF remains controversial, and reports of surgical treatment of this complication are infrequent.[10,12,15] We wished to determine the incidence of GGF in our patient population of 1,763 morbidly obese patients who underwent primary divided LRYGB to determine the indications for intervention and to evaluate a novel surgical approach to symptomatic GGF. We present our results on laparoscopic remnant gastrectomy (LRG) with tract excision or exclusion without interference with the gastrojejunostomy in the management of patients with symptomatic GGF after LRYGB.

Methods

Review of a prospectively maintained database and medical records of consecutive patients undergoing primary LRYGB from January 2001 to October 2006 was undertaken. All procedures were performed by two surgeons (S. S. and R.J.R.) in accordance with the National Institute of Health consensus criteria.[16] Study permission was obtained from the Institutional Review Board. All patients had a Gastrografin upper gastrointestinal study (GUGI) on postoperative day (POD) 1, and oral intake commenced if normal. Patients were discharged on POD 2 to 4 on a 3-month course of a proton pump inhibitor (PPI). Patients were reviewed at 2 weeks, 2 and 6 months, and yearly thereafter. All data including demographic data, weight, body mass index (BMI), co-morbidities, prior surgery, reason for revision, complications, and outcome, including mortality, morbidity, readmission rate, and weight loss, were analyzed.

Surgical Technique of Laparoscopic Roux-en-Y Gastric Bypass

A standard seven-trocar LRYGB was performed.[17] A 15- to 20-ml pouch was created with a linear stapler with reinforcement of the last three vertical firings with bovine pericardial strips. A 50-cm biliopancreatic and >100-cm antecolic antegastric (AA) alimentary limb determined by BMI were fashioned. GJA and pouch staple-line integrity was confirmed by air insufflation, methylene blue instillation, and esophagogastroduodenoscopy (EGD).

Diagnosis and Management of Patients with GGF

Patients with persistent nausea, vomiting, failure of weight loss, weight regain, intractable GJA ulceration, persistent epigastric pain, recurrent upper gastrointestinal hemorrhage, and GJA stricture underwent surgeon-performed EGD, GUGI, barium contrast study with supine and lateral decubitus views, and/or double contrast abdominal CT (Fig. 1). All patients with a GGF were treated with a PPI regardless of symptoms, with the addition of sucralfate for concomitant marginal ulceration and/or stricture. Indications for surgery were failed medical management in a symptomatic patient, weight regain with non-resolution of comorbidity, recurrent or non-healing GJA ulceration with persistent abdominal pain and/or hemorrhage, and recurrent GJA stricture.

Surgical Technique of Laparoscopic Remnant Gastrectomy

Trocar site placement was identical to primary LRYGB.[17] The greater curve vessels were divided to the GEJ, the postgastric space entered with remnant mobilization, and a window was created separating pouch and remnant. Intraoperative EGD was performed to delineate the fistula. The distal antrum was transected with a linear stapler proximal to the pylorus. The pouch was vertically transected medial to the GGF over an Ewald tube with a linear stapler. In the presence of a small pouch, the remnant was vertically transected lateral to the GGF, leaving a narrow stomach margin. All staple lines were over-sewn. Repeat EGD was performed to confirm fistula excision or exclusion, fol-

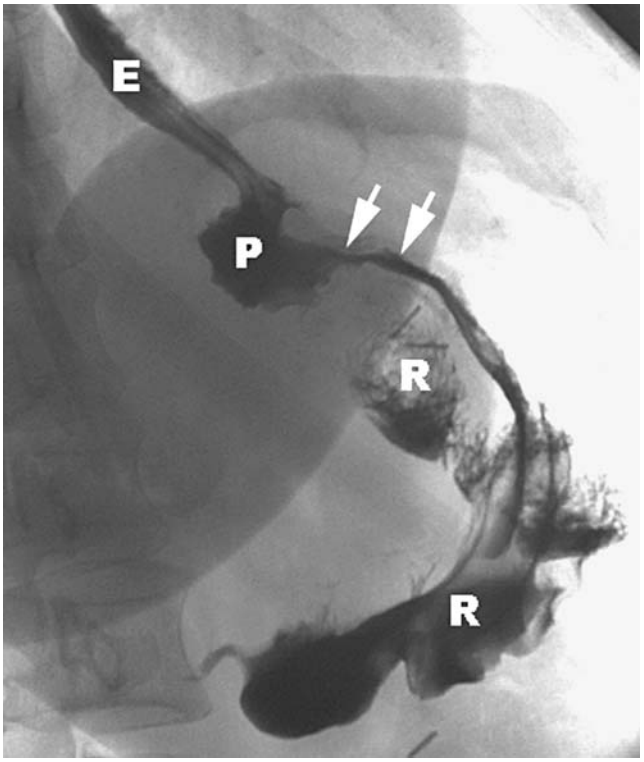


Figure 1 Gastrografin upper gastrointestinal contrast study demonstrating contrast extravasation from the lateral aspect of the gastric pouch (*P*) through a fistulous tract (*arrows*) into the remnant stomach (*R*) after laparoscopic Roux-en-Y gastric bypass; *E* esophagus.

lowed by air insufflation to check staple-line integrity. The gastric remnant was extracted through the umbilicus.

Results

Over a 70-month period from January 2001 to October 2006, 1,763 patients underwent LRYGB for morbid obesity. Of the 1,763 procedures performed, 27 patients (1.5%) developed a GGF. All LRYGB procedures in these 27 patients were performed in a standard fashion with an AA approach, and all were completed laparoscopically. All 27 patients were prescribed a treatment course of a PPI. In addition, sucralfate was commenced in patients with concomitant GJA ulceration and/or stenosis. Ten patients (37%) with GGF after LRYGB responded to medical treatment with symptom resolution. The remaining 17 patients (63%) had persistent symptoms despite maximum medical treatment and required surgical intervention.

Of the 17 patients who required surgical intervention, the majority were women with a male/female ratio of 1:5. At the time of their primary LRYGB, their mean age was 42 years (range, 30–58), with a mean weight of 325 lb (range 215–570), and a mean BMI of 49.7 kg/m^2 (range, 35–61; Table 1). Three patients had a history of previous abdominal surgery. One patient had a prior open cholecystectomy, appendicectomy and two previous caesarian sections; the second, had a laparoscopic cholecystectomy and bilateral tubal ligation; and the third, had a total abdominal hysterectomy with bilateral salpingoophorectomy. Concomitant surgery was performed at the time of LRYGB in two patients, umbilical hernia repair in one, and laparoscopic cholecystectomy in the other. All procedures were completed laparoscopically (100%). The mean length of hospital stay was 3.7 days (range, 3–5). During follow-up, three patients (18%) developed acute cholecystitis requiring laparoscopic cholecystectomy.

The indications for surgery were failure of medical management in 17 (100%), weight regain in 9 (53%), persistent epigastric pain in 10 (59%), vomiting in 5 (29%), persistent GJA ulceration in 13 (76%) with significant hemorrhage in 3 (18%), and non-resolving GJA stenosis in 8 (47%) patients (some patients had more than one indication). Surgery was performed at a mean of 24.9 months after primary LRYGB (range, 4–57). LRG was performed in all 17 patients and completed laparoscopically in 16 (94%). One patient required conversion (6%) because of excess intraluminal air in the gastrointes-

Table 1 Patient Characteristics at Primary Laparoscopic Roux-en-Y Gastric Bypass

Patients with gastro–gastric fistula requiring surgery (*n*)	17/27 (63%)
Gender (*n*)	
Male	14 (82)
Female	3 (18)
Age (year)	
Mean	42
Range	30–58
Weight (lb)	
Mean	325
Range	215–570
BMI (kg/m^2)	
Mean	49.7
Range	35–61
Comorbidities (*n*)	
Hypertension	13 (76)
Ischemic heart disease	2 (12)
Hyperlipidemia	8 (47)
Diabetes	7 (41)
Osteoarthritis	9 (53)
Chronic muscle and joint pain	7 (41)
Obstructive sleep apnoea	11 (65)
Gastroesophageal reflux	7 (41)
Deep venous thrombosis	2 (12)
Pulmonary embolus	2 (12)
Depression	4 (23)
Hypothyroidism	1 (6)
Others	4 (23)

Data in parentheses are percentages.
BMI Body mass index

tinal tract after an intraoperative EGD. Remnant gastrectomy with pouch trimming and GGF excision was performed in 12 patients (71%); four (23.5%) of these patients required GJA excision and reanastomosis for stomal obliteration secondary to longstanding marginal ulceration. LRG without pouch trimming was performed in 5 patients (29%) for exclusion of GGF. Five of 17 (29.4%) patients developed early postoperative complications that delayed discharge. One patient required 3 days of intravenous antibiotics for a wound infection. A second patient developed unexplained pyrexia, nausea, and tachycardia. A GUGI and abdominal CT scan were normal with no evidence of a leak or collection, and the patient responded to conservative treatment. The third patient discharged purulent fluid from his surgical drain on POD 7. An anastomotic or staple-line leak was suspected, but a GUGI and abdominal CT were entirely normal. He was discharged home on oral antibiotics with the drain in situ, remained well, and the drain was subsequently removed in the outpatient clinic. Hemorrhage from the gastric staple line occurred in a single patient who was taking an oral anticoagulant before surgery. This patient underwent an urgent exploratory laparoscopy that required conversion to an open approach to achieve hemostasis with over-sewing of the pouch staple line. A fifth patient developed pneumonia, which responded to oral antibiotics. The mean length of stay for the 17 patients was 6.1 days (range, 3–10).

An additional seven patients were referred for surgery from other centers with symptomatic GGF after open RYGB in five (71%), and LRYGB in two (29%). Four patients had a RYGB with GJA ring reinforcement (57%) and two a non-divided RYGB with staple-line disruption (28.5%). All patients were female. Incomplete data was available for weight, BMI, and comorbidity at the time of primary RYGB, and this data, was not included. The patients presented for surgery at a mean of 7.8 years (range, 2–20) from the time of primary RYGB at a mean age of 42 years (range, 27–52). Indications for surgery were intractable epigastric pain in four (57%), non-resolving GJA stenosis in one (14%), recurrent GJA ulceration in three (43%) with hemorrhage in one (14%), coexistent jejuno–gastric fistula in one (14%), and vomiting in four (57%). Six of the seven patients underwent RG (86%). The remaining patient had a prior ring reinforcement of an open retrocolic retrogastric (RR) RYGB. At laparotomy, pouch outlet obstruction with ring erosion and GGF was evident. The eroded ring was removed, the GJA was excised and reanastomosed, the GGF transected, and a tube gastrostomy inserted. LRG was attempted in four patients and completed successfully in two (50%). An open approach was used in the remaining two patients. Remnant gastrectomy with pouch trimming and GGF excision was performed in five patients (71%). In four (57%) patients, the gastric bypass was converted from a RR to an AA RYGB with excision and reanastomosis of the GJA, and insertion of a tube gastrostomy in addition to pouch trimming and GGF excision. Remnant gastrectomy with GGF exclusion was performed in one patient. In addition, an appendicectomy was performed in one patient. Three complications were observed, a subcapsular splenic hematoma, pneumonia, and a superficial wound infection. The mean duration of hospital stay was 9.4 days (range, 3–27).

Our incomplete follow-up is promising with symptom resolution in the majority of patients (87%), resolution of GGF and GJA ulceration in all 24 patients, and further weight loss of an average of 27 lb in 21 patients (87%). Four patients required surgical intervention for late complications after LRG, including open adhesiolysis for small bowel obstruction at 1 month, laparoscopic adhesiolysis for small bowel obstruction at 4 months, incarcerated umbilical port site hernia repair at 13 months, and a converted procedure for an internal hernia at the jejunojejunal anastomosis at 21 months.

Discussion

There are many factors responsible for GGF formation after LRYGB (Table 2). Non-divided RYGB procedures have been associated with an unacceptably high incidence of GGF because of breakdown of the staple line with reestablishment of continuity between the gastric seg-

Table 2 Pathogenesis of Gastro–Gastric Fistula After Laparoscopic Roux-en-Y Gastric Bypass

	Description
Iatrogenic	Poor surgical technique
	Incomplete gastric transection
Anastomotic Leak	Pouch staple line disruption
	Gastrojejunal anastomotic disruption
	Coagulation injury
	Ischemic necrosis due to foreign body: VBG, LAGB
	Incomplete gastric transection
Operation type	Non-divided gastric bypass
Marginal ulcer, perforation	Tissue ischemia
	Staple migration
	Use of non-absorbable suture material
Foreign body erosion	Preanastomotic rings in banded gastric bypass
	Bovine pericardial strips
Natural tendency	Natural gastric migration to reattach to the remnant

LAGB Laparoscopic adjustable gastric banding, *VBG* vertical banded gastroplasty

ments.[10] In our series, two patients referred to us for surgical management of symptomatic GGF from other centers had a prior non-divided RYGB with staple-line disruption (28.5%). Subsequent technical variations with reinforcement of divided RYGB procedures with bands or rings to increase restriction and prevent stomal and pouch dilation were also plagued with a high incidence of GGF.[7,10] Intragastric migration of the band or ring with erosion of the staple line was implicated in the evolution of GGF in these procedures.[7,10] Four of the patients referred to us from other centers with symptomatic GGF had a prior RYGB with GJA ring reinforcement (57%). At laparotomy, two of the four rings had completely eroded through the gastric staple line, whereas the other two were densely adhered to the gastric wall. Ischemic necrosis because of the presence of a constricting ring or band may have been responsible for GGF in the latter two cases.

In the current era of divided RYGB, the majority of GGF are caused by poor surgical technique with failure to completely divide the stomach during pouch creation with maintenance of continuity between the pouch and remnant. Cucchi et al.[13] reported a 6% incidence in divided gastric bypass and recommended meticulous oversewing of staple lines, careful anastomotic technique with good bites of healthy tissue, avoidance of alimentary limb obstruction, and intraoperative confirmation of GJA integrity using methylene blue. Another common cause of GGF is an acute leak from the GJA or the pouch staple-line disruption, which is reported in up to 4.3% of patients after LRYGB.[18] We have previously reported a 1.7% incidence of GJA leak, of whom 27% subsequently developed a GGF.[14] Malfunctioning of linear staplers can also occur, although this complication has become uncommon with the advent of more sophisticated devices.[19] Various techniques have been used to reduce the occurrence of pouch staple-line leak and GGF, including jejunal and/or omental interposition, suture reinforcement of the staple line, vapor-heated fibrin sealant, and more recently, bovine pericardial strips.[20–23]

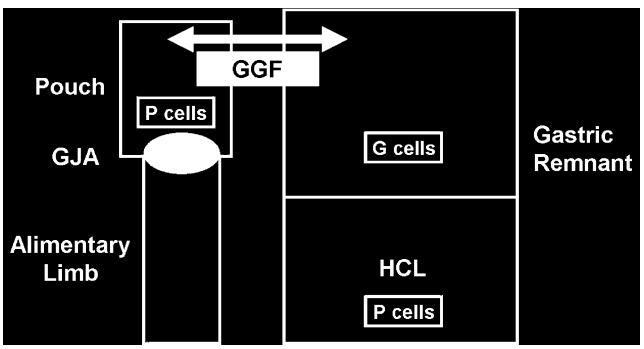


Figure 2 Schematic representation of a gastro–gastric fistula after laparoscopic Roux-en-Y gastric bypass; *GJA* gastrojejunal anastomosis, *GGF* gastro–gastric fistula, *HCL* hydrochloric acid, *P cells* parietal cells, *G cells* gastrin cells.

Table 3 Surgical Management of Gastro–Gastric Fistula

n=24 patients	
Remnant gastrectomy, *n*=23 (96)	Remnant gastrectomy with GGF excision, *n*=9 Remnant gastrectomy with GGF exclusion, *n*=6 Remnant gastrectomy with redo GJA, *n*=8
Additional procedures	Gastrostomy, *n*=4 Appendicectomy, *n*=1 Conversion from RR RYGB to AA RYGB, *n*=4
Fistula transection, *n*=1 (4)	Removal of eroded ring, GGF transection, redo GJA, tube gastrostomy, *n*=1

Data in parentheses are percentages.
GGF Gastro–gastric fistula, *RR* retrocolic retrogastric, *AA* antecolic antegastric, *RYBG* Roux-en-Y gastric bypass

In our series, the incidence of symptomatic GGF of 1.5% after 1,763 primary LRYGB is relatively low compared to other published series.[13,15,24] Of these 27 patients, 37% resolved without further intervention. We believe this is because of standardization of our surgical approach to LRYGB. At the beginning of the procedure, dissection commences high on the gastric fundus to expose the angle of His and the gastroesophageal junction. This exposure allows the creation of a small lesser curve-based pouch and ensures exclusion of the fundus with complete separation of the gastric segments under direct vision. Incomplete division of the apical portion of the stomach during pouch construction can predispose to GGF formation.[25] We routinely perform a posterior wall stapled GJA and close the anterior enterotomy in two layers with an absorbable suture creating a narrow 1.5-cm outlet. To reduce the risk of staple-line leak and hemorrhage, the lateral pouch staple line is reinforced with bovine pericardial strips. The integrity of the GJA and pouch staple line are then confirmed by a combination of intraoperative EGD, air insufflation, and methylene blue instillation. Non-absorbable suture use, staple migration, and tissue ischemia have all been implicated in the development of stomal ulceration.[10,14,24] Although peristrips could act as a foreign body resulting in localized erosion and/or ulceration with subsequent GGF formation, no cases have been recorded in our series. We also use diathermy judiciously, as a localized coagulation injury may predispose to GGF formation. In our institution, we routinely perform GUGI study on POD 1, facilitating the detection of acute leaks and permitting early intervention.[26]

Persistent ulceration at the GJA predisposes to a localized perforation and subsequent GGF formation. We have previously reported a 4.2% incidence of marginal ulceration after LRYGB, with a significant increase up to

53.3% in patients with a demonstrable GGF.[14] To reduce the risk of GJA ulceration, we preoperatively test and treat patients positive for *Helicobacter pylori*. Eradication of *H. pylori* has been demonstrated to significantly reduce the incidence of marginal ulceration.[27,28] Patients are also encouraged to stop smoking. In addition, after LRYGB, patients are discharged on a 3-month course of a PPI.[29]

A number of patients with symptomatic GGF will respond to conservative management.[30] The aim of medical treatment is to attenuate the increased acid production in the remnant stomach because of stimulation of parietal and antral G-cells by food entering through the fistula (Fig. 2). The acid from the remnant stomach spills over through the fistula into the pouch and contributes to marginal ulceration formation.[31] Acid production, although significantly reduced, has been observed in the gastric pouch by stimulation of residual parietal cells.[32,33] PPI significantly decrease acid production in the excluded gastric remnant. In our unit, patients are commenced on a 6-week treatment course of a PPI, with the addition of sucralfate in the presence of marginal ulceration. Sucralfate provides a protective barrier to the gastric pouch and jejunal mucosa, reducing damage by refluxed acid from the remnant stomach through the GGF.[14,30] Patients are reevaluated after 6 weeks to assess symptoms, and a repeat EGD is performed. If patients fail to respond to maximal medical therapy and develop GGF-related complications, surgery is indicated. Currently, there is no accepted surgical technique to manage symptomatic GGF. In our unit, we favor a LRG with trimming of the gastric pouch and excision or exclusion of the fistulous tract. This approach does not interfere with the gastrojejunal anastomosis. In our series, 23 of 24 patients (96%) underwent a RG with GGF excision in 74% and GGF exclusion in 26% (Table 3). The pouch size determines the need for fistula excision or exclusion. In the presence of an adequately sized small pouch, we exclude the tract by vertical transection of the gastric remnant just lateral to the fistula. To date, there has been no evidence of ischemia of the narrow cuff of the stomach left in situ lateral to the GGF. It is important to excise as much of the antrum as possible to avoid the creation of a retained antrum and the theoretical risk of hypergastrinemia. Therefore, the distal stomach is transected just proximal to the pylorus. Remnant gastrectomy can be performed successfully by a laparoscopic approach in the majority of patients. In our series, a laparoscopic approach was attempted in 21 patients (91%) and completed in 18 (78%). As expected, the conversion rate for remnant gastrectomy was higher in patients referred from other centers, the majority of whom had a primary open RYGB. Excision of the GJA with reanastomosis is required in the presence of significant marginal ulceration with stomal stenosis or prior RYGB, where complete pouch revision is required. Eight patients (35%) in our series required excision of the GJA with reanastomosis, of whom four (50%) were converted from a RR to AA RYGB. After RG, adverse events were observed in the early postoperative period in six patients (25%), and our surgical reintervention rate was 4.1%. A leak was suspected in one patient but not proven, and a second patient developed pyrexia of unknown origin. No deaths were recorded in this series.

Conclusion

In summary, GGF formation can complicate divided LRYGB. Asymptomatic GGF can be managed conservatively. There is no standardized surgical treatment approach for symptomatic GGF. Reports of surgical treatment for this complication are rare. In this study, we present a novel surgical procedure to treat GGF, which consists of a laparoscopic approach with RG with or without trimming of the gastric pouch and/or fistulous tract, while leaving the GJA intact in the majority of patients. Based on our early experience, we recommend LRG with fistula excision or exclusion as an effective option with a low morbidity and no mortality in the management of symptomatic GGF after LRYGB.

References

1. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG. Meta-analysis: surgical treatment of obesity. Ann Intern Med 2005;142(7):547–559.
2. DeMaria EJ, Jamal MK. Surgical options for obesity. Gastroenterol Clin North Am 2005;34(1):127–142.
3. Rosenthal RJ, Szomstein S, Kennedy CI, Soto FC, Zundel N. Laparoscopic surgery for morbid obesity: 1,001 consecutive Bariatric operations performed at The Bariatric Institute, Cleveland Clinic Florida. Obes Surg 2006;16(2):119–124.
4. Cottam DR, Nguyen NT, Eid GM, Schauer PR. The impact of laparoscopy on Bariatric surgery. Surg Endosc 2005;19(5):621–627.
5. Nguyen NT, Silver M, Robinson M, Needleman B, Hartley G, Cooney R, Catalano R, Dostal J, Sama D, Blankenship J, Burg K, Stemmer E, Wilson SE. Result of a national audit of Bariatric surgery performed at academic centers: a 2004 University HealthSystem Consortium Benchmarking Project. Arch Surg 2006;141(5):445–449.
6. Wittgrove AC, Clark GW. Laparoscopic gastric bypass, Roux-en-Y-500 patients: technique and results, with 3–60 month follow-up. Obes Surg 2000;10(3):233–239.
7. Gomez CA. Gastroplasty in morbid obesity. Surg Clin North Am 1979;59(6):1113–1120.
8. Mason EE. Vertical banded gastroplasty for obesity. Arch Surg 1982;117(5):701–706.
9. Mason EE, Doherty C, Cullen JJ, Scott D, Rodriguez EM, Maher JW. Vertical gastroplasty: evolution of vertical banded gastroplasty. World J Surg 1998;22(9):919–924.
10. Capella JF, Capella RF. Gastro–gastric fistulas and marginal ulcers in gastric bypass procedures for weight reduction. Obes Surg 1999;9(1):22–27.

11. Fobi MA, Lee H, Igwe D, Jr, Stanczyk M, Tambi JN. Prospective comparative evaluation of stapled versus transected silastic ring gastric bypass: 6-year follow-up. Obes Surg 2001;11(1):18–24.
12. Stanczyk M, Deveney CW, Traxler SA, McConnell DB, Jobe BA, O'Rourke RW. Gastro–gastric fistula in the era of divided Roux-en-Y gastric bypass: strategies for prevention, diagnosis, and management. Obes Surg 2006;16(3):359–364.
13. Cucchi SG, Pories WJ, MacDonald KG, Morgan EJ. Gastrogastric fistulas. A complication of divided gastric bypass surgery. Ann Surg 1995;221(4):387–391.
14. Carrodeguas L, Szomstein S, Soto F, Whipple O, Simpfendorfer C, Gonzalvo JP, Villares A, Zundel N, Rosenthal R. Management of gastrogastric fistulas after divided Roux-en-Y gastric bypass surgery for morbid obesity: analysis of 1,292 consecutive patients and review of literature. Surg Obes Relat Dis 2005;1(5):467–474.
15. Gumbs AA, Duffy AJ, Bell RL. Management of gastrogastric fistula after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2006;2(2):117–121.
16. Gastrointestinal surgery for severe obesity. Consens Statement 1991;9(1):1–20.
17. Szomstein S. How we do it: laparoscopic Roux-en-Y gastric bypass. Contemp Surg 2007;62(3):106–111.
18. Hamilton EC, Sims TL, Hamilton TT, Mullican MA, Jones DB, Provost DA. Clinical predictors of leak after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Surg Endosc 2003;17(5):679–684.
19. Favretti F, Segato G, De MF, Pucciarelli S, Nitti D, Lise M. Malfunctioning of linear staplers as a cause of gastro–gastric fistula in vertical gastroplasty]. G Chir 1990;11(3):157–158.
20. Shikora SA, Kim JJ, Tarnoff ME. Reinforcing gastric staple-lines with bovine pericardial strips may decrease the likelihood of gastric leak after laparoscopic Roux-en-Y gastric bypass. Obes Surg 2003;13(1):37–44.
21. Sapala JA, Wood MH, Schuhknecht MP. Anastomotic leak prophylaxis using a vapor-heated fibrin sealant: report on 738 gastric bypass patients. Obes Surg 2004;14(1):35–42.
22. Lee MG, Provost DA, Jones DB. Use of fibrin sealant in laparoscopic gastric bypass for the morbidly obese. Obes Surg 2004;14(10):1321–1326.
23. Zorrilla PG, Salinas RJ, Salinas-Martinez AM. Vertical banded gastroplasty–gastric bypass with and without the interposition of jejunum: preliminary report. Obes Surg 1999;9(1):29–32.
24. Filho AJ, Kondo W, Nassif LS, Garcia MJ, Tirapelle RA, Dotti CM. Gastrogastric fistula: a possible complication of Roux-en-Y gastric bypass. JSLS 2006;10(3):326–331.
25. Gould JC, Garren MJ, Starling JR. Lessons learned from the first 100 cases in a new minimally invasive Bariatric surgery program. Obes Surg 2004;14(5):618–625.
26. Sims TL, Mullican MA, Hamilton EC, Provost DA, Jones DB. Routine upper gastrointestinal Gastrografin swallow after laparoscopic Roux-en-Y gastric bypass. Obes Surg 2003;13(1):66–72.
27. Rasmussen JJ, Fuller W, Ali MR. Marginal ulceration after laparoscopic gastric bypass: an analysis of predisposing factors in 260 patients. Surg Endosc 2007 19.
28. Carrodeguas L, Szomstein S, Zundel N, Lo ME, Rosenthal R. Gastrojejunal anastomotic strictures following laparoscopic Roux-en-Y gastric bypass surgery: analysis of 1291 patients. Surg Obes Relat Dis 2006;2(2):92–97.
29. Gumbs AA, Duffy AJ, Bell RL. Incidence and management of marginal ulceration after laparoscopic Roux-Y gastric bypass. Surg Obes Relat Dis 2006;2(4):460–463.
30. Gustavsson S, Sundbom M. Excellent weight result after Roux-en-Y gastric bypass in spite of gastro–gastric fistula. Obes Surg 2003;13(3):457–459.
31. MacLean LD, Rhode BM, Nohr C, Katz S, McLean AP. Stomal ulcer after gastric bypass. J Am Coll Surg 1997;185(1):1–7.
32. Siilin H, Wanders A, Gustavsson S, Sundbom M. The proximal gastric pouch invariably contains acid-producing parietal cells in Roux-en-Y gastric bypass. Obes Surg 2005;15(6):771–777.
33. Hedberg J, Hedenstrom H, Nilsson S, Sundbom M, Gustavsson S. Role of gastric acid in stomal ulcer after gastric bypass. Obes Surg 2005;15(10):1375–1378.

J Gastrointest Surg (2007) 11:1680–1685
DOI 10.1007/s11605-007-0235-7

Repeat Transarterial Chemoembolization (TACE) for Progressive Hepatic Carcinoid Metastases Provides Results Similar to First TACE

Kimberly A. Varker · Edward W. Martin · Dori Klemanski · Bryan Palmer · Manisha H. Shah · Mark Bloomston

Received: 5 June 2007 / Accepted: 30 June 2007 / Published online: 25 September 2007

Abstract
Background Transarterial chemoembolization (TACE) is commonly used to treat metastatic carcinoid tumors; however, the management of progressive disease is less clear. We sought to determine if patients with disease progression after TACE would benefit from repeat TACE.
Methods The records of 27 patients undergoing repeat TACE for radiologic or symptomatic progression after TACE for metastatic carcinoid were reviewed and compared to 122 undergoing first TACE. Overall and progression-free survivals were estimated by the Kaplan–Meier method.
Results Mean disease-free interval after first TACE was 11.8 months. Radiologic response was observed in 61% compared to 82% after first TACE (p=0.058); hormone response in 64% compared to 80% (p=0.159); and symptomatic response in 77% compared to 92% (p=0.053). The complication rate after repeat TACE was lower than after first TACE (p=0.03). Median overall survival was similar after repeat (28.1 months) and first TACE (33.3 months) (p=0.53). Progression-free survival was shorter after repeat TACE but not significantly so. No factor examined could predict survival after repeat TACE.
Conclusion Repeat TACE for patients with hepatic carcinoid metastases failing first TACE or having evidence of disease progression is safe and offers a viable treatment option.

Keywords Carcinoid tumor · Hepatic metastases · Transarterial chemoembolization

Presented at the 48th Annual Meeting of The Society for Surgery of the Alimentary Tract, Washington, DC, May, 2007.

K. A. Varker · E. W. Martin · D. Klemanski · B. Palmer · M. H. Shah · M. Bloomston
Division of Surgical Oncology, Department of Surgery, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA

M. H. Shah
Division of Hematology-Oncology, Department of Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA

M. Bloomston (✉)
Division of Surgical Oncology, Department of Surgery, The Ohio State University Medical Center, N924 Doan Hall, 410 W. 10th Avenue, Columbus, Ohio 43210, USA
e-mail: Mark.Bloomston@osumc.edu

Introduction

Carcinoid tumors are neuroendocrine malignancies characterized by an indolent growth pattern. The most frequent primary sites include the gastrointestinal tract, commonly ileum, and the bronchopulmonary system.[1] The most frequent site of distant metastasis of carcinoid tumors is the liver, and the involvement is typically multicentric and diffuse.[1] The presence of hepatic metastases is an important determinant of survival, with a 5-year survival of only 40% in patients having carcinoid liver metastases, compared to 100% in those without metastases.[2] The optimal treatment for carcinoid hepatic metastases is complete resection, but at most 10% of patients have resectable disease.[3] To realize benefit from cytoreduction, all of the primary tumor and at least 90% of the metastatic disease must be removed.[3,4] Thus, although cytoreduction is recommended management, it is not achievable in the majority of patients. Systemic chemotherapy such as streptozotocin has provided disappointing results for the treatment of neuroendocrine

tumors.[5] Octreotide analogs are effective for management of symptoms related to the carcinoid syndrome by inhibition of polypeptide release, although their ability to inhibit tumor growth is mostly theoretical.[6] However, over time the disease can become refractory to octreotide treatment.[7]

The use of hepatic artery embolization or chemoembolization (TACE) for neuroendocrine metastases has evolved over time. Hepatic metastases provide an ideal setting for regional therapies because tumors are preferentially supplied by branches of the hepatic artery; thus, selective devascularization can induce ischemia within the tumor while preserving normal parenchyma. This strategy is particularly useful for neuroendocrine tumors because they are highly vascular and thus particularly sensitive to ischemia.[8,9] Thus, regional therapies such as TACE have been found to be efficacious in patients with symptoms refractory to octreotide and are the treatment of choice in patients whose disease is not amenable to resection.[9–11]

Although TACE has an established role in the treatment of hepatic neuroendocrine metastases, the management of patients who fail to respond to TACE or develop progressive disease after response to TACE remains a clinical challenge. Whereas most well-experienced centers advocate repeat TACE for progressive disease, the efficacy of such an approach has not been reported. We sought to determine if patients with disease progression after TACE could derive similar benefit from a second TACE procedure. The goal of this study was to determine the rate of response and overall survival in patients undergoing repeat TACE for hepatic carcinoid metastases. Furthermore, we wished to determine whether any factors related to the tumor or to the response to the first TACE procedure could predict survival after repeat TACE.

Materials and Methods

Patients

From the group of patients undergoing TACE for inoperable hepatic carcinoid metastases at the Ohio State University Medical Center between 1992 and 2004 (n=122), a subset of patients (n=27) underwent a second TACE procedure between January 1997 and May 2006 for treatment of radiologic or symptomatic progression. Patients undergoing TACE as a planned staged second procedure were not included. Both computerized records and paper charts were examined. Results were compared to those for first TACE. Approval for this study was obtained from the Institutional Review Board of the Ohio State University.

Eligibility Criteria and Patient Follow-Up

The eligibility criteria for initial TACE for metastatic carcinoid were detailed previously.[12] Briefly, eligible patients were those with well- or moderately differentiated (atypical carcinoid) neuroendocrine carcinoma who had poorly controlled carcinoid-related symptoms on octreotide therapy, evidence of tumor progression in the liver, or significant tumor burden such that any progression could result in hepatic insufficiency rendering the patient ineligible for regional therapy. Patients with uncontrolled symptoms on octreotide therapy or asymptomatic patients with radiologic evidence of tumor progression in the previously treated region after first TACE were considered for repeat TACE. Patients undergoing planned stage TACE were not included in this study. Additional eligibility criteria included preserved hepatic and renal function (serum bilirubin <2 mg/dL and serum creatinine <2 mg/dL), normal coagulation profile, and adequate hematologic profile (leukocyte count >2,000/mL and platelet count >100,000/mL). Lobar portal vein occlusion was an absolute contraindication to TACE. All treatment decisions were made by a multidisciplinary team including the treating surgeon, medical oncologist, and interventional radiologist. After treatment, patients underwent clinical and radiologic evaluation at the discretion of the attending physician.

Embolization Procedure

Our approach to TACE has been described previously.[12] Briefly, diagnostic angiography via the femoral approach at the time of TACE was first performed to review the hepatic arterial anatomy and confirm portal vein patency. A microcatheter was subsequently advanced through a 5-French sheath into the left or right hepatic artery. An emulsion of doxorubicin 30 mg, mitamycin 30 mg, cisplatin 50 mg, ioxaglate sodium, and ethiodized oil (37%) was injected. Additional embolic materials consisting of gelfoam, polyvinyl alcohol (PVA) particles, or Embospheres (Biosphere Medical, Inc., Rockland, MD) were then injected until flow in the hepatic artery ceased. Patients remained hospitalized as their clinical course dictated.

Assessment of Response

Radiologic response was assessed by computed tomography (CT), and was defined as any decrease in the size or number of hepatic lesions, or the development of significant calcifications within the lesions. Radiologic progression was defined as any increase in size or number of lesions at any time during follow-up. Symptomatic progression was defined as the worsening of symptoms or the requirement

of increasing doses of octreotide to control symptoms. Finally, biochemical response to therapy was determined by assessment of serum pancreastatin levels.[13]

Statistical Analysis

Overall survival was determined from the time of repeat TACE until time of death from any cause as determined by hospital records or the Social Security Death Index (http://ssdi.rootsweb.com). Progression-free survival was calculated from the time of repeat TACE until radiologic, symptomatic, or serologic evidence of disease progression. Categorical data were compared using Fisher's exact test and continuous data were compared using the Mann–Whitney *U* test. Overall survival and progression-free survival were estimated by the Kaplan–Meier method and curves were compared by log-rank analysis. The Cox proportional hazards model was used to determine prognostic variables. All analyses were completed using SPSS v.14 software (SPSS, Chicago, IL).

Results

Patients

The multidisciplinary team of the Neuroendocrine Tumor Program at The Ohio State Medical Center coordinates the treatment of patients undergoing TACE. We previously reported on 122 patients with inoperable hepatic carcinoid metastases who underwent TACE between January 1992 and December 2004.[12] Of these 122 patients, a total of 27 (13 male, 14 female; median age 53) underwent a second TACE procedure for treatment of radiologic or symptomatic progression. This group of patients constituted the population for the present study. Patient characteristics are summarized in Table 1. The most common site of primary tumor was the small bowel, and half of these were in the ileum. The primary tumor had been resected in three-quarters of the patients. Before initial TACE, most patients were treated with somatostatin analogs. In the majority of patients (59%), the indication for repeat TACE was palliation of recurrent/progressive symptoms (Table 2).

Treatment Administered

Our traditional approach to TACE has been to treat all tumor-bearing portions of the liver in one sitting. Unilateral TACE was considered selectively in patients with particularly high tumor burden or those with poor underlying health. As such, two-thirds of the patients underwent whole liver TACE, and 26% underwent a unilateral (right or left) approach (Table 2).

Table 1 Patient Characteristics

Characteristic	Number of patients (percent)
Gender	
Male	13 (48.1)
Female	14 (51.9)
Age (median, range)	53 (33–83)
Primary tumor site	
Small bowel	13 (48.1)
Ileum	6
Other	7
Pancreas	4 (14.8)
Colon	2 (7.4)
Lung	2 (7.4)
Rectum	1 (3.7)
Stomach	1 (3.7)
Unknown	4 (14.8)
Primary resected	
Yes	20 (74.1)
No	7 (25.9)

Adverse Effects

As expected, all patients experienced transient (maximum duration 2–4 weeks) pain, fever, nausea, or fatigue after TACE (the so-called post-embolization syndrome). These were not considered complications. However, three patients (11%) developed complications, all of which resolved with medical management. One patient developed transient

Table 2 Characteristics of Repeat TACE

Characteristic	Number of patients (percent)
Indication for repeat TACE	
Symptoms	16 (59.3)
Radiologic progression	10 (37.0)
Not specified	1 (3.7)
Extent of TACE	
Whole liver	18 (66.7)
Right	6 (22.2)
Left	1 (3.7)
Unknown	2 (7.4)
Radiologic response to repeat TACE*	
Yes	11 (61.1)
No	7 (38.9)
Hormone response to repeat TACE†	
Yes	14 (63.6)
No	8 (36.4)
Symptomatic response to repeat TACE†	
Yes	17 (77.3)
No	5 (22.7)

*Total evaluable patients, $n=18$
† Total evaluable patients, $n=22$

hyperbilirubinemia, one had hepatic encephalopathy, and one had supraventricular tachycardia. In contrast, among the original 122 patients undergoing the first TACE, complications occurred in 28 (23%). The difference in the rate of complications between first and repeat TACE was statistically significant (p=0.03). Mortality of repeat TACE was nil, whereas mortality among the patients undergoing first TACE was 5% (6 patients) (p=NS).

Response to TACE

Radiologic response was observed in 61% (11 of 18) compared to 82% after first TACE (p=0.058); hormone response was seen in 64% (14 of 22) compared to 80% after first TACE (p=0.159); and symptomatic response was observed in 77% (17 of 22) compared to 92% after first TACE (p=0.053).

Survival and Prognostic Factors

Overall median survival after repeat TACE (28.1 months) was similar to that after first TACE (33.3 months; p=0.53, Fig. 1). Progression-free survival (median 5.0 months) was shorter after repeat TACE compared to initial TACE, but this difference was not statistically significant. No factor including age, comorbidity, site of primary tumor, resection of primary tumor, symptoms of carcinoid syndrome, or radiologic, hormone, or symptomatic response to the first TACE could predict survival after repeat TACE.

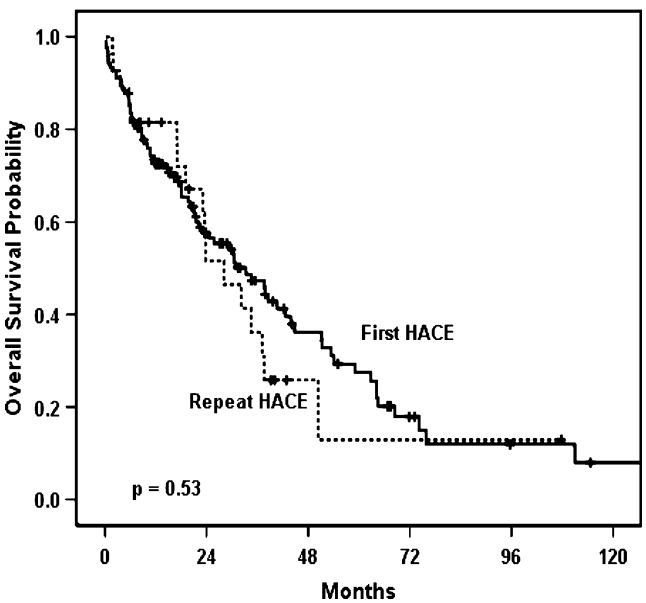


Figure 1 Overall survival as estimated by the Kaplan–Meier method. Survival for first TACE is represented by the solid black line, and survival for repeat TACE is represented by the dotted line.

Discussion

Regional embolic therapy such as TACE is widely accepted for the management of hepatic metastases from carcinoid. In the era of novel regional therapies such as selective internal radiation therapy (SIRT), it remains to be seen whether repeat TACE or strategies such as SIRT should be considered in patients with disease progression after TACE. Whereas most well-experienced centers offer repeat TACE for patients failing initial TACE or having evidence of disease progression, the efficacy of repeat TACE relative to first-time treatment has not been described. Herein we report the results of 27 patients undergoing repeat TACE for radiologic or symptomatic progression. Repeat TACE was well tolerated, with only three patients (11%) experiencing complications. Survival was not different from first TACE.

Despite examination of several factors relating to the primary tumor and to response after initial TACE, we were unable to identify any factor predictive of survival. Nevertheless, long-term survival was possible in some patients. Factors examined as potential prognostic variables were age; presence of comorbidity; site of primary tumor; resection of primary tumor; symptoms of carcinoid syndrome; radiologic, hormone, or symptomatic response to the initial TACE; and radiologic, hormone, or symptomatic response to repeat TACE. In our previous report of patients undergoing initial TACE, pre-TACE levels of pancreastatin >5,000; the occurrence of complications; and lack of radiologic, symptomatic, or biochemical response to TACE were associated with decreased overall survival by univariate analysis.[12] By multivariate analysis, only lack of symptomatic improvement after TACE was predictive of poor outcome.[12] None of these factors was able to predict survival in the group of patients undergoing repeat TACE. Similarly, although others have suggested that carcinoid as compared to islet cell primary or resection of the primary before the need to address hepatic metastases were associated with survival advantage after liver-directed therapy, we have not found either of these to be prognostic in our experience.[11,14]

Serum level of pancreastatin, a split-product of chromogranin A, has proven utility as a sensitive marker for carcinoid tumors.[15,16] Calhoun *et al* studied 31 patients with carcinoid tumors.[17] Serum pancreastatin was elevated in 81% of patients, and was the only elevated peptide in 57%. Levels of multiple other peptides, including vasoactive intestinal peptide, pancreatic polypeptide, neurotensin, substance P, gastrin-releasing peptide, calcitonin, and gastrin were not consistently elevated.[17] Similarly, we observed inconsistent elevation of tumor markers other than pancreastatin in a group of patients with metastatic neuroendocrine tumors treated on a Phase II trial of thalidomide.[25] Our group previously found that decreased pancreastatin levels after TACE treatment may correlate with response to treatment,

and proposed that an increase in pancreastatin level after a previous decrease may provide an indication for repeat TACE.[13] Seventy-eight percent of patients treated with TACE experienced decreased or stable levels of pancreastatin after treatment; those whose pancreastatin levels did not decrease at least 20% after treatment all died within 8 months.[13] The fact that pancreastatin response to TACE treatment was not able to predict survival in the present group of patients may be caused by the relatively small number of patients in this study.

The rates of radiologic, hormone (*i.e.*, pancreastatin), and symptomatic response to TACE in this study were 61%, 64%, and 77%, respectively. Whereas these response rates were lower than after initial TACE, statistical significance was not reached. The rate of radiologic response, defined as any decrease in the size or number of hepatic lesions, was 61%. This compares favorably with results in the literature. There is inherent difficulty in objectively measuring radiographic response after regional therapy. Standardized criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) assume equal distribution of drug to all areas of the tumor in a given organ and equate response to therapy with decrease in tumor size. Such assumptions do not hold true in regional therapy because drug distribution is less predictable and necrotic tumors often do not change (or may even increase in size) in response to therapy. Nevertheless, we currently track RECIST in our prospective database. In this study, we relied on the interpretation of the attending radiologist to determine response to therapy. Whereas this introduces a potential bias in this retrospective review, all radiologists were blinded to clinical information. Reported rates of symptom response vary between 66% and 100%, of marker response between 50% and 91%, and of morphologic (radiologic) response between 33% and 80%.[18] Gupta *et al.* reviewed recent series of TACE for various neuroendocrine tumors and found the average rate of complete or partial radiologic response to be 32% (31 of 96 patients).[11,19–24] Finally, symptomatic response was observed in 77% of patients in the present study. This is a particularly encouraging result given that most patients were on octreotide before TACE, and corroborates the results of others demonstrating the role of TACE in patients with octreotide-refractory symptoms.[9–11]

The median survival of 28.1 months in this study was not significantly different than survival of the larger group after the initial TACE procedure (33.3 months). This result again underscores the indolent nature of carcinoid tumors and the long-term survival possible, even with metastatic disease. Importantly, this finding suggests that repeat TACE has an important role in the management of progressive carcinoid metastases after initial TACE, providing symptom control and extension of survival similar to the first TACE procedure. Repeat TACE may be especially useful because patients with longstanding carcinoid metastases often have disabling symptoms refractory to medical management. Furthermore, the procedure was well tolerated with a low incidence of complications, making it well suited to a group of patients with advanced malignancy. Although we analyzed multiple factors related to the extent of primary tumor and patient response to first TACE, we were unable to identify any prognostic factors. Further studies in larger groups of patients may help to identify prognostic factors among this unique group of patients.

Conclusion

In this group of 27 patients undergoing repeat TACE for radiologic or symptomatic progression of hepatic carcinoid metastases, the procedure was well tolerated, with a small percentage of patients experiencing transient adverse effects. Interestingly, the incidence of complications was significantly lower in this group than in patients undergoing the first TACE. Radiologic, hormone, and symptomatic responses to repeat TACE were 60–80%; these results were not significantly different than among patients undergoing first TACE. The median overall survival of 28.1 months for repeat TACE was not different than that of patients undergoing first TACE, suggesting that repeat TACE is a useful and effective treatment for patients with progression of hepatic carcinoid metastases after previous regional embolic therapy. Repeat TACE should be considered at any point in the treatment algorithm of patients with progressive hepatic carcinoid metastases.

References

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–959.
2. Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou JF, Vilgrain V, Belghiti J, Bernades P, Ruszniewski P. Prognostic factors in patients with endocrine tumors of the duodenopancreatic area. Gut 1998;43:422–427.
3. McEntee GP, Nagorney DM, Kvols LK, Moertel CG, Grant CS. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990;108:1091–1096.
4. Osborne DA, Zervos EE, Strosberg J, Boe BA, Malafa M, Rosemurgy AS, Yeatman TJ, Carey L, Duhaine L, Kvols LK. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol 2006;13:572–581.
5. Moertel CG, Johnson CM, McKusick MA, Martin JK Jr, Nagorney DM, Kvols LK, Kunselman S. The management of patients with advanced carcinoid tumors and islet cell carcinomas. Ann Intern Med 1994;120:302–309.
6. Schnirer II, Yao JC, Ahani HA. Carcinoid—a comprehensive review. Acta Oncol 2003;42:672–692.

7. Arnold R, Trautmann ME, Creutzfeldt W, Benning R, Neuhaus C, Jurgensen R, Stein K, Schafer H, Bruns C, Dennler HJ. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. Gut 1996;38:430–438.
8. O'Toole D, Ruszniewski P. Chemoembolization and other ablative therapies for liver metastases of gastrointestinal tumours. Best Pract Res Clin Gastroenterol 2005;19:585–594.
9. Drougas JG, Lowell BA, Blair TK, Lopez RR, Wright JK, Chapman WC, Webb L, Mazer M, Meranze S, Pinson CW. Hepatic artery chemoembolization for management of patients with advanced metastatic carcinoid tumors. Am J Surg 1998;175:408–412.
10. Eriksson BK, Larsson EG, Skogseid BM, Lofberg AM, Lorelius LE, Oberg KE. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. Cancer 1998;83:2293–2301.
11. Gupta S, Yao JC, Ahrar K, Wallace MJ, Morello FA, Madoff DC, Murthy R, Hicks ME, Ajani JA. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J 2003;9:261–267.
12. Bloomston M, Al-Saif O, Klemanski D, Pinzone JJ, Martin EW, Palmer B, Guy G, Khabiri H, Ellison EC, Shah MH. Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned. J Gastrointest Surg 2007;11:264-271.
13. Desai DC, O'Dorisio TM, Schirmer WJ, Jung SS, Khabiri H, Villanueva V, Martin EW Jr. Serum pancreastatin levels predict response to hepatic artery chemoembolization and somatostatin analogue therapy in metastatic neuroendocrine tumors. Regul Pept 2001;96:113–117.
14. Yao KA, Talamonti MS, Nemcek A, Angelos P, Chrisman H, Skarda J, Benson AB, Rao S, Joehl RJ. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. Surgery 2001;130:677–685.
15. Oberg K. The ultimate biochemical diagnosis of gastroenteropancreatic tumours. Digestion 1996;57(suppl 1):45–47.
16. Stidsberg M, Oberg K, Li Q, Engstrom U, Lundqvist G. Measurements of chromogranin A, chromogranin B (secretogranin 1), chromogranin C (secretogranin II) and pancreastatin in plasma and urine from patients with carcinoid tumors and endocrine pancreatic tumors. J Endocrinol 1995;144:49–59.
17. Calhoun K, Toth-Fejel S, Cheek J, Pommier R. Serum peptide profiles in patients with carcinoid tumors. Am J Surg 2003;186:28–31.
18. Ruszniewski P, Malka D. Hepatic arterial chemoembolization in the management of advanced digestive endocrine tumors. Digestion 2000;62(Suppl I):79–83.
19. Roche A, Girish BV, de Baere T, Baudin E, Boige V, Elias S, Lasser P, Schlumberger M, Ducreux M. Trans-arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumors. Eur Radiol 2003;13:136–140.
20. Dominguez S, Denys A, Madeira I, Hammel P, Vilgrain V, Menu Y, Bernades P, Ruszniewski P. Hepatic arterial chemoembolization with streptozotocin in patients with metastatic digestive endocrine tumours. Eur J Gastroenterol Hepatol 2000;12:151–157.
21. Hajarizadeh H, Ivancev K, Mueller CR, Gletcher WS, Woltering EA. Effective palliative treatment of metastatic carcinoid tumors with intra-arterial chemotherapy/chemoembolization combined with octreotide acetate. Am J Surg 1992;163:479–483.
22. Kim YH, Ajani HA, Carrasco CH, Dumas P, Richli W, Lawrence D, Chuang V, Wallace S. Selective hepatic arterial chemoembolization for liver metastases in patients with carcinoid tumor or islet cell carcinoma. Cancer Investig 1999;17:474–478.
23. Ruszniewski P, Rougier P, Roche A, Legmann P, Sibert A, Hochlaf S, Ychou M, Mignon M. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors. A prospective Phase II study in 24 patients. Cancer 1993;71:2624–2630.
24. Therasse E, Breittmayer F, Roche A, DeBaere T, Indushekar S, Ducreux M, Lasser P, Elias D, Rougier P. Transcatheter chemoembolization of progressive carcinoid liver metastases. Radiology 1993;189:541–547.
25. Varker KA, Campbell J, Shah MH. Phase II study of thalidomide in patients with metastatic carcinoid and islet cell tumors. Cancer Chemother Pharmacol; DOI 10.1007/s00280-007-0521-9.

J Gastrointest Surg (2007) 11:1686–1691
DOI 10.1007/s11605-007-0278-9

Laparoscopic Deployment of Biliary Self-Expandable Metal Stent (SEMS) for One-Step Palliation in 23 Patients with Advanced Pancreatico-Biliary Tumors—a Pilot Trial

Everson L. A. Artifon · Airton Z. Rodrigues · Sergio Marques · Bhawna Halwan · Paulo Sakai · Claudio Bresciani · Atul Kumar

Received: 20 May 2007 / Accepted: 24 July 2007 / Published online: 29 September 2007

Abstract
Background Exploratory laparoscopy is commonly undertaken in patients with highly suspicious biliary and pancreatic lesions to facilitate diagnosis and staging cancer is present. If an unresectable tumor is identified, a second endoscopic procedure may be required do deploy a self-expandable metal stent (SEMS) for palliation. As endoscopic retrograde cholangio pancreatography (ERCP) may be unsuccessful in up to 20% of patients, we evaluated the feasibility and safety of deployment of self-expandable metal stents at the same time as the initial laparoscopy.
Patients and Methods A total of 23 eligible patients (8 male and 15 female) with malignant obstruction of the common bile duct underwent deployment of SEMS at laparoscopy. Primary outcome measure was the successful laparoscopic deployment of stent and secondary outcome measure was complications rates.
Results Indications for stent deployment were unresectable pancreatic cancer in 18, cholangiocarcinoma in two, neuroendocrine tumor in one and ampullary adenocarcinoma in two patients. The median age was 73 years (range 49–93). Twenty-two of 23 stents were deployed successfully: 17 stents were deployed transcystically and five via a choledochotomy. Median times for laparoscopic exploration and SEMS deployment were 165 min (range 105–230) and 20 min (range 10–50), respectively. Pre- and post-procedures median total bilirubin were 9.4 mg/dl (range 5.4–17.5) and 4.0 (range 2.6–7.1). The median size of the pancreatic mass was 3 cm (range 2–5 cm) and that of the common bile duct (CBD) from 9.2 mm (range 7.2–17.4). The mean duration of laparoscopy was 170 min (range 120–230 min) and that for stent deployment 23 min (range 10–50 min). Complications included bleeding, obstruction, and wound infection. Bleeding occurred on day 7 in two patients and on day 30 in one patient; bleeding occurred at the gastrojejunal anastomosis site and was successfully treated with endoscopic hemostasis. A total of three stent obstructions were identified: one each at 60, 90, and 120 days follow-up. All complications were successfully managed endoscopically. There were a total of seven deaths, six as a result of progressive cancer and one of surgical wound infection and ensuing complications.
Conclusion This study demonstrates that laparoscopic deployment of self-expandable metal bile duct stents is feasible and safe. This option appears to be a reasonable option in patients with inoperable malignant obstruction of the distal common bile duct.

E. L. A. Artifon · A. Z. Rodrigues · S. Marques · P. Sakai · C. Bresciani
Hospital Ana Costa, Santos and Hospital Estadual de Sapopemba, University of São, Paulo School of Medicine, São Paulo, Brazil

B. Halwan
Division of Gastroenterology & Hepatology, SUNY-Downstate, Brooklyn, NY 11203, USA

A. Kumar (✉)
Northport VA Medical Center, Stony Brook University, 79 Middleville Road, Northport, NY 11768, USA
e-mail: atul.kumar2@va.gov

Keywords Self-expandable metal stent · Pancreatic cancer · Laparoscopic surgery

Introduction

Pancreatic cancer is the fifth leading cause of cancer death and accounts for about over 30,000 deaths annually.[1] Once diagnosed, the condition is universally fatal. In fact, the mortality rate from pancreatic cancer is the highest among all cancers and exceeds 95% at 5 years. Our ability to rapidy diagnose and treat pancreatic cancer is quite dismal despite

significant progress in our understanding of this disease.[2] Only 10–15% of patients have surgically resectable cancers at time of diagnosis.[3] Despite the availability of several imaging and tissue acquisition modalities such as CT scan, ultrasound-guided fine-needle aspiration cytology (CT/US-FNAC), endoscopic retrograde cholangio pancreatography (ERCP) with brushings, and endoscopic ultrasound-guided fine-needle aspiration cytology (EUS-FNAC), a large cohort of patients require laparoscopic surgical biopsy for confirmatory diagnosis. In patients with unresectable pancreaticobiliary tumors, ERCP for insertion of metal bile duct stents for palliation, is often indicated

Palliative measures such as biliary bypass surgery, endoscopic or percutaneous stent placement across the area of involvement are currently the cornerstone of therapy as it improves quality of life by relieving obstructive symptoms and prolongs survival by preventing development of cholangitis. In a metaanalysis of nearly 2000 patients collectively with malignant obstructive jaundice, although success rates were similar for percutaneous, endoscopic, and surgical modalities, short-term morbidity, mortality, and length of hospital stay were higher in the surgical bypass group.[4,5] Endoscopic stent deployment provides complete relief of jaundice, itching, dyspepsia, and anorexia and has similar survival outcomes and lower complication rates as compared to surgical treatment.[6] Self-expandable metal stents (SEMS) are also preferred in comparison to plastic stents as they are associated with fewer complications such as migration and occlusion and hence are cost-effective. Expandable metallic stents for palliation may be placed endoscopically or percutaneously under radiological guidance. Alternatives to endoscopic deployment of SEMS include percutaneous hepatic drainage, which is useful only for short-term drainage and associated with a greater complication rate.[7] Yoshida, et al., have described a simple one step percutaneous transhepatic insertion of a SEMS for treatment of unresectable malignancies in 14 patients; however, the catheter in this technique has to be left in place to prevent bleeding in the liver after its removal. We evaluated, for the first time, the feasibility of deploying a SEMS during laparoscopy as a one-step procedure in patients with unresectable pancreatic cancer.

Methods

Patients

The study was conducted at a single tertiary care referral center at Hospital Ana Costa, Santos and Hospital Estadual de Sapopemba at the University of Sao Paulo School of Medicine, Sao Paulo, Brazil between July 2005 and November 2006. The local institutional review committee approved the study protocol and informed consent was obtained from all patients before enrollment. Twenty-three patients meeting eligibility criteria were prospectively enrolled in the study. Eligible patients included those with a pancreatic mass on computed tomography (CT) scan imaging and scheduled to undergo laparoscopic biopsy for further evaluation. Patients had advanced pancreatic or biliary cancer and diagnosis suspected clinically by CT scan and prior EUS. Exclusion criteria included any contraindication to laparoscopic intervention such as uncorrected coagulopathy, severe cardiopulmonary abnormalities, and objection to study participation. Demographic, laboratory, and clinical data were obtained before and 7, 30, 60, 90, and 120 days post-procedure. The primary outcome measure was the successful deployment of the stent and secondary outcomes included short- and long-term complication rates, procedure time, total Bilirubin and Alkaline Phosphatase before and after the procedure.

Technique of SEMS Insertion During Laparoscopy

Antibiotics were administered prophylactically to all patients 12 hours before surgery. A nasogastric tube was inserted and the stomach lumen aspirated to the fullest extent possible. After the creation of a pneumoperitoneum using a Veress needle in the supraumbilical and previously not operated area, patients were positioned with a head-up tilt. The surgeon operated from the left side of the patient with a cameraman at his side and the assistant and scrub nurse on the opposite side of the operating table. Four conventional ports were used: 11 mm optical, 5 mm and 11 mm operating, and a 5-mm assistance port. The optical port was located near the umbilicus and a 30° laparoscope was used. An initial 360° scan of the whole abdomen was performed to exclude any preexisting abnormalities. The dissection of the cystic pedicle was carried out as follows. With traction on the anterior edge of Hartmann's pouch, the peritoneum off the superior aspect of the cystic pedicle was dissected superficially as far back as the liver. Blunt dissection around the cystic duct pedicle was performed using a pledget. The cystic artery was dissected away from the cystic duct using a Maryland grasper or electrosurgical hook knife. The cystic artery was then double-clipped and divided by hook scissors. The dissection of the cystic pedicle was completed by placement of a clip to occlude the cystic duct at its junction with the gallbladder. An opening in the cystic duct was made on its antero-superior aspect in 18 patients (Fig. 1). Correct alignment of the cystic duct and infusion of saline into the cystic duct facilitated opening of the cystic duct lumen for insertion of the SEMS for deployment. Insertion was noted to be difficult if the opening in the cystic duct was made too close to the gallbladder. Contrast medium was injected

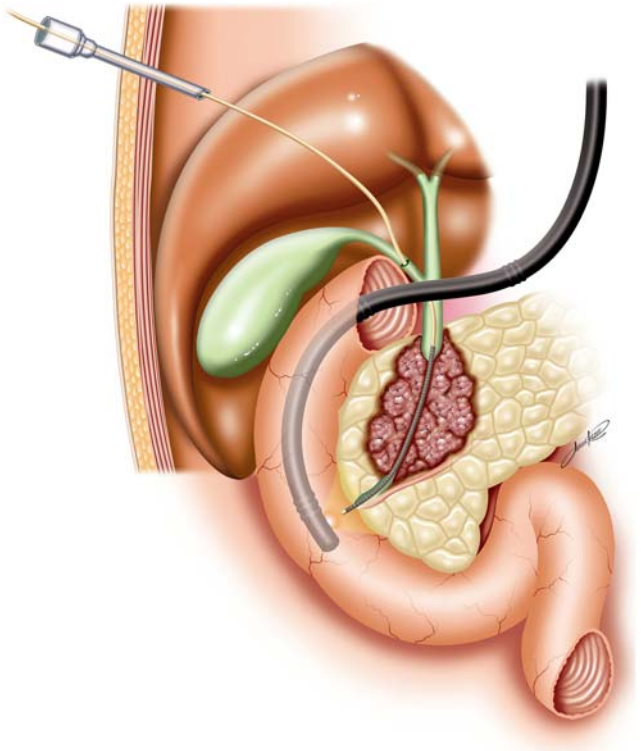


Figure 1 A schematic of opening in cystic duct to enable passage of a guidewire.

slowly with the patient in a slight Trendelenburg position and the table rotated slightly to the right to outline the entire common bile duct (Fig. 2). The cholangiogram was reviewed to identify the extent of the bile duct involvement and to identify the appropriate stent size for deployment. Choledochotomy of the anterior surface of the common hepatic duct close to the insertion of the cystic duct was performed in five patients (Fig. 3). The guidewire was advanced into the duodenum where it was endoscopically seen exiting the ampulla antegrade (Fig. 4). The metallic stent, (Wall Stent, Boston Scientific, Natick, MA, USA) was passed through the 5-mm port in the right midclavicular line. Using a grasper, the SEMS was directed to the narrow passage of the cystic duct orifice and/or choledochotomy. The angulation of the cystic duct was adjusted by traction on the gallbladder to facilitate advancement of the stent over the 0.035-inch teflon wire. A duodenoscope, model TJF-140 (Olympus, Melville, NY, USA) was utilized to verify positioning before stent deployment (Fig. 5). The stent was deployed in the usual way under fluoroscopy guidance (Figs. 6, 7, and 8). No conversion to laparotomy was necessary in any patient. The patients remained in the hospital for 2–5 days after the procedure.

Patients underwent urgent endoscopy for clinical suspicion of bleeding, obstruction, and other complications such as stent migration. For active bleeding, endoscopic hemostasis was performed by first injecting the bleeding area and using hemoclips (Olympus, Melville, NY) or coaptive coagulation using gold probe (Boston Scientific, Natick, MA). Stent occlusion was treated with passage of plastic stent through the existing stent and/or APC (ERBE, Marietta, GA, USA) of the stent lumen to debulk ingrowing tumor.

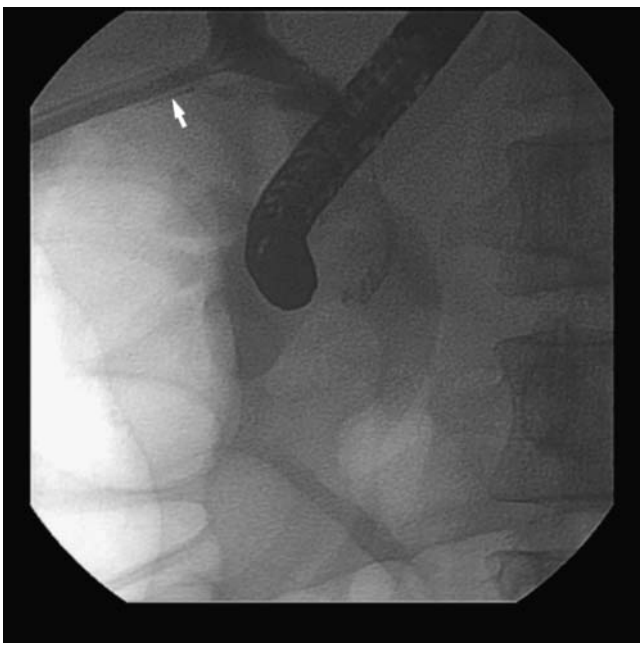


Figure 2 Contrast medium is injected in the cystic duct/common bile duct opening to outline the common bile duct and area of tumor involvement.

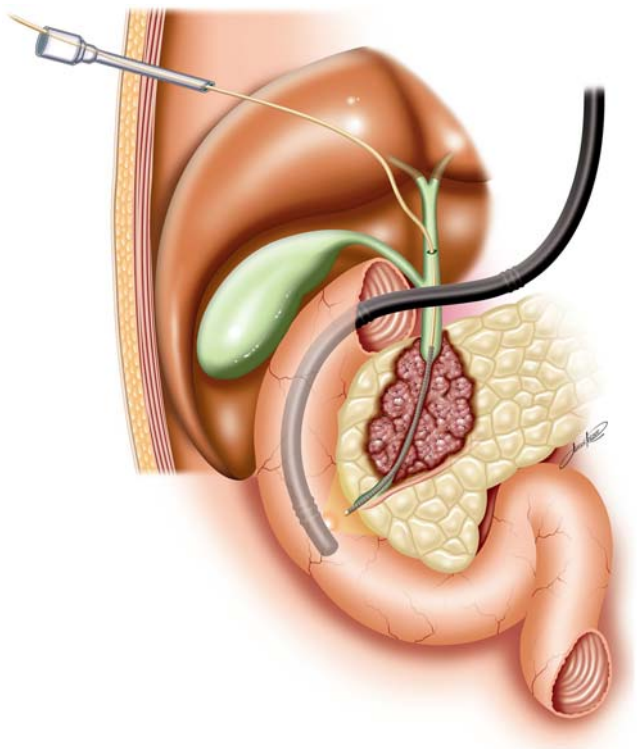


Figure 3 A schematic of opening in common bile duct to enable passage of a guidewire.

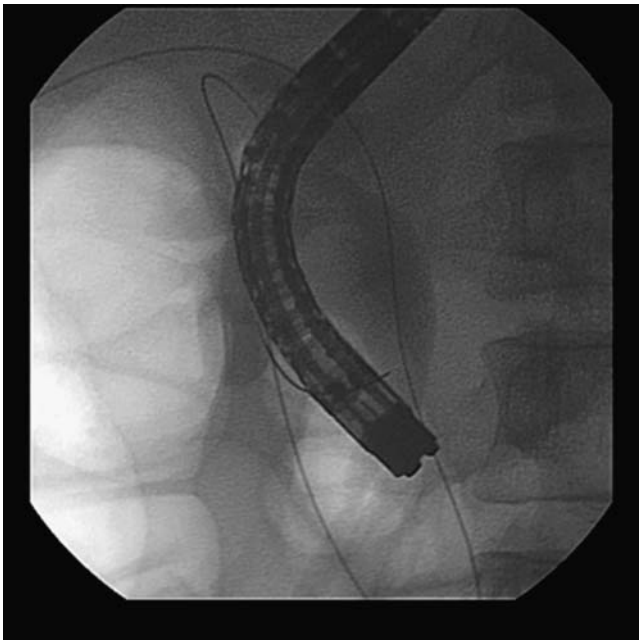


Figure 4 The guidewire is passed through the cystic duct/common bile duct opening into the ampulla antegrade. Fluoroscopic and endoscopic confirmation of course of wire.

Statistical Analysis

Statistical analysis of outcomes was performed using chi-square test or Fisher's exact test. Wilcoxon Mann–Whiney test was utilized for comparison of means between two continuous variables. A single-tailed *p* value of greater than 0.05 was considered significant.

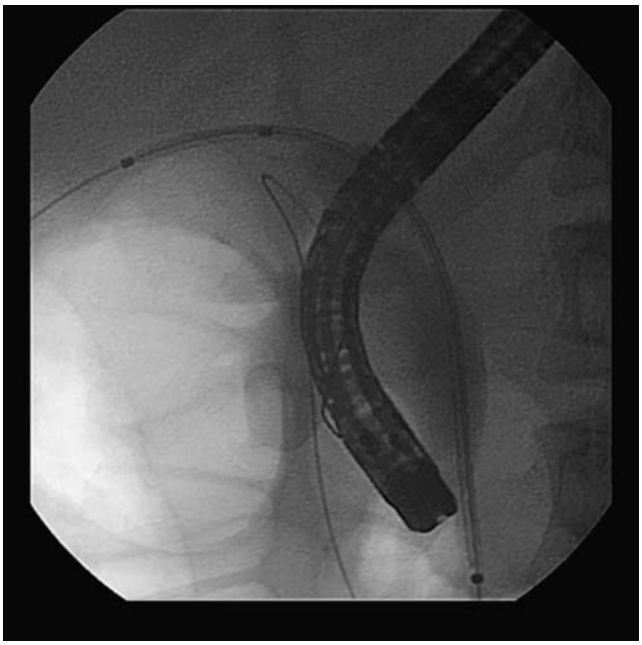


Figure 5 Stent device is passed over wire and its position is confirmed endoscopically.

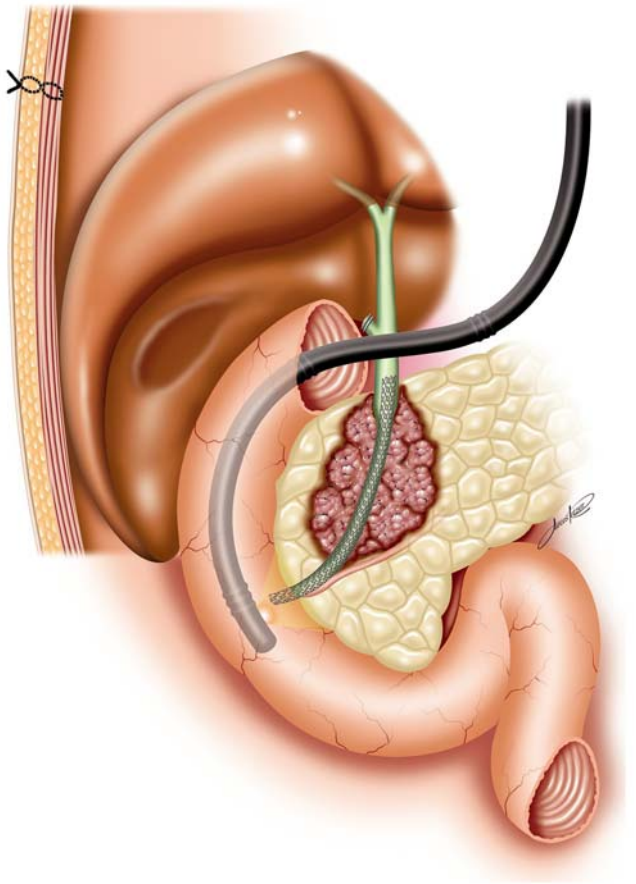


Figure 6 Schematic of stent post deployment in the area of tumor involvement.

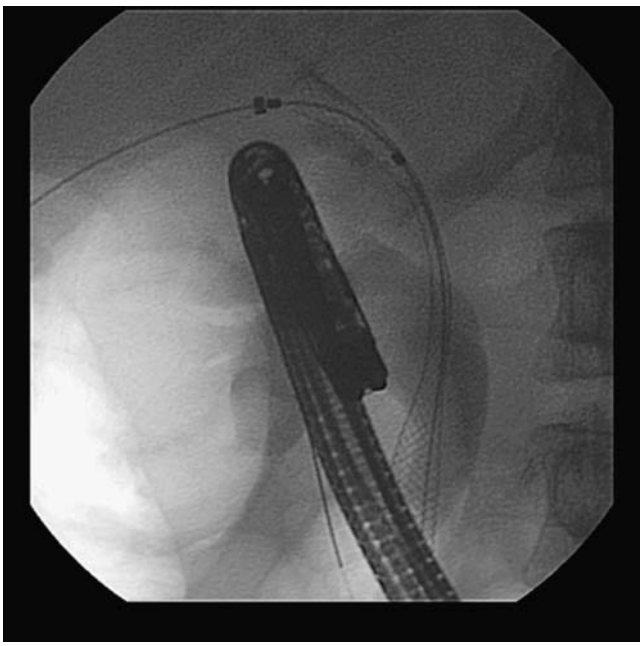


Figure 7 Fluoroscopic appearance of successfully deployed stent.

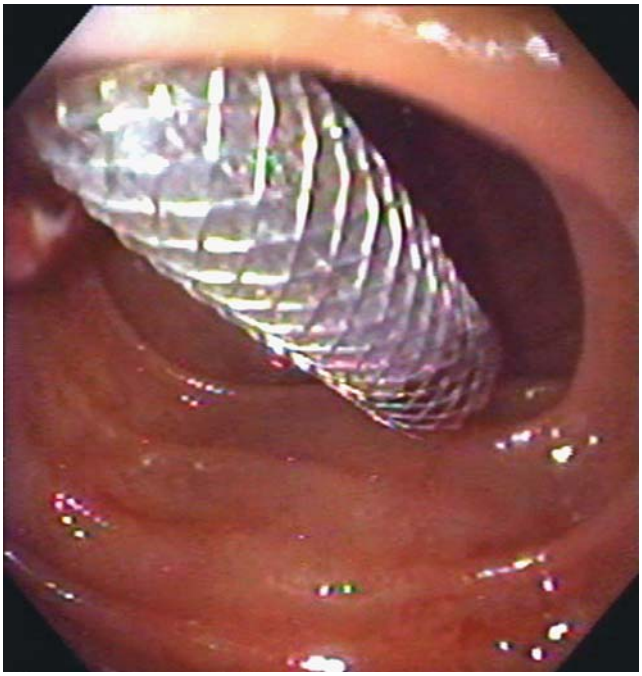


Figure 8 Position of stent is confirmed endoscopically.

Results (Table 1)

There were eight male and 15 female patients. The final histological diagnosis was as follows: pancreatic adenocarcinoma in 18 patients, ampullary adenocarcinoma in two patients, cholangiocarcinoma in one patient, hepatic hilar lymph nodes metastasis from lung cancer causing extrinsic obstruction in one patient, and neuroendocrine tumor in one patient. After evaluation of the pancreatic mass by CT scan and EUS, patients underwent exploratory laparotomy. Median time for laparoscopic exploration and SEMS deployment was 165 min (range 105–230) and 20 min (range 10–50), respectively. Eighteen stents were deployed transcystically and four via choledochotomy. The stent could not be deployed in one patient via a choledochotomy as we were unable to passage the guidewire through the area of the narrowing. Median pre-procedure total bilirubin (TB) and alkaline phosphatase (AP) were 9.4 mg/dl and 470 IU/l, respectively. After stent deployment, median TB and AP at days 7, 30, 60, 90, and 120 were 6.1, 4.1, 3.3, 2.9, and 3.1 mg/dl and 358, 295, 205, 190, and 183 IU/l, respectively. Complications included bleeding, stent obstruction, and wound infection. At 7 days, two cases of bleeding occurred, which required endoscopic hemostasis, at 30 days there was another case of bleeding from the gastrojejunal anastomosis site; all were controlled endoscopically. Stent obstruction was noted in three patients at 60, 90, and 120 days follow up, respectively, and all responded to endoscopic intervention. There were seven deaths, six as a result of progressive cancer and one as a

Table 1 Patient Characteristics

Pt.	Age	Gender	Pre- TB	Pre- AP	Diagnosis	Success	TB at 30 days	AP at 30 days	Complications
1	67	F	11	470	Pancreatic adenocarcinoma	Y	7.1	217	Bleeding within 7 days
2	83	F	14.2	516	Pancreatic adenocarcinoma	N			Death within 30 days
3	71	M	9.4	417	Metastatic lung cancer	Y	4.2	240	None
4	59	F	7.7	527	Pancreatic adenocarcinoma	Y	3.1	215	None
5	81	F	11.4	718	Pancreatic adenocarcinoma	Y	4.9	318	None
6	78	M	6.1	415	Papilla neoplasia	Y	2.7	270	Death within 60 days
7	73	M	14.7	817	Pancreatic adenocarcinoma	Y	5.3	315	None
8	64	F	9.2	547	Pancreatic adenocarcinoma	Y	2.9	195	Death within 90 days
9	86	F	7.1	321	Neuroendocrine tumor	Y	3.2	200	None
10	93	M	17.5	720	Pancreatic adenocarcinoma	Y	5.4	300	Death within 120 days
11	49	F	9.1	520	Pancreatic adenocarcinoma	Y	5	390	Obstruction within 60 days
12	58	F	10.2	715	Pancreatic adenocarcinoma	Y	4	470	None
13	65	F	10.4	418	Pancreatic adenocarcinoma	Y	2.9	195	Death within 60 days
14	77	F	11.7	405	Papilla neoplasia	Y	4.1	390	Bleeding within 7 days
15	70	M	11	470	Pancreatic adenocarcinoma	Y	4.2	400	Obstruction within 120 days
16	61	F	8.1	495	Pancreatic adenocarcinoma	Y	2.9	315	None
17	81	F	5.4	291	Pancreatic adenocarcinoma	Y	2.6	150	Death within 90 days
18	84	M	8.1	417	Cholangiocarcinoma	Y	3.5	290	None
19	75	M	13.5	610	Pancreatic adenocarcinoma	Y	5.1	400	Death within 120 days
20	72	F	8.2	418	Pancreatic adenocarcinoma	Y	4	250	Obstruction within 90 days
21	84	M	12	470	Pancreatic adenocarcinoma	Y	4.3	300	None
22	87	F	5.9	319	Pancreatic adenocarcinoma	Y	2.9	310	Bleeding within 30 days
23	56	F	7.85	515	Cholangiocarcinoma	Y	5.12	290	None

TB=Total bilirubin, AP=Alkaline phosphatase

result of surgical complication but unrelated to SEMS deployment. There were no complications or adverse events related to deployment of SEMS. The median size of lesions on CT was 3.0×3.5 cm (2.0–2.5 cm×4.5–5 cm). Placement of stent failed in one patient as we were unable to negotiate the guidewire through the area of CBD involvement into the duodenum.

Discussion

Twenty two out of twenty three stents were successfully deployed laparoscopically without any immediate complications. Stents were effective at restoring biliary drainage as assessed by total bilirubin and alkaline phopshatase. Stent deployment lengthened the laparoscopic procedure by 10–50 min (median 20 min). Stent deployment is straightforward and the learning curve is not steep. It may be expected that with experience the deployment time may further decline.

Lange, et al.[8] first reported laparoscopic CBD stenting for retained CBD stone to avert follow-up endoscopic intervention. Up to 10% of patients undergoing laparoscopic surgery for gallstone disease may have retained stones or impaired biliary drainage at the end of operation. Martin, et al.[9] successfully deployed stents at laparoscopy in these patients via the transcystic approach. Fanelli, et al.[10] reported successful laparoscopic deployment of a plastic stent in 16 patients with CBD stone and concluded that the technique reduced operative morbidity, complications of T-tubes, and enhanced postoperative recovery. In another study by Fanneli, et al., 48 patients with CBD stones at intraoperative cholangiogram underwent laparocopic deployment of stents. The method was technically less challenging than surgical alternatives, averted conversion to open surgery, and was safe and effective. Furthermore, placement of stent during laparoscopy averted urgent endoscopic intervention and facilitated selective cannulation at ERCP, thus eliminating the need for repeated attempts at ERCP, referral to specialty centers, use of transhepatic techniques, or repeat surgery for retained bile stones.[11] Endoscopy was not performed to confirm the transpapillary positioning of the stent in these studies.

Complications included bleeding, wound infection, and stent occlusion (Table 1). Complication rates associated with laparoscopic stent deployment was within that expected with endoscopic deployment of stents. Complication rates with SEMS deployment for malignant bile duct obstruction are mainly occlusion, migration, and bleeding. Three patients developed bleeding and the stent was obstructed as a result of tumor growth in three patients. Earlier studies have reported early occlusion rates of 7–42% and late occlusion rates of 12–38% with a mean patency of 6–9 months. Bleeding complications were successfully managed by endoscopic hemostasis. Stent obstruction was treated endoscopically by passing a plastic stent and/or Argon Plasma Coagulation. Twenty-day death rates in our study were 30%. Deaths were not related to the deployment of stent and related to progression of cancer in six patients and surgical complication in one patient. These rates are similar to those reported in earlier studies. Reported 30-day mortality after metal stent deployment in three studies have been 14 of 49 patients, five of 86, and 13 of 31 patients, respectively.[12–14]

In conclusion, we successfully demonstrate that deployment of metallic stents during laparoscopy is feasible, safe, and a reasonable alternative for palliative stenting in patients with unresectable malignant bile duct obstruction.

References

1. DiMagno EP, Reber HA, Tempero MA. Epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. Gastroenterology 1999;117:1463–1484.
2. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics 2003. Cancer J Clin 2003;53:5–26.
3. DiMagno EP, Reber HA, Tempero MA. Epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. Gastroenterology 1999;117:1463–1484.
4. Sarr MG, Cameron JL. Surgical management of unresectable carcinoma of pancreas. Surgery 1991;161:120–125.
5. Watanapa P, Williamson RC. Surgical palliation for pancreatic cancer: developments during past two decades. Br J Surg. 1992;79:8–20.
6. Ballinger AB, McHugh M, Catnach SM, et al. Symptom relief and quality of life after stenting for malignant bile duct obstruction. Gut 1994;35:467–470.
7. Burke DR, Lewis CA, Cardella JF, Citron SJ, Drooz AT, Haskal ZJ, Husted JW, McCowan TC, Van Moore A, Oglevie SB, Sacks D, Spies JB, Towbin RB, Bakal CW. Quality improvement guidelines for percutaneous transhepatic cholangiography and biliary drainage. J Vasc Interv Radiol 2003;Sep;14(9 Pt 2):S243–246.
8. Lange V, Rau HG, Schardey HM, Meyer G. Laparoscopic stenting for protection of common bile duct sutures. Surg Laparosc Endosc 1993;Dec;3(6):466–469.
9. Martin CJ, Cox MR, Vaccaro J. Laparoscopic trancystic bile duct stenting in the management of common bile duct stones. ANZ J Surg 2002;72(4):252–253.
10. Fanelli RD, Gersin KS. Laparoscopic endobiliary stenting: a simplified approach to the management of occult common bile duct stones. J Gastrointest Surg 2001;Jan–Feb;5(1):74–80.
11. Fanelli RD, Gersin KS, Mainella MT. Laparoscopic endobiliary stenting significantly improves success of postoperative endoscopic retrograde cholangiopancreatography in low-volume centers. Surg Endosc 2002 Mar;16(3):487–491.
12. Davids PH, Groen AK, Rauws EA, et al. Randomized trial of self expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet 1992;340:1488–1492.
13. Carr-Locke DL, Ball TJ, Connors PJ, et al. Multi-center randomized controlled trial of Wallstent biliary endoprosthesis versus plastic stents. Gastrointest Endosc 1993;39:310–316.
14. Knyrim K, Wagner HJ, Pausch J, et al. A prospective randomized controlled trial of metal stents for malignant obstruction malignant obstruction of the common bile duct. Endoscopy 1993;25: 207–212.

J Gastrointest Surg (2007) 11:1692–1698
DOI 10.1007/s11605-007-0298-5

Clinical Factors Contributing to Rapid Reoperation for Crohn's Disease Patients Undergoing Resection and/or Strictureplasty

David G. Binion · Kenneth R. Theriot · Sushrut Shidham · Sarah Lundeen · Ossama Hatoum · Hyun J. Lim · Mary F. Otterson

Published online: 17 October 2007

Abstract Although surgically induced remission of Crohn's disease following segmental resection/strictureplasty is effective and durable, a subpopulation of patients will require rapid reoperation. We reviewed our inflammatory bowel disease center's database to identify patients who underwent multiple laparotomies. A retrospective analysis of consecutive Crohn's disease patients (1998–2004) was performed, and patients requiring repeat laparotomy were identified. Rapid reoperation was defined as repeat intestinal surgery within 2 years. Demographic data and medical treatment were recorded. Clinical factors contributing to rapid reoperation were defined as (1) symptomatic adhesion, (2) residual strictures/technical error, (3) lack of effective medical therapy, and (4) severe disease despite medical treatment. Of 432 patients, 65 required two or more abdominal explorations, with 32 patients requiring rapid reoperation (50 surgeries). Residual strictures and technical error accounted for 20% of procedures; ineffective medical therapy was identified in 64%, whereas severe disease despite medical therapy was a contributing factor in 14%. Adhesions were found in a single patient. Kaplan–Meier analysis confirmed that rapid reoperation patients had significant and consistently shorter intervals between surgical procedures (i.e., interval between procedures 1 and 2 and 2 and 3). Residual strictures manifest during postop year 1, whereas recurrence of severe disease was the dominant contributing factor during year 2. Our data suggest that operative strategies emphasizing occult stricture detection and adequate medical therapy in Crohn's disease patients may improve outcome and decrease the need for rapid re-exploration.

Keywords Crohn's disease · Surgery · Strictureplasty · Azathioprine · 6-Mercaptopurine · Methotrexate · Infliximab · Adhesions · Complications

Introduction

Despite advances in medical treatment, the majority of Crohn's disease patients will require intestinal surgery during their lifetime.[1–5] Although not curative, surgery is necessary to correct complications of intestinal inflammation, including symptomatic luminal stenosis, fistula, abscess, perforation, or manage fulminant disease uncontrollable with medical treatment. For obstructing intestinal Crohn's disease, surgical approaches typically require either resection of the affected bowel with primary anastomosis or strictureplasty to reestablish patency of the intestinal lumen. Crohn's disease patients requiring segmental resection with

D. G. Binion · K. R. Theriot · O. Hatoum
Division of Gastroenterology and Hepatology,
Department of Medicine, Digestive Disease Center,
Froedtert Hospital, Milwaukee VA Medical Center,
Medical College of Wisconsin,
Milwaukee, WI, USA

S. Shidham
Department of Pathology, Digestive Disease Center,
Froedtert Hospital, Milwaukee VA Medical Center,
Medical College of Wisconsin,
Milwaukee, WI, USA

S. Lundeen · M. F. Otterson (✉)
Department of Surgery, Digestive Disease Center,
Froedtert Hospital, Milwaukee VA Medical Center,
Medical College of Wisconsin, 9200 West Wisconsin Ave,
Milwaukee, WI 53226, USA
e-mail: otterson@mcw.edu

H. J. Lim
Division of Biostatistics, Digestive Disease Center,
Froedtert Hospital, Milwaukee VA Medical Center,
Medical College of Wisconsin,
Milwaukee, WI, USA

reanastomosis and/or strictureplasty will invariably have recurrence of disease, with the remission and symptom-free interval varying between patients.[6,7] After their first operation, 33 to 82% of Crohn's disease patients will require further surgical intervention, which may occur at early, as well as late, time periods.[8–11]

In the setting of intestinal segmental resection and/or strictureplasty, the majority of Crohn's disease patients will experience a prolonged time period between surgeries. One third of Crohn's disease patients will require reoperation by 10 years.[12,13] However, a subgroup of Crohn's disease patients demonstrates a more problematic clinical course, requiring a rapid return to the operating room, at an interval of less than 2 years. Patients who demonstrate a pattern of rapid reoperation are arguably one of the most severe phenotypes, as the repeat resections become technically more challenging and place the individual at risk for gut failure. The percentages of Crohn's disease patients who face rapid reoperation, as well as clinical factors that contribute to a rapid return to surgery, are presently not defined.

The underlying reasons contributing to rapid reoperation in Crohn's disease are heterogeneous and may include symptomatic intra-abdominal adhesions, retained strictures not addressed at the preceding procedure, technical errors, intra-abdominal septic complications (i.e., abscess, anastomotic leak, enterocutaneous fistula) occurring rapidly after an initial abdominal procedure, and rapid recurrence of severe intestinal inflammation leading to complications and refractory disease. We hypothesized that Crohn's disease patients who undergo rapid reoperation (i.e., repeat intestinal surgery within 2 years of an operation) represent a distinct, high-risk subgroup of patients with a unique natural history. Furthermore, we sought to characterize the clinical factors that correlated with rapid reoperation in an attempt to devise improved surgical and medical algorithms for care. In this paper, we define the subgroup of Crohn's disease patients who have required rapid reoperation, as well as clinical patterns that are linked to this poor outcome. We demonstrate that technical errors, primarily linked to retained strictures not addressed at the preceding operation and insufficient medical therapy required for the maintenance of remission in Crohn's disease, are important contributing factors. Our findings suggest that surgical approaches to address occult small intestinal strictures, as well as optimizing immunomodulator therapy for maintenance of remission, may provide strategies for improved clinical outcome in this high-risk subgroup of Crohn's patients.

Methods

A review of consecutive Crohn's disease patients followed at a tertiary referral inflammatory bowel disease center between 1998 and 2004 was performed. Patients undergoing multiple abdominal procedures involving resection with primary intestinal anastamosis and/or strictureplasty were eligible for analysis. Operations performed at outside institutions and at our facility were analyzed. Crohn's disease patients undergoing colectomy in the absence of small intestinal disease were not included in our analysis as we wished to focus our review on small intestinal disease. Individuals requiring procedures limited to the perineum were excluded from this study.

We performed a retrospective review of the peri-operative clinical course and surgical outcomes. Demographic and medical treatment for the Crohn's disease was recorded. Clinical factors contributing to rapid reoperation were defined as (1) symptomatic adhesions not requiring intestinal resection, (2) technical error (re-exploration for hemorrhage or sepsis within 2 weeks and/or retained strictures and stenotic anastamoses), (3) inadequate immunomodulator therapy, or (4) severe disease in the presence of what was judged to be adequate immunomodulator therapy. Immunmodulator therapy included azathioprine or 6 mercaptopurine (6MP), methotrexate and/or infliximab, agents with demonstrated efficacy to maintain remission in moderate to severe Crohn's disease.[14–16] Crohn's disease patients on either azathioprine or 6MP therapy with insufficient 6MP metabolites (rapid metabolizers) were included as inadequate therapy. For this study, red blood cell 6-thioguanine levels of <150 pmol/8×10^8 cells were arbitrarily defined as insufficient or inadequate Crohn's disease therapy.[17]

Adequate medical therapy was not achieved due to a variety of reasons, which include drug intolerance, drug allergy, failure of compliance, rapid metabolism of purine analogs (6MP, azathioprine), and failure of the physician to prescribe immunomodulator therapy. We defined Crohn's disease with nutritional deterioration, quality of life deterioration as measured by the Short Inflammatory Bowel Disease Questionnaire,[18] or severe disease requiring surgery as moderate to severe disease. All patients treated at our center with moderate to severe disease are candidates for immunomodulator therapy, but this may not have been achieved.

For the purpose of this retrospective analysis, only one clinical factor could be designated for each rapid reoperation. The clinical factors listed above were arbitrarily ranked by priority in the following order: (1) symptomatic adhesions, (2) technical error, (3) inadequate immunomodulator therapy, and (4) severe disease in the presence of immunomodulator therapy. Therefore, a patient with adhesions listed as the postoperative diagnosis could not also be included in the category of inadequate immunomodulator therapy. A review of the operative record and discharge summary was performed initially by a neutral research member (K.R.T.) who had not participated in the care of

Table 1 Demographics Data

	Total Patients (n=65)	Surgery w/in 2 Years (n=32)	Surgeries >2 Years (n=33)	
Gender				
M	35 (54%)	18 (56%)	17 (52%)	n.s.
F	30 (46%)	14 (44%)	16 (48%)	
Smokers	23 (35%)	11 (34%)	12 (36%)	n.s.
Location of disease				
SB	36 (55%)	20 (63%)	16 (48%)	
SB/LB	20 (31%)	8 (25%)	12 (36%)	
LB	8 (12%)	3 (9%)	5 (15%)	
Upper GI	1 (2%)	1 (3%)	0	n.s.
Age of onset				
<40 years	63 (97%)	30 (94%)	33 (100%)	
>40 years	2 (3%)	2 (6%)	0	n.s.
Disease behavior				
Inflammation	0	0	0	
Stricture	58 (89%)	28 (87%)	30 (91%)	
Fistula	7 (11%)	4 (13%)	3 (9%)	n.s.

patients during the operative time period. Once the clinical factors for the rapid reoperation had been designated, experienced medical personnel (D.G.B.) and surgical staff (M.F.O.) verified the ranking.

Analysis was carried out with SAS statistical software (The SAS Institute, Cary, NC, USA) and LogXact software (Cytel Software, Cambridge, MA, USA). The Medical College of Wisconsin's human research review committee approved this study.

Results

During the study period, 432 Crohn's disease patients were identified in the database. Sixty five patients had required more than a single surgical intervention. A total of 200 abdominal surgeries had been performed in these 65 patients. Thirty two of these patients required rapid reoperation within 2 years (7% of our Crohn's disease population). A total of 50 abdominal procedures had been performed in the rapid reoperation patients. In the cohort of patients requiring rapid reoperation, the average number of surgical procedures was 3.0+1.2 (mean+SD) and the operative interval was 2.9+4.5 years (mean+SD). The 33 Crohn's disease patients in our center requiring repeat surgery who never required rapid reoperation had a mean of 2.9+1.3 surgical procedures (not significant) with an average interval of 7.6+4.9 years (p<0.05).

Analysis of demographic data revealed no significant difference between patients who had undergone rapid reoperation when compared to patients with longer time intervals between the repeat surgical procedures (Table 1).

Kaplan–Meier analysis followed by Wilcoxson testing confirmed that the intervals between procedures 1 and 2 and between procedures 2 and 3 were significantly shorter in patients who had ever been categorized as rapid reoperative patients (p<0.001, Figs. 1 and 2). The interval between procedures 3 and 4 did not reach statistical significance between these two groups due to the limited number of patients requiring four surgical procedures. We repeated the Kaplan–Meier analysis after excluding procedures that had been judged to be technical error and adhesions. Again, Kaplan–Meier analysis followed by Wilcoxson testing confirmed that the intervals between procedures 1 and 2 and between procedures 2 and 3 were significantly shorter in patients who had ever been categorized as rapid reoperative patients (p<0.001, Figs. 3 and 4).

Next, we evaluated the clinical factors that contributed to rapid reoperation. There were 27 rapid reoperation procedures in the first postoperative year. The contributing clinical factors were as follows: symptomatic adhesions (1 procedure, 4%), technical error (8 procedures, 7 missed strictures, 1 evacuation of hematoma, 30%), inadequate immunomodulator therapy (13 procedures, 2 on azathioprine with inadequate drug levels, 11 who were on no drug, 1 of the 11 had an intra-abdominal abscess, 47%), and severe disease despite immunomodulator therapy (5 procedures, 19%). Between years 1 and 2, there were 23 rapid reoperation procedures. In this group, technical error contributed to 13% (3 procedures), whereas severe disease despite immunomodulator therapy was responsible for two procedures (9%); inadequate immunomodulator therapy was linked to the majority of these rapid reoperations (18 procedures, 78%). Symptomatic adhesions were not seen during the second postoperative year in our cohort of rapid reoperation patients. In summary, during the first 2 years, adhesions were responsible for 2%, technical error for 22%, severe disease with inadequate therapy for 62%, and severe disease despite adequate therapy for 14% of rapid reoperations.

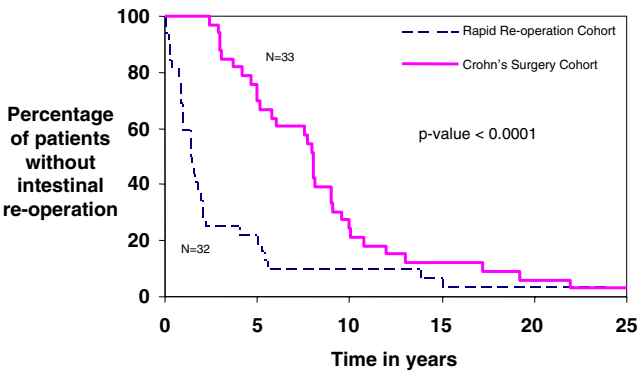


Figure 1 Intervals between surgery 1 and 2 in the rapid reoperation Crohn's surgery cohorts.

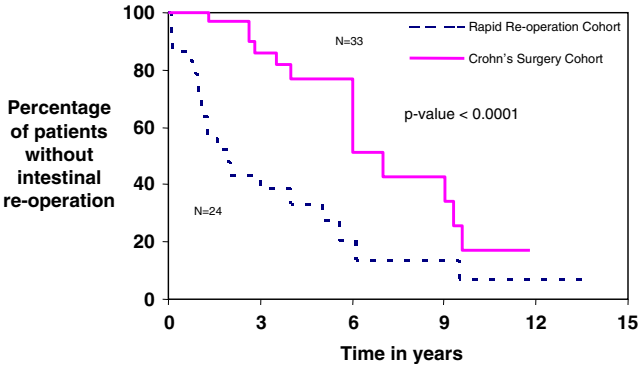


Figure 2 Intervals between surgery 2 and 3 in the rapid reoperation Crohn's surgery cohorts.

Interestingly, nine patients who were categorized in the rapid reoperation group were initiated on immunomodulator therapy for the first time (three on azathioprine, one on leflunomide,[19] and five on infliximab maintenance therapy). Since initiating immunomodulator therapy, eight out of nine patients have not required additional surgical intervention, with a mean duration of elapsed time of 4.7 years and a range of 1.4 to 9.4 years since prior surgery. Fifty two of the 65 Crohn's disease patients who required repeat abdominal operation (80%) are currently maintained on immunomodulator therapy. The remaining patients are not on immunomodulator therapy due to multiple drug intolerances or refusal to comply with therapy.

Three of the Crohn's disease patients requiring repeat abdominal operations included in this study have subsequently died, giving this population a mortality rate of 4.6%. Each of these deceased patients had at least five surgeries. One patient died at age 39 following repeat hip replacement surgery for avascular necrosis. A second patient died at the age of 71 years with a cardiac event attributed to electrolyte disturbances, and the third patient died at the age of 53 years of complications of line infection on chronic total parenteral nutrition.

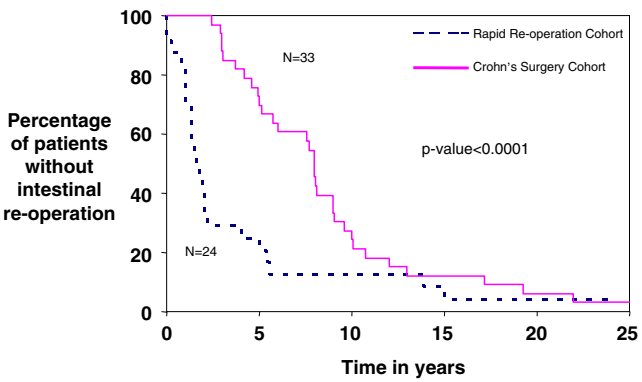


Figure 3 Intervals between surgery 1 and 2 with elimination of surgical procedures judged to be due to technical error and adhesions. These data demonstrate problems associated with lack of effective/adequate medical maintenance therapy in the rapid reoperative cohort.

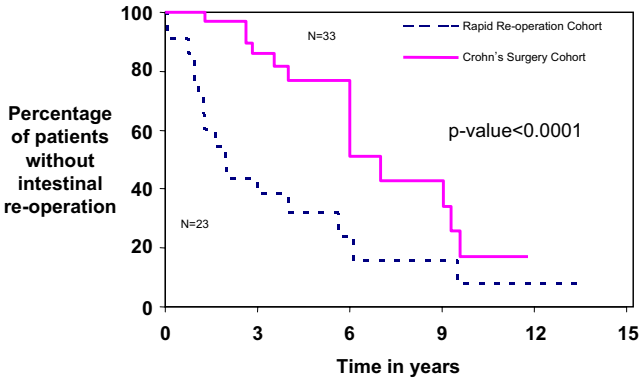


Figure 4 Interval between surgery 2 and 3 with elimination of surgical procedures judged to be due to technical error and adhesions.

Discussion

Although surgery is the most rapid treatment modality to induce remission in Crohn's disease, patients who undergo segmental resection and reanastomosis and/or strictureplasty will experience relapse at high rates. Surgically induced remission may last numerous years in fortunate individuals, whereas other patients with Crohn's disease will experience symptomatic clinical relapse within months of laparotomy. We report that a subgroup of patients who require a rapid return to surgery within 2 years of the prior procedure constitute a distinct high-risk subgroup of Crohn's disease patients who are significantly more likely to face additional rapid reoperations. In addition, we highlight clinical factors related to surgical technique and adjunctive medical therapy, which were linked to rapid reoperation. These findings suggest that improved operative strategies to address occult intestinal strictures and maximizing immunomodulator maintenance of remission therapy appropriate for moderate to severe Crohn's disease may improve clinical outcomes in this high-risk subgroup of patients.

Improved medical management strategies for Crohn's disease have established a central role for immunomodulators such as azathioprine, 6MP, and methotrexate in the management of moderate to severe Crohn's disease.[15,20] Biologic therapy with the anti-TNF-α chimeric monoclonal antibody infliximab has also been identified as effective in resolving Crohn's disease inflammation and maintaining remission.[21,22]

Our study suggests that patients whose illness is severe enough to warrant repeat surgery will benefit from the use of immunomodulator agents typically used in moderate to severe Crohn's disease. Furthermore, patients with a rapid return to the operating room represent a more ill subset of patients, and care must be taken to assure compliance, adequate therapeutic drug levels, and ongoing therapy.

Studies have estimated that postoperative complications and morbidity associated with strictureplasty or bowel

resection with anastomosis for Crohn's disease range from 13 to 22%.[23–26] The most serious immediate complications are fistula, abscess, and anastomotic leak, which typically occur within 1 month of the intestinal procedure. We recently demonstrated a lack of association between immunomodulator agents and infectious complications in the setting of Crohn's disease surgery.[27] This has been confirmed in other centers.[28] These data suggest that Crohn's disease patients requiring abdominal surgery may benefit during the initial postoperative month with immunomodulator therapy to provide medical control of the disease process. These findings also suggest that the initiation of medical treatment in patients who are facing the prospect of surgery due to symptomatic complications (i.e., intermittent partial small bowel obstruction) may benefit from the initiation of immunomodulator treatment in the short term, as well as with the potential benefit of preventing postoperative recurrence of disease.[29]

In our analysis, we also defined a subgroup of patients where technical issues during the initial procedure contribute to a rapid return to surgery. We broadly categorized stenotic anastamoses and retained strictures as technical error. Much has been written in the literature about the superiority of either stapled or hand sewn anastamoses; however, our technical errors included both types of anastamoses and no meaningful conclusion can be made regarding that argument from these data.[30–32] There were no prior laparoscopic surgical procedures for Crohn's disease in the cohort that we evaluated. However, it must be noted that the frequency of laparoscopic resections for Crohn's disease is very small in our region.

Small intestinal Crohn's disease may manifest with "skip" areas scattered in the intestine, as well as diffuse disease throughout the small bowel. In patients with these more extensive patterns of disease, the capability to accurately determine a "dominant" stricture(s) that requires surgical treatment is difficult. The ability to adequately gauge the level of severity of strictures may be made more challenging by laparoscopic approaches. Surgeons have historically relied on small bowel barium radiographs to provide an accurate map of the pathologic intestinal anatomy, which will require resection or strictureplasty. Previous studies have suggested that radiographic imaging may underestimate up to 1/3 of strictures in 1/3 of the patients.[33] This high rate of occult strictures may play a contributing role in the Crohn's patients who required rapid reoperation in our study, particularly those who required repeat surgery within 1 year. The adoption of intraoperative plans to diagnose and correct all luminal stenoses with resection/strictureplasty will potentially address this mechanism linked to rapid reoperation.

We realize that our study was limited by its retrospective design and was not the ideal method for demonstrating the direct therapeutic effect of regimens. We depended upon documentation of the previous surgeon and analyzed results with incomplete knowledge of the prior pathology. In spite of this, retrospective analysis can demonstrate significant correlations, which may generate hypotheses that can be further defined with prospective trials.

Our analysis of Crohn's disease patients requiring rapid reoperation has attempted to characterize a high-risk subgroup of patients who have a relatively defined starting point for an analysis of their natural history (i.e., postoperative clinical course). Unfortunately, clinical trials in patients with Crohn's disease have been severely hampered by the heterogeneity of the disease process, where interpatient variability regarding anatomic location of disease, duration of disease, unique histories of drug treatment and medication intolerance, and variable strategies employed with surgical intervention are typically not taken into consideration. The result of this comingling of patients with different levels of disease severity, at various stages in their natural history of illness, is typically a nonsignificant clinical result. We believe that the identification of this rapid reoperation Crohn's disease cohort is an important contribution of this study.

By limiting the population of postoperative patients to those who have undergone segmental resection and/or strictureplasty, we were able to both identify a unique natural history, which is linked again to heterogeneous clinical contributing factors (i.e., occult strictures, lack of early immunomodulator therapy, and lack of effective maintenance immunomodulator therapy over the initial two postoperative years). Using our criteria for patients with a history of rapid reoperation, we identified 7% of the total Crohn's disease cohort followed in our center. Although this is not the majority of Crohn's disease, this approximation appears to be consistent with the subgroup that has extensive small intestinal disease and will be at risk for intestinal failure due to repeated surgery. Our study suggests that this cohort of patients can be readily identified based on their clinical history (repeated small intestinal surgery at rapid intervals) and should have continuous medical treatment with more potent immunomodulator agents maintained on a long-term basis. The argument that medical treatment may be successfully weaned off in postoperative Crohn's disease patients does not apply to the rapid reoperation subgroup, where surgical risk (i.e., intra-abdominal septic complications), as well as an aggressive form of disease that rapidly recurs with clinically symptomatic illness, is highly likely. Our study suggests that a surgical approach which strives to diagnose and repair intestinal strictures in combination with a medical approach which emphasizes maintenance immunomodulator therapy will lead to improved outcomes in the management of this high-risk Crohn's disease population.

Our case series suggests that Crohn's disease patients who require rapid reoperation represent a subset who require greater health care resources. Early identification of these patients as being at risk may allow improved strategies for medical interventions. Maintaining remission with immunomodulator therapy may represent a key variable that can be optimized to improve surgical outcome in these Crohn's disease patients.

References

1. Mekhjian HS, Switz DM, Watts HD, Deren JJ, Katon RM, Beman FM. National cooperative Crohn's disease study: Factors determining recurrence of Crohn's disease after surgery. Gastroenterology 1979;77:907–913.
2. Whelan G, Farmer RG, Fazio VW, Goormastic M. Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. Gastroenterology 1985;88:1826–1833.
3. Sachar DB, Subramani K, Mauer K, Rivera-MacMurray S, Turtel P, Bodian C, Greenstein AJ. Patterns of postoperative recurrence in fistulizing and stenotic Crohn's disease: A retrospective cohort study of 71 patients. J Clin Gastroenterol 1996;22:114–116.
4. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg 2000; 231:38–45.
5. DeDombal FT, Burton I, Goligher JC. The early and late results of surgical treatment for Crohn's disease. Br J Surg 1971;58:805–816.
6. D'Haens G, Rutgeerts P. Postoperative recurrence of Crohn's disease: pathophysiology and prevention. Inflamm Bowel Dis 1999;5:295–303.
7. D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology 1998;114:262–267.
8. Krupnick AS, Morris JB. The long-term results of resection and multiple resections in Crohn's disease. Semin Gastrointest Dis 2000;11:41–51.
9. Heimann TM, Greenstein AJ, Lewis B, Kaufman D, Heimann DM, Aufses AH Jr. Comparison of primary and reoperative surgery in patients with Crohns disease. Ann Surg 1998;227:492–495.
10. Fazio VW, Marchetti F, Church M, Goldblum JR, Lavery C, Hull TL, Milsom JW, Strong SA, Oakley JR, Secic M. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. Ann Surg 1996;224:563–571; discussion 571–573.
11. Lautenbach E, Berlin JA, Lichtenstein GR. Risk factors for early postoperative recurrence of Crohn's disease. Gastroenterology 1998;115:259–267.
12. Michelassi F, Balestracci T, Chappell R, Block GE. Primary and recurrent Crohn's disease. Experience with 1379 patients. Ann Surg 1991;214:230–238; discussion 238–240.
13. Lock MR, Farmer RG, Fazio VW, Jagelman DG, Lavery IC, Weakley FL. Recurrence and reoperation for Crohn's disease: the role of disease location in prognosis. N Engl J Med 1981;304:1586–1588.
14. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut 1995;37:674–678.
15. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med 2000;342:1627–1632.
16. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–1549.
17. Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Theoret Y, Seidman EG. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology 2000;118:705–713.
18. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol 1996;91:1571–1578.
19. Prajapati DN, Knox JF, Emmons J, Saeian K, Csuka ME, Binion DG. Leflunomide treatment of Crohn's disease patients intolerant to standard immunomodulator therapy. J Clin Gastroenterol 2003;37:125–128.
20. Stein RB, Lichtenstein GR. Medical therapy for Crohn's disease: the state of the art. Surg Clin North Am 2001;81:71–101, viii.
21. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–1035.
22. Rutgeerts PJ, Targan SR. Introduction: anti-TNF strategies in the treatment of Crohn's disease. Aliment Pharmacol Ther 1999;13 (Suppl 4):1.
23. Yamamoto T, Keighley MR. Factors affecting the incidence of postoperative septic complications and recurrence after strictureplasty for jejunoileal Crohn's disease. Am J Surg 1999;178:240–245.
24. Dietz DW, Laureti S, Strong SA, Hull TL, Church J, Remzi FH, Lavery IC, Fazio VW. Safety and longterm efficacy of strictureplasty in 314 patients with obstructing small bowel Crohn's disease. J Am Coll Surg 2001;192:330–337; discussion 337–338.
25. Broering DC, Eisenberger CF, Koch A, Bloechle C, Knoefel WT, Durig M, Raedler A, Izbicki JR. Strictureplasty for large bowel stenosis in Crohn's disease: quality of life after surgical therapy. Int J Colorectal Dis 2001;16:81–87.
26. Tichansky D, Cagir B, Yoo E, Marcus SM, Fry RD. Strictureplasty for Crohn's disease: meta-analysis. Dis Colon Rectum 2000;43:911–919.
27. Tay GS, Binion DG, Eastwood D, Otterson MF. Multivariate analysis suggests improved perioperative outcome in Crohn's disease patients receiving immunomodulator therapy after segmental resection and/or strictureplasty. Surgery 2003;134:565–572; discussion 572–573.
28. Colombel JF, Loftus EV Jr., Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, Harmsen WS, Schleck CD, Sandborn WJ. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol 2004;99:878–883.
29. Hanauer SB, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. Gastroenterology 2004;127:723–729.
30. Resegotti A, Astegiano M, Farina EC, Ciccone G, Avagnina G, Giustetto A, Campra D, Fronda GR. Side-to-side stapled

anastomosis strongly reduces anastomotic leak rates in Crohn's disease surgery. Dis Colon Rectum 2005;48:464–468.
31. Scarpa M, Angriman I, Barollo M, Polese L, Ruffolo C, Bertin M, D'Amico DF. Role of stapled and hand-sewn anastomoses in recurrence of Crohn's disease. Hepatogastroenterology 2004;51:1053–1057.
32. Yamamoto T, Bain IM, Mylonakis E, Allan RN, Keighley MR. Stapled functional end-to-end anastomosis versus sutured end-to-end anastomosis after ileocolonic resection in Crohn disease. Scand J Gastroenterol 1999;34:708–713.
33. Otterson MF, Lundeen SJ, Spinelli KS, Sudakoff GS, Telford GL, Hatoum OA, Saeian K, Yun H, Binion DG. Radiographic underestimation of small bowel stricturing Crohn's disease: a comparison with surgical findings. Surgery 2004;136:854–860.

Discussion

694. Rapid Re-Operation for Crohn's Disease. Paper presented by Mary Otterson, M.D., Milwaukee, WI.

E-mail: otterson@mcw.edu

Discussion by Susan Gearhart, M.D., Maryland.
E-mail: sdemess1@jhmi.edu.

Dr. S. Gearhart (Baltimore, MD): I want to thank the authors, first of all, for the opportunity to discuss this paper and for their timely submission. I also want to congratulate you on an interesting and important study examining the clinical risk factors associated with reoperation for Crohn's disease. I have questions on several specific aspects of your study.

First, the aim of your study was to identify clinical factors that are associated with the rapid reoperation for Crohn's disease. Yet the clinical data with regards to the initial surgery type as it directly related to the need for rapid reoperation, for example, strictureplasty or no strictureplasty, laparoscopic, which you touch on in your manuscript, emergent or elective, is missing. Could you please elaborate on that? It also would be important to list factors which may affect healing in Crohn's disease, such as nutritional status of the patient or steroid use. Furthermore, in your mention in the manuscript about patients with colonic disease you decided to exclude them, and I didn't understand why you did, and then you did actually mention them when you described demographic data. Could you just touch on whether or not you were discussing colonic disease?

Second, you defined one of your clinical factors contributing to rapid reoperation for Crohn's disease as inadequate immunomodulator therapy. I agree with you that there is certainly data to support the use of immunomodulator therapy in active Crohn's disease and preventing clinical recurrence of the disease. However, the data is not compelling in the support of the use of immunomodulators in the prevention of surgical recurrence and the need to go back to the operating room for surgery for Crohn's disease. And could you comment on your data with respect to randomized clinical trials and the use of immunomodulator therapy on the prevention of recurrence of Crohn's disease postoperatively?

Finally, in your conclusions you suggest that this study supports the use of immunomodulators in patients who require rapid reoperation for Crohn's disease. This study is retrospective and lacks a control group and therefore this claim may be a bit premature. Do you have plans to look at this in a more prospective fashion?

Thank you.

Dr. Otterson: Thank you very much for your comments. I hope I remember all the questions in the appropriate order.

Regarding strictureplasty versus resection, we have looked at strictureplasty versus resection with recurrence and not seen any issues in the past. I think that the majority of the outside procedures are performed as resections and a very small minority are done as strictureplasties. At our institution most of our procedures are actually a combination of both strictureplasty and resection. So it is going to be difficult for us to give a conclusive result on that.

We do routinely pull a Foley catheter and inflate it to 2 cm through our intestine looking for missed strictures. In a paper that we wrote several years ago, we found that radiology underestimated a third of the strictures in a third of the patients. So if you have single strictures in first-time resections, the data is pretty good for radiology, but after that, if they have multiple resections or if they have had multiple strictures identified, you really need to look for additional strictures.

The nutritional factors, I don't have data on that. We have looked in the past, and we did not see a difference with albumins down to a level of 3. The VAH study suggests that 2.5 is the magic number. We didn't see any difference at a level of 2.5 for complications, postoperative intra-abdominal septic complications, but we did not specifically look at that with this.

Steroid use, most of the patients who came in with partial obstructive issues were on steroids to try to control their obstructive symptoms, but the majority of our patients, 80%, are on immunomodulator therapy before they come to the operating room. The patients who are not on drug therapy are those patients who are multiply drug intolerant, leading to novel concoctions of drugs, or who are noncompliant.

As far as randomized clinical trials, methotrexate, azathioprine, or 6-MP have all been shown in randomized prospective trials to be the only drugs that are capable of inducing prolonged remission with Crohn's disease. The ACCENT II trials with infliximab and REMICADE are also supporting the data that good medical care prior to the surgical procedures are the way to go as far as maintaining disease-free intervals.

J Gastrointest Surg (2007) 11:1699–1703
DOI 10.1007/s11605-007-0258-0

Pancreatojejunal Leakage After Pancreas Head Resection: Anatomic and Surgeon-Related Factors

O. Kollmar · M. R. Moussavian · M. Bolli · S. Richter · M. K. Schilling

Received: 27 May 2007 / Accepted: 19 July 2007 / Published online: 2 September 2007

Abstract
Leakage of pancreatojejunostomies after pancreatic resections remains a challenge even at high volume centers. We here utilized a simple pancreas anatomy classification to study the effect of pancreatic anatomy on the development of pancreatic fistula after pancreas resection and pancreatojejunostomies. Also, the effect of surgical experience on the development of pancreatic fistulas was studied. Three hundred ninety-one patients undergoing pancreatic resections and reconstruction with a pancreatojejunostomy were studied. Closed suction drain was placed behind the anastomosis, and drainage fluid was collected postoperatively. A twofold increase over the serum amylase level was considered a fistula and was classified as described by the International Study Group on Pancreatic Fistula Definition. In 67 patients, the structural quality of the pancreatic parenchyma and the diameter of the pancreatic duct were classified as being <2 mm (2 points), between 2 and 5 mm (1 point), or >5 mm (0 points). The pancreatic parenchyma was assessed as being soft (2 points), intermediate (1 point), or hard (0 points). Pancreatic leakage as a function of surgeons' experience was also studied. Leakage was found in 25.1%, 8.9% being of type A, 10.2% being of type B, and 5.9% of type C. Pancreatic fistulas were only observed in patients with a score of 2 points or more. Age over 70 years, operations >6 h, and extended lymphadenectomy or surgeons experience were not associated with a higher leakage rate. In this study, leakage after pancreatojejunostomy was only associated with pancreatic anatomy, classified with a simple score. That score might improve comparability of studies on pancreatic leakage. Furthermore, drainage of pancreatic anastomosis might safely be omitted in patients with a low risk score for leakage.

Keywords Pancreatic anastomosis · Anatomy · Score

Introduction

Leakage of pancreatic juice out of anastomosis or along parenchymal suture lines occurs in 5 to 30% and remains a challenge even at high volume centers for pancreatic surgery. The problem has been studied in a number of well-designed trials that addressed surgical techniques,[1–3] modified drainage regimens,[4] administered somatostatin and analogues,[4–6] or altered the definition of pancreatic leakage. To address the problem of definition of pancreatic leakage, an International Study Group on Pancreatic Fistula Definition (ISGPF) divided pancreatic fistula in three grades depending on the need of treatment.[7] To further improve the comparability of various techniques and trials, we utilized a simple pancreas anatomy classification that includes pancreatic consistency and the diameter of the pancreatic duct and studied the development of pancreatic fistula after pancreas resection and pancreatojejunostomies as a function of that classification. Furthermore, the experience (cases performed) of individual surgeons on the development of pancreatic fistulas was studied.

O. Kollmar · M. R. Moussavian · M. Bolli · S. Richter · M. K. Schilling (✉)
Department of General, Visceral, Vascular and Pediatric Surgery, University of Saarland, 66421 Homburg/Saar, Germany
e-mail: martin.schilling@uniklinik-saarland.de

Patients and Methods

Between 2002 and 2006, 391 consecutive patients underwent abdominal exploration for pancreatic pathologies

followed by a resection of the pancreas either as partial duodenopancreatectomy (pylorus preserving Whipple or classical Whipple), duodenum preserving pancreatic head resections, or central pancreatic resections. Reconstruction was performed as pancreatojejunostomy in duct to mucosa technique in all patients. Initially, all anastomoses were performed by one surgeon, and all subsequent pancreatic surgeons were trained by that single surgeon. One closed suction drain was placed behind the pancreatojejunal anastomosis and was kept in place for 7 days in patients that did not develop fistulas. In patients developing fistulas, drains were kept until spontaneous closure of the fistula. Drainage fluid was collected on days 3, 5, and 7 and measured for pancreas amylase and lipase. Postoperative pancreatic fistula (POPF), according to ISGPF criteria,[7] was defined as any measurable drainage from an operatively or subsequently percutaneous placed drain with an amylase content greater than three times the upper limit of normal serum amylase level (>300 IU/l). Three grades of POPF severity were classified as described by the ISGPF clinical criteria.[7]

Data from all patients were entered in a database on an ISH-Med SAP (St. Leon, Germany) platform. Data included all biographic and perioperative data as well as postoperative outcome. In addition, patients after June 2003 were treated along in IT-based clinical pathway for the treatment of pancreatic neoplasms or inflammatory alterations of the pancreas, allowing for the retrieval of process management data as well. The total cohort of 391 patients was divided in a group of patients (n=65) operated on by surgeons having performed 0–10 pancreatic resections, a group of patients (n=88) operated by surgeons having performed 11–29 resections, a group of patients (n=108) having been operated by surgeons with an experience of 30–50 resections. Also, results for one surgeon who performed >100 pancreatic resections are included (n=130).

Out of those 391 patients, a consecutive cohort of 67 patients undergoing partial duodenopancreatectomy was classified intraoperatively for the structural quality of the pancreatic parenchyma and the diameter of the pancreatic duct according to Table 1. To keep resection technique, extent of resection, and reconstruction technique constant, only patients undergoing pancreaticoduodenectomy were included. After resection of the pancreatic head, the widest diameter of the duct of the pancreatic remnant was measured and categorized as being <2 mm, between 2 and 5 mm, or >5 mm. The pancreatic parenchyma was assessed by one surgeon (MKS) as being soft, like in an unobstructed native pancreas or hard like in chronic pancreatitis or intermediate.

Table 1 Pancreas Anastomosis Score (PAS; range 0–4 points)

	Score
Pancreas parenchyma	
Soft	2
Intermediate	1
Hard	0
Pancreatic duct	
<2 mm	2
2–5 mm	1
>5 mm	0

Table 2 Biographic Data of 391 Consecutive Patients Undergoing Pancreatic Resection (67 Consecutive Patients were Assessed for Pancreatic Anatomy and Scored According to Table 1)

	Total	PAS subgroup	P
Patients	391	67	
Age (years)	59.7±0.7	62.2±1.4	NS
Age (>70 years)	122 (28.1 %)	12 (17.9 %)	NS
Gender (w/m)	166/225	26/41	NS
ASA score	2.46±0.03	2.29±0.06	0.027
Malignancy	224 (57.3 %)	43 (64.2 %)	NS
Chronic pancreatitis	125 (31.9 %)	17 (25.4 %)	NS
Benign pancreatic tumor	42 (10.7 %)	7 (10.4 %)	NS

Data are given as absolute numbers, mean and standard error of the mean, or as median (range) unless indicated otherwise. Differences between groups were calculated by chi-square test or Fisher's exact test using the SIGMA STAT® software and SAS Analytics (SAS Institute GmbH, D-69043 Heidelberg, GERMANY).

Results

Biographic data of the total cohort of 391 patients as well as the 67 patients assessed for pancreatic anatomy are detailed in Tables 2 and 3. Leakage in the total cohort was found in 25.1%, 8.9% being of type A, 10.2% being of type B, and 5.9% requiring extensive additional management equaling type C (Table 4). Leakage was comparable in patients over 70 years or after operations lasting longer than 6 h when compared to patients under 70 years or to operations lasting shorter than 6 h. Likewise, leakage in the PAS subgroup was no different to the total cohort (Table 4). Consistency of the pancreatic parenchyma in the PAS subgroup was classified as 1.02±0.11, consistent with an intermediate pancreas on average (Table 5). The average diameter of the pancreatic duct was 3.7±0.25 mm, giving an average score of 2.2±0.2. Pancreatic fistulas were only observed in patients with a score of more than 1 (Fig. 1). Patients without a fistula had an average score of 1.97±0.20; patients who developed a fistula had an average score of 2.67±0.21 (p=0.078). Subgroup analysis of the PAS cohort concerning risk factors for POPF is shown in detail in

Table 3 Operative Details for 391 Consecutive Patients Undergoing Pancreatic Resection (67 Consecutive Patients were Assessed for Pancreatic Anatomy and Scored According to Table 1)

	Total	PAS subgroup	*p*
Patients	391	67	
pp Whipple	204 (52.2%)	62 (92.5%)	<0.001
Classic whipple	31 (7.9%)	5 (7.5%)	NS
Other resections[a]	156 (39.9%)		
Extended lymphadenectomy	174 (44.5%)	49 (73.1%)	<0.001
Orthotope reconstruction	187 (47.8%)	60 (89.6%)	<0.001
Arterial/portal venous reconstruction	58 (14.8%)	5 (7.5%)	0.025
OR time (min)	260±5	313±10	<0.001
Blood loss (ml)	613±35	675±53	NS

[a] Duodenum preserving resections, segmental, and central pancreatic resections, cystojejunostomies

Table 6. As demonstrated, the structure of the pancreatic parenchyma directly correlates significantly with the appearance of POPF in these patients undergoing pancreatic head resection. The number and severity of pancreatic fistula as a function of surgeon experience is detailed in Table 7. Neither the overall incidence of fistula nor the severity of pancreatic fistulas correlated with the number of pancreatic resections performed by the individual surgeon.

Discussion

In this study of leakage after pancreatojejunostomy in a series of nearly 400 resections, we found leakage to be strongly associated with pancreatic anatomy. The cohort studied was kept constant for various parameters that have been associated with pancreatojejunal leakage like surgical technique (here, duct to mucosa technique was used in all patients, 100%),[8–11] omission of somatostatin (52%),[12–14] stents (63%) or duct occlusion techniques (0%) and a persistent use of closed suction drains placed behind the pancreatojejunostomy (100%).[15] With that technique, an overall leakage rate of ~25% and a type C leakage rate of ~5% was found, which compares favorably with previous reports of similar leakage classifications.[7,16,17] Only minor non-significant differences were seen between the total fistula rate or the severity of leakage in experienced surgeons and surgeons in training. Although volume and outcome correlates for pancreatic surgery, no difference in surgical complications have been reported for individual surgeons within a high volume center, and we have not found a difference in anastomotic leakage when anastomoses were performed by high or low volume surgeons in our high volume center. However, leakage was found only in patients with a PAS of 2 or higher. The association of leakage and pancreatic consistency has been described in previous studies, but no score was developed out of those data.[15,17] Interestingly, no difference was found between a score of 2, 3, or 4, indicating an "all or nothing mechanism" of development of pancreatojejunal leakage. That mechanism remains unclear from this study, but might be leakage of

Table 4 POPF in 391 Consecutive Patients Undergoing Pancreatic Resection and in 67 Consecutive Patients Undergoing Pancreatic Head Resection and Pancreas Anatomy Classification (PAS group)

	Total	PAS group	*P*
Leakage (%)	25.1	22.4	NS
POPF Grad A (%)	8.9	8.9	NS
POPF Grad B (%)	10.2	10.4	NS
POPF Grad C (%)	5.9	3.0	NS
Patients >70 years (%)	31.1	25	NS
Patients <70 years (%)	22.3	21.8	NS
OR time >6 h (%)	16.4	23.5	NS
OR time <6 h (%)	26.7	22	NS
Standard resection (%)	13.1	18.8	NS
Extended lymphadenectomy (%)	25	23.5	NS

Table 5 Pancreatic Anatomy Classification for 67 Consecutive Patients Undergoing Pancreatic Head Resection

	Values
Pancreas parenchyma	1.02±0.11
Diameter pancreatic duct (mm)	3.67±0.25
Score pancreaticojejunostomy	2.17±0.16

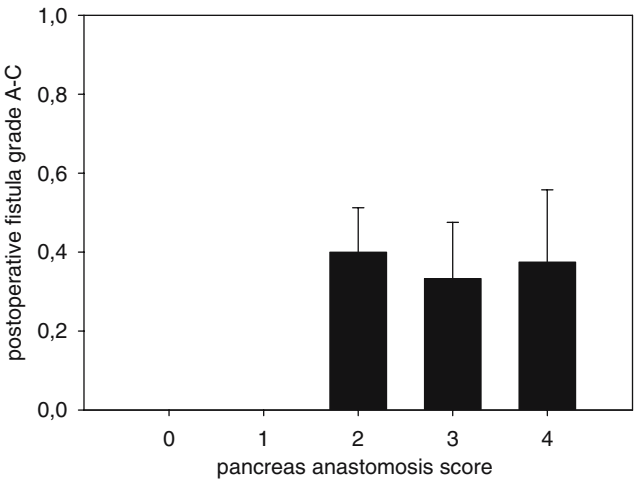


Figure 1 Correlation between anastomosis score and leakage at the pancreaticojejunostomy. POPF was classified according to the definition of ISGPF.[7] Statistical analysis: POPF grade A=1, POPF grade B=2 and POPF grade C=3; the graph shows the regression line of the second order.

Table 6 Risk Factors for POPF in 67 Consecutive Patients Undergoing Pancreatic Head Resection (Univariate Analysis)

	POPF n=15	No POPF n=52	p
Gender			NS
Male, n (%)	7 (46.7)	33 (63.5)	
Female, n (%)	8 (53.3)	19 (36.5)	
Age (years)	62.7±2.5	62.1±1.7	NS
>70, n (%)	3 (20)	9 (17.3)	NS
<70, n (%)	12 (80)	43 (82.7)	
ASA grade, n (%)	2.3±0.1	2.3±0.1	NS
I	0	2 (4%)	
II	11 (73.3%)	31 (62%)	
III	4 (26.7%)	17 (34%)	
Chronic pulmonary disease, n (%)	2 (13.3)	25 (48.1)	0.022
Body mass index (BMI: kg/cm^2)	26.8±1.1	26.3±0.7	NS
Preoperative biliary drainage, n (%)	3 (20)	36 (69.2)	0.002
Surgical indication, n			NS
Malignant	8 (53.3%)	35 (67.3%)	
Benign	7 (46.7%)	17 (32.7%)	
Pancreatic parenchyma, n			0.016
Hard	0	15	
Intermediate	7	14	
Soft	7	9	
Pancreatic duct (mm)	3.21±0.37	3.84±0.32	NS
OR time (min)	322.9±14.9	310.7±12.2	NS
Blood loss (ml)	590.0±88.0	700.0±63.2	NS
Reoperation (patients), n (%)	5 (33.3)	3 (5.8)	0.009
Anastomotic bile leakage (patients), n (%)	3 (20)	1 (1.9)	0.007
Reoperation due to bleeding (patients), n (%)	2 (13.3)	1 (1.9)	NS
Amylase out of suction drain 5th POD (U/L)	4,015.4±2538.9	89.0±30.5	<0.001
Lipase out of suction drain 5th POD (U/L)	11,463.5±5013.3	603.8±394.9	<0.001

pancreatic juice along suture lines with subsequent arrosion of the anastomosis (like in type A of B leakage) or the rare complete breakdown of the anastomosis (like in type C leakage). The sleeve technique should avoid leakage–arrosion along suture lines, and Peng et al.[18] reported no leakage in nearly 150 pancreatic head resections. However, no other study confirmed that result. Routine somatostatin prophylaxis was not given due to the conflicting results of prophylactic somatostatin treatment and the negative effect of somatostatin on gastrointestinal perfusion and bowel motility.[19,20] Furthermore, we have not altered our technique of pancreatic anastomosis in soft pancreata or small ducts in our institution. Whether ductal drainage or sleeve techniques would be of benefit in those patients remains speculative.

In summary, pancreatic anastomosis performed in a duct to mucosa technique with a score of 2 and higher are much more likely to leak. Drainage might safely be omitted in patients with a score less than 2. Furthermore, future studies on pancreatic leakage should include such a score to allow for comparability.

Table 7 Leakage of the Pancreaticojejunostomy and Case Load

Case load	Number of operations		Leakage (n)		
	Performed	Total	Grade A	Grade B	Grade C
0–10	65 (16.6%)	18 (27.7%)	6 (9.2%)	10 (15.4%)	2 (3.1%)
11–29	88 (22.5%)	18 (20.5%)	7 (8.0%)	8 (9.1%)	3 (3.4%)
30–50	108 (27.6%)	33 (30.5%)	12 (11.1%)	13 (12.0%)	8 (7.4%)
>100	130 (33.2 %)	29 (22.3%)	10 (7.7%)	9 (6.9%)	10 (7.7%)
Total	391 (100%)	98 (25.1%)	35 (8.9%)	40 (10.2%)	23 (5.9%)

References

1. Winter JM, Cameron JL, Campbell KA, Chang DC, Riall TS, Schulick RD, Choti MA, Coleman J, Hodgin MB, Sauter PK, Sonnenday CJ, Wolfgang CL, Marohn MR, Yeo CJ. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2006;10:1280–1290.
2. Duffas JP, Suc B, Msika S, Fourtanier G, Muscari F, Hay JM, Fingerhut A, Millat B, Radovanowic A, Fagniez PL; French Associations for Research in Surgery. A controlled randomized multicenter trial of pancreatogastrostomy or pancreato-jejunostomy after pancreatoduodenectomy. Am J Surg 2005;189:720–729.
3. Bassi C, Falconi M, Molinari E, Mantovani W, Butturini G, Gumbs AA, Salvia R, Pederzoli P. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. Surgery 2003;134:766–771.
4. Suc B, Msika S, Fingerhut A, Fourtanier G, Hay JM, Holmieres F, Sastre B, Fagniez PL; French Associations for Surgical Research. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: prospective randomized trial. Ann Surg 2003;237:57–65.
5. Tran K, Van Eijck C, Di Carlo V, Hop WC, Zerbi A, Balzano G, Jeekel H. Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. Ann Surg 2002;236:422–428.
6. Nakatsuka A, Yamaguchi K, Chijiiwa K, Tanaka M. Octreotide inhibits pancreatic exocrine secretion and prevents pancreatoenterostomy leakage. Int Surg 2000;85:124–129.
7. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Büchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an International Study Group (ISGPF) definition. Surgery 2005;138:8–13.
8. Arnaud JP, Tuech JJ, Cervi C, Bergamaschi R. Pancreaticogastrostomy compared with pancreaticojejunostomy after pancreaticoduodenectomy. Eur J Surg 1999;165:357–362.
9. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005;11:2456–2461.
10. Munoz-Bongrand N, Sauvanet A, Denys A, Sibert A, Vilgrain V, Belghiti J. Conservative management of pancreatic fistula after pancreaticoduodenectomy with pancreaticogastrostomy. J Am Coll Surg 2004;199:198–203.
11. Gouillat C, Gigot JF. Pancreatic surgical complications—the case for prophylaxis. Gut 2001;49 Suppl 4:32–39.
12. Nakatsuka A, Yamaguchi K, Chijiiwa K, Tanaka M. Octreotide inhibits pancreatic exocrine secretion and prevents pancreatoenterostomy leakage. Int Surg 2000;85:124–129.
13. Büchler M, Friess H, Klempa I, Hermanek P, Sulkowski U, Becker H, Schafmayer A, Baca I, Lorenz D, Meister R, Kremer B, Wagner P, Witte J, Zurmayer EL, Saeger HD, Riecx B, Dollineer P, Glaser K, Teichmann R, Konradt J, Gaus W, Dennier HJ, Welzer D, Beger HG. Role of octreotide in the prevention of postoperative complications following pancreatic resection. Am J Surg 1992;163:125–130.
14. Sarr MG; Pancreatic Surgery Group. The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: a prospective, multicenter, double-blinded, randomized, placebo-controlled trial. J Am Coll Surg 2003;196:556–564.
15. Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Coit DG, Merchant N, Brennan MF. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg 2001;234:487–493.
16. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA, Hruban RH. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002;236:355–366.
17. Lermite E, Pessaux P, Brehant O, Teyssedou C, Pelletier I, Etienne S, Arnaud JP. Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. J Am Coll Surg 2007;204:588–596.
18. Peng SY, Mou YP, Liu YB, Su Y, Peng CH, Cai XJ, Wu YL, Zhou LH. Binding pancreaticojejunostomy: 150 consecutive cases without leakage. J Gastrointest Surg 2003;7:898–900.
19. Hansen L, Hartmann B, Mineo H, Holst JJ. Glucagon-like peptide-1 secretion is influenced by perfusate glucose concentration and by a feedback mechanism involving somatostatin in isolated perfused porcine ileum. Regulatory Pept 2004;118:11–18.
20. Di Francesco V, Angelini G, Zoico E, Zamboni M, Frulloni L, Cavallini G. Effect of native somatostatin on Sphincter of Oddi motility in patients with acute recurrent pancreatitis. A pilot study with ultrasound-secretin test. Dig Liver Dis 2006;38:268–271.

J Gastrointest Surg (2007) 11:1704–1711
DOI 10.1007/s11605-007-0369-7

ORIGINAL ARTICLE

Long-term Anastomotic Complications After Pancreaticoduodenectomy for Benign Diseases

Kaye M. Reid-Lombardo · Antonio Ramos-De la Medina · Kristine Thomsen · William S. Harmsen · Michael B. Farnell

Received: 1 June 2007 / Accepted: 20 September 2007 / Published online: 11 October 2007

Abstract
Background The study of long-term complications after pancreaticoduodenectomy (PD) for malignant disease has been problematic given the paucity of patients with long-term survival after diagnosis and surgical resection. We therefore studied patients who were surgically treated with a PD for a benign diagnosis to evaluate long-term anastomotic durability.
Methods A retrospective analysis of 122 patients who had PD performed in the interval 1993–2003 inclusive for benign pancreatic diseases was undertaken. Long-term morbidity and mortality (specifically biliary, pancreaticojejunostomy [PJ], and gastrojejunostomy [GJ] strictures) were evaluated.
Results Gender was equally represented with 53% female and 47% male. The median age at surgery was 55 years (range 15–81 years). The three most frequent diagnoses were chronic pancreatitis (40%), intraductal papillary mucinous neoplasm (16%), and cystic neoplasms (9%). Median follow-up in the 95 patients alive at last follow-up was 4.1 years (10 days–12.6 years). The 5- and 10-year survival rates were 83% (76, 91%) and 62% (49%, 78%), respectively. The observed survival was significantly lower than the expected survival in an age- and gender-matched U.S. white population, $p<0.001$ (one-sample log-rank test). The 5- and 10-year cumulative probability of biliary stricture was 8% (2%, 14%) and 13% (4%, 22%), respectively. For pancreatic strictures the 5- and 10-year rates were 5% (0%, 9%) and 5% (0%, 9%), respectively. No GJ strictures were noted. The management of biliary strictures was primarily with dilatation and stent (78%) and less commonly operative intervention (22%). Pancreatic strictures required surgery alone (25%), surgery followed by endoscopic intervention (25%), or endoscopic therapy alone (50%).
Conclusion Intervention for anastomotic strictures after pancreaticoduodenectomy is uncommon. Biliary strictures can usually be treated nonoperatively with dilation and stent. Our study likely underestimates the incidence of stricture formation. Prospective imaging studies may be warranted for a more accurate assessment of the rate of long-term anastomotic complications.

Keywords Pancreaticoduodenectomy · Anastomoses · Hepaticojejunostomy · Stricture · Pancreaticojejunostomy · Whipple

K. M. Reid-Lombardo · A. Ramos-De la Medina · M. B. Farnell (✉)
Division of Gastroenterologic and General Surgery, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905, USA
e-mail: farnell.michael@mayo.edu

K. Thomsen · W. S. Harmsen
Division of Biostatistics, Mayo Clinic, Rochester, MN, USA

Abbreviations

CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreatography
F	female
IR	interventional radiology
IPMN	intraductal papillary mucinous neoplasm
GJ	gastrojejunostomy
M	male
MCN	mucinous cystic neoplasms
MRCP	magnetic resonance cholangiopancreatography
PD	pancreaticoduodenectomy
PJ	pancreaticojejunostomy
PPPD	pylorus preserving pancreaticoduodenectomy
PTC	percutaneous transhepatic cholangiogram
SD	standard deviation

Introduction

Over the last two decades, a dramatic improvement in operative mortality after pancreaticoduodenectomy (PD) and pylorus-preserving pancreaticoduodenectomy (PPPD) has been observed for pancreatic and periampullary adenocarcinomas, especially in high-volume centers.[1,2] This has led to an expansion of the operative indications to include various benign diseases such as chronic pancreatitis and, more recently, intraductal papillary mucinous neoplasm (IPMN).[3] A recent report from a high-volume center estimated that 9.2% of all PDs performed were to treat benign disorders.[4] The expanded inclusion criteria to include more patients with benign disease allows for the examination of the long-term anastomotic durability (pancreaticojejunostomy, gastrojejunostomy/duodenojejunostomy, and biliary–enteric) after PD or PPPD. Heretofore, the assessment of long-term anastomotic complications has been compromised by the limited survival observed among patients with pancreatic adenocarcinoma, the most frequent indication for PD or PPPD.

There is a large body of literature that describes the short-term complications (e.g., pancreatic or biliary anastomotic leaks) that occur after PD, but little has been published regarding long-term anastomotic complications. Recently, House et al. from John Hopkins reported long-term biliary stricture rates seen at their institution in patients with both benign and malignant pathologies.[5] However, long-term outcome relative to the pancreaticojejunostomy (PJ) and gastrojejunostomy/duodenojejunostomy (GJ/DJ) anastomoses were not reported and the median follow-up period was only 2.3 years. This study addresses the prevalence of strictures for the biliary, pancreatic, and gastric/duodenal anastomoses after PD and PPPD for benign disorders.

Methods

Patient Selection

After approval by the Mayo Clinic Institutional Review Board, a retrospective chart review for all patients in whom a PD or PPPD for benign diseases at Mayo Clinic in Rochester, Minnesota during the time period inclusive of 1993 to 2003 was performed. Each patient's chart was abstracted for demographic information, preoperative evaluation, intraoperative technique, postoperative complications, and follow-up to assess long-term morbidity and mortality after pancreaticoduodenectomy. Further follow-up data was supplemented by patient contact utilizing mailed survey or phone contact with assistance from the Survey Research Center at Mayo Clinic.

Surgical Technique and Diagnosis of Strictures

After completion of the PD, reconstruction of the PJ consisted of a two-layer duct-to-mucosa anastomosis with either a monofilament or polyfilament absorbable suture. An unsecured silastic stent was frequently used to stent the anastomoses and prevent complete closure of the duct during the creation of the anastomosis. The construction of the hepaticojejunostomy varied with either running or interrupted using monofilament or polyfilament absorbable suture. The majority of patients did not have a stent placed during the hepaticojejunostomy. Two surgical drains were placed one near the hepaticojejunostomy and another near the PJ.

All strictures were defined by the need for endoscopic, percutaneous, or surgical intervention in symptomatic patients.

Statistical Analysis

The characteristics of patients are reported using standard descriptive statistics, number (percent) for the discrete factors, and the mean (±standard deviation) or median with range, as appropriate for continuous factors. Pearson chi square analysis was used to compare survey response rates by gender and the two-sample *t*-test to compare age. Survival and cumulative probability of strictures were estimated using the Kaplan–Meier survival method. Gender was assessed as a risk factor for stricture using Cox proportional hazard regression. Survival to death was also compared to expected survival of an age- and gender-matched U.S. white population; significance was tested with a one-sample log-rank test. The alpha level was set at $p<0.05$ for statistical significance.

Results

Patient Characteristics

In the interval 1993 to 2003, 122 patients had a PD ($n=26$)/PPPD ($n=96$) performed for benign pancreatic, periampullary, biliary, or duodenal diseases. Sixty-four (52%) of the patients were female. The median age at surgery was 55 years with a range of 15 to 81 years. For patients with chronic pancreatitis, the median age was younger than those with other benign diagnoses, 51 vs 63 years ($p=0.003$) (Table 1).

The surgical indications included chronic pancreatitis, 49 (40.2%); IPMN, 20 (16.4%); mucinous cystadenoma, 11 (9.0%); villous adenoma, 6 (4.9%); serous cystadenoma, 5 (4.1%); and other, 31 (25%) (for the complete list, see Table 2). The technique most used for fashioning the pancreaticojejunostomy was a duct-to-mucosa anastomosis

Table 1 Patient Characteristics

	Chronic pancreatitis	Other diagnoses	Overall	
			N	%
Age (median)	51 years	63 years	55 years	
Gender				
Female	24	40	64	52.5
Male	25	33	58	47.5
Procedure				
PD	12	14	26	21.3
PDDD	37	59	96	78.6

(*n*=104, 85.2%). Stents were used to aid in the creation of the PJ anastomosis in 43% of the patients. Biliary stents were rarely used (*n*=17, 13.9%) during the performance of the hepaticojejunostomy.

The median pancreatic duct size was 4.0 mm (range 1–8 mm), and the median bile duct size was 10 mm (range 6.0–30.00 mm). The majority of patients did not suffer from a postoperative morbidity (*n*=83, 68%). The most frequent postoperative complications were pancreaticojejunostomy leaks (*n*=19, 15.6%), bile leaks (*n*=8, 6.6%), and delayed gastric emptying (*n*=14, 11.5%). All postoperative complications are listed in Table 3. Short term morbidity and long term morbidity were not statistically different between those with a diagnosis of chronic pancreatitis versus those without (*p*=0.15; Table 3). The number of patients with a leak were more frequent in the "other" group when compared to those with chronic pancreatitis (*n*=14, 19.2% vs *n*=5, 10.2%); however, no statistical significance was noted (*p*=0.18).

Table 2 Benign Diagnosis of all 122 Patients who Underwent a PD or PPPD

Diagnosis	*N*	%
Chronic pancreatitis	49	40
Other		
Intraductal papillary mucinous neoplasm	20	16
Mucinous cystadenoma	6	5
Villous adenoma	6	5
Serous cyst adenoma	5	4
Gastrointestinal stromal disease	2	2
Islet cell adenoma	5	4
Duodenal adenoma	4	3
Ampullary adenoma	2	2
Benign Inflammatory process	4	3
Duodenal duplication cyst	1	1
Duodenal fistula	2	2
Ampullary stenosis	1	1
Angiolipoma	1	1
Choledochocyst	1	1
Disconnected ampulla	1	1
Lymphocytic sclerosing pancreatitis	1	1
Nesidioblastosis	1	1
Peptic ulcer disease	1	1

Table 3 Thirty-day Morbidity and Mortality After PD and PPPD for Benign Diseases in 122 Patients

Morbidity	Chronic pancreatitis[a]	Other diagnoses	Total	
	N=49	*N*=73	*N*	%
No complications	37	46	83	68.0
Pancreaticojejunostomy leak[a]	5	14	19	15.6
Bile leak	4	4	7	5.7
Gastric delayed emptying	4	10	14	11.5
Intraabdominal abscess	0	2	2	1.6
Acute renal failure	1	0	1	0.8
Bile duct obstruction	0	1	1	0.8
Cardiac arrest open thoracotomy	0	1	1	0.8
Chylous leak	1	0	1	0.8
Enteric fistula	1	0	1	0.8
Hepatic necrosis	0	1	1	0.8
Intraabdominal hemorrhage	0	1	1	0.8
Pancreaticojejunostomy anastomotic hemorrhage	0	1	1	0.8
Mortality	2	3	5	4.1

[a]No statistical difference in having a 30-day morbidity between those with chronic pancreatitis and those without (*p*=0.18).

Thirty-day mortality in this group was 4% (*n*=5). During the decade that was examined, 12 surgeons performed the surgical procedures with 1 surgeon performing 43% of the cases. The median follow-up time was 4.1 years (range 10 days–12.6 years) with 95 patients (77.9%) alive at follow-up.

Biliary Strictures

Biliary strictures were observed in a total of nine patients who had a PD/PPPD. Preoperative bile duct size was available in two patients that developed a stricture (1.2 and 6 mm, respectively). Of the nine patients with biliary strictures, two had preoperative stents and only one had an intraoperative stent placed. Cumulative probability of biliary stricture at 1 year was 2.9% (range 0–6.0%) and at 5 years was 8.2% (range 1.9–14.1%). Among the nine patients with biliary strictures, the median time to diagnosis of biliary strictures after PD was 18 months (range 1–69 months) (Fig. 1). Male gender was not significantly associated with the development of biliary stricture (*p*=0.84) with four females and five males developing a biliary stricture, OR=1.1 (95%CI=0.3, 4.3). Six patients had a PPPD and three patients had a PD. The indication for PD in

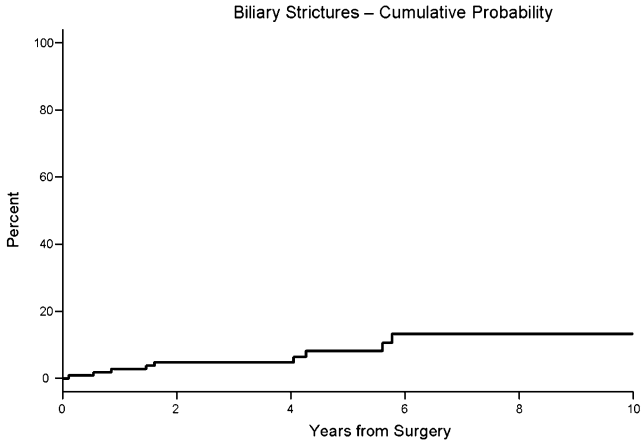


Figure 1 Cumulative probability for intervention of biliary stricture after PD/PPPD.

these nine patients was chronic pancreatitis (n=3), IPMN (n=2), angiomyolipoma (n=1), ampullary stenosis (n=1), insulinoma (n=1), and villous adenoma of the ampulla (n=1). Thirty-day morbidity included one patient with a postoperative abdominal collection, one patient with a bile leak that was controlled with a drain, and one patient with a PJ leak that was controlled with the drain that was placed intraoperatively. The presenting sign or symptoms of biliary strictures were cholangitis in four patients, an increase in liver function tests in three patients, whereas four patients presented with jaundice. The initial diagnostic tool was abdominal computed tomography (CT) in all but one patient who was first evaluated with an ultrasound. Each patient was then subsequently evaluated with percutaneous transhepatic cholangiogram (PTC; n=7) or endoscopic retrograde cholangiopancreatography (ERCP; n=2). In the PTC group, three were found to have choledocholithiasis.

The management of biliary strictures was primarily dilatation and stenting, which was performed in seven patients, four by the percutaneous transhepatic route and three endoscopically. Multiple dilations were required in four of the seven patients treated nonoperatively. Two patients required surgical intervention: one had a revision of the choledochojejunostomy and the other a conversion to a hepaticojejunostomy because of failure of nonoperative management.

Pancreatic Strictures

Pancreaticojejunostomy strictures required intervention in four patients. Cumulative probability of PJ stricture at 1 year was 2.8% (range 0–5.9%) and at 5 years was 4.6% (range 0–9.2%). Pancreatic duct size at the time of surgery was available for only two of the four patients. Their duct size was 2.5 and 4 mm, respectively. Among the four patients with PJ strictures, the median time to PJ strictures was 3 months (range 1–56 months) (Fig. 2). Three of the patients with PJ were males and one was female. They carried the diagnosis of mucinous cystic neoplasm (MCN; n=2), chronic pancreatitis (n=1), and periampullary polyposis (n=1). All except one had a PPPD. Two of the patients had an uncomplicated postoperative course, another had a PJ leak and one suffered from delayed gastric emptying. The presenting signs and symptoms of pancreatic strictures in these four patients were abdominal pain and diarrhea and/or steatorrhea in three and a pseudocyst seen on an imaging study in one. Analysis of fecal fat was performed and found to be increased in one of the three patients that presented with diarrhea. The management of PJ strictures was diverse with two patients requiring operative revision. The first patient had an operative revision with a takedown and redo of the PJ whereas the other had a conversion to a side-to-side lateral PJ because of inability to treat nonoperatively and persistent pain. The other two were treated with dilation and stent and needle knife, respectively, to relieve the stricture endoscopically. All four of these patients were alive at the time of the study with minimal to no symptoms related to the treated anastomosis. Steatorrhea was resolved in all three patients with suspected steatorrhea at time of presentation at the time of last follow-up.

Gastrojejunostomy Stricture

No patients were diagnosed with a gastrojejunostomy (GJ) stricture. One patient did develop a GJ anastomotic ulcer and was treated with proton-pump inhibition and a gastric mucosa protective agent. He was pain-free on his last follow-up, but did state on the subsequent survey that he had “quite a bit of pain”. He has not had a repeat esophagoscopy.

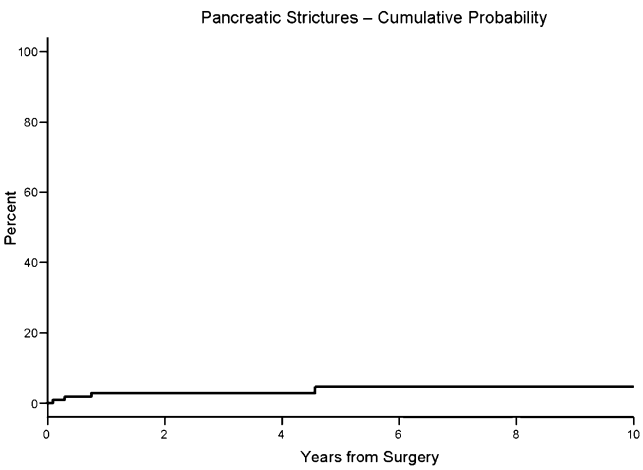


Figure 2 Cumulative probability for intervention of pancreaticojejunostomy stricture after PD/PPPD.

Survival

The overall 5- and 10-year survival for the entire cohort was 83% (range 76–91%) and 62% (range 49–78%), respectively. When we compared survival to the general U.S. population, the observed survival rate was significantly lower than the expected survival rate ($p<0.001$) (Fig. 3). Observed and expected rates at 5 years were 82.7% (range 75.7–90.5%) and 90.3%, respectively, and at 10 years were 61.7% (range 48.7–78.3%) and 78.8%, respectively. To assess whether the inclusion of patients with a diagnosis of chronic pancreatitis may have caused this observation, we also compared the observed survival with the expected survival separately for the chronic pancreatitis patients and those with any other diagnosis (Figs. 4 and 5). Survival was significantly lower for chronic pancreatitis ($p<0.001$) but not significant for all "other" diagnoses in our patient population ($p=0.22$).

Figure 4 Survival of other nonchronic pancreatitis patients ($n=73$) in our study cohort compared to the general population, age- and gender-matched.

Discussion

The expansion of operative indications to include benign diseases for PD has allowed us to evaluate the durability of the anastomoses performed during this surgical procedure. Our results suggest that the anastomoses performed during a PD/PPPD are quite durable (Table 4) with a 5-year cumulative probability of biliary stricture rate of 8.2% and a 5-year cumulative probability of PJ stricture of 4.6%. If we exclude the one patient with a nonanastomotic stricture in the right biliary tree that was later found to have sclerosing cholangitis, our cumulative probability of biliary stricture falls. House et al.[5] reported a lower frequency of biliary strictures after PD for benign diseases. In their study, the rate of biliary strictures was 2.6% (10/392). A difference in biliary stricture rates between patients with benign and malignant diseases was not observed in their study. Our follow-up period was longer, which may have contributed to the higher rate of biliary stricture observed in our study. However, when we compare our 1-year cumulative probability with the data of House et al., it is quite similar at 2.9%. A 5-year cumulative probability was not reported in their study.

Most of the data in the literature regarding the prevalence of biliary strictures after hepaticojejunostomy stems from the orthotopic liver transplant experience. In a recent study comparing Roux-en-Y hepaticojejunostomy with duct-to-duct anastomosis after adult-to-adult living donor liver transplantation, the biliary stricture rate was found to be 5.3% after 4.7 years of follow-up.[6] This is similar to the rate of biliary strictures seen in our study at 4 years (4.8%).

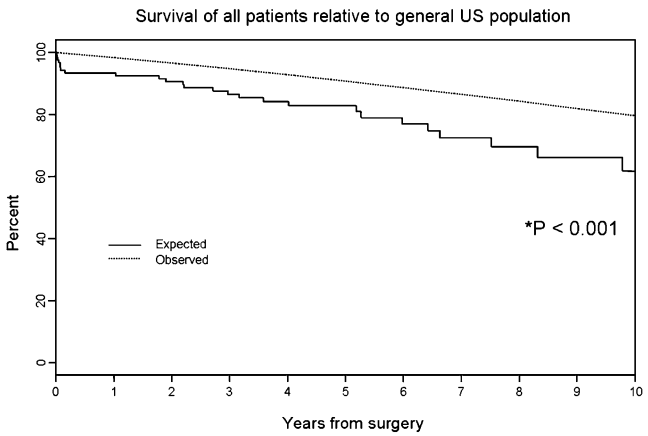


Figure 3 Survival of study cohort ($n=122$) compared to general population, age- and gender-matched.

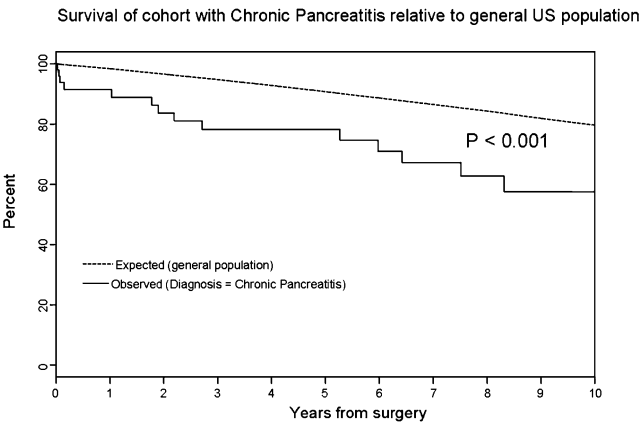


Figure 5 Survival of chronic pancreatitis patients in our study cohort compared to the general population, age- and gender-matched. $p<0.05$ is statistically significant.

Table 4 Stricture Rates After PD/PPPD

Stricture type	*N*	%
Biliary	9	7.4
Pancreaticojejunostomy	4	3.3
Gastrojejunostomy	0	0

The clinical presentation of biliary stricture more often than not included cholangitis, and the evaluation most frequently began with abdominal CT and followed by a more invasive diagnostic tool such as PTC or ERCP. The management of the majority of these strictures was nonoperative, mirroring the experience reported by House et al.[5] and by transplant surgeons that utilize the hepaticojejunostomy method for bile duct reconstruction.[7] Several patients did require reintervention with upwards of five balloon dilations, a rather high reintervention rate but with good to excellent outcomes. Even with our small sample size of biliary stricture patients, the reintervention rate is higher than that reported in the transplant literature. Alazmi et al. reported a stricture recurrence rate of almost 20% in patients after endoscopic dilation, and suggested recurrence is responsive to repeat dilation.[8] In contradistinction, one of the only reports addressing biliary stricture after pancreaticoduodenectomy reported that all four patients required surgical revision after failure of endoscopic management.[9]

Upon clinical presentation, most of the biliary stricture patients in this series were treated nonoperatively and more often by interventional radiologic techniques than by endoscopy. Difficult endoscopic access to the biliary enteric anastomosis inherent with the complex anatomy of the proximal gastrointestinal tract after PD/PPPD reconstruction may explain this difference. Interventional radiology (IR) has been shown in many reports to be a successful way to treat biliary strictures after PD.[10–13] Our median number of balloon dilatation was one but many report a higher frequency of repeat dilatations in the literature. In our patient population, two of nine with biliary stricture required surgical intervention. In one study comparing the utility of percutaneous transhepatic and endoscopic modalities for the treatment of benign biliary strictures, 15% of the patients reviewed required surgical intervention. The authors concluded that these nonsurgical interventions were good short-term and long-term options for patients with benign biliary strictures.[14]

There was a lot of variability in the treatment offered to patients with PJ strictures; but because of our small sample size (n=4), we cannot make a definitive recommendation on how to manage these patients. Attempts of endoscopic intervention were successful in only one of the three patients in which it was attempted and the remaining two proceeded to surgical intervention. We currently place a medium titanium clip at the PJ anastomosis, which is identifiable at fluoroscopy to facilitate endoscopic access. A prospective, radiographic study would be required to answer if there are subclinical PJ strictures that go undetected as most of these patients are treated medically for presumed pancreatic insufficiency and not radiographically evaluated.

Other notable findings from our study include the mortality rate of 4%, which is higher than expected. After close examination of the five deaths that occurred, there were some notable differences to normal practice. One patient had an orthotropic liver transplant, developed a choledochojejunostomy dehiscence and a duodenal leak with subsequent duodenal necrosis. This patient required a damage control operation in the form of a Whipple operation, and after this procedure developed failure of the transplanted organ and died. It seems reasonable that this patient can be excluded, which would make our 30-day mortality rate 3.3% closer to what is expected based on the reported rates in the literature. The four remaining deaths were because of a myocardial infarction in an elderly patient and complications related to a pancreatojejunal anastomotic dehiscence in three patients. The mortality reported herein is higher than our recently reported operative mortality rate of 1.4% after pancreatoduodenectomy for adenocarcinoma of the pancreas.[15] The higher mortality rate seen in this benign cohort is likely because of two observations. First, in those patients with a soft pancreas that is frequently encountered in benign disorders, the risk of anastomotic dehiscence is much higher than in a patient with a firm pancreas, which is often seen with malignancy. Second, a number of patients in this series had chronic pancreatitis. The intense inflammatory reaction and fibrosis in the peripancreatic tissues makes dissection technically more difficult, which may lead to more intraoperative hemorrhage and subsequent postoperative morbidity.

The rate of DGE in this series (11.5%) is lower than most reports in the literature;[16,17] however, it is on par with the rate of DGE (12.5%) in a recent report of a pancreatic database that contains 1,500 patients who had PD/PDDD for both benign and malignant disease at high volume centers across the world.[18] It is unclear why the rate of DGE is lower in our cohort of patients with benign disease; however, it might be speculated that pancreatic adenocarcinoma elaborates factors that worsen delayed gastric emptying after a pancreaticoduodenectomy. The observation of lowered morbidity and mortality that is observed at high-volume centers with this procedure might also explain the lower DGE rate.[19]

We did observe a difference in survival when compared to population controls (age- and gender-matched). This decrease in survival is largely because of the subpopulation of patients with chronic pancreatitis and has been previ-

ously documented.[20–22] In our study, 64% reported having at least some abdominal pain. The etiology of this pain was not assessed, but analysis revealed that 59.5% of the patients who reported having abdominal pain on the survey had a diagnosis of chronic pancreatitis. After PD or PPPD, 8–54% of patients with chronic pancreatitis can experience chronic pain.[23,24]

An obvious limitation of this study is that we did not prospectively evaluate all patients alive at follow-up with imaging studies to detect subclinical strictures. Instead, our analysis included patients who came to clinical attention. Presumably, all patients with medically significant biliary strictures present with symptoms of jaundice or cholangitis and, therefore, we should be accounting for at least the majority of "at-risk" individuals. This, however, is not the case in patients with pancreatic strictures, as many can go undetected with symptoms, which may be treated medically, such as abdominal pain or steatorrhea. In the case of IPMN, the distinction between recurrent disease and pancreatic stricture might be aided by the analysis of stool fat or fecal fat, both of which should be increased in the presence of a stricture. Future direction might include prospective imaging to obtain an accurate estimate of biliary stricture and PJ strictures.

Conclusion

Intervention for anastomotic strictures after pancreaticoduodenectomy is uncommon. Intervention for biliary anastomotic strictures occurs later and apparently more frequently than PJ strictures after pancreaticoduodenectomy. Biliary anastomotic strictures can usually be managed by balloon dilatation and stents alone whereas PJ strictures may more often require operative intervention because of persistent abdominal pain or failure of medical management. Future studies that utilize prospective imaging would be useful in more accurately identifying postoperative long-term anastomotic complications.

References

1. Birkmeyer JD, Warshaw AL, Finlayson SRG, Grove MR, Tosteson AN. Relationship between hospital volume and late survival after pancreaticoduodectomy. Surgery 1999;126:178–183.
2. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg 2003;237:509–514.
3. Balcom JH, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391–398.
4. Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK, Hruban RH. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all 'chronic pancreatitis'? Am J Surg Pathol 2003;27:110–120.
5. House MG, Cameron JL, Schulick RD, Campbell KA, Sauter PK, Coleman J, Lillemoe KD, Yeo CJ. Incidence and outcome of biliary strictures after pancreaticoduodenectomy. Ann Surg 2006;243:571–576.
6. Yi NJ, Suh KS, Cho JY, Kwon CH, Lee KU. In adult-to-adult living donor liver transplantation hepaticojejunostomy shows a better long-term outcome than duct-to-duct anastomosis. Transpl Int 2005;18:1240–1247.
7. Graziadei IW, Schwaighofer H, Koch R, Nachbaur K, Koenigsrainer A, Margreiter R, Vogel W. Long-term outcome of endoscopic treatment of biliary strictures after liver transplantation. Liver Transpl 2006;12:718–725.
8. Alazmi WM, Fogel EL, Watkins JL, McHenry L, Tector JA, Fridell J, Mosler P, Sherman S, Lehman GA. Recurrence rate of anastomotic biliary strictures in patients who have had previous successful endoscopic therapy for anastomotic narrowing after orthotopic liver transplantation. Endoscopy 2006;38:571–574.
9. Ammori BJ, Joseph S, Attia M, Lodge JP. Biliary strictures complicating pancreaticoduodenectomy. Int J Pancreatol 2000;28:15–21.
10. Moore AV, Illescas FF, Mills SR, Wertman DE, Heaston DK, Newman GE, Zuger JH, Salmon RB, Dunnick NR. Percutaneous dilation of benign biliary strictures. Radiology 1987;163:625–628.
11. Vos PM, van Beek EF, Smits NJ, Rauws EA, Gouma DJ, Reeders JW. Percutaneous balloon dilatation for benign hepaticojejunostomy strictures. Abdom Imaging 2000;25:134–138.
12. Gervais DA, Fernandez-del Castillo C, O'Neill MJ, Hahn PF, Mueller PR. Complications after pancreatoduodenectomy: imaging and imaging-guided interventional procedures. Radiographics 2001;21:673–690.
13. Schumacher B, Othman T, Jansen M, Preiss C, Neuhaus H. Long-term follow-up of percutaneous transhepatic therapy (PTT) in patients with definite benign anastomotic strictures after hepaticojejunostomy. Endoscopy 2001;33:409–415.
14. Born P, Rosch T, Bruhl K, Sandschin W, Allescher HD, Frimberger E, Classen M. Long-term results of endoscopic and percutaneous transhepatic treatment of benign biliary strictures. Endoscopy 1999;31:725–731.
15. Schnelldorfer T, Ware AL, Smyrk TC, Zhang L, Qin R, Gullerud RE, Sarr MG, Donohue JH, Nagorney DM, Farnell MB. Long-term survival of surgically treated pancreatic adenocarcinoma: the unique features. Gastroenterology 2007;132:A871–A872.
16. Bames S, Lillemoe K, Kaufman H, Sauter P, Yeo C, Talamini M, Pitt H, Cameron J. Pancreaticoduodenectomy for benign disease. Am J Surg 1996;171:131–134.
17. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006;244:10–15.
18. Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C, Traverso LW; Members of the Pancreatic Anastomotic Leak Study Group. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: a report from the Pancreatic Anastomotic Leak Study Group. J Gastrointest Surg 2007; in press.
19. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221:43–49.
20. Porter GA, Pisters PW, Mansyur C, Bisanz A, Reyna K, Stanford P, Lee JE, Evans DB. Cost and utilization impact of a clinical pathway for patients undergoing pancreaticoduodenectomy. Ann Surg Oncol 2000;7:484–489.

21. Sakorafas GH, Farnell MB, Nagorney DM, Sarr MG, Rowland CM. Pancreatoduodenectomy for chronic pancreatitis: long-term results in 105 patients. Arch Surg 2000;135:517–523.
22. Buhler L, Schmidlin F, de Perrot M, Borst F, Mentha G, Morel P. Long-term results after surgical management of chronic pancreatitis. Hepatogastroenterology 1999;46:1986–1989.
23. Martin RF, Rossi RL, Leslie KA. Long-term results of pylorus-preserving pancreatoduodenectomy for chronic pancreatitis. Arch Surg 1996;131:247–252.
24. Jimenez RE, Fernandez-del Castillo C, Rattner DW, Chang Y, Warshaw AL. Outcomes of pancreaticoduodenectomy with pylorus preservation or with antrectomy in the treatment of chronic pancreatitis. Ann Surg 2000;231:293–300.

J Gastrointest Surg (2007) 11:1712–1721
DOI 10.1007/s11605-007-0314-9

Protein Kinase C-Zeta (PKC-ζ) Regulates Kupffer Cell Apoptosis During Experimental Sepsis

Yanhua Peng · Celia A. Sigua · Cynthia Karsonovich · Michel M. Murr

Received: 9 May 2007 / Accepted: 18 August 2007 / Published online: 25 September 2007

Abstract
Background Kupffer cells play an important role in sepsis-mediated liver injury. We tested the hypothesis that PKC-ζ plays a critical role in Kupffer cell apoptosis during sepsis.
Methods Sepsis was induced in rats by cecal ligation and puncture (CLP); 12 h later, livers were assayed for PKC-ζ, IKKα, IKKβ, IKKγ, NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation. Kupffer cells from control rats were infected with AdPKC-ζ DN to inhibit PKC-ζ, or transfected with pCMVPKC-ζ to overexpress PKC-ζ, and then treated with lipopolysaccharide (LPS). Cellular extracts were assayed for PKC-ζ, IKKα, IKKβ, IKKγ, NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation.
Results During sepsis, PKC-ζ localized in cells positive for the macrophage marker (F4/80). CLP upregulated PKC-ζ protein and activity, IKKβ, IKKγ, NF-κB, Fas/FasL, Caspase-3, and increased DNA fragmentation in rat livers (all $p<0.001$). AdPKC-ζ DN attenuated the LPS-induced upregulation of PKC-ζ activity, IKKβ, IKKγ, NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation in Kupffer cells (all $p<0.001$), whereas overexpression of PKC-ζ augmented LPS-induced upregulation of IKKβ, IKKγ, NF-κB, Caspase-3, and DNA fragmentation ($p<0.001$).
Conclusion PKC-ζ plays an important role in sepsis-induced apoptosis of Kupffer cells via activation of NF-κB and Fas/FasL. Manipulating the response of Kupffer cells to cellular stress may have important therapeutic implications.

Keywords Apoptosis · Kupffer cells · Liver injury · PKC-ζ · Sepsis

Abbreviations

ABTS	2, 2′azino-di [3-ethylbenzthiazoline sulfonate (6)] and H_2O_2 in glycine/citric acid buffer
AdPKC-ζ DN	adenovirus which expresses domain negative protein kinase C zeta
AdLacZ	adenovirus which expresses LacZ gene
DAPI	4-6-Diamidino-2-phenylindole
FBS	fetal bovine serum
IKKα	IκB kinase α
IKKβ	IκB kinase β
IKKγ	IκB kinase γ
LPS	lipopolysaccharide
NF-κB	nuclear factor kappa-B
NP-40	non-ionic surfactant
PCMVcDNA3.1	empty expression vector driven by cytomegalovirus (CMV) promoter
PCMVPKC-ζ	expression plasmid of protein kinase C zeta driven by CMV promoter
PKC-ζ	protein kinase C Zeta
TNF-α	tumor necrosis factor-α
SDS	sodium dodecyl sulfate
RIPA buffer	PIPA buffer (50 mM Tris–HCl (pH 7.5), containing 1% Nonidet P-40, 0.05% SDS, 0.5% sodium deoxycholate, 1 mM EDTA, 150 mM NaCl, and protease inhibitors)

Presented as a poster during Digestive Disorders Week, Washington, DC, May 2007.

Y. Peng · C. A. Sigua · C. Karsonovich · M. M. Murr (✉)
Department of Surgery, James A. Haley Veterans Affairs Medical Center, University of South Florida Health Sciences Center, C/O Tampa General Hospital, Suite F-145, P.O. Box 1289, Tampa, FL 33601, USA
e-mail: mmurr@health.usf.edu

PMSF	phenylmethylsulfonyl fluoride
PRKC	primary rat Kupffer cells

Introduction

Liver injury is a clinical prognostic indicator in acute pancreatitis, trauma, and sepsis. Kupffer cells play a central role in the hepatic manifestations of a number of diseases including sepsis,[1] acute pancreatitis,[2] nonalcoholic fatty liver disease,[3] and ischemia/reperfusion.[3,4] We have demonstrated that Kupffer-cell-derived cytokines, such as TNF-α and Fas/FasL, mediate parenchymal liver injury and hepatocyte death during experimental pancreatitis.[5,6]. On the other hand, Fas/FasL induce apoptosis of their originator, the Kupffer cell, through transcriptional regulation of NF-κB.[7] This stress-induced Kupffer cell apoptosis may have a protective effect by reducing the number of activated Kupffer cells and overall cytokine production in the liver.

NF-κB and protein kinase C (PKC) share various cell signaling networks and target genes; the atypical PKC isoforms, PKC-ζ and PKC-λ, are essential in TNF-α/IL 1-β signaling pathways[8] and regulate Fas ligand-induced apoptosis.[9] Therefore, we hypothesize that the interactions between PKC-ζ and NF-κB are critical for programmed cell death in activated Kupffer cells. This study was undertaken to investigate the role of PKC-ζ in Kupffer cells apoptosis during cecal ligation and puncture-induced experimental sepsis.

Materials and Methods

All experiments were conducted with the prior approval of the Institutional Animal Care and Use Committee at the University of South Florida College Of Medicine.

Experimental Sepsis

Sepsis was induced in adult male Sprague–Dawley rats (240–260 g) by cecal ligation and puncture (CLP); sham operation was used as a ligation control (n=5 each). Briefly, rats were anesthetized with intraperitoneal injection of sodium pentobarbital solution (10 mg/kg, Abbott Laboratories, Chicago, IL, USA). Under sterile conditions, the cecum was exposed through a 1- to 2-cm incision in the left lower abdomen, ligated with a 5-0 silk suture below the ileocecal valve, and punctured. The abdomen was closed with surgical staples. The rats were injected with 2 ml of saline subcutaneously for fluid resuscitation and placed on a heating pad until they recovered from anesthesia. The animals were killed 24 h later, and their livers were collected and frozen at −80°C. Liver homogenates were processed for PKC-ζ, IKKα, β and γ, p65/NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation.

Isolation of Fresh Primary Rat Kupffer Cells

Fresh primary rat Kupffer cells (PRKC) were isolated from un-operated adult male Sprague–Dawley rats and provided by the Research Center for Alcoholic Liver and Pancreatic Diseases, Los Angeles, Keck School of Medicine University of Southern California.[10] Cells were grown in RPMI 1640 with 10% fetal bovine serum (FBS), 1% non-essential-amino acids, and 0.03% glutamine.

Overexpression of PKC-ζ

PKC-ζ was overexpressed in PRKC by transfection with a CMV-promoter-driven PKC-ζ gene expression plasmid (pCMVPKC-ζ) using lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Briefly, 15 μg pCMVPKC-ζ or control expression vector pCMVcDNA3.1 were separately transfected into 1×10^7 PRKC; 36–48 h after gene transfection, cells were treated with lipopolysaccharide (LPS; 1 μg/ml, Sigma, St. Louis, MO, USA) for 2 h to simulate conditions of acute inflammation. The dose of LPS has been validated in our lab with human mononuclear cells, lung macrophages, and Kupffer cells.[2] The experiments were grouped as follows:

PRKC+No Treatment
PRKC+LPS
PRKC+pCMVcDNA3.1
PRKC+pCMVcDNA3.1+LPS
PRKC+pCMVPKC-ζ
PRKC+pCMVPKC-ζ+LPS

Cellular extracts were processed for PKC-ζ, IKKα, β and γ, p65/NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation.

Inhibition of PKC-ζ Expression

PKC-ζ activity was inhibited by infection of PRKC with an adenovirus that expresses a domain negative PKC-ζ driven by CMV promoter (AdPKC-ζ DN). AdPKC-ζ DN and control AdLacZ were kindly provided by Dr. Robert Farese, James A. Haley Veterans Affairs Medical Center, University of South Florida, Tampa, FL.

Amplification and Purification of Adenovirus

Human embryonic kidney cell line 293 (HEK-293) is a gift from William Gower, Jr., Ph.D., James Haley Veterans Affairs Medical Center, University of South Florida, Tampa, Florida. HEK-293 cells were grown in 15-cm tissue

plates at 90% confluence and were infected at a MOI of eight to ten per cell. The infected cells were grown in Dulbecco modified eagles' media with 10% FBS for 72 h until a very strong cenotaphic effect could be observed and approximately 75% cells were detached. The cells then were collected by centrifugation at 3,000 rpm for 5 min; viral particles were released by five cycles of freezing in liquid nitrogen and rapid thawing at 40–50°C and purified using Virakit TM Adenomini-24 adenoviruses purification kit (Virapur, San Diego, CA, USA). Determination of virus infectivity was made by viral plaguing assay. Concentration of viruses was measured by colorimetry; X-gal staining was used to determine efficiencies of viral infection.

Primary rat Kupffer cells (1×10^7) were plated overnight before infection with AdPKC-ζ DN or AdLacZ at 100 plaque-forming units/cell or at 50–100 MOI. To enhance the infection efficiency of adenoviruses, FBS concentration was kept in 3% during the first 2 h of infection, adding FBS back to 10% afterwards. Twenty-four hours later, cells were treated with LPS (1 μg/ml, Sigma, St Louis, MO) for 2 h. The experimental groups were as follows:

PRKC+No treatment
PRKC+LPS
PRKC+AdPKC-ζ DN
PRKC+AdPKC-ζ DN+LPS
PRKC+AdLacZ
PRKC+AdLacZ+LPS

Cellular extracts were processed for PKC-ζ, IKKα, β and γ, p65/NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation.

Reverse Transcription-Polymerase Chain Reaction

Fas/FasL mRNA was measured by semi-quantitative differential reverse transcription-polymerase chain reaction (RT-PCR). Briefly, total liver or Kupffer cells mRNA was isolated by Trizol solution (Invitrogen, Carlsbad, CA). One microgram of RNA was primed using oligo (dT; Gibco, Gaithersburg, MD, USA) and subsequently reverse-transcribed with reverse transcriptase (SuperscriptII, Gibco). cDNA production was amplified in the presence of rat specific Fas, FasL, and βMG primers for 30 cycles of PCR in a UNO-Thermo block (Biometra, Tampa, FL, USA).

The sequences for the Fas primers were: sense 5′ GTATGCTGTGGATCATGGC 3′ and antisense 5′ AACTTTTCGTTCACCAG3′ (Invitrogen). FasL primers were: sense 5′ ATGGAACTGCTTTGATCTCTGG3′, and antisense 5′ ATTCCTCAAAATTGATCAGAG3′. The βMG primers were: sense 5′CTCCCCAAATTCAAGTG TACTCTCG3′ and antisense 5′GAGTGACGTGTT TAACTCTGCAAGC3′. The PCR products were separated with electrophoresis in 4% low melting temperature agarose gel containing ethidium bromide and were photographed digitally (UVP, GDS 8000 Upland, CA, USA).

Immunoblotting

Cells were lysed in RIPA buffer [phosphate-buffered saline (PBS)] with 0.1% sodium dodecyl sulfate (SDS), 1%NP40, 0.5% sodium deoxycholate; 50–100 μg protein was fractionated by 10% SDS polyacrylamide gel electrophoresis (SDS-PAGE), transferred to nitrocellulose membrane (Amersham, Pharmacia Biotech), blocked for 1 h with PBS containing 5% instant non-fat dry milk and 0.1% Tween-20, then incubated for 2 h in blocking buffer containing antibodies to either Fas, FasL (BD Biosciences, San Diego, CA, USA), Caspase-3, PKC-ζ, p-IKKα, p-IKKβ, p-IKKγ or β-actin (Cell Signaling Technology, Beverly, MA, USA). Bound primary antibody was detected by incubation with horseradish peroxide goat anti-mouse IgG or anti-rabbit IgG. The membranes were developed using Super Signal (Pierce, Rockford, IL, USA) ECL reagent, and quantified using densitometry.

PKC-ζ Activity

Briefly, PKC-ζ from Kupffer cells or from rat livers was immunoprecipitated with rabbit PKC-ζ monoclonal antibody[11] (Cell Signaling Technology), collected on Sepharose-A and G beads (Amersham Pharmacia Biotech, Sweden), and incubated in 100 μl $Na_4P_2O_7$, 1 mM NaF, 100 μM PMSF, 4 μg phosphatidylserine (Sigma), 50 μM [γ-^{32} P] ATP (Amersham Pharmacia Biotech, NJ, USA), 5 mM $MgCl_2$, and 40 μM serine analog of the PKC pseudosubstrate (Biosource Technologies, Inc., Camarillo, TX, USA). ^{32}P-ATP-labeled substrate was trapped on P-81 filter papers and quantified using scintillation counter.

DNA Fragmentation

DNA fragmentation was determined using enzyme-linked immunosorbent (ELISA)-based assay (Roche Molecular Biochemicals, Indianapolis, IN, USA). Briefly, 10^4 cells were lysed, incubated with 80 μl of immunoreagent for 2–4 h at room temperature or 4°C overnight. After adding ABTS (2, 2′azino-di [3-ethylbenzthiazoline sulfonate (6)] and H_2O_2 in glycine/citric acid buffer), the samples were quantified using colorimetry at 425 nm.

Enzyme-Linked Immunosorbent Assay for Measuring Nuclear Translocation of p65/NF-κB

Kupffer cell pellets or homogenates of liver tissue were lysed with 1% NP-40 and centrifuged at 14,000 rpm. Nuclear extracts were used for determination of protein

concentration and ELISA (Imgenex, San Diego, CA, USA) using colorimetry at 425 nm.

Immunofluorescence Staining for Macrophage Markers F4/80 and PKC-ζ

Double immunofluorescent staining was used to localize the macrophage marker F4/80 and PKC-ζ. Liver tissues were fixed in 10% formalin solution and subsequently deparaffinized and hydrated with xylene, ethanol, and PBS. Tissue sections were then treated with 0.1–0.2% trypsin in 0.4% $CaCl_2$ for 1 h and incubated with anti-F/80 and PKC-ζ antibodies (1:200 in PBS plus 10% normal goat serum) for 2–4 h. The slides were washed with PBS+0.1% Triton X-100, incubated with fluorescein isothiocyanate goat anti-mouse, rat, or rabbit IgG in PBS +10% normal goat serum for 1 h, and mounted with anti-fade solution and DAPI. Photomicrographs were taken with a Nikon microscope and merged by Image-Pro-Express (Image Processing Solutions, North Reading, MA, USA).

Data Analysis

All experiments were repeated at least in triplicates. Analysis of variance was used to compare means of the various experimental groups; if $p<0.05$, then a t test was used to compare means of two different arms, e.g., control vs LPS. Bonferroni's correction was used to correct for multiple comparisons. Generally, we used six different controls or treatment arms per experiment; therefore, the corrected p value for statistical significance was set at $p=0.05/6=0.008$. Data are mean+standard deviation.

Results

Upregulation of PKC-ζ Expression and Activity in Both Rat Liver and LPS-Treated PRKC

Total PKC-ζ protein and activity were significantly increased in rat livers 24 h after CLP-induced acute sepsis compared to sham control (all $p<0.001$, Figs. 1 and 2). Similarly, PKC-ζ protein and activity were increased in LPS-treated PRKC (all $p<0.001$, Figs. 1 and 2).

In vitro, AdPKC-ζ DN increased LPS-induced expression of PKC-ζ protein in PRKC ($p<0.001$, Fig. 1); however, the activity of the mutant PKC-ζ was significantly decreased ($p<0.001$; Fig. 2). Viral infection control experiments demonstrated the specificity of AdPKC-ζ DN (PKC-ζ protein: 3,657±37 vs 1,354±19, AdPKC-ζ DN+LPS vs AdLacZ+LPS, $p<0.001$; PKC-ζ activity: 1.5±0.1 vs 2.1±0.1-folds; AdPKC-ζ DN+LPS vs AdLacZ+LPS, $p<0.001$).

In contrast, transfection of PRKC with PKC-ζ expression vector pCMVPKC-ζ further augmented the LPS-induced upregulation of PKC-ζ ($p<0.001$, Figs. 1 and 2). Transfection with pCMVcDNA3.1 as a control demonstrat-

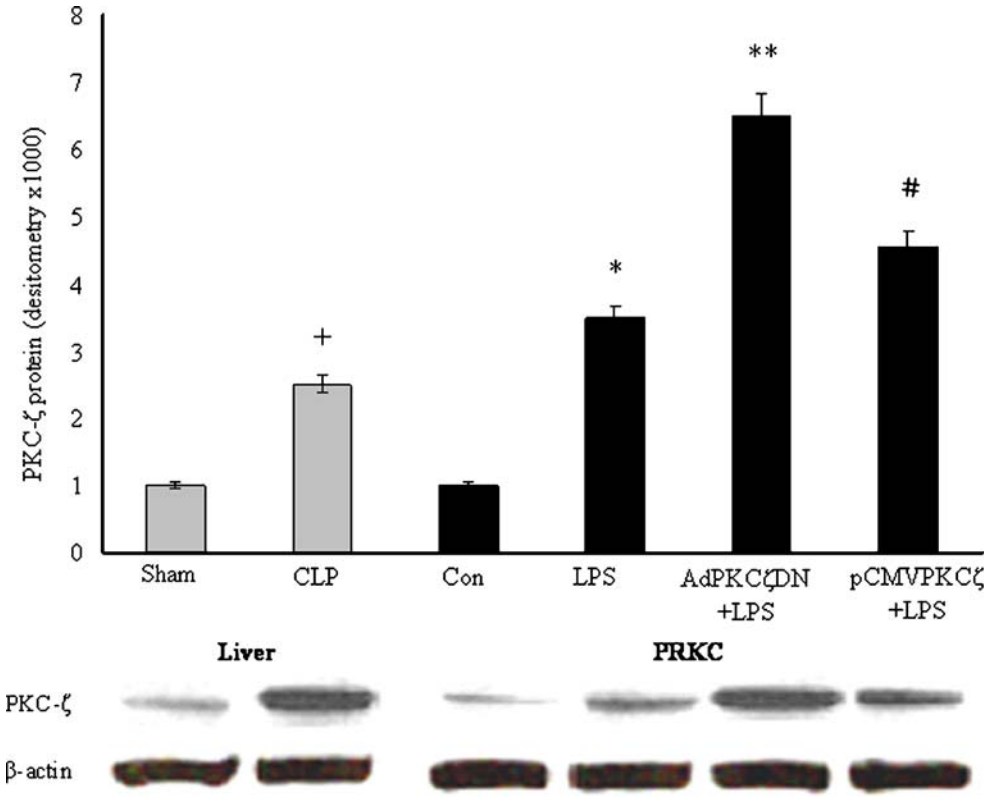


Figure 1 PKC-ζ protein expression increased in livers after sepsis (CLP) and LPS-treated PRKC (+,*$p<0.001$ vs sham). AdPKC-ζ DN increased (**$p<0.001$ vs AdLacZ + LPS, not shown), and pCMVPKC-ζ augmented ($^{\#}p<0.001$ vs pCMV. cDNA3.1 + LPS, not shown) the LPS-induced expression of PKC-ζ. *Panel* is a representative gel of PKC-ζ protein; the *bar graph* is densitometric quantification of $n\geq3$ immunoblots.

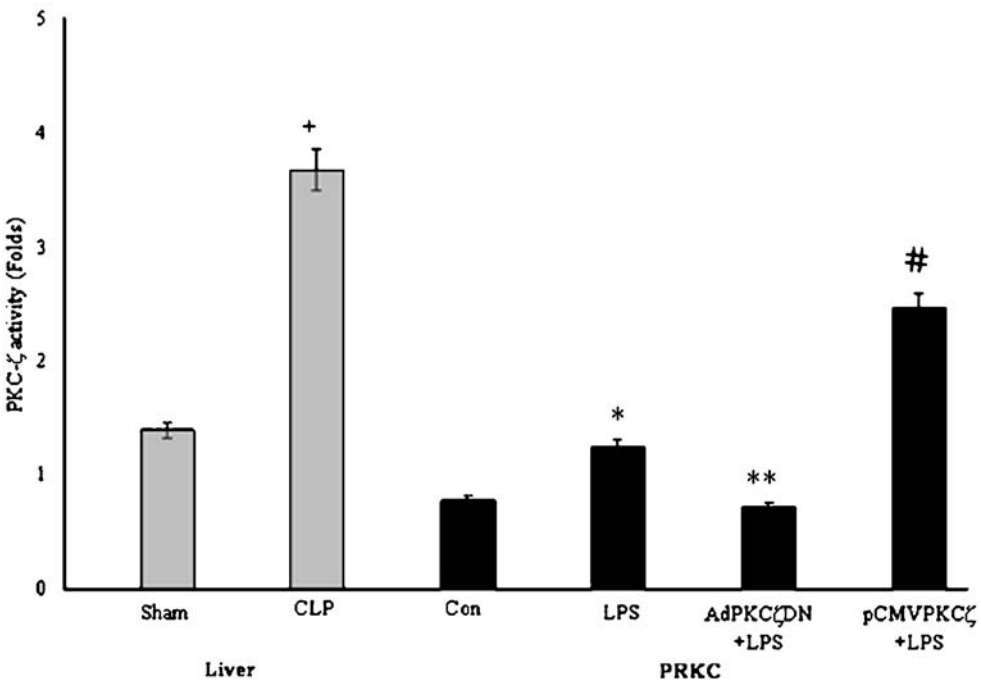


Figure 2 PKC-ζ activity increased in livers after sepsis (CLP) and LPS-treated PRKC (+,*$p<0.001$ vs Con). AdPKC-ζ DN attenuated (**$p<0.001$ vs AdLacZ + LPS, not shown), whereas pCMVPKC-ζ augmented ($^{\#}p<0.001$ vs pCMVcDNA3.1 + LPS, not shown) the LPS-induced upregulation of PKC-ζ activity.

ed the specificity of pCMVPKC-ζ (PKC-ζ protein: 2,468±30 vs 1,578±23, pCMVPKC-ζ+LPS vs pCMVcDNA3.1+LPS, $p<0.001$; PKC-ζ activity: 3.1±0.1 vs 4.6±0.2-folds; pCMVPKC-ζ+LPS vs pCMVcDNA3.1+LPS, $p<0.001$; data not shown).

Upregulation of Protein Kinases IKKβ and IKKγ but not IKKα in Both Rat Liver During CLP-Induced Sepsis and LPS-Treated PRKC

IKKβ and IKKγ were significantly increased in rat livers within 24 h after CLP compared to sham control ($p<0.001$, Fig. 3). IKKα was not upregulated by CLP-induced sepsis ($p>0.05$; data not shown).

Similarly, IKKβ and IKKγ were dramatically increased in LPS-treated PRKC (all $p<0.001$, Fig. 3). Infection with AdPKC-ζ DN attenuated the LPS-induced upregulation of IKKβ and IKKγ ($p<0.001$, Fig. 3). Viral infection control experiments confirmed the specificity of AdPKC-ζ DN (IKKβ protein: 698±18 vs 536±10; IKKγ protein: 768±18 vs 545±34, AdPKC-ζ DN+LPS vs AdLacZ+LPS, all $p<0.001$). Transfection with pCMVPKC-ζ augmented the LPS-induced upregulation of IKKβ and IKKγ, but not IKKα ($p<0.001$, Fig. 3).

Increasing Nuclear Translocation of p65/NF-κB in Both Rat Liver During CLP-Induced Sepsis and LPS-Treated PRKC

Nuclear translocation of p65/NF-κB significantly increased in rat liver during CLP-induced sepsis and LPS-treated PRKC compared to control ($p<0.001$, Fig. 4). Infection with AdPKC-ζ DN attenuated the LPS-induced nuclear translocation of p65/NF-κB ($p<0.001$, Fig. 4). In contrast, transfection with pCMVPKC-ζ augmented the LPS-induced nuclear translocation of p65/NF-κB translocation ($p<0.05$, Fig. 4).

Upregulation of Fas/FasL in Rat Liver During CLP-Induced Sepsis and LPS-Treated PRKC

Fas/FasL protein and mRNA were significantly upregulated in rat livers during CLP-induced sepsis and in LPS-treated PRKC compared to control (all $p<0.001$, Fig. 5). Infection with AdPKC-ζ DN dramatically attenuated the LPS-induced upregulation of Fas/FasL in PRKC (all $p<0.001$, Fig. 5). In contrast, transfection with pCMVPKC-ζ did not increase Fas/FasL in PRKC, but increased LPS-induced Fas/FasL mRNA (all $p<0.001$, Fig. 5).

Upregulation of Apoptosis in Rat Liver During CLP-Induced Sepsis and in LPS-Treated PRKC

Caspase-3 was significantly increased in rat livers 24 h after CLP-induced sepsis and in LPS-treated PRKC ($p<0.001$, Fig. 6). Infection with AdPKC-ζ DN inhibited the LPS-induced activation of Caspase-3 ($p<0.001$, Fig. 6). In contrast, transfection with pCMVPKC-ζ increased the LPS-induced activation of Caspase-3 ($p<0.001$, Fig. 6).

DNA Fragmentation

DNA fragmentation was increased in livers of rats with CLP-induced sepsis ($p<0.001$, Fig. 7). Similarly, DNA

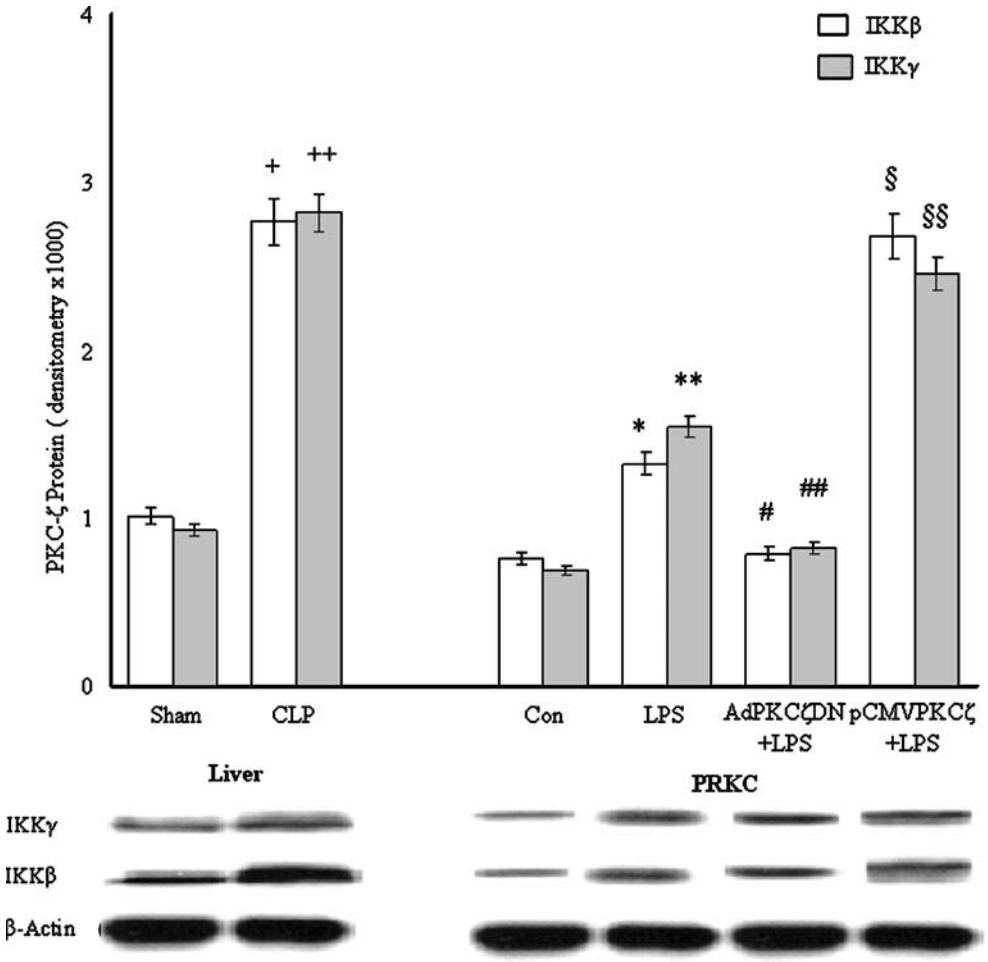


Figure 3 IKKβ/IKKγ protein increased in livers after sepsis (CLP; +, ++$p<0.001$ vs sham) and in LPS-treated PRKC (*, **$p<0.001$ vs Con). AdPKC-ζ DN attenuated ($^{\#}$, $^{\#\#}p<0.001$ vs AdLacZ + LPS, not shown), whereas pCMVPKC-ζ augmented (§, §§ vs pCMVcDNA3.1 + LPS, not shown) the LPS-induced upregulation of IKKβ/IKKγ. *Panel* is a representative gel of IKKβ/IKKγ/β-actin; the *bar graph* is densitometric quantification of $n \geq 3$ immunoblots.

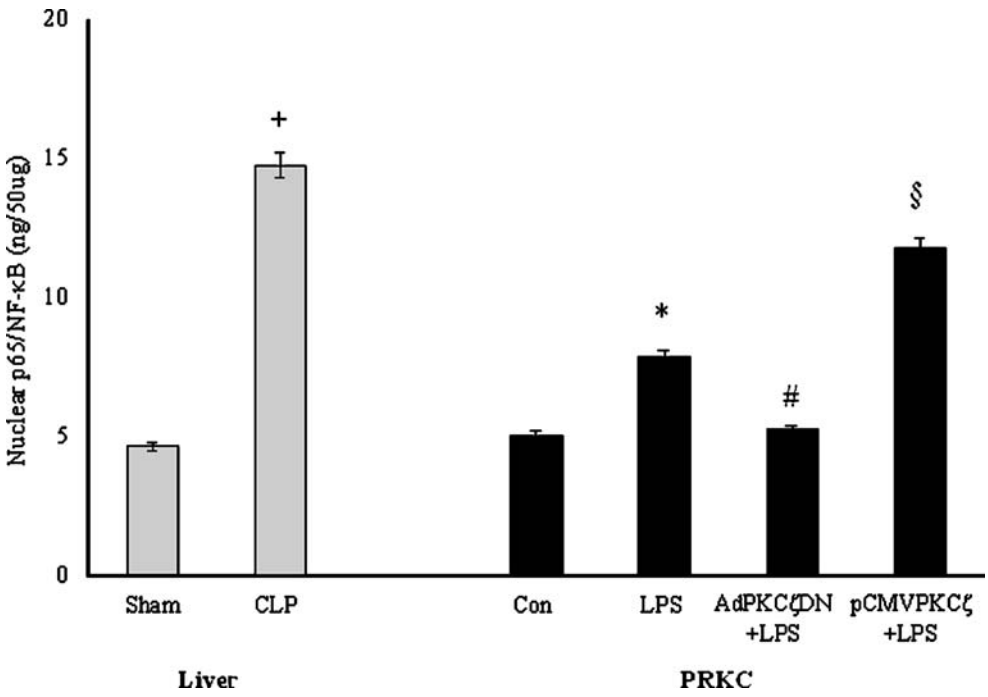


Figure 4 Nuclear translocation of p65/NF-κB increased in livers after sepsis (CLP; +$p<0.001$ vs sham) and in LPS-treated PRKC (*$p<0.001$ vs Con). AdPKC-ζ DN attenuated ($^{\#}p<0.001$ vs AdlacZ + LPS, not shown), and pCMVPKC-ζ augmented ($^{\S}p<0.05$ vs pCMVcDNA3.1 + LPS, data not shown) the LPS-induced activation of p65/NF-κB.

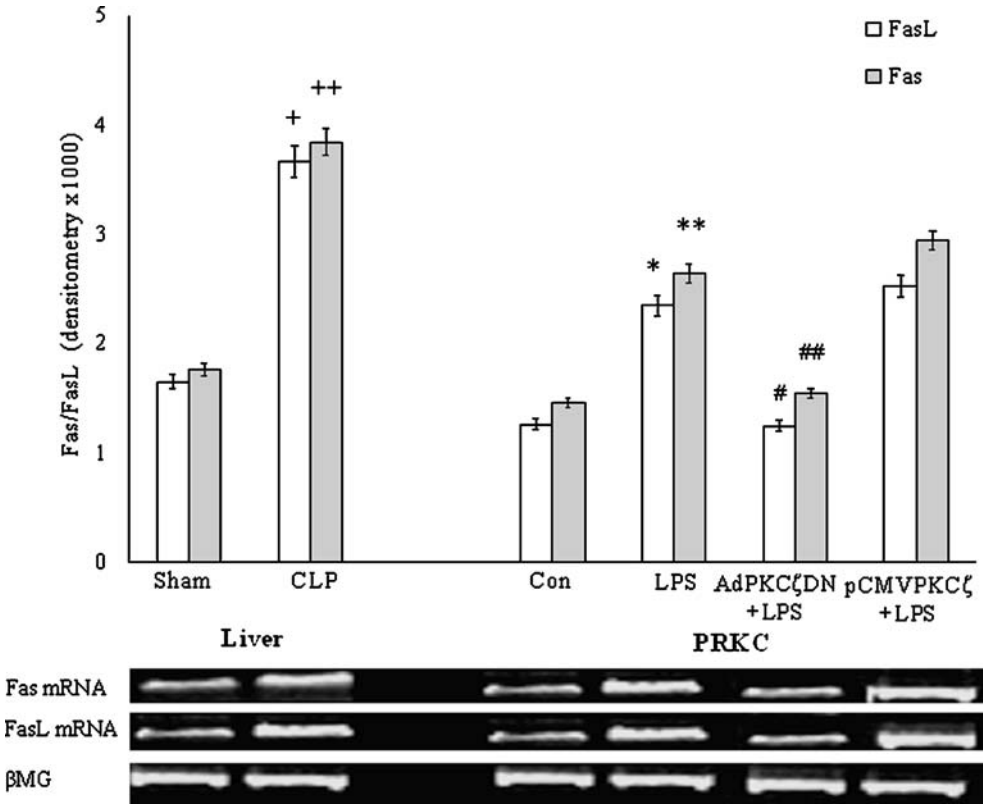


Figure 5 Fas/FasL protein and mRNA increased in livers after acute sepsis (CLP; +, ++$p<$ 0.001 vs sham), and in LPS-treated (LPS) PRKC (*, **$p<$ 0.001 vs Con). AdPKC-ζ DN attenuated the LPS-induced upregulation of Fas/FasL protein and mRNA (#, ## Fas/FasL protein, $p<0.001$ vs AdLacZ + LPS, not shown); whereas pCMVPKC-ζ did not augment the LPS-induced upregulation of Fas/FasL protein ($p>0.05$ vs pCMVcDNA3.1, data not shown), but augmented Fas/FasL mRNA. *Panel* is a representative RT-PCR; *bar graph* is densitometric quantification of $n\geq3$ immunoblots.

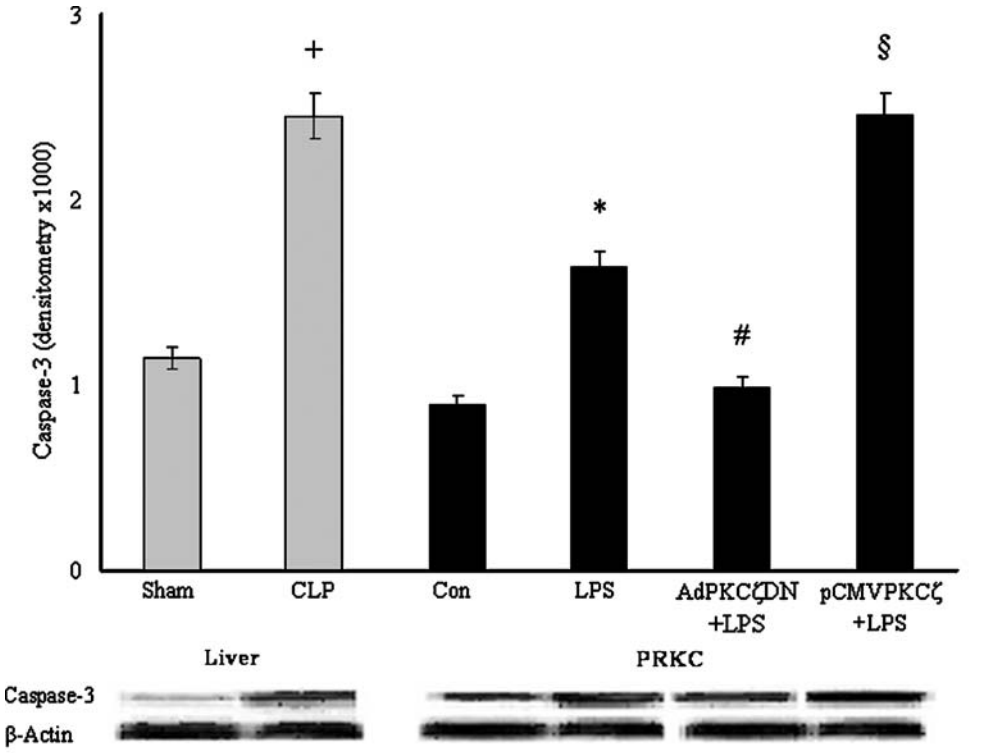


Figure 6 Cleaved Caspase-3 increased in livers after acute sepsis (CLP; +$p<0.001$ vs sham) and in LPS-treated (LPS) PRKC (*$p<0.001$ vs Con). AdPKC-ζ DN attenuated ($^{\#}p<$ 0.001 vs AdLacZ + LPS, data not shown), whereas pCMVPKC-ζ augmented ($^{\S}p<$ 0.001 vs pCMVcDNA3.1 + LPS, not shown) the LPS-induced Caspase-3 cleavage. *Panel* is a representative gel of cleaved Caspase-3; *bar graph* is densitometric quantification of $n\geq3$ immunoblots.

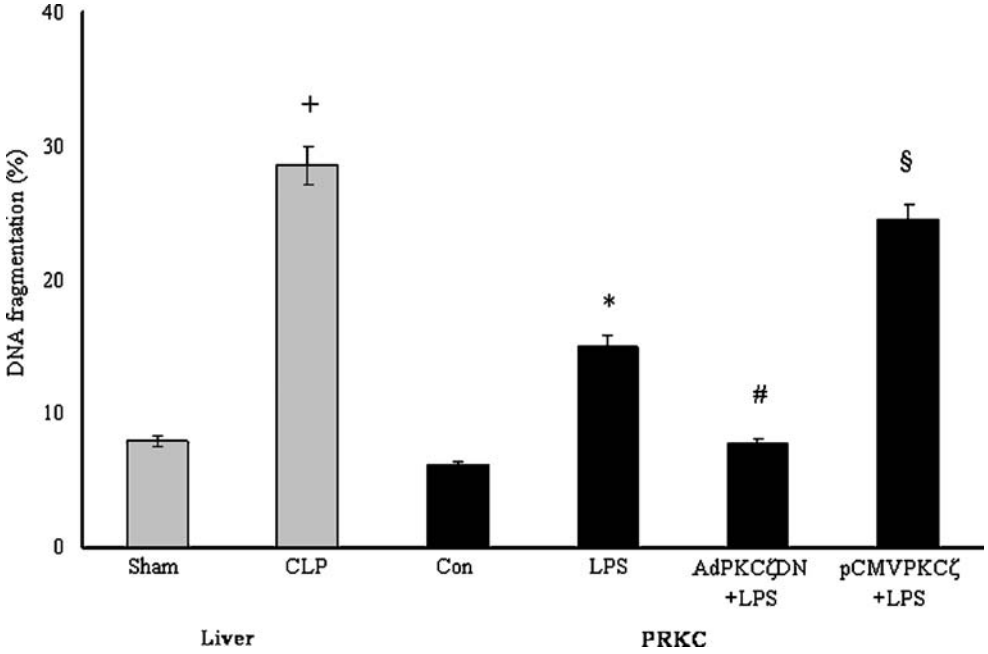


Figure 7 DNA fragmentation increased in livers after acute sepsis (CLP; $+p<0.001$ vs sham), and in LPS-treated (LPS) PRKC ($*p<0.001$ vs control). AdPKC-ζ DN attenuated ($^{\#}p<0.001$ vs AdLacZ + LPS, data not shown), whereas pCVMPKC-ζ augmented ($^{\S}p<0.001$ vs pCMVcDNA3.1 + LPS, data not shown) the LPS-induced DNA fragmentation.

fragmentation increased in PRKC treated with LPS ($p<0.001$, Fig. 7). Infection with AdPKC-ζ DN attenuated, while transfection with pCMV PKC-ζ increased the LPS-induced DNA fragmentation in PRKC (all $p<0.001$, Fig. 7).

F4/80 and PKC-ζ Co-Localize in Kupffer Cells

CLP-induced sepsis increased immunostaining for PKC-ζ in liver tissue (Fig. 8). CLP-induced PKC-ζ expression was predominantly localized in F4/80 positive cells, suggesting that Kupffer cells are the main source of PKC-ζ during CLP-induced sepsis.

Discussion

Liver injury is an important prognostic indicator in acute pancreatitis, trauma, and sepsis. Previously, we demonstrated that Kupffer-cell-derived TNF-α and Fas/FasL induce liver injury and hepatocyte apoptosis via NF-κB-dependent pathways.[2,5–7,12] Nonetheless, activated Kupffer cells upregulated their Fas receptors and underwent accelerated apoptosis, thereby suggesting that Kupffer cells modulate their stress response by upregulating their own cell death ligand receptors.[6,13,14] In these models of acute pancreatitis, we found that PKC-ζ plays a critical role in regulating both Kupffer cell stress response as well as apoptosis, similar to what others have previously reported.[15,16]

Although experimental acute pancreatitis induces many features of the septic response, it lacks the persistent and infectious nature of endotoxic shock. Therefore, we undertook this study to characterize the role of PKC-ζ in Kupffer cell apoptosis in an established model of sepsis.

Our data demonstrate that the activity of PKC-ζ is significantly increased in rat livers after CLP. Similarly, key signaling systems such as IKKβ, IKKγ, and p65/NF-κB are upregulated; Fas/FasL, cleaved Caspase-3, and DNA

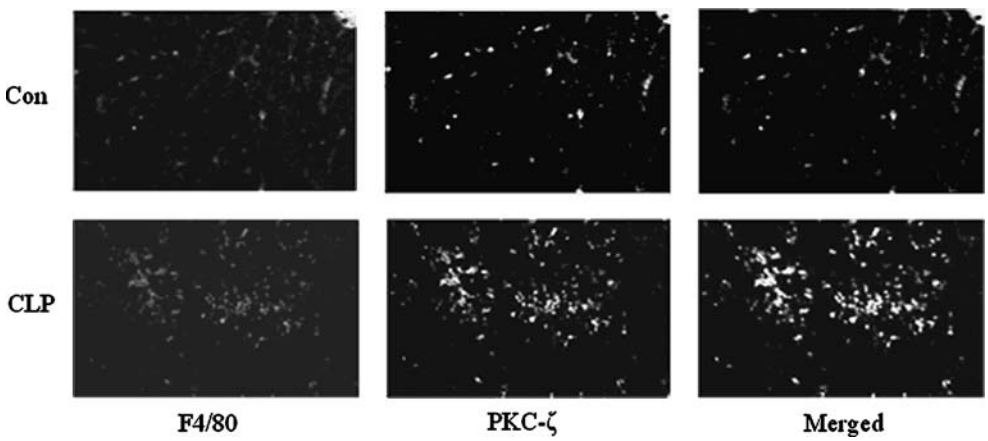


Figure 8 Sepsis (CLP) increased staining for PKC-ζ in livers compared to control. Staining for PKC-ζ localizes in cells stained for F4/80 as indicated by the merged photomicrographs. In color photomicrographs PKC-ζ is *green*, F4/80 is *red*, and the merged color is *yellow*.

fragmentation are also increased during sepsis compared to sham controls. The origin of the activated PKC-ζ is within Kupffer cells as demonstrated by co-localization of PKC-ζ and the macrophage marker F4/80 by immunofluorescence.

To further test the hypothesis that Kupffer cells are the source of PKC-ζ, we treated Kupffer cells with LPS in vitro. LPS mimicked CLP-induced sepsis by upregulating PKC-ζ, IKKβ, IKKγ, p65/ NF-κB, and Fas/FasL and increased cleaved Caspase-3 and DNA fragmentation within Kupffer cells. We confirmed the role of PKC-ζ in the response of Kupffer cells to LPS using a PKC-ζ dominant negative adenovirus; although AdPKC-ζ DN increased PKC-ζ protein, the activity of the mutant PKC-ζ was significantly reduced. Similarly, AdPKC-ζ DN attenuated the LPS-induced upregulation of IKKβ, IKKγ, p65/NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation. As expected, overexpression of PKC-ζ by infection with pCMVPKC-ζ augmented the LPS-induced upregulation of PKC-ζ activity, IKKβ, IKKγ, p65/NF-κB, Fas/FasL, Caspase-3, and DNA fragmentation.

These findings, similar to what we have reported in experimental acute pancreatitis,[6,7,17,18] give further insight into the role of PKC-ζ. PKC-ζ and NF-κB share many signaling systems and target genes that are important in sepsis and inflammation. Moreover, the two members of the subfamily of protein kinase C, atypical, PKC-ζ and PKC-λ, have been implicated in the activation of NF-κB in vitro in response to several stimuli[15,19]; specifically, PKC-ζ regulates NF-κB by phosphorylation of RelA Ser 311.[16]

Most likely, PKC-ζ phosphorylates IKKβ, IKKγ and activates NF-κB; however, we cannot be certain whether PKC-ζ directly modifies p65/NF-κB at some potential phosphorylation sites.[16] In a model of acute pancreatitis, we demonstrated that PKC-ζ interacts physically with ERK1/2 and not directly with NF-κB in Kupffer cells.[17]

Although IKKβ and γ are upregulated, IKKα exhibited no change in Kupffer cells. Despite structural and biochemical similarities, IKKα and IKKβ have distinctly different functions. Whereas IKKβ is essential for NF-κB activation in response to pro-inflammatory and innate immune stimuli, IKKα is not required for such response.[20]

These observations suggest that PKC-ζ may be a critical upstream regulator of NF-κB and are corroborated by the fact that we were not able to abolish cytokine production from Kupffer cells utilizing adenoviral gene transfection and siRNA to silence NF-κB.[7] These findings are consistent with other reports that PKC-ζ is essential for endotoxin-induced activation of macrophages and nuclear translocation of NF-κB.[21]

Modulating the expression of PKC-ζ has a direct effect on Kupffer cells apoptosis and consequently on their cytokine production; the ability of Kupffer cells to autoregulate their stress response warrants further investigation.

Acknowledgment This study was supported by the VA Merit Award (MM) and Dr. Bob Haines Pancreatitis Research Fund (MM).

References

1. Keller SA, Paxian M, Ashburn JH, Clemens MG, Huynh T. Kupffer cell ablation improves hepatic microcirculation after trauma and sepsis. J Trauma 2005;58(4):740–749; discussion 749–751.
2. Murr MM, Yang J, Fier A, Kaylor P, Mastorides S, Norman JG. Pancreatic elastase induces liver injury by activating cytokine production within Kupffer cells via nuclear factor-Kappa B. J Gastrointest Surg 2002;6(3):474–480.
3. Diehl AM. Nonalcoholic steatosis and steatohepatitis IV. Nonalcoholic fatty liver disease abnormalities in macrophage function and cytokines. Am J Physiol Gastrointest Liver Physiol 2002;282 (1):G1–5.
4. Tsung A, Hoffman RA, Izuishi K, Critchlow ND, Nakao A, Chan MH, Lotze MT, Geller DA, Billiar TR. Hepatic ischemia/ reperfusion injury involves functional TLR4 signaling in nonparenchymal cells. J Immunol 2005;175(11):7661–7668.
5. Murr MM, Yang J, Fier A, Gallagher SF, Carter G, Gower WR, Jr, Norman JG. Regulation of Kupffer cell TNF gene expression during experimental acute pancreatitis: the role of p38-MAPK, ERK1/2, SAPK/JNK, and NF-kappaB. J Gastrointest Surg 2003;7 (1):20–25.
6. Gallagher SF, Peng Y, Haines K, Baksh K, Epling-Burnette PK, Yang J, Murr MM. Fas/FasL play a central role in pancreatitis-induced hepatocyte apoptosis. J Gastrointest Surg 2005;9(4):467–474; discussion 474–475.
7. Peng Y, Gallagher SF, Haines K, Baksh K, Murr MM. Nuclear factor-kappaB mediates Kupffer cell apoptosis through transcriptional activation of Fas/FasL. J Surg Res 2006;130(1):58–65.
8. Duran A, Rodriguez A, Martin P, Serrano M, Flores JM, Leitges M, Diaz-Meco MT, Moscat J. Crosstalk between PKCzeta and the IL4/Stat6 pathway during T-cell-mediated hepatitis. EMBO J 2004;23(23):4595–4605.
9. Leroy I, de Thonel A, Laurent G, Quillet-Mary A. Protein kinase C zeta associates with death inducing signaling complex and regulates Fas ligand-induced apoptosis. Cell Signal 2005;17 (9):1149–1157.
10. Xiong S, She H, Sung CK, Tsukamoto H. Iron-dependent activation of NF-kappaB in Kupffer cells: a priming mechanism for alcoholic liver disease. Alcohol 2003;30(2):107–113.
11. Standaert ML, Galloway L, Karnam P, Bandyopadhyay G, Moscat J, Farese RV. Protein kinase C-zeta as a downstream effector of phosphatidylinositol 3-kinase during insulin stimulation in rat adipocytes. Potential role in glucose transport. J Biol Chem 1997;272(48):30075–30082.
12. Yang J, Gallagher SF, Haines K, Epling-Burnette PK, Bai F, Gower WR, Jr, Mastorides S, Norman JG, Murr MM. Kupffer cell-derived Fas ligand plays a role in liver injury and hepatocyte death. J Gastrointest Surg 2004;8(2):166–174.
13. Canbay A, Feldstein AE, Higuchi H, Werneburg N, Grambihler A, Bronk SF, Gores GJ. Kupffer cell engulfment of apoptotic bodies stimulates death ligand and cytokine expression. Hepatology 2003;38(5):1188–1198.
14. Chung CS, Song GY, Lomas J, Simms HH, Chaudry IH, Ayala A. Inhibition of Fas/Fas ligand signaling improves septic survival: differential effects on macrophage apoptotic and functional capacity. J Leukoc Biol 2003;74(3):344–351.
15. Moscat J, Diaz-Meco MT, Rennert P. NF-kappaB activation by protein kinase C isoforms and B-cell function. EMBO Rep 2003;4 (1):31–36.

16. Duran A, Diaz-Meco MT, Moscat J. Essential role of RelA Ser311 phosphorylation by zetaPKC in NF-kappaB transcriptional activation. EMBO J 2003;22(15):3910–3918.
17. Peng Y, Sigua CA, Gallagher SF, Murr MM. Deletion of toll-like receptor-4 downregulates protein kinase C-zeta and attenuates liver injury in experimental pancreatitis. Surgery 2007 (under revision).
18. Peng Y, Sigua CA, Gallagher SF, Murr MM. Protein kinase C-zeta is critical in pancreatitis-induced apoptosis of Kupffer cells. J Gastrointest Surg 2007;11:1253–1261.
19. Moscat J, Diaz-Meco MT. The atypical protein kinase Cs. Functional specificity mediated by specific protein adapters. EMBO Rep 2000;1(5):399–403.
20. Ruocco MG, Karin M. IKK{beta} as a target for treatment of inflammation induced bone loss. Ann Rheum Dis 2005;64 Suppl 4:iv81–85.
21. Dallot E, Mehats C, Oger S, Leroy MJ, Breuiller-Fouche M. A role for PKCzeta in the LPS-induced translocation NF-kappaB p65 subunit in cultured myometrial cells. Biochimie 2005;87 (6):513–521.

J Gastrointest Surg (2007) 11:1722–1727
DOI 10.1007/s11605-007-0320-y

Gallbladder Cancer with Duodenal Infiltration: Is it still resectable?

Anil K. Agarwal · Sanjoy Mandal · Shivendra Singh · Puja Sakhuja · Sunil Puri

Received: 14 May 2007 / Accepted: 3 September 2007 / Published online: 29 September 2007

Abstract
Objective To assess the resectability and the long-term survival in patients of gallbladder cancer with duodenal involvement.
Background Duodenal infiltration in patients of carcinoma gallbladder is generally regarded as a sign of advanced disease and an indicator of unresectable disease.
Methods A total of 252 patients of gallbladder cancer (GBC) who underwent surgery over a 5-year period were studied for duodenal involvement. Patients with duodenal infiltration on per-operative assessment were analyzed for resectability, postoperative morbidity, mortality and disease free survival.
Results Forty-three patients were detected to have duodenal infiltration on per-operative assessment out of which 17 had unresectable disease (39.54%), whereas the remaining 26 patients underwent R0 resection (61.9%). Of these, nine underwent distal gastrectomy with resection of the first part of the duodenum (34.62%), 16 underwent duodenal sleeve resection (61.54%), and in one patient pancreatoduodenectomy (HPD) (3.85%) was performed. With regard to the extent of liver resection, two underwent extended right hepatectomy, whereas the remaining 24 underwent segment IVB and V resection. Bile duct and adjacent viscera were resected when involved. Of the resected patients, eight underwent bile duct excision, seven had colonic resection, and three had vascular resection and reconstruction. The postoperative morbidity and mortality was 15 (34.9%) and three (6.97%), respectively, in the resected group of patients. The overall actual survival in the resected group was a mean of 15.87 months, median of 14 months (range 3 to 56 months).
Conclusion Duodenal infiltration is neither an indicator of unresectability nor an indication to perform Hepato-pancreatoduodenectomy (HPD). In most of these patients, an oncologically adequate R0 resection can be performed with either a duodenal sleeve resection or distal gastrectomy with resection of the first part of the duodenum.

Keywords Gall bladder cancer (GBC) · GBC with duodenal infiltration · Advanced gall bladder cancer · Carcinoma gall bladder

A. K. Agarwal (✉) · S. Mandal · S. Singh
Department of Gastrointestinal Surgery,
GB Pant Hospital & Maulana Azad Medical College,
JLN Marg,
New Delhi 110002, India
e-mail: aka.gis@gmail.com

P. Sakhuja
Department of Pathology,
GB Pant Hospital & Maulana Azad Medical College,
New Delhi, India

S. Puri
Department of Radiology,
GB Pant Hospital & Maulana Azad Medical College,
New Delhi, India

Introduction

Gallbladder cancer (GBC) has long been known to have a poor outcome.[1,2] It is generally believed that only early stage tumors limited to the mucosa or muscle layer can have a satisfactory outcome with simple cholecystectomy or extended cholecystectomy with lymph node clearance.[3,4] Despite great advancement in diagnostic techniques, majority of gall bladder malignancies are diagnosed at advanced stages, when radical surgery is either not feasible

or when feasible is noncurative with only a limited increase in survival.[5–7] A significant number of these advanced cases include tumors that infiltrate the duodenum. Duodenal infiltration in patients of gall bladder cancer has been regarded as a sign of advanced disease and an indicator of unresectability.[8,9] Most of these studies have documented unresectability in these groups of patients and those in whom it has been resectable, the long-term survival has been very poor. However, recently some authors, especially from Japan, have shown improved survival with aggressive resection. These studies from Japan and some also from the west have reported that gall bladder cancer with duodenal infiltration merits an associated pancreatoduodenectomy (PD) to accomplish R0 resection and allow good long-term survival.[10–14]

We have analyzed our prospectively collected data of gall bladder cancer to assess the resectability in patients with duodenal involvement, the necessity of hepatopancreatoduodenectomy (HPD) in these patients and the long-term survival.

Materials and Methods

The prospectively collected data of patients undergoing surgery for carcinoma of the gall bladder between January 2000 and December 2004 in the Department of Gastrointestinal Surgery, Gobind Ballabh Pant Hospital, New Delhi, a tertiary care referral and teaching hospital of Northern India, was analyzed. The standard preoperative workup included abdomen ultrasound with Doppler for the assessment of portal vein and hepatic artery involvement and contrast-enhanced computed tomography (CT) of the abdomen. Magnetic Resonance Imaging with Magnetic Resonance Cholangio-pancreatography (MRCP) was obtained in selected patients, particularly those with associated bile duct involvement. All the patients underwent an upper gastrointestinal tract endoscopy (UGIE) to look for any gastroduodenal involvement. UGIE evidence of involvement was defined as external compression, obvious infiltration of tumor into the lumen, or gastric outlet obstruction. Assessment of involvement on UGIE was further categorized into two types: "A" when there was only external compression but no evidence of gastric outlet obstruction (GOO); and "B" when there was obvious infiltration of the tumor into the lumen or gastric outlet obstruction. Endosonography for evaluation of the tumors was not performed in our study. Patients who appeared to be resectable on preoperative imaging underwent surgery with a curative intent, whereas some of the patients considered to have unresectable disease underwent palliative procedure. Those patients with distant metastasis, who otherwise did not require palliation, were not operated upon. Informed consent was taken of all patients in accordance with ethical standards of our institution (ethical standards of the Helsinki Declaration of 1975). Routine staging laparoscopy was introduced in the later part of the study (from September 2002) during which all subsequent patients underwent staging laparoscopy before definitive surgery under the same anesthesia to detect occult distant metastasis. Doubtful lesions were biopsied and sent for frozen section. Laparoscopic ultrasound and extensive mobilization was not included. Patients who were subsequently considered to be resectable or required palliation underwent laparotomy. Patients who proceeded to laparotomy underwent routine sampling of the inter-aortocaval lymph node for frozen section analysis. Wide kocherization of the duodenum and division of the gastrocolic omentum was performed and involvement of the pyloroduodenal area and head of the pancreas was assessed. In patients with a small area of duodenal infiltration where it was expected that there would be no luminal compromise after sleeve resection of the duodenum, we would perform the same. In the presence of more significant duodenal infiltration but no evidence of pancreatic involvement, where luminal compromise was expected after a simple sleeve resection, we would perform a distal gastrectomy with resection of the first part of the duodenum (D1). Bowel continuity in such case would be restored by a gastro-jejunostomy (GJ). We would perform pancreatoduodenectomy (PD) only if there was extensive peripancreatic lymph nodes, which could not be otherwise cleared, or direct involvement of the head of pancreas.

Resected specimens were analyzed histopathologically. Pathological staging was done according to the 6th edition of the AJCC TNM staging handbook[14] and the long-term survival of the patients who underwent R0 resection was analyzed. Resectabilty of the tumors with regards to the preoperative imaging was analyzed.

Statistical analysis has been carried out with the help of statistical software SPSS 10.0, copyright© SPSS, Inc, USA, 1989–1999. Survival was calculated by Kaplan–Meier method and statistical significance by Log rank test and Fisher's exact test.

Results

The total number of patients of GBC operated during this period was 252. The male-to-female ratio was 1:3. The mean age of our patients was 49.8 years (20 to 80 years). On preoperative workup, 65 patients (25.79%) were suspected to have duodenal infiltration on cross-sectional imaging (CECT and/or MRI). Out of these 19 patients were found to have gastroduodenal involvement on endoscopy (Type B) in the form of gastric outlet obstruction or obvious

infiltration (7.54%, 19 of 252; 29.23%, 19 of 65). Only external compression on endoscopy (Type A) was seen in 21 (8.33%, 21 of 252; 32.3%, 21 of 65) of our patients.

On per-operative assessment, 43 out of the 252 (17.06%) were found to have duodenal involvement. Out of the 65 patients with duodenal involvement on CT or MR, 35 actually had duodenal involvement out of which 18 were resectable (51.42%). All (100%) of the 19 patients who had type B involvement on endoscopy had actual involvement, and out of these only two (10.53%) were resectable. Out of the 21 patients with type A involvement, six had actual involvement of the duodenum, whereas 15 did not. Of these six patients, four were resectable, whereas two were unresectable. There were eight patients who had duodenal involvement, which was neither detected on imaging nor on endoscopy, and all eight of them were resectable (Table 1).

The sensitivity and specificity of CT and MRI for detecting duodenal involvement was 81.4% and 85.64%, whereas for UGIE it was 75.76% and 93.15% (Table 2).

The mean age in this group of patients with duodenal involvement (n=43) was 50.16 years (range 22–70 years). The male-to-female ratio was 1:3. Out of the 43 patients, 17 (39.54%) were unresectable on account of locally unresectable disease in 10 patients, positive inter-aortocaval lymph node in three, noncontiguous liver metastasis in two, and peritoneal metastasis in two patients. Out of these 17 patients, five were considered to have unresectable disease on preoperative imaging and hence were taken up for surgery with palliative intent. The rest 26 (61.9%) patients were resectable and underwent R0 resection. Among the patients who underwent resection, segment IVB and V resection was performed in 24, whereas two patients underwent extended right hepatectomy. All 26 patients underwent standard lymph node dissection. Common bile duct excision was performed in 15 patients, in eight on account of bile duct involvement by the tumor, in five for adequate lymph node clearance, in one for positive cystic duct margin, and in one on account of associated choledochal cyst. Reconstruction was done in the form of roux-en-Y hepaticojejunostomy. Segmental colonic resection was performed in seven and vascular resection and reconstruction in three patients. With regard to the duodenal resection in 26 patients, 16 underwent sleeve resection of the duodenum, nine underwent distal gastrectomy and excision of the first part of the duodenum (DG & D1), whereas only one patient underwent PD (Table 3). Four patients underwent completion radical cholecystectomy for incidental GBC, two of which underwent duodenal sleeve resection, whereas the other two underwent DG & D1 resection.

Among the unresectable group, only gastrojejunostomy (GJ) was performed in 10, gastrojejunostomy with segment III bypass in six, and feeding jejunostomy (FJ) in one. Overall, 18 out of 43 patients (41.86%) had postoperative complications. In the resected Group, 15 out of 26 patients had complications (57.69%), whereas in the palliative group, three out of 17 (17.65%) had complications. The details of the morbidity are given in Table 4 Overall mortality was 6.97% (three out of 43 patients). All the deaths were in the resected group—three out of 26patients (11.54%). The cause of death was anastomotic leak and sepsis in two patients (one from RYHJ site and the other from the duodenal stump) and postoperative bleed in one. The mean hospital stay of our patients was 14.38 days, median of 12 days, and range of 9 to 97 days.

Twenty-four patients resected had evidence of histopathologic involvement of the duodenum with varying depths of

Table 1 Preoperative Investigation

Investigation modality	Suspected involvement	Actual involvement	Resectable
CT/MR	65	35 (53.85%)	18 (51.42%)
UGIE* (combined)	40	25 (62.5%)	6 (24%)
UGIE* (Type B)	19	19 (100%)	2 (10.53%)
UGIE* (Type A)	21	6 (28.57%)	4 (66.67%)
Unsuspected	–	8	8 (100%)

*Upper gastrointestinal endoscopy

Table 2 Sensitivity, Specificity, and Predictive Value of Preoperative Investigations

Investigation	Sensitivity (%)	Specificity (%)	Predictive value (%)	
			Negative	Positive
CT/MR	81.4	85.64	95.72	53.85
UGIE (combined)	75.76	93.15	96.23	62.5
UGIE*(Type B)	44.19	100	89.7	100
UGIE*(Type A)	42.86	93.7	96.54	28.57

*Upper gastrointestinal endoscopy

Table 3 Extent of Resection Performed (n=26)

Extent of resection	*N*
1. Extent of liver resection	
a. Seg IVB & V wedge	24
b. Extended right hepatectomy	2
2. CBD excision	
a. Associated jaundice	8
b. LN clearance	5
c. Positive cystic duct margin	1
d. Choledochal cyst	1
3. Duodenum excision	
a. Sleeve	16
b. Distal gastrectomy & D1 excision	9
c. Pancreatoduodenectomy (as a part of HPD)	1
4. Colon resection	7
5. Vascular reconstruction	3

Table 4 Postoperative Complications in the Resected and Palliative Group

Complication	Palliative surgery (n=17)	Resected group (n=26)	Combined (n=43)	P value
Wound infection	3 (17.65%)	8 (30.77%)	11 (25.58%)	0.480 (NS)
Chest infection	0 (0%)	5 (19.23%)	5 (11.63%)	0.139 (NS)
Bile leak	2 (11.77%)	3 (11.54%)	5 (11.63%)	0.685 (NS)
Acsites leak	2 (11.77%)	3 (11.54%)	5 (11.63%)	0.685 (NS)
Sepsis	0 (0%)	2 (7.69%)	2 (4.65%)	0.511 (NS)
Bleeding	0 (0%)	1 (3.85%)	1 (2.33%)	1.000 (NS)
Overall	3 (17.65%)	15 (57.69%)	18 (41.86%)	0.013 (Sig)

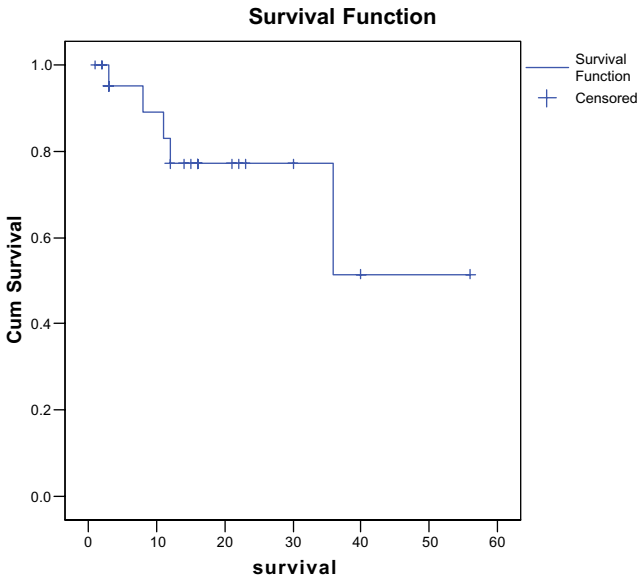


Figure 1 Kaplan–Meier survival curves (overall survival; n=23).

invasion. Involvement of only the serosa was seen in 10 (one patient of incidental GBC had few atypical cells in the serosa), infiltration up to the muscularis in seven, up to the submucosa in three, and up to the mucosa in four. Whereas, the remaining two patients did not have any evidence of tumor in the specimen (both these patients had incidental GBC). Stagewise distribution of the disease of the 26 resected patients showed four patients in stage IIA, three in stage IIB, 18 in III, and one in IV. Of the 23 patients who were discharged, we have a complete follow up available of 17 patients.

The overall actual survival in the 23 patients was a mean of 15.87 months, median of 14 months, range of 3 to 56 months and a 1- and 3-year actual survival of 60.87% and 13.04%, respectively. The 1, 2, and 3 years overall actuarial survival in our patients was 76.64%, 76.64%, and 51.09%, respectively.

Survival calculated from the Kaplan–Meier survival curves for all the patients (n=23) (Figs. 1 and 2) was a mean of 40 months (95% Confidence Interval [CI] of 29 and 52). The same for stage IIA disease was a mean of 31 months (95% CI of 24 and 38) and median of 36 months (95% CI of 2 and 70). By log-rank test survival when compared with different stages of disease survival was statistically significant (p value 0.0364).

Discussion

Duodenal involvement was seen in 17.06% (n=43) of GBC patients who underwent surgery at our institution. Duodenal infiltration was detected in 35 out of the 43 patients (81.4%) on preoperative imaging, whereas in eight patients it was neither detected on imaging nor on endoscopy. All these eight patients, were found to be resectable. On the other hand, out of the 65 patients who had suspected involvement on imaging, only 35 (53.85%) had actual involvement. Out of these 35 patients, 18 (51.42%) were resectable. In comparison, out of the 19 patients who had type B involvement on endoscopy, all 19 had actual involvement, two of which (10.53%) were resectable. On the contrary, patients with type A involvement on UGIE had a lower incidence of actual infiltration (28.57%) and a higher resectability (66.67%). These data would imply patients who were incidentally detected to have duodenal infiltration had higher probability of having a resectable disease. Patients with limited involvement on endoscopy (external compression alone) were more likely to have

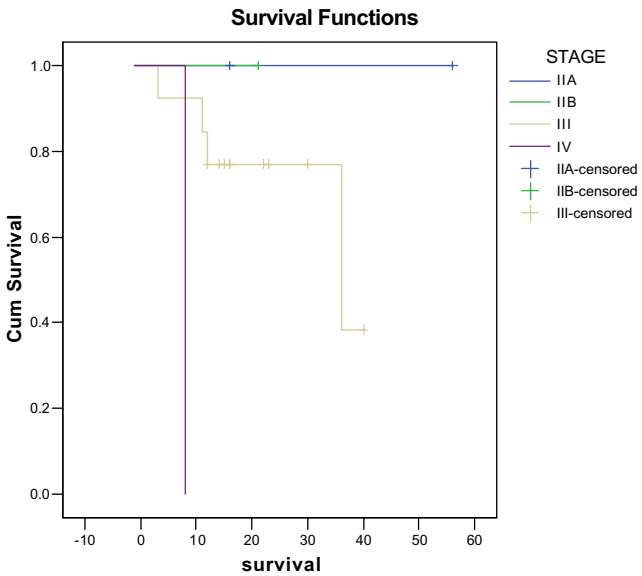


Figure 2 Kaplan–Meier survival curves (stage-wise survival).

resectable diseases compared to patients with more extensive involvement in form of mucosal involvement or complete duodenal obstruction.

It is apparent that although these investigations help in preoperative detection of duodenal infiltration and to some extent the resectability, the overall management does not change.

Imaging is more sensitive, whereas endoscopy has high specificity and a high positive predictive value. With regard to the type of involvement on UGIE, type B is more sensitive and specific and has greater positive predictive value, whereas type A has greater negative predictive value. Simple external compression is a poor positive predictor of duodenal involvement (28.57%). This would imply that in several patients, because of the anatomical proximity, a large mass in the gall bladder could create an impression on the duodenum without actual tumor infiltration. To this end, endosonography may be more reliable. However, although there are studies that have dealt with endosonography in the assessment of the T-stage of GBC, but none has assessed duodenal infiltration with this modality.[16,17]

All the patients in our series underwent a R0 resection. The majority of our resections were segment IVB & V wedge resection, only two underwent extended right hepatectomy. With regard to the resection performed on the duodenum most underwent either duodenal sleeve resection or distal gastrectomy and D1 resection, only one patient underwent pancreatodudenectomy.

The stage-wise distribution of our patients has shown that most of our patients were in stage III (Table 5). The best survival was seen in patients with stage IIA disease. Stage of disease was a significant factor in predicting survival (p value 0.0364).

Some of the older studies that have dealt with this entity have essentially concluded that gastric outlet obstruction in gall bladder cancer is an advanced disease and can only be palliated.[18,19] These studies have not specifically analyzed the spectrum of duodenal infiltration, which can occur without gastric outlet obstruction being present. Our study reveals that in the absence of symptomatic duodenal infiltration the resectability is high and that although patients with gastric outlet obstruction have a high chance of unresectability, it should not be used as the sole criteria for unresectability. Most studies do not analyze the involvement of the duodenum in gall bladder cancer. Most Japanese literature recommends performing HPD for involvement of the duodenum, pancreas, and lymph node clearance. Majority of these studies have not clearly defined the incidence of duodenal infiltration and comparisons with our study cannot be made.[13–15,20,21] Kondo et al., have shown that radical surgery in GBC patients with duodenal involvement had a postoperative mortality of 28%, which was higher than those without duodenal infiltration but was not statistically significant. This higher mortality rate as compared to our study (11.54%) could be caused by the fact they had performed extended right hepatectomy, HPD with or without portal vein resection in a significant number of their patients. Among their patients with duodenal involvement, the 3-year survival was 14%, which is similar to the 13.04% in our study.[10] Nakamura et al, in their patients of advanced GBC infiltrating the duodenum and pancreas (seven patients) who had undergone HPD, reported that the 1- and 2-year survival rates were 57% and 28.6%, respectively, with a median survival time of 12 months.[22] Nimura et al. in their 14 patients of advanced GBC, who underwent HPD, reported a median survival of 12.4 months and a 2-year survival rate of 20.8%.[23] Nagakawa et al., in a collective review of Japanese literature of HPD being performed in 355 GBC patients with surrounding organ infiltration over a period of 10 years, reported a 5-year survival of more than 10%.[24]

The long-term survival advantage of this policy has been debated. In fact, some studies have shown that the overall long-term survival is limited, with only very limited survival advantage seen in patients with positive lymph nodes but no obvious hepatoduodenal infiltration (21). There are, however, other studies that have shown that resection of such advanced GBC leads to significant increase in survival and a better quality of life (20). Thus, in view of the current literature and our results, we believe that minor duodenal infiltration with no luminal compromise can be resected with sleeve resection, whereas advanced involvement of a significant portion of the circumference with the possibility of luminal compromise requires distal gastrectomy and excision of the first part of the duodenum, and pancreatoduodenectomy is only reserved for more extensive involvement. We do not perform HPD unless there are extensive peripancreatic lymph nodes,

Table 5 Correlating Actual Survival with Stage of Disease (6th Edition AJCC TNM)

Stage	*N*	Minimum	Maximum	Range	Mean	Std. deviation	Median	Std. error of mean
IIA	3	3	56	53	25.00	27.622	16.00	15.948
IIB	3	2	21	19	8.67	10.693	3.00	6.173
III	16	1	40	39	16.00	11.770	14.50	2.943
IV	1	8	8	0	8.00	–	8.00	–
Total	23	1	56	55	15.87	13.981	14.00	2.915

which cannot be otherwise cleared, tumor extension into the head of pancreas or advanced duodenal infiltration where pancreas preserving duodenectomy is not possible.

Conclusion

Duodenal infiltration in gall bladder cancer does not preclude resection. It should not be taken as sole indicator of performing HPD. R0 resection can be achieved with limited surgical procedure without resorting to HPD in most cases, and survival depends on the overall stage of the disease.

References

1. Chattopadhyay TK, Kumar A, Kapoor VK, Sharma LK, Kapur MM, Kapur BM, Dhawan IK. Carcinoma of the gall bladder—can we do anything? Postgrad Med J 1988;64(754):593–595.
2. Hawkins WG, DeMatteo RP, Jarnagin WR, Ben-Porat L, Blumgart LH, Fong Y. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. Ann Surg Oncol 2004 Mar;11(3):310–315.
3. Ouchi K, Suzuki M, Tominaga T, Saijo S, Matsuno S. Survival after surgery for cancer of the gallbladder. Br J Surg 1994 Nov;81 (11):1655–1657.
4. Frezza EE, Mezghebe H. Galbladder carcinoma: a 28-year experience. Int Surg 1997;82:295–300.
5. Okamoto A, Tsuruta K, Ishiwata J, Isawa T, Kamisawa T, Tanaka Y. Treatment of T3 and T4 carcinomas of the gallbladder. Int Surg 1996;81(2):130–135.
6. Ruckert JC, Ruckert RI, Gellert K, Hecker K, Muller JM. Surgery for carcinoma of the gallbladder. Hepatogastroenterology;43 (9):527–533.
7. Benoist S, Panis Y, Fagniez PL. Long-term results after curative resection for carcinoma of the gallbladder. French University Association for Surgical Research. Am J Surg 1998;175(2):118–122.
8. Cubertafond P, Gainant A, Cucchiaro G. Surgical treatment of 724 carcinomas of the gallbladder. Results of the French Surgical Association Survey. Ann Surg 1994;219(3):275–280.
9. Wilkinson DS. Carcinoma of the gall-bladder: An experience and review of the literature. Aust N Z J Surg 1995;65(10):724–727. Review.
10. Kondo S, Nimura Y, Kamiya J, Nagino M, Kanai M, Uesaka K, Yuasa N, Sano T, Hayakawa N. Factors influencing postoperative hospital mortality and long-term survival after radical resection for stage IV gallbladder carcinoma. World J Surg 2003;27(3):272–277. Epub 2003 Feb 27.
11. Dixon E, Vollmer CM Jr, Sahajpal A, Cattral M, Grant D, Doig C, Hemming A, Taylor B, Langer B, Greig P, Gallinger S. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. Ann Surg 2005;241(3):385–394.
12. Greene FL. TNM staging for malignancies of the digestive tract: 2003 changes and beyond. Semin Surg Oncol 2003;21(1):23–29. Review.
13. Miyazaki M, Itoh H, Ambiru S, Shimizu H, Togawa A, Gohchi E, Nakajima N, Suwa T. Radical surgery for advanced gallbladder carcinoma. Br J Surg 1996;83(4):478–481.
14. Todoroki T, Takahashi H, Koike N, Kawamoto T, Kondo T, Yoshida S, Kashiwagi H, Otsuka M, Fukao K, Saida Y. Outcomes of aggressive treatment of stage IV gallbladder cancer and predictors of survival. Hepatogastroenterology 1999;46 (28):2114–2121.
15. Nakamura S, Suzuki S, Konno H, Baba S, Baba S. Outcome of extensive surgery for TNM stage IV carcinoma of the gallbladder. Hepatogastroenterology 1999;46(28):2138–2143.
16. Fujita N, Noda Y, Kobayashi G, Kimura K, Yago A. Diagnosis of the depth of invasion of gallbladder carcinoma by EUS. Gastrointest Endosc 1999;50(5):659–663.
17. Inui K, Nakazawa S. Diagnosis of depth of invasion of gallbladder carcinoma with endosonography. Nippon Geka Gakkai Zasshi 1998;99(10):696–699.
18. Chaudhary A, Dhar P, Sachdev A, Agarwal A. Gastric outlet obstruction in carcinoma gall bladder. Indian J Gastroenterol 1999;18(3):101–103.
19. Singh B, Kapoor VK, Sikora SS, Kalawat TC, Das BK, Kaushik SP. Malignant gastroparesis and outlet obstruction in carcinoma gall bladder. Trop Gastroenterol 1998;19(1):37–39.
20. Nakamura S, Nishiyama R, Yokoi Y, Serizawa A, Nishiwaki Y, Konno H, Baba S, Muro H. Hepatopancreatoduodenectomy for advanced gallbladder carcinoma. Arch Surg 1994;129(6):625–629.
21. Yoshikawa T, Ohta T, Araida T, Azuma T, Takasaki K. Indications for and operative outcome of hepato-pancreatoduodenectomy in the treatment of carcinoma of the gallbladder. Nippon Geka Gakkai Zasshi 1998;99(10):717–721.
22. Nakamura S, Nishiyama R, Yokoi Y, Serizawa A, Nishiwaki Y, Konno H, Baba S, Muro H. Hepatopancreatoduodenectomy for advanced gallbladder carcinoma. Arch Surg 1994;129(6):625–629.
23. Nimura Y, Hayakawa N, Kamiya J, Maeda S, Kondo S, Yasui A, Shionoya S. Hepatopancreatoduodenectomy for advanced carcinoma of the biliary tract. Hepatogastroenterology 1991;38 (2):170–175.
24. Nagakawa T, Kayahara M. Indication for and problems of hepatopancreatoduodenectomy for carcinoma of the biliary tract based on the statistical registry in Japan. Nippon Geka Gakkai Zasshi 2001;102(2):199–202.

J Gastrointest Surg (2007) 11:1728–1731
DOI 10.1007/s11605-007-0281-1

Jaundice in the *Hippocratic Corpus*

Niki Papavramidou · Elizabeth Fee · Helen Christopoulou-Aletra

Received: 18 May 2007 / Accepted: 29 July 2007 / Published online: 25 September 2007

Abstract The Hippocratic physicians were among the first who described jaundice (icterus). The *Hippocratic Corpus* has numerous appearances of the condition, where its etiology, description, prognosis, and treatment are provided. The connection made between the liver and jaundice was remarkable, bearing in mind that the Hippocratic physicians had not performed dissections and that their medical views were based on observation. The Hippocratic doctors described five kinds of jaundice. The etiology was, as in most cases of diseases mentioned in the *Hippocratic Corpus*, "humoral" imbalance. The diagnosis and prognosis were based on the color of the skin, the urine, the feces, and several other factors, such as the season of the year during which the disease first appeared or the coexisting diseases. The treatment, finally, consisted of herbal medications, baths, diet, and blood-letting, depending on the type of jaundice in question. Finally, an attempt is made to correlate modern diseases with the Hippocratic types of jaundice.

Keywords Icterus · Hippocratic Corpus · History of liver diseases · Ancient medicine

Introduction

"Icterus" (jaundice) was mentioned for the first time in clay tablets of Mesopotamia and repeatedly in the Old Testament,[1] but the Hippocratic doctors were the first to describe this disease in detail and to relate it to a pathological condition of the liver. At that time, jaundice, like "fever", was considered to be a separate and independent disease, not merely a symptom. The *Hippocratic Corpus* refers to five types of jaundice, having in common a yellow or greenish pigmentation of the skin. For each type, the Hippocratic physicians described separate etiologies, clinical manifestations, and treatments, all in full compliance with the Hippocratic humoral theory. Here, we will present each type and make an attempt to correlate the Hippocratic view of jaundice with modern knowledge about the diseases that provoke it.

Paper presented as poster at the 6th World Congress of the Hepato-Pancreato-Billiary Association, Washington, June, 2004

N. Papavramidou (✉) · H. Christopoulou-Aletra
History of Medicine Division, School of Medicine,
Aristotle University of Thessaloniki,
P.O. Box 356, 54006 Thessaloniki, Greece
e-mail: papavramidou@hotmail.com

E. Fee
History of Medicine Division, National Library of Medicine,
National Institutes of Health,
Bldg 38, Rm 1E-21, 8600 Rockville Pike,
Bethesda, MD 20894, USA

Present address:
N. Papavramidou
30 Koritsas St., Panorama,
55236 Thessaloniki, Greece

The Hippocratic Types of Jaundice

The Hippocratic physicians refer to jaundice several times in the *Hippocratic Corpus*. Jaundice was considered at that time a disease in itself, rather than a symptom occurring because of a disease. The most complete and detailed descriptions can be found in the *Diseases* treatises. The writers provide us with the clinical manifestations of each type, along with the appropriate treatments, according to the Hippocratic physiology.

The First Type of Jaundice

The first type of jaundice described by the Hippocratic physicians is characterized as "acute and rapidly fatal".[2] The skin becomes green, "greener than green lizards",[2] a reddish sediment appears in the urine, and the patient experiences fever and mild shivering. The patient also suffers from irritation, in such a degree that "he couldn't even tolerate a blanket". In the morning, before breakfast, pain strikes the patient in the abdomen and bowels.[2] The prognosis of this type of jaundice is not good, as the patient usually dies within 14 days. Nevertheless, if he survives that far, he has a chance of full recovery. As for the treatment of this type of jaundice, the Hippocratic physicians advise the use of warm baths. Furthermore, the patient should drink "melicrat" (a mixture of milk and honey) with equal amounts of almonds and wormwood leaves and half as much sifted anise. The patient should drink this mixture as soon as he wakes up in the morning and just before retiring at night. Before going to bed, he should also drink light old wine and gruel.[2]

The Second Type of Jaundice

This type of jaundice occurs, according to the Hippocratic physicians, mainly in summer when, according to the "humoral" theory, bile is set in motion due to the excessive heat of the sun. The bile is responsible for the color of the skin; bile is said to gather under the skin and in the head, causing the yellowish color of the skin. The eyes become pale yellow, and a kind of incrustation appears under the hair and on the scalp, while the patient experiences chills and fever.[2] The color of the urine is also pale yellow. In the early morning, before breakfast, there is a rumbling in the abdomen and bowels, and the patient is extremely irritated. Finally, the stools are yellow and foul-smelling. The prognosis of this jaundice is not good, as the patient usually dies within 14 days.

The recommended treatment is as follows: when the patient's fever remits, he has to be washed with very hot water, and drink "melicrat" and barley–water gruel with honey, until the crucial 14th day has passed. From that day on, the patient has to bathe twice a day and has to be fed very well. He can drink white wine in large amounts throughout the day. If, after many days have gone by, the color of his body remains pale yellow, vomiting has to be provoked by means of foods.[2] If the disease does not disappear after all these measures, the patient has to drink hellebore, a plant known for its cathartic properties. After that, he has to eat soft barley cake or the inner part of a loaf of bread, or soup with well-boiled chicken, onion, coriander, cheese, salt, sesame, and white raisins, and drink a very old, dry, white wine. On the following day, the lower part of the abdomen has to be emptied with the aid of juice from white chickpeas and honey.[2] After the third day, the patient should drink daily water boiled with a pinch of peeled roots of mulberry trees and water boiled with white chickpeas. The patient can mix this water with wine and drink it. If the patient refuses to drink the aforementioned water, he can have boiled dried white figs with water, either alone or mixed with wine.[2]

The Third Type of Jaundice

This kind of jaundice occurs mainly in winter and is caused by drunkenness and chills. The clinical manifestations of the disease begin, according to the Hippocratic doctors, with chills and fever. "The subcutaneous moisture in the patient's body congeals with the blood", as is clear from the fact that "the body becomes livid and hard, the vessels through it are stretched, pale yellow, larger than they were before, and wider",[2] while other vessels are stretched and darker. Incision of a vessel will provide pale yellow blood if the vessel is pale yellow or dark blood if the vessel is dark. The patient experiences irritation and itching and is immobilized in bed by extreme weakness and thirst.[2] The prognosis for this type of jaundice is better than the previous ones but, unless the patient recovers in 7 days, the condition may be prolonged for a long time, usually for 8–9 months. In such a case, the patient may fall into bed due to intense pain and weakness and sudden death may occur.[2]

The treatment consists of special diet and purging. After 7 days have passed, from the first appearance of jaundice, the patient should drink hellebore, and purging of the bowels should be provoked with the use of the same medications described in the previous cases. Blister-beetles should also be administered, with their wings and heads removed: "grind four, dissolve in (...) white wine, immediately add a little honey, and give thus to drink; let the patient drink this potion two or three times a day".[2] If the disease is prolonged, the patient should undergo baths and steam baths. The patient can eat whatever he wants and drink dry white wine to overcome his weakness. Although this type of jaundice is easier to cure, its prolongation may prove to be fatal.

The Fourth Type of Jaundice

The Hippocratic physicians call this type of jaundice "common" because it may occur in every season of the year. They believe that it is caused by excessive food intake or drunkenness, combined with chills. Immediately, the patient's body and eyes become yellow and "the disease

invades beneath the hair and nails".[2] Chills, mild fever, headache, and weakness are present, and the patient's urine becomes thick, pale yellow. The prognosis of this type of jaundice is even better than the previous one and, if promptly treated, the patient will totally recover.

The treatment used by the Hippocratic physicians is as follows: they incise the patient's elbows to draw blood. Then, they recommend a steam bath and have the patient drink cucumber juice. On the third day, they purge his bowels by using ass's milk and his head by using the aforementioned drinks and foods to cause vomiting. The patient should also drink soup made from plovers (a wading bird) and is advised to have copious hot baths, after this treatment until the day he recovers.[2]

The Fifth Type of Jaundice

This type of jaundice mainly occurs in winter because of the surplus of phlegm produced by the cold weather. The patient's color becomes ashen and "his chest fills up with phlegm".[2] He expectorates copious sputum and, while coughing, he often suffers from hiccups; his urine is thick and white. The prognosis of this type of jaundice is a very good one, as it is rarely fatal, and the patient usually recovers quickly.

The management again concerns diet and baths. The patient should drink "Cnidian berry" (a berry found in Cnidos, in Asia Minor) which provokes purging. Afterwards, he has to drink barley–water gruel with honey which also produces vomiting, to clean the phlegm from his lungs and bronchial tubes. For the rest, the patient must undergo the same treatments administered for the other types of jaundice: medications, steam baths, baths, and gruel. If done as advised, the patient will soon recover.[2]

Discussion

For the Hippocratic physicians, health is a state of equilibrium among the factors responsible for the proper functioning of the body. Disease results from the alteration of the equilibrium of factors like the climate and the seasons, the habits of the patient, and the surplus or deficiency of any of the body "humors". The lack of post mortem examinations is the main reason why the Hippocratic physicians were unable to form etiopathogenic theories closer to the clinical reality. Nonetheless, it is impressive that at such an early period jaundice was divided into several types; it is difficult not to admire the care and detail of the Hippocratic observations.

A modern physician reading the clinical symptoms of each type of jaundice described in the *Hippocratic Corpus* will certainly come to think of the symptoms described in modern Atlases of Medicine. Even if the descriptions are not always accurate, even if the era lacked clinical and laboratory tests, even if the treatments proposed might have treated only the superficial manifestations of jaundice, like pain and fever, it is worthy of admiration that we can correlate the Hippocratic types of jaundice with possible modern diseases. Such an attempt, of course, is full of danger but yet challenging for the modern researcher. Thus, it can be speculated that *the first Hippocratic type of jaundice* might be hepatic jaundice. Patients suffering from hepatitis A and also from acute cholangitis resulting from stasis of the bile and from its infection by microbes usually appearing in cases of choledocholithiasis and neoplasm of the biliary tree and of the pancreas may be identified. Patients with hemolysis provoked by other causes such as cyamosis or poisoning could also be included in this category. *The second Hippocratic type of jaundice* could be correlated with posthepatic jaundice. The poor prognosis leads us to the conclusion that it may be about Ca of the head of pancreas, as well as Ca of ampulla of Vater and extrahepatic cholangiocarcinoma. *The third Hippocratic type of jaundice* might be equated with posthepatic jaundice, having a better prognosis than the previous type. It resembles intrahepatic biliary diseases, such as alcoholic cirrhosis, intrahepatic lithiasis, primary or metastatic liver cancer, and sclerosing cholangitis. Chronic hemolytic disorders and Gilbert Syndrome along with several cases of chronic pancreatitis may also be included. *The fourth Hippocratic type of jaundice* could refer to cases of posthepatic jaundice including the most common cases of nonmalignant jaundice, such as cholelithiasis and choledocholithiasis, and diseases such as hepatitis A, cirrhosis, Gilbert syndrome, and familial unconjugated hyperbilirubinemia. Finally, *the fifth Hippocratic type of jaundice* might be recognized as "pseudo-jaundice," because it is hard for anyone to distinguish if the color of the skin is icteric, sub-icteric, or just pale, and, furthermore, it is connected with inflammation of the lungs. Some types of jaundice may be related to these symptoms, such as those caused by viruses (i.e., the common cold, acute cholecystitis) or systematic use of alcohol.

Paleopathology would be the only science able to affirm such speculations, but the close similarities between "jaundice" described plainly in the *Hippocratic Corpus* and some of the clinical manifestations of modern diseases allow us to provide the reader with possible matches. The therapeutic treatments of the Hippocratic physicians may have little to do with modern medical reality, but we can nonetheless admire their observational powers in describing the different types of jaundice they

encountered in their clinical practices, so many centuries ago.

Acknowledgment We would like to thank Prof. S. Papavramidis for his contribution in identifying the possible matches of the Hippocratic types of jaundice to modern diseases.

References

1. Rosner F. Yerakon in the Bible and Talmud: jaundice or anemia. Am J Clin Nutr 1972;25:626–628.
2. Potter P. Hippocrates (trans). Volume 6. Cambridge, MA: Harvard University Press, 1988:23–25, 189–199.

J Gastrointest Surg (2007) 11:1732–1740
DOI 10.1007/s11605-007-0302-0

Roux-en-Y Reconstruction after Distal Gastrectomy to Reduce Enterogastric Reflux and *Helicobacter pylori* Infection

De-Chuan Chan · Yu-Ming Fan · Chih-Kung Lin · Cheng-Jueng Chen · Ching-Yuan Chen · You-Chen Chao

Received: 22 May 2007 / Accepted: 12 August 2007 / Published online: 18 September 2007

Abstract Enterogastric reflux (EGR) is regarded as an unavoidable consequence of distal gastrectomy. We evaluated the efficacy of Roux-en-Y (RY) gastrojejunostomy and Braun enteroenterostomy (BEE) for preventing EGR. Between January 2002 and January 2005, 60 patients who underwent distal gastrectomy for gastric cancer or peptic ulcers were divided into RY, Billroth II reconstruction (BII) without or with BEE (BII+B) according to reconstructive method. After 12 months, EGR and mucosal alterations of the remnant stomach were evaluated using biliary scintigraphy, endoscopy, and histology. Scintigraphy showed fasting and postprandial EGR into the remnant stomach occurred in 5.3% and 21.1% of the RY group, 62.1% and 93.1% of the BII group, and 50.0% and 91.7% of the BII+B group, respectively. Endoscopy showed bile reflux occurred in 15.8% of the RY group, 75.9% of the BII group, and 83.3% of the BII+B group. In addition, the prevalence of *Helicobacter pylori* (HP) infection in the RY group was less than in the other groups ($P<0.02$). Therefore, RY after distal gastrectomy was effective in reducing EGR and HP infection. BEE was ineffective in diverting bile flow away from the gastric remnant.

Keywords Enterogastric reflux · Roux-en-Y gastrojejunostomy · Braun enteroenterostomy · *Helicobacter pylori*

The study was supported by a grant from the Research Foundation of The Tri-Service General Hospital (TSGH-C96-14-S05).

D.-C. Chan · C.-J. Chen
Division of General Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Y.-M. Fan · C.-Y. Chen
Department of Nuclear Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

C.-K. Lin
Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Y.-C. Chao (✉)
Division of Gastroenterology, Tri-Service General Hospital, National Defense Medical Center, National Defense University, Taipei 114, Taiwan
e-mail: chrischan1168@yahoo.com.tw

Introduction

Distal gastrectomy is a common and effective treatment for complicated peptic ulcers and most distal gastric cancers. Billroth II (BII) reconstruction is the most common method of reconstruction after distal gastrectomy because of its simplicity.[1] However, enterogastric reflux (EGR) is regarded as an unavoidable consequence of this procedure. Many disorders of the gastric remnant are associated with EGR. Reflux gastritis is a syndrome that occurs mainly in gastrectomized patients, causing distress over long periods and impairing their quality of life.[2] Importantly, the presence of bile acids in the gastric remnant may contribute to mucosal injury and may cause cancer in the gastric remnant.[3] It was believed that diversion of bile flow away from gastric remnant would prevent reflux gastritis and reduce the risk of stump carcinoma. Therefore, various reconstruction procedures, including Roux-en-Y (RY) gastrojejunostomy and Braun enteroenterostomy (BEE), were developed to replace or supplement conventional BII reconstruction and prevent EGR.[4,5] However, the optimal reconstruction method has not been defined.

We performed RY reconstruction or BII reconstruction with BEE (BII+B) in patients who underwent distal gastrectomy for treatment of complicated peptic ulcers or stomach cancer. We determined the efficacies of the two reconstructive procedures for preventing EGR and the correlation between endoscopic and histological features of gastric remnants and the type of reconstructive procedure.

In recent years, *Helicobacter pylori* infection has emerged as a major risk factor for the development of peptic ulcer disease and gastric cancer, but the role of *H. pylori* in the development of gastric remnant cancer is still uncertain. Therefore, this study compared the incidence of *H. pylori* infection between several reconstructive procedures associated with distal gastrectomy.

Patients and Methods

Patients

Sixty patients who underwent distal gastrectomy for complicated peptic ulcer or stomach cancer at the Tri-Service General Hospital in Taipei, Taiwan between January 2002 and January 2005 were enrolled. All patients had undergone operation 12 months previously. The subjects were divided into three groups according to the gastrointestinal reconstructive procedures, including RY gastrojejunostomy, BII without or with BEE reconstructions. None of the patients took drugs that alter gastric motility. The characteristics of the three groups of patients are summarized in Table 1. Delayed gastric emptying was defined as the patient who could not tolerate semiliquid diet more than 10 days after operation. This work was performed as a prospective study and approved by the ethics committees of Tri-Service General Hospital.

Table 1 Patient Groups and Characteristics

	BII (n=29)	BII+B (n=12)	RY (n=19)	P
Mean age (years)	64.5	68	55.9	NS
Mean age (range)	(31–85)	(51–78)	(24–80)	
Gender (M/F)	17/12	8/4	12/7	NS
Primary disease				
Peptic ulcer	19	6	4	**
Gastric cancer	10	6	15	
Nasogastric drainage (ml/day)	435± 241	330± 218	58±47	***
Delayed gastric emptying	2	0	1	NS
Marginal ulcer	1	1	1	NS

BII: Billroth II
BII+B: Billroth II with Braun's procedure
RY: Roux-en-Y
*Average amount of nasogastric drainage in the first three postoperative day
**p<0.01: RY vs BII or BII+B,
***p<0.05: RY vs BII or BII+B,

Operation

In most patients, the length of the remnant stomach was about 2 cm at the lesser curvature and 7 cm at the greater curvature. Patients underwent various reconstructions at the discretion of the surgeon. Twenty-nine of the 60 patients underwent BII reconstructions, 12 underwent BII+B reconstructions, and 19 underwent RY reconstructions. In the patients subjected to BII, the jejunum was lifted through the antecolic route and the gastrojejunostomy was made about 25 cm from the Treitz ligament. In the patients subjected to BII+B, the jejunum was lifted through the antecolic route, the gastrojejunostomy was made about 40 cm from the Treitz ligament, and the BEE was done about 15 cm distal to the gastrojejunostomy. In patients subjected to RY, the jejunum was lifted up through the retrocolic route; the length between the gastrojejunostomy and the Y-anastomosis was about 40 cm.

Kinetics of Bile Juice According to Biliary Scintigraphy

A modification of a previously reported method was used for scintigraphic evaluation of EGR.[6] After an overnight fast (12 h), patients received an intravenous injection of 8 mCi Tc-99 m DISIDA (Disofenin™). Patients were placed in a supine position immediately after injection of the radiopharmaceutical and instructed to lie under the Hawkeye system (Millencium VG 5/8; GE Medical Systems, Milwaukee, WI, USA). The detector of the system was aimed at the liver, gallbladder, stomach, and bowel. Scintigraphic images were acquired in the dynamic mode at 1-min intervals for 60 min and image data were analyzed using a computer. After this procedure, the subjects consumed a fatty meal consisting of one piece of buttered bread (379 kcal, 17 g fat, 48 g carbohydrate, 8 g protein) and 240-ml whole milk (192 kcal, 12 g fat, 13 g carbohydrate, 9 g protein). An additional 60 min of imaging (60 s/frame) was then acquired after the patients had been placed in a supine position. Images were processed to determine the areas of interest in the stomach and small intestine and to visualize the distribution of radioactivity in these areas as a function of time. The 3-dimensional position of the gastric remnant was determined using a single-photon emission computed tomography (SPECT)/computed tomography (CT) system (Fig. 1). The following formula was used to derive a quantitative EGR index (EGRI) [7]:

$$\mathrm{EGRI} = S/(S + SI) \times 100,$$

where S=counts per minute in the stomach and SI=counts per minute in the small intestine.

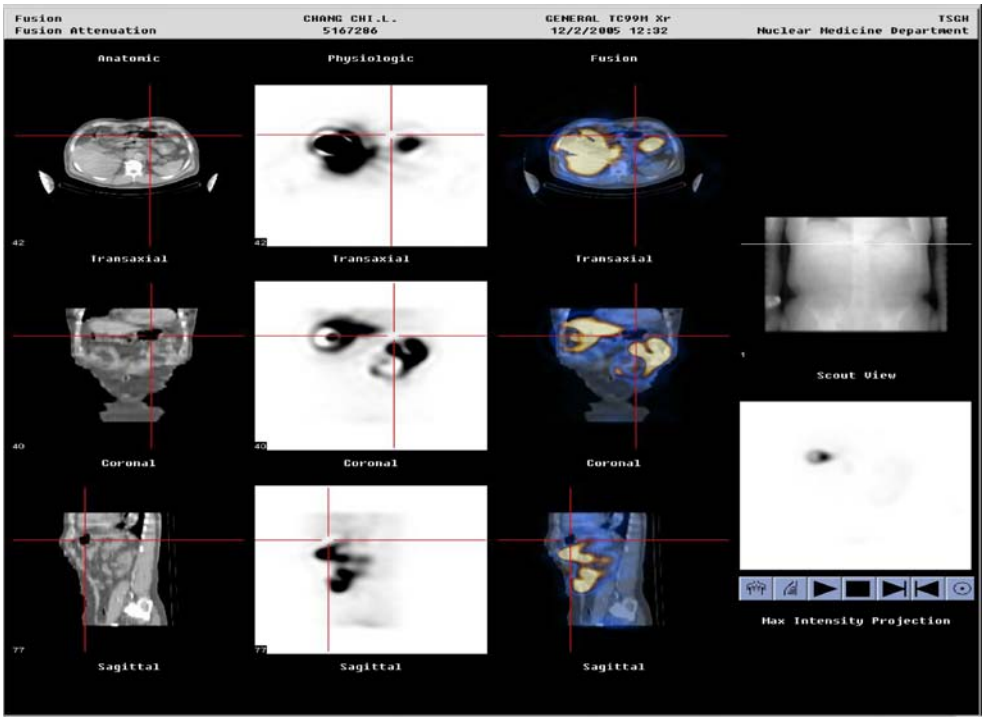


Figure 1 Localizing of gastric remnants using biliary scintigraphy with a single-photon emission computed tomography (SPECT)/computed tomography (CT) system.

Counts per minute at peak radioactivity in the stomach were used to calculate the EGRI.

Postoperative Endoscopy

Endoscopy was conducted for all patients to determine whether the properties of the mucosa of the remnant stomach had changed since the operation and whether bile reflux into the gastric remnant had occurred. Endoscopic examinations were conducted by a senior gastroenterologist (WK Chang) who was blinded to the results of hepatobiliary scintigraphy. The absence of bile reflux was defined as an absence of a bile stain or a bile lake in the gastric remnant (Fig. 2a). A yellow or green bile lake (Fig. 2b,c) or a bile stain coating the gastric mucosa (Fig. 2d) of the remnant stomach was regarded as evidence of bile reflux. Remnant gastritis was classed into four categories according to the extent of erythematous changes in the gastric mucosa: grade 0, normal mucosa without erythema (Fig. 3a); grade 1, erythema confined to the anastomotic area (Fig. 3b); grade 2, intermediate between grades 1 and 3 (Fig. 3c); and grade 3, erythema of the entire remnant stomach (Fig. 3d). During endoscopy, four or more biopsy specimens were taken for histological analysis from an area near the stoma of the gastrojejunostomy. *H. pylori* infection was confirmed using the Campylobacter-like organism (CLO) test and by high-magnification examination of samples for the presence of short, curved *H. pylori* rods by a pathologist. In most instances, *H. pylori* was identified using hematoxylin and eosin staining; when none of the bacteria were positive for hematoxylin and eosin, the Giemsa stain was used. The patients were considered uninfected when both the CLO test and the histological examination were negative for *H. pylori*; other patients were considered infected.

Histological Assessment of Biopsy Specimens

Biopsy specimens from the stoma of the stomach were placed on filter paper and immediately fixed in 10% buffered formalin. Paraffin-processed sections were cut at three levels and stained with hematoxylin and eosin. The sections were examined by one pathologist (CK Lin), who was blinded to the endoscopic and scintigraphic results. The severity of foveolar hyperplasia, inflammation, intestinal metaplasia, and dysplasia was assessed. The presence of foveolar hyperplasia was classified on a scale of absent to severe. Gastric mucosal inflammation was classified according to the degree of infiltration of interstitial inflammatory cells and glandular involvement as mild, moderate, or severe. Intestinal metaplasia and dysplasia were classified as absent or present.

Questionnaire Survey on Clinical Symptoms

We selected five major symptoms of postgastrectomy symptoms as our questionnaire survey. All patients were given a questionnaire before undergoing endoscopic examination and biliary scintigraphy, to assess the following clinical symptoms (Table 2): epigastric pain, heartburn, biliary vomiting, postprandial bloating, and nausea. Each of these

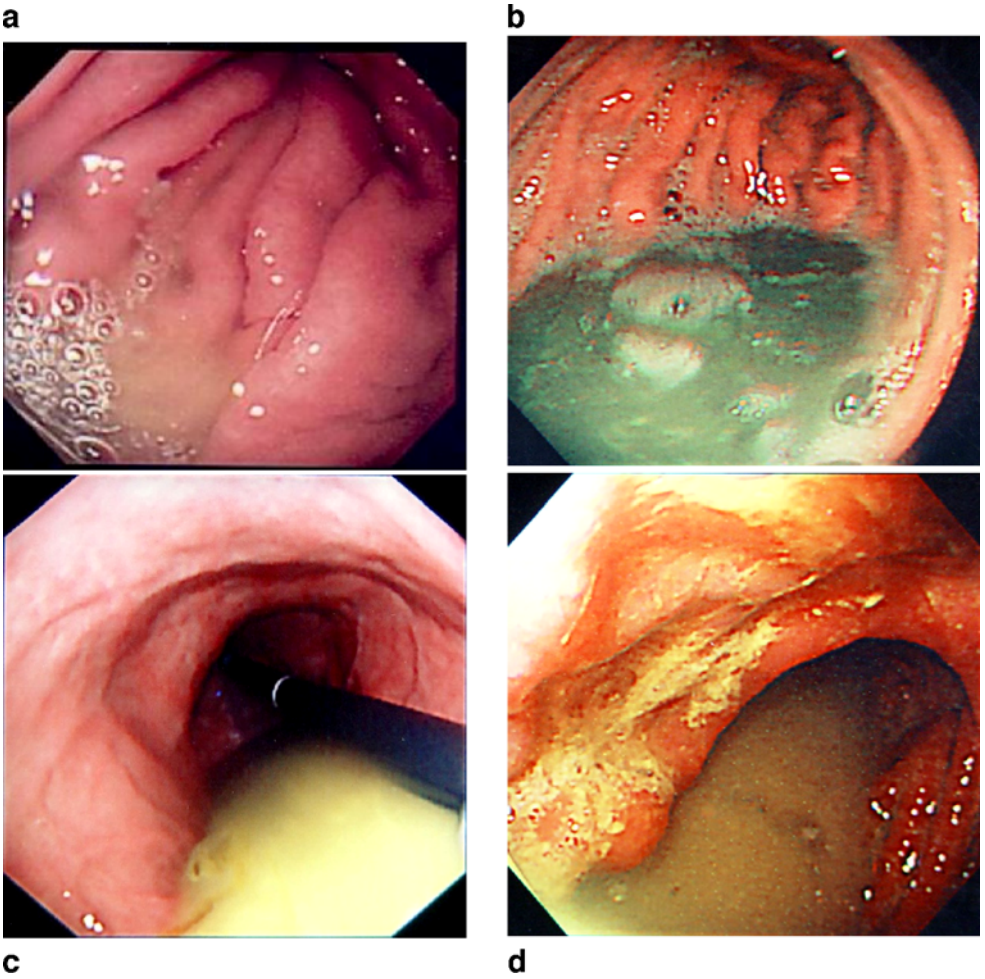


Figure 2 Endoscopic evidence of bile reflux. **a** No bile reflux; **b** greenish bile; **c** yellowish bile; **d** bile stain.

five items was scaled from 0 to 5 points, and the grade of clinical symptom was based on the total score as follows (Fig. 4): Grade 0: 0; Grade 1: 1–5 points; Grade 2: 6–10 points; Grade 3: 11–15 points; and Grade 4: 16–25 points.

Statistical Analysis

Differences between groups were tested for significance using Student's *t* test and the Kruskal–Wallis probability test. A one-way ANOVA and the χ^2 test were used to compare the difference in EGR assessment between hepatobiliary scintigraphy and endoscopy. Differences in mucosal inflammation between groups were evaluated using the Mann–Whitney *U* test. Differences were considered statistically significant at $P<0.05$.

Results

There were no significant differences in age and sex between the three groups. However, the RY group contained more patients with gastric cancer ($P<0.05$) than the other groups. In the first 3 days after surgery, patients who underwent RY reconstruction had a mean gastric output of 58 ml/day; patients with BII or BII+B had gastric outputs of 430 ml/day and 335 ml/day, respectively. The RY group had the less postoperative output from the nasogastric tube than the other groups ($P<0.01$) (Table 1). In all three groups, there was no significant difference in the incidence of delayed gastric emptying and marginal ulcer.

Kinetics of Bile According to Biliary Scintigraphy

Fasting and postprandial biliary scintigraphy showed that EGR was present in 5.3% and 21.1% patients of the RY group, respectively (Table 3). In the BII group, EGR was present in 62.1% and 93.1% of patients during fasting and after the meal, respectively. In the BII+B group, EGR was present in 50.0% and 91.7% of patients during fasting and after the meal, respectively; the mean EGRI was 24%. The incidence of EGR differed between the RY group and the BII and BII+B groups, irrespective of the time of the evaluation ($P<0.001$). However,

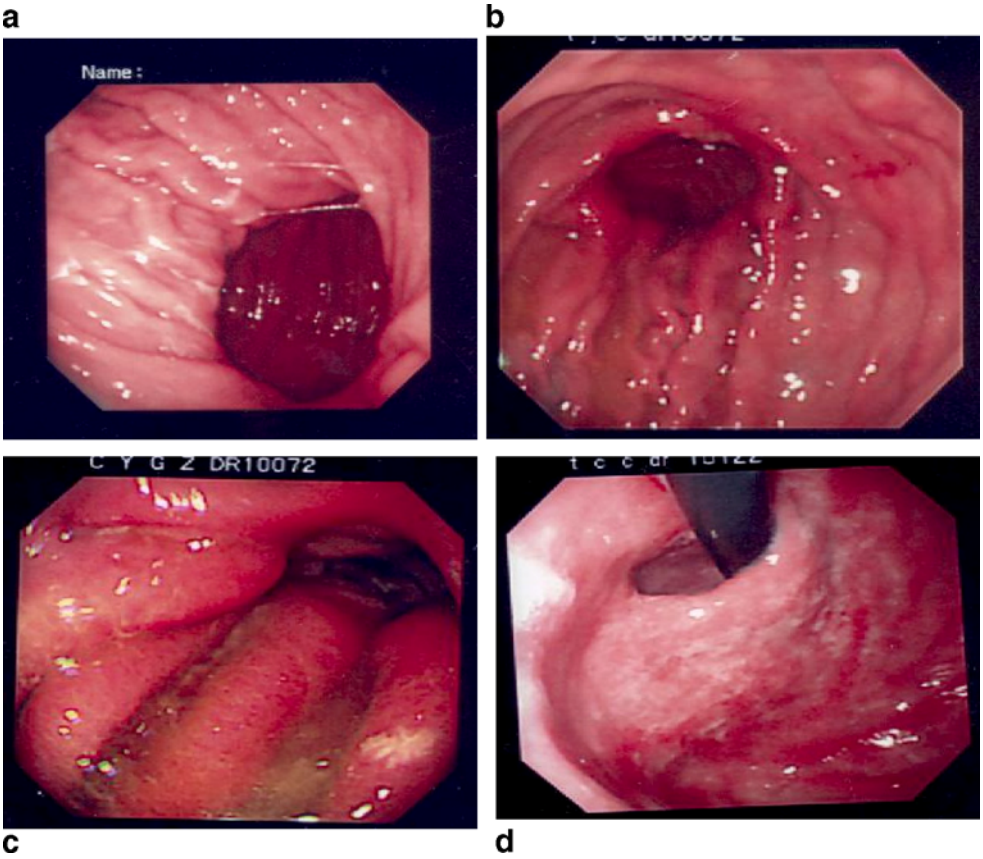


Figure 3 Endoscopic grade of remnant gastritis. **a** Grade 0, no erythema of remnant gastric mucosa; **b** grade 1, mild erythema around the anastomosed region; **c** grade 2, comb-shaped marked erythema of the greater curvature on the oral side of the anastomosed area; **d** grade 3, diffuse severe redness and marked edema.

there was no difference in the incidence of EGR between the BII and BII+B groups (P=0.722 and P=0.992 during fasting and after the meal, respectively). The incidence of reflux increased after the fatty meal in all three groups (P<0.001). The mean postprandial EGRI was 8±4% in the RY group, 29±7% in the BII group, and 24±4% in the BII+B group. The lowest EGRI was observed in the RY group.

Postoperative Endoscopy

Endoscopic findings related to the gastric stump are summarized in Table 4. Bile reflux was observed in 15.8% of the RY group, 75.9% of the BII group, and 83.3% of the BII+B group. Patients of the RY group had significantly less bile reflux than those of the BII and BII+B groups (P<0.001). Grade 1 or greater remnant gastritis occurred in 96.6% (28/29) of patients with BII reconstruction and 91.7% (11/12) of patients with BII+B reconstruction. Of the 19 RY patients, 14 (73.7%) had grade 0 remnant gastritis. The endoscopic severity of remnant gastritis was significantly milder for RY than for BII (P<0.001) or BII+B (P<0.001). However, no significant differences in the endoscopic severity of remnant gastritis were observed between BII and BII+B patients.

Questionnaire Survey on Clinical Symptoms

According to the results of the questionnaire survey on clinical symptoms, 18 (62%) patients in the BII group and 7 (58%) of patients in the BII+B group had symptoms of grade 1 or higher, although there was no patient with grade 4 symptoms in the two groups. On the other hand, 17 (89%) of the RY group patients had grade 0 symptom. There was statistically significant difference among the three groups (Fig. 4).

Histological Assessment of Biopsy Specimens

The severity of foveolar hyperplasia of biopsy specimens taken from sites near the stoma did not differ significantly between the three groups (P>0.05) (Table 5). Mild inflammation of the gastric stump was observed in 15 (79.0%) RY patients, 16 (55.2%) BII patients, and 8 (66.7%) BII+B patients. The severity of inflammation differed between the RY and BII groups (P=0.034). Intestinal metaplasia of the remnant stomach was observed in three patients (15.8%) of the RY group, 11 patients (37.9%) of the B-II group, and seven patients (58.3%) of the BII+B group. The incidence of intestinal metaplasia in the RY group was less than that in the other groups (P=0.042). However, dysplasia of the

Table 2 Clinical Symptom Scores Based on the Questionnaire Survey

Symptom / Frequency	Epigastric pain	Heartburn	Biliary vomiting	Postprandial bloating	Nausea
No symptom	0				
1-3/month	1				
1/week	2				
2-3/week	3				
1/day	4				
>1/day	5				

The score of each symptom was defined according to the frequency of symptom. The grade of clinical symptom was based on the total score of the five items as follows. Grade 0: 0; Grade 1: 1–5 points; Grade 2: 6–10 points; Grade 3: 11–15 points; and Grade 4: 16–25 points.

remnant stomach was observed in three patients (10.3%) of the BII group, one patient (8.3%) of the BII+B group, and two patients (10.5%) of the RY group ($P>0.05$).

Presence of *H. pylori*

The CLO or histology tests were positive for *H. pylori* in five (26.3%) of the 19 subjects in the RY group, 16 (55.2%) of the 29 subjects in the BII group, and nine (75.0%) of the 12 subjects in the BII+ B group. The prevalence of *H. pylori* infection was less in RY patients than in BII or BII+B patients ($P=0.024$) (Table 5).

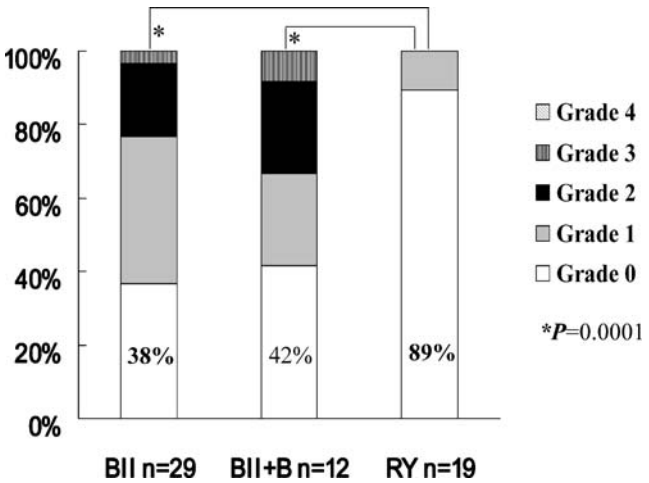


Figure 4 Questionnaire assessment of the five major clinical symptoms following distal gastrectomy; namely, epigastric pain; heartburn; biliary vomiting; postprandial bloating; and nausea. Most of the patients in RY group are free of these symptoms.

Association Between the Histological Change in Gastric Remnant Mucosa and the Presence of H. pylori or EGR

The patients were classified into four groups according to the presence of *H. pylori* and their EGR status (Table 6). When EGR was present, patients with *H. pylori* infection had significantly more severe inflammation and more metaplasia than those without *H. pylori* infection ($P=0.046$ and $P=0.041$, respectively). In patients with *H. pylori* infection, the presence of EGR resulted in a numerically higher incidence of metaplasia compared with those in whom EGR was absent (59.1% vs. 25%, respectively), but the difference was not statistically significant (Table 6). The groups did not differ significantly in the incidence of foveolar hyperplasia or dysplasia.

Table 3 DISIDA Study of the Remnant Stomach

	B II ($n=29$)	B II+B ($n=12$)	RY ($n=19$)
DISIDA EG reflux			
Fasting			
Negative	11 (37.9%)	6 (50.0%)	18 (94.7%)
Positive	18 (62.1%)	6 (50.0%)	1 (5.3%)
Postmeal			
Negative	2 (6.9%)	1 (8.3%)	15 (78.9%)
Positive	27 (93.1%)	11 (91.7%)	4 (21.1%)
EGRI	29 ± 7%	24 ± 4%	8 ± 4%

EG: enterogastric; EGRI: enterogastric reflux index; BII: Billroth II; BII+B: Billroth II with Braun's procedure; RY: Roux-en-Y
RY vs BII or BII+B, $p<0.001$ (ANOVA)

Table 4 Relationship between Reconstruction Procedure and Endoscopic Gastritis and Bile Reflux in the Remnant Stomach

	BII (n=29)	BII+B (n=12)	RY (n=19)	P
Endoscopic bile reflux				*
Absence	7 (24.1%)	2 (16.7%)	16 (84.2%)	
Presence	22 (75.9%)	10 (83.3%)	3 (15.8%)	
Endoscopic grade of gastritis				*
0	1 (3.4%)	1 (8.3%)	14 (73.7%)	
1	10 (34.5%)	3 (25.0%)	3 (15.8%)	
2	12 (41.4%)	5 (41.7%)	2 (10.5%)	
3	6 (20.7%)	3(25.0%)	0 (0.0%)	

B II: Billroth II; BII+B: Billroth II with Braun's procedure; RY: Roux-en-Y
*RY vs BII or BII+B, $p<0.001$

Discussion

Although many distal gastrectomies have been performed to treat complicated peptic ulcers and gastric antrum cancer, the optimal reconstruction method has not been established. The most common method of reconstruction, BII, often causes serious postgastrectomy symptoms. Patients with this type of reconstruction often experience EGR, which is associated with reflux gastritis.[8] EGR is also associated with the development of stump cancer after gastrectomies performed with BII reconstructions.[9] Consequently, reconstruction procedures such as RY and BEE were developed to replace or supplement conventional BII reconstruction and prevent EGR.[4,5]

In our study, almost all patients in the BII group showed evidence of EGR. In contrast, the incidence of EGR in patients who underwent RY was low. These findings are consistent with those of other investigations.[10–12] BEE was ineffective in preventing bile reflux into the gastric remnant after a fatty meal.

Stephen *et al.* concluded that BEE diverts a substantial amount of bile from the stomach and that the alkaline reflux gastritis syndrome can be prevented by performing BEE during gastric resection or bypass in a variety of operations.[5] However, 47% of their BEE patients experienced EGR while fasting, which is similar to our result (50%). Although half our patients did not develop EGR after fasting, 11 out of 12 patients who underwent BII with BEE experienced reflux into the residual stomach after a fatty meal. Therefore, BEE is ineffective in preventing bile reflux into the gastric remnant after a fatty meal, which is concordant with previous reports.[13,14]

Remnant gastritis was more severe in the patients who underwent BII with or without BEE than in those who underwent RY. The endoscopic severity of remnant gastritis in RY patients was mainly grade 0 (73.7%). Conversely, the proportion of patients with grade 0 remnant gastritis was less in BII and BII+B patients than in RY patients.

Endoscopy of the remnant stomach during the early postoperative stage typically reveals signs of acute inflammation such as edema and redness. Most of these signs disappear within 3 months. We selected patients who had undergone gastrectomies more than 1 year before the study and were in a stable postoperative condition. After BII and BII+B, remnant stomachs showed significantly more severe gastritis than after RY ($P<0.001$), which suggests that the

Table 5 Results of Histological Study and HP Infection of the Remnant Stomach

	BII (n=29)	BII+B (n=12)	RY (n=19)	P
Foveolar hyperplasia				NS
Absence	5 (17.2%)	4 (33.3%)	7 (36.8%)	
Mild	9 (31.0%)	2 (16.7%)	7 (36.8%)	
Moderate	10 (34.5%)	4 (33.3%)	5 (26.4%)	
Severe	5 (17.2%)	2 (16.7%)	0 (0.0%)	
Inflammation				0.034*
Mild	16 (55.2%)	8 (66.7%)	15 (79.0.%)	
Moderate	10 (34.5%)	1 (8.3%)	2 (10.5%)	
Severe	3 (10.3%)	3 (25.0%)	2 (10.5%)	
Dysplasia				NS
Absence	26 (89.7%)	11 (91.7%)	17 (89.5%)	
Presence	3 (10.3%)	1 (8.3%)	2 (10.5%)	
Metaplasia				0.042**
Absence	18 (62.1%)	6 (50.0%)	17 (89.5%)	
Presence	11 (37.9%)	6 (50.0%)	2 (10.5%)	
HP infection				0.024**
Negative	12 (41.4%)	4 (33.3%)	14 (73.7%)	
Positive	17 (58.6%)	8 (66.7%)	5 (26.3%)	

BII: Billroth II; BII+B: Billroth II with Braun's procedure; RY: Roux-en-Y; HP: *Helicobacteria pylori*
*RY *vs* BII
**RY *vs* BII or BII+B

Table 6 Association of Histological Finding with EGR and HP Infection for the Remnant Stomach

	EGR− HP− (n=17)	EGR − HP+ (n=8)	EGR + HP − (n=13)	EGR + HP + (n=22)
Foveolar hyperplasia				
Absence	6 (35.3%)	0 (0.0%)	3 (23.1%)	7 (31.8%)
Mild	6 (35.3%)	2 (25.0%)	4 (30.8%)	6 (27.3%)
Moderate	5 (29.4%)	5 (62.5%)	5 (38.5%)	4 (18.2%)
Severe	0 (0.0%)	1 (12.5%)	1 (7.7%)	5 (2.7%)
Inflammation				
Mild	13 (76.5%)	5 (62.5%)	11(84.6%)*	10 (45.5%)*
Moderate	3 (17.6%)	2 (25.0%)	1 (7.7%)	7 (31.8%)
Severe	1 (5.9%)	1 (12.5%)	1 (7.7%)	5 (22.7%)
Dysplasia				
Absence	16 (94.1%)	7 (87.5%)	13 (100%)	20 (90.9%)
Presence	1 (5.9%)	1 (12.5%)	0 (0.0%)	2 (9.1%)
Metaplasia				
Absence	15 (88.2%)**	6 (75.0%)	11(84.6%)	9 (40.9%)**
Presence	2 (11.8%)	2 (25.0%)	2(15.4%)***	13 (59.1%)***

EGR: enterogastric reflux; HP: *Helicobacteria pylori*
*p=0.046
**p=0.013
***p=0.041

macroscopic severity of remnant gastritis is determined by EGR, not the type of surgery.

Scintigraphy using Tc99 m DISIDA is a standard noninvasive technique for quantifying bile reflux and is a reliable means observing reflux in real time.[15,16] We used a single-photon emission computed tomography (SPECT)/computed tomography (CT) system to localize the gastric remnant in three dimensions. It is a more effective method for localization of the gastric remnant than x-rays and barium solutions, which only provide data in two dimensions. Reflux of bile into the remnant stomach was rarely visualized in the RY group, which is similar to the results of the endoscopic evaluation in which only three of 19 patients of the RY group showed evidence of bile stains or bile lakes in the gastric stump. On the other hand, most patients in the BII (93.1%) and BII+B (91.7%) groups had postprandial scintigraphic bile reflux, which coincided with the relevant endoscopic findings.

A high percentage of gastric cancer and peptic ulcer patients have *H. pylori* infections (98% and 94–97%, respectively).[17–19] There are few reports on *H. pylori* and Roux-en-Y diversions. Several studies reported that the prevalence of *H. pylori* is low in patients who have undergone distal gastrectomy (22–47%).[20–25] The decrease in the prevalence of *H. pylori* infection in patients who have undergone gastrectomy compared with those who have peptic ulcers or gastric cancer may be explained by a reduction in *H. pylori* survival after surgical resection of the antrum, which is likely to be colonized by *H. pylori*, and by increased bile reflux and elevated pH associated with gastrectomy.[20,24] When a patient undergoes a reconstruction procedure that minimizes bile reflux (such as RY), the level of *H. pylori* infection is elevated, but when patients undergo a reconstruction procedure that is associated with bile reflux (such as BI or BII), the rate of *H. pylori* infection is low. However, Nakagawara et al. reported that duodenogastric reflux facilitates the survival of *H. pylori* in the gastric stump after distal gastrectomy.[26] In their study, the *H. pylori* infection rate in RY (29%) and jejunal pouch interposition (JPI) (28%) patients was lower than in BII (73%) and BI (60%) patients (88%). They speculated that the lower prevalence of *H. pylori* infection in RY and JPI patients might be related to inhibition of the proliferation of *H. pylori* by other bacteria.

Our study showed that the prevalence of *H. pylori* infection decreased in patients who underwent gastrectomies. The ratio of *H. pylori* infection was significantly less in the RY group (26.3%) than that in the BII (58.6%) or BII+B (66.7%) groups, which indicates there are other factors besides bile reflux and antrum resection that inhibit colonization of *H. pylori*.

Bechi et al.[27] and Niemela et al.[28] showed that bile reflux is correlated with hyperplastic changes of the foveolar epithelium. Our study showed that there was a trend for more severe foveolar hyperplasia in BII and BII+B patients than in RY patients, but the difference was not statistically significant. Patients who underwent RY had a lower incidence of inflammation and intestinal metaplasia than those who underwent BII (P=0.034 and P=0.042, respectively), indicating there might be a positive association between EGR and inflammation and intestinal metaplasia. Associations between bile reflux and intestinal metaplasia have been reported,[29,30] but the mechanism underlying this association is unclear. One hypothesis is that intestinal metaplasia is caused by divergent differentiation of regenerating epithelium consequent to erosion or ulceration.[31] Intestinal metaplasia seems to originate during the regenerative process after gastric erosion and usually regresses with time.[32,33] When injury is repetitive, as in *H. pylori*-associated chronic gastritis, intestinal metaplasia may be extensive and permanent.

Our study failed to show a significant difference in foveolar hyperplasia and dysplasia among groups. However, as the observation period was short, our results do not preclude the possibility of significant differences in foveolar hyperplasia and dysplasia of the remnant stomach among the reconstruction techniques after a longer observation period.

It is intriguing that the prevalence of inflammation and intestinal metaplasia was greatest in patients with *H. pylori* infection and EGR (Table 6). The presence of concurrent *H. pylori* infection and EGR may be responsible for the severe histological inflammation and metaplasia in patients who underwent BII or BII+B reconstructions. A synergistic

effect of EGR and *H. pylori* infection has been suggested,[34,35] as high levels of inflammation[26,36] and intestinal metaplasia[37] are found in patients with both conditions.

Although the number of patients enrolled in this study was small, the study revealed some important differences in the condition of the remnant stomach between various methods of reconstruction. RY reconstruction was effective in preventing EGR and reducing *H. pylori* infection. Braun's enteroenterostomy was ineffective in diverting bile flow from the gastric remnant, especially after eating a fatty meal.

References

1. Yoshino K. History of gastric cancer surgery. J Jpn Surg Soc 2000;101:855–860.
2. Fiore AC, Malangoni MA, Broadie TA, Madura JA, Jesseph JE. Surgical management of alkaline reflux gastritis. Arch Surg 1982;117:689–694.
3. Northfield TC, Hall CN. Carcinoma of the gastric stump: Risks and pathogenesis. Gut 1990;31:1217–1219.
4. Buhl K, Lehnert T, Schlag P, Herfarth C. Reconstruction after gastrectomy and quality of life. World J Surg 1995;19:558–564.
5. Vogel SB, Drane WE, Woodward ER. Clinical and radionuclide evaluation of bile diversion by Braun enteroenterostomy: Prevention and treatment of alkaline reflux gastritis. An alternative to Roux-en-Y Diversion. Ann Surg 1994;219:458–466.
6. Fisher RS, Malmud LS, Roberts GS, Lobis IF. Gastroesophageal (GE) scintiscanning to detect and quantitate GE reflux. Gastroenterology 1976;70(3):301–308.
7. Niemela S. Duodenograstric reflux in patients with upper abdominal complaints or gastric ulcer with particular reference to reflux-associated gastritis. Scand J Gastroenterol 1985;20:1–56.
8. Dixon MF, O'Connor HJ, Axon ATR, King RFJG, Johnston D. Reflux gastritis: distinct histopathological entity? J Clin Pathol 1986;39:524–530.
9. Furukawa H, Iwanaga T, Hiratsuka M, Imaoka S, Ishikawa O, Kabuto T, et al. Gastric remnant cancer as a metachronous multiple lesion. Br J Surg 1993;80:54–56.
10. Obradovic VB, Artiko V, Chebib HY, et al. Estimation of the enterogastric reflux by modified scintigraphic method. Gastroenterology 2000;47:738–741.
11. Mackie CR, Hulks G, Cuschieri A. Enterogastric reflux and gastric clearance of refluxate in normal subjects and in patients with and without bile vomiting following peptic ulcer surgery. Ann Surg 1986;204:537–542.
12. Karlqvist P, Norrby K, Svedberg J, Sjodahl R. Enterogastric reflux after gastric surgery: A comparison between gastroduodenostomy and Roux diversion. Scand J Gastroenterol 1985;20:861–867.
13. Lindecken KD, Salm B. The effectiveness of Braun's anastomosis in Billroth II surgery. The role of hepatobiliary sequence scintigraphy (HBSS) in the diagnosis of bile flow following stomach resection. Rofo 1993;159(2):158–160.
14. Shinoto K, Ochiai T, Suzuki T, Okazumi S, Ozaki M. Effectiveness of Roux-en-Y reconstruction after distal gastrectomy based on an assessment of biliary kinetics. Surg Today 2003;33(3):169–177.
15. Mackie CR, Wisbey ML, Cuschieri A. Milk 99Tcm-EHIDA test for enterogastric bile reflux. Br J Surg 1982;69(2):101–104.
16. Tolin RD, Malmud LS, Stelzer F, Menin R, Makler PT Jr, Applegate G, Fisher RS. Enterogastric reflux in normal subjects and patients with Bilroth II gastroenterostomy. Measurement of enterogastric reflux. Gastroenterology 1979;77(5):1027–1033.
17. Uemura N. The magnitude of association between *Helicobacter pylori* infection and the development of gastric cancer. Scand J Gastroenterol 2002;37:869–870.
18. Uemura N, Mukai T, Okamoto S. *Helicobacter pylori* infection and the background gastric mucosa in the patients with gastric cancer. Rinsho Geka 1997;52:161–168.
19. Enomoto H, Watanabe H, Nishikura K, Umezawa H, Asakura H. Topographic distribution of *Helicobacter pylori* in the resected stomach. Eur J Gastroenterol Hepatol 1998;10:473–478.
20. O'Connor HJ, Dixon MF, Wyatt JI, Axon AT, Ward DC, Dewar EP, et al. Effect of duodenal ulcer surgery and enterogastric reflux on *Campylobacter pyloridis*. Lancet 1986;ii:1178–1181.
21. Robles-Campos R, Lujan-Mompean JA, Parrilla-Paricio P, Bermejo-Lopez J, Liron-Ruiz R, Torralba-Martinez JA, et al. Role of *Helicobacter pylori* infection and duodenogastric reflux in the pathogenesis of alkaline reflux gastritis after gastric operations. Surg Gynecol Obstet 1993;176:594–598.
22. Nagahata Y, Kawakita N, Azumi Y, Numata N, Yano M, Saitoh Y. Etiological involvement of *Helicobacter pylori* in 'reflux' gastritis after gastrectomy. Am J Gastroenterol 1996;91:2130–2134.
23. Leivonen M, Haglund C, Nordling S. *Helicobacter pylori* infection after partial gastrectomy for peptic ulcer and its role in relapsing disease. Eur J Gastroenterol Hepatol 1997;9:371–374.
24. Kuipers EJ, Thijs JC, Festen PM. The prevalence of *Helicobacter pylori* in peptic ulcer disease. Aliment Pharmacol Ther 1995;9 (suppl 2):59–69.
25. Offerhaus GJA, Rieu PNMA, Jansen JBMJ, Joosten HJM, Lamers CBHW. Postoperative comparative study of the influence of postoperative bile reflux on gastric mucosal histology and *Campylobacter pylori* infection. Gut 1989;30:1552–1527.
26. Nakagawara H, Miwa K, Nakamura S, Hattori T. Duodenogastric reflux sustains *Helicobacter pylori* infection in the gastric stump. Scand J Gastroenterol 2003;38(9):931–937.
27. Bechi P, Amorosi A, Mazzanti R, Romaqnoli P, Tonelli L. Gastric histology and fasting bile reflux after partial gastrectomy. Gastroenterology 1987;93(2):335–343.
28. Niemela S, Karttunen T, Heikki la J, Lehtola J. Characteristics of reflux gastritis. Scand J Gastroenterol 1987;22(3):349–354.
29. Houghton PWJ, Mortensen NJMcC, Thomas WEG, Cooper MJ, Morgan AP, Burton P. Intragastric bile acids and histological changes in gastric mucosa. Br J Surg 1986;74:354–356.
30. Ishii T. Experimental study on the atrophic gastritis especially on the cause of the postoperative gastritis and on the histogenesis of experimentally induced atrophic gastritis. Jpn Gastroenterol 1966;63:1323–1337.
31. Smith GM. An experimental study of the relation of bile to ulceration of the mucous membrane of the stomach. J Med Res 1914;30:147–184.
32. Mukawa K, Nakamura T, Nakano G, Nagamachi Y. Histopathogenesis of intestinal metaplasia: minute lesions of intestinal metaplasia in ulcerated stomachs. Clin Pathol 1987;40:13–18.
33. Silva S, Filipe MI, Pinho A. Variants of intestinal metaplasia in the evolution of chronic atrophic gastritis and gastric ulcer. A follow-up study. Gut 1990;31:1097–1104.
34. Leivonen M, Nordling S, Haglund C. Does *Helicobacter pylori* in the gastric stump increase the cancer risk after certain reconstruction types? Anticancer Res 1997;17:3893–3896.
35. Lynch DAF, Mapstone NP, Clarke AMT, et al. Cell proliferation in the gastric corpus in *Helicobacter pylori* associated gastritis and after gastric resection. Gut 1995;36:351–353.
36. Abe H, Murakami K, Satoh S, Sato R, Kodama M, Arita1 T, Fujioka T. Influence of bile reflux and *Helicobacter pylori* infection on gastritis in the remnant gastric mucosa after distal gastrectomy. J Gastroenterol 2005;40:563–569.
37. Sobala GM, O'Connor HJ, Dewar EP, King RF, Axon AT, Dixon MF. Bile reflux and intestinal metaplasia in gastric mucosa. J Clin Pathol 1993;46:235–240.

J Gastrointest Surg (2007) 11:1741–1743
DOI 10.1007/s11605-007-0292-y

Combined Resection of the Liver and the Inferior Vena Cava for Hydatid Disease

Kristin L. Mekeel · Alan W. Hemming

Published online: 15 September 2007

Abstract Hydatid disease can result in cystic liver disease. If a conservative treatment fails, these cysts require resection. Involvement of the inferior vena cava requiring resection for hydatid disease is unusual. We present a case of hydatid disease with complete caval obstruction and resultant portal hypertension that required combined liver resection and inferior vena cava replacement.

Keywords Hydatid disease · Echinococcus · Liver resection · Inferior vena cava resection

Introduction

Zoonotic infection by *Echinococcus granulosus* and *Echinococcus multilocularis* result in hydatid cyst disease in human. Echinococcal cysts occur predominately in the liver (60–70%) but can arise in the lungs, other abdominal organs, and even the thyroid.[1] Initial treatment for cyst echinococcal disease of the liver is albendazole, which has limited efficacy. Cysts have also been managed with either percutaneous drainage alone or with percutanous aspirations along with alcohol injection.[2] However, operative intervention, ranging from cyst evacuation to hepatic lobectomy, is generally recommended.

Liver resection or cyst evacuation with or without the addition of scolicidal agents remains the standard of care for hydatid disease, with excellent results. Hydatid involvement of the inferior vena cava is a rare event with the need for resection of the inferior vena cava even more unusual. Compression of the inferior vena cava by hydatid cysts can generally be dealt with by decompression and cyst evacuation, without caval resection. We present a case of hydatid disease with complete caval obstruction and resultant portal hypertention that require combined liver resection and inferior vena cava replacement.

K. L. Mekeel · A. W. Hemming
Division of Transplantation and Hepatobiliary Surgery,
Department of Surgery,
University of Florida College of Medicine,
Gainesville, FL, USA

K. L. Mekeel
e-mail: mekeek1@surgery.ufl.edu

A. W. Hemming (✉)
University of Florida Center for Hepatobiliary Disease,
P.O. Box 100286, Gainesville, FL 32610-0286, USA
e-mail: hemming@surgery.ufl.edu

Case Report

A 38-year-old male presented with a 6.5×5-cm hepatic cyst, which occluded the retro-hepatic inferior vena cava at the junction of the inferior vena cava and hepatic veins. The patient was born and raised in the Middle East and spent several years in a refugee camp. He became symptomatic over 3 years prior to his visit. His symptoms included severe right-upper-quadrant pain and fullness, shortness of breath, and weight loss. He was unable to work because of these symptoms. He was otherwise healthy. He did not have lower-extremity swelling or edema. He had been evaluated at another institution, where the lesion was considered unresectable and he was listed for liver transplantation.

Triphasic computed tomography and magnetic resonance (MR) arteriorgraphy and venography scans of the abdomen were obtained, which confirmed a large cystic mass in the caudate lobe of the liver, between the hepatic veins and inferior vena cava. It appeared to completely obstruct the inferior vena cava just below the hepatic veins (Fig. 1).

Venous flow was bypassed through a large right inferior hepatic vein, which then shunted through the liver and out the left hepatic vein (Fig. 2). The cyst had a calcified wall with a solid component, thought to be consistent with echinococcal disease. However, echinococcal serologies by radioimmunoassay were negative. Liver function test and creatinine were normal. The decision was made to proceed with operative intervention, knowing that caval resection might be necessary, because of his severe symptoms and the unclear etiology of the complex cyst.

At surgery, the liver was quite abnormal in shape and had a shrunken right lobe and a hypertrophic left lobe. An intraoperative ultrasound demonstrated massive venous shunting through the liver. The vena cava was completely obstructed with flow redirected through a large inferior hepatic vein on the right and then shunted around the mass through the liver and out the left hepatic vein. The right and middle hepatic veins were occluded at the level of the inferior vena cava. There was moderate portal hypertension presumably because of the shunting of the caval flow through the liver. The liver was then mobilized and a plastic sheet was sewn onto the liver around the cyst. The cyst was then opened, carefully keeping the contents out of the peritoneal cavity. A large amount of gelatinous material was found in the cyst, with a clear laminar membrane comprising the cyst wall. The cyst was then filled with 3% saline for 10 min. Even with cyst decompression, there was no flow through the inferior vena cava, and the portal hypertension was not improved. The liver was then mobilized off the inferior vena cava to the wall of the cyst.

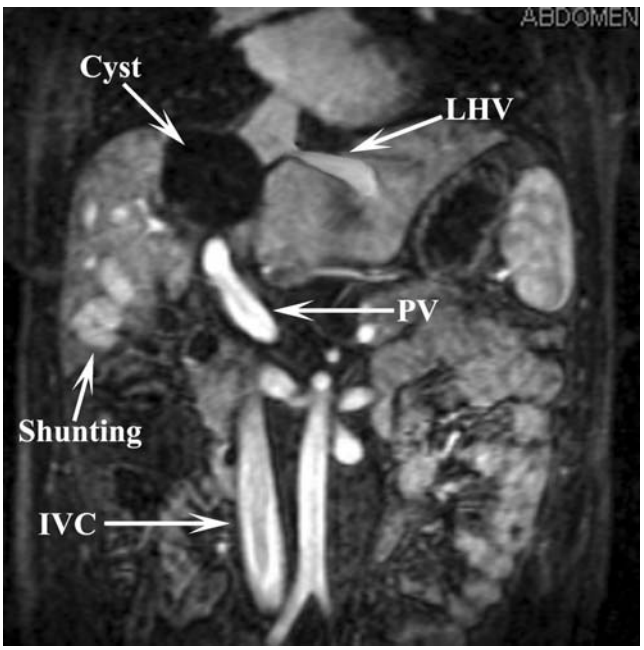


Figure 1 MR-venogram of the liver showing a large cyst adjacent to the right hepatic vein and compressing the inferior vena cava. The intrahepatic shunting is also demonstrated.

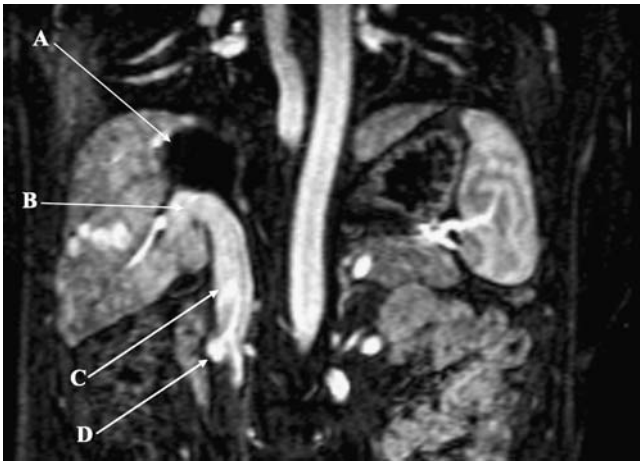


Figure 2 MR-venogram of the liver, showing complete diversion of the caval flow through the large inferior hepatic vein through the liver and out of the left hepatic vein, which is slightly narrowed by the cyst wall. A = cyst, B = diversion of caval flow through large inferior vein, C = inferior vena cava, D = right renal vein.

The edge of the cyst was just to the right of the falciform ligament, and the parenchyma was then divided as for a right trisegmentectomy (right trisectionectomy, segments 4–8 plus segment 1). The right lobe was quite atrophic with hypertrophic segments 2 and 3 resulting in a relatively large planned liver remnant. The portal pedicle was isolated and divided. The large inferior hepatic feeding vein was then ligated intrahepatically, and the suprahepatic and infrahepatic vena cava were isolated and clamped. The inferior vena cava was opened, confirming complete fibrous obstruction from the cyst in the retrohepatic portion of the cava. A cholecystectomy was performed, and intraoperative cholangiogram demonstrated no involvement of the biliary tree. The right trisegmentectomy specimen and the occluded inferior vena cava were removed en bloc. A 20-mm ringed Gore-Tex graft was then sewn end to end to the supra- and infrahepatic vena cava (Fig. 3). After the clamps

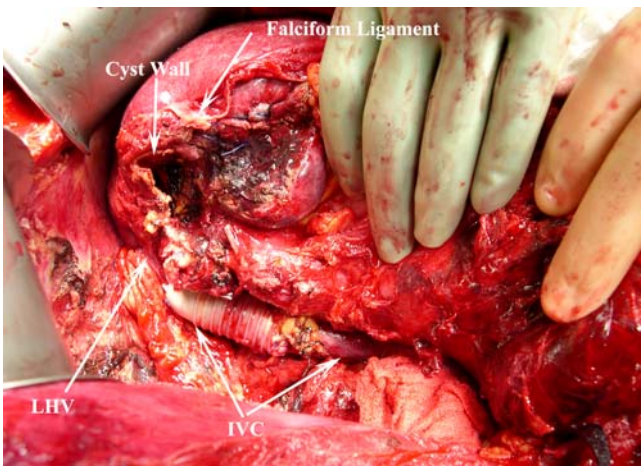


Figure 3 Intraoperative photograph demonstrating the gortex graft replacement of the inferior vena cava with the pericyst wall superiorly along the edge of the left vein.

were released, there was excellent flow through the graft. The portal hypertension was relieved.

The pathology confirmed that the histologic features of the cyst contents and the laminated membranes were consistent with echinococcal infection, although viable parasites were not identified. The patient was treated with albendazole. He was discharged from the hospital on postoperative day 8 and is currently doing well at home, back at work, and without recurrence of his symptoms at 1-year follow-up. Imaging studies demonstrate a patent inferior vena cava graft with no recurrence of his hydatid disease.

Discussion

A review of the English literature lists four case reports of hydatid cyst involving the vena cava resulting in thrombosis, embolization to the lungs, and even vena cava rupture into the cyst resulting in death.[3–6] There is a single case report of obstruction of the vena cava by a cyst, which resolved with percutaneous treatment.[7] In another series of 11 patients, 8 (73%) had complete obstruction of the inferior vena cava and 3 (27%)[1] had partial obstruction secondary to hydatid cysts.[8] Only four (36%) exhibited signs of chronic venous insufficiency of the lower extremities; one patient had a pulmonary embolism. Five patients (45%) in this series had evidence of abdominal collateralization, with main drainage through the lumbar, azygous, and hemiazygous veins. None of these patients required surgical intervention.

Most of the studies concerning hydatid involvement of the inferior vena cava refer to patients with alveolar echinococcus, which has a more widespread and invasive pattern than the simple hydatid cyst disease seen in this patient. As a result, inferior vena caval involvement is more common, but it is also harder to treat successfully. One study published experience with 18 patients who required liver resection for alveolar echinococcus.[9] Four of the nine patients underwent trisegmentectomy, but for involvement of the hepatic duct and not of the inferior vena cava. Inferior vena caval involvement was an indication for palliative resection in this series. Nine patients underwent palliative resection, of which two died from echinococcal disease during the follow-up period. They did find that radical resection of all disease had a survival advantage for patients with the alveolar form of echinococcus but did not undertake radical resections in patients with inferior vena cava involvement.

There are two case reports describing inferior vena caval invasion treated with radical resection and one case with replacement with a Dacron graft. The first describes a hydatid cyst invading the inferior vena cava from the hepatic portion of the inferior vena cava to the right atrium–inferior vena cava function.[8] The resection involved portions of the inferior vena cava and right atrium, which was then closed primarily with Prolene suture, after placing the patient on cardio-pulmonary bypass. The patient was well 4 months after surgery. Another case report describes resection of the inferior vena cava and Dacron graft replacement for hydatid disease involving the anterior wall of the retrohepatic inferior vena cava.[10] This patient also recovered uneventfully and had a patent graft without recurrence 24 months after surgery. To our knowledge, there are only two previous reports of hydatid disease that have undergone successful combined resection of the liver and inferior vena cava.

This case report illustrates that a hydatid cyst with caval involvement may rarely require a combined procedure of hepatic lobectomy and caval resection. Cyst drainage alone in this patient would not have treated the caval obstruction, venous shunting, and resultant portal hypertension, thus making the combined resection necessary.

References

1. Hamamci EO, Besim H, Korkmaz A. Unusual locations of hydatid disease and surgical approach. ANZ J Surg 2004;74:356–360.
2. Filice C, Pirola F, Brunetti E et al. A new therapeutic approach for hydatid liver cysts. Aspiration and alcohol injection under sonographic guidance. Gastroenterology 1990;98:1366–1368.
3. Anuradha S, Agarwal SK, Khatri S et al. Spontaneous rupture of hepatic hydatid cyst causing inferior vena cava thrombosis. J Gastroenterol 1999;18:34.
4. Berthet B, N'Guema R, Assadourian R. An unusual complication of hydatid disease of the liver: spontaneous operative rupture of the inferior vena cava into the cyst wall. Case report. Eur J Surg 1994;160:447–448.
5. Gruttadauria S, Luca A, Cintorino D et al. Hepatic hydatid cyst causing thrombosis of the inferior vena cava and complicated by hemobilia: a multimodal sequential approach in the treatment. Dig Dis Sci 2003;48:358–364.
6. Caballero J, Arana R, Calle G et al. A hydatid cyst in the vena cava inferior and right atrium with venous flow obstruction and pulmonary dissemination. Rev Esp Cardiol 1999;52:281–284.
7. Rajagopal Kv, Bishwas R. Hydatid cyst of the liver presenting as an inferior vena cava obstruction. J Clin Ultrasound 2002;30:114–116.
8. Karunajeewa HA, Jones RM, Hardy KJ et al. Hydatid disease invading the inferior vena cava: successful combined medical and surgical treatment. ANZ J Surg 2002;72:159–160.
9. Partensky C, Landraud R, Valette PJ et al. Radical and nonradical hepatic resection for alveolar echinococcosis: report of 18 cases. World J Surg 1990;14:654–659.
10. Landra Garcia JI, Moreno Azcoita M, Moreno Gonzalez E et al. Resection of suprarenal inferior vena cava and dacron graft replacement without right nephrectomy for echinococcal cyst. Case report and review of the literature. Ital J Surg Sci 1984;14:327–332.

J Gastrointest Surg (2007) 11:1744–1751
DOI 10.1007/s11605-007-0232-x

Salvage Surgery After Failed Chemoradiation For Anal Canal Cancer: Should The Paradigm Be Changed For High-Risk Tumors?

David Stewart · Yan Yan · Ira J. Kodner · Elisa Birnbaum · James Fleshman · Robert Myerson · David Dietz

Received: 14 May 2007 / Accepted: 26 June 2007 / Published online: 6 September 2007

Abstract It is common belief that patients failing chemoradiation therapy (CRT) for squamous cell cancer of the anus (SCCA) can be salvaged with subsequent surgery. The aim of this study was to examine our experience with abdominoperineal resection (APR) in cases of persistent or recurrent SCCA with an emphasis on survival and morbidity. All patients between 1985 and 2001 undergoing salvage APR were reviewed. Details of CRT, surgery, tumor characteristics, postoperative complications, and survival were obtained from medical records. There were 22 patients (13 women, 9 men) with a mean age of 62 years (range=42–87). Initial tumors were AJCC stage 2 (16 cases), 3A (3 cases), and 4 (1 case). Mean radiation dose was 47.6 Gy (30–60) and most received concomitant 5-FU. In 20 patients, APR was felt to be "curative" but only 13 (65%) had negative margins on final pathology. Thirteen (59%) perineal wounds broke down with a median time to healing of 7 months. Tumor differentiation (p=0.02) and positive resection margins (p=0.004) were significantly associated with DFS (5-year DFS of 37%). Salvage APR in patients with poorly differentiated tumors or positive resection margins has a high morbidity and poor survival and may warrant a *planned* APR after CRT instead.

Keywords Anal cancer · Abdominoperineal resection · Chemoradiation therapy · Salvage surgery

This manuscript was presented at the poster session of the 2002 ASCRS meeting.

D. Stewart · I. J. Kodner · E. Birnbaum · J. Fleshman · D. Dietz (✉)
Section of Colon and Rectal Surgery, Department of Surgery,
Barnes-Jewish Hospital,
Washington University School of Medicine,
660 S. Euclid Ave., Suite 14102 Queeny Tower,
Campus Box 8109, St. Louis, MO 63110, USA
e-mail: dietzd@wudosis.wustl.edu

Y. Yan
Division of Urologic Surgery, Department of Surgery,
Washington University School of Medicine,
4960 Children's Place, Campus Box 8242,
St. Louis, MO 63110, USA

R. Myerson
Department of Radiation Oncology,
Washington University School of Medicine,
660 S. Euclid Avenue, Campus Box 8224,
St. Louis, MO 63110, USA

Introduction

Since the introduction of the Nigro protocol in 1974, non-surgical treatment of squamous cell carcinoma of the anal canal (SCCA) with chemoradiation therapy (CRT) has become the standard approach to this disease.[1] The change from primary surgical resection to primary CRT has resulted in significant improvements in patient outcomes compared to historical results seen with abdominoperineal resection (APR), which had local recurrence rates from 20% to 50%[2,3] and 5-year survival rates as low as 40%.[4,5] However, it is still estimated that between 10% and 15% of patients will fail primary CRT[6] and up to 30%[6–8] of those who initially respond to CRT will recur. Traditionally, patients who developed persistent or recurrent disease have undergone "salvage" APR, but because of the rarity of SCCA, there is a paucity of literature on outcomes after APR for CRT treatment failures.[9,10] Furthermore, the outcomes listed in these studies range from poor to encouraging regarding survival with no clear predictors of outcome after salvage APR emerging. The aim of this study was to examine our experience with salvage APR in cases of persistent (reappear-

Table 1 Patient Information

Patient descriptor	Value
Gender	
Male	9
Female	13
Age (years)	
Mean (±SD)	62 (±11.9)
Range	42–87
Mean for patients who died (±SD)	656±14
Mean for patients alive at end of study (±SD)	58.1±7.3
T stage before CRT	
T1	0
T2	9 (42.8%)
T3	11 (52.3%)
T4	1 (4.5%)
Unknown	1 (4.5%)
Nodal status before CRT	
Negative	13 (61.9%)
Positive	8 (38.1%)
Unknown	1 (4.5%)
Presence Of distant metastases before CRT	
Yes	1 (4.5%)
No	21 (95.5%)
AJCC stage	
Stage I	0
Stage II	16 (76.1%)
Stage IIIa	3 (14.2%)
Stage IIIb	1 (4.5%)
Stage IV	1 (4.5%)
Unknown	1 (4.5%)
Radiation dose (Gy)	
Mean	47.6
Range	30–60
Complete clinical response	
Yes	12
No	8
Unknown	2
Tumor differentiation	
Well	1
Moderate	8
Moderate–poor	3
Poor	7
Unknown	3
Time to recurrence (months)	
Mean (±SD)	9.7 (±10.6)
Range	0–38
Mean TTR for patients who died (±SD)	5.5±11.6
Mean TTR for patients alive at end of study (±SD)	14.7±12.3
Category of disease before APR	
Persistent (<6 months)	9
Recurrent (>6 months)	13

ance of the cancer <6 months after CRT) and recurrent (reappearance of the cancer >6 months after CRT) SCCA with particular attention on morbidity and oncologic outcome. Predictors of survival were also sought.

Materials and Methods

This was a retrospective study undertaken with the approval from our institution's Investigational Review Board (IRB). All patients who underwent a salvage APR for SCCA from 1985 to 2001 were reviewed using our institution's IRB approved departmental database. Patient demographics, initial tumor staging, details of chemoradiation therapy, pattern of failure, and details of the APR, including intraoperative and postoperative complications, were gathered from medical records. Disease status at last follow-up was obtained through the tumor registry of the Siteman Cancer Center at the Washington University School of Medicine and by reviewing Medicare lists. Statistical analysis of factors related to recurrence and survival was performed by chi-square analysis, the Fisher's exact test, and comparison of means by the Student's *t*-test as appropriate. Kaplan–Meier (KM) curves were generated to plot time to recurrence and overall survival, and comparison of KM curves was performed by log-rank analysis.

Results

Patient Demographics and Details of Primary Tumors

A total of 22 patients (13 women, 9 men) were included in this study. All patients had anal canal cancers; no cancers of the anal margin were included. The median age of all patients was 60.5 years (mean=62±11.9 years; range=42–87 years). Patient demographics, initial treatment, and recurrence information is summarized in Table 1. Histology before CRT revealed that 21 of the cancers were squamous cell type whereas one lesion had adenosquamous histology. The T stage of each patient before CRT was reviewed. No patients had T1 cancers (≤2 cm in greatest dimension), 9 patients (42.8%) had T2 cancers (2–5 cm in greatest dimension), 11 patients (52.3%) had T3 cancers (≥5 cm in greatest dimension), 1 patient (4.5%) had a T4 cancer (tumor invades deep structures such as muscle, bone or

Table 2 Results of Pretreatment Transrectal Ultrasound (TRUS)

Stage by TRUS	Number
uT Stage	
uT1	0
uT2	2
uT3	2
uT4	1
uN Stage	
uN0	2
uN1	3

Table 3 Initial Staging and Treatment of Patients with Persistent and Recurrent Anal Cancers After CRT

Disease type	*N*	Male/female ratio	Stage I	Stage II	Stage III	Stage IV	Unknown	Mean (Gy)
Persistent	9	5/4	0	4 (44%)	3 (33%)	1 (11%)	1 (11%)	46.9 (30–60)
Recurrent	13	3/10	0	12 (92%)	1 (7.6%)	0	0	48.2 (30–60)

cartilage), and 1 (4.5%) patient's T stage was unknown. Five (23%) patients underwent a pretreatment transrectal ultrasound (TRUS) with the results recorded in Table 2. The single patient with a uT4 lesion was found to have invasion into the prostate before CRT. All patients underwent a pretreatment CT scan of the abdomen and pelvis to identify metastatic disease.

Four patients were noted to have clinically positive inguinal lymph nodes at the time of diagnosis, and the inguinal nodal basins were included in the field of radiation during CRT. Three of those patients were found to have suspicious perirectal lymph nodes based on TRUS. A single patient had distant metastatic disease involving the liver on CT, which was diagnosed before CRT, and this patient underwent a subsequent liver resection of the metastasis at the time of salvage APR. Two of the patients had anal condylomata, and none of the patients studied were HIV positive. Using the American Joint Committee on Cancer (AJCC) staging system, the pretreatment breakdown of staging for all patients was as follows: stage I (0), stage II (16/22, 76.1%), stage IIIa (3/22, 14.2%), stage IIIb (1/22, 4.5%), and unknown stage (1/22, 4.5%).

Details of Initial CRT

All patients received CRT as initial treatment of their anal cancer with 7 (32%) patients receiving their CRT at an institution other than Washington University. The median radiation dose was 47 Gy (mean=47.6±7.87 Gy; range=30–60 Gy). The breakdown of chemotherapy was as follows: 21 (95.4%) patients received 5-FU, 16 (72.7%) patients received mitomycin-C (MMC), and 2 (9%) patients received cyclophosphamide (CP). After the initial CRT for the primary tumor, 12 (54.5%) patients were noted to have a complete clinical response (CCR) to CRT, 8 (36.3%) had residual tumor after CRT, and the response of 2 patients (9%) was unknown.

Timing and Presentation of Persistent/Recurrent Disease

Table 3 reports the stage and radiotherapy information for persistent and recurrent anal cancers. Persistence of disease (9/22, 41%) was defined as the reappearance of the anal canal cancer less than 6 months after CRT, whereas reappearance of anal cancer 6 months after CRT was considered to be a recurrence (13/22, 59%). Within 6 months after CRT, 14 patients had a surveillance examination under anesthesia with biopsies of the anal canal. Of these 14 patients, 9 (64%) had a positive biopsy for anal canal cancer whereas 5 (36%) patients had negative biopsy results. Of these 14 patients, 8 (57%) were eventually diagnosed with recurrent disease, whereas the remaining 6 (43%) demonstrated persistent disease.

The manner in which each persistent or recurrent cancer presented during surveillance after CRT was reviewed. Twenty-one (95%) patients with failure after CRT were found to have a mass; in two of these patients (one with recurrent and one with persistent disease), the mass was located in the inguinal region whereas the remainder were within the anal canal. Of these 21 patients who presented with a mass, 12 (57%) had recurrent disease and 9 (43%) had persistent disease. Additional presenting complaints included anal pain (n=2, both with recurrent disease) and bleeding (n=1, recurrent disease).

The median time to the reappearance (TTRe) of disease for all patients after CRT, whether persistent or recurrent, was 7 months (mean=9.7±10.6 months; range=0–38 months). For recurrent disease, the median TTRe was 15 months (mean=15±10.6 months; range=2–38 months), and for persistent anal canal cancers, the median TTRe was less than 1 month (mean=1.72±2.84 months; range=0–7 months). The median TTRe after CRT for patients who eventually died during the study period was 2.5 months (mean=5.5±11.6 months; range=0–21 months), and for those alive at the end of the study, the median TTRe was 12 months (mean=14.7±12.3 months; range=0–38 months). The difference in TTRe between those alive and dead at the conclusion of the follow-up period was significant (Student's t-test, p=0.039).

Details of "Salvage" APR

All patients in this study failed CRT and were subsequently treated with APR. The median interval to salvage APR for all patients was 10 months (mean=12.1±9.76 months;

Table 4 Disease Status at Last Follow-up

Disease status	Number of patients
Disease-free	11
Local recurrence	7
Local+distant recurrence	1
Distant recurrence	3

Table 5 Univariate Predictors of Overall Survival

Variable	Significance (p value)
Gender	1.00
Pretreatment T stage	0.428
Pretreatment N stage	0.673
AJCC stage before CRT	0.397
Complete clinical response to CRT	1.00
Intent of surgery (curative vs palliative)	0.48
Groin metastases at time of APR	1.00
Presence of distant disease at time of APR	1.00

range=1–38 months). For patients with recurrent disease, the median time to APR was 15 months (mean=16.2± 10 months; range=2–38 months) and for those with persistent disease, the median time to surgery was 3 months (mean=5.61±5.78 months; range=1–19 months). Patients with persistent disease had a significantly shorter time interval between CRT and salvage APR than those with recurrent cancers (Student's t-test, p=0.01).

Operative records were reviewed for each patient. In 20 (91%) cases, APR was performed with curative intent, whereas 2 (9%) APR's were palliative (1 recurrent cancer, 1 persistent). Only one patient (persistent disease) had positive inguinal lymph nodes noted at salvage APR. In 4 (18%) cases, an en bloc resection of an adjacent organ was performed, each case involving a partial vaginectomy; all of these were recurrent cancers. No other adjacent organs were involved at the time of salvage APR. One (4.5%) patient who had persistent disease was known before surgery to have a metastatic lesion involving the liver and underwent a right hepatic lobectomy at the time of APR.

Intraoperative blood loss (EBL) was recorded for 13 patients (6 with recurrent and 7 with persistent disease) with a median blood loss of 400 cc (mean=542±315 cc; range= 200–1,100 cc) for all patients. One patient required flap reconstruction of the perineum, whereas the remainder of the patients had their perineal wounds closed primarily. The median postoperative length of stay (LOS) in the hospital was 7.5 days (mean=8±4.1 days; range=3–20 days).

Surgical Pathology

Surgical pathology revealed that 20 (91%) patients had SCCA and 2 (9%) patients had adenosquamous histology. The median size of all resected tumors was 3 cm (mean= 3.11±1.71 cm; range=0–7 cm). For recurrent cancers, the median size was greater than for persistent tumors (recurrent-median=3.5 cm [mean=3.74±1.56 cm; range= 1.5–7 cm] vs persistent-median=2 cm [mean=2.22± 1.60 cm; range=0–4.5 cm]; p=0.038). Only 2/22 (9%) patients had positive perirectal lymph nodes on pathology. The median number of nodes examined in each specimen was 2 (mean=4.32±4.44; range=0–15). Nine patients had either lymphovascular or perineural invasion on histology, and there was no significant difference in lymph node involvement or the presence of lymphovascular or perineural invasion between recurrent and persistent cancers.

The most common tumor differentiation was moderate (n=8), followed by poor (n=7), moderate–poor (n=3), and well-differentiated (n=1). In three patients, tumor differentiation was not reported. Thirteen (59%) patients had negative surgical margins, 7 (31.8%) patients had margins involved with cancer, and the margin status of 2 patients was unknown.

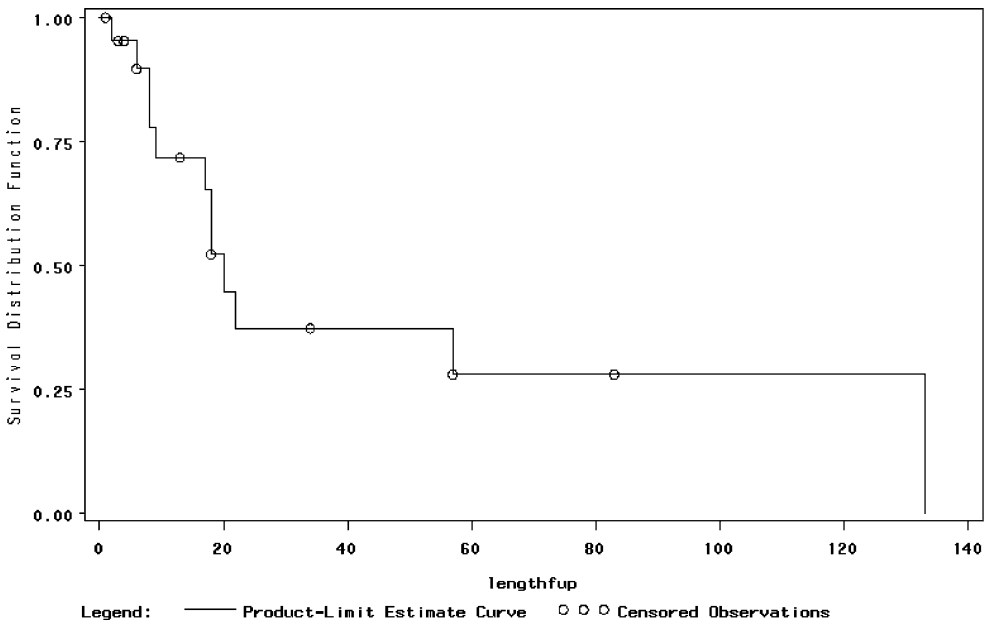


Figure 1 Kaplan–Meier curve for overall survival for all patients with anal cancer.

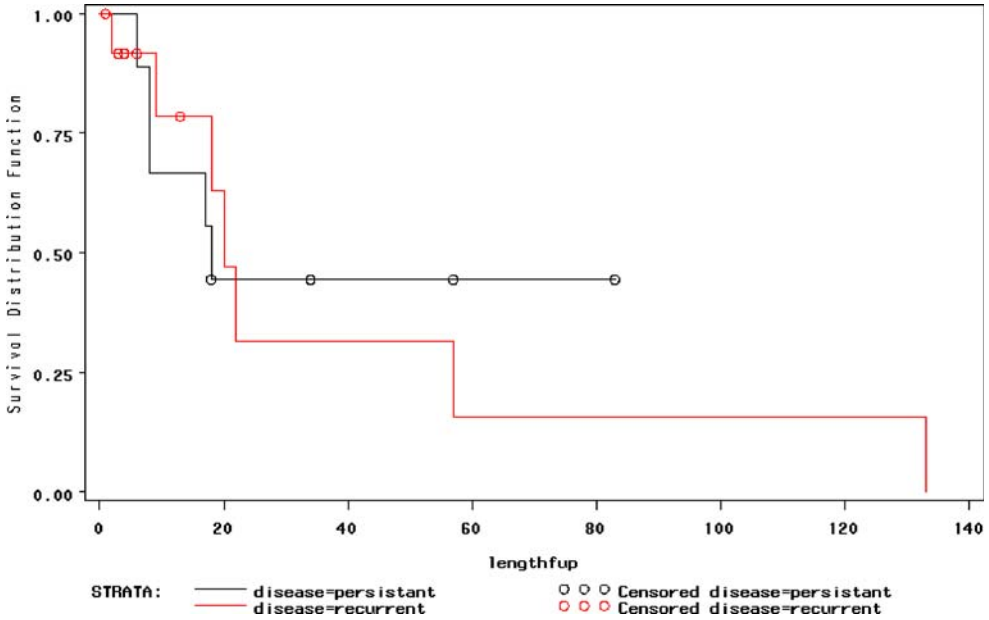


Figure 2 Kaplan–Meier curves comparing overall survival in patients with recurrent vs persistent disease. Log-rank, p=0.77.

Using the Fisher's exact test, no significant difference in the status of the surgical margins between recurrent and persistent disease was demonstrated (p=0.174).

Complications of "Salvage" APR

There were no intraoperative complications or perioperative deaths in this series. The overall postoperative complication rate was 78%. Early postoperative complications, defined as occurring within 30 days from the date of surgery, were observed in 18 (81%) patients. Early complications included perineal wound breakdown (13/22, 59%), one of which required reoperation. Other complications included pelvic abscess (n=1), an enterotomy requiring reoperation (n=1), urinary retention (n=2), and erectile dysfunction (n=2). Late postoperative complications (beyond 30 days after surgery) occurred in 4/22 (18%) patients. Late complications included a small bowel obstruction requiring laparotomy (n=1), an incisional and parastomal hernia in the same patient with both requiring repair (n=1), an obstructed left ureter (n=1), and a colostomy prolapse that was managed nonoperatively (n=1).

The time required for perineal wound healing was recorded for 12/13 patients who had a breakdown of their perineal wound. The median time to wound healing was 7 months (mean=7.16±2.82 months; range=3–12 months).

Oncologic Outcomes After "Salvage" APR

The final disease status of all patients is listed in Table 4. After salvage APR, 11/22 (50%) patients developed a recurrence of their cancer. Time to recurrence (TTR) information was recorded in 8/11 cases. The median TTR for all patients after salvage APR was 9 months (mean=12.9±15.4 months; range=2–50 months). For patients who had a recurrence after CRT, the median TTR was 11.5 months (mean=20.2±19.9 months; range=8–50) and for patients who had persistent disease after CRT, the median TTR was 5 months (mean=5.5±3.42; range=2–10 months). The difference between the TTR for recurrent and persistent cancers was not significant (Student's t-test, p=0.194).

Although information on patient symptoms at the time of recurrence was incomplete, the most common symptom was pain (n=5), followed by either the presence of a mass (n=1) or a nonhealing perineal wound (n=1). Recurrences included the pelvis (n=6), liver (n=2), bone (n=2), vulva (n=1), and mesentery (n=1). Recurrences were isolated local recurrences in 9 (81%) of these patients. Out of the 11 recurrences, 6 (54%) occurred in patients who had undergone salvage APR for recurrent disease. Comparing recurrence rates after salvage APR between those who had persistent and recurrent disease after CRT revealed no significant difference between these two groups (Fisher's exact test, p=1.00).

Table 6 Univariate Predictors of Disease-free Survival

Variable	Significance (p value)
Pretreatment T stage	0.359
Pretreatment N stage	1.00
AJCC stage before CRT	0.467
Complete clinical response to CRT	0.669
Presence of nodal metastases	0.214
Lymphovascular and/or perineural invasion	0.405
Tumor differentiation	0.02
Status of resection margin	0.004

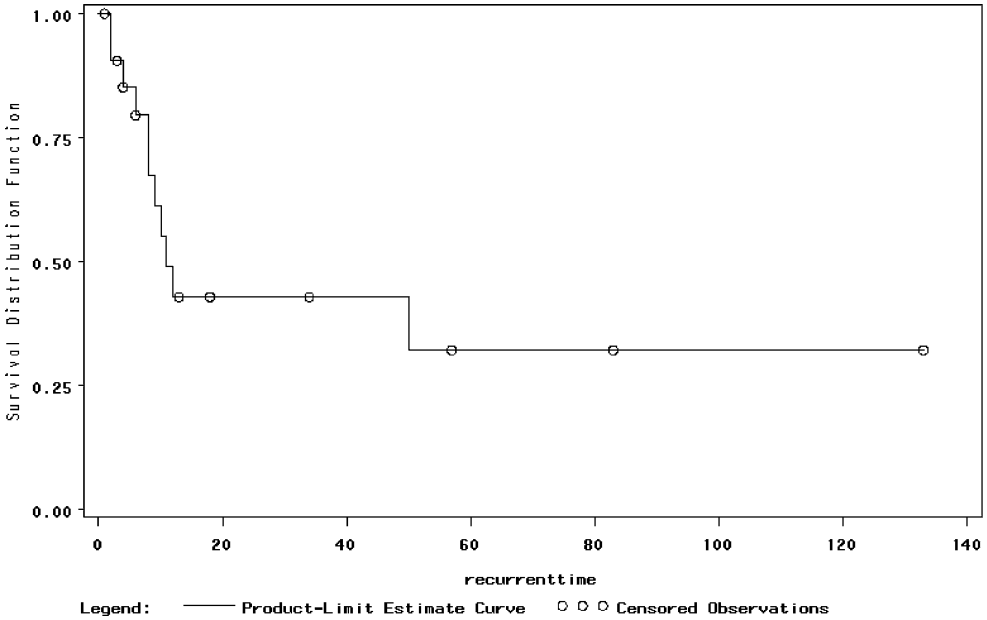


Figure 3 Kaplan–Meier curve for disease-free survival for all patients with anal cancer.

Survival Analysis

The median follow-up time for all patients was 15 months. By the end of the follow-up period, 12 patients were dead from anal cancer with a median age of 70 years (mean age=68.2±16.9 years; range=42–98 years) and 10 patients were still alive with no evidence of disease with a median age of 58 years (mean age=58.1±7.3 years; range=42–67 years).

Univariate analysis was performed to determine which variables influenced overall survival (OS). A list of univariate analysis for overall survival is given in Table 5. Using the Fisher's exact test to calculate two-tailed probabilities, gender (p=1.00), pretreatment N stage (p=0.673), complete clinical response to CRT (p=1.00), intent of surgery (p=0.48), the presence of inguinal nodal metastases at the time of APR (p=1.00), and the presence of distant disease at time of APR (p=1.00) did not have a significant influence on OS. Using the chi-squared test, pretreatment T stage (p=0.428) and AJCC stage before CRT (p=0.397) were also non-predictive. Analysis of continuous variables including age, time to recurrence, and interval to salvage APR was performed with respect to OS. Age (p=0.141) and interval

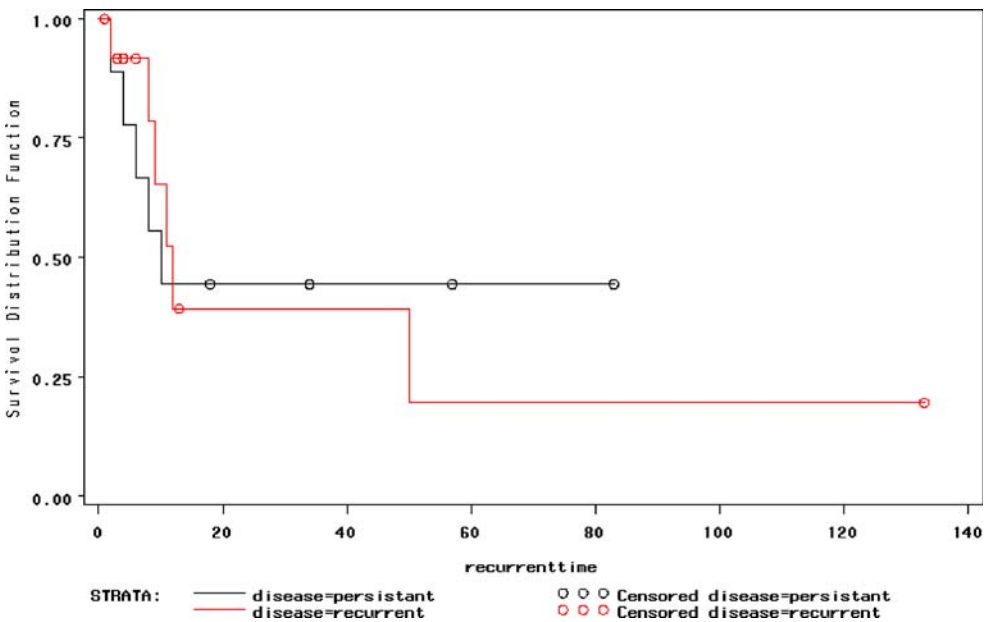


Figure 4 Kaplan–Meier curves comparing disease-free survival in patients with recurrent vs persistent disease. Log-rank, p=0.943.

to salvage APR (p=0.129) did not influence OS. A shorter time to recurrence after salvage APR, however, was associated with a shorter OS (p=0.038).

A Kaplan–Meier curve for OS in all patients is seen in Fig. 1. The median OS for all patients was 18 months. Figure 2 shows the KM curves for OS in patients with persistent vs recurrent disease after CRT. The median OS for all patients with persistent disease was 17.5 months, whereas all patients with recurrent disease had a median survival of 18.5 months. Using log-rank analysis to compare the two survival curves demonstrated no significant differences between them (p=0.77).

The same analysis was performed for factors related to DFS (Table 6). Using univariate analysis with the Fisher's exact test, the status of the resection margin (p=0.004) impacted DFS, whereas pretreatment N stage (p=1.00), CCR (p=0.669), nodal metastases (p=0.214), and lymphovascular or perineural invasion on histology (p=0.405) did not influence DFS. Using the chi-squared test, tumor differentiation (p=0.02) impacted DFS whereas pretreatment T stage (p=0.359) and AJCC stage before CRT (p=0.467) did not. Analyzing the tumor size as a continuous variable did not reveal a significant impact on DFS (p=0.126). Based on a KM curve including all patients, the median DFS for all patients was 10.5 months (Fig. 3). For persistent cancers, the median DFS was 8.5 months, and for recurrent cancers, the median DFS was 11.5 months (Fig. 4). Using log-rank analysis to compare DFS between persistent and recurrent cancers revealed no significant difference in survival (p=0.943).

Discussion

Although APR as the initial treatment for SCCA has fallen from favor because of the superior results of CRT, APR has remained a commonly used treatment for patients who fail CRT from persistent or recurrent cancers. As mentioned earlier, despite the high response rates to CRT, there are still a substantial number of patients who eventually fail primary therapy and will require "salvage therapy" of some type. In the previously cited study by Akbari,[6] the median overall survival in all patients undergoing salvage surgery was 34 months with a median follow-up time of 24 months; other studies report similar findings.[8–10]

A recent paper by Myerson et al. reviewed the oncologic outcomes of 106 patients who underwent radiation therapy for epidermoid anal canal carcinomas between 1975and 1997.[11] Because of the time period covered in this study, the treatment of patients ranged from radiation alone or combined with surgery to CRT followed by surgery or CRT alone. The most important predictor of freedom from disease at 5 years after treatment was the extent of disease at the time of diagnosis with 87% of T1/T2N0 cancers having a 5-year ultimate freedom from cancer. In this series, planned surgery after CRT offered no survival advantage compared to surgery after diagnosis of a recurrent cancer. One of the main conclusions of this paper was that for early stage (T1/T2N0) cancers, moderate doses of radiation combined with combination chemotherapy are adequate treatment, whereas advanced cancers (T4N0 and node positive disease) require further investigation to evaluate the most effective dosage of radiation and the most effective CRT protocols.

Morbidity was a significant problem for patients undergoing salvage APR in this series with a 78% overall complication rate. By far, perineal wound healing was the most common complication regardless of the time elapsed after surgery, making up 60% of all early complications. The time required for perineal wound healing averaged over 7 months. This coincides with other series that mark perineal wound healing as the most common complication after salvage APR, much as it is for APR in other settings.[12] CRT likely plays a role in the widespread wound healing delays seen in salvage APR for anal cancer, as may the location of the wound in a weight bearing area.

Conclusion

Salvage abdominoperineal resection after failed chemoradiation therapy for SCCA has a high morbidity rate and poor overall and disease-free survival. Poorly differentiated cancers, positive resection margins, and a short time interval between CRT and failure are predictors of poor outcome after salvage APR. With this in mind, patients with primary tumors at high risk for local failure (i.e., poorly differentiated and higher stage anal cancers) may benefit from a planned APR after CRT. Although this may not improve survival, it is plausible that morbidity rates might be lower with a planned surgery rather than surgery after reappearance of the cancer. Furthermore, the success of achieving negative margins of resection may also be improved. Patients with persistent or recurrent disease after CRT had no significant differences in complications or survival, and therefore both groups may benefit from planned APR after neoadjuvant therapy.

References

1. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum 1974;17:354–356.
2. Schraut WH, Wang CH, Dawson PJ, Block GE. Depth of invasion, location, and size of cancer of the anus dictate operative treatment. Cancer 1983;51:1291–1296.

3. Dougherty BG, Evans HL. Carcinoma of the anal canal: a study of 79 cases. Am J Clin Pathol 1985;83:159–164.
4. Bowman BM, Moertel CG, O'Connell MJ, Scott M, Weiland LH, Beart RW, Gunderson LL, Spencer RJ. Carcinoma of the anal canal. A clinical and pathological study of 188 cases. Cancer 1984;54:114–125.
5. Pintor MP, Northover JM, Nicholls RJ. Squamous cell carcinoma of the anus at one hospital from 1948 to 1984. Br J Surg 1989;76:806–810.
6. Akbari RP, Paty PB, Guillem JG, Weiser MR, Temple LK, Minsky BD, Saltz L, Wong WD. Oncologic outcomes of salvage surgery for epidermoid carcinoma of the anus initially managed with combines modality therapy. Dis Colon Rectum 2004;47:1136–1144.
7. Longo WE, Vernava AM, Wade TP, Coplin MA, Virgo KS, Johnson FE. Recurrent squamous cell carcinoma of the anal canal. Predictors of initial treatment failure and results of salvage therapy. Ann Surg 1994;220:40–49.
8. Ellenhorn JD, Enker WF, Quan SH. Salvage abdominoperineal resection following combined chemotherapy and radiotherapy for epidermoid carcinoma of the anus. Ann Surg Oncol 1994;1:105–110.
9. Pocard M, Tiret E, Nugent K, Dehni N, Parc R. Results of salvage abdominoperineal resection for anal cancer after radiotherapy. Dis Colon Rectum 1998;41:1488–1493.
10. Zelnick RS, Haas PA, Ajlouni M, Szilagyi E, Fox TA. Results of abdominoperineal resections for failures after combination chemotherapy and radiation therapy for anal canal cancer. Dis Colon Rectum 1992;35:574–578.
11. Myerson RJ, Kong F, Birnbaum EH, Fleshman JW, Kodner IF, Picus J, Ratkin GA, Read TE, Walz BJ. Radiation therapy for epidermoid carcinoma of the anal canal, clinical and treatment factors associated with outcome. Radiother Oncol 2001;61(1):15–22.
12. Nilsson PJ, Svensson C, Goldman S, Glimelius B. Salvage abdominoperineal resection in anal epidermoid cancer. Br J Surg 2002;89:1425–1429.

J Gastrointest Surg (2007) 11:1752–1754
DOI 10.1007/s11605-007-0231-y

Gastroduodenal Artery Pseudoaneurysm Associated with Hemosuccus Pancreaticus and Obstructive Jaundice

Jaime L. Bohl · Lesly A. Dossett · Ana M. Grau

Received: 8 June 2007 / Accepted: 17 June 2007 / Published online: 17 July 2007

Abstract A 42-year-old male was admitted with recurrent gastrointestinal bleeding and new-onset jaundice. Computed tomography showed a persistent gastroduodenal artery pseudoaneurysm and dilated intrahepatic and extrahepatic ducts consistent with obstructive jaundice. This patient had two previous coil embolizations, which failed to prevent recurrent bleeding. The patient underwent pancreaticoduodenectomy for definitive treatment of his pseudoaneurysm. We report this case and review the literature.

Keywords Hemosuccus pancreaticus · Pseudoaneurysm · Pancreaticoduodenectomy · Pancreatitis

Introduction

Hemosuccus pancreaticus (HP), defined as bleeding through the pancreatic duct, is a rare cause of gastrointestinal (GI) bleeding that usually develops from complications of pancreatitis. Causes of bleeding in patients with pancreatitis are multiple; however, as many as 10% of patients with pancreatitis develop pseudoaneurysms of peripancreatic arteries. Commonly involved arteries are the splenic, gastroduodenal (GDA), and pancreaticoduodenal arteries.[1,2] We report a patient with recurrent HP and associated obstructive jaundice secondary to a GDA pseudoaneurysm who required pancreaticoduodenectomy.

J. L. Bohl · L. A. Dossett
Department of Surgery, Vanderbilt University,
Nashville, TN, USA

A. M. Grau (✉)
Department of Surgery, Division of Surgical Oncology
and Endocrine Surgery, Vanderbilt University,
2220 Pierce Ave, 597-PRB,
Nashville, TN 37232-6860, USA
e-mail: ana.grau@vanderbilt.edu

Case Report

A 42-year-old male with a 10-year history of alcohol-induced pancreatitis and a presumed pancreatic head pseudocyst presented in May 2005 with an acute GI bleed, characterized by melena and a hematocrit of 14.0%. The patient had an esophagogastroduodenoscopy and colonoscopy which did not reveal the source of GI bleeding. A computed tomography (CT) was performed, which demonstrated contrast within a cystic mass of the pancreas consistent with a pseudoaneurysm arising from the GDA. During the next 4 months, the patient required coil embolization of the pseudoaneurysm on two occasions due to HP and GI bleeding.

A month after his second embolization, he presented with recurrent bleeding, obstructive jaundice, and a 20-lb weight loss. Repeat CT demonstrated increased size of the GDA pseudoaneurysm from 4 to 6 cm with active blood flow and replacement of the pancreatic head. The patient was also noted to have dilated pancreatic and extrahepatic biliary ducts, as well as pancreatic calcifications (Fig. 1). The patient was taken for pancreaticoduodenectomy with en-bloc excision of the GDA pseudoaneurysm. Laparotomy revealed a large pseudoaneurysm arising from the GDA with active blood flow despite the presence of coils within the neck of the pseudoaneurysm. A short segment of normal-caliber GDA was identified (Fig. 2); preoperative CT scan had shown this small segment to be free from coils. This allowed for safe ligation and transection of the GDA. Pancreaticoduodenectomy was performed demon-

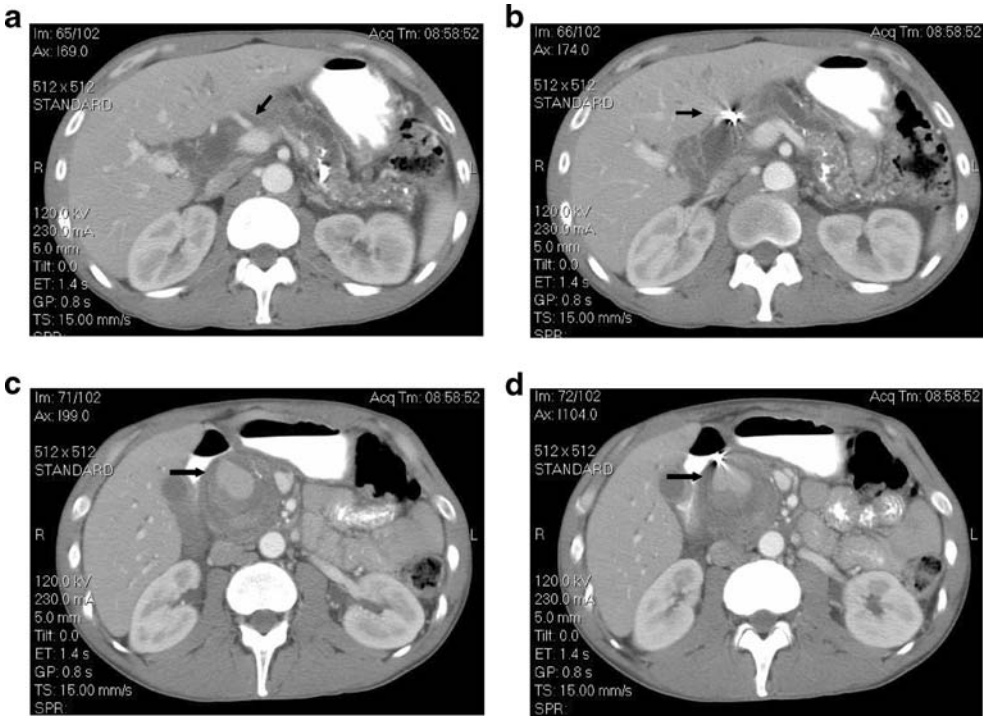


Figure 1 CT scan of abdomen. **a** and **b** consecutive sections showing pancreatic body an tail with dilated pancreatic duct and calcifications, *arrow* in **a** indicates the location of the common hepatic artery, and *arrow* in **b** indicates artifact from coils in the origin of the GDA. **c** and **d**, *arrows* demonstrate the GDA pseudoaneurysm with active blood flow.

strating a superior mesenteric vein that abutted but did not adhere to the pseudoaneurysm. Dilated pancreatic and common bile ducts were identified. Figure 3 demonstrates the resected specimen with a dilated pancreatic duct that had a small remnant of pancreatic tissue proximal to the GDA pseudoaneurysm. Gross inspection of the tumor revealed a 7×6×5.5-cm mass that adhered to the duodenum. On section, a hemorrhagic center surrounded by a thick, yellowish 1.5-cm wall was identified. The pancreatic duct was dilated measuring 1 cm in diameter and disappearing into the mass. Pathologic assessment was consistent with a pseudoaneurysm. The patient had an uneventful postoperative course and was discharged 1 week following his operation. His abdominal pain improved significantly but did not completely resolve, consistent with his chronic pancreatitis. He remains with pancreatic exocrine insufficiency and requires pancreatic enzyme replacement. A CT at 12 months after pancreaticoduodenectomy revealed no evidence of recurrent pseudoaneurysm.

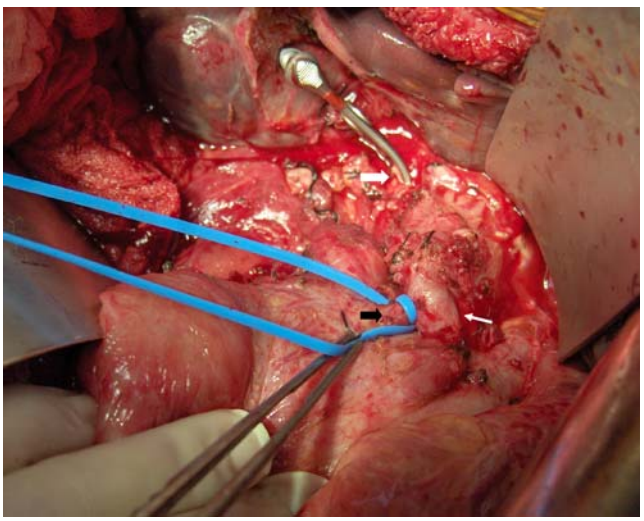


Figure 2 Intraoperative photograph with stomach and duodenum deflected caudal after Kocher maneuver. *White block arrow* indicates the location of the clamped transected hepatic duct. *Black block arrow* and *vessel loop* show the neck of the GDA pseudoaneurysm with the short segment of unaffected GDA off the hepatic artery (*white arrow*).

Discussion

HP, defined as bleeding through the pancreatic duct, is a rare cause of GI bleeding that usually develops from

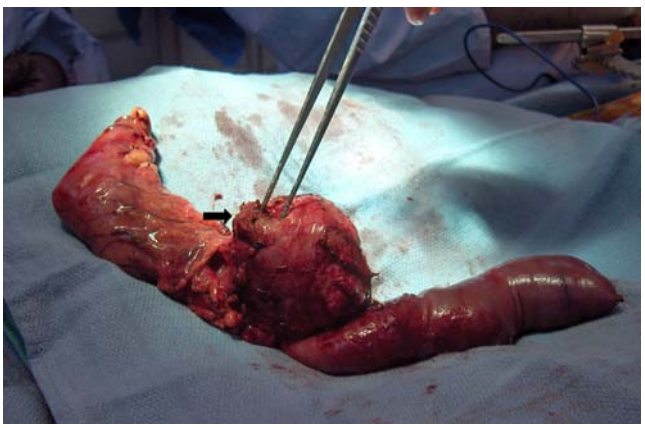


Figure 3 Resected pancreaticoduodenectomy specimen with dilated pancreatic duct showed on small remnant of pancreatic tissue proximal to the GDA pseudoaneurysm.

complications of pancreatitis. Causes of bleeding in patients with pancreatitis are multiple; however, as many as 10% of patients with pancreatitis develop pseudoaneurysms of peripancreatic arteries. Commonly involved arteries are the splenic, GDA, and pancreaticoduodenal arteries.[1,2] We report a patient with recurrent HP and associated obstructive jaundice secondary to a GDA pseudoaneurysm who required pancreaticoduodenectomy.

Diagnosis of HP can be difficult. Patients present with nonspecific symptoms and signs of increased abdominal pain, melena, hematochezia or hematemesis, anemia, hyperamylasemia, and hemodynamic instability. Endoscopic diagnosis of HP is made when blood is seen coming from the ampulla of Vater. This finding is uncommon because bleeding is intermittent. Endoscopic retrograde cholangiopancreatography may show a pancreatic duct with focal filling defects or with communication to a pseudocyst.[3] Ultrasound (US) with Doppler or CT may aid in the diagnosis. US may demonstrate "a cyst within a cyst" (a cystic structure within a larger anechoic mass). The addition of Doppler may show turbulent arterial blood flow within or adjacent to a pseudocyst.[1] CT may show simultaneous opacification of an aneurysmal artery and pseudocyst or persistence of contrast within a pseudocyst after the arterial phase. Again, these findings are only suggestive of the diagnosis.[1] Ultimately, angiography is the diagnostic gold standard. Angiography identifies the causative artery and allows for delineation of the arterial anatomy and therapeutic intervention.[1] Overall, the diagnosis of HP requires a high index of suspicion in patients with pancreatitis and GI bleeding.

Treatment of HP requires a multidisciplinary approach. Catheter embolization of a pseudoaneurysm can serve as definitive treatment in up to 78% of patients.[1,4] Failure of catheter embolization may result from inability to isolate the bleeding vessel, incomplete arterial occlusion, or misidentification of the bleeding vessel.[4] A recent case series by Zyromski et al.[5] reported the outcomes of 24 patients with visceral artery pseudoaneurysms in the setting of pancreatitis of which 24% had a GDA pseudoaneurysm. Transcatheter interventional therapy was successful in controlling bleeding in all patients. There was 1 patient who required repeat embolization for recurrent bleeding, 5 patients had complications (splenic abscess, hepatic abscess, or hemobilia), and 12 patients underwent surgery directed towards resolving the pancreatic inflammatory process during the same admission. This study emphasizes the utility of transcatheter therapy in patients with HP.[5] In some cases, embolization can act as a preliminary treatment to stabilize a patient's hemodynamics prior to operative intervention.

Operative treatment is reserved for patients who fail embolization (continued or recurrent bleeding), have other indications for operative intervention (pseudocyst, pancreatic abscess, gastric outlet obstruction, obstructive jaundice, or incapacitating pain), and are otherwise appropriate surgical candidates.[1,3] Operative treatment includes management of the pseudoaneurysm, drainage of the pseudocyst, and bypass of any biliary or GI obstruction. A pseudoaneurysm may be treated by transcystic or extracystic arterial ligation or by aneurysm resection. Pseudocysts may be externally or internally drained or resected en bloc with the aneurysm. Overall, resection is recommended in the appropriate surgical candidate, as *rebleeding* and other complications are higher with pseudoaneurysm ligation and drainage.[6]

Pseudoaneurysms of the GDA may be more difficult to manage than other peripancreatic pseudoaneurysms. These pseudoaneurysms are most likely to develop secondary to pancreatitis. Once present, they rarely remain asymptomatic and usually cause GI bleeding.[2] After transcather embolization of a GDA pseudoaneurysm, additional procedures to embolize arterial branches are frequently required.[3] Limited surgical approaches may also have a higher failure rate. Transcystic ligation frequently fails to completely occlude the aneurysmal vessel, and rebleeding is common. Extracystic ligation may be impossible secondary to inflammatory phlegmon around the pseudoaneurysm. Failure to control a GDA pseudoaneurysm by angiography or direct aneurysm ligation mandates resection or pancreaticoduodenectomy.[6]

Our patient developed HP secondary to pancreatitis and a pseudoaneurysm of his GDA. His recurrent GI bleeding after two embolizations, obstructive jaundice, and good baseline performance status made him a candidate for pancreaticoduodenectomy. Ultimately, we think operative treatment has improved this patient's quality of life with decreased pain and no new episodes of GI bleeding.

References

1. Boudghene F, L'Hermine C, Bigot JM. Arterial complications of pancreatitis: diagnostic and therapeutic aspects in 104 cases. J Vasc Interv Radiol 1993;4:551–558.
2. Eckhauser FE, Stanley JC, Zelenock GB, Borlaza GS, Freier DT, Lindenauer SM. Gastroduodenal and pancreaticoduodenal artery aneurysms: a complication of pancreatitis causing spontaneous gastrointestinal hemorrhage. Surgery 1980;88:335–344.
3. Sakorafas GH, Sarr MG, Farley DR, Que FG, Andrews JC, Farnell MB. Hemosuccus pancreaticus complicating chronic pancreatitis: an obscure cause of upper gastrointestinal bleeding. Langenbecks Arch Surg 2000;385:124–128.
4. Gambiez LP, Ernst OJ, Merlier OA, Porte HL, Chambon JP, Quandalle PA. Arterial embolization for bleeding pseudocysts complicating chronic pancreatitis. Arch Surg 1997;132:1016–1021.
5. Zyromski NJ, Vieira C, Stecker M, Nakeeb A, Pitt HA, Lillemoe KD, Howard TJ. Improved outcomes in postoperative and pancreatitis-related visceral pseudoaneurysms. J Gastrointest Surg 2007;11:50–55.
6. Bender JS, Bouwman DL, Levison MA, Weaver DW. Pseudocysts and pseudoaneurysms: surgical strategy. Pancreas 1995;10:143–147.

J Gastrointest Surg (2007) 11:1755–1757
DOI 10.1007/s11605-007-0215-y

Metastatic Melanoma Causing Jejunal Intussusception

Tania Mucci · William Long · Agnes Witkiewicz · Michael J. Mastrangelo · Ernest L. Rosato · Adam C. Berger

Received: 10 June 2007 / Accepted: 10 June 2007 / Published online: 10 July 2007

Abstract The gastrointestinal (GI) tract is a common site of melanoma metastases although reports of small bowel intussusception are relatively rare. Most patients with intussusception will be symptomatic and resection will provide significant palliation. In rare instances, patients will have solitary metastases to the small intestine, and resection can provide long-term palliation and chance for cure. We describe a case of a patient with a widely metastatic melanoma who presented with crampy abdominal pain and CT findings of small bowel metastases. Exploration revealed jejunojejunal intussusception and resection provided excellent palliation.

Keywords Malignant melanoma · Intussusception · Palliation

Case Report

This patient is a 53-year-old male with a history of malignant melanoma diagnosed in September 1996. Initially, a melanoma of 1.3 mm thickness and level IV invasion was removed from his left posterior shoulder. A second melanoma, measuring 0.7 mm in thickness, was removed from his lower back in February of 2002. In October 2004, he was found to have melanoma metastatic to the gall bladder at the time of laparoscopic cholecystectomy for what was suspected to be an acute attack of cholecystitis. Subsequent CT scans revealed numerous subcutaneous metastatic lesions to his chest and abdominal wall. Between December 2004 and May 2006, he received several different chemotherapeutic regimens, including oral temozolamide (Temodar®) and the Dartmouth regimen. In May 2006, he began having symptoms of intermittent crampy abdominal pain and his physical exam was significant for diffuse abdominal tenderness to palpation. CT scan at that time showed numerous small bowel metastases. The patient underwent an exploratory laparotomy with lysis of adhesions and two small bowel resections with primary anastomosis. There was an area of intussusception in the distal small bowel (Fig. 1) as well as multiple areas of metastases in the proximal small bowel. He underwent two separate resections of intestine of approximately 100 cm. Surgical pathology revealed small bowel metastatic melanoma with multiple polypoid masses ranging in size from 2.5 to 5.0 cm (Fig. 2) predominantly involving the mucosa with focal extension to the submucosa and muscularis propria. Immunohistochemical stains showed tumor cells to be positive for S100, HMB45, and Melan A. He was discharged on postoperative day number eight on a regular diet and in good condition. The patient is currently alive with metastatic disease 12 months later, having achieved excellent palliation of his symptoms.

Discussion

The GI tract is one of the most common sites to which metastatic melanoma spreads with reported incidences ranging from 35% to 50%.[1] In addition, the most common cause of small bowel metastasis is malignant melanoma. A study at Memorial Sloan Kettering in the late 1960s reported a breakdown of the incidence of GI melanoma metastases as follows: liver 68%, small bowel 58%, colon

T. Mucci · W. Long · A. Witkiewicz · M. J. Mastrangelo · E. L. Rosato · A. C. Berger (✉)
Department of Surgery, Thomas Jefferson University,
1100 Walnut Street, MOB, Suite 500,
Philadelphia, PA 19107, USA
e-mail: adam.berger@jefferson.edu

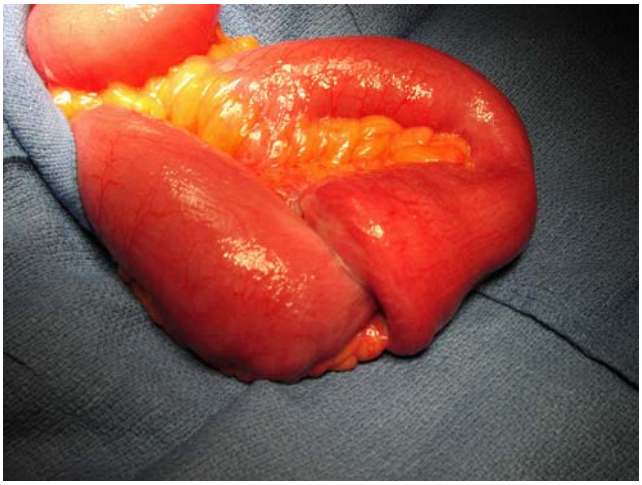


Figure 1 Intraoperative photograph demonstrating jejunojejunal intussusception.

22%, stomach 20%, duodenum 12%, rectum 5%, esophagus 4%, and anus 1%, based on the review of a number of autopsies.[2] A similar study performed 14 years later at the Roswell Park Memorial Institute reported similar results.[1]

Whereas all subtypes of cutaneous melanoma may metastasize to the GI tract, superficial spreading melanoma is the most common, in part because of the fact that it is the most prevalent.[3] Additional risk factors for spread include: an axial primary tumor site, Clark level III or IV, a high degree of histological regression, presence of ulceration, and high mitotic rate.[4] Metastatic disease is often not clinically detectable in the early stages, and diagnosis is often made only when complications occur. These include chronic GI blood loss, obstruction, abdominal pain, nausea, vomiting, and weight loss.[5] Recent studies have reported that two-thirds of patients present with abdominal pain and 50% with bleeding; equally occult and gross.[6]

Diagnosis is made predominantly by CT scans with contrast, although more recently, PET has been useful to identify sites. The sensitivity of CT for detecting metastases is 60–70%, indicating the need for further work-up if the scan is negative. Barium swallow and enteroclysis exams may also be useful to detect lesions in relatively inaccessible areas of the small bowel.[6] Biopsy of masses during surgery secures the diagnosis, and immunohistochemical stains including HMB-45 and S100 are useful in confirmation.

Less than 20 cases of small bowel intussusception secondary to metastatic skin melanoma have been reported, and their presentations are varied. One such case revealed intussusception of the lower part of the ileum secondary to the presence of an ileal tumor. Laparotomy did not reveal any additional pathology aside from four mesenteric lymph nodes.[7] The patient survived the procedure and was free of recurrence 3 months after the operation. In another case, a patient with a large, fungating mass on his back presented with abdominal pain, and laparotomy revealed a jejunal intussusception, which was successfully resected.[8] A recent case report concerned a patient who presented 10 years after resection of a Clark Level III malignant melanoma with a 4-month history of anemia, melena, abdominal pain, and anorexia, secondary to an ileal intussusception from malignant melanoma. Complete resection of the involved ileum and mesentery was successful, and follow-up chest and abdominal CT scans were negative for recurrence or metastasis.[5]

The prognosis of patients with metastatic melanoma is poor with a mean survival of 6–8 months in patients with systemic metastases. Five-year survival rates are reported as less than 10%. However, studies have shown a survival advantage to individuals capable of undergoing complete resection of all intraabdominal disease. Survival times have ranged from 23.5 to 48.9 months in the literature.[6,9] A retrospective study performed at M.D. Anderson Cancer Center revealed that both symptomatic and asymptomatic patients benefit equally from surgical resection, especially those that involve non-GI viscera. For patients with symptoms, quality of life improved and symptom-free survival time was lengthened.[10] In a report from the John Wayne Cancer Institute, patients who underwent curative resection had a median survival of 49 months compared to 5.4 months for those undergoing palliative surgical procedures.[9] It is now widely accepted that aggressive surgical resection in patients with metastatic melanoma is the treatment plan of choice, conferring both palliative and survival advantages.

Conclusion

Metastatic melanoma of the small bowel should be suspected in any patient with a history of malignant melanoma who develops GI symptoms or chronic anemia. Studies have

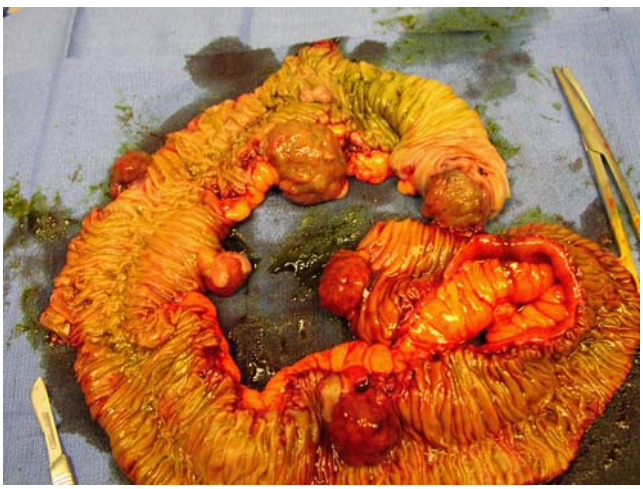


Figure 2 Small bowel malignant melanoma with multiple polypoid masses, which serve as potential lead points for intussusception.

shown that surgical intervention not only provides palliative care, but also provides a survival advantage. Because of the vast range in time between the presence of a primary lesion and the progression of metastatic disease, careful follow-up and observation of patients with high-risk primary cutaneous melanoma is warranted.

References

1. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. Am J Surg 1978;135:807–810.
2. Dasgupta TK, Brasfield RD. Metastatic melanoma of the gastrointestinal tract. Arch Surg 1964;88:969–973.
3. Schuchter LM, Green R, Fraker D. Primary and metastatic diseases in malignant melanoma of the gastrointestinal tract. Curr Opin Oncol 2000;12:181–185.
4. Liang KV, Sanderson SO, Nowakowski GS, Arora AS. Metastatic malignant melanoma of the gastrointestinal tract. Mayo Clin Proc 2006;81:511–516.
5. Rampone B, Roviello F, Marrelli D, De Marco G, Rossi S, Corso G, Cerullo G, Pinto E. Late recurrence of malignant melanoma presenting as small bowel intussusception. Dig Dis Sci 2006;51:1047–1048.
6. Berger AC, Buell JF, Venzon D, Baker AR, Libutti SK. Management of symptomatic malignant melanoma of the gastrointestinal tract. Ann Surg Oncol 1999;6:155–160.
7. Gatsoulis N, Roukounakis N, Kafetzis I, Gasteratos S, Mavrakis G. Small bowel intussusception due to metastatic malignant melanoma. A case report. Tech Coloproctology 2004;8(Suppl 1):s141–s143.
8. Bilello JF, Peterson WM. Retrograde jejunojejunal intussusception secondary to metastatic melanoma. Mayo Clin Proc 2005;80:1098.
9. Ollila DW, Essner R, Wanek LA, Morton DL. Surgical resection for melanoma metastatic to the gastrointestinal tract. Arch Surg 1996;131:975–979.
10. Gutman H, Hess KR, Kokotsakis JA, Ross MI, Guinee VF, Balch CM. Surgery for abdominal metastases of cutaneous melanoma. World J Surg 2001;25:750–758.