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The Durability of Laparoscopic Nissen Fundoplication: 11-Year Outcomes

Craig B. Morgenthal · Matthew D. Shane · Alessandro Stival · Nana Gletsu · Graham Milam · Vickie Swafford · John G. Hunter · C. Daniel Smith

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Abstract Laparoscopic Nissen fundoplication (LNF) has become the most commonly performed antireflux procedure since its introduction in 1991. There are few studies with greater than 5-year outcomes. Herein we report a series of 312 consecutive patients who underwent primary LNF before 1996. Follow-up of more than 6 years was available in 166 patients, and the mean follow-up was 11 years (median 11.1 years, range 6.1–13.3 years). Prospective data collection included preoperative and current symptom scores (scale 0=none to 3=severe), as well as the level of patient satisfaction and use of antireflux medications. Total symptom score for each patient was summed from seven symptoms for a maximum value of 21. Heartburn and regurgitation were the most improved symptoms; however, all symptoms were significantly improved ($P<0.01$). The total symptom score at follow-up was 2.6 down from 7.5 at baseline, with a mean difference of −4.9 (range −12 to 3). The percentage of patients stating they would have the procedure again was 93.3%, and 70% were off daily antireflux medications. Outcomes at a mean of 11 years after LNF are excellent, and the majority of patients had their symptoms resolved or significantly improved and are satisfied with their results.

Keywords Laparoscopic Nissen fundoplication · GERD · Antireflux surgery · Long-term outcomes

Introduction

Gastroesophageal reflux disease is one of the most common gastrointestinal conditions, with approximately 7% of people experiencing daily symptoms.[1,2] The first 360-degree fundoplication for GERD was performed by Rudolf Nissen in December 1955.[3,4] The first laparoscopic Nissen fundoplication (LNF) was reported in 1991 by Dallemagne et al.[5]

Shortly afterwards, in 1992, the results of the VA GERD Study Group were published. In this randomized trial of patients with complicated GERD, surgical treatment by open Nissen fundoplication (NF) was found to be significantly more effective than medical therapy at controlling symptoms and endoscopic signs of esophagitis.[6]

The acceptance of the laparoscopic approach and the confirmation of the surgical approach as more effective than medical treatment were two major contributors to the growth in popularity of the NF. Between 1990 and 1997, the annual rate of antireflux surgery more than doubled from 4.4 to 12.0 per 100,000.[7]

Our early outcomes for LNF in 126 patients was published in 1996.[8] Heartburn was absent or rare in 93% of patients at 1- to 2-year follow-ups, whereas preoperatively, it was severe in 70%. Only 3% were back on medical therapy to control daily symptoms. More recently, our experience with reoperation after antireflux surgery was published, with 2.8% of 1,892 patients requiring fundopli-

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C. B. Morgenthal · M. D. Shane · A. Stival · N. Gletsu · G. Milam · V. Swafford
Department of Surgery, Emory Endosurgery Unit, Emory University School of Medicine, Atlanta, GA, USA

C. D. Smith (✉)
Department of Surgery, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA
e-mail: smith.c.daniel@mayo.edu

J. G. Hunter
Department of Surgery, Oregon Health Sciences University, Portland, OR, USA

cation revision.[9] Other series of LNF have similarly shown excellent outcomes.[10,11]

The long-term outcomes from the VA GERD Study Group were published in 2001 and called the results of NF into question. Over 60% of surgical patients were on antireflux medications, with 32% on proton pump inhibitor (PPI). An additional antireflux procedure was necessary in 16%.[12] Over the past few years, the annual rate of antireflux surgery has declined, from a peak of 15.6 per 100,000 (32,900) in 2000 down by approximately 27% to 11.2 per 100,000 in 2003 (24,000).[13] Although there are a number of reasons for the decline, the results of the highly visible VA trial have contributed to this trend.

The aims of this study were to review the long-term outcomes from our large experience in performing LNF over the past 14 years. Specifically, we wanted to look at symptom outcomes, use of antireflux medications, and the need for further surgical or procedural intervention. A secondary goal was to identify patients with recurrent symptoms, antisecretory medication use, or dissatisfaction and have them return to clinic for objective assessment.

Material and Methods

This study was approved by our Institutional Review Board. Data on all patients undergoing foregut operations are collected prospectively and maintained in a computer database (Microsoft Access, Microsoft, Seattle, WA, USA). Information includes patient demographics, preoperative presentation and symptoms, type of operation, postoperative course, any subsequent foregut operation or intervention, and postoperative symptoms. The database is maintained by a full-time research nurse.

Indications for surgery, preoperative evaluation, and operative technique have been described previously.[8] Essentially, the short gastric vessels are mobilized, the esophagus is dissected from the mediastinum to allow an intra-abdominal length of 2–3 cm, the crura is closed, and a 2-cm floppy NF is created around a large (54–60 French) dilator.

Three hundred twelve consecutive patients underwent primary LNF at Emory University Hospital between November 1992 and December 1995. None of these patients had prior gastric or esophageal operations. Of these, 166 patients with at least 6 years of follow-up were available for inclusion in this study. There were 31 patients (9.9%) who died during the follow-up period, with 29 of them excluded from analysis and the two with follow-up greater than 6 years included. None of these patients died secondary to their original operation or from known gastrointestinal pathology. One patient refused to participate in the database and is excluded. Eighteen of the 166 patients underwent revisional fundoplication (10.8%). Revised patients are included in analysis on an intention-to-treat basis.

Each patient who undergoes operation is asked to complete a standardized questionnaire every 2 to 3 years, either in clinic or by mail or phone. Phone survey was completed by the research nurse or a physician, neither of whom participated in the diagnosis or treatment of the patients. When a patient cannot be found through contact information maintained in the database or in hospital records, a search is conducted through a national phone information service and the Internet. A patient's death was confirmed through phone contact with family members and an Internet search of the social security death index.

Symptom scores were obtained at baseline and follow-up for seven typical and atypical symptoms using a standardized questionnaire. Typical symptoms included heartburn, regurgitation, and dysphagia, whereas atypical symptoms included chest pain, hoarseness, cough, and asthma. Each symptom is scored on a four-point scale (0 none, 1 mild, 2 moderate, and 3 severe). Total symptom score (TSS) for each patient is summed from the seven symptoms, for a maximum value of 21. All symptom scores and TSS were compared at baseline and recent follow-up to assess durability of clinical response. Information was also obtained on patient satisfaction and use of antireflux medications.

If patients were asymptomatic, no further tests to evaluate GERD were performed. On the other hand, patients with "poor" outcomes were invited back to the clinic to undergo an objective assessment. Our definition of "poor" outcomes was liberal: the presence of any moderate or severe symptoms, the daily use of either PPI or H2 antagonists (H2-A), or the lack of patient satisfaction. A separate analysis was conducted in these patients.

Statistical analysis was performed with Statistica 7.1 software (StatSoft, Tulsa, OK, USA) using *T* tests to analyze continuous data, Chi-square for categorical data, and the Wilcoxon matched pairs test or Mann–Whitney U test for nonparametric data. A Kaplan–Meier survival curve was constructed to assess the actuarial proportion of repairs that "survived" to current-follow-up. All values are calculated using the 166 patients with recent follow-up unless otherwise stated. Results are reported as mean values with standard deviation, and values in tables are expressed as percentages unless otherwise specified. Statistical significance is accepted at $P<0.05$.

Results

Between November 1992 and December 1995, primary LNF was completed in 312 consecutive patients. This series

represents our institution's early operative experience for LNF. Out of 282 patients available for inclusion, we have greater than 6 years of follow-up in 166 (58.9%). Mean duration of follow-up is 11.0±1.2 years (median 11.1 years, range 6.1–13.3 years). A frequency table of duration of follow-up is listed in Table 1. Although all operations were before 1996, there are 12 patients with less than 10 years of follow-up. These patients are included in the analysis, as we have data available for at least 6 years after their operation. Patient demographics are listed in Table 2. The mean age at operation was 46.8 years (range 12–77 years), and current body mass index (BMI) is significantly increased over preoperative BMI.

Preoperative and current symptom scores, mean symptom scores, and symptom change vs baseline are listed in Tables 3, 4, and 5, respectively. Heartburn and regurgitation score distributions are displayed graphically in Figs. 1 and 2. Typical symptoms, as expected, were the most prevalent symptoms at baseline, with 93% of patients complaining of heartburn. Atypical symptoms ranged from 15% prevalence for asthma to 51% for cough.

Typical symptoms had the greatest improvement over baseline. Heartburn preoperatively was moderate to severe in 86% of patients. At follow-up, 89% of patients had either no or mild symptoms. Heartburn resolved in 65% of patients and improved in 90% of patients, whereas only 3% had this symptom worsen.

All symptoms improved significantly over baseline ($P<0.01$) except for asthma ($P=0.36$). As seen in Table 4, atypical symptoms improved, although to a lesser degree than typical symptoms. However, when only those patients who had asthma at baseline were evaluated ($N=22$), there was a significant improvement in this symptom ($P<0.01$). The percent of patients with moderate to severe chest pain, hoarseness, and cough decreased from baseline by 64, 76, and 63%, respectively.

Global parameters were all significantly improved over baseline. Total symptom score decreased from 7.48 to 2.61, at follow-up, a reduction of 65%. The mean difference in TSS was −4.93 (median −5, range −12 to 3). Approximately 92% of patients had improvement in TSS over baseline and 24% of patients had complete resolution of all symptoms.

The percent of patients stating they would have the operation again was 93.3%, whereas 5.4% said they would not and 1.2% did not know. The percent of patients that were very satisfied or satisfied with the results of the operation was 92.5% (75.3% very satisfied and 17.1% satisfied), with 7.5% stating they were unsatisfied.

Esophageal dilatation was required in 14% of patients. Antireflux medications (either PPIs or H2-A) are currently used daily in 29.7% of patients, whereas 70.3% are not using any antisecretory medications. Of those on daily antireflux medications, 83% would undergo the operation again and 84% were satisfied or very satisfied with their results (see Table 6).

A revisional antireflux procedure was necessary in 18 patients (10.8%). The Kaplan–Meier survival curve for LNF in our patient cohort is shown in Fig. 3. Out of the original 312 patients, we know of 26 patients (8.3%) who underwent a revisional fundoplication, giving us a follow-up rate of 69.2% in the revision group (18/26). For all revisions, the mean time to reoperation was 4.4±3.6 years (range postop day 4 to 11 years). There were 22 attempted redo LNFs (one with Collis gastroplasty), with two converted to open NF, one open NF, and three laparoscopic Toupet fundoplications (one with Heller myotomy). Three of the redo patients required a third operation, with two undergoing a second redo NF and one requiring esophagectomy for persistent dysphagia despite Heller myotomy with Toupet and multiple esophageal dilatations. One additional patient had Barrett's esophagus preoperatively and required esophagectomy for high-grade dysplasia 9 years after LNF. Throughout his follow-up, he was asymptomatic, and serial esophagogastroduodenoscopy (EGD) confirmed an intact wrap.

Of the patients undergoing reoperation with recent follow-up, 81% were satisfied or very satisfied with their outcomes, which was statistically similar to the satisfaction level of those that did not have reoperation. The symptom

Table 1 Years of Patient Follow-up

Years FU	# (%)
6	2 (1)
7	3 (2)
8	1 (1)
9	6 (4)
10	29 (17)
11	67 (40)
12	50 (30)
13	8 (5)

FU=follow-up

Table 2 Patient Demographics

Characteristic	Value
Males	94 (57%)
Females	72 (43%)
Age at OR	46.8 years
Current age	57.6 years
Preop weight	181.2 lb
Preop BMI	27.9 kg/m^2
Current weight	188.0 lb
Current BMI	29.2 kg/m^2

Table 3 Preoperative and Current Symptoms

Symptom (%)	None	Mild	Moderate	Severe	None/Mild	Mod/Severe
Heartburn preop	7.2	7.2	48.0	37.5	14.4	85.5
11 years	65.7	22.9	10.2	1.2	88.6	11.4
Regurgitation preop	37.9	10.0	32.9	19.3	47.9	52.2
11 years	78.9	15.1	4.2	1.8	94.0	6.0
Dysphagia preop	41.7	17.9	29.1	11.3	59.6	40.4
11 years	70.5	17.5	10.2	1.8	88.0	12.0
Chest pain preop	49.7	18.5	26.5	5.3	68.2	31.8
11 years	72.3	16.3	10.2	1.2	88.6	11.4
Hoarseness preop	55.6	17.2	23.2	4.0	72.8	27.2
11 years	74.1	19.3	4.2	2.4	93.4	6.6
Cough preop	49.0	20.5	24.5	6.0	69.5	30.5
11 years	68.7	19.9	8.4	3.0	88.6	11.4
Asthma preop	85.4	6.0	5.3	3.3	91.4	8.6
11 years	84.3	9.6	4.8	1.2	93.9	6.0

response of these patients was also similar, with the TSS reduced to 3.33 at follow-up. There was also no increased use of antireflux medications.

Esophageal dilatation was associated with a higher current TSS than those not receiving any dilatation (3.8 vs 2.4; $P=0.04$); however, preoperative TSS in the dilatation group was also higher (8.3 vs 7.3; $P=0.26$) and the overall decrease of −4.9 in TSS for both groups was equivalent. Of the patients undergoing dilatation, 83% would undergo the operation again and 81% were very satisfied or satisfied with their results, and both of these values are significantly decreased.

There were 69 patients (41.6%) at follow-up who had at least one moderate or severe symptom, were on antireflux medications, would not do the operation again or were unsatisfied with their outcomes. Of these patients, 71% were taking antireflux medications. Despite repeated attempts to have patients return to our institution for pH studies and EGD, results of EGD were available in 27 of these patients (39%). Nine of the 27 had pH studies completed. Only six patients were demonstrated to have either a loose wrap or pathological reflux on pH studies (22.2%).

Table 4 Preoperative and Current Mean Symptom Scores

Symptoms	Baseline	Current	Change
Heartburn	2.16	0.47	−1.68
Regurgitation	1.34	0.29	−1.10
Dysphagia	1.10	0.43	−0.69
Chest pain	0.87	0.40	−0.47
Hoarseness	0.75	0.35	−0.37
Cough	0.87	0.46	−0.42
Asthma ($N=22$)	0.26 (1.82)	0.23 (0.77)	−0.06 (−1.09)
TSS	7.48	2.61	−4.93

Symptom scores are based on a four-point scale, 0=none to 3=severe. Baseline and current asthma scores were analyzed for all patients and for those patients who had asthma at baseline ($N=22$).

Discussion

Laparoscopic Nissen fundoplication is currently the gold standard for the surgical correction of GERD. Several series have shown the early outcomes of LNF to be excellent, with minimal morbidity and mortality, marked reduction in distal esophageal acid exposure, and symptom control for the overwhelming majority of patients.[8,14,15] There have been multiple series with approximately 5-year outcomes following LNF (see Table 7).[10,11,16,17] Heartburn was controlled in approximately 90% of patients, the revision rate was between 1 and 14%, and 86–92% of patients were off antireflux medications.

There have been few series to date with 10-year outcomes for NF. Grande et al. reported the results of open NF in patients with up to 20 years follow-up. Approximately 80% of patients were completely free of symptoms and 89% would have the operation again.[18]

Dallemagne et al. recently reported the results of 100 consecutive patients undergoing fundoplication in 1993, 68 of whom underwent LNF, with 45 of these having 10 years of follow-up.[19] Although their first LNF was in 1991, they chose this separate cohort of patients to avoid the effect of the learning curve on outcomes. About 93% of patients were free of significant reflux symptoms. Out of their 100 patients operated on, 4% required reoperation, whereas only 1.4% of the LNF patients required revision.

This series of 166 patients undergoing primary LNF shows good results at 11 years of follow-up, with 92.1% of patients experiencing improvement in their TSS and 92.5% satisfied or very satisfied with their results. Different from

Table 5 Symptom Change vs Baseline

Symptom (%)	None BL/FU	Resolved	Improved	Same	Worse	New
Heartburn	5.3	64.6	89.6	7.6	2.8	2.0
Regurgitation	33.6	73.1	87.1	5.4	7.5	4.3
Dysphagia	35.1	56.1	75.5	10.2	14.3	6.0
Chest pain	42.4	50.6	63.2	20.7	16.1	7.3
Hoarseness	50.3	48.5	65.3	17.3	17.3	5.3
Cough	40.4	47.3	60.0	22.2	15.6	8.6
Asthma	77.5	34.4	52.9	8.8	38.2	7.9
TSS	0	23.9	92.1	2.9	5.0	–

This table excludes patients who had a score of none for each symptom at both baseline and follow-up. For example, of the 95% of patients with heartburn at BL or follow-up, 65% have resolved this symptom, 90% have had some improvement, etc. New represents the percent of all patients with new onset of that symptom after LNF.
BL = baseline, FU = follow-up

the Dallemagne data mentioned above, this series is our initial experience, which includes our "learning curve."

All symptoms were improved over baseline, with atypical symptoms appearing to be less responsive to LNF. When analysis takes into consideration only those patients who have atypical symptoms, there is a more significant response. For example, in all patients, the asthma score improved by 12%, whereas if only the 22 patients (13%) who suffered from asthma preoperatively were evaluated, there was a 58% improvement in asthma score. When patients who had a score of none for each symptom at both baseline and follow-up are excluded, approximately 60% of patients saw their atypical symptoms improve and 84% had their typical symptoms improve.

Regarding use of antireflux medications, in this series 70% of patients were off daily PPI or H2-A at recent follow-up. In comparison to rates of 86–92% in other series, this number may seem low; however, the series by Bammer et al. and Dallemagne et al. do not include the use of H2-A. Most of these series have been conducted outside of the United States where prokinetics such as cisapride are still available and could impact on the need for PPIs to control symptoms. Additionally, our patients in the U.S. have seemingly unlimited access to highly marketed, over-the-counter PPI and H2-A.

There has been considerable debate in the literature as to what it means to "fail" antireflux surgery. For example, some patients and physicians have erroneously interpreted the regular use of antireflux medications in 62% of patients in the VA study as a marker of failure. Clearly, the use of antireflux medications in the majority of patients does not necessarily diagnose recurrent GERD. In our group of 69 patients with recurrent symptoms, 71% of whom were taking daily PPI or H2-A, only 22% were demonstrated to have evidence of wrap failure or reflux. Although most patients that were studied had only EGD completed, a study by Lord et al. found that wrap disruption or malposition was 53 times more likely to have increased esophageal acid exposure, with 75% of these patients having an abnormal pH study.[20]

Our findings are supported by several studies showing medication use is a poor indicator of recurrent GERD. Anvari and Allen studied 181 patients with 24-h pH study 5 years after LNF, and only 5% of all patients had an abnormal test.[16] In this series, only three of 21 patients on medications had an abnormal pH study (14%). The USC group evaluated 86 symptomatic patients post Nissen by 24-h pH at 28 months, and 43% were on PPI. Twenty-three percent of all patients and 24% of patients on PPI were found to have an abnormal study.[20] Khajanchee et al. found 58 of 209 patients (28%) complained of symptoms of reflux

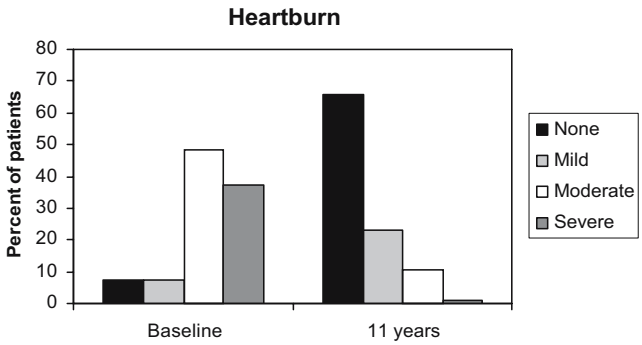

Figure 1 Heartburn symptom scores.

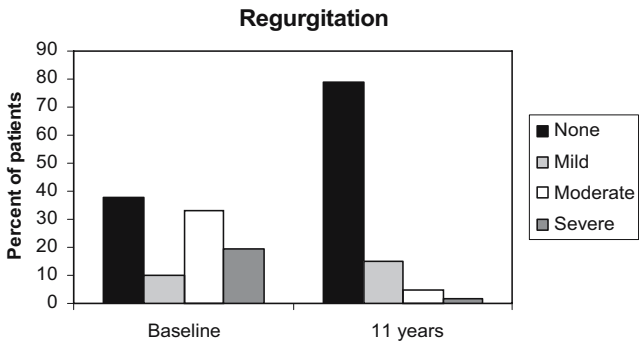

Figure 2 Regurgitation symptom scores.

Table 6 Comparison of Clinical Outcomes in the Poor-results Groups

	N	Current TSS	Redo	Diln	Mod/Sev sympts	VS/S	Do again	Off PPI + H2-A
All patients	166	2.61	10.8	14.0	29.5	92.5	93.3	70.3
Reoperation	18	3.33	–	6.3	38.9	81.3	83.3	72.2
Dilatation	23	3.82*	4.4	–	52.2*	81.0*	82.6*	34.8*
Mod symptom	46	6.31*	13.0	26.1*	–	81.4*	82.6*	40.0*
Sev symptom	13	9.54*	23.1	15.4	–	61.5*	69.2*	38.5*
Unsat/not again	12	7.50*	25.0	33.3	91.7*	–	–	33.3*
Antireflux meds	49	4.63*	10.2	31.3*	59.2*	84.4*	83.3*	–

Mod=moderate, Sev=severe, VS=very satisfied, S=satisfied, Unsat=unsatisfied
*Statistical significance $P<0.05$

8 months after fundoplication, and only 17 of these patients (29%) had abnormal DeMeester scores.[21]

These studies suggest that postoperative symptoms and the use of antireflux medications do not correlate with true recurrent reflux in the majority of patients. However, there is a significant decrease in patient satisfaction associated with the presence of moderate or severe symptoms. The level of patient satisfaction decreases from 93% in all patients to 81% in patients with moderate symptoms, and to 62% in those with severe symptoms.

Why are patients having symptoms without recurrent reflux? There were 12 patients (8%) who developed new-onset asthma during the follow-up period of this study. It is unlikely that all of these patients developed symptoms of asthma from recurrent GERD when preoperatively they had documented GERD but did not have asthma. Some of them simply developed asthma, cough, etc. over the last 10 years. For the subset of patients whose symptoms never improved despite control of their reflux, some of these patients were misdiagnosed as having GERD as the cause of their symptoms, despite having proven reflux preoperatively.

We cannot blame the patient for their persistent symptoms. Although many surgeons would like to think that it is true, patients complaining of problems after antireflux surgery do not have a higher level of psychological disturbances than those that are satisfied with their outcomes.[22] The fact that the majority of patients with symptoms do not have wrap failure highlights the importance of a thorough preoperative work-up that emphasizes the exclusion of other causative factors for their symptoms.

The patients that required reoperation had high levels of satisfaction with their outcomes. Their current symptom

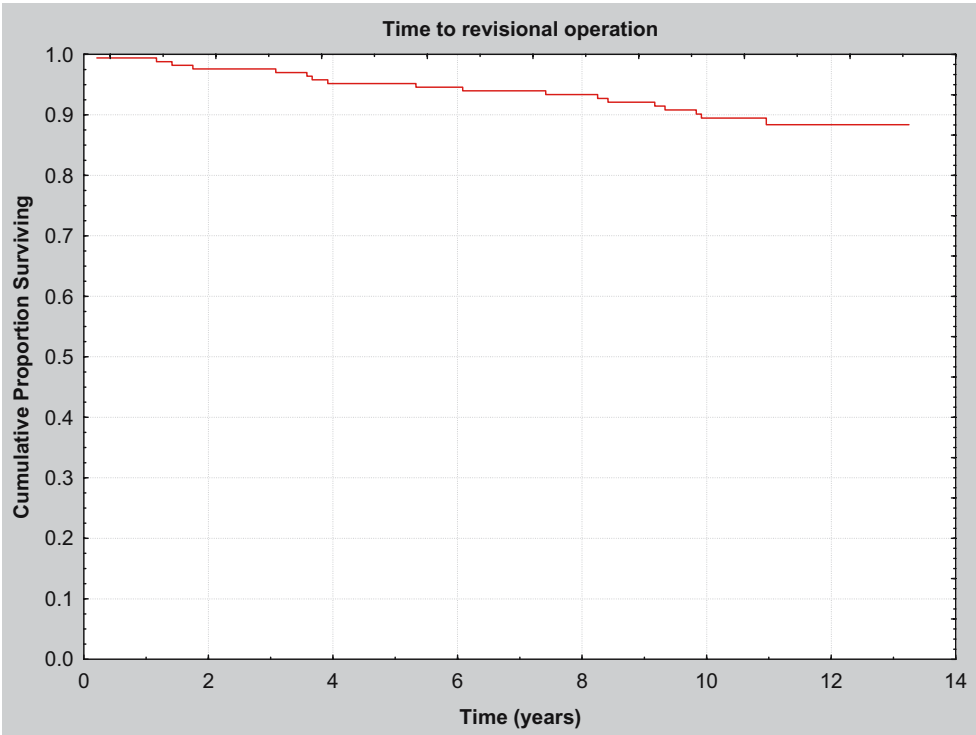

Figure 3 Kaplan–Meier survival curve for LNF.

Table 7 Laparoscopic Nissen Fundoplication Series

Series	FU (years)	*N* (%FU)	% HB Relief (0–1)	Revision (%)	Off PPI + H2-A
Emory	11.0	166 (59)	89	10.8	70
Dallemagne et al. 2006 (Belgium)	10.3	45 (66)	96	1.4	92[a]
Bammer et al. 2001 (Mayo, FL, USA)	6.4	171 (59)	94	1.0	86[a]
Lafullarde et al. 2001 (Australia)	6	166 (93)	87	14.2	89
Anvari, Allen 2003 (Ontario, Canada)	5	181 (48)	–	3.6	88
Booth et al. 2002 (England)	4	140 (78)	90	6.3	86

FU = follow-up, HB = heartburn, 0–1 = none–mild
[a] Does not include patients on H2-A

scores, dilatation rate, and medication use were statistically similar to the overall group of patients. These data confirm previous studies showing that redo patients can have a high degree of satisfaction and good outcomes.[9,23] This is in contradistinction to patients that undergo dilatation. They do have a significantly lower level of satisfaction and a worse overall symptom score. Perhaps having a single operative reintervention with subsequent relief of symptoms is less of a negative experience than having continued dysphagia and, in some instances, repeated dilatations. The implication here is that it might be better to offer these patients reoperation rather than long-term dilatation.

It is difficult to know what the actual revision rate is in our original group of 312 patients. The only thing we can be certain of is that 10.8% of our current group of 166 patients had a revisional procedure. Including redo patients who have been lost to follow-up, we are aware of 26 reoperations out of the 312 (8.3%). This cannot be considered the true statistical value because we are not sure if any of the fundoplications in patients lost to follow-up have been revised.

When all patients who are lost to follow-up are excluded from the survival analysis at 13 years, the calculated reoperation rate is 14.9%. This includes the eight additional patients that we know had a revision (18+8/166+8). This number is also inaccurate because it assumes that none of the patients lost to follow-up currently have an intact fundoplication. If we assume that all patients lost to follow-up simply moved or changed their phone numbers, but did not fail, and that we know of all of the failures because for over 10 years we have been the primary center in the region performing revisions, the redo rate is the previously mentioned 8%. In support of this value, of the 166 patients we have recently contacted, only two had a second operation at another institution (1.2%). To summarize, the 15% rate is falsely elevated, whereas 8% may be too optimistic; therefore, the most statistically accurate value for our series is an 11% redo rate at 11 years.

This redo fundoplication rate takes into account our learning curve during our early experience. In addition, anatomic failure was demonstrated in another six patients (3.6%) with recurrent symptoms. The redo rate is similar to the revision rates of 6.3–14.2% by groups who included their early experience.[10,17] With our accumulated experience of approximately 1,900 fundoplications, the redo rate came down to 2.8%.[9] This number takes into account all patients, with a variable rate of follow-up. It is likely that, over time, a higher percentage of these cases will have anatomic failure, but with experience and proper surgical technique, the number of revisions can be minimized.

A possible criticism of this study could be that the results were skewed by interviewer bias. Approximately 80% of the questionnaires were completed by direct interview of patients in clinic or by phone, whereas the remainder completed them by mail. Every effort was made to avoid influencing the patient's response. A study by Ludemann et al. examined whether methodology of follow-up impacted study outcomes. They found that patients responding to questionnaires by mail had similar results when subsequently interviewed, whereas nonresponders were found to have a lower satisfaction level and worse symptoms when contacted by phone. Studies relying solely on mailed questionnaires may falsely elevate success rates, especially if follow-up is incomplete, as patients with worse outcomes may be disinclined to return the questionnaires.[24] Another criticism may concern our follow-up rate of only 59%. We have employed a full-time research nurse for the past 10 years and we attempt to maintain constant contact with these patients. When patient addresses and all phone numbers were changed, we then searched through internet and phone listings. Only when all efforts failed did we consider a patient lost to follow-up.

Conclusion

This series currently has the longest follow-up data in the literature for LNF. Our results compare favorably with other series with extended follow-up. In patients undergoing LNF, outcomes at a mean of 11 years are excellent and the overwhelming majority of patients had their symptoms resolved or significantly improved and are satisfied with their results.

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Normal Lower Esophageal Sphincter Pressure and Length Does Not Impact Outcome After Laparoscopic Nissen Fundoplication

Sarah M. Cowgill · Mark Bloomston · Sam Al-Saadi · Desiree Villadolid · Alexander S. Rosemurgy II

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Abstract Intuitively, a manometrically normal lower esophageal sphincter (LES) will promote dysphagia after laparoscopic Nissen fundoplication. This study was undertaken to compare outcomes after laparoscopic Nissen fundoplication for patients who had normal and manometrically inadequate LES preoperatively. Before fundoplication, the length and resting pressures of LES were determined manometrically in 59 patients with documented gastroesophageal reflux disease (GERD). Twenty-nine patients had a manometrically normal LES, with resting pressures >10 mm Hg and length >2 cm. Thirty patients had resting pressures of ≤10 mm Hg and length of ≤2 cm. Before and after fundoplication, patients graded the frequency and severity of symptoms of GERD utilizing a Likert scale (0 = never/not bothersome to 10 = always/very bothersome). DeMeester scores and symptom scores before and after fundoplication were compared. Before fundoplication, the manometric character of the LES did not impact the elevation of DeMeester scores or the frequency/severity of reflux symptoms. All symptoms improved significantly with fundoplication independent of LES pressure/length. Prefundoplication, manometric character of the LES did not impact the frequency or severity of reflux symptoms after fundoplication. Preoperative manometric character of the LES does not impact the presentation of GERD or the outcome after fundoplication. Symptoms globally and significantly improve after fundoplication, independent of manometric LES character. Normal LES manometry does not impact outcome and, specifically, does not promote dysphagia, after laparoscopic Nissen fundoplication.

Keywords Nissen fundoplication · Lower esophageal sphincter · GERD

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S. M. Cowgill · S. Al-Saadi · D. Villadolid · A. S. Rosemurgy II
Digestive Disorders Center,
Tampa General Hospital and the Department of Surgery,
University of South Florida College of Medicine,
Tampa, FL, USA

M. Bloomston
Division of Surgical Oncology,
Ohio State University Medical Center,
Columbus, OH, USA

A. S. Rosemurgy II (✉)
Division of General, Tampa General Hospital,
University of South Florida,
P.O. Box 1289, Suite F-145,
Tampa, FL 33601, USA
e-mail: arosemur@health.usf.edu

Introduction

Gastroesophageal reflux disease (GERD) is the most common foregut disorder in the Western world and is believed to impact up to 20% of Americans on a weekly basis.[1,2] It is one of the most frequent complaints of patients in the office setting and can lead to long-term sequelae such as fibrosis, esophagitis, stricture, and Barrett's esophagus. Causes of GERD are multifactoral and can be divided broadly into dysfunctional esophageal body peristalsis, abnormal gastric function, and dysfunctional lower esophageal sphincter (LES) function. Over 60% of the time, GERD is caused by a defective LES, which is further damaged by inflammatory changes.[3]

Most surgeons who evaluate patients referred for refractory GERD will request preoperative esophageal manometry to qualify esophageal motility and to document a dysfunctional LES. Factors contributing to LES dysfunction are complex and are comprised of, to varying degrees,

total LES length, intra-abdominal length, and resting sphincter pressure, all parameters measured by manometry. Correction of GERD and the symptoms of GERD secondary to a dysfunctional LES can only occur with surgical intervention.

Intuitively, a manometrically normal LES will prevent GERD and promote dysphagia after laparoscopic Nissen fundoplication, with minor improvement of reflux. This study was undertaken in patients with GERD and manometrically normal or inadequate LES to characterize their reflux and symptoms before and their symptoms after laparoscopic Nissen fundoplication. Our hypotheses were that patients with manometrically normal LESs and GERD would have less severe acid reflux and associated symptoms before laparoscopic Nissen fundoplication and would be more likely to suffer dysphagia after fundoplication, with generally poorer outcomes after laparoscopic Nissen fundoplications.

Materials and Methods

Patient Selection

More than 800 patients with GERD underwent laparoscopic Nissen fundoplications from 1991 to 2005 and are followed through a prospectively maintained registry system. Before fundoplication, patients underwent esophageal motility testing, by stationary water perfusion esophageal manometry and/or barium-laden food bolus esophagram, and 24-h pH monitoring using commercially available instrumentation.[4] Patient data collection and study design were conducted in concordance with a protocol approved by the Institutional Review Board of the University of South Florida College of Medicine.

Standard esophageal manometry was undertaken by using a conventional catheter with pressure-sensitive transducers. The catheter was withdrawn across the cardia to identify the higher-pressure zone of the LES. At the respiratory inversion point, the amplitude of the LES pressure and length of the sphincter exposed to abdominal pressure was measured. Resting sphincter pressure and LES abdominal length were documented. Manometry tracings were interpreted by experienced gastroenterologists. "Normal" LES pressures were considered to be greater than 10 mm Hg, in concordance with published medians in normal subjects.[5] "Normal" LES length was considered to be greater than 2 cm, also in concordance with published values.[5] A manometrically inadequate LES was defined as an LES with resting pressures of 10 mm Hg or less (i.e., hypotensive) and total length of 2 cm or less (i.e., short). Patients who had undergone laparoscopic Nissen fundoplications were excluded if they had no reported manometry data or incompletely recorded preoperative manometric measurements.

Before and after laparoscopic Nissen fundoplication, the frequency and severity of symptoms of reflux (e.g., dysphagia, regurgitation, choking, heartburn, chest pain) were scored using a Likert scale (0 = never/not bothersome to 10 = always/very bothersome) (Table 1).[6] Symptoms of gas/bloating and inability to belch were surveyed before and after fundoplication as well. In addition, patients reported their outcomes as "excellent" (complete resolution of symptoms), "good" (symptoms occurring once per month or less frequently), "fair" (symptoms weekly or less frequently), or "poor" (symptoms daily or more often or as severe as prior to fundoplication). In addition, to assess satisfaction with their original decision, patients were asked if they would undergo the operation again, if necessary, knowing what they know now.

Technique of Fundoplication

Our technique of laparoscopic Nissen fundoplication has been previously described.[4] Briefly, laparoscopic Nissen fundoplication was undertaken with the patient supine using a five-port technique. The gastrohepatic omentum

Table 1 Patients were Asked Before and After Fundoplication to Grade the Frequency and Severity of their Symptoms of GERD Utilizing a Likert Scale and to Declare How Their Lifestyle Has Changed After Fundoplication

Representative Questions
How often do you experience
Food gets stuck
Postprandial chest pain
Forceful vomiting
Regurgitation
Choking
Coughing
Heartburn
Severity of symptoms
Heartburn postprandial/while sleeping
Nausea/vomiting/regurgitation after meals
Food stuck in throat/chest
Difficulty swallowing
Bitter taste in mouth postprandial/while sleeping
Asthma/coughing
Gas/Bloating
Have you had dietary changes for
Spicy foods
Bread
Meat
Coffee
Alcohol

was opened widely in a stellate manner. Dissection was carried along the edge of the right crus, working to reduce any hiatal hernia and free an adequate (approaching 8 cm) length of intra-abdominal esophagus. The stomach was then rolled to the patients' right and the short gastric vessels were divided. Dissection was carried along the edge of the left crus and into the mediastinum, such that any hiatal hernia was completely reduced. A generous window dorsal to the esophagus was established. A posterior cruroplasty was sutured with 0-gauge braided polyester sutures (Surgidac, US Surgical Corporation, Norwalk, CT, USA) to close the esophageal hiatal defect. The gastroesophageal fat pad and hernia sac were routinely removed. The posterior fundus was brought behind the esophagus with a 52F to 60F bougie placed per os into the stomach, and the fundoplication was constructed. The anterior fundus was secured to the esophagus and to the posterior fundus well above the gastroesophageal junction twice. A third suture brought the anterior fundus and the posterior fundus together at the gastroesophageal junction. A lateral gastropexy was constructed, suturing the dorsal-most portion of the posterior fundus behind the esophagus to the esophagus and to the right crus to remove tension, which might otherwise result in twisting of the lower esophagus or promote the "unwrapping" of the fundoplication. This final suture also augments the angle between the stomach and esophagus, augmenting the angle of His. All trocar sites were closed with monofilament absorbable suture under laparoscopic visualization using the Endo Close® device (US Surgical Corporation). Patients routinely began a liquid diet when awake, and were generally discharged home within 24 h of their operation.

Data Analysis

Data are maintained on an Excel (Microsoft, Redmond, WA, USA) spreadsheet and are analyzed by Wilcoxon matched pairs test or Mann–Whitney U-test, when appropriate, using GraphPad InStat version 3.06 (GraphPad Software, San Diego, CA, USA). Significance was accepted with 95% probability. Where appropriate, data are presented as median, mean ± standard deviation.

Results

Of over 800 patients undergoing laparoscopic Nissen fundoplications in a single institution, 447 of them did not have documented manometry preoperatively. Of the 353 remaining patients with manometry, 9 patients who underwent "redo" fundoplications were excluded and only 59 patients were identified who had manometrically documented LES resting pressures and lengths preoperatively. Of those 59 patients, 29 patients had manometrically normal LES and 30 patients had resting pressure of 10 mm Hg or less and length of 2 cm or less. The gender and age of patients with manometrically normal LES and those with inadequate LES are noted in Table 2. Median length of follow-up after laparoscopic Nissen fundoplication was 23 months (28±27.5) for patients with manometrically normal LES and 31 months (39±38.0) for patients with inadequate LES.

Before fundoplication, all patients had elevated DeMeester scores (Table 2). Patients with isolated upright reflux (defined if they had a pH of less than 4.0 for more than 8.3% of the time spent in an upright position) were identified in 23% of the patients with normal LES pressures and length and in 18% of those patients with inadequate LES (p=NS). All patients underwent successful laparoscopic Nissen fundoplications.

Before fundoplication, patients with manometrically normal LES had symptom scores that were similar to those of patients with inadequate LES (Table 3). Scored particularly high were severity and frequency of heartburn and regurgitation (Table 3).

Scores of "obstructive" symptom severity and frequency were similar for patients with manometrically normal LES or inadequate LES (Table 4). Patients' scoring of gas/bloating was high, but did not differ after laparoscopic Nissen fundoplication (Table 4). Patients' scoring of inability to belch was not high preoperatively, and did not worsen significantly postoperatively. Overall, "obstructive" symptoms in both groups generally did not improve significantly postoperatively.

With laparoscopic fundoplication, symptoms scores of gastroesophageal reflux improved for patients with manometrically normal or inadequate LES (Table 3). Only chest

Table 2 Demographic and Descriptive Data of Patients with Manometrically Normal LES vs Inadequate LES

	Normal LES (n=29)	Inadequate LES (n=30)	p Value
Gender	41% (males)	57% (males)	NS
Age	56 (54±14.2)	51 (50±15.1)	NS
DeMeester score	38 (43±30.4)	52 (77±71.6)	NS
LES length (cm)	4.0 (4.2±1.03)	2.0 (1.3±0.87)	<0.0001[a]
LES resting pressure (mm Hg)	18.0 (19.1±5.57)	5.0 (4.3±3.86)	<0.0001[a]
Follow up length (months)	23 (28±27.5)	31 (39±38.0)	NS

Data format median (mean ± SD)
SD = standard deviation
[a] Significantly different using Mann–Whitney U-test

Table 3 Reflux Symptom Severity and Frequency was Scored by Patients with Manometrically Normal and Inadequate LESs

	Normal LES (n=29)	Inadequate LES (n=30)	p Value[a]
Chest pain frequency			
Preop	4.0 (4.6±3.93)	4.0 (4.5±2.78)	NS
Postop	2.0 (3.7±3.71)	2.0 (3.0±2.73)	NS
p value	NS	NS	
Choking frequency			
Preop	2.0 (3.2±3.24)	4.0 (4.0±3.86)	NS
Postop	0.0 (1.3±2.72)	0.0 (1.5±2.37)	NS
p value	0.0156[b]	0.0313[b]	
Heartburn frequency			
Preop	8.0 (6.5±2.96)	8.0 (7.6±2.66)	NS
Postop	0.0 (2.1±3.04)	2.0 (2.3±2.82)	NS
p value	0.0005[b]	0.0005[b]	
Regurgitation frequency			
Preop	6.0 (6.0±3.24)	6.0 (5.6±3.12)	NS
Postop	0.0 (2.2±3.46)	1.0 (2.3±3.09)	NS
p value	0.0015[b]	0.0010[b]	
Regurgitation severity			
Preop	7.0 (5.9±3.30)	7.0 (6.1±3.33)	NS
Postop	0.0 (1.7±2.71)	0.0 (1.4±2.69)	NS
p value	0.0006[b]	0.0005[b]	
Heartburn severity			
Preop	7.5 (6.4±3.36)	8.5 (7.7±2.71)	NS
Postop	1.0 (2.0±3.07)	1.0 (2.0±2.63)	NS
p value	0.0001[b]	<0.0001[b]	
Choking severity			
Preop	5.0 (5.2±3.48)	3.5 (4.1±3.56)	NS
Postop	0.0 (1.7±2.60)	1.0 (1.5±1.88)	NS
p value	0.0067[b]	0.0034[b]	
Chest pain severity			
Preop	1.0 (3.1±3.60)	1.0 (2.7±3.20)	NS
Postop	0.0 (1.4±2.43)	1.0 (1.1±1.38)	NS
p value	0.0322[b]	0.0059[b]	

Data format median (mean ± SD)
SD = standard deviation
[a] All preop vs preop and postop vs postop were not significantly different using Mann–Whitney U-test
[b] Significant using Wilcoxon matched-pairs test

pain frequency for patients with both inadequate LES and manometrically normal LES failed to improve. In addition, scores of dysphagia severity significantly improved for patients with inadequate and adequate LES, but dysphagia frequency did not improve for patients with manometrically normal LES or inadequate LES. After fundoplication, reflux and obstructive symptom scores were not different for patients with manometrically normal vs inadequate LES (Tables 3 and 4).

When evaluating outcomes after fundoplication, 82% of the patients with GERD and manometrically normal LES reported "excellent" or "good" outcomes and 82% of the patients with GERD and inadequate LES noted "excellent" or "good" outcomes (Fig. 1). When asked if they would repeat the fundoplication if necessary, 82% of patients with manometrically normal LES and 86% with inadequate LES reported that they would repeat the laparoscopic fundoplication, if necessary (Fig. 2).

Discussion

Prior to undertaking laparoscopic Nissen fundoplications, surgeons appropriately obtain esophageal manometry studies. Reviewing these preoperatively, surgeons will note that LES length and pressure in some patients is normal. That leaves surgeons to wonder if LES function can be improved and if augmentation of LES function by fundoplication will promote dysphagia. This study documents that patients with manometrically normal LES pressures and length can have severe gastroesophageal reflux and can undergo augmentation of LES function by fundoplication without experiencing relatively increased frequency or severity of obstructive symptoms (e.g., dysphagia).

Patients with GERD are not a homogeneous population. Variables of gastric function, esophageal dysmotility, and LES function and position contribute differently to a given patient's reflux profile. With this variability in pathophysiology, it can be expected that patients will have disparate outcomes after laparoscopic fundoplications to control reflux. Experience with laparoscopic fundoplication in

Table 4 "Obstructive" Symptoms of Dysphagia, Gas/Bloating, and Inability to Belch were Scored by Patients with Manometrically Normal or Inadequate LESs

	Normal LES (n=29)	Inadequate LES (n=30)	p Value[a]
Dysphagia frequency			
Preop	4.0 (4.0±3.16)	5.0 (4.4±3.59)	NS
Postop	2.0 (3.4±3.80)	2.0 (2.4±2.41)	NS
p value	NS	NS	
Dysphagia severity			
Preop	3.5 (3.3±3.03)	2.5 (3.9±3.65)	NS
Postop	0.0 (1.3±2.08)	1.0 (1.0±1.13)	NS
p value	0.0098[b]	0.0010[b]	
Gas/bloating			
Preop	4.0 (5.3±3.96)	7.0 (5.9±3.66)	NS
Postop	3.0 (4.6±3.99)	4.0 (4.7±3.51)	NS
p value	NS	NS	
Inability to belch			
Preop	2.0 (3.7±4.21)	1.0 (1.4±1.62)	NS
Postop	1.0 (2.3±3.13)	1.0 (2.8±3.41)	NS
p value	NS	NS	

Data format median (mean ± SD)
SD = standard deviation
[a] All preop vs preop and postop vs postop were not significantly different using Mann–Whitney U-test
[b] Significant using Wilcoxon matched-pairs test

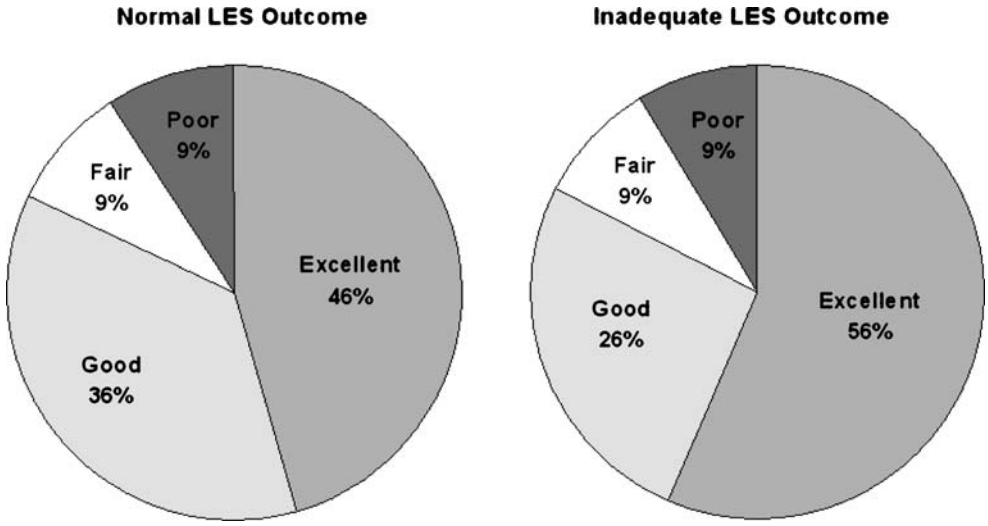

Figure 1 Outcomes after fundoplication were scored as "excellent," "good," "fair," or "poor." Patients reported their outcomes as "excellent" for complete resolution of symptoms, "good" when symptoms occurred once per month or less frequently, "fair" when symptoms occurred weekly or less frequently, or "poor" when symptoms occurred daily or more often or as severe as prior to fundoplication.

patients with normal LES pressures and length is limited. Intuitively, we expected patients with normal LES pressures and length to have more dysphagia and gas-bloating after a full 360° (i.e., Nissen) fundoplication. This single institutional outcome study represents a relatively large series of patients with GERD and normal LES manometry that have been successfully treated by laparoscopic Nissen fundoplication. This study documents that a manometrically normal LES does not compromise outcome after laparoscopic Nissen fundoplication.

This study consists of predominantly middle-aged men and women with excessive, but widely varying degrees of, acid reflux. All patients in the study had symptoms despite appropriate medical therapy. Laparoscopic Nissen fundoplication brought about significant reduction in median symptom frequency and severity scores for the representative symptoms queried. Surprisingly, dysphagia severity scores generally improved after laparoscopic Nissen fundoplication despite or without regard to the preoperative manometric character of the LES. The number of patients who would not undergo fundoplication again, if necessary, was small, but they undoubtedly had many of the same disappointments that other dissatisfied patients have reported.[7] Notably, dissatisfaction is often, if not generally, due to factors not directly related to symptom relief or medical/surgical issues.

Why use esophageal manometry? Manometry allows surgeons to diagnose a concomitant esophageal dysmotility disorder. However, it may be safe to undertake antireflux operations based upon symptomatology or by upper gastrointestinal fluoroscopy.[4] Frantzides et al. evaluated the selective use of esophageal manometry in patients who underwent a "floppy" 360° Nissen fundoplication, and he identified a very reasonable 0.8% rate of persistent postoperative dysphagia.[8] These investigators believe that patients with typical GERD symptoms should be able to successfully undergo laparoscopic Nissen fundoplication, and manometry can be selective utilized preoperatively. We have selectively utilized esophagography with barium-laden food boluses to assess esophageal motility and clearance before laparoscopic Nissen fundoplication.[4]

The need for fundoplication for patients with excessive gastroesophageal reflux who have failed medical therapy and have normal manometric LES function is not intuitive. Pathologic gastroesophageal reflux can occur in patients with manometrically normal LES function. Transient LES relaxation is one mechanism thought to cause this phenomenon.[9–11] If transient LES relaxation does not occur during the time of manometry, the manometry tracing will appear normal, although the LES will subsequently behave abnormally and inadequately. Interestingly, there are other proposed mechanisms to explain the occurrence of pathologic gastroesophageal reflux in the setting of normal manometric LES function. For example, it has also been shown that gastric distention can shorten the length of the

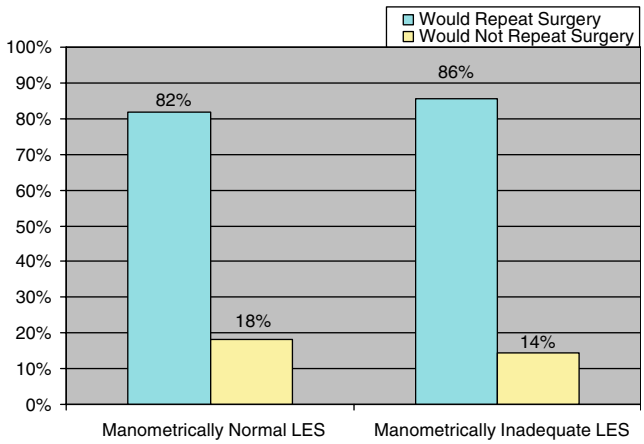

Figure 2 Patients were asked if they would undergo laparoscopic Nissen fundoplication again if they knew then what they know now.

LES, rendering it an incompetent barrier to gastroesophageal reflux.[12] Nissen fundoplication prevents shortening of the sphincter and reduces the amount of reflux that occurs during gastric distention. In a series of 14 patients known to have transient LES relaxation, laparoscopic Nissen fundoplication significantly reduced the median number of gastroesophageal reflux episodes and transient LES relaxations during gastric distention.[13] Furthermore, it is established that excessive reflux occurs most often in the upright position. Manometric studies conducted for brief time periods in the supine position may not identify LES relaxations thought to give rise to gastroesophageal reflux in the upright position. In addition BMI, smoking, medications, alcohol, caffeine, and a host of other factors are recognized to impact LES function. Given the complex nature of LES function, it is not surprising that, in one series, one half of patients with excessive gastroesophageal reflux and normal LES function were eventually able to discontinue medical therapy without the need for operative intervention.[14] Moreover, the theoretical possibility of worsening dysphagia with fundoplication makes surgeons reluctant to undertake fundoplication in this group of patients.

The outcomes after laparoscopic Nissen fundoplication reported in this study are similar to those reported by others. Ritter et al. evaluated the outcome of laparoscopic Nissen fundoplication in 33 patients with functionally normal LES.[15] They reported that 82% had excellent or good results after fundoplication. In addition, Patti et al. reported outcomes of 41 patients with normal or increased LES pressures undergoing partial or total fundoplication.[16] Outcomes after fundoplication were similar for patients undergoing either total or partial, with de novo postoperative dysphagia occurring in only 7%. This was also similar to the rate of new-onset dysphagia in patients undergoing fundoplication with decreased preoperative LES pressures. For patients with dysphagia, it resolved in the majority of patients within 4 months or improved with dilation.

In our patients, prefundoplication dysphagia was moderately bothersome for patients with manometrically normal LES and for those with manometrically inadequate LES. Notably, dysphagia severity generally improved with fundoplication. In contrast, Blom et al., in an effort to evaluate all patients with postoperative dysphagia following laparoscopic Nissen fundoplication, found that normal and increased preoperative LES pressures were risk factors for postoperative dysphagia.[17]

Undoubtedly, GERD occurs in patients with normal manometric LES function more commonly than we used to believe. It can be severe and refractory to medical management. Laparoscopic Nissen fundoplication relieves symptoms of excessive gastroesophageal reflux in patients with GERD and manometrically normal LES function. For these patients, the risk of developing new or worsening dysphagia after laparoscopic Nissen fundoplication is minimal. In patients with symptoms of excessive gastroesophageal reflux and GERD, normal manometric LES function should not deter the application of Nissen fundoplication.

Conclusion

Normal LES pressure does not impact the presentation of GERD or the outcome after laparoscopic Nissen fundoplication. Symptoms significantly improve after laparoscopic Nissen fundoplication even with a manometrically normal LES before fundoplication. A manometrically normal LES does not predispose to dysphagia after fundoplication.

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Effect of Location and Speed of Diagnosis on Anastomotic Leak Outcomes in 3828 Gastric Bypass Cases

Sukhyung Lee · Brennan Carmody · Luke Wolfe · Eric DeMaria · John M. Kellum · Harvey Sugerman · James W. Maher

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Abstract
Introduction Leaks after Roux-en-Y gastric bypass are a major cause of mortality. This study attempts to define the relationship between the leak site, time from surgery to detection, and outcome.
Methods Retrospective review of 3,828 gastric bypass procedures.
Results Of the leaks (3.9% overall), 60/2,337 (2.6%) occurred after open gastric bypass, 57/1,080 (5.2%) after laparoscopic gastric bypass, and 33/411 (8.0%) after revisions. Overall leak-related mortality after Roux-en-Y gastric bypass was 0.6% (22/3,828). Mortality rate from gastrojejunostomy leaks (38 in the open gastric bypass, and 43 in the laparoscopic) was higher in the open group than the laparoscopic group (18.4 vs 2.3%, $p=0.015$). Median time of detection for a gastrojejunostomy leak in the open group was longer than in the laparoscopic group (3 vs 1 days, Wilcoxon score $p<0.001$). Jejunojejunostomy (JJ) leak was associated with a 40% mortality rate. Initial upper gastrointestinal series did not detect 9/10 jejunojejunostomy leaks. Median detection time was longer in the jejunojejunostomy leak group than the gastrojejunostomy leak group (4 vs 2 days, $p=0.037$).
Discussion Leak mortality and time of detection was higher after open gastric bypass than laparoscopic gastric bypass. GBP patients with normal upper gastrointestinal (UGI) studies may harbor leaks, especially at the JJ or excluded stomach. Normal UGI findings should not delay therapy if clinical signs suggest a leak.

Keywords Gastric bypass · Morbid obesity · Gastric bypass leak complications · Gastric bypass mortality

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S. Lee · B. Carmody · L. Wolfe · E. DeMaria · J. M. Kellum · H. Sugerman · J. W. Maher (✉)
Department of Surgery, Virginia Commonwealth University, Richmond, VA, USA
e-mail: jwmaher@vcu.edu

S. Lee
Department of Surgery, William Beaumont Army Medical Center, El Paso, TX, USA

B. Carmody
Department of Surgery, Walter Reed Army Medical Center, Washington, DC, USA

Introduction

Obesity is a serious and growing medical problem in the United States, affecting more than 30% of the adult population[1]. Medical treatment of morbid obesity is relatively ineffective[2]. Surgical procedures for weight reduction have been evolving since the 1960s. Roux-en-Y gastric bypass (GBP) is currently the most common weight reduction procedure in the United States[3]. Laparoscopic Roux-en-Y gastric bypass (LGB) is gaining popularity because it has similar outcomes to open Roux-en-Y gastric bypass (OGB) and the advantages of lower wound complication rates, shorter hospital stays, and lower incidence of incisional hernia[4,5].

Leak after GBP is a feared complication and a major cause of mortality. The incidence of leaks varies between 2 to 5%[6,7], with most occurring at the gastrojejunostomy (GJ) anastomosis. However, leaks at other sites, such as the jejunojejunostomy (JJ) anastomosis, excluded stomach or staple line, are not infrequent[7,8].

This study attempts to elucidate the relationships between leak site, time from surgery to detection, methods of diagnosis, and outcome, using a large prospective database of nearly 4,000 cases to improve the understanding of leak diagnosis and management.

Materials and Methods

Institutional review board approval was obtained before the study. A database of 3,828 cases of OGB or LGB at Virginia Commonwealth University from 1982 to April 2005 was analyzed. The database was started in 1987 and has been prospectively maintained and updated using inpatient and clinic records. Data before 1987 were retrospectively entered into the database.

Leaks were defined as anastomotic disruptions at either the GJ or JJ, intestinal perforations or staple line disruptions. Leaks were diagnosed by the extravasation of contrast material on an upper gastrointestinal contrast study (UGI), abdominal computed tomography (CT), or identification of intestinal spillage during laparoscopy or laparotomy that was performed based on the patient's clinical picture. Basic demographic data, including age, sex, and type of surgery (OGB, LGB, or revisional surgery [RGB]), were collected from the database. There was a mix of different surgical techniques within each surgical group. The OGB group included patients with proximal, long-limb, and distal OGB. The LGB group contained only de novo LGBs. The RGB group contained patients whose GBPs were revised due to malnutrition, staple line disruptions, or weight loss failure. Some of these patients had previous horizontal or vertical banded gastroplasties. Each group also contained patients who underwent either retrocolic or antecolic approaches for the GJ. The GJ anastomosis was created with a stapler and two-layer hand-sewn technique in both LGB and OGB groups. The JJ anastomosis was created with a GIA-60 linear stapler and either stapler or hand sewing to close the resulting enterotomy. In most laparoscopic cases, a closed suction drain was placed in the GJ area.

We retrospectively reviewed medical records that included the location of the leak (GJ, JJ anastomosis, or elsewhere), method of diagnosis (UGI study, CT scan, or clinical), time from surgery to detection, vital signs at the time of diagnosis (temperature and heart rate), laboratory data at the time of diagnosis (white blood cell count), and in-hospital mortality directly related to the leak. Patients in the GJ leak group and the JJ leak group were compared with respect to age, sex, preoperative BMI, preoperative weight, average time from surgery to detection, method of diagnosis, in-hospital mortality rate, and method of intervention (surgical vs nonsurgical). Nonsurgical management consists of close suction drainage or percutaneous drainage, NPO, total parenteral nutrition, and broad spectrum antibiotics. The Fisher exact test and Pearson's Chi-square test were used to determine statistical significance between groups. The Wilcoxon rank-sum test was used to compare the time from surgery to detection, due to its abnormal distribution. *P*-values less than 0.05 were considered significant.

Results

Overall

The overall leak rate was 3.9% (150 leaks out of 3,828 GBPs). There were 61 leaks among the 2,337 OGBs (2.6%), 56 leaks among the 1,080 LGBs (5.2%), and 33 leaks among the 411 RGBs (8.0%). Table 1 showed leak and mortality rate in OGB, LGB, and RGB. The overall leak rate was higher in the LGB group than the OGB group ($p<0.001$). The overall leak rate in the RGB group was higher than in the LGB group ($p=0.049$). The overall leak related mortality after GBP was 0.6% (22/3,828), and the mortality associated with leaks was 14.7% (22/150).

Demographics of Patients With Leaks

Demographic information for patients with and without leaks is presented in Table 2. Leaks were more common in

Table 1 Incidence of Leaks

	Total	Leaks	Leak-related Death	GJ Leak	JJ Leak
OGB	2,337	61 (2.6%)	15 (0.6%)	40 (1.7%)[a]	11 (0.5%)[a]
LGB	1,080	56 (5.2%)	5 (0.5%)	44 (4.1%)[b]	5 (0.5%)[b]
RGB	411	33 (8.0%)	2 (0.5%)	20 (4.9%)[c]	3 (0.7%)
Total	3,828	150 (3.9%)	22 (0.6%)	104 (2.7%)	19 (0.5%)

Patients who had leaks at more than one location were classified as others in Table 3.

OGB Open gastric bypass, *LGB* laparoscopic gastric bypass, *RGB* revisional gastric bypass, *GJ* gastrojejunostomy, *JJ*, jejunojejunostomy

[a] Two patients had both GJ and JJ leak. One patient had both JJ and excluded stomach leaks.

[b] One patients had both GJ and JJ leak.

[c] One patient had both GJ and staple line leaks.

Table 2 The Demographic Data of All GBP Performed

	Leak Group (N=150)	Nonleak Group (N=3678)	P value
Age	45.3±10.4	40.6±10.3	<0.001
Preop BMI	49.2±10.4	50.0±10.1	0.354
Preop Weight	307.5±77.0	307.5±69.3	1.000
Percentage male	43 (28.7%)	670 (18.2%)	0.003

GBP Roux-en-Y gastric bypass, *BMI* body mass index

older patients and males. The average age of patients with leaks was 45.3±10.4 years, compared to 40.6±10.3 years for patients without leaks (p<0.001). Twenty-nine percent of patients with leaks were male, compared to 18% of patients without leaks (p=0.003). BMI and preoperative weight were similar in patients with and without leaks.

Comparison of OGB and LGB Leak Complications

In the OGB group, there were 40 leaks at the GJ and 11 at the JJ (1.7 and 0.5% of all OGBs, respectively, Table 1). In the LGB group, there were 44 leaks at the GJ and 5 at the JJ (4.1 and 0.5% of all LGBs, respectively, Table 1). The LGB group had a higher overall leak rate than the OGB group (5.2 vs 2.6%, p<0.001), which was due to a two times higher GJ leak rate (4.1 vs 1.7%, p<0.001). There was no significant difference between the two groups in JJ leak rate (p=0.975). Mortality among leak patients in the OGB group was higher than in the LGB group (24.6% [15/61] vs 8.9% [5/56], p=0.025). However, overall mortality rate due to leaks in OGB and LGB was similar (0.6 vs 0.5%, p=0.53). Patients who had only GJ or JJ leaks are presented in Table 3. Patients who had leaks at more than one location were classified as others in this table. Mortality from a GJ leak was higher in OGB than LGB (18.4 vs 2.3%, p=0.015). Mortality from a JJ leak was similar in OGB and LGB (50.0 vs 50.0%, p=1.000).

Median time from surgery to detection for GJ leaks in the OGB group was longer than in the LGB group (3 vs 1 days, Wilcoxon score p<0.0001, mean 5.0±6.7 vs 2.2±2.6 days, p=0.02, Table 4). Median time from surgery to detection of JJ leaks was not statistically different between the OGB and LGB groups.

Comparison of GJ and JJ Leaks

A total of 115 patients had either GJ (100 patients) or JJ leaks (15 patients). JJ leaks were associated with a 40% mortality rate, compared to 9% for GJ leaks (p=0.005). Sixty-eight percent of GJ leaks underwent reoperation (71% [27/38] OGB, 67% [29/43] LGB, and 63% [12/19] RGB), while 32% of GJ leaks were managed nonoperatively with closed suction drainage or percutaneous drainage, NPO, total parenteral nutrition, and broad spectrum antibiotics. None of 68 patients who underwent reoperations were subjected to conservative management before the reoperations. None of the patients who had nonoperative management of leaks required surgical management, and there were no deaths in the nonoperative group (32 patients). We attempted to analyze patients who were treated nonoperatively to see what characteristics were associated with successful nonoperative management. There were no significant differences in heart rate, temperature, or white count between the nonoperative and operative group (heart

Table 3 Type of Procedures, Leak Locations, and Associated Mortality

	All		OGB		LGB		RGB	
	Leak	Death	Leak	Death	Leak	Death	Leak	Death
GJ only	100	9 (9.0)	38	7 (18.4)	43	1 (2.3)	19	1 (5.3)
JJ only	15	6 (40.0)	8	4 (50.0)	4	2 (50.0)	3	0 (0.0)
Others	35	7 (20.0)	15	4 (26.7)	9	2 (22.2)	11	1 (9.1)
Total	150	22 (14.7)	61	15 (24.6)	56	5 (8.9)	33	2 (6.1)

Numbers in parenthesis are percentages. Others in OGB group: both GJ and JJ leaks (2), JJ leak and excluded stomach perforation (1, death), staple line leak (4), esophageal leak (4), jejunum perforation (1, death), gastroileostomy leak (1), esophagus and staple line leak (1, death), leak location unidentified (1, death). Others in LGB group: both GJ and JJ leaks (1), staple line leak (1), esophageal leak (1), excluded stomach perforation (3, 1 death), jejunal perforation (3, 1 death). Others in RGB group: GJ and staple line leak (1), staple line leak (3), esophageal leak (3), excluded stomach perforation (1, death), esophageal jejunostomy leak (3).

OGB Open gastric bypass, *LGB* laparoscopic gastric bypass, *RGB* revisional gastric bypass, *GJ* gastrojejunostomy leak, *JJ* jejunojejunostomy leak.

Table 4 Comparison of Leak Types and Time From Surgery to Detection

Type of Leak	GJ (N=81[a])			JJ (N=12[a])		
Type of Surgery	OGB (N=38)	LGB (N=43)	P value	OGB (N=7[b])	LGB (N=4)	P value
Mean (days)	4.9±6.7	2.3±2.6	0.021[c]	4.6±1.9	10±9.8	0.350
Median (days)	3	1	<0.001[c]	4	8	0.922

Continuous data were shown as the mean ± the standard deviation.
GJ Gastrojejunostomy, *JJ* jejunojejunostomy, *OGB* open gastric bypass, *LGB* laparoscopic gastric bypass
[a] GJ and JJ leaks in RGB were not included in this table.
[b] One patient does not have a detection time recorded in OGB JJ leak group (1989 surgery).
[c] Statistically significant with $p<0.05$.

rate: 126+19 operative, 120.7+20 nonoperative, $p=0.283$; temperature: 99.1+3.1 operative, 99.7+3.1 nonoperative, $p=0.911$; WBC: 9.0+2.2 operative, 7.8+2.1 nonoperative $p=0.121$). It is noteworthy that with the exception of the pulse, these are all normal mean values. We also attempted to determine whether operative placement of a drain correlated with successful conservative management. There were no differences between the groups (67% of drained patients required reoperation, while 78% of undrained patients required reoperation). In the undrained patients with successful nonoperative management, percutaneous radiologically guided drains were successful. There was also no difference in mortality between GJ leaks with drains placed at initial surgery versus undrained patients.

All 15 patients who had JJ leaks required reoperation. Initial UGI failed to detect 9 of 10 JJ leaks (90.0%), compared to 16 of 89 GJ leaks (19.1%, $p<0.001$). Median time from surgery to detection was longer for JJ leaks than for GJ leaks (4 vs 2 days, respectively, $p=0.037$ Wilcoxon score). Average detection times were similar in both groups (GJ: 4.3±5.6 days, JJ: 5.9±5.6 days, $p=0.294$). Patients with JJ leaks had a higher BMI than those with GJ leaks (JJ: 55.3±10.0 kg/m^2, GJ: 48.8±10.0 kg/m^2, $p=0.021$).

Tachycardia, defined as pulse rate greater than 120, was seen in 65% (45/69) of GJ leaks and 83% (10/12) of JJ leaks ($p=0.320$). Other clinical signs, including maximal temperature and white blood cell count, were also similar in GJ and JJ leaks. Age, male gender, and race were also similar between groups (Table 5). Comparison of GJ and JJ leak in de novo OGB and LGB without RGB are presented in Table 6. Modalities used in the diagnosis of leaks are presented in Table 7. Seventy-nine leaks were detected by UGI. Nine leaks were detected by computerized axial tomography (CT) scan. Twenty-seven leaks were detected by laparotomy as a result of suggestive clinical signs without radiological studies. Leaks identified by clinical signs had the highest mortality, 29.6% (8/27), while leaks identified by UGI had the lowest mortality rate of 7.6% (6/79).

Table 5 Comparison of GJ and JJ Leaks

	GJ (N=100)	JJ (N=15)	P value
In-hospital death	9 (9.0%)	6 (40.0%)	0.005[a]
Surgical intervention	68 (68.0%)	15 (100.0%)	0.010[a]
Death in surgical repair group	9 (13.2%)	6 (40.0%)	0.025[a]
Number of UGI performed	89	10	
Initial UGI read as normal	17 (19.1%)	9 (90.0%)	<0.001[a]
Mean, detection time (days)	4.3±5.6	5.9±5.6	0.294
Median, detection time (days)	2	4	0.037[a]
Heart rate >120 BPM	45 (65.2%)	10 (83.3%)	0.320
Mean, maximal temperature	38.3±0.9	38.7±1.1	0.190
Mean, WBC (K/μL)	12.3±6.2	12.6±5.9	0.892
Age	43.9±10.2	46.8±13.6	0.339
Preoperation BMI (kg/m^2)	48.8±10.0	55.3±10.0	0.021[a]
Preoperation weight (lbs)	304.2±76.0	338.9±69.5	0.099
Gender, male	26 (26.0%)	4 (26.7%)	1.000
Race, white	83 (83.0%)	13 (86.7%)	0.691
Mode of diagnosis	UGI (78) CT(7) Clinical (15)	UGI (1), CT (2), Clinical (12)	

Continuous data were shown as the mean ± the standard deviation.
GJ Gastrojejunostomy, *JJ* jejunojejunostomy, *UGI* upper gastrointestinal study, *BPM* beats per minutes, *WBC* white blood cell count, *BMI* body mass index, *CT* computerized axial tomography
[a] Statistically significant with $p<0.05$.

Table 6 Comparison of GJ and JJ Leaks in de novo OGB and LGB Without RGB

	GJ (N=81)	JJ (N=12)	P value
In-hospital death	8 (9.9%)	6 (50.0%)	0.002[a]
Surgical intervention	56 (69.1%)	15 (100.0%)	0.032[a]
Death in surgical repair group	8 (14.3%)	6 (40.0%)	0.012[a]
Number of UGI performed	74	10	
Initial UGI read as normal	14 (18.9%)	9 (90.0%)	<0.001[a]
Mean, detection time (days)	3.5±5.1	6.5±6.2	0.078
Median, detection time (days)	2	4	0.006[a]
Heart rate >120 BPM	39/60 (65.0%)	9/11 (81.8%)	0.484
Mean, maximal temperature	38.3±0.9	38.7±1.1	0.153
Mean, WBC (K/μL)	11.6±5.9	13.2±5.8	0.426
Age	43.4±10.2	44.1±13.5	0.829
Preoperation BMI (kg/m^2)	50.7±8.5	57.0±9.7	0.020[a]
Preoperation weight (lbs)	316.1±70.3	350.2±70.1	0.120
Gender, male	21 (26.3%)	3 (25.0%)	1.000
Race, white	68 (84.0%)	11 (91.7%)	0.685
Mode of diagnosis	UGI (66) CT(2) Clinical (13)	UGI (1), CT (2), Clinical (9)	

Continuous data were shown as the mean ± the standard deviation.
GJ Gastrojejunostomy, *JJ* jejunojejunostomy, *UGI* upper gastrointestinal study, *BPM* beats per minutes, *WBC* white blood cell count, *BMI* body mass index, *CT* computerized axial tomography
[a] Statistically significant with $p<0.05$.

Discussion

Overall

Leaks after GBP are a major cause of mortality[9]. Our overall leak rate was 3.9%, similar to rates from 2 to 5% reported in the literature[6,7]. RGB carries a higher risk of leak, and we noted 8.0% incidence in our study.

Fernandez has reported that occurrence of postoperative leak, higher weight, procedure type, and hypertension are associated with increased risk of early death after surgery[9]. Age, male gender, sleep apnea, and procedure type have been shown to be independent risk factors for leaks[9]. Our study confirms that leaks are more common in older patients and males. Preoperation BMI and weight did not differ between patients with and without leaks. Male patients may have more central obesity (android)[10], with thickened mesentery and enlarged liver causing technical difficulties during surgery. This may contribute to their higher leak rates. Advanced age has also been shown to be associated with delayed wound healing[11], and thus may increase the risk of postoperation complications, specifically leaks.

OGB vs LGB

The overall leak rate after OGB was lower than after LGB. However, leak-associated mortality was significantly higher in the OGB group. OGB patients had their surgery at earlier time periods in our series, and heavier patients (BMI >50 kg/m^2) were offered only OGB in the beginning of our LGB experience, which might partially explain its higher leak-associated mortality. However, a more likely explanation for the lower mortality in the LGB group was the earlier detection of leaks.

Gastrojejunostomy leaks were more common after LGB than OGB. This may have been partially due to technical difficulties associated with implementing the laparoscopic approach. Even though there was a higher GJ leak rate in the LGB group, mortality after GJ leak was higher in the OGB group (18.4 vs 2.3%, p=0.015). Sixty-eight percent of GJ

Table 7 Modality of Detection

	All (N=115)		GJ (N=100)		JJ (N=15)	
Modality	Time	Death	Time	Death	Time	Death
UGI	3.7±5.0	6/79 (7.6%)	3.7±5.0	6/78 (7.7%)	4	0/1 (0.0%)
CT	9.0±6.3	1/9 (11.1%)	7.1±3.8	0/7 (0.0%)	22	1/2 (50.0%)
Clinical	5.2±6.4	8/27 (29.6%)	5.6±8.0	3/15 (20.0%)	4.8±3.5	5/12 (41.7%)
All	4.5±5.6	15/115 (13.0%)	4.3±5.6	9/100 (9.0%)	5.9±5.6	6/15 (40.0%)

Continuous data were shown as the mean ± the standard deviation. Time is in days.
GJ Gastrojejunostomy, *JJ* jejunojejunostomy, *UGI* upper gastrointestinal study, *CT* computerized axial tomography

leaks required reoperation, while 32% of GJ leaks were managed conservatively with close suction drainage or percutaneous drainage, NPO, total parenteral nutrition, and broad-spectrum antibiotics. Conservative management of leaks by closed suction drainage in patients who were clinically stable appears to be safe, with no deaths occurring in this subgroup.

Time from surgery to detection of a GJ leak in the OGB group was longer than in the LGB group. In the OGB era, water soluble contrast studies were obtained on postoperative day 2, while in the LGB era they were typically obtained on postoperative day 1. The earlier diagnosis of leaks in the LGB group could explain their better outcomes. Furthermore, most LGB patients had juxta-anastomotic (GJ) drains facilitating nonoperative management of leaks.

GJ vs JJ Leak Complications

Jejunojejunostomy leaks had a higher mortality rate than GJ leaks and surgical interventions were performed for all JJ leak cases because all patients showed hemodynamic instability or clinical deterioration. Our mortality rate of 40% after JJ leaks is similar to a previous report[7]. UGI was unreliable in diagnosing JJ leaks. Nine out of 10 UGI studies did not detect JJ leaks, and 75% of JJ leaks were diagnosed clinically. Median times from surgery to detection of JJ leaks were longer than for GJ leaks. From our experience, UGI is usually limited to identifying leaks at the esophagus, proximal pouch, and GJ. The high rate of UGI false negatives for JJ leaks may have contributed to the delay in diagnoses and poor outcomes. Furthermore, a GJ leak cannot be completely ruled out even with a normal UGI. Therefore, patients with clinical signs or symptoms of a leak require further investigation or operation.

Clinical signs of leak include tachycardia (exceeding 120 beats per minute) and respiratory distress[8]. In our study, 65 and 83% of patients with GJ and JJ leaks, respectively, showed tachycardia. Although tachycardia has been found to be the most accurate independent predictor of leak, it is of limited use in this obese population because many GBP patients without leaks are also often tachycardic from other sources[8]. It should be also noted that tachycardia did not have to be persistent to herald leaks. Our current practice is to aggressively study patients with tachycardia, decreased urine output, hypoxia, or abdominal pain with UGI and/or CT scan if patients' weight can be accommodated by the scanner. We have also found that an elevated drain amylase levels (>400 U/L) to be a sensitive indicator of GJ leaks[12]. We presently utilize selective contrast studies in patients with elevated drain amylase or clinical signs suggestive of a leak; however, normal UGI finding should not delay therapy if clinical signs suggest a leak.

We were unable to define from our data characteristics that would allow us to predict which GJ leaks could be treated nonoperatively. The same characteristics that define successful management of leaks in the gastrointestinal tract in general apply: good drainage (this can be provided by operatively placed drains or percutaneous drains), bowel rest, and broad-spectrum antibiotic therapy. Success is judged by clinical improvement.

Conclusion

Leak mortality and time from surgery to detection were higher in OGB patients than in LGB patients. Age, male gender, and operation type were predictors of leaks. JJ leak carries a higher mortality rate than GJ leak, likely because UGI is inadequate to rule out a JJ leak, leading to a delay in diagnosis. GBP patients with normal UGI studies may harbor leaks, especially at the JJ or excluded stomach. Normal UGI findings should not delay therapy if clinical signs suggest a leak.

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Hyperbilirubinemia in Appendicitis: A New Predictor of Perforation

Joaquin J. Estrada · Mikael Petrosyan · Jordan Barnhart · Matthew Tao · Helen Sohn · Shirin Towfigh · Rodney J. Mason

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Abstract This study examines the relationship between hyperbilirubinemia and appendicitis. It was hypothesized that an association exists between the presence of appendiceal perforation and hyperbilirubinemia. Patients with liver function tests on admission and pathologically confirmed appendicitis were included in the study. Age, duration of symptoms, temperature, white blood cell counts, systemic inflammatory response score, and bilirubin levels were independent variables in a logistic regression analysis assessing factors predicting the presence or absence of appendiceal gangrene/perforation. Elevated total bilirubin levels (>1 mg/dl) were found in 59 (38%) of 157 patients. Patients with gangrene/perforation were significantly (p=0.004) more likely to have hyperbilirubinemia than those with acute suppurative appendicitis. No statistical differences were observed for any of the other variables. On logistic regression the only significant relationship between the presence or absence of appendiceal gangrene and perforation was the presence of hyperbilirubinemia (p=0.031, 95% confidence interval 1.11–7.6). The odds of appendiceal perforation are three times higher (odds ratio 2.96) for patients with hyperbilirubinemia compared to those with normal bilirubin levels. Hyperbilirubinemia is frequently associated with appendicitis. Elevated bilirubin levels have a predictive potential for the diagnosis of appendiceal perforation.

Keywords Hyperbilirubinemia · Appendicitis · Jaundice · Peritonitis

Introduction

An association between elevated serum bilirubin levels and a variety of infectious diseases has been noted.[1–4] This finding most commonly occurs in neonates with gram-negative bacterial infections.[5–8] It has also been described in patients with severe intraabdominal infections. The pathogenesis is thought to be because of bacteremia or endotoxemia causing impaired excretion of bilirubin from the bile canaliculi.[1,9]

Appendicitis is one of the most commonly diagnosed surgical conditions, with *Escherichia coli* being one of the most frequent bacterial isolates in the disease. The association of hyperbilirubinemia in patients with appendicitis is largely unknown. There are only a few case reports in the literature that describe the finding of hyperbilirubinemia in patients with either severe postoperative infection after appendectomy or with complicated appendicitis.[4,10–16]

The aim of the present study was to determine the frequency with which elevated bilirubin levels are associated with appendicitis. Furthermore, we hypothesized that appendiceal perforation might favor the development of hyperbilirubinemia and designed a study to compare clinical factors important in distinguishing patients with nonperforated appendicitis to those with perforation.

Poster of Distinction presented at the 47th annual meeting of the Society for Surgery of the Alimentary Tract held in Los Angeles, CA on 22 May 2006.

J. J. Estrada · M. Petrosyan · J. Barnhart · M. Tao · H. Sohn · S. Towfigh · R. J. Mason (✉)
Division of Emergency (Non-Trauma) Surgery,
Department of Surgery, Keck School of Medicine of the University of Southern California and Los Angeles County,
USC Medical Center,
1200 North State Street, Room 10-850,
Los Angeles, CA 90033, USA
e-mail: rmason@surgery.usc.edu

Patients and Methods

A retrospective review was performed for all patients who presented with clinical features of appendicitis to the Emergency Surgical Services of the Los Angeles County Hospital, University of Southern California Medical Center between January 2005 to December 2005. Patients were included in the study if they had an appendectomy (laparoscopic or open) and liver function tests performed on admission. Patients were excluded if they had documented liver disease, history of alcoholism, hemolytic disease, and other acquired or congenital biliary disease.

One hundred and seventy patients met all inclusion and exclusion criteria. There were 69 female and 101 male patients. The median age of the patients was 32 years (range 5–66 years). The patients were then stratified into two groups based on final tissue histopathology: those with acute suppurative appendicitis and those with gangrenous/perforated appendicitis.

Patients were analyzed based on the following factors: demographics, duration of symptoms, preoperative liver function tests, systemic inflammatory response score (SIRS), microbiology, and pathology. Systemic inflammatory response score was calculated using the defined categories for systemic inflammation [temperature, heart rate, respiratory rate, and white blood cell (WBC) count]. Fever was defined as a temperature >38°C. An elevated WBC count was defined as 10.3 K/cumm or greater and an elevated bilirubin level was defined as a total bilirubin >1 mg/dl, which corresponds to our clinical laboratory's normal range of values.

Microbiological specimens, including aerobic and anaerobic cultures, were obtained from the blood in 75 patients preoperatively and from the peritoneal cavity in 111 patients at the time of appendectomy.

Statistical Analysis

Data were reported as median and interquartile range unless otherwise specified. Fisher's exact test was used for categorical data, whereas continuous variables were analyzed using the Mann–Whitney U-test. Factors potentially predictive of appendiceal perforation on the basis of the pathological analysis were accessed using univariate analysis and included duration of symptoms (≤24 and >24 h), pyrexia (≤38 and >38°C), SIRS score (≤2 and >2), inflammatory response (WBC count ≤10.3 and >10.3 K/cumm), age (≤18 and >18), and total bilirubin (≤1 and >1mg/dl). These factors were then entered into a multivariable model as independent parameters. Forward stepwise logistic regression was performed to assess the joint effect of the variables and to define those that were independently associated with the appendiceal perforation. The results are presented as adjusted odds ratio (OR) with 95% confidence interval (CI) and p values from the adjusted Wald's test. The Wald's test was computed in SPSS (version 10) using the square of the coefficient divided by the standard error for the independent variables. All analyses were two-sided with significance set at 0.05.

Results

Appendicitis was found and confirmed histologically in 157 (92%) of 170 patients. Thirteen patients had a pathological diagnosis not consistent with appendicitis. Hyperbilirubinemia was found in 59 of the 157 (38%) patients. One hundred and sixteen patients (74%) had evidence of acute suppurative appendicitis and 41 patients (26%) had gangrenous/perforated appendicitis on final histopathologic analysis (see Fig. 1).

Demographics

The median age was 33 years (range 5–66 years) for patients with acute suppurative appendicitis and 31 years (range 7–61 years) for patients with gangrenous perforated appendicitis (p=0.95). Ten percent of the population in both groups were 18 years or younger (p=0.94). The prevalence of male patients with an acute suppurative appendicitis (68%) was similar (p=0.229) to the prevalence in those with a gangrenous/perforated appendix (57%).

Duration of Symptoms

The median duration of symptoms was slightly shorter for patients with an acute suppurative appendicitis (1 day, range 1–4) compared to those with a gangrenous/perforated appendix (2 days, range 1–5), although it did not reach statistical significance. The proportion of patients with symptoms for greater than 24 h was similar in both groups (p=0.65).

Pyrexia

Twenty-two percent of patients with acute suppurative appendicitis and 31% of patients with a gangrenous/perforated appendicitis presented with a fever. Statistical analysis failed to reveal a difference between the two groups.

Inflammatory Response

Seventeen (15%) patients with acute suppurative appendicitis had a SIRS >2 compared to nine patients (22%) with a gangrenous/perforated appendicitis (p=0.28). An elevated WBC count on admission was found in 89 (77%) patients

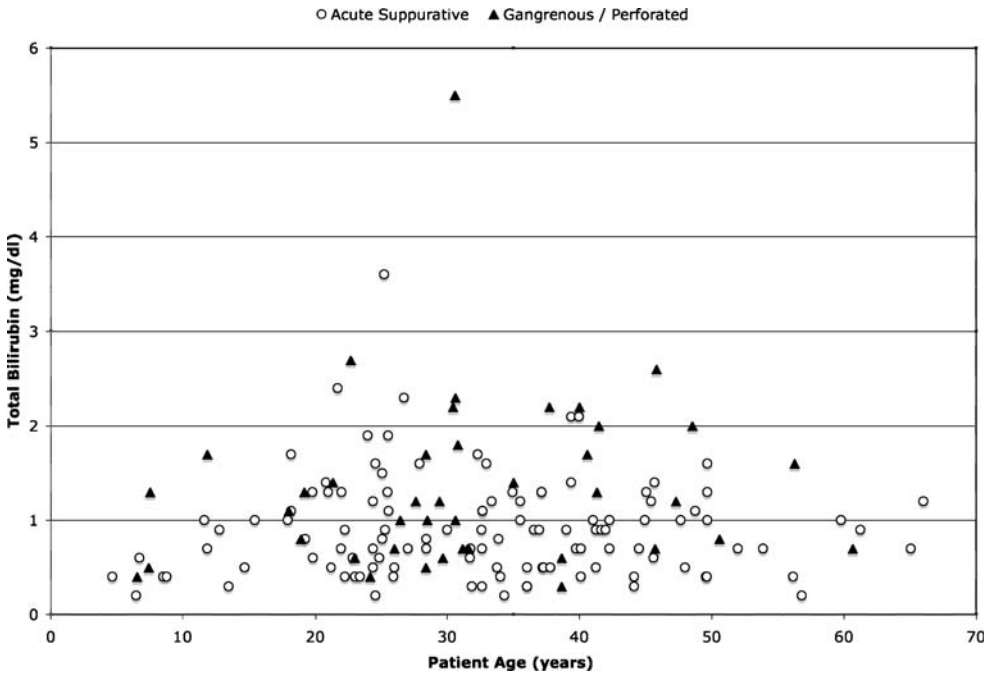

Figure 1 Scatter plot showing the relationship of serum bilirubin levels to patients' age. Data stratified into those patients with acute suppurative appendicitis (open circles) and gangrenous perforated appendicitis (solid triangle).

in the acute suppurative appendicitis group and in 30 (73%) in the gangrenous/perforated group. Comparison between the two groups failed to reveal statistical significance.

Liver Function Tests

Thirty-six (31%) of the patients with acute suppurative appendicitis and 23 (56%) of the patients with a gangrenous/perforated appendix had elevated bilirubin values (p=0.004). Direct bilirubin levels showed identical findings to total bilirubin levels. On logistic regression the only significant relationship between the presence or absence of appendiceal gangrene/perforation was the presence of hyperbilirubinemia (p=0.031, 95% CI 1.11–7.6). The odds of appendiceal gangrene/perforation were three times higher (OR 2.96) for patients with hyperbilirubinemia compared to those with normal bilirubin levels. Only 14 patients out of the total study population had bilirubin levels elevated greater than 2 mg/dl. Abnormal liver transaminases were found in only 6 of 116 (5%) patients in the acute suppurative group and 2 of 41 (5%) patients in the gangrenous/perforated group (p=0.94).

Bacterial Cultures

A positive blood culture was detected in 15 of the 75 patients (20%). The prevalence of elevated bilirubin was significantly higher in those patients with a positive blood culture compared to those with a negative blood culture (p=0.011, see Fig. 2).

There was no growth seen from intraabdominal cultures of patients with a histologically normal appendix. The prevalence of bacterial growth from the peritoneal culture was significantly higher in the gangrenous/perforated group compared to the acute suppurative group (p=0.031, see Fig. 3). All patients except for one had multiple bacterial isolates from the peritoneal cultures. The commonest isolates were *E. coli* and Bacteroides, each of which occurred in 70% of the specimens. The prevalence of a positive peritoneal culture was similar between patients with normal bilirubin compared to those with elevated bilirubin levels.

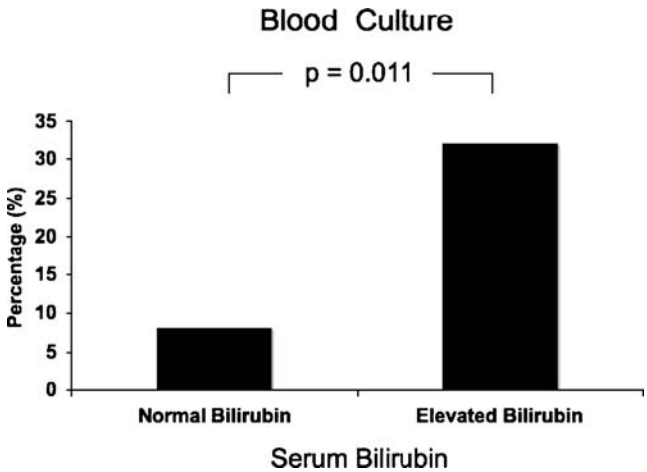

Figure 2 Prevalence of a positive blood culture in patients with normal and elevated bilirubin levels (p=0.011).

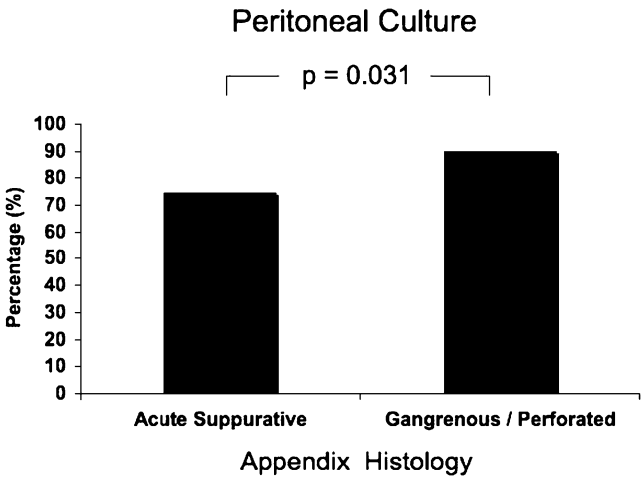

Figure 3 Prevalence of positive peritoneal culture in patients with acute suppurative appendicitis and gangrenous/perforated appendicitis.

Discussion

In this study, we have found that in a series of patients with appendicitis, hyperbilirubinemia was found in well over one third of all patients, and in more than half of the patients with a perforated appendix. In the past, no other investigators have addressed the significance of hyperbilirubinemia in appendicitis. This is probably related to the fact that clinically the signs and symptoms of the appendicitis overshadow the bilirubin abnormality. Only 5% of patients had abnormal liver transaminases, and therefore, hyperbilirubinemia was independent of other liver function abnormalities. This observation has also been reported with other gram-negative infections.[1]

As these finding were documented on admission to the hospital, it is unlikely that liver injury because of anesthetic agents, blood transfusions, or medications were the cause of elevated bilirubin levels. Septic shock with subsequent ischemic liver injury was not a major factor as only 17% of patients had a SIRS of >2. The most likely explanation is because of the circulating endotoxemia related to the appendiceal infection. Utili et al.[17–19] have shown with an in vitro infusion of endotoxin into an isolated rat liver that there is a dose-dependant decrease in the bile–salt excretion from the liver, and that it is possible that *E. coli* endotoxin exerts direct damage at the cholangiolar level.

This study shows that hyperbilirubinemia is an independent predictor of appendiceal perforation, with nearly a threefold risk of perforated appendicitis in patients with total bilirubin levels greater than 1 mg/dl. The other factors we examined are indirect markers of inflammation and are therefore unreliable, whereas the cause for elevated bilirubin is directly related to the pathogenesis of appendicitis.

Sisson et al.[20] demonstrated that mucosal ulceration in appendicitis occurs early in the evolution of the disease before dilation of the appendix. This facilitates invasion of the bacteria into muscularis propria of the appendix, causing classical acute suppurative appendicitis. Subsequent events cause a nonspecific host immune response, which leads to edema, elevated intraluminal pressure, and subsequent ischemic necrosis of mucosa, causing tissue gangrene and perforation.[21,22] This process is associated with progressive bacterial invasion most likely facilitated by bacteria cytotoxins. The number of organisms isolated from patients with gangrenous appendicitis is five times greater than those with acute suppurative appendicitis.[23,24] This is supported by the observation in our study that the prevalence of a positive peritoneal culture was significantly higher in patients with gangrenous/perforated appendicitis.

These elevated levels of bacteria in the appendix cause either the direct invasion or translocation into the portal venous system. This was demonstrated in a large animal model of colonic ischemia, using systemic and portal venous sampling of blood combined with hepatic tissue cultures. In this model, Bennion et al.[21,22] showed a stepwise progression of bacterial invasion from the ischemic organ into the portal venous system, the liver, and subsequently into the arterial system. Direct invasion of bacteria into the hepatic parenchyma interferes with the excretion of bilirubin into the bile canaliculi by a mechanism that is thought to be caused by the bacterial endotoxin and is biochemical in nature rather than obstructive. Our in vivo study supports this evolution as proposed by Bennion et al. Ninety percent of our patients with a gangrenous/perforated appendicitis had positive intraabdominal cultures, 56% had elevated bilirubin levels, and 32% of these patients had a positive blood culture.

The limitation of this study are that it was a retrospective study with a possible selection bias as not all patients with appendicitis seen at our institution during this period had liver function tests on admission. Furthermore, ultrasonography of the portal vein was not routinely performed to exclude the presence of a septic thrombosis in the portal vein. Gilbert's syndrome occurs in approximately 3–8% of the general population and it is likely that some of the patients in this study may have had Gilbert's syndrome as a cause for their hyperbilirubinemia. However, the prevalence in each group would be expected to be similar.

Historically perforated appendicitis cannot be reliably distinguished from acute appendicitis based on admission criteria.[25] However, the likelihood of appendiceal perforation is three times higher for patients with elevated serum bilirubin levels. Therefore, obtaining serum bilirubin values upon admission can be used in conjunction with more modern diagnostic tests, such as CT scan and ultrasound, to

help determine the presence of perforation and thus aid in proper clinical management.

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Enteral Immunonutrition During Sepsis Prevents Pulmonary Dysfunction in a Rat Model

Joerg Glatzle · Michael S. Kasparek · Mario H. Mueller · Fiedrich Binder · Tobias Meile · Martin E. Kreis · Alfred Konigsrainer · Wolfgang Steurer

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Abstract
Background Sepsis often results in severe pulmonary dysfunction. Via the thoracic duct, the lung is the first organ exposed to gut-derived inflammatory mediators released into mesenteric lymph during sepsis.
Aim To investigate whether an enteral immunonutrition during sepsis improves pulmonary function.
Methods Mesenteric lymph was obtained from lymph fistula donor rats after intra peritoneal (i.p.) saline (control lymph) or lipopolysaccharide (sepsis lymph) injection. Sepsis lymph was also collected during enteral immunonutrition with ω-3 enriched, long-chain fatty acids (SMOF lipid). Control, sepsis, or sepsis-SMOF lymph was reinfused into the jugular vein of separate recipient rats. The lungs were then harvested, stained with hematoxylin-eosin, and analyzed for: (1) perpendicular parenchyma thickness of the alveolar wall; (2) myeloperoxidase-positive cells; and (3) terminal deoxynucleotidyl transferase Biotin-dUTP nick end labeling (TUNEL)-positive cells.
Results Enteral immunonutrition during sepsis reduced the release of TNFα into mesenteric lymph by about 4.5-fold within the first 2 h. Infusion of sepsis lymph into recipient rats induced thickening of alveolar walls, inflammatory reaction, and apoptosis. Infusion of sepsis lymph obtained during enteral immunonutrition did not cause anatomical changes, induced only a mild inflammatory reaction, and prevented apoptosis in the lungs of recipient rats.
Conclusions Mediators in sepsis lymph induce pulmonary dysfunction such as an increased distance for oxygen transport, inflammatory reaction, and apoptosis. The lung may be protected by an enteral immunonutrition containing long-chain fatty acids.

Keywords Mesenteric lymph · Lung · Sepsis · Fish oil · Cytokines · Immunonutrition

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J. Glatzle (✉) · M. S. Kasparek · F. Binder · T. Meile · A. Konigsrainer · W. Steurer
Department of General and Transplantation Surgery,
University Hospital of Tuebingen,
Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany
e-mail: joerg.glatzle@med.uni-tuebingen.de

M. H. Mueller · M. E. Kreis
Dept. of General Surgery,
Ludwig-Maximilians-University of Munich,
Munich, Germany

Introduction

Gut-derived inflammatory mediators play a major role in lung injury during acute insults to the gastrointestinal tract and include trauma, hemorrhagic shock, and sepsis.[1,2] Via the thoracic duct, the lung is the first organ exposed to mesenteric inflammatory mediators. It has been demonstrated in several studies that diversion of the thoracic duct prevents acute lung injury, neutrophil activation, endothelial cell apoptosis, and red blood cell dysfunction.[3–5] Recently, we developed a new animal model to investigate the release of mediators into mesenteric lymph during sepsis. We have shown that during abdominal sepsis inflammatory mediators such as tumor necrosis factor-α (TNFα) are released in high concentrations into mesenteric lymph. This indicates that TNFα is a good parameter for

monitoring the release of inflammatory mediators from the gut into mesenteric lymph during sepsis.[6]

Recently, Leite et al. showed that an enteral nutrition containing olive oil benefits the survival of mice during sepsis.[7] The aim of the present study was to reduce the release of gut-derived, inflammatory mediators during sepsis using an enteral, immune-modulating nutrition containing long-chain triglycerides enriched in ω-3 fatty acids. For the enteral nutrition in the present study, we used a combination of soybean, olive, and fish oil, containing high amounts of ω-3 fatty acids. These fatty acids rely on metabolic pathways that use eicosapentaenoic acid (EPA) as a precursor for the synthesis of five-series leucotriens and three-series prostaglandins mediating vasodilatation, bronchodilatation, and inhibition of the inflammatory cascade. Therefore, an enteral immunonutrition containing ω-3 fatty acids might in itself have anti-inflammatory potential.

Recent studies using immunonutrition in critically ill patients were carried out with an array of immuno-active substances, including arginine, glutamine, nucleotides, vitamins, trace elements, and ω-3 fatty acids. However, conclusions regarding the contribution of a single substrate to the observed beneficial sum effect could not be drawn. In the present study, we investigate the immune-modulating effect of ω-3 fatty acids during sepsis and use the term "immunonutrition" for enteral nutrition that contains ω-3 fatty acids. We hypothesize that an enteral immunonutrition during sepsis reduces the release of inflammatory mediators from the gut into mesenteric lymph and therefore ameliorates pulmonary dysfunction during sepsis.

Methods

Animals

Male Sprague-Dawley rats (Charles River, Kieslegg, Germany) maintained on regular laboratory chow were housed under controlled conditions of illumination (12: 12 h light/dark cycle starting at 7:00 PM.), humidity and temperature (21°C). Rats were not fed overnight but allowed water ad libitum before all surgical and experimental procedures. We followed institutional guidelines for the care and use of laboratory animals throughout the study.

Mesenteric Lymph Collection

The method of mesenteric lymph duct cannulation has been previously published by the authors.[6,8] In brief, rats weighing 260–300 g were anaesthetized with methohexital sodium (60 mg/kg intraperitoneally [i.p.], Brevital, Jones Pharma Inc., St. Louis, MO) and the superior mesenteric lymph duct was cannulated with a polyvinyl tube (Medical Grade, 0.50 mm ID, 0.80 mm OD; Dural Plastics, Australia), fixed in place with a drop of cyanoacrylate glue (Krazy Glue, Elmers Products Inc., Columbus, OH) and externalized through the right flank. A second cannula (Silastic, 1 mm ID, 2.15 mm OD) was passed through the fundus of the stomach, extended 3 cm into the duodenum, secured in place with a silk suture and externalized through the left flank. After surgery, rats were placed in Bollman cages, and a glucose–saline solution (glucose 0.2 mol/l, NaCl 145 mmol/l, and KCL 4 mmol/l with or without 4% or 1% SMOF lipid; Fresenius Kabi, Germany) was infused continuously through the duodenal cannula at a rate of 3 ml/h to equalize volume and energy losses via the lymph. SMOF lipid contains 30% ω-6 fatty acids in the form of soy oil, 30% medium-chain triglycerides, 25% ω-9 fatty acids in the form of olive oil, and 15% ω-3 fatty acids in the form of fish oil. A steady lymph flow of 2.5±0.5 ml/h confirmed that lymph flow was not obstructed and that the cannula was appropriately positioned.

Mesenteric lymph was collected from four different experimental groups:

1 Control lymph: rats were intestinally infused with a glucose saline solution and saline was injected i.p. after the recovery period (n=6).
2 Sepsis lymph: rats were intestinally infused with a glucose–saline solution and lipopolysaccharide (LPS, *E. coli* serotype 0111:B1, Sigma, 5 mg/kg in 1 ml) was injected i.p. after the recovery period (n=6).
3 Sepsis-SMOF lymph: rats were intestinally infused with 4% SMOF lipid and LPS was injected i.p. after the recovery period (n=6).
4 Sepsis-SMOF lymph: rats were intestinally infused with 1% SMOF lipid and LPS was injected i.p. after the recovery period (n=6).

After a 24-h recovery period from surgical procedures, mesenteric lymph was continuously collected for a 12-h period in 2-h time intervals in all aforementioned groups. Lymph was collected in ice-chilled tubes, centrifuged, frozen, and stored at −80°C for further experiments.

Detection of Mediators in Mesenteric Lymph

Control, sepsis, and sepsis-SMOF lymph were sampled at 2-h intervals for detection of the pro-inflammatory cytokine TNFα (ELISA Kit, No. KRC 3012, Biosource, CA) to monitor adequate septic response after i.p. LPS injections. Because all animals responded adequately, no animals were excluded from the experiments.

Mesenteric Lymph Infusion

The lymph samples of the six donor rats from each group were pooled for the collection period 1–12 h. Mesenteric lymph was then infused in separate groups of healthy recipient rats through a catheter in the jugular vein (PE10, SIMS Portex, UK), which was emplaced 1 day before the lymph infusion experiments. Either NaCl, control lymph, sepsis lymph, or sepsis-SMOF (4%) lymph was infused for 90 min in fasted recipient rats at an infusion rate of 2.0 ml/h (n=6 for each group). The lung was harvested immediately after the termination of lymph infusion and fixed in paraformaldehyde (4%, Sigma, Steinheim, Germany) for histological staining.

Histological Analysis of Lung Tissue

The lung tissue was embedded in paramatoxylin eosin (H&E), H&E in combination with myeloperoxidase (MPO) or H&E in combination with TUNEL. For each animal 30 optical sections (24,300 μm^2) in 15 different specimens were analyzed using the Quantimet System (Leica, magnification ×40) to determine the thickness of the alveolar walls and assess for MPO-positive and TUNEL-positive cells. The average value of the 30 optical sections of one specimen was calculated and used as a single value for the statistical calculations.

The MPO immunohistochemistry was performed in paraffin-embedded lung tissue. In brief, the endogenous peroxidase was blocked by pre-incubation with hydrogen peroxide (120 ml methanol, 2 ml hydrogen peroxide, for 15 min). Nonspecific background staining was blocked by incubation with 20% swine serum for 20 min. Thereafter, the lung tissue was incubated overnight with a rabbit anti-MPO antibody (1:50; Dianova, Germany) at room temperature. The tissue was washed in phosphate-buffered saline and incubated with a biotinylated, swine anti-rabbit antibody (1:600; DAKO, Germany) for 60 min at room temperature. MPO immunoreactivity was demonstrated by the avidin–biotin complex (ABC) method with 3,3′diaminobenzidine 0.05%/hydrogen peroxide 0.033%) serving as chromagen. TUNEL-positive cells in the lung tissue were detected using the "In Situ Cell Death Detection Kit" (POD, Roche, Penzberg, Germany).

Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM). Differences between independent groups were determined by a two-tailed unpaired Student's t test and differences within a group were determined by a two-tailed paired Student's t test using the software package of GraphPad Prism 3.02 (San Diego, CA). A probability of $p<0.05$ was taken as significant.

Results

Effects of an Enteral Immunonutrition on Mediator Release into Mesenteric Lymph During Sepsis

During sepsis, TNFα was significantly increased in mesenteric lymph by about 200-fold within the first 2 h. In contrast, enteral immunonutrition with 4% SMOF lipid significantly reduced the TNFα release from the gastrointestinal tract into mesenteric lymph during sepsis. An enteral immunonutrition containing 1% SMOF lipid failed to reduce the inflammatory mediator release during sepsis (Fig. 1).

Effects of an Enteral Immunonutrition on Septical Anatomical Alterations in the Lung Parenchyma

Sepsis lymph infusion into healthy recipient rats induced a significant increase in alveolar wall thickness by about 30%. In contrast, infusion of sepsis-SMOF (4%) lymph did not cause anatomical changes of the alveolar walls in recipient rats (Fig. 2). Sepsis-SMOF (1%) lymph was not used for reinfusion into healthy recipient rats as an enteral immunonutrition containing 1% SMOF lipid did not change the release of inflammatory mediator from the gut during sepsis.

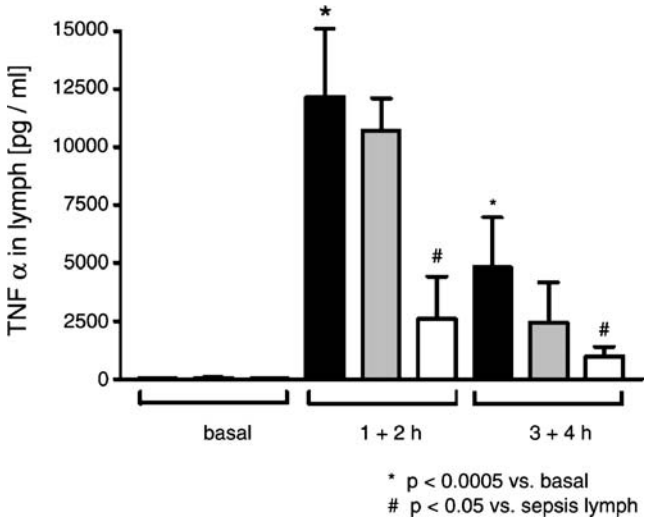

Figure 1 TNFα was significantly increased in mesenteric lymph during sepsis (black bars) compared to baseline levels. Intestinal lipid absorption (4% SMOF lipid) during sepsis significantly reduced the release of TNFα from the gastrointestinal tract into mesenteric sepsis-SMOF lymph (white bars), being significantly lower at 1+2 h and 3+4 h after the onset of sepsis compared to sepsis lymph. However, 1% SMOF lipid did not reduce TNFα output into mesenteric lymph during sepsis (gray bars).

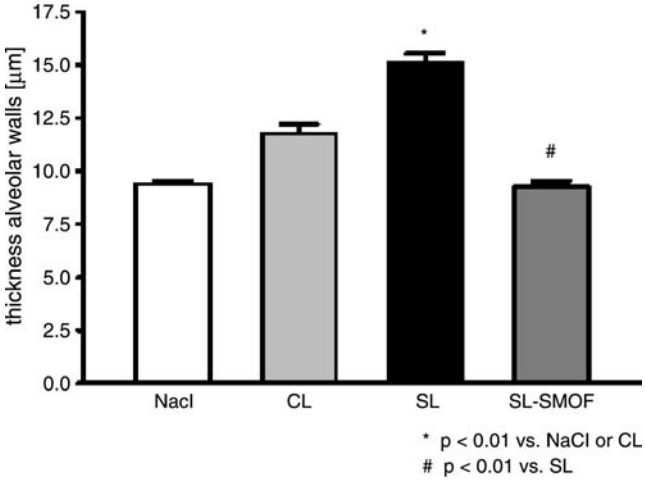

Figure 2 Sepsis lymph (SL, black bars) significantly increased the thickness of the alveolar walls in recipient rats, whereas control lymph (CL, light gray bars) or sepsis lymph collected during lipid absorption (SL-SMOF, dark gray bars) did not thicken the alveolar walls in recipient rats compared to the control group receiving NaCl (white bars).

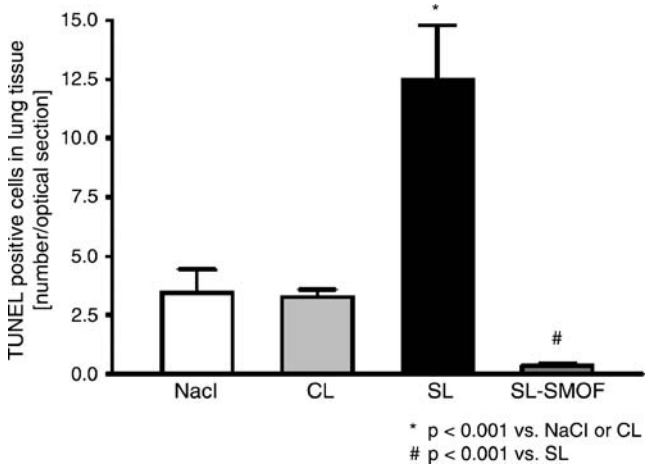

Figure 4 Sepsis lymph (SL, black bars) caused apoptosis (TUNEL immunoreactivity) in the lungs of recipient rats, whereas no changes were observed after infusion of control lymph (CL, light gray bars). Sepsis-SMOF (dark gray bars) lymph failed to induce apoptosis in the lungs of recipient rats. The control group receiving NaCl is shown in the white bars.

Effects of an Enteral Immunonutrition on Invasion of Immune Cells into the Lung Parenchyma During Sepsis

Infusion of sepsis lymph increased the number of MPO-positive cells in the lungs of healthy recipient rats compared to control lymph or saline. However, infusion of control lymph also caused invasion of immune cells into the lungs of recipient rats. In contrast, infusion of sepsis-SMOF lymph produced a significantly reduced inflammatory reaction compared to sepsis lymph, comparable to the inflammatory response caused by control lymph (Fig. 3).

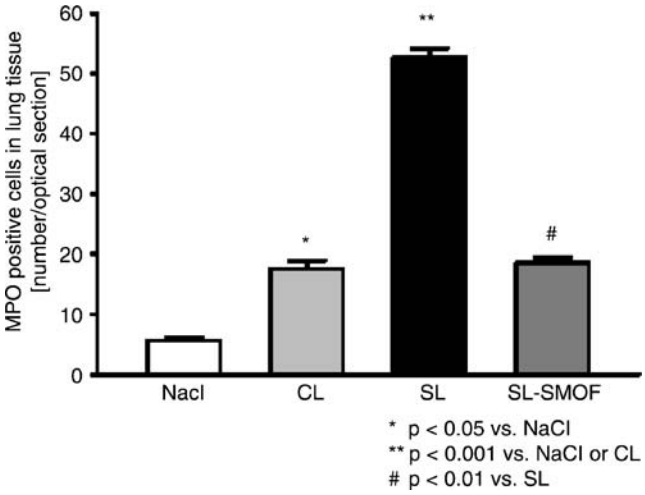

Figure 3 Infusion of sepsis lymph (SL, black bars) significantly increased the number of myeloperoxidase (MPO) positive cells in the lung of recipient rats. Infusion of control lymph (CL, light gray bars) also increased the inflammatory response in the lungs of recipient rats compared to the control group (NaCl, white bars), but to a much lower extent. The ability of sepsis lymph to cause inflammatory response in the lungs of recipient rats was significantly reduced when collected during lipid absorption (SL-SMOF, dark gray bars).

Effects of an Enteral Immunonutrition on Apoptosis in Lung Parenchyma During Sepsis

Sepsis lymph collected during enteral glucose saline infusion significantly increased the number of apoptotic cells in the lung parenchyma of healthy recipient rats compared to control lymph or NaCl infusion. However, infusion of sepsis-SMOF lymph collected during active fat resorption failed to cause apoptosis in the lung parenchyma of healthy recipient rats (Fig. 4).

Discussion

The present study demonstrates that inflammatory mediators are released into mesenteric lymph during sepsis and that these mediators are associated with septic pulmonary dysfunctions. The release of inflammatory mediators into mesenteric lymph during sepsis could be significantly reduced by an enteral immunonutrition containing ω-3 fatty acids. Sepsis lymph causes pulmonary dysfunction such as an increased distance for oxygen transport, inflammation, and apoptosis. In contrast, sepsis lymph collected during fat absorption attenuated septic pulmonary dysfunction.

In the United States, about 500,000 individuals develop sepsis annually and in Germany sepsis ranks as the third most frequent cause of death after acute myocardial infarction and cancer.[9,10] Multiple organ dysfunction syndrome (MODS) is typically present in severe sepsis and respiratory

failure is a particularly common sequela. The mortality rates during acute respiratory distress syndrome (ARDS) range from 30 to 40%, indicating the severity of the disease.[11] Further therapeutical approaches in abdominal sepsis to reduce pulmonary dysfunction would be desirable.

Bacterial sepsis and septic shock usually result from an overproduction of inflammatory mediators as a consequence of the interaction between the host immune system and the bacteria or bacterial wall components. Lipopolysaccharide (LPS), a glycolipid component of the gram-negative bacteria membrane, is commonly used in experimental sepsis models, as recognition of LPS by the host immune system initiates an inflammatory cascade similar to a gram-negative infection.[12] In the present study, we used 5 mg/kg LPS, a dose that is clearly sublethal, as none of the animals died during sepsis. However, this dose was sufficient to induce an inflammatory response in the gut wall of the donor rats and resulted in the release of significantly increased amounts of pro-inflammatory mediators such as TNFα. Sepsis lymph likely consists of a "cocktail" of gastrointestinal inflammatory and anti-inflammatory mediators released from the gut during sepsis. Therefore, TNFα seems to represent one of several inflammatory cytokines whose level increases in sepsis lymph. In the present study, we mainly measured TNFα in sepsis lymph to ensure the integrity of the sepsis model of the donor rats.

It is widely accepted that during sepsis pulmonary dysfunction occurs.[13,14] However, the mechanisms of the inflammatory lung injury induced by abdominal sepsis remain to be determined. There is strong evidence that the mesenteric lymph system, which drains the lymph of the gut via the thoracic duct into the systemic circulation, is involved in mediating septic pulmonary dysfunction, as diversion of mesenteric lymph significantly increased pulmonary function and survival during sepsis and hemorrhagic shock.[15] In the present study, we used an animal model that allowed us to investigate the release of mediators into mesenteric lymph during sepsis and the ability of these mediators to induce septic pulmonary dysfunction in healthy recipient rats. The aim was to reduce the inflammatory mediator release from the gut during sepsis using an immune-modulating diet enriched in ω-3 fatty acids to ameliorate septic pulmonary dysfunction caused by mesenteric lymph.

Several clinical studies have shown that ω-3 fatty acids improved the clinical outcome of critically ill patients.[16–18] In a prospective multiple-center trial parenteral nutrition that included fish oil as a source of ω-3 fatty acids reduced the length of hospital stay and lowered the hospital mortality rate.[16] However, the comparison of the treated patients in this open-label clinical trial was made against a predicted Simplified Acute Physiology Score II (SAPSII) and not against a proper placebo or control group. Gadek et al.[17] reported that an enteral immunonutrition enriched in ω-3 fatty acids and gamma-linolenic acid improved pulmonary function, reduced the length of stay in the intensive care unit, and prevented additional organ failure in patients with adult respiratory distress syndrome (ARDS).

The pathway by which an enteral immunonutrition with long-chain fatty acids mediates its immune-modulating effect remains uncertain. Recently, Tracey et al. discovered that the vagus nerve has an immunoregulatory function, which is termed the "cholinergic anti-inflammatory pathway".[19–21] The parasympathetic nervous system inhibits macrophage activation through the binding of acetylcholine to the nicotinic receptors located on macrophages.[20] Surgical dissection of the vagus nerve in rats enhanced systemic production of TNFα and accelerated the development of shock during sepsis. On the other hand, electrical stimulation of the vagus nerve decreased serum and hepatic TNFα levels.[21] Thus, mortality is increased in vagotomized rats during sepsis.[22] Interestingly, administration of high-fat nutrition reduced circulating TNFα and IL-6 levels in rats subjected to hemorrhagic shock.[23] However, when these experiments were repeated in vagotomized animals, administration of a high-fat diet no longer prevented the increase in TNFα or IL-6.[23] According to the present findings the cholinergic, anti-inflammatory pathway may, to some extent, explain the reduced TNFα released into mesenteric lymph during sepsis when the rats were intestinally infused with long-chain fatty acids. Therefore, sepsis lymph obtained during infusion of intestinal lipid might have a reduced inflammatory potential to cause septic pulmonary dysfunction. This recently discovered, cholinergic, anti-inflammatory pathway opens up several possibilities for experimental and clinical studies in critically ill patients.

Conclusion

During sepsis inflammatory mediators are released into mesenteric lymph. These gut-derived mediators result in septic pulmonary dysfunction such as increased distance of oxygen transport, inflammation, and apoptosis. An enteral immune-modulating diet containing long-chain ω-3 fatty acids reduces the release of gut-derived mediators during sepsis. Furthermore, sepsis lymph collected during enteral immunonutrition did not cause septic pulmonary dysfunction. However, the optimal use, timing, and dose of immune-modulating drugs such as ω-3 fatty acids in septic patients remain to be addressed.

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"How I do It" Session of the Pancreas Club

Carlos Fernández-del Castillo

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Middle Pancreatectomy

One of the few things that is guaranteed to spur controversy among surgeons is the discussion of new surgical procedures. On Sunday, May 21, 2006, the Pancreas Club held its 40th Annual Meeting, at the UCLA Faculty Center in Los Angeles. The topic for this year's "How I do It" symposium was Middle Pancreatectomy. This operation, which has also been referred to as median, segmental, and central, was first described in Europe in 1993, and five years later in the United States. A PubMed search yielded 27 papers on this topic, including some novel aspects such as various reconstruction techniques and a laparoscopic approach. Claudio Bassi, from Verona, Italy, gave an excellent description of the surgical technique and highlighted the PRO side, whereas Howard Reber, our host at UCLA, gave a very thoughtful presentation on the CON side. This was followed by a hearty discussion from the audience.

The following article was inadvertently published without its companion pieces. The section appears here in its entirety:
1. Fernández-del Castillo
2. Bassi
3. Reber

C. Fernández-del Castillo (✉)
Division of General Surgery, Massachusetts General Hospital,
15 Parkman Street,
Boston, MA, USA
e-mail: cfernandez@partners.org

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Middle Segment Pancreatectomy: A Useful Tool in the Management of Pancreatic Neoplasms

Claudio Bassi

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Abstract
Small, benign or low grade malignant tumours located in the neck of the pancreas are usually treated with enucleation. However if enucleation is too risky because of possible damage to the main pancreatic duct, standard pancreatic resections are performed. Such operations can lead to impaired long term exocrine-endocrine function. Middle segment pancreatectomy consists of a limited resection of the midportion of the pancreas and can be performed in selected patients affected by tumours of the pancreatic neck. Middle segment pancreatectomy is a safe and feasible procedure for treating tumours of the pancreatic neck; in experienced hands it is associated with no mortality but with high morbidity; the rate of "clinical" pancreatic fistula is about 20%. Moreover, it allows the surgeon to preserve pancreatic parenchyma and consequently long term endocrine and exocrine pancreatic function.

Keywords Pancreatic resection · Middle segment pancreatectomy · Pancreatic tumours · Surgical complications · Pancreatic function

Introduction

While neoplastic lesions located in the pancreatic head or body-tail are usually resected by pancreaticoduodenectomy or distal pancreatectomy, tumours in the neck represent a real challenge for the surgeon. In these cases, standard or extended pancreatectomies performed for benign or borderline cases, can result in the loss of a great amount of glandular tissue, significantly increasing the risk of diabetes, impaired exocrine function and splenic loss[1–6].

Enucleation would be an adequate alternative for small, benign and low-grade malignant tumours, such as endocrine and cystic neoplasms of the pancreas. Unfortunately this conservative procedure is not always applicable. When the neoplastic lesion measures up to 2 cm or more, or is encased within the pancreatic gland, enucleation is associated with a high risk of Wirsung's duct damage; moreover in the case of tumours with uncertain biological behaviour this approach shuld be avoided because of the risk of tumour recurrence[1–5].

Letton and Wilson reported for the first time in the English literature in 1959 two cases of traumatic mid-pancreatic transection followed by a reconstruction with a Roux-en-Y jejunal loop anastomized to the distal part of the gland[7]. Dagradi and Serio, form our own Department of Surgery, were the first in 1984 to propose middle pancreatectomy with an "oncological" indication, treating a pancreatic insulinoma[8]. Subsequently, other Authors reported cases of resection of the middle pancreas, of varying extent, using various terms such as "central pancreatectomy", "middle segment pancreatectomy", "segmental pancreatectomy" and "intermediate pancreatectomy"[9–13]. The underlying indications for surgery ranged

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1. Fernañdez-del Castillo
2. Bassi
3. Reber

C. Bassi
Department of Surgery, Policlinico "GB Rossi",
University of Verona,
Verona, Italy

C. Bassi (✉)
Department of Surgery - Chirurgia Generale B,
Policlinico "GB Rossi" - University of Verona,
Piazzale L.A. Scuro 10,
37134 Verona, Italy
e-mail: claudio.bassi@univr.it

from chronic pancreatitis to benign, uncertain behaviour or low- grade malignant exocrine and endocrine neoplasms[1–19]. Different tecniques were adopted for gastrointestinal reconstruction including jejunal anastomosis of boh the proximal and distal stump, or of only the distal stump, with pancreaticojejunal or pancreaticogastric anastomosis[1–21].

Surgical Technique

The abdomen is entered through a midline incision. The gastrocolic ligament is opened, preserving the gastroepiploic vessels, and the pancreatic gland is exposed. The posterior peritoneum along the superior and inferior margin of the pancreas is incised. The superior mesenteric vein and the portal vein must be identified and their surfaces cleared below the gland. The plane between the superior mesenteric and portal vein should be teased apart. The splenic artery and vein are dissected free and separated from the gland. Some venous tributaries to the portomesenteric axis and some minor collaterals of the splenic artery can be ligated. Then, the posterior surface of the pancreatic neck is isolated from the portomesenteric axis and a ribbon is passed behind the gland to elevate it. Sutures are placed along the superior and inferior margins to indicate where the proximal and distal transection should be performed and to ligate those wessels running along the margins. The segment of the pancreas with the tumour is subsequently transected through a knife or a stapler to the left and to the right of the lesion. The cephalic stump is sutured with interrupted stitches after elective ligation of Wirsung's duct or by means of a stapler. A small stent is placed in the main pancreatic duct while performing pancreojejunal or pancreogastric anastomosis; the stent can be left in place. Two closed-system suction drains are used to drain the cephalic stump of the gland and the pancreojejunostomy or pancreogastrostomy.

Discussion

It has been demonstrated that standard pancreatic resections are nowadays associated with low mortality and morbidity if performed in high-volume centres by experienced surgeons[22–24]. It is also known that this type of surgery can lead to long-term complications, such as diabetes, exocrine insufficiency and late postsplenectomy infection[25,26].

The incidence of postoperative exocrine and endocrine impairment is not predictable in patients with apparently "normal pancreas". Factors such as fibrosis of the remnant, Wirsung duct obstruction, preexisting chronic pancreatitis, benign or malignant disease and subclinical diabetes may play a role as "risk factors"[1–3]. After a standard left-sided resection there is an increased incidence of endocrine impairement and diabetes onset reported in from 17 to 85% of patients: it is obvious that the extent of the resection is strictly related to the incidence of endocrine-exocrine long-term insufficiency[27–31].

For all these reasons, more conservative surgical techniques have been advocated for small, benign or low-grade malignant tumours located in the neck of the gland, aimed at sparing as much as possible of pancreatic parenchyma; whenever neoplastic lesions are not small and superficial enought to be simply enucleated, middle segment pancreatectomy should be considerated[1–6].

Middle segment pancreatectomy accounts for only 3% of the pancreatic resections performed at our Institution and about 100 cases have been reported in the English literature[1–21,32–34]: this means carefull patients selection. The small number of patients who have undergone this type of opeation is related to different factors: specific localization of the neoplasm, well selected indications (benign or low-grade malignant tumours) and a distal pancreatic stump of at least 5 cm in length.

Some authors[1,3] have reported that this operation should be performed only for small tumours (<5 cm in diameter); in our experience, although the mean diameter of the resected lesions is 27.4 mm, we have safely performed middle segment resection for tumours measuring more than 5 cm, arising from the anterior surface of the pancreas.

We have also used middle segment pancreatectomy occasionaly for malignant disease: two islet cell carcinomas, one vipoma who subsequently developed hepatic metastases, one cystadenocarcinoma and one carcinoma in situ[2,3,10–12].

In the past, we have also performed this operation for more malignant tumours, but we have had pancreatic recurrence of the tumor in two patients (one affected by metastasis and one by IPMN with in situ carcinoma); moreover two patients with adenoma and borderline main duct IPMN, had a tumour recurrence in the pancreatic gland. Thus, we believe that in patients affected by primary or metastastic malignant tumours, a standard resection would be more appropriate. Moreover, middle pancreatectomy in our experience should be avoided also in patients affected by IPMN, especially main-duct type, because of their potential malignancy and the possibility of different degrees of dysplasia along the duct.

The surgeon must be sure to achieve tumor-free proximal and distal resection margins after performing middle segment pancreatectomy and for this reason frozen section examination is mandatory.

Middle segment pancreatectomy is a meticolous procedure. There is the possibility of leaks from both the closed cut edge of the head and the pancreojejunostomy, particu-

larly since in most patients we are dealing with a normal soft pancreatic texture with a small Wirsung duct. Thus, not only great care must be taken in selecting the patients who will benefit from this operation, but also an experienced pancreatic surgeon working in a high-volume centre is required for performing the procedure[1–4,6,32,33].

Median panceatectomy is reported to be associated with no mortality but with a high postoperative morbidity, particularly pancreatic fistulas[6]. In our experience the "clinical" pancreatic fistula rates after pancreaticoduodenectomy and left pancreatectomy are 10 and 20%, respectively[23,35–37]. Between January 1990 and December 2005 61 patients underwent middle segment pancreatectomy at our Institution. The incidence of pancreatic fistula - according to the ISGPF definition[22] - was 51%. It is remarkable that most patients had a Grade A fistula, which is a "biochemical" fistula without any clinical impact, while 13 patients (21%) developed a Grade B or C fistula which required prolonged in-hospital stay. In all patients the conservative management was successfull: no one underwent reoperation and in four cases intra-abdomnal collections were treated with ultrasounds guided drainage. The mortality rate was zero.

The risk of developing a pancreatic fistula must be taken into account in the preoperative decision making; we believe that this risk is acceptable when the procedure is performed in a high-volume centre and for patients with a long-life expectancy, such as young or middle aged people affected by benign or low-grade tumours.

The most important advantage of middle segment pancreatectomy is the good endocrine and exocrine long-term function[1–6,10]. Iacono et al.[1] in a series of 13 patients demonstrated that postoperative oral glucose tolerance, pancreolauryl and fecal fat excretion were normal in all cases. They studied six patients pre- and postoperatively with an OGTT, showing no significant differencies before and after surgery. Moreover, Sperti et al.[3] showed, in a review of the literature, no case of impaired endocrine function in 59 evaluable patients while exocrine function was reported to be normal in 56 out of 59.

Another advantage of this procedure is the possibility to preserve the spleen, avoiding the risk of postsplenectomy sepsis and hematologic disorders, which is low but exists in adults[38,39].

In conclusion, middle segment pancreatectomy is a safe and technically feasible surgical approach for removing pancreatic neck tumours in well selected patients; in experienced hands it is associated with no mortality but with high morbidity. Most of the complications do no require reoperation or prolonged in-hospital stay and can be successfully managed conservatively. Moreover, it allows the surgeon to preserve pancreatic parenchyma and consequently long term endocrine and exocrine function.

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Middle Pancreatectomy: Why I Rarely Do It

Howard A. Reber

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Proponents of middle pancreatectomy have presented its theoretical advantages, and Professor Bassi has done that eloquently. The principal ones are that it 1) preserves pancreatic exocrine and endocrine function, thus avoiding pancreatic exocrine insufficiency and diabetes, and 2) preserves the spleen and avoids the life-threatening complication of post splenectomy sepsis. Those who have expressed concern about the operation point out its disadvantages. The main ones are that it 1) doubles the risk of pancreatic fistula, and 2) risks the inadequate resection of malignant pancreatic tumors. In the discussion that follows, I will review each of these issues.

Theoretical Advantages

Preservation of Exocrine Function In 1973, DiMagno et al.[1] published a now classic paper that related the degree of malabsorption to the severity of pancreatic enzyme insufficiency. They showed convincingly that clinically significant malabsorption did not occur until 85–90% of pancreatic enzyme output was lost. This could occur via a variety of mechanisms, including destruction of functional pancreatic parenchyma (e.g., chronic pancreatitis), duct obstruction (e.g., pancreatic tumor), or pancreatic resection (e.g., distal pancreatectomy). Indeed, in a recent review of the effects of pancreatic resection on pancreatic exocrine function, Ghaneh and Neoptolemos[2] concluded that 5–10% of normal pancreatic enzyme output is enough for adequate absorption to occur. Thus, I would conclude that in patients with a previously normal pancreas, a distal (75–80%) pancreatic resection would not be expected to produce clinically significant exocrine insufficiency.

Preservation of Endocrine Function Slezak and Anderson[3] also recently reviewed the effects of varying degrees of pancreatic resection on glucose metabolism. They concluded that there was usually little change in what they termed "metabolic status" unless more than 80% of the pancreas was resected in patients with previously normal function. In other words, the situation is quite similar to that with exocrine function: the normal pancreas provides an excess capacity for both, and diabetes would be expected to be unusual after a major distal resection, as long as function in the remaining pancreas is normal.

There are very little data in the literature that address this question; almost all of the papers that deal with it assess patients who underwent distal pancreatectomy for complications of chronic pancreatitis. Of course, this group would be expected to have a higher rate of diabetes after pancreatic resection than the population that would be a candidate for middle pancreatectomy. For that reason, we reviewed the UCLA patients (n=128) who underwent distal pancreatectomy for a variety of indications from January 1992 through March 2006. New onset diabetes appeared in 10 patients (7.8%). Four of these patients had underlying chronic pancreatitis. If they were removed from consideration, then only 6/124 patients (4.7%) developed new-onset diabetes mellitus (insulin or oral agents) after 70–80% distal pancreatectomy. Again, the argument that middle

The following article was inadvertently published without its companion pieces. The section appears here in its entirety:
1. Fernández-del Castillo
2. Bassi
3. Reber

H. A. Reber (✉)
UCLA Center for Pancreatic Diseases,
David Geffen School of Medicine at UCLA,
10833 Le Conte Avenue, Los Angeles, CA, USA
e-mail: hreber@mednet.ucla.edu

pancreatectomy should be done because it avoids the endocrine insufficiency associated with a major resection would appear to be overstated for most patients.

Avoidance of Post Splenectomy Sepsis Although it occurs rarely in otherwise normal adults, there can be no question that splenic preservation avoids this usually fatal complication. It is a more persuasive argument in children than in adults, however. And of course, preservation of the spleen is often possible with conventional distal pancreatectomy.

Disadvantages

Pancreatic Fistula Middle pancreatectomy requires that a pancreaticojejunostomy be done to drain the preserved distal pancreas. Thus, both that anastomosis and the transected and closed resection margin at the head of the gland are at risk for leakage. Although occasional small series have been reported without any leaks, this is not the rule. In fact, in the hands of even the most experienced pancreatic surgeons around the world, fistula rates as high as 60% have been reported. Proponents of middle pancreatectomy generally dismiss this as an insignificant problem, suggesting that it is more of an annoyance, that almost all fistulas can be managed easily, and that they usually close without the need for another operation. I agree that the majority do close spontaneously. However, sometimes they do create significant morbidity, and they almost always increase the cost of care.

In a recent article, our moderator and his colleagues found that complications derived from pancreatic fistulas doubled the cost and significantly increased health care resource utilization.[4] They went on to conclude that there was an urgent need to develop strategies that reduced the incidence of that complication. This would also seem a persuasive argument against the use of middle pancreatectomy in many instances.

Inadequate Resection of Cancer Middle pancreatectomy is not a cancer operation. It is not performed with an extensive soft tissue and node dissection. It does not remove the putative lymphatic and venous drainage bed along the distal pancreas and at the splenic hilum where many malignant pancreatic tumors are thought to spread. Nevertheless, the list of lesions that have been removed in recent published series of middle pancreatectomy include serous and mucinous cystic neoplasms, intraductal papillary mucinous tumors (IPMN), pseudopapillary neoplasms, a malignant insulinoma, and numerous nonfunctional neurendocrine tumors.

There are several problems here. What appear to be serous cystic neoplasms preoperatively may turn out to be mucinous tumors with malignant potential. A number of surgical series give no indication that frozen section examination of the lesion and the resection margins are obtained as a routine. All resected pancreatic tumors should be managed in that way. Mucinous cystic neoplasms and IPMNs are both premalignant neoplasms in which invasive malignancy may be overlooked at the time of a limited resection. In part, this is related to sampling error, an intrinsic issue whenever the pathologist is required to perform a frozen section on a small portion of a larger lesion. With IPMN, the problem is compounded by the fact that the disease affects the entire gland, which cannot be sampled. Pseudopapillary tumors rarely metastasize, but they do tend to recur locally, which suggests that a limited local excision may be inadvisable.

The diagnosis of invasive malignancy in pancreatic neuroendocrine tumors is associated with a different complexity that is still not recognized widely. Thus, according to the *Armed Forces Institute of Pathology Guidelines (1995)*, the presence of microscopic vascular invasion alone by the neoplasm is viewed as sufficient for the diagnosis of invasive cancer. Metastases or invasion of adjacent structures is not required. Vascular invasion is often not possible to demonstrate on frozen section examination and it may only become evident in the postoperative period after the final pathology report is available. In a recent review of the UCLA experience with these lesions, 3/4 of 50 *nonfunctioning* pancreatic neuroendocrine tumors were malignant, according to these criteria (metastases and/or direct invasion of adjacent structure, or vascular invasion alone).[5] For these reasons, I am reluctant to perform a limited resection of any nonfunctional pancreatic neuroendocrine tumor. Functional tumors, especially insulinomas, which are likely to be benign, are an exception. Nevertheless, even the occasional malignant insulinoma may be overlooked (see above) because of the limitations of frozen section assessment already mentioned.

Conclusions

In general, the value of middle pancreatectomy has been overstated. With a previously normal pancreas, the loss of the body and tail of the gland causes malabsorption or diabetes only rarely. In certain cases (e.g., children) the preservation of the spleen may be desirable, but this is often possible by more conventional operations, which should be considered. Middle pancreatectomy doubles the risk of pancreatic fistula, which increases morbidity and the cost of care. The ability to diagnose cancer intraoperatively is limited, and middle pancreatectomy is an inadequate cancer operation. When the operation is done, patients should be chosen more carefully than what the literature suggests has been the practice to date. Be especially cautious about using it for nonfunctioning neuroendocrine tumors, because of the high frequency with which these turn out to be malignant. Always get frozen sections of the lesion itself and the resection margins, but realize the limitations of that assessment.

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Co-morbidity is a Strong Predictor of Early Death and Multi-organ System Failure among Patients with Acute Pancreatitis

Charles Frey · Hong Zhou · Danielle Harvey · Richard H. White

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Abstract A small but significant percentage of patients with acute pancreatitis die within 2 weeks of hospitalization, usually with multiorgan system failure. To determine the effect of chronic medical comorbidities on early death, we conducted a retrospective analysis of all patients who were hospitalized in California with first-time pancreatitis between 1992 and 2002. Among 84,713 patients, 1514 (1.8%) died within 2 weeks. In a risk-adjusted multivariate model, the strongest predictors of early death were age 65 to 75 years (OR=2.6, 95% CI: 2.2–3.1 versus <55 years), age over 75 years (OR=5.2, 95% CI: 4.4–6.1), and the presence of either two chronic comorbid conditions (OR=3.5, CI: 2.7–4.6) or three or more comorbidities (OR=7.4, 95% CI: 5.7–9.5). Among the 14,280 patients younger than 55 years who had no chronic comorbid conditions, only 14 (0.1%) died in the first 14 days compared to 701 (5.9%) of 24,852 patients 64 years or older who had three or more comorbidities (RR=29, 95% CI: 17–50). Comorbid conditions associated with early death included recent cancer, heart failure, renal disease, and liver disease. We conclude that advancing age and the number of chronic comorbid conditions are very strong predictors of early death among patients with acute pancreatitis.

Keywords Pancreatitis · Mortality · Epidemiology · Multiple-organ failure

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C. Frey
Department of Surgery, UC Davis,
Davis, CA, USA

H. Zhou · R. H. White
Department of Medicine, UC Davis,
Davis, CA, USA

D. Harvey
Department of Public Health Sciences, UC Davis,
Davis, CA, USA

R. H. White (✉)
Division of General Medicine,
Suite 2400, PSSB 4150 V Street,
Sacramento, CA 95817, USA
e-mail: rhwhite@ucdavis.edu

Introduction

Acute pancreatitis is a significant medical and surgical problem.[1] Estimates of the incidence vary widely, but it is approximately eight to 30 cases per 100,000 persons based on studies in Europe.[2–7] The reported case-fatality rate ranges between 2 and 9% depending on the exact case definition, with approximately half of the deaths occurring very early within 2 weeks of hospitalization, with the majority manifesting multiple organ system failures.[8–12] After this early phase, most studies suggest that sepsis and other complications are the principal causes of late deaths.[12,13]

Most studies of patients with pancreatitis have been observational in nature, usually case series of patients hospitalized at large university medical centers.[10–13] Clinical studies aimed at defining risk factors associated with death in the first 1 or 2 weeks after presentation have generally looked at the interrelationships between clinical features, laboratory findings, extent of pancreatic necrosis, and the development of acute organ system failure or death. The goal has been to identify patients at high risk for early multiorgan system dysfunction and death.[14] These studies have analyzed an array of clinical parameters collected at the time of admission or

during the first 48 h, such as APACHE II parameters score,[15,16] or Ranson score,[17] or Imrie (Glasgow) score,[14,17,18] and laboratory test findings,[19–21] with the goal of accurately determining not only the severity of the pancreatitis, but also short-term prognosis. Unfortunately, researchers have not been able to develop and validate a prediction tool that is useful in individual patients.[14,22] Clinically, aggressive fluid replacement and supportive care are the cornerstones of treatment, with many experts recommending transfer of sicker patients to specialty centers as rapidly as possible.[22]

Although some studies of mortality in patients with acute pancreatitis have analyzed the effect of age together with crude measures of prior medical health,[14,23,24] there have been no comprehensive studies that have determined the effect of preexisting chronic medical conditions on either early or late mortality in patients with acute pancreatitis. The only specific comorbidity that has been reported to be associated with increased mortality is obesity.[14,25] A parallel situation exists in the study of cancer patients, as most oncology studies tend to focus on the effect of the type of cancer, the stage, and the histology and treatment effects on mortality. However, recent studies have shown that the number and severity of preexisting comorbid conditions strongly influence survival of cancer patients in a dose-dependent fashion, with an effect independent of cancer stage.[26–30]

The current study was undertaken to determine if age, ethnicity/race, sex, and presence of chronic morbid medical conditions are significantly predictors of death among patients with acute pancreatitis.

Materials and Methods

Data Base

The California Patient Discharge Data Set has been described in detail in other manuscripts.[31,32] Except for 12 Veteran Administration and two military hospitals, all acute care hospitals (N=470) supply specific information about each inpatient, including basic demographic data, the principal diagnosis, up to 24 secondary diagnoses, a principal procedure, and up to 20 secondary procedures using *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes. Use of an encrypted record linkage number allows serial hospitalizations to be linked. The study was approved by the California Health and Welfare Agency Committee for the Protection of Human Subjects, and the University of California, Davis Human Subjects Committee.

Study Cohort

The study cohort was made up of all cases admitted for the first time with a principal diagnosis of acute pancreatitis (ICD-9-CM, 577.0) between Jan 1, 1992 and Sept 31, 2000 and without a secondary diagnosis of chronic pancreatitis (578.0). Cases that had a prior diagnosis of either acute or chronic pancreatitis (principal or secondary) during the previous 4-year period were excluded. Cases with a secondary diagnosis of acute pancreatitis were excluded included (n=6565, 7.5%), as were cases with human immunodeficiency virus infection. To validate the predictive value of a principal diagnosis of acute pancreatitis, 277 consecutive records at the UC Davis Medical Center that were coded as having a principal diagnosis of acute pancreatitis were reviewed.

For each case, a specific etiologic subtype of acute pancreatitis was determined based on the presence of a commonly recognized risk factor(s). Subtypes were assigned in an ordered hierarchical fashion. First, cases that had coexisting *pancreatic cancer* (157.*x*) were assigned as subtype 1; remaining cases that had systemic lupus or a *systemic rheumatic disease* (710.0, 714.0) were assigned as subtype 2; then all cases that underwent *endoscopic retrograde cholecystoscopy <1 month before admission* (51.10, 51.11) were assigned as subtype 3; then cases with both *biliary disease* (574, 575.0, 575.1, 576 at time of 3 or ≤3 months before admission) *and chronic alcohol abuse* (codes at the time of hospitalization or <1 year=291, 303, 305.0, 357.5 ,425.5, 571.0, 5711, 5712, 5713,9800, V113) were categorized as subtype 4; all remaining cases with *biliary disease* alone (*cholelithiasis or cholecystitis*) were assigned as subtype 5; remaining cases with chronic *alcoholic abuse* (codes listed above) were assigned as Subtype 6; then cases with *hyperlipidemia* (272) *or hyperparathyroidism* (252.0) were assigned as subtype 7; then cases with other *abdominal surgery within 3 months* (biliary, stomach, bowel or splenectomy defined using DRG codes) were called subtype 8, and finally, all remaining cases were assigned as having *idiopathic* pancreatitis, or subtype 9. Any case hospitalized for longer than 91 days (<1%) was excluded as an outlier.

Comorbidity

We determined the presence of comorbid medical disorders using a modification of the Healthcare Costs and Utilization Project (or Elixhauser) comorbidity software.[33,34] This index is made up of 29 groups of ICD-9-CM codes that identify specific chronic medical conditions such as chronic congestive heart failure, renal failure, chronic pulmonary disease, diabetes, etc. For almost all of the conditions included in the index, the codes for chronic comorbidity specifically exclude acute medical illness. However, three groups of codes were deemed to more likely reflect acute illness rather than chronic illness, and these groups were not included (fluid and electrolyte disorder, blood loss anemia, coagulation defect).[35] Also excluded were two psychiatric diagnoses that were judged to be unlikely to affect early mortality (psychosis,

depression). Two of the comorbidity variables were combined into just one variable (diabetes with or without complications). A variable use to identify acquired immune deficiency syndrome (AIDS) was removed as these cases were excluded from the pancreatitis cohort, and the variables for chronic alcohol abuse and collagen vascular disease were removed because these codes were used to define two of the subtypes of pancreatitis, alcohol-related and systemic-lupus-erythematosus-related pancreatitis. There were 20 remaining groups of codes that defined the presence of a specific chronic comorbid condition (see Appendix A). Information from the index hospital and any hospitalizations in the previous 12 months was used to define the presence of a comorbid condition.[36] Studies of the validity of comorbidity data indicate that there is minimal misclassification, and the agreement between chart review and the administrative data is very good.[37,38]

Hospitals (N=470) were categorized as large university or university affiliated hospitals (N=9), hospitals with over 350 beds (N=27), hospitals with 251–350 beds (N=67), hospitals with 125–250 beds (N=106), and hospitals with fewer than 125 beds (N=261).

Outcomes

The time between the hour of admission and midnight of that day is defined as day 0, whereas day 1 is the first full day in the hospital. Principal outcomes were death on day 0 to day 14, and death within days 15 and 28. In some analyses, death in the first 91 days was the outcome. The number of cases with organ system failures (up to seven systems) was determined using a modifications of a validated index developed by Sands et al.[39] Codes for acute organ failure were selected and codes for bowel ischemia or infarction were added (see Appendix B).[40–42] Death was determined using the linked California master death registry.[43] Pancreatic surgery was defined as all ICD-9-CM procedure codes 52.*x*, excluding 52.22, 52.6, 52.93, but including 54.11, 54.19, and 54.5.

Statistical Analysis

Data were analyzed using SAS. Continuous variables were compared using Student's t test, and categorical data were analyzed using the Chi-square test or Fisher's exact test. Linear regression was used to test for a trend in the incidence of pancreatitis in California. Logistic regression was used to model predictors of death within 14 days of presentation or the development of two or more organ system failures during the initial hospitalization. A separate model using the cases that survived the first 2 weeks of illness was created to predict death 15 to 28 days after admission. Specific risk factors were forced into the model including age, race/ethnicity, sex, hospital size, and type of pancreatitis. Other comorbidity variables were allowed to leave the model using backward stepwise elimination with $p>0.05$.

Analyses were adjusted for the clustering of observations within hospitals using a Generalized Estimating Equations (GEE) approach, with robust sandwich estimators of variance and an independent within-group correlation structure assumed. Age was modeled in discrete age groups, using age less than 35 years as the referent.

Results

Between Jan 1, 1992 and Sept 30, 2001 a total of 84,713 cases met the study criteria for incident (first-time) acute pancreatitis. Overall, 53.9% of the cases were women, median age was 54.5 years, and 18.5% were over the age of 75 years. Mean length of hospital stay was 6.0±8 days (±S.D.), and 3.4% of all cases were hospitalized for 20 or more days.

Table 1 shows the number and demographic characteristics of the different pancreatitis subgroups. Cases with biliary tract disease or cholelithiasis made up 32% of the cohort, and, as expected, over two-thirds of these cases were women. Twenty-one percent of the cases had alcohol-related pancreatitis and an additional 2.5% had biliary tract

Table 1 Characteristics of the Subgroups of Patients with Acute Pancreatitis

Group	*N*	Percent of Total	Mean Age (yrs)	Percent Women	Mean LOS
Idiopathic	31,579	37.3	56.9	58.5	5.5
Biliary	26,821	31.7	57.6	68.7	6.3
Alcoholic	17,655	20.8	45.8	25.5	6.1
Hyperlipidemia	5,183	6.1	52.4	50.0	6.4
Biliary + Alcohol	2,082	2.5	54.3	31.5	7.4
Systemic lupus	569	0.7	49.5	89.6	7.5
Pancreatic cancer	488	0.6	65.7	48.4	6.7
Other	336	0.4	54.2	67.3	7.2
Total	84,713	100	54.5	53.9	6.0

Table 2 Incidence of Comorbidity and Death in Major Pancreatitis Subgroups

Subgroup	*N*	Number of Comorbidities			Death ≤3 mo	Percentage of early deaths in Specified Time Period			≥2 Organ System Failures ≤3 mo	Pancreatic Surgery ≤3 mo
		=0 (%)	1 or 2 (%)	>3 (%)	*N* (%)	Weeks 1–2	Weeks 3–4	Weeks 5–12	*N* (%)	*N* (%)
Idiopathic	31,579	29.3	42.9	27.8	1,611 (5.1%)	45.2	16.5	38.3	446 (1.4%)	343 (1.1%)
Biliary	26,821	36.9	42.0	21.1	978 (3.6%)	43.4	16.5	40.2	394 (1.5%)	349 (1.3%)
Alcohol	17,655	4.9	55.2	39.9	555 (3.1%)	46.3	21.8	31.9	262 (2.1%)	229 (1.3%)

disease plus alcohol abuse. The cases with alcoholic pancreatitis were significantly younger, with a mean age of 46 years, and 75% of these cases were men. Thirty-seven percent of the cases that did not meet criteria for a specific etiology were classified as idiopathic pancreatitis.

The frequency of comorbidity among the subgroups with biliary, alcohol, and idiopathic pancreatitis, and other measured outcomes is shown in Table 2. Over 60% of all pancreatitis cases carried a diagnosis of one or more comorbid condition. Cases with alcohol-related pancreatitis had the highest percentage of cases (95%) that had one or more comorbid condition, and 40% of these cases had three or more conditions. In bivariate analysis, the 91-day mortality rate was highest in the idiopathic pancreatitis group, 5.1%, and this was significantly higher compared with the biliary (3.6%, $p<0.001$) and alcoholic groups (3.1%, $p<0.001$). Less than 1.5% of the cases in each group underwent major surgery on the pancreas during the index hospitalization. In the biliary pancreatitis group, 11,198 cases (41.8%) underwent biliary surgery or a biliary procedure during the index hospitalization.

Figures 1, 2, and 3 show the number of deaths on each of the first 14 days of hospitalization in the cohorts with idiopathic pancreatitis, alcoholic pancreatitis, and biliary pancreatitis, respectively. Included in each figure is the distribution of the number of coexisting comorbid conditions among the cases that died on each day. For the entire cohort, 38% of all deaths in the first 14 days occurred on day 0, 1, or 2. Only 69 (4.6%) of 1,514 cases that died in the first 14 days had no underlying comorbid condition compared to 25% for the cases that did not die ($p<0.001$).

Table 3 shows the incidence of death and multiorgan system failure among the pancreatitis cases that had 0, 1, 2, or ≥3 chronic comorbid conditions and the incidence of adverse outcomes among the cases that had one (or more)

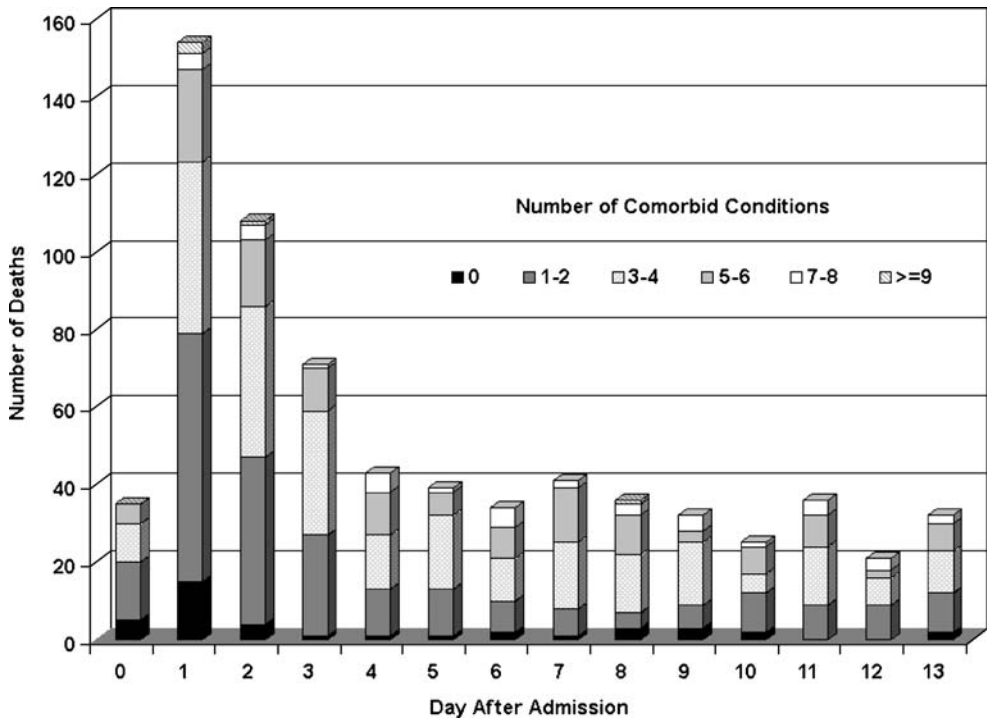

Figure 1 Distribution of deaths in the first 14 days among cases with idiopathic pancreatitis, and the corresponding frequency of comorbid conditions.

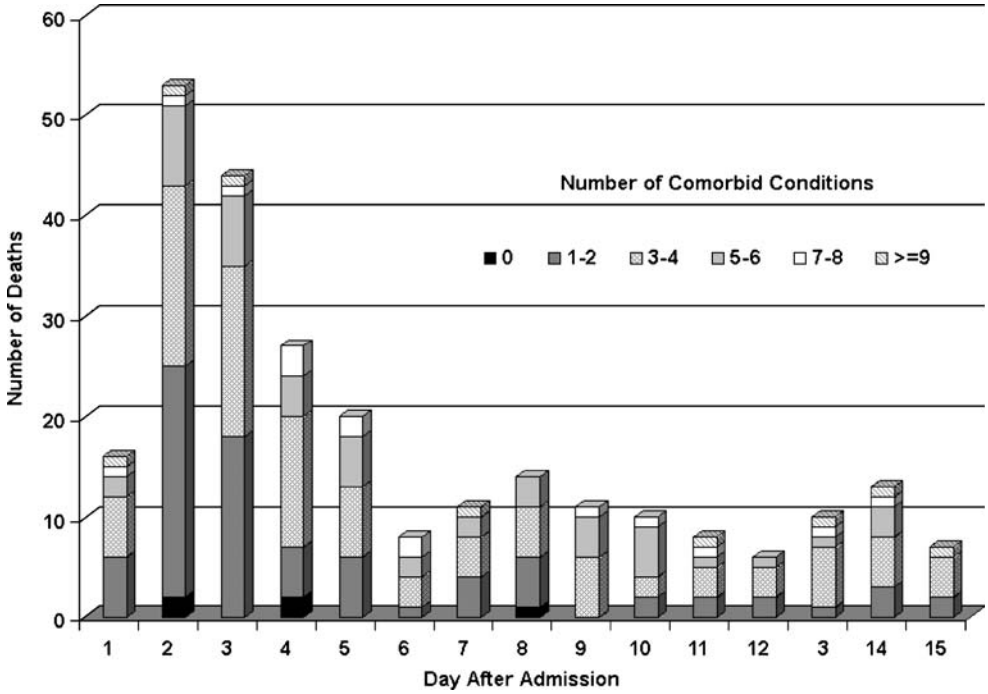

Figure 2 Distribution of deaths in the first 14 days among cases with alcoholic pancreatitis, and the corresponding frequency of comorbid conditions.

of the ten most common chronic comorbid conditions. It is important to recognize that a significant percentage of the cases that had a specific comorbid condition also had one or more additional comorbidities.

Among the 21,096 cases that had no identified comorbid condition, there were 70 (0.3%) deaths in the first 14 days and 170 (0.8%) deaths in the first 91 days; only 28 (0.08%) of these cases developed organ failure affecting two or more systems. In comparison, 24,852 (29.3%) cases had three or more comorbidities and 947 (3.8%) of these died in the first 14 days (RR=11.5, $p<0.001$), and 2,337 (9.4%) died within 91 days; 999 (2.5%) of these cases developed organ failure of two or more organ systems (RR=30.3, $p<0.001$). Specific comorbid conditions associated with the highest incidence of death within 91 days were recent cancer, chronic heart failure, chronic renal failure, and malnutrition. The incidence of organ failure affecting two or more systems was highest for cases with heart failure, malnutrition, and renal failure.

Table 4 shows the results of the multivariate regression analysis of potential risk factors leading to either death within 2 weeks of admission or failure of two or more organ system

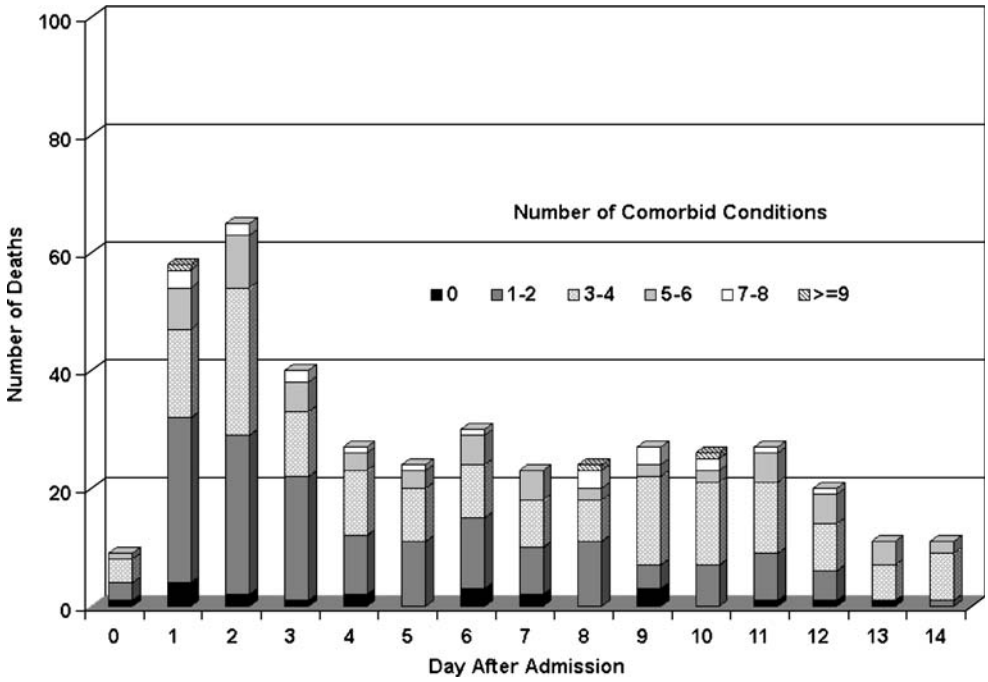

Figure 3 Distribution of deaths in first 14 days among cases with biliary pancreatitis, and the corresponding frequency of comorbid conditions.

Table 3 Frequency of Number and Type of Comorbidity on Organ System Failure and Early or Late Death

Comorbidity[a]—Number or Type	Number of Cases (Total= 84,713)	Percent of Total Cases	Death Days 0–14 (%)	Death Days 15–91 (%)	≥2 Organ Failures in Index Hosp (%)
0	21,096	24.9	0.3	0.5	0.1
1	21,470	25.3	1.0	1.0	0.6
2	17,295	20.4	1.6	2.0	1.2
3 or more	24,852	29.3	3.8	5.6	4.0
Chronic heart failure	5,124	6.0	7.2	10.5	5.3
Malnutrition	2,443	2.9	4.8	11.7	8.4
Chronic kidney disease	3,225	3.8	5.7	9.8	4.7
Chronic liver disease	4,649	5.5	2.4	4.3	2.9
Chronic anemia	11,986	14.1	2.7	6.1	3.3
Diabetes mellitus	14,997	17.7	2.3	3.3	2.7
Metastatic cancer	902	1.1	8.9	20.1	1.8
Solid cancer	890	1.1	5.8	9.7	2.8
Obesity	5,887	6.9	1.7	1.6	2.1
Chronic lung disease	9,632	11.4	3.6	5.7	2.8

[a] Many subjects with a specified comorbidity had one or more additional comorbid conditions.

during the index hospitalization. Separate models are shown that incorporated: a) specific comorbid conditions and b) the number of comorbid conditions. In all of the models, Hispanic ethnicity and African Americans were associated with a modest but statistically significant lower odds of dying.

In the models that incorporated specific comorbidities, the strongest predictors were male sex, increasing age (particularly age over 75 years), and classification as either alcoholic or idiopathic pancreatitis (compared to biliary pancreatitis). When the total number of comorbid conditions was modeled instead of specific conditions, the odds of dying increased considerably as the number of conditions increased, with cases having three or more comorbid conditions having 7.4-fold higher odds compared to cases with no comorbidity. Male sex, and advancing age remained significant, but only idiopathic pancreatitis was associated with significantly higher odds of early death. In a model not shown, risk factors for death 2 to 4 weeks after admission were similar to the risk factors associated with death during the first 2 weeks, with the exception that hospitalization in an academically affiliated medical centers was associated with significantly lower odds of dying (OR=0.5, CI 0.3–0.7).

The models predicting failure of two or more organ systems were similar to the models predicting death, with several notable exceptions. Presence of nonmetastatic cancer, metastatic cancer, and lymphoma were not significant predictors of organ failure, whereas malnutrition and diabetes were significant predictors of organ system failure. In the models that incorporated the number of comorbid conditions, the presence of three or more conditions was associated with 36-fold higher odds (95% CI: 25–52) of organ system failure.

During a 4-year period between 1996 and 2000, 373 (1.9%) of 19,767 cases with idiopathic pancreatitis were transferred from the index hospital to a different hospital; 281 (1.4%) of these were transferred within 7 days of the index admission. There were 68 (0.3%) transfers to an academic medical center, and only 43 (0.2%) of these were within 7 days of hospitalization.

Discussion

There were several clinically important findings in this study of patients with first-time pancreatitis. First, the presence of an increasing number of chronic comorbid medical conditions, particularly three or more, was a very strong predictor of early death, and presence of comorbidity was an even stronger predictor of multiorgan system failure. Conversely, the absence of any chronic comorbid condition was associated with a very low incidence of death, just 0.3% during the first 2 weeks compared to a tenfold higher rate of 3% among the cases with three or more comorbidities. Advancing age was also a very strong independent predictor of early death, especially in patients who had one or more comorbidities. For example, only 14 (0.1%) of 14,279 patients age 54 years or younger who had no underlying comorbid condition died within 2 weeks compared with 492 (7.1%) of 6,917 cases 75 years or older that had three or more underlying chronic medical problems (RR=73, $p<0.001$).

The unadjusted 91-day mortality rate among patients with alcoholic pancreatitis was lower than the rate in patients with idiopathic or biliary pancreatitis, as shown in Table 2. However, after adjustment for age, race, and sex, patients with alcoholic pancreatitis had the highest 91-day-mortality rate. This is because the alcoholic pancreatitis group had highly skewed demographic characteristics, with a much lower mean age and greater percentage of males and African Americans compared to patients with idiopathic or biliary pancreatitis.[44] In the current study, after adjusting for the

Table 4 Multivariate Analysis of Predictors of Death within 2 Weeks of Hospitalization or Failure of Two or More Organ Systems

Variable	Models with Specified Comorbid Conditions				Models with Number of Comorbid Conditions			
	Odds of death in Wks 1–2 (*N*=1514)	95% CI	Odds of ≥2 Organs Failing (N=5172)	95% CI	Odds of Death in Wks 1–2 (N=1514)	95% CI	Odds of ≥2 Organs Failing (N=5172)	95% CI
Men versus women	1.2*	1.1–1.5	1.5*	1.3–1.7	1.3*	1.2–1.5	1.5*	1.4–1.7
Age (versus <55 years)								
55–64	1.6*	1.3–1.9	1.3	1.1–1.5	1.4	1.2–1.7	1.1	0.9–1.3
65–74	3.0*	2.6–3.6	1.7	1.5–2.0	2.6*	2.1–3.1	1.3	1.1–1.6
>75	6.2*	5.2–7.4	1.4	1.2–1.7	5.1*	4.3–6.2	1.1	0.9–1.2
Race-ethnicity (versus Caucasian)								
African American	0.7*	0.6–0.9	0.5*	0.4–0.6	0.7	0.6–0.9	0.5*	0.4–0.7
Hispanic	0.7*	0.6–0.8	0.7	0.6–0.8	0.7*	0.6–0.8	0.7	0.7–0.9
Asian-Pacific Islander	0.6	0.5–0.8	1.0	0.8–1.2	0.7	0.5–0.8	1.1	0.9–1.4
Other	1.0	0.7–1.5	0.9	0.6–1.2	1.0	0.7–1.5	1.0	0.7–1.3
Hospital size (versus >350 beds)								
Academic (*N*=8)	0.7	0.5–1.1	1.0	0.7–1.5	0.7	0.5–1.1	1.1	0.8–1.5
Moderate 250–350 beds	0.9	0.7–1.2	0.8	0.7–1.0	0.9	0.7–1.1	0.9	0.7–1.0
Standard 125–250 beds	1.0	0.8–1.2	0.8	0.7–1.0	0.9	0.8–1.2	0.9	0.7–1.0
Community <125 beds	1.0	0.8–1.3	0.7	0.5–0.9	1.0	0.8–1.3	0.7	0.6–0.9
Pancreatitis group (vs biliary)								
Alcoholic	1.8*	1.5–2.1	1.5*	1.3–1.8	1.2	1.0–1.4	0.8	0.6–0.9
Idiopathic	1.4*	1.3–1.6	0.9	0.8–1.0	1.4*	1.2–1.6	0.8	0.7–1.0
Systemic lupus	1.9	1.0–3.5	2.0	1.2–3.3	1.4	0.8–2.5	1.2	0.7–2.0
Pancreatic cancer	1.5	0.9–2.3	0.9	0.4–1.8	1.8	1.1–2.7	0.7	0.3–1.3
Biliary + Alcohol	0.3	0.2–0.6	1.5	1.1–2.0	0.3*	0.1–0.5	0.8	0.6–1.2
Hyperlipidemia	1.0	0.7–1.3	1.1	0.8–1.4	0.8	0.6–1.0	0.8	0.6–1.0
Other	0.8	0.3–2.1	0.7	0.2–2.3	0.8	0.3–2.1	0.7	0.2–2.2
Comorbid conditions								
Specific co morbid condition# (versus not present)								
Metastatic cancer	4.0*	3.1–5.3	ns					
Cancer	1.8*	1.3–2.4	ns					
Lymphoma	2.2	1.3–3.7	ns					
Congestive heart failure	2.3*	2.0–2.7	2.6*	2.1–3.1				
Chronic renal failure	2.1*	1.7–2.6	1.8*	1.4–2.2				
Chronic liver disease	1.8*	1.4–2.2	1.3	1.1–1.6				
Obesity	1.2	1.0–1.5	1.3	1.0–1.6				
Malnutrition	1.7*	1.3–2.1	4.2*	3.5–4.9				
Anemia not caused by blood loss	ns		1.7	1.5–2.0				
Peripheral vascular disease	1.5*	1.2–1.7	ns					
Paralysis	1.5*	1.2–2.0	1.4	1.0–1.8				
Neurologic disease	1.4*	1.1–1.7	1.7*	1.4–2.0				
Drug abuse (not alcohol)	ns		ns					
Chronic lung disease	ns		1.2	1.0–1.4				
Diabetes	ns		1.6*	1.4–1.8				
Comorbidity score								
Number of comorbidities (versus 0)								
1					2.5*	1.9–3.3	4.6*	3.1–7.0
2					3.6*	2.7–4.7	9.4*	6.4–14.0
≥3					7.4*	5.7–9.7	35.3*	23.7–52.4

OR = Odds ratio; MODS= Multiorgan system dysfunction
*$P<0.0001$, otherwise $P<0.05$.

number of underlying comorbidities, the specific etiologic subgroup of pancreatitis had only a modest effect on both survival and the development of multiorgan system dysfunction. In fact, although patients with idiopathic pancreatitis had a modest but significantly higher risk of dying within 91 days compared to patients with biliary pancreatitis, with there was no significant difference between alcoholic pancreatitis and either biliary or idiopathic pancreatitis. The reason that the adjusted risk of death in this model was much lower among the patients with alcoholic pancreatitis was that a much larger percentage of these patients had multiple chronic comorbidities (as shown in Table 2). Thus, although patients with alcoholic pancreatitis had a relatively low 91-day mortality rate, when age, race, and sex were accounted for, their risk of early death was relatively high, but when the presence of multiple comorbidities was also taken into account, the 91-day mortality risk was comparable to patients with idiopathic or biliary pancreatitis.

Taken together, these findings strongly suggest that the exact etiology of the pancreatitis has minimal effect on early survival, and that early death is most strongly associated with older age and the number of chronic comorbid conditions. Using only administrative data, the effect of laboratory and physiologic findings at the time of admission could not be assessed in this study. Further studies are needed to determine the relative importance of initial clinical data compared to the presence or absence of specific medical comorbidities as predictors of death.

As noted in other studies,[10] there was a spike in the incidence deaths in the first 2 full days of hospitalization followed by a rapid decline to a relatively stable rate after day 5, with 45% of all deaths in the first 91 days occurring during the first 2 weeks. Perhaps the most striking finding of this study was the very strong association between the presence of preexisting comorbidity and death in the first 3 days after hospitalization. Only 33 (5.7%) of the 574 cases that died on days 0, 1, or 2 had no underlying comorbidity.

These findings suggest that acute pancreatitis presents a major stress that may be tolerated reasonably well by otherwise healthy younger individuals. However, among older patients or patients who have chronic underlying comorbid conditions, such as chronic heart failure, chronic kidney disease, or malnutrition, a significant percentage rapidly decompensate and die within a short period of time. Further research is needed to determine if the patients most likely to develop multiorgan system failures and death can be identified at the time of admission and treated aggressively leading to a reduction in mortality. The findings of this study suggest that initial mortality risk assessment of patients with pancreatitis might be improved by including not only physiologic data, but increments of age and the presence or absence of chronic medical illnesses.

Interestingly, the risk-adjusted models suggested that hospitalization in either a large or academic hospital was not associated with a significantly reduced risk of early death. It is unlikely that the transfer of sicker patients from smaller hospitals to larger hospitals affected the findings because fewer than 2% of patients were transferred, and the majority of these were transferred after 7 days. Being hospitalized in an academic medical center was, however, associated with a significantly reduced risk of dying in the second 2-week period, a time that has been reported to be associated with a higher incidence of sepsis and other complications among the small percentage of cases that require prolonged hospitalization.

Limitations of this study include the retrospective design and reliance on administrative data assembled by the hospital coders who review physician notes. It is possible that sicker patients had more details regarding underlying medical conditions charted than healthier patients, leading to some bias. However, validation studies indicate very good agreement between data bases that include clinical data and administrative data alone,[45] except for asymptomatic conditions.[37] In addition, there are other studies that have shown that age and comorbidity are strong predictors of adverse outcomes.[26] Finally, a number of studies have reported that advancing age with its attendant infirmities is a strong predictor of death among patients with pancreatitis.[3,14,46,47] In a study by Halonen and colleagues, the presence of chronic medical comorbidity, defined as the use of any medication for a chronic medical illness, was associated with over a threefold higher risk of death.[14]

Analyzing the effect of comorbidity by using the number of comorbid conditions present rather than specific comorbidities has been shown to be very useful and simple, providing good explanatory power.[48,49] However, it should be kept in mind that when the total number of comorbidities is used, all the conditions are treated equally without any weighting. Using the number of comorbidities has the advantage of taking into account some interaction between comorbidities, which is not possible when individual comorbidities are modeled as main effects. Thus, patients with chronic hypertension, diabetes, and chronic congestive heart failure may be at even greater risk for death caused by pancreatitis than the additive risk based on the effect of individual comorbid conditions.

Conclusion

In conclusion, death in the first 2 weeks after the diagnosis of first-time pancreatitis was strongly associated with advancing age and the number of underlying chronic medical conditions, whereas the etiology of the pancreatitis and the size of the treating hospital had minimal impact. Future studies should take into account the types and severity of these conditions with the aim of identifying the strongest predictors of organ

system failure and death, and then targeting early intensive treatment in patients with these risk factors.

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Appendix A

Terms Used in the Comorbidity Index:[34]

Congestive Heart Failure
Cardiac Valvular Disease
Pulmonary Circulation Disorder
Peripheral Vascular Disease
Hypertension, with or without complication
Paralysis
Other Neurological Disease
Chronic Pulmonary Disease
Diabetes, with or without complications
Hypothyroidism
Renal Failure
Liver Disease
Chronic Peptic Ulcer Disease
Morbid Obesity
Malnutrition
Chronic Anemia
Drug Dependence
Lymphoma
Metastatic Cancer
Solid Tumor without Metastasis

Appendix B

ICD-9-CM Codes Used to Define MODS: Multiorgan Dysfunction Syndrome

1) Circulation: Hypotension or Shock
   785.50 Shock, unspecified failure of peripheral circulation
   785.51 Cardiogenic shock
   785.59 Other shock: endotoxic gram-negative hypovolemic
   458.8 Other specified hypotension
   458.9 Hypotension, unspecified hypotension (arterial) NOS
2) Lung: Pulmonary insufficiency
   518.4 Acute edema of lung, unspecified
   518.81 Acute respiratory failure Respiratory failure NOS
   799.1 Respiratory arrest
   518.82 Acute respiratory distress syndrome, other pulmonary insufficiency,
   PLUS Mechanical ventilation
   96.70 Continuous mechanical ventilation of unspecified duration
   96.71 Continuous mechanical ventilation for less than 96 consecutive hours
   96.72 Continuous mechanical ventilation for 96 consec utive hours or more
3) Neurologic: Encephalopathy
   348.30 Encephalopathy, unspecified
   348.31 Metabolic encephalopathy, Septic encephalopathy
   348.39 Other encephalopathy
   Or Psychosis
   293.0 Acute delirium
   293.1 Subacute delirium
   293.8 Other specified transient organic mental disorders
   293.9 Unspecified transient organic mental disorder
   348.1 Anoxic brain damage
4) Blood: Coagulation abnormalities
   287.4 Secondary thrombocytopenia,
   287.5 NOS, thrombocytopenia
   286.9 Coagulopathy NOS
   286.6 Disseminated intravascular coagulation
5) Liver: Acute Liver injury
   570 Hepatic failure Acute only
   573.4 Hepatic infarction
6) Kidney: Acute renal failure
   584.5 With lesion of tubular necrosis
   584.6 With lesion of renal cortical necrosis
   584.7 With lesion of renal medullary [papillary] necrosis
   584.8 With other specified pathological lesion in kidney
   584.9 Acute renal failure, unspecified
7) Bowel: Ischemic bowel
   557.0 Acute vascular insufficiency of intestine
   557.1 Chronic vascular insufficiency of intestine
   557.9 Unspecified vascular insufficiency of intestine

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Stomach-Preserving Distal Pancreatectomy with Combined Resection of the Celiac Artery: Radical Procedure for Locally Advanced Cancer of the Pancreatic Body

Shoichi Hishinuma · Yoshiro Ogata · Moriaki Tomikawa · Iwao Ozawa

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Abstract To enhance the resectability of cancer of the pancreatic body, a new surgical technique should be developed. Of 25 patients with cancer of the pancreatic body who underwent distal pancreatectomy with curative intent, seven with cancer invasion around the celiac artery underwent stomach-preserving distal pancreatectomy with combined resection of the celiac artery. This procedure secured arterial blood supply to the whole stomach and liver via the inferior pancreaticoduodenal artery without arterial reconstruction. There was no postoperative mortality. One patient developed transient passage disturbance in the duodenum. Another one developed a minor pancreatic fistula. No patients had serious complications related to ischemia of the stomach or liver. The quality of life of the patients after surgery was well maintained, and planned adjuvant therapy was accomplished. Local recurrence was evident in only two patients. The median survival time of patients who underwent distal pancreatectomy with (n=7) or without (n=18) resection of the celiac artery was 19 and 25 months, respectively. The overall survival rate was not significantly different between the two groups (P=0.5300). The present study suggests that this surgical procedure is a rational approach to locally advanced pancreatic body cancer invading around the celiac artery. In view of the feasibility of this procedure, it can also be adopted for less advanced cancer of the pancreatic body to enhance local control and survival.

Keywords Cancer of the pancreas · Cancer of the pancreatic body · Distal pancreatectomy · Celiac artery resection · Preservation of the stomach

Introduction

Because the only long-term survivors with cancer of the pancreatic body have been those who have undergone resection, surgery still remains the only hope for prolonged survival. Results of surgical treatment, however, have not improved in recent years.[1,2] The resectability rate for cancer of the pancreatic body also remains poor despite the use of modern imaging techniques.[3] Most patients with cancer of the pancreatic body are unresectable at the time of diagnosis due to cancer invasion of large arteries. To increase resectability rates, surgical challenge against such an advanced pancreatic cancer is necessary.

Cancer of the pancreatic body often invades the origin of the common hepatic and/or splenic arteries arising from the celiac artery. More advanced cancer further invades the celiac artery itself with cancer infiltration of the surrounding nerve plexus. For such a case, we first performed stomach-preserving distal pancreatectomy with combined resection of the celiac artery (SP-DP-CA) in 1987. This operative procedure successfully secured arterial blood supply to the whole stomach and liver only via the inferior pancreaticoduodenal artery (IPDA) arising from the superior mesenteric artery (SMA). In 1991, we reported on two patients who underwent SP-DP-CA without any complications, showing the feasibility of SP-DP-CA for locally advanced cancer of the pancreatic body.[4] In that report, it was clarified that the whole stomach can be safely preserved without arterial reconstruction even if the celiac and common hepatic arteries are severed. We believe that preservation of the whole stomach significantly contributes

S. Hishinuma (✉) · Y. Ogata · M. Tomikawa · I. Ozawa
Department of Surgery, Tochigi Cancer Center,
4-9-13, Yohnan, Utsunomiya, Tochigi 320-0834, Japan
e-mail: shishinu@tcc.pref.tochigi.jp

to a better quality of life for patients who have undergone radical pancreatectomy. In the present study, we report our experience with SP-DP-CA for locally advanced cancer of the pancreatic body.

Material and Methods

Patient Number and Indication for SP-DP-CA

Between July 1987 and April 2003, 149 patients with cancer of the pancreatic body were admitted to the Tochigi Cancer Center Hospital. Among them, 25 patients underwent distal pancreatectomy with curative intent, and seven of these 25 patients underwent SP-DP-CA. SP-DP-CA was indicated for patients who had cancer invasion around the celiac artery and origins of the common hepatic artery and/or splenic artery, without tumor involvement of the SMA (Fig. 1). In all patients, preoperative angiography was carried out and variations of the IPDA were examined to safely perform SP-DP-CA.

Surgical Procedure

The abdominal cavity is explored through a wide upper midline incision. After confirming the absence of distant metastasis, the spleen and pancreatic tail and body are retracted medially from the retroperitoneum. To expose the origin of the celiac artery at the abdominal aorta, the left celiac ganglion, celiac nerve plexus, and a part of the left crus of the diaphragm are excised with en bloc dissection of the lymph nodes around the celiac artery and abdominal aorta. A polyester tape is then applied to the origins of the celiac artery and SMA that appears just below the celiac artery. In cases with tumors invading near the origin of the celiac artery, another polyester tape is also applied to the abdominal aorta just below the diaphragm, which enables the control of arterial bleeding by total clamping of the aorta. During these procedures, frozen section examination of surgical margins is repeatedly carried out to determine the curability of this operation.

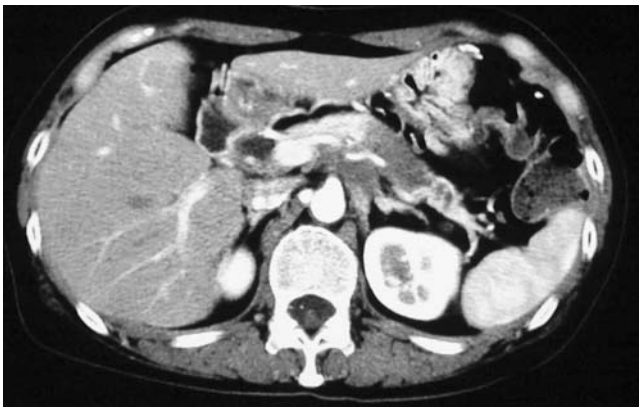

Figure 1 Computed tomography scan demonstrating a tumor mass invading around the bifurcation of the splenic and common hepatic arteries (patient 5).

Following division of the short gastric vessels, the peripheries of the left gastric artery and vein are divided near the gastric wall, preserving the ascending branches of the left gastric vessels. By lifting the stomach upward, an anterior approach to the tumor is facilitated. Dissecting the lymph nodes and neural plexus around the common hepatic artery, the confluence of the gastroduodenal artery and common hepatic artery is exposed. The right gastric and gastroepiploic arteries should be preserved with certainty. The common hepatic artery is then severed with a transfixing suture just proximal to the origin of the gastroduodenal artery after confirming a well-palpable pulsation of the proper hepatic artery during a 3-min-long occlusion of the common hepatic and celiac arteries with vascular clamps.

The portal vein (PV) is dissected above and below the pancreas and finally freed from the dorsal side of the pancreas. The pancreas is divided over the right side of the PV. The pancreatic margin is routinely investigated by frozen section. The splenic vein is divided immediately before the junction with the superior mesenteric vein (SMV). When tumor invasion of the SMV–PV confluence is encountered or suspected, portal reconstruction is required.

Lifting up the cut end of the caudal pancreas with the tumor, the SMA is dissected from the surrounding lymph nodes and nerve plexus toward its origin. Great care should be taken to preserve the IPDA arising from the SMA or first jejunal artery. Therefore, dissection at the right side of the SMA is relatively compromised. The origin of the celiac artery is then totally dissected with excision of the right celiac ganglion and celiac nerve plexus. Pulling the polyester tape, already applied to the origin of the celiac artery, makes this dissection safe without difficulty. Finally, the celiac artery is divided at its origin via transfixing suture. When the tumor threatens the origin of the celiac artery, a side vascular clamp is applied to the aorta and then the celiac artery is severed at its origin. In such a case, the cut end of the celiac artery at the aorta is closed with sutures. The status after completion of SP-DP-CA is shown in Figs. 2 and 3.

Survival Time and Statistical Analysis

To evaluate the survival time of SP-DP-CA patients, the 18 patients with cancer of the pancreatic body who underwent distal pancreatectomy without combined resection of the celiac artery were used as a control.

Survival time was measured from the time of surgery and recorded in months. Cumulative survival rates were estimated based on the Kaplan–Meier method. The log-rank test

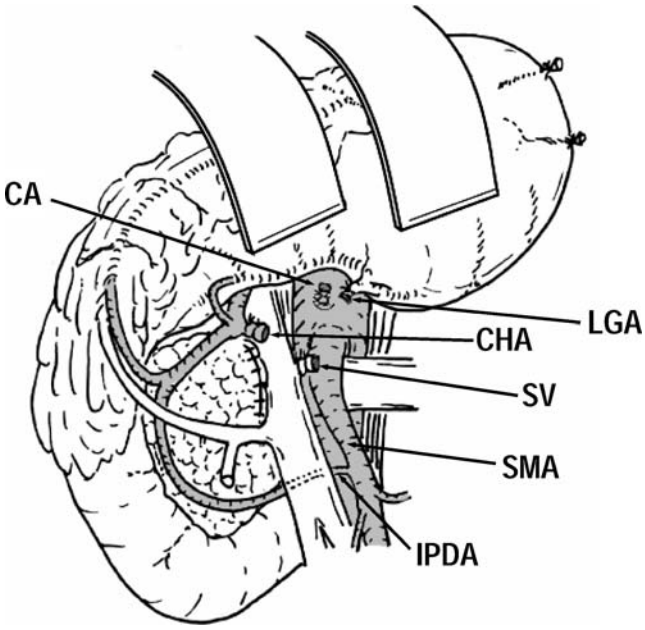

Figure 2 Completion of SP-DP-CA. The stomach is lifted upward. The blood supply to both the stomach and liver is maintained via the IPDA arising from the SMA. *CA* stump of the celiac artery, *LGA* distal stump of the left gastric artery, *CHA* stump of the common hepatic artery, *SV* stump of the splenic vein.

was used to compare the outcome between the two patient groups, and significance was accepted at the 5% level.

Results

Details of Patients and Surgical Procedures

Involved major vessels confirmed by preoperative imaging studies and/or by surgery are listed in Table 1. Patient 2 underwent combined resection of the involved SMV–PV confluence with end-to-end anastomosis. Patient 1, who also had cancer of the transverse colon, underwent additional transverse colectomy. In four patients (patients 2, 4, 5, and 7), adjacent structures were resected en bloc because of tumor invasion (Table 1). Patients 4 and 7 with invasion of the stomach underwent partial resection of the gastric wall. In three patients (patients 2, 5, and 7), en bloc resection of the transverse mesocolon, preserving the transverse colon with marginal vessels, was performed because of tumor invasion of the mesocolon near the ligament of Treitz. Prophylactic cholecystectomy was carried out in four patients (patients 1, 2, 4, and 6). In two patients (patients 2 and 6), repeat frozen section examination of the pancreatic cut margins disclosed cancer deposits in the small pancreatic ducts. We finally abandoned the idea of an additional resection of the pancreas because of the risk of sacrificing the pancreaticoduodenal arterial arcade, and we consequently administered intraoperative electron beam radiotherapy.

Pathological Findings of the Resected Specimens

The sixth edition of the International Union Against Cancer pTNM classification[5] was used to determine the stage grouping (Table 1). In patient 1, the dissected margin adjacent to the SMA wall was found to be positive for cancer, and the stage, therefore, was judged to be stage III (pT4, pN0, M0). In two patients (patients 2 and 6), positive pancreatic margins were reconfirmed. As a result, three of seven patients were found to have positive surgical margins. Four patients were found to have regional lymph node metastasis. Minute peritoneal nodules near the primary lesion proved to be cancer dissemination in patient 7, who was judged to have stage IV disease. In all patients, pathological examination of the resected specimens disclosed cancer infiltration of the nerve plexi encompassing the celiac, common hepatic, and/or splenic arteries. No patients, however, had direct cancer invasion of the celiac arterial wall.

Adjuvant Therapy Performed

One patient (patient 4) had not been scheduled for adjuvant therapy because of her poor general condition before surgery (Table 1). Adjuvant therapy could be delivered as scheduled in the remaining six patients. Intraoperative electron beam radiotherapy (16 to 30 Gy) was delivered in six patients, excluding patient 4 (Table 1). In addition, patients 1 and 2 received planned 45 and 40.5 Gy of postoperative external

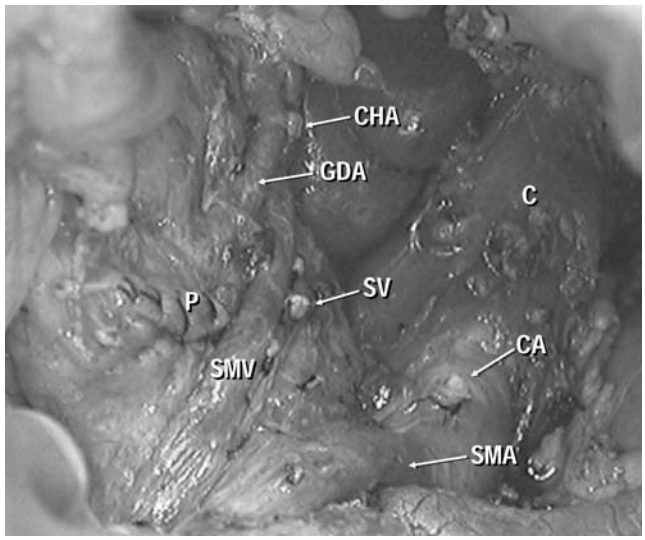

Figure 3 Operative field following SP-DP-CA. *CHA* stump of the common hepatic artery, *C* crus, *GDA* gastroduodenal artery, *SV* stump of the splenic vein, *CA* stump of the celiac artery, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *P* stump of the pancreas.

Table 1 Patient Characteristics

Patient no.	Age and Gender	Preoperative Epigastric and/or Back Pain	Involved Major Vessels	Other Resected Structures	Surgical Margin	UICC Stage					Adjuvant Therapy
						pT	pN	Positive Nodes	pM	pTNM	
1	62 M	+	CHA, SA, CA	Transverse colon, gallbladder	Positive	4	0	(0/33)	0	III	IORT (20 Gy), EBRT (45 Gy)
2	60 F	+	SA, CA, SMV/PV	Transverse mesocolon, gallbladder	Positive	3	1	(3/41)	0	IIB	IORT (16 Gy), EBRT (40.5 Gy)
3	79 M	+	CA	None	Negative	3	1	(1/33)	0	IIB	IORT (30 Gy), PHI (20 Gy)
4	74 F	+	SA	Stomach (partial), left adrenal, left kidney (partial), jejunum, gallbladder	Negative	3	0	(0/7)	0	IIA	None
5	54 F	+	CHA, SA	Transverse mesocolon, left adrenal, left kidney	Negative	3	1	(2/51)	0	IIB	IORT (30 Gy), PHI (22 Gy)
6	73 M	+	CHA, SA, CA	Gallbladder	Positive	3	0	(0/29)	0	IIA	IORT (30 Gy)
7	45 M	+	CHA, SA	Transverse mesocolon, stomach (partial), left adrenal	Negative	3	1	(3/21)	1	IV	IORT (30 Gy), chemotherapy with GEM

CHA = common hepatic artery, SA = splenic artery, CA = celiac artery, SMV = superior mesenteric vein, PV = portal vein, IORT = intraoperative radiotherapy, EBRT = postoperative external beam radiotherapy to the tumor bed, PHI = prophylactic hepatic irradiation, GEM = gemcitabine

beam radiotherapy to the tumor bed, respectively. Patients 3 and 5 were able to receive planned 20 and 22 Gy of postoperative prophylactic hepatic irradiation, respectively.[6] Patient 7 received postoperative chemotherapy with three courses of full-dose gemcitabine.

Of the 18 patients in the control group, four received no adjuvant therapy. The remaining 14 received adjuvant therapy as follows, similarly to the SP-DP-CA patients: 14, intraoperative electron beam radiotherapy (16 to 30 Gy); seven, postoperative prophylactic hepatic irradiation (19.8 to 20 Gy); two, postoperative external beam radiotherapy to the tumor bed (39.6 and 25.2 Gy, respectively); two, postoperative chemotherapy with gemcitabine and 5-fluorouracil, respectively.

Postoperative Complications

There was no postoperative mortality. Postoperative complications occurred in two patients (patients 3 and 6) (Table 2). Patient 3 developed transient passage disturbance in the second portion of the duodenum, resulting in the delayed start of oral intake (Table 2). An upper gastrointestinal series showed decreased motility of the duodenum without stenosis. The passage disturbance was conservatively improved. Patient 6 developed a minor pancreatic fistula, but it spontaneously closed without surgical intervention. Although two patients (patients 6 and 7) showed a transient elevation of serum transaminase levels that peaked on postoperative day 2 and promptly declined thereafter, no patients showed significant evidence related to ischemia of the stomach or liver (Table 2).

Long-term Outcome and Survival

Diarrhea, which sometimes needed loperamide and/or opium tincture to be controlled, was observed in five patients (Table 2). No patients developed insulin-dependent diabetes mellitus. Until death, all but one patient (patient 6) showed a complete resolution of epigastric and/or back pain that they had preoperatively had (Table 1). Patient 6 developed epigastric and back pain along with local recurrence that was confirmed by computed tomography (CT) scan 13 months after surgery. Patient 2 committed suicide without follow-up examinations. The reason for suicide was mental and not related to severe postoperative morbidity. The other six patients had been able to maintain a good quality of life until they required readmission due to the progression of recurrent lesions.

Table 2 Postoperative Course

Patient no.	Start of Oral Intake (POD)	Early Postoperative Complication	Diarrhea	Insulin-dependent Diabetes Mellitus	Epiagstric/ Back Pain	Pattern of Recurrence				Autopsy	Survival Time (months)	Cause of Death
						Local	Liver	Lung	Peritoneum			
1	9	None	Controllable	None	Disappeared	None	None	None	+	+	42	DOC
2	8	None	Controllable	None	Disappeared	Unknown	Unknown	Unknown	Unknown	None	4	Suicide
3	29	Transient passage disturbance in the duodenum	Controllable	None	Disappeared	None	None	None	+	+	17	DOC
4	18	None	None	None	Disappeared	None	+	None	None	None	21	DOC
5	11	None	Controllable	None	Disappeared	+	None	+	None	+	78	DOC
6	10	Pancreatic fistula, transaminase elevation POD2 (AST=641, ALT=443)	None	None	+	+	+	+	+	+	19	DOC
7	8	Transaminase elevation POD2 (AST=1546, ALT=1680)	Controllable	None	Disappeared	None	None	None	+	None	13	DOC

POD = postoperative day, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DOC = died of cancer

Patterns of recurrence confirmed by CT and/or autopsy are listed in Table 2. Local recurrence was clarified in two (patients 5 and 6) of four patients who underwent autopsy, one (patient 6) of whom had had a positive surgical margin. Patient 5, with negative surgical margins, was first found at autopsy to have had local recurrence around the stump of the celiac artery, which had not been detected by CT scan before death. This patient developed pulmonary metastasis and was administered more than 10 courses of full-dose gemcitabine. As a result, patient 5 could survive for more than 6 years. The local control achieved in patient 1 may have been attributed to adjuvant radiotherapy composed of intraoperative electron beam radiotherapy (20 Gy, 9 MeV) and postoperative external beam radiotherapy (45 Gy). The median survival times of patients who underwent distal pancreatectomy with (n=7) or without combined resection of the celiac artery (n=18) were 19 and 25 months, respectively. The overall survival rate was not significantly different in the two groups (P=0.5300, Fig. 4).

Discussion

Some instances of locally advanced cancer of the pancreatic body show invasion around the bifurcation of the common hepatic, splenic, and celiac arteries without cancer involvement of the SMA. For such a case, the Appleby operation.[7] might be a radical procedure. The Appleby operation, devised for advanced gastric cancer, allows en bloc resection of the stomach, caudal pancreas, and common hepatic and celiac arteries with surrounding lymph nodes. Using the Appleby operation, cancer of the pancreatic body invading around the celiac artery can theoretically be resected without any arterial reconstructions because

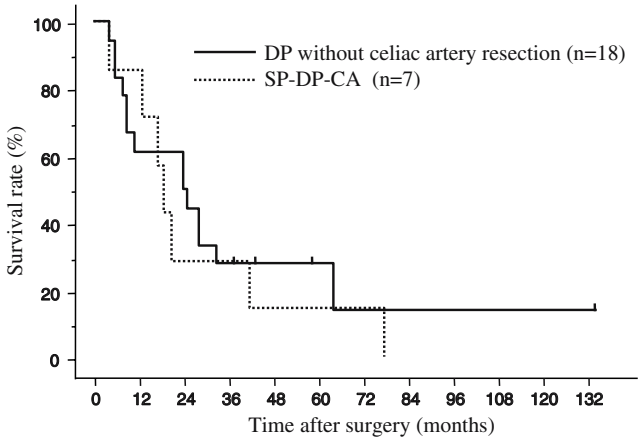

Figure 4 Survival curves of patients who underwent distal pancreatectomy with or without celiac artery resection for cancer of the pancreatic body. There was no significant difference in the survival rate between the two groups (P=0.5300).

arterial blood supply to the liver is maintained via the IPDA arising from the SMA. There have been several reports on the Appleby operation adopted for patients with advanced cancer of the pancreatic body.[8–12] The greatest disadvantage of the Appleby operation, when adopted for cancer of the pancreatic body, is that an intact stomach is totally resected. Total gastrectomy that might be unrelated to the surgical radicality for pancreatic cancer inevitably has negative effects upon the quality of life of patients undergoing pancreatectomy. As a result, such patients may lose the chance to receive adjuvant therapy that is likely to enhance postoperative survival. The Appleby operation provided us with some useful hints for developing SP-DP-CA. SP-DP-CA, however, fundamentally differs from the Appleby operation in terms of preserving the whole stomach. We believe that the preservation of the whole stomach maintains a more normal gastrointestinal hormonal milieu, which in turn results in a better nutritional status. It is our policy that a good nutritional status is necessary for resected patients to complete planned postoperative adjuvant therapy. On the basis of these concepts, we first performed SP-DP-CA for locally advanced cancer of the pancreatic body in 1987. Our primary concern was arterial blood supply to the liver and stomach only via the IPDA. Fortunately, a postoperative arteriogram of the SMA showed sufficient blood flow to the liver and stomach via the IPDA, and the clinical course of the patient following the first SP-DP-CA was uneventful.[4] Patients fulfilling the indication criteria for SP-DP-CA have been very limited. A majority of patients with locally advanced cancer of the pancreatic body had tumor invasion not only around the celiac artery, but also around the SMA. Furthermore, CT with arterial portography often disclosed small liver metastases in patients who were supposed to be candidates for SP-DP-CA. Our series, therefore, includes only seven patients who underwent SP-DP-CA. On the other hand, owing to precise preoperative evaluation by imaging studies, we never experienced a patient in whom planned SP-DP-CA was discontinued before completing the resection because of local disease or positive intraoperative biopsies.

Several investigators have reported on SP-DP-CA with or without modification.[13–19] The major items of concern involve blood flow of the proper hepatic artery following resection of the common hepatic artery because abrupt reduction of blood flow of the proper hepatic artery may result in both hepatic and gastric ischemia. Of four patients in the series of Konishi et al.[15], two patients underwent reconstruction of the hepatic artery using a graft of the splenic artery taken from the resected specimen between the cut end of the common hepatic and celiac arteries because of weak pulsation of the proper hepatic artery. Lin et al.[17] modified SP-DP-CA by reanastomosis between the stump of the celiac and common hepatic arteries without a vascular graft. Kondo et al.[18] reported that preoperative embolization of the common hepatic artery was successfully performed to enhance the collateral arterial flow via the IPDA. Kondo et al.[18] also showed that postoperative gastric ulcer was rare in patients who underwent preoperative embolization of the common hepatic artery. None of the seven patients in our series underwent reconstruction of the hepatic artery or any attempts to enhance arterial blood flow via the IPDA. Well-palpable pulsation of the proper hepatic artery after occlusion of the common hepatic and celiac arteries can be considered valid evidence for a sufficient arterial flow to the liver and stomach. Intraoperative Doppler ultrasonography may be useful to evaluate hepatic arterial flow after occlusion, especially in cases with poor pulsation of the proper hepatic artery.[11] To ensure hepatic and gastric arterial flow following SP-DP-CA, accidental intraoperative injury to the IPDA must be avoided. Clearance of the lymph nodes and nerve plexus around the SMA is, therefore, inevitably compromised to secure the IPDA arising from the SMA. Preoperative evaluation for individual variation of the IPDA by angiography is also recommended to safely perform SP-DP-CA. We have never had a patient in whom SP-DP-CA was aborted because of poor pulsation of the proper hepatic artery after occlusion of the common hepatic and celiac arteries.

It is well known that extended pancreatectomy with the combined resection of major arteries, so-called regional pancreatectomy, is associated with high morbidity and mortality rates.[20] In contrast to regional pancreatectomy, SP-DP-CA does not require any arterial or gastrointestinal reconstruction. Kondo et al.[18] showed that the morbidity rate following SP-DP-CA was as high as 62%, but there was no mortality in their series. In addition, postoperative mortality following SP-DP-CA has not been documented in any other report on SP-DP-CA.[14–17,19] Zero mortality following SP-DP-CA may be attributed to the absence of arterial, pancreatico-biliary, and gastrointestinal reconstruction in this procedure. Furthermore, our SP-DP-CA patients were able to survive for as long as those who underwent distal pancreatectomy without resection of the celiac artery. These results show that SP-DP-CA is justified as a radical procedure for locally advanced cancer of the pancreatic body. Gagandeep et al.[19] also conclude that SP-DP-CA can result in prolonged survival and should be considered in central and distal pancreatic cancers invading the celiac artery. Adjuvant therapy performed following SP-DP-CA may also contribute to the survival of SP-DP-CA patients. SP-DP-CA patients in this series were able to complete planned adjuvant therapy or receive full-dose chemotherapy after cancer recurrence, owing to their well-maintained performance status following surgery. As a result, 3- and 5-year survivors could be obtained.

Recently, we reported that autopsy of patients with resectable pancreatic cancer revealed a high rate of local recurrence even after curative resection.[21] The control of local recurrence is one of the major goals of surgery for pancreatic cancer. It is noteworthy that local recurrence was evident in only two patients (patients 5 and 6), although all patients in this series had locally advanced pancreatic cancer involving major arteries. Furthermore, SP-DP-CA that is associated with a low mortality rate and good local control has the possibility of becoming a standard procedure for cancer of the pancreatic body without cancer invasion of the major arteries.

Conclusion

This study showed that SP-DP-CA is a rational approach to locally advanced pancreatic body cancer that invades around the celiac artery. Using SP-DP-CA, the resectability of advanced cancer of the pancreatic body will be improved without increased mortality rates. If limited to one institute, the accumulation of candidates for SP-DP-CA with the present indication criteria, however, will take a long time because the majority of locally advanced cancer of the pancreatic body is associated with not only the celiac artery but also SMA involvement. To determine the implications of SP-DP-CA for locally advanced cancer, multicentric clinical studies will be necessary. In view of the feasibility of SP-DP-CA, it may also be worthwhile to adopt SP-DP-CA for less advanced cancer of the pancreatic body to enhance local control and survival.

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A Novel Biodegradable Biliary Stent in the Normal Duct Hepaticojejunal Anastomosis: an 18-month Follow-up in a Large Animal Model

Johanna M. Laukkarinen · Juhani A. Sand · Pierce Chow · Hanne Juuti · Minna Kellomäki · Päivi Kärkkäinen · Jorma Isola · Sidney Yu · Satchithanantham Somanesan · Irene Kee · In Chin Song · Teck Hin Ng · Isto H. Nordback

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Abstract Creating a well-functioning hepaticojejunostomy (HJ) anastomosis with non*dilated* bile ducts remains a challenge. Our aim was to study the use in a large animal model of a novel, braided polylactide barium sulfate biodegradable biliary stent (BDBS) without external connection and with no need for later removal. Fifty swine were randomly operated on for Roux-Y HJ with or without BDBS in the anastomosis, and followed up (dynamic biligraphy, x-ray, serum determinations, anastomosis inner diameter, and histology) for 1.5, 3, 6, 12, and 18 months. During the follow-up, one nonstented animal died because of anastomotic leakage. In x-ray BDBS was seen in place until 1.5 months in all of the stented animals. In the nonstented animals HJ anastomosis inner diameter was decreased at 18 months [6.3 (5.0–7.0) mm vs 7.4 (7.0–9.0) mm, $p=0.05$] and liver clearance reduced at 12 and 18 months compared to stented animals. Serum liver values and liver and bile duct histology did not differ between the groups. We conclude that this novel BDBS is easy to insert into the HJ anastomosis with nondilated ducts. It is nontoxic, dissolves safely, and may be associated with a larger and better draining anastomosis at 18-month follow-up. These results encourage us to proceed to clinical studies.

J. M. Laukkarinen · J. A. Sand · I. H. Nordback
Department of Gastroenterology and Alimentary Tract Surgery,
Tampere University Hospital,
Tampere, Finland

J. M. Laukkarinen · P. Chow · I. Kee · I. C. Song · T. H. Ng
Department of Experimental Surgery,
Singapore General Hospital,
Singapore, Singapore

P. Chow
Department of General Surgery, Singapore General Hospital,
Singapore, Singapore

H. Juuti · M. Kellomäki
Institute of Biomaterials, Tampere University of Technology,
Tampere, Finland

P. Kärkkäinen
Department of Pathology, Helsinki University Hospital,
Helsinki, Finland

J. Isola
Department of Pathology, Tampere University Hospital,
Tampere, Finland

S. Yu · S. Somanesan
Department of Nuclear Medicine, Singapore General Hospital,
Singapore, Singapore

I. H. Nordback (✉)
Division of Surgery, Gastroenterology and Oncology,
Tampere University Hospital,
Teiskontie 35, P.O. Box 2000, Tampere 33521, Finland
e-mail: isto.nordback@pshp.fi

Keywords Hepaticojejunostomy anastomosis · Bile ducts · Biodegradable biliary stent

Introduction

Hepaticojejunostomy (HJ) is a common procedure used to establish continuity when bypassing obstructed bile duct and after resections for various diseases and injuries. The early and late complications of HJ anastomosis with nondilated bile ducts, such as leak and stricture formation, remain a challenging problem in biliary surgery.[1–5] Controversy persists regarding which operative technique best prevents problems in this anastomosis. Selective use of transanastomotic stents has been recommended by some authors.[6,7] The disadvantages of percutaneous drainage placed pre- or intraoperatively include discomfort for the patient as well as the risk of infections, hemorrhage, and bile leakage.[8] These disadvantages of stenting may be explained, at least partly, by the direct external connection of the stent. This connection may be avoided when an internal biodegradable biliary stent (BDBS) is used without external connection and still without need for later removal. Previously we have shown in pilot patients that a spiral-shaped version of the biodegradable stent seemed promising in pancreaticojejunal anastomosis after Whipple operation,[9] but the radial force, inner/outer diameter ratio, and biodegradation of the stent were far from optimal. Because of this pilot study the stent has been improved. The current biodegradable polylactide (PLA) stent is braided in configuration, which generates a better radial force. Also, a thinner PLA wire has been generated to reduce the thickness of the stent wall. This enables us to generate stents with smaller diameters, and these novel stents can also be used in smaller caliber ducts. Furthermore, the current stent degrades faster than the earlier stent, and in general the degradation time can be adjusted during the manufacturing process to meet the needs of the indication. The new stent has not so far been studied in biliary applications.

The aim of the present study was to investigate the use of a novel BDBS in HJ performed in nondilated hepatic duct in a large animal model, and to follow the patency of the HJ and the possible changes in biliary dynamics and histology.

Methods

The braided, gamma-sterilized BDBS were manufactured at the Institute of Biomaterials, Tampere University of Technology, Tampere, Finland. The manufacturing was done using melt spinning of 96L/4D PLA blended with 23wt% barium sulfate ($BaSO_4$) for radio-opacity.[10–12] After melt spinning, the manufacturing was followed by solid-state drawing to create oriented structure to the fiber to enhance the mechanical properties. The fiber was braided over a mandrel to form tubular mesh and the mesh was heat-threaded to stabilize the structure. Finally, the stents were cut to appropriate length from the tubular mesh. The stent wall thickness was 0.30 mm, length 20 mm, and the outer diameter 6, 7, 8, and 9 mm when fully expanded to match the inner diameter of the HJ anastomosis (Fig. 1).

Fifty Yorkshire swine [weight median 59 (range 51–77) kg] were used. Before all the experiments the animals fasted for 2 days. The anesthesia was induced after 2 days' fast by 5% halothane inhalation after ketamine (Ketalar, Pfizer, Hameln Pharmaceuticals GmbH, Hamelin, Germany) 100 mg/10 kg, i.m., premedication. Anesthesia was maintained with 2% halothane inhalation vaporized with 100% oxygen. The animals received amoxicillin (Amoxin, Merckle GmbH, Blaubeuren, Germany) 5 mg/10 kg, i.v., during anesthesia induction.

Blood samples aspirated from the femoral vein were analyzed for full blood count. The samples were partly centrifuged to obtain serum. Serum samples were analyzed for sodium (S-Na, method: ion selective electrode), potassium (S-K, method: ion-selective electrode), creatinine (S-Crea, method: Jaffe reaction), glucose (S-Gluc, method: enzymatic determination), amylase (S-Amyl; method: kinetic, substrate ED-PNP-maltoheptaoside), total bilirubin (S-Bil, method: diazo reaction), direct bilirubin (S-Bil-Dir, method: diazo reaction), bile acid (method: enzymatic, colorimetric), Alanine transferase (S-ALT, method: kinetic, according to European Committee for Clinical Laboratory Standards

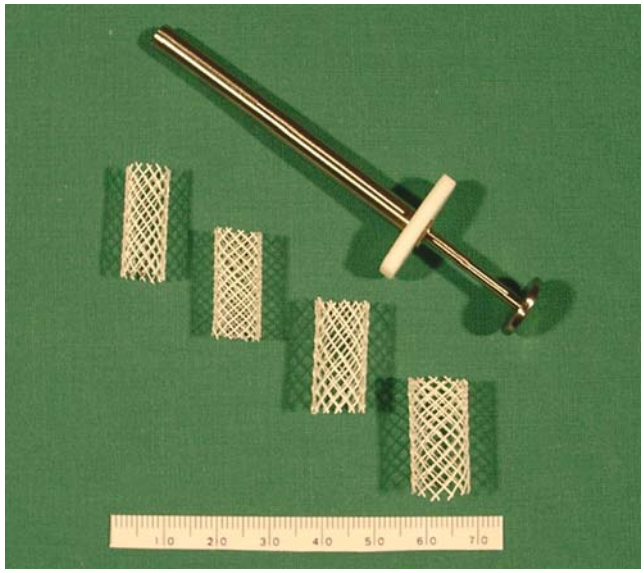

Figure 1 The braided, self-reinforced, gamma-sterilized PLA–$BaSO_4$ BDBSs (length 20 mm, outer diameters 6, 7, 8, and 9 mm when fully expanded) used in the HJ anastomosis in group I animals and the custom-made applicator for introducing the stent.

[ECCLS] reference), alkaline phosphatase (ALP, method: kinetic, substrate *p*-nitrophenyl phosphate in AMP), glutamyltransferase (S-GT; method: kinetic, according to ECCLS reference), lactate dehydrogenase (S-LDH; method: kinetic, according to Nordic reference), total cholesterol (fS-T-Chol, method: enzymatic), HDL-cholesterol (fS-HDL-C, method: direct enzymatic), LDL-cholesterol (fS-LDL-C, method: Friedewald formula), triglycerides (fS-TG, method: enzymatic), total protein (S-Prot, method: photometric), and albumin (S-Alb, method: immunoturbidimetric).

In dynamic biligraphy, ^{99m}Technetium diethyliminodiacetic acid (Tc-HIDA) (volume 1.5 ml, radioactivity 3 mCi) was injected into the cannulated ear vein, and the study was performed by obtaining serial analogous images for 90 min at 1-min intervals with the gamma camera (Starcam, GE Medical Systems, Huntley, USA). The regions of interest (ROI) were drawn for liver, liver hilum, and duodenum/jejunum at bile duct entrance (before/after HJ, respectively), after which the registered counts per minute per ROI were corrected for ^{99m}Tc decay and background radiation. Hepatic maximal uptake, hepatic clearance at 15, 30, 45, and 60 min, appearance of radioactivity in the liver hilum and in the intestine, and the hilum intestine transit time were determined.

An upper midline laparotomy was performed, liver was sampled, and gallbladder bile aspirated and kept anaerobic on ice until bacterial analysis. The cystic duct was closed by clamping and the common bile duct was cannulated with 24 G polyethene tubing. Four milliliters of bile were aspirated from the hepatic duct. Cholecystectomy was performed. The bile duct was cut proximal to the cystic duct and the distal end was ligated. The jejunum was transected 15 cm distal to ligament Treitz, and an end-to-side HJ was performed with interrupted 5–0 polytrimethylene carbonate (Maxon, Syneture, Norwalk, USA) sutures in one layer. The diameter of the HJ anastomosis was measured by probing through the still open distal end of the jejunum (site of the transection of the jejunum). The 50 animals were divided in two groups: group I with a BDBS in the HJ (n=25) and group II (n=25) without any stent in the anastomosis (n=25).

In group I (stent) a 20-mm-long BDBS with an appropriate outer diameter [6 (n=11), 7 (n=11), 8 (n=2), or 9 (n=1) mm] was inserted into the HJ anastomosis with a metallic applicator through the still open jejunal end, leaving 10 mm of the stent outside the anastomosis in the jejunal lumen (Fig. 2a–c). In group II animals the applicator was also introduced into the HJ anastomosis, but no stent was used. Then the jejunal end was closed and an end-to-side jejunojejunal anastomosis (Roux-Y) was made 50 cm distal to the HJ anastomosis in two layers with 4–0 polytrimethylene carbonate (Maxon) sutures. In both groups I and II the abdominal cavity was washed with saline, and the abdomen was closed in two layers. All the operations were performed by a single surgeon.

Aliquots of bile from the bile duct were frozen for subsequent analysis of bile acids and phospholipids (method: end-point enzymatic assay; kit by WakoCorp, Osaka, Japan). Determinations of cholesterol and bilirubin concentrations, pH (method: test strips by QA Supplies, Norfolk, VA, USA), and the culture for aerobic and anaerobic bacteria were done immediately after the retrieval of bile.

The animals were followed up for 1.5, 3, 6, 12, or 18 months (five animals from both groups were killed at each follow-up time) by repeated blood and serum analysis, abdominal radiograph, ^{99m}Tc-HIDA dynamic biligraphy, gallbladder and bile duct bile analysis, and histological analysis of the liver and bile duct samples. The determinations were performed preoperatively, 2 weeks postoperatively, and at the end of the follow-up time. The animals were fed with standard pig chow and were allowed free access to water and free movement in their cages. Ketorolac tromethamine (Toradol, Roche, Basel, Switzerland) 6 mg/10 kg, i.m., was given for postoperative pain medication, and the daily intramuscular injections were continued for the 3 days.

During the follow-up, the placement, visualization, and degradation of the stent was evaluated by repeated abdom-

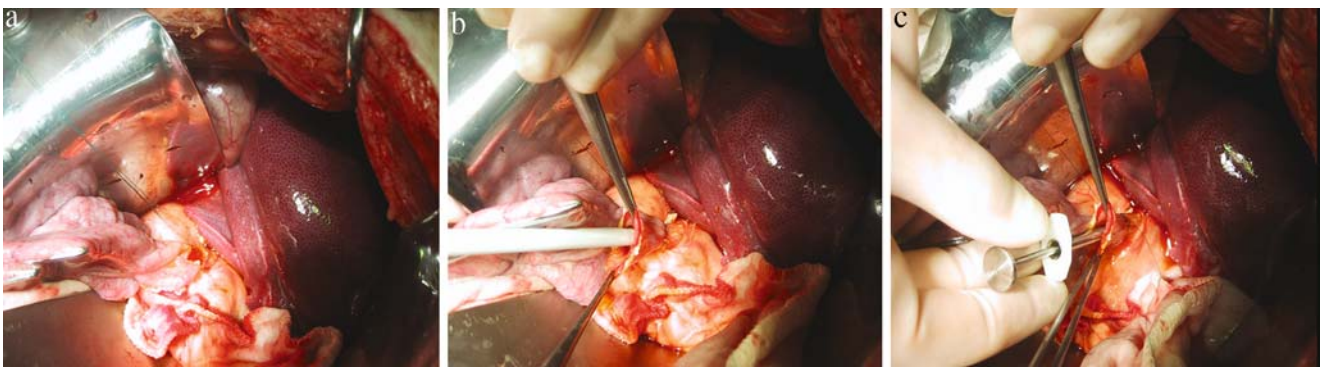

Figure 2 In the operation, the HJ anastomosis was performed **(a)** and measured by probing **(b)**, and in group I animals a BDBS was inserted into the anastomosis with an applicator **(c)**.

inal radiographs. At the end of the follow-up time at 1.5, 3, 6, 12, or 18 months (five animals from both groups I and II at each time point), a blood sample was taken and dynamic biligraphy was performed as described above. A laparotomy was performed, and the inner diameter of the HJ anastomosis was measured through the opened jejunum by probing. Thereafter the hepatic duct and liver were sampled for histology. The animals were then overdosed with sodium pentobarbital (Nembutal, Abbot Laboratories, Chicago, IL, USA) 100 mg/kg and killed by exsanguination.

Analysis of histology was performed blind for the group from the formalin-fixed, paraffin-embedded liver (stained with hematoxylin and eosin, Masson–Goldner's trichrome and Gomori's reticuline) and hepatic (stained with hematoxylin and eosin) specimens by a specialized pathologist. Semiquantitative analysis of liver histology was performed by grading the samples for (1) periportal and/or bridging necrosis, (2) intralobular degeneration and focal necrosis, (3) portal inflammation, (4) fibrosis, and (5) centrilobular and periportal cholestasis. Steps 1 to 4 were done according to the histological activity index (HAI, the Knodell score)[13] originally designed for the grading of chronic hepatitis. The overall HAI scores were broken into individual components of necrosis, inflammation, and fibrosis to yield additional information not provided by conventional composite scales for grading necroinflammatory liver diseases. Centrilobular and periportal cholestasis (step 5) were graded according to Desmet[14] (see Table 1 for definitions and grading). In

Table 1 Description and Scores Used for the Semiquantitative Grading of the Liver Histological Samples

Score	Description
I	Periportal and/or bridging necrosis (part of HAI[a])
1	None
2	Mild piecemeal necrosis
3	Moderate piecemeal necrosis (involves less than 50% of the circumference of most portal tracts)
4	Marked piecemeal necrosis (involves more than 50% of the circumference of most portal tracts)
5	Moderate piecemeal necrosis plus bridging necrosis[b]
6	Marked piecemeal necrosis plus bridging necrosis[b]
7	Multilobular necrosis[c]
II	Intralobular degeneration and focal necrosis[d] (part of HAI[a])
1	None
2	Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis <1/3 of lobules and nodules)
3	Moderate (involvement of 1/3 to 2/3 of lobules or nodules)
4	Marked (involvement of >2/3 of lobules and nodules)
III	Portal inflammation (part of HAI[a])
1	No portal inflammation
2	Mild (sprinkling of inflammatory cells in <1/3 of portal tracts)
3	Moderate (increased inflammatory cells in 1/3–2/3 of portal tracts)
4	Marked (dense packing of inflammatory cells in >2/3 of portal tracts)
IV	Fibrosis (part of HAI[a])
1	No fibrosis
2	Fibrous portal expansion
3	Bridging fibrosis (portal–portal or portal–central linkage)
4	Cirrhosis[c]
V	Centrilobular and periportal cholestasis (modified from Desmet 1994)
1	No cholestasis
2	Mild cholestasis (acute stage). Parenchymal biliary bacteriostasis (hepatocellular canalicular and possibly in Kupffer cells)
3	Moderate cholestasis (chronic stage). Cholestatic liver cell rosettes, clusters and xanthomatous cells with foamy appearing cytoplasm, and features of acinar zone 1 cholate stasis. Decrease in number of interlobular bile ducts (ductopenia; interlobular bile duct number to portal tract number ratio less than 0.5)
4	Severe cholestasis (advanced stage). Periportal parenchymal changes of cholate-stasis is fully developed, including cellular swelling, coarse granularity, occurrence of Mallory bodies, storage of copper and copper-binding protein, infiltration by some inflammatory cells including neutrophils, and pericellular fibrosis. Periportal fibrosis may be present.
5	Close to biliary cirrhosis. Biliary type fibrosis with fibrous septal connections between adjacent portal tracts.
6	Biliary cirrhosis[e]

[a] HAI is the combined scores for necrosis, inflammation, and fibrosis.[13]
[b] Bridging is defined as ≥2 bridges in the liver biopsy specimen; no distinction is made between portal–portal and portal–central linkage.
[c] Two or more continuous lobules with panlobular necrosis.
[d] Degeneration—acidophilic bodies, ballooning, focal necrosis—scattered foci of hepatocellular necrosis.
[e] Loss of normal hepatic lobular architecture with fibrous septa separating and surrounding nodules.

hepatic duct histology, atrophy, mucosal inflammation, submucotic vascularization, submucotic fibrosis, scar formation, foreign body granuloma, and stent material were all analyzed semiquantitatively on a scale none, mild, and marked.

The data are shown as median and range, except the histological scoring, which is given as sum scores per group and mean scores per animal. To calculate the statistical significance of the differences, chi-square test was used for cross-tabulated variables, Mann–Whitney *U*-test for linear nonparametric variables between the study groups, as well as general linear model variance analysis for repeated measures within the groups. Differences of $p \leq 0.05$ were considered statistically significant.

The study was conducted in accordance with the Helsinki Declaration for Scientific Experimentation on Animals. The experiments were approved by the experimental laboratory animal ethical committee of the Singapore General Hospital, Singapore.

Results

Preoperatively groups I (stent) and II (no stent) were well comparable for weight [54 (50–58) vs 55 (52–59) kg], bile duct inner diameter [7.0 (5.5–8.0) vs 6.7 (5.0–8.0) mm], and for blood, serum, and bile determinations. In dynamic biligraphy, too, there was no difference between groups I and II preoperatively in any of the study parameters.

During the follow-up, one group II (no stent) animal died on the second postoperative day because of leakage in the HJ anastomosis. The rest of the animals remained healthy and gained weight during the follow-up period, with no difference between the two groups. Blood and serum determinations did not differ from the preoperative values, or between the two groups at any time points (Table 2).

In abdominal radiograph the BDBS was seen in place right after the operation and at 2 weeks in all 25 animals in Group I. From 1.5 months on, none of the 25 group I pigs had the stent in place in the radiograph (Fig. 3). In the laparotomy at the end of the follow-up the finding was identical, i.e., no stents were seen from 1.5 months onward.

The inner diameter of the HJ anastomosis did not differ between the groups at 1.5 and at 3 months. Thereafter the diameter decreased in group II (no stent) to 6.3 (5.0–7.0) mm at 18 months, but did not change in group I (stent) remaining 7.4 (7.0–9.0) mm at 18 months ($p=0.05$ between groups I and II). Because the animals gained weight during the experiment, we also studied the weight-related diameter of the anastomosis. This also showed a similar difference between the two groups at 18 months in favor of the stent group.

Liver clearance was significantly reduced in group II compared to group I both at 12 and 18 months (Table 3).

The hepatic duct bile concentrations of cholesterol, phospholipids, bile acids, and bilirubin were significantly decreased and the pH had a tendency to increase compared to the preoperative values in both groups I and II, but without difference between the two groups (data not shown).

In the gallbladder or hepatic duct bile no bacteria could initially be isolated. In the follow-up, 22 of 25 (88%) of the group I (stent) animals and 19 of 24 (79%) of the group II (no stent) animals had postoperative bacterial growth in hepatic duct bile. The groups did not differ as to the bacterial species, where *Escherichia coli* was predominant.

In liver histology, all the parameters studied (Table 1) were graded as normal (total score per five animal) in both groups I and II preoperatively. In group I (stent) 13 of 25 (52%) and in group II (no stent) 12 of 24 (50%) of the animals had an abnormal grading of at least one of the parameters. The cases with an abnormal liver histology grading were evenly distributed in the different follow-up groups with no difference between groups I and II.

In the hepatic duct histological analysis all the parameters studied were considered normal in 20 of 25 (80%) of the group I (stent) and 19 of 24 (79%) of the group II (no stent) animals. In group I there was mild inflammation reaction of the mucosa in 8% (2/25), mild submucotic vascularization in 8% (2/25), and both in 4% (1/25) of the animals, the representative percentages being 13% (3/24), 4% (1/24), and 4% (1/24) for group II (no stent). Mucosal atrophy, submucotic fibrosis, scar formation, foreign body granuloma, or stent material were not seen in the histological analysis of the hepatic duct samples. The few cases with abnormal hepatic duct histology were evenly distributed in the different follow-up time groups with no difference between groups I and II.

Discussion

The early and late complications of the HJ anastomosis with no dilated bile ducts, such as leak and stricture formation, remain a challenging problem in biliary surgery. Selective use of transanastomotic stents has been recommended by some authors.[6,7] When HJ is performed after a long-term biliary obstruction, the need for a temporary stent is negligible because of the ease of handling a large duct. In small ducts this problem is more evident, but reasonable long-term results have earlier been reported to be achieved both with[15,16] and without[17,18] anastomotic stents. At present some authors recommend the use of transanastomotic stents especially when there is a question of ischemic, scarred ducts with a diameter of less than 4 mm.[6] An inert silicone stent creates an outside connection into the biliary tree, needs to be removed later, and sometimes causes obstruction.[19,20] The administration of ursodeoxycholic acid does

Table 2 Animal Weight, Blood, and Serum Concentrations in Groups I (Stent) and II (No Stent) at 0.5, 1.5, 3, 6, 12, and 18 Months Postoperatively [Median and Range; No Statistical Difference Between the Groups (Weight), or Between or Inside the Groups (Blood and Serum Determinations)]

	0.5 Months (n=25)		1.5 Months (n=5)		3 Months (n=5)		6 Months (n=5)		12 Months (n=5)		18 Months (n=5)	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
Group I (stent)												
Weight (kg)	56	51–62	60	52–64	62	56–66	73	60–77	91	88–118	134	112–142
WBC ($\times 10^9$/l)	11.9	10.6–12.4	12.0	10.6–14.2	13.2	10.1–14.9	11.9	8.9–16.2	12.9	10.1–15.1	11.8	9.8–13.4
S-Bil total (μmol/l)	6.2	4–11	6.4	5.8–6.7	8.1	4–11	6.9	6–8	5.2	2–7	4.9	2–10
S-Bil direct (μmol/l)	0	0–1	0	0–2	0	0–2	0	0–1	0	0–2	0	0–2
S-Bile acids	14	4.23	11	6–15	16	6.23	14	9–28	17	6–29	15	10–19
S-ALT (GPT) (U/l)	27	16–36	30	23–35	32	21–36	38	29–39	29	16–37	25	16–39
S-ALP (U/l)	69.2	60–100	73.1	68.2–77.4	63.9	30–100	55	49–78	56	31–67	54	35–65
S-GT (U/l)	39.7	22–60	42.9	39.3–47.7	44.5	20–46	36.2	20–52	32	14–46	31	29–44
S-LDH (U/l)	887	666–982	954	886–1034	899	834–1020	774	666–848	816	712–910	745	578–799
Group II (no stent)												
Weight (kg)	56	53–62	50	54–66	64	58–68	77	65–80	89	86–112	129	118–143
WBC ($\times 10^9$/l)	13.2	8.0–16.1	12.0	10.1–13.8	11.2	8.2–16.1	11.0	8.0–16.1	10.2	8.2–16.1	11.4	8.2–16.1
S-Bil total (μmol/l)	5.4	4–12	5.7	3–1	3.9	4–10	6.3	4–12	6.7	4–8	6.6	3–11
S-Bil direct (μmol/l)	0	0–1	0	0–2	0	0–2	0	0–1	0	0–0	0	0–2
S-Bile acids	18	4–18	19	5–20	12	5–20	11	4–24	10	6–22	11	5–20
S-ALT (GPT) (U/l)	39	24–42	33	21–46	38	21–46	39	24–42	41	24–42	38	21–46
S-ALP (U/l)	74.8	37–87	71.9	36–78	61.2	36–78	49	37–87	47	39–53	49	32–84
S-GT (U/l)	32	21–39	30	21–39	38	19–49	42	21–39	40	31–49	46	21–39
S-LDH (U/l)	789	666–868	689	544–724	721	557–865	945	565–889	772	603–829	677	647–862

not prevent the obstruction of the transanastomotic stent.[6,21] Metallic endobiliary stents are recommended not to be used in patients with a predicted life expectancy greater than 2 years because they are virtually irremovable and may also cause obstruction.[22] The disadvantages of the percutaneous drainage (infections, hemorrhage, and external bile leakage) may be partly prevented if an internal stent is used instead.[8]

Because of the similarities of its hepatobiliary system to the human counterpart (e.g., bile duct diameter), the present study was carried out on the Yorkshire swine model widely used in the preclinical hepatobiliary studies.

It was found that the insertion of the stent was easy, including the probing for selecting appropriate stent size and then the insertion of the stent. This was done in the end-to-side HJ via the transsected jejunum before the closure of this transection line. If an automatized stapler is used for jejunal transection, a separate small hole needs to be opened in the jejunal wall to pass the stent inside the anastomosis. An alternative would have been to use stay sutures inserted first in the entire circumference of the anastomosis, then to insert the stent before tightening the sutures. It would also be possible to perform the anastomosis so that the applicator is already inside the lumen, which might help with the smallest ducts, and then to release the self-expanding stent into the ready-made anastomosis. In this first series we preferred to do the anastomosis and then to insert the stent.

One of the 25 (4%) nonstented animals died of anastomotic leak and peritonitis soon after the operation, whereas none of the stented animals died in this way. Because of the small number, this difference was not significant. We consider the possible use of a stent for preventing stricture rather than early leakage. Theoretically a self-reinforcing stent with a radial force to maintain it in place could stretch the anastomosis too much to induce leakage. This did not appear to be the case. It might be suggested, however, that the use of the stent does not increase the likelihood of early leakage.

In abdominal radiograph the BDBS was seen in place until 6 weeks in all animals, whereafter the stents could not

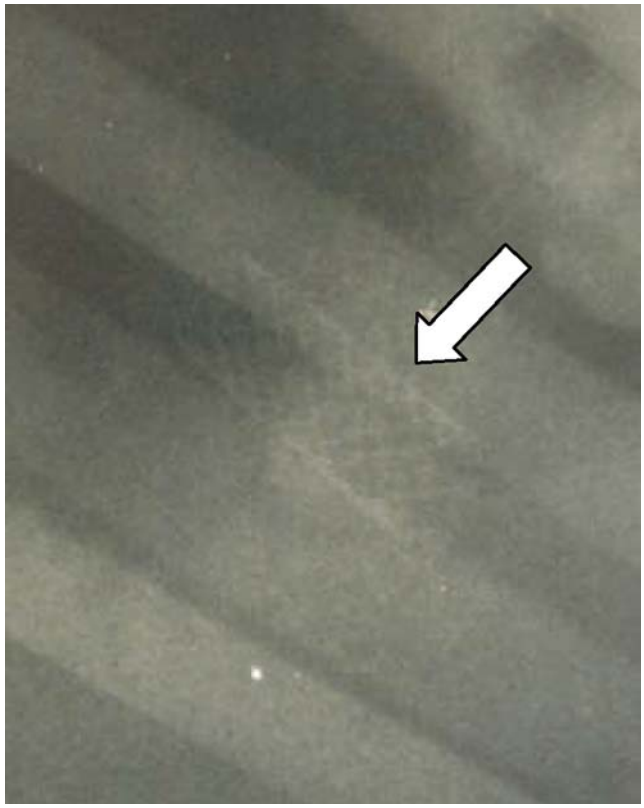

Figure 3 The BDBS visualized in the abdominal radiograph in one of the group I animals at 2 weeks postoperatively.

be detected in the radiograph or in the autopsy. Earlier in vitro experiments have demonstrated complete degradation of the stent within 6–12 months, but the degradation started much earlier depending on the medium used.[9] When a stent modified for vascular purposes is inserted into an artery it will soon be covered by endothelium.[23] In our experiments the stents remained in the lumen, and were not covered by mucosal epithelium. Therefore, already partial degradation of the stent followed by the clearance of the fragments from the biliary tree with the bile flow could explain the disappearance of the stent. Theoretically this fragmentation might result in a retained part of the stent within the duct with consequent stone formation, as has been seen in endoscopically inserted partly biodegradable stents.[24] This stent, however, differed considerably from our stent, which did not contain nonbiodegradable materials. Therefore, if the degradation is fairly rapid, as was the case in our stent, even such a retained part might degrade rapidly enough to prevent obstructive complications.

In patients, an optimal time for the stent to stay in place might be something between 2 and 3 months—long enough to ensure the healing of the anastomosis, but short enough to prevent stent obstruction. The degradation time of the stent can be modified with the manufacturing method: It is possible to produce stents with a longer or shorter degradation time.[9,11,12] For the current indication, stents with a longer degradation time will probably be used when the studies are carried forward to clinical trials in the future. Somewhat longer time may also be needed when this kind of a stent is used for other purposes, such as endoscopic stenting for benign biliary stricture, and shorter degradation time when used for the endoscopic stenting for cystic duct leakage.

Some authors have suggested that the use of an intraanastomotic stent should not be recommended because the stent may promote fibrosis of the anastomosis because

Table 3 Hilum Intestine Transit Time, Liver Maximum, and Liver Clearance at 45 and 60 Min After the ^{99m}Tc i.v. Injection in Dynamic Biligraphy in the Group I (Stent) and II (No Stent) Animals at 0.5, 1.5, 3, 6, 12, and 18 Months Postoperatively (Median and Range)

	0.5 Months (n=25)		1.5 Months (n=5)		3 Months (n=5)		6 Months (n=5)		12 Months (n=5)		18 Months (n=5)	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
Group I (stent)												
Hilum intestine time (min)	3	2–3	3	2–3	3	2–3	2.5	2–4	3	2–4	3	2–4
Liver max (min)	10	9–11	10	8–11	9	7–11	10	8–12	9.5	8–11	10	7–12
Liver clearance 45min (%)	68.2	62.6–72.7	67.2	62.3–70.4	75.6	73.0–77.2	74.8	72.3–77.9	74.9*	70.2–80.5	75.7*	73.4–78.9
Liver clearance 60min (%)	72.0	69.0–75.2	71.9	65.4–74.2	79.4	76.7–85.2	79.2	75.1–84.2	79.6*	72.9–85.1	80.0*	75.5–84.7
Group II (no stent)												
Hilum intestine time (min)	3	2–3	3	2–4	3	1–3	3	2–4	3	2–4	3	2–4
Liver max (min)	8	7–11	10	9–12	10	8–12	9	8–11	11	9–12	10	9–12
Liver clearance 45min (%)	67.8	62.6–71.8	66.9	65.1–70.0	74.9	69.2–77.3	67.0	63.3–72.9	67.2*	63.2–78.2	66.1*	63.3–69.2
Liver clearance 60min (%)	72.1	69.4–74.4	71.9	67.9–74.0	78.4	71.1–81.2	70.0	66.8–74.9	71.9*	68.0–86.2	70.2*	65.6–74.2

*$p \leq 0.05$ between the two groups at the time points.

of long-term irritation of ductal mucosa, thereby inhibiting rather than increasing drainage.[18,25,26] In the present study, the ductal histology did not show any signs of irritation induced by the stent. Nor did the stent increase the prevalence of bacterial colonization of the hepatic duct. In the histology and serum liver function tests it also showed no toxicity for liver, compared with nonstented animals. On the contrary, the diameter of the anastomosis was larger at 18 months in the stented compared to nonstented animals. Furthermore, in ^{99m}Tc-HIDA imaging, the liver clearance was significantly better at 12 and 18 months in the stented compared to the nonstented animals. Although during the 18-month follow-up time none of the nonstented animals showed a late failure in the anastomosis with impairments in the serum liver function tests or histology, the larger late diameter of the anastomosis and the improved drainage in ^{99m}Tc HIDA in the stented animals might also speak for the benefits of the BDBS. The clinical significance of the differences in the outcomes is uncertain. In patients the circumstances for creating the anastomosis are usually less optimal compared to these healthy animals, which had undergone no previous surgery. It is thus likely that nonstented patients might not do as well during the follow-up as in our study. Our opinion is that the biodegradable stent may bring real benefits when HJ anastomosis is created in small caliber ducts in patients. These good experimental results point to clinical trials in the near future.

In conclusion, in HJ with nondilated ducts the novel BDBS seems to be easy to insert, nontoxic, disappears safely from the anastomosis, and may be associated with larger and better draining anastomosis in 18-month follow-up.

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A Review of Resistance Patterns and Phenotypic Changes in Gastrointestinal Stromal Tumors Following Imatinib Mesylate Therapy

Kai Bickenbach · Rebecca Wilcox · Jula Veerapong · Hedy Lee Kindler · Mitchell C. Posner · Amy Noffsinger · Kevin King Roggin

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Abstract Gastrointestinal stromal tumors are neoplastic lesions that arise from the interstitial cells of Cajal and are associated with somatic mutations in the tyrosine kinase receptor, KIT. The only known curative therapy is complete surgical resection. Unfortunately, postsurgical recurrence rates exceed 50% and most tumors are resistant to standard chemotherapy and radiation. Imatinib mesylate, a novel tyrosine kinase inhibitor, holds promise as a potential adjuvant therapy to prevent recurrence and improve long-term survival. However, as resistance data emerge, it appears that a potential "escape pathway" may originate from secondary mutations in the KIT receptor. This paper reviews the historical clinical experience with imatinib mesylate and discusses resistance patterns following targeted therapy. We highlight this review with an interesting case report that illustrates unique phenotypic tumoral changes associated with imatinib mesylate resistance.

Keywords Gastrointestinal stromal tumors · Imatinib mesylate · Resistance

Drs. Bickenbach and Wilcox share joint first authorship

K. K. Roggin
Division of Biological Sciences,
University of Chicago Pritzker School of Medicine,
Chicago, IL, USA

K. Bickenbach · J. Veerapong · M. C. Posner · K. K. Roggin (✉)
Department of Surgery,
University of Chicago Pritzker School of Medicine,
5841 S. Maryland Avenue, MC5031,
Chicago, IL 60637, USA
e-mail: kroggin@surgery.bsd.uchicago.edu

R. Wilcox · A. Noffsinger
Department of Pathology,
University of Chicago Pritzker School of Medicine,
Chicago, IL, USA

H. L. Kindler
Section of Hematology/Oncology,
University of Chicago Pritzker School of Medicine,
Chicago, IL, USA

Case Report

History

A 70-year-old Caucasian male with a past medical history of non-insulin dependent diabetes mellitus, hyperlipidemia, and chronic tobacco use was found to have a normochromic, normocytic anemia on routine serum chemistries in December 2002. He complained of mild fatigue and a 10-lb weight loss. Esophagogastroduodenoscopy demonstrated two submucosal lesions along the greater curvature of the stomach. Preoperative fine needle aspiration biopsy was consistent with a spindle cell neoplasm. He had an uncomplicated sleeve gastrectomy in December of 2002 at a community hospital. Pathologic examination revealed two distinct submucosal lesions: a 9× 7 cm gastrointestinal stromal tumor (GIST) neoplasm (CD-34 and CD-117/c-*kit* positive) and a 4×2×0.8 cm mass consistent with benign lymphatic tissue. All surgical margins were microscopically negative and the perigastric lymph nodes did not harbor microscopic metastatic GIST.

The patient was followed clinically with serial imaging studies and did not receive any adjuvant treatment. In January 2003, a positron emission tomography (PET) scan demonstrated increased [^{18}F] flurodeoxyglucose (FDG) uptake adjacent to the prior surgical field. The patient was started

on imatinib mesylate (Gleevec™) at a dose of 400 mg per day. His disease remained stable for 2 years (April 2005) when both a computed tomography (CT) and PET scan demonstrated a mass with FDG-uptake in the splenic hilum and enlarged regional lymphadenopathy. The mass continued to increase in size despite dose escalation of imatinib mesylate to a maximum daily dose of 800 mg. A follow-up CT scan (August 2005) showed further progression of the mass with displacement of the body of the pancreas. The tumor appeared to involve the tortuous splenic artery, but did not invade the main trifurcation of the celiac axis (Fig. 1). He presented to a tertiary care referral hospital for a second opinion with complaints of a 40-lb weight loss (25% of his original body weight), severe anorexia, and fatigue.

The patient underwent a radical resection of the left upper quadrant mass in October of 2005. The tumor was 10×10 cm and adherent to the greater curvature of the stomach, distal pancreas, spleen, and left adrenal gland. The postoperative course was complicated by paroxysmal hypoglycemia, self-limited *Clostridium difficile* colitis, and failure to thrive. His negative nitrogen balance and severe cachexia were ultimately corrected with supplemental nasojejunal enteral nutrition.

Pathology

The patient's original tumor (December 2002) was received as a partial gastrectomy specimen with a 9×7 cm centrally ulcerated tumor mass. Histology of this mass revealed a spindle cell neoplasm of moderate cellularity with elongated, cigar-shaped nuclei. Nuclear pleomorphism was minimal, and mitotic activity was brisk [counts ranging from 5 to 20 per 10 high power field (hpf)]. Focal necrosis was present. Immunohistochemistry (IHC) showed expression for CD34 and CD117 in the neoplastic cells (Fig. 2, panel A). Tumor cells were negative for actin, desmin, and S-100 protein. These IHC results, in conjunction with the tumor size and high mitotic activity, were diagnostic of a malignant GIST. All lymph nodes were found to be negative for neoplasia. However, tumor cells were present at the radial margin.

The patient's second specimen (October 2005) was received as a distal pancreatectomy, splenectomy, left adrenalectomy, and partial omentectomy (Fig. 3). Within the soft tissue, a bulging, nodular mass measuring 11.5 cm in greatest dimension was abutting both the hilum of the spleen and the pancreatic resection margin. Sectioning the mass revealed a firm, gritty cut surface. There was prominent invasion into the spleen, with the mass occupying greater than 50% of the splenic parenchyma. The pancreas was spared.

Histology of this recurrent mass showed a mildly cellular spindle cell tumor with extensive formation of bone and cartilage (Fig. 4). Also present was a single focus of tumor cells with epithelioid differentiation and marked cytological atypia. IHC staining for CD117 and CD34 was negative in all cell types within this tumor (spindle, epithelioid, bone, and cartilage) (Fig. 2, panel B). Overall, the histological findings in this recurrent tumor were most consistent with an imatinib-mesylate-treated GIST. However, the distinctively different histology and the presence of extensive bone and cartilage formation was a finding not previously described in these tumors (Fig. 4). Despite its dramatic change in morphology, this lesion was genetically similar by c-*kit* mutational analysis (Corless lab; OHSU Cancer Institute) to the original GIST. A homozygous KIT gene exon 11 deletion was established in the primary gastric tumor (WK 557-558). Samples from two morphologically distinct (spindle cell vs cartilage) post-imatinib mesylate nodules were found by denaturing high performance liquid chromatography (DHPLC) to share the same KIT gene exon 11 deletion. Given that no wild-type allele was found in the primary GIST mutation, it can be assumed that the heterogeneity found in the recurrent nodules is a reflection

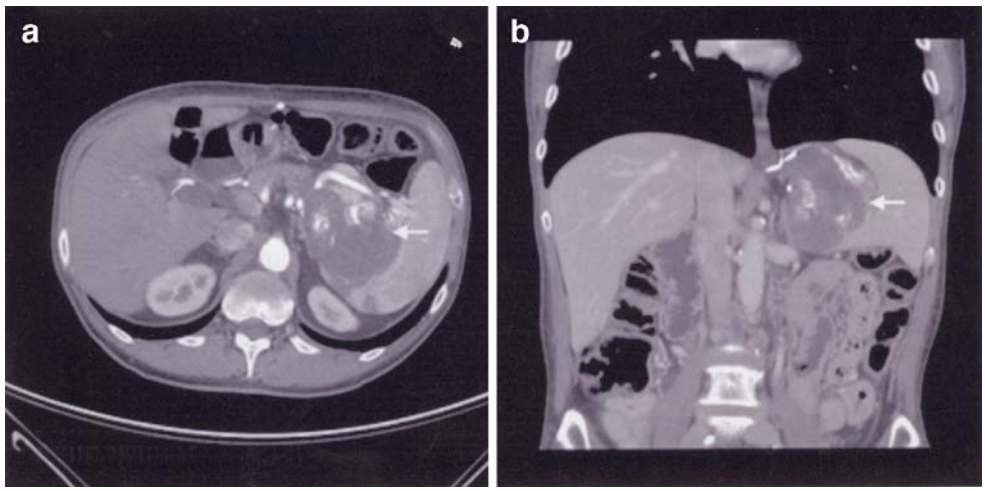

Figure 1 An infused computed tomography scan of the abdomen demonstrates a large mass (*white arrows*) in the *left upper quadrant*. The mass appears to involve the left adrenal gland, distal pancreas, and spleen.

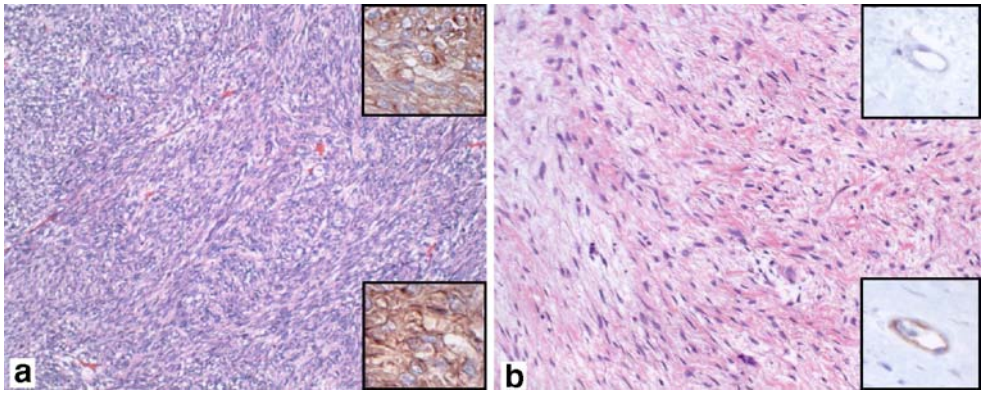

Figure 2 Primary and recurrent GIST. **a** Histology section from primary tumor revealing a moderately cellular spindle cell neoplasm (20×, hematoxylin and eosin preparation). Immunohistochemical staining for both CD117 (*inset*; *upper*) and CD34 (*inset*; *lower*) were strongly positive. **b** Histology section from spindled area of recurrent tumor shows marked decrease in cellularity (20×, hematoxylin and eosin preparation). Immunoreactivity for both CD117 (*inset*; *upper*) and CD34 (*inset*; *lower*) was lost.

of tissue heterogeneity even despite best efforts to prepare DNA from homogenous tissue type.

Background

Gastrointestinal stromal tumors (GIST) are uncommon mesenchymal tumors of the gastrointestinal tract with a median age of diagnosis at 58 years[1]. GIST commonly arise in the stomach (70%), followed by the small intestine (20–30%) and colon/rectum (10%). They occur less frequently in the esophagus, gallbladder, and appendix. They are typically composed of spindle cells and are thought to originate from the interstitial cells of Cajal (ICC) which function as the pacemaker of the GI tract[2]. Until 20 years ago, they were previously categorized as neoplasms of smooth muscle or neural origin and were considered part of the same category of tumors that included leiomyoma and leiomyosarcoma[3]. GIST typically lack the histologic features of Schwann cells and have different ultrastructural characteristics from smooth muscle cells[4]. In the last 10 years, Hirota et al.[5] made the landmark discovery that GIST are associated with gain of function mutations in the c-*kit* proto-oncogene. As a result, they typically stain positive for KIT (CD117) and CD34, with variable reactivity for SMA, desmin, and S-100; this immunohistochemistry profile is similar to ICC[3].

The only known curative therapy for GIST is complete surgical resection. Five-year survival rates from retrospective series of resected patients approach 65%[1]. Historically (pre-Gleevec® era), over half of the GIST patients had advanced disease at presentation and were not amenable to curative resection[1,6,7]. Many more (40–80%) tended to recur despite complete surgical resection[1,6,8]. This underscores the importance of effective systemic therapy. Unfortunately, historical data have shown that nearly all GIST were highly resistant to cytotoxic chemotherapy and/or radiation[9,10]. The recent development of the new small molecule tyrosine kinase inhibitor, imatinib mesylate, holds promise as an effective neoadjuvant, adjuvant, and palliative therapy for GIST.

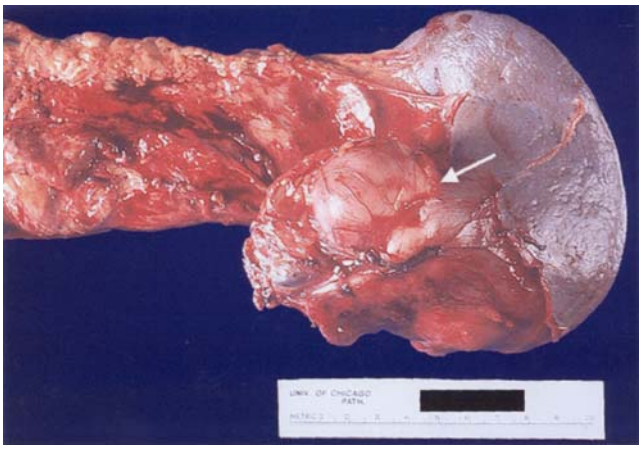

Figure 3 Gross specimen of the recurrent GIST. This photograph illustrates the *ex vivo* specimen consisting of the left adrenal gland, distal pancreas, spleen, and tumor mass (*white arrow*).

The KIT Receptor and Imatinib Mesylate

KIT is a receptor tyrosine kinase that belongs to the Type III family. It is structurally similar to other receptor tyrosine kinases such as platelet-derived growth factor receptor A and B (PDGFR), CSF1R, and FLT3. KIT is expressed in hematopoietic stem cells, mast cells, melanocytic cells, germ cells, and interstitial cells of Cajal (ICC). KIT is thought to play a key role in the differentiation of ICCs, and without it, a functional ICC network fails to develop[11–13]. KIT is a transmembrane receptor whose extracellular portion binds stem cell factor, which is also known as steel factor, mast cell growth factor, and the Kit ligand[14]. The binding of stem cell factor to KIT causes homodimerization, conformational

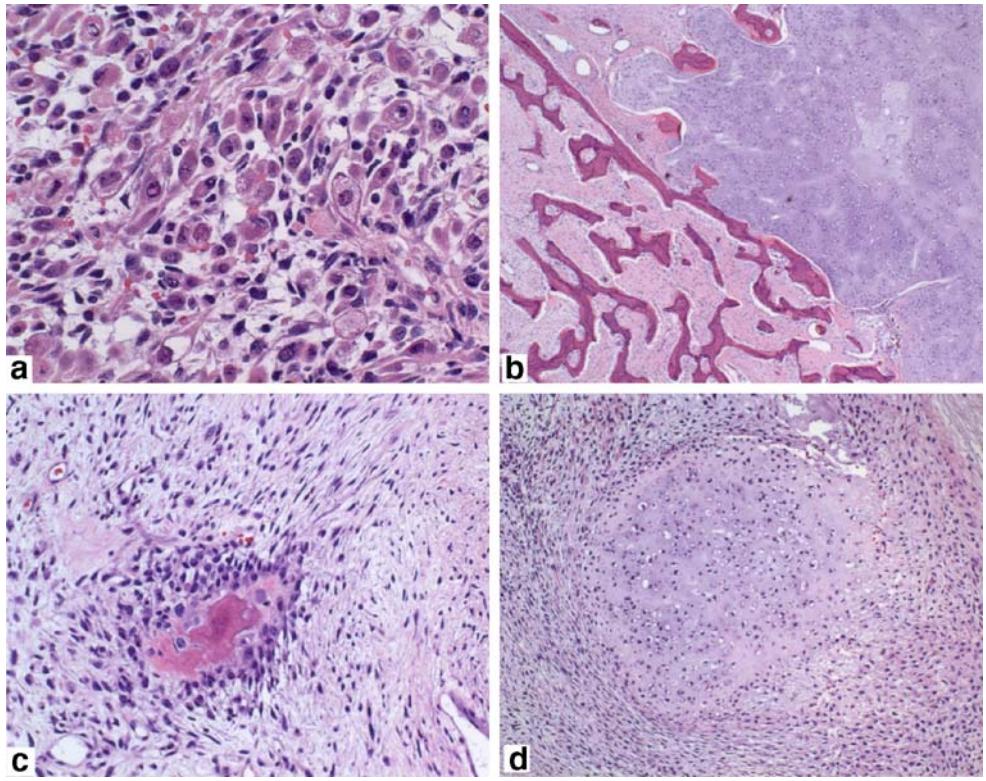

Figure 4 Heterogeneous morphology in recurrent GIST. **a** Single focus of tumor cells with epithelioid differentiation. **b** Representative histological section showing both bone and cartilage. **c** Bone formation by tumor cells. **d** Tumor cells producing cartilage.

changes, and activation of its kinase sites. Each KIT receptor then cross-phosphorylates its opposing dimer's tyrosine residues (cytoplasmic interface). These phosphotyrosine residues then serve as binding sites for the signal proteins downstream of KIT that include MAP kinase, PI3 kinase, STAT5, Ras, and Jak2[15,16]. These effectors lead to multiple signal cascades that regulate cell functions such as adhesion, proliferation, differentiation, and apoptosis.

The association between KIT and GIST was first made by Hirota et al.[5] who noted that 78% of GIST expressed both CD34 and KIT. Polymerase chain reaction (PCR) analysis demonstrated that five of six GIST samples had mutations in the juxtamembrane region of the KIT receptor. All five of these mutations activated the KIT receptor without the addition of its substrate stem cell factor. Transfection of the cDNA of these mutant KIT receptors into Ba/F3 murine lymphoid cell line resulted in malignant transformation. Rubin et al.[17] demonstrated that 48 consecutive GIST at the Brigham and Women's Hospital showed histologic evidence of constitutively active KIT receptor. Subsequent retrospective studies have confirmed that activating KIT mutations are present in 80–90% of GIST[3,18]. There are 21 exons in the KIT gene, and it appears that the most common site of mutation is in the 5′ end of exon 11. PCR analysis has demonstrated that mutations appear in roughly 50–78% of GIST at this site[5,19]. Exon 11 encodes the juxtamembrane region of the receptor which normally functions as a negative regulator of KIT's enzymatic site; activating mutations at this site therefore release KIT from its own autoinhibition. Other sites of mutation are exon 9 (extracellular region) and in the intracellular regions of exons 13 and 17. Exon 9 mutations appear in 3–18% of GIST, while exon 13 and 17 alterations are uncommon[20–23].

KIT activation appears to be an early step in the development of GIST. Studies have shown that many benign GIST have KIT mutations, suggesting that activation of KIT is an early event in carcinogenesis. KIT mutations often appear before other cytogenetic abnormalities occur[17,24]. Furthermore, familial forms of GIST have been defined in which there appears to be a germ line mutation of KIT[25–28]. Studies have demonstrated that the type of KIT mutation has prognostic significance. Miettinen et al.[29] demonstrated that in gastric GIST, deletions in exon 11 predicts a worse prognosis than point mutations in exon 11. A similar study showed that GIST with exon 11 single amino acid point substitutions had a 5-year recurrence free survival rate of 89%, while exon 11 insertion/deletion mutations had a 5-year recurrence free survival rate of 37%[30]. The lowest survival rate was seen in exon 13 mutations whose 5-year recurrence free survival rate was 0%[30].

Understanding KIT and other receptor tyrosine kinases has led to the development of specific inhibitors for these proteins. Imatinib mesylate, or Gleevec®, is an orally available agent that inhibits tyrosine receptor kinases such as BCR-ABL, PDGFR, and KIT[31,32]. Imatinib mesylate

functions by binding to the ATP-binding pocket of the KIT-receptor and blocking ATP from its receptor. This prevents phosphorylation of the downstream effectors that are essential for normal cell signaling. It has an oral bioavailability of >97% and is metabolized in the liver by CYP3A4, a *P*450 enzyme[33]. The half-life of imatinib mesylate is 13–16 h, which allows for once daily dosing. *In vitro* studies have demonstrated a 50% inhibiting concentration (IC50) of 413 nM for KIT, 188 nM for c-ABL, and 386 nM for PDGFR-β[32,34]. Studies suggest that a serum level of 1 ìmol/l is necessary for optimal therapy. This level can easily be reached with a dose of 300 mg[35].

Clinical Experience

Imatinib mesylate was originally used in the treatment of chronic myelogenous leukemia (CML). In CML, a fusion protein BCR-ABL is formed by chromosomal rearrangement that results in the "Philadelphia Chromosome"[36]. This fusion protein contains the tyrosine kinase portion of ABL, which is made constitutively active by the linkage to BCR[37]. Imatinib mesylate selectively inhibits this fusion protein, and *in vitro*, it inhibits the proliferation of lymphoid cells that had been transformed with the BCR-ABL fusion protein[31]. Druker et al.[33] demonstrated that 98% (53/54) of patients treated with 300 mg of imatinib mesylate developed a complete hematological response.

Imatinib mesylate was first used clinically in the treatment of GIST by Joensuu et al.[38], who treated a single 50-year-old patient with metastatic GIST who recurred despite aggressive surgical resection and systemic chemotherapy. Mutational analysis demonstrated an activating mutation of KIT in exon 11. The patient was started on 400 mg of imatinib mesylate daily. The patient had a radiological tumor response, with the sum of the cross-sectional area of her liver tumors decreasing from 112.5 to 28 cm^2 by 8 months of treatment. Six of 28 of her metastases disappeared, and no new lesions appeared. In addition, several hepatic and renal metastases that had FDG uptake on pretreatment PET scanning became FDG-negative 1 month after therapy. Serial biopsy specimens demonstrated myxoid degeneration and necrosis[38].

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase I toxicity trial of imatinib mesylate from August to December 2000[39]. Forty patients (36 with GIST) were randomized to receive imatinib mesylate at doses of 400 mg daily, 300 mg twice daily, 400 mg twice daily, and 500 mg twice daily. Objective responses as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) were observed in 25 of the 36 patients with GIST[40]. Seven patients had stable disease, and only four progressed. Fourteen patients were evaluated by PET scan on days 8 and 28. After 8 days of treatment, eight patients had no FDG-uptake in their GIST and two had a decreased FDG-uptake. After 28 days, 10 of 14 patients' tumors were FDG-negative. One patient had unchanged FDG uptake, and three patients showed increased FDG-uptake in their tumors[39].

Based on these results, the collaborative phase II US–Finland trial recruited 147 patients with advanced GIST[41]. Patients were randomly assigned to be treated with either 400 or 600 mg of imatinib mesylate daily. After a median follow-up of 9 months, 53.7% of those treated had a partial response (range: 50–96% tumor volume reduction); no complete responses were observed. Stable disease was observed in 27.9% of patients, and progression was noted in 13.6% of patients. A reduction of FDG-uptake on PET scan was noted in all patients within 24 h of treatment. Although the median survival had not been reached by the time of the report, the estimated 1-year survival rate was 88%. There was no statistically significant difference in survival or response rate between the two treatment groups[41].

The EORTC conducted a subsequent trial that randomized 946 patients with advanced or metastatic GIST to 400 mg of imatinib mesylate either once or twice daily[42]. There was no statistically significant difference in the objective response rate by RECIST criteria between treatment groups (400 vs 800 mg daily). The entire study population had a complete response rate of 5% and a partial response rate of 47%. Stable disease was observed in 32% and progression was noted in 11%. After a median follow-up of 760 days, 56% of the patients with the once daily dose had progression, while only 50% of the twice daily dose had progression ($p<0.026$). There was no significant difference in overall survival. The most frequent toxicities were gastrointestinal symptoms, edema, and nausea. These were mild in both treatment groups; however, there was an increase in dose reductions and interruptions in patients who received the higher dose of imatinib mesylate[42].

The North American Sarcoma Intergroup Study S0033 also examined the appropriate dose of imatinib mesylate by randomizing 746 patients to receive either 400 or 800 mg of imatinib mesylate daily[43]. The results of the trial were reported at the 2004 American Society of Clinical Oncology (ASCO) meeting after a median follow-up of 14 months. There was no statistically significant difference in progression-free survival, overall survival, or response rates in the study groups. The 2-year progression-free survival estimate was 50% in the 400 mg dose and 53% in the 800 mg dose ($p=0.13$). Overall survival was 78% in the 400 mg dose and 73% in the 800 mg dose ($p=0.87$). The partial response rate was 45%, and only 3% had a complete clinical response[43].

In summary, four separate prospective phase I/II clinical trials have examined the palliative role of imatinib mesylate

Table 1 Clinical Trial Summary for the Use of Palliative Imatinib Mesylate in Patients with Locally Advanced or Metastatic GIST

Trial	Date	Number of Patients	Phase	Daily Imatinib Mesylate Dose (mg)	PR (%)	CR (%)	Notes
EORTC	2001	36	I	400–1,000	–	–	25/36 (70%) objective RR
US-Finland	2002	147	II	400 vs 600	53.7	0	No Δ in RR and OS
EORTC	2004	946	II	400 vs 800	47	5	No Δ in OS
S0033	2004	746	II	400 vs 800	45	3	No Δ in PFS, RR, or OS
TOTAL		1,875					

N Number of patients, *mg* milligrams, *PR* partial response rate, *CR* complete response rate, *EORTC* European Organization for Research and Treatment of Cancer, *RR* response rate, *Δ* delta or difference, *OS* overall survival, *PFS* progression-free survival

in 1,875 patients with locally advanced or metastatic GIST (Table 1). The studies have shown that imatinib mesylate is relatively safe at doses up to 800 mg per day and that over half of patients with locally advanced or metastatic GIST will have clinical and radiographic disease stabilization or regression at short-term follow-up. Unfortunately, objective tumor response rates have not been associated with significant improvements in either progression-free or overall survival in this patient population.

The use of imatinib mesylate in the *adjuvant* setting is currently being examined in several randomized multicenter, cooperative-group trials. The recently completed ACOSOG Z9000 trial examined the potential survival benefit of adjuvant imatinib mesylate (400 mg daily) after complete resection of high-risk GIST (tumors>10 cm in diameter, evidence of tumor rupture, intraperitoneal hemorrhage, or presence of intraperitoneal tumors) compared to historical controls. The ongoing ACOSOG Z9001 is a randomized phase III trial designed to determine the impact of adjuvant imatinib mesylate (400 mg daily) vs placebo on the recurrence-free survival after complete resection of GIST (>3 cm). Imatinib mesylate is also being tested as a potential cytoreductive neoadjuvant therapy in patients with locally advanced GIST in both the Radiation Therapy Oncology Group (RTOG) S0132 and the MD Anderson Cancer Center (MDACC) ID03-0023 trials.

Mutations and Imatinib Mesylate Resistance

Although imatinib mesylate can have dramatic clinical responses in patients with GIST, initial resistance to therapy ranges from 9–13%[39,41,42]. In addition, many patients who are treated with imatinib mesylate may develop an acquired resistance to imatinib mesylate. There are several possible mechanisms for development of acquired resistance to imatinib mesylate. There is evidence that the oral bioavailability of imatinib mesylate decreases in patients with chronic use. One putative mechanism is via up-regulation of hepatic *P*450 enzymes that metabolize the drug[44]. Tumor cells may contribute to this form of resistance by metabolizing imatinib mesylate. In CML, increases in the multidrug resistant-1 (MDR-1) gene and multidrug related protein-1 (MRP-1) expression have been correlated with resistance to imatinib mesylate[45,46]. Increased expression of MDR proteins in GIST has recently been demonstrated in tumors that are not resistant to imatinib mesylate[47]. Putative mechanisms of imatinib mesylate resistance include increasing the copy number of c-*kit* or secondary mutations to the receptor. Most studies have failed to demonstrate increases in copy number as a source of resistance[48–50]. However, an abstract presented at ASCO in 2003 showed that a two- to fourfold increase in copy number was seen in two of 13 patients that developed resistance[51]. Secondary mutations can include mutations that either block the interaction of imatinib mesylate with its target site on the ATP-binding pocket or that further stabilize the active form of c-*kit*.

Debiec-Rychter et al.[48] screened 26 imatinib mesylate-resistant GIST for mutations in the KIT and platelet-derived growth factor receptor, alpha polypeptide (PDGFRA) kinase domains. Clinically, 15 of those patients had an initial partial response, 10 had stable disease, and 1 patient discontinued imatinib mesylate due to early resistance. Nineteen patients had exon 11 mutations, six patients had exon 9 mutations, and one patient had no identifiable KIT or PDGFRA mutations. Fluorescent in situ hybridization (FISH) analysis demonstrated an increase in c-*kit* copy number in only two of 26 (7.7%) patients. The authors showed that resistance developed by reactivation of KIT in eight of 10 patients. This was confirmed by immunoblot for activated KIT. The authors hypothesized that the reactivation of KIT was mediated through secondary mutations, as there were no primary mutations in the kinase regions before imatinib mesylate therapy. After a median treatment time of 77 weeks, there were six distinct secondary site mutations identified in 12 patients; four patients had a V654A mutation, and there were individual cases of D716N, D816G, D820Y, D820E, and N822K mutations. Another three patients had T670I substitutions. One patient also developed a new mutation on PDGFRA. It is possible

that these mutations may activate other kinase regions of KIT that are not sensitive to imatinib mesylate.

A similar study was performed by Antonescu and colleagues[49] in which they performed mutational analysis on tumor samples of 31 patients with GIST. Thirteen patients were nonresistant to imatinib mesylate, while 3 patients had primary resistance, and 15 patients who were initially sensitive to imatinib mesylate acquired resistance during treatment. Of the patients that acquired resistance, ten patients had an initial partial response, and five had stable disease that subsequently progressed on therapy. In this selected series, 14 of 15 (93%) patients that acquired resistance to imatinib mesylate initially had an exon 11 mutation. Of the 15 patients that acquired resistance, 7 patients (46%) also developed secondary mutations. The majority of these mutations were in exon 17 (six of seven patients) that encodes the second KIT kinase domain. Additional mutations were detected in the exon 13 in one patient and exon 14 in another patient. A study by Chen et al.[50] also confirmed that secondary KIT mutations may contribute to imatinib mesylate resistance. Six peritoneal implants were identified from five patients that had an initial near complete response to imatinib mesylate and then subsequently developed acquired resistance. All six implants harbored the same secondary mutation in exon 13 of KIT. This mutation was not present in any of the nonresistant patients.

GIST may also acquire resistance to imatinib mesylate by activating genes that control the downstream signal transduction pathways of KIT. Up-regulation or uncontrolled activation of the downstream effectors of KIT may allow clones to become resistant to imatinib mesylate. For example, secondary mutations in PDGFRA have been reported in cases of acquired resistance to imatinib mesylate[48,51]. Up to 35% of GIST with a wild-type KIT gene also have mutations in PDGFRA[52]. It is possible that activating mutations to these downstream effectors may allow resistance tumor cells to act independently of the KIT-receptor. This may explain the mechanism of acquired resistance in patients who did not have secondary mutations in the aforementioned studies[48,49].

Imatinib mesylate typically induces the formation of pyknotic nuclei and reduced cytoplasmic volume in residual GIST cells[38,41]. A single report describes three different patterns of phenotypic variation in response to imatinib mesylate therapy. Pauwels et al.[53] described three patients with spindle-cell GIST tumors that recurred after treatment. One case involved the transformation into an epithelioid pattern consistent with carcinoma, melanoma, or histiocytic proliferation. Another tumor showed a tubulopapillar and epithelioid pattern that was similar to a carcinoma or mesothelioma. The third GIST had an epithelioid pattern with eosinophilic cytoplasm. In all three patients, KIT expression was lost after treatment, and no secondary mutations were identified.

Our report is the first published account of the discovery of bony and cartilaginous elements within a GIST specimen following imatinib mesylate therapy. Previous reports have described the ability of imatinib mesylate to induce changes in GIST, such as necrosis and apoptosis. In light of those findings, we hypothesize that the morphologic changes found in our patient's tumor specimen may be due to alterations resulting from imatinib mesylate treatment itself or from secondary mutations in the KIT pathway. We speculate that KIT alterations may lead to the phenotypic expression of more highly differentiated mesenchymal elements, such as bone and cartilage. Although the specific mechanism for these phenotypic changes has not been identified, it is possible that differential activation of downstream effectors of the KIT pathway may influence cellular differentiation to express more mature mesenchymal elements such as cartilage and bone. Alternatively, a secondary mutation within the kinase domain of KIT or a mutation in PDGFRA may be responsible for the observed phenotypic changes in this patient. This case may represent an atypical presentation of Carney's Triad, which is a constellation of disorders including GIST (usually gastric), extra-adrenal paraganglionomas, and pulmonary chondromas[54,55]. This disorder usually affects young women and is inherited in an autosomal dominant pattern, but the exact etiology remains unknown. Although GIST in the Carney Triad typically stain positive for KIT, none of the usual germ line mutations has been previously observed[56,57]. It is possible that our patient's tumor developed imatinib mesylate resistance by developing mutations similar to the germ line mutations present in Carney's Triad. However, this theory cannot be proven until the origin of the Triad is fully explained.

Conclusion

The development of imatinib mesylate is a triumph in molecular targeting of cancer therapy. Studies have demonstrated that there is a clear clinical response to the drug, although no difference in progression-free survival or overall survival has been demonstrated in the palliative setting. Its role in the adjuvant setting is currently being examined in several trials. The understanding of how resistance develops to imatinib mesylate will aid investigators in developing future targeted therapies and strategies to treat GIST.

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Functional Results Following Elective Laparoscopic Sigmoidectomy After CT-Proven Diagnosis of Acute Diverticulitis Evaluation of 43 Patients and Review of the Literature

Patrick Ambrosetti · Karim Francis · Dominique Weintraub · Jonathan Weintraub

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Abstract We performed a prospective study to analyze the functional results following elective laparoscopic sigmoidectomy for computed tomography (CT)-proven diagnosis of acute diverticulitis and review the literature. Forty-three of 45 available patients (96%) who had laparoscopic sigmoidectomy for CT-proven acute diverticulitis answered, after a mean time of 40 months, a questionnaire exploring new abdominal symptoms, bowel function, and the patient's own judgement of the surgical outcome. Surgical technique aimed at removing all the sigmoid by taking down the splenic flexure and do a colorectal anastomosis. Four patients (9%) complained of new abdominal pain. Bowel function was reported as better for 24 patients (56%), unchanged for 16 patients (37%), and worse for 3 (7%). Twenty patients (47%) considered their final result as excellent to good, 17 patients (40%) as satisfying, and 6 patients (13%) as mediocre. Male gender, absence of preoperative history compatible with an irritable bowel syndrome, length of resected sigmoid and residual acute inflammation on histology are statistically predictive of a better postoperative degree of satisfaction. After elective laparoscopic sigmoidectomy for CT-proven diverticulitis, a great majority of patients are very satisfied with their postoperative general comfort.

Keywords Laparoscopic sigmoidectomy · Diverticulitis · CT · Postoperative functional results

Elective surgery is now considered reasonable in patients with recurrent attack(s) of diverticulitis, patients with complicated disease (stricture, fistula, abscess), and immunocompromised patients after one episode of diverticulitis. The practice to recommend elective resection in young patients after one well-documented episode of uncomplicated diverticulitis remains debatable[1–3]. While some indications for elective sigmoidectomy remain controversial and are not yet evidence-based, we now know that the most important factor is the quality of candidate selection for elective colectomy. At present, it is still quite common to accept the diagnosis of diverticulitis without computed tomography (CT) demonstration. Indeed, diagnosis of diverticulitis remains based on bioclinical indices (tenderness in the left iliac fossa in combination with fever, sedimentation rate or C-reactive protein, or white blood cell count above normal values). We also know that this bioclinical approach, when verified by CT, is associated with a 50% incidence of failure[4,5]. Unfortunately, most series reporting functional results of patients after elective colectomy are either retrospective and/or do not include computed tomography (CT) evidence of diverticulitis. Consequently, the cohort of studied patients is largely altered by false positive cases that weigh considerably on the interpretation of the results. The purpose of this study was to determine the final results (bowel function, abdominal symptoms, and subjective appreciation) of elective laparoscopic sigmoidectomy in patients whose acute diverticulitis was, in all cases, objectively demonstrated by CT.

P. Ambrosetti · K. Francis
Clinique Générale Beaulieu,
Geneva, Switzerland

D. Weintraub · J. Weintraub
Laboratoire Weintraub S.A.,
Geneva, Switzerland

P. Ambrosetti (✉)
4, rue Emile Yung,
1205 Geneva, Switzerland
e-mail: p_ambrosetti@bluewin.ch

Material and Methods

Between November 1998 and January 2005, 48 consecutive patients registered in a prospective database had elective laparoscopic sigmoidectomy for diverticulitis of the left colon. A postoperative questionnaire concerning recurrent diverticulitis, bowel function, abdominal new pain, and the patient's own judgement of the surgical outcome was sent to 45 patients. Two patients who died from non-colorectal cancer a few months after surgery and one for whom a subtotal colectomy was necessary could not be included in this postoperative assessment. Forty-three patients (96%) (22 women and 21 men with a mean age of 59.5 years) returned the questionnaire after a mean follow-up of 40 months (3–76) and were included in this study. These 43 patients had one or more episode of acute diverticulitis confirmed by CT. Thirty- eight patients had diverticulitis without CT signs of perforation, two had small mesocolic abscesses that were not drained, and three had an inflammatory sigmoid stenosis on colonoscopy of whom two were symptomatic. All patients were treated successfully, ambulatory, with oral antibiotics. Indications for surgical treatment, according to the recommendations of the American and European Consensus[1–3], were as follow: 40 patients (93%) after 2 or more episodes of acute diverticulitis, 2 patients after 1 episode of diverticulitis with an associated abscess, and 1 patient after 1 episode of acute diverticulitis followed by chronic pain in the left iliac fossa not responding to conservative means. The mean time between surgery and the last episode of acute diverticulitis was 110 days (4–1,172).

Surgical Technique

All patients had preoperative mechanical bowel preparation 2 and 1 day before the operation with 2×90 ml solution of Sodium Phosphate (Colophos®, Spirig) and 24 h parenteral antibiotics active against Gram-negative and anaerobic bacteria, started at the anesthesiological induction. A urinary catheter was inserted in the patient in the lithotomy position, and compressing lower leg boots were made to be worn by the patient. Regularly, four to five ports were used. Full mobilization of the descending and sigmoid colon was obtained by completely taking down the splenic flexure in *all cases*. The inferior mesenteric vein was divided at the Treitz angle, while the inferior mesenteric artery (IMA) was divided during the early period of the study and then preserved when technically possible. The proximal rectum was divided intracorporeally with a linear stapler under the reunion of the taeniae. The colon was then exteriorized via a short (3–5 cm) horizontal suprapubic muscle-splitting incision. After placing the anvil of the circular stapler in the proximal colon, the anastomosis was done intracorporeally and was routinely tested by intrarectal air insufflation. Abdominal drainage was never done. After discharge from the hospital, all patients were followed-up ambulatory for at least 6 months. Groups of patients were compared using BMDP Statistical Software (BMDP Statistical Software Incorporated, Los Angeles; California, USA)[4].

Results

There was no postoperative in-hospital mortality. Morbidity occurred in three patients (7%): one patient was reoperated 12 h after the first operation for a hemoperitoneum, one patient had a parietal abscess, and the third patient had an auricular flutter. No patient had an anastomotic leak.

Five patients (12%) had partial conversion. All of them had laparoscopic take down of the splenic colonic angle, while the liberation of the sigmoid and the rectal division needed to be done by laparotomy (by a Pfannenstiehl incision for four patients and by an infraumbilical median incision for one). The reasons to do a conversion were difficult identification and dissection of the left ureter due to a chronic inflammation of the sigmoid mesentery in three patients and technical difficulty in doing an intracorporeal anastomosis for two patients. The mean length of the resected colon was 23.3 cm (range: 14–50).

Results of the Postsurgery Inquiry

An overall view of the results is reported on Table 1.

These results can be presented as follow:

1. Recurrent diverticulitis

   No patient had recurrence of diverticulitis
2. Bowel function

   Twenty-four patients (56%) considered their bowel function to be better than before surgery, 16 patients (37%) considered this function to have remained unchanged, while only 3 patients (7%) considered their bowel function to be worse than before surgery.
3. Degree of satisfaction

   Twenty patients (47%) considered their final result as excellent to good, 17 patients (40%) as satisfying, and 6 patients (13%) as mediocre. Five of the latter patients belong to a group of 16 patients who had a preoperative history compatible with an irritable colon (altered bowel habits with an irregularity in frequency and/or in form of stool). Finally, we found that male gender, absence of preoperative history compatible with an irritable bowel syndrome, and length of resected sigmoid were statistically predictive of a better postoperative degree of satisfaction (Table 2).
4. New abdominal symptoms

   Four patients (9.3%) described new postsurgical symptoms. Due to the very small number of patients complaining

Table 1 Overall Postoperative Results (43 Patients)

Results	Number of Patients (*N*)	Percentage (%)
Bowel function		
Better	24	56
Unchanged	16	37
Worse	3	7
New abdominal pain	4	9.3
Degree of satisfaction		
Excellent	20	47
Good	17	40
Mediocre	6	13
Would you go back to surgery	41	95
Recurrence	0	

of new symptoms, no differences could be found between these patients and the 39 others in terms of bowel function, self-appreciation of the surgical outcome, type of anastomosis, length of resected colon, and conversion to laparotomy. Nevertheless, we noted that female gender and absence of acute inflammation on histology were constant for these four patients.

5. Histological findings

In every case, histological analysis reported signs of inflammation: acute for 20 patients (45%) and chronic for 23 patients (55%). The mean delay between the last episode of acute diverticulitis and surgery was shorter for the patients who had acute inflammation than for the others (57 vs 157 days), and the proportion of patients who had still occasional abdominal pain at the time of surgery was statistically greater for the patients with acute inflammation than for the others (15/20 vs 7/23, $p=0.009$) The comparison between these two groups is reported on Table 3. Patients with residual acute inflammation on histology had statistically better postoperative results (better degree of satisfaction and absence of postoperative new abdominal pain). Finally, 41 patients (95%) said that they would go back to surgery, while 2 patients (5%) did not answer to this question.

Discussion

Evaluation of postoperative results of elective sigmoidectomy cannot be dissociated from the notion of diagnosis of acute diverticulitis and indications for elective colectomy:

1. Diagnosis and severity of acute diverticulitis

We know now the lack of accuracy of bioclinical criteria both to confirm the suspected diagnosis of diverticulitis[4,5], and moreover, to define its severity keeping in mind that the finding of CT-diagnosed abscess is not rare, with an incidence between 15 and 20%[5–7]. We know today that CT is the best performing technique to make both the diagnosis of diverticulitis and definition of its severity, in particular, the presence of an associated abscess[8–10]. Moreover, by grading precisely the severity of diverticulitis, CT plays a predominant role in the evaluation of the risk of a complicated evolution after a first episode of acute diverticulitis successfully treated conservatively[11]. CT evaluation helps the surgeon to better determine the indications for secondary elective colectomy[11–13].

2. The place of elective sigmoidectomy

The place of elective sigmoidectomy for colonic diverticular disease is still openly debated in the literature[14,15]. The discussion is probably biased by the introduction of laparoscopy, which is met with general acceptance both by patients and physicians. Moreover, the fact that sigmoidectomy for diverticular disease is the privileged field of training for laparoscopy learners could probably widen the indications to surgery. Finally, the evidence that postoperative immediate results are excellent in terms of medico-surgical morbidity/mortality, and in terms of cosmetic results, could also play a role by strengthening the disposition to propose elective surgery[16]. Most authorities agree that the indications for elective surgery include: (1) patients with two or more previous acute attacks who were treated conservatively; (2) patients with one attack that is to be associated either with a contained perforation, or colonic obstruction, or with a fistula; and (3) patients with a suspicion of colonic cancer that cannot be excluded by other means. Immunocompromised patients should have surgery after the first episode. Surgery for younger patients after a first episode of acute diverticulitis is still a controversial topic[1–3]. These recommendations were essentially based on Parks's study finding that chances of successful conservative treatment of acute diverticulitis were decreasing with recurrences[17]. After frightening warnings reported by some authors about severe morbidity and even mortality related to recurrences after first successful conservative treatment of acute diverticulitis[18,19], new trends appeared in the recent literature strongly

Table 2 Parameters Statistically Favoring Excellent/Satisfying vs Mediocre Degree of Satisfaction

Degree of Satisfaction	Women	Preoperative History of Irritable Bowel Syndrome	Length of Resected Sigmoid (cm)
Excellent/good (37 patients)	16 (43%)	11 (28%)	23.2
Mediocre (6 patients)	6 (100%)	5 (83%)	20.1

Table 3 Postoperative Results: Comparison Between Patients with Histological Signs of Acute Inflammation vs Patients with Chronic Signs of Inflammation

Parameters	Acute Inflammation (20 Patients)	Chronic Inflammation (23 Patients)	P
New abdominal pain	0	4	
No pain	20	19	0.05
Bowel function			
Better	13	11	Ns
Unchanged	5	11	Ns
Worse	2	1	Ns
Degree of satisfaction			
Excellent to good	14	6	0.004
Satisfying	5	12	Ns
Mediocre	1	5	Ns
Would go back to surgery	20	21	Ns

refuting these assertions. Guzzo et al., studying retrospectively a group of 196 patients aged 50 years or younger successfully treated conservatively for a sigmoid diverticulitis, found after a median follow-up of 5.2 years that only one patient (0.5%) presented at a later date with perforation[20]. On the other hand, we reported results from 118 patients with long-term follow-up after a first acute episode of sigmoid diverticulitis treated successfully by conservative means and found after a median follow-up of 9.5 years that no patient died from evolutive complications of the disease and that no patient subsequently required emergency surgical treatment[11]. Large recent multicentric retrospective studies questioning the outcome of patients whose first episode of acute diverticulitis was conservatively treated also confirmed this tendency to a much more benign evolution[21,22]. In the end, using statistical models, Richards and Hammitt[23] determined that the optimal timing for elective colectomy is after a third episode of diverticulitis, whereas Salem et al.[24] concluded that elective colectomy should be considered after a fourth attack for it to be cost-effective. This radically new trends about the natural evolution of acute diverticulitis, published in the literature and found in our prospective studies, modified considerably the recent recommendations proposed by the American Society of Colon and Rectal Surgeons about the place of elective colectomy after a first episode of diverticulitis successfully treated conservatively[25].

In summary this is what they propose:

1. After recovery from acute diverticulitis: the recommendation is to do a case-to-case decision based on age, medical condition, frequency, and severity of attack(s), and persistent symptoms
2. After nonoperative treatment of an episode of complicated diverticulitis: elective colectomy should typically be advised...
3. Long-term results after sigmoidectomy

Only a few studies, mostly retrospective, centered their interest on functional postoperative results, and none of them had CT-proven diverticulitis[26–30]. These studies found that 7 to 27% of patients followed-up between 11 and 48 months were still complaining of abdominal symptoms after colectomy. Authors attributed these persistent symptoms to irritable bowel syndrome[26,27], insufficient length of resected colon[27], or inappropriate indications to surgery[28]. Thörn et al.[26], questioning by mail 64 patients who had elective colectomy for diverticular disease, found after a mean follow-up of 4 years that 14 patients (22%) had a fair to poor self assessment of surgical outcome. Functional symptoms or symptoms suggestive of irritable bowel syndrome before the operation predicted a less successful result. Diagnosis of diverticulitis was based on bioclinical parameters and radiography with barium enema or colonoscopy. CT investigation was never done. Munson et al. followed retrospectively 65 patients for a mean time of 1.9 year. Diagnosis of diverticulitis was not routinely based on CT examination. Indications for surgical treatment were not described. Of the 33 patients who were surgically treated, 9 (27.2%) reported continuing symptoms with pain being at the same location for all of them. The character of pain was unchanged in two-thirds, while one-third stated that the pain was completely different from the pain for which they were hospitalized. Surprisingly, all of these symptomatic patients had histological signs of diverticulitis, and five had perforation. The only statistically significant difference between the symptomatic patients vs the asymptomatic ones was the length of the resected colon which was an average of 17.6 cm for the first group of patients compared to 19.3 cm for the other group ($p=0.002$). The authors are drawing our attention to the fact that symptoms may be largely unchanged after operation for reasons that are poorly understood and that could simply represent presence of irritable bowel disease[27]. Breen et al.[28] reported retrospectively their experience on 82 patients followed for a mean time of 37 months. Radiological evaluation of diverticulitis and indications for elective colectomy were not defined. Twenty-two patients (27%) had postoperative complaints: 17 of them (21%) had minor complaints and 5 (6%) had major ones. Much more interesting is the fact that 60% of the 20 patients who had histological diverticulosis had complaints compared to 16% of the 62 patients who had histological diverticulitis! Male patients, histological signs of inflammation, preoperative bowel complaints of less than 1 year duration, preoperative pain localized on the left iliac fossa, and barium-enema findings consistent with diverticulitis were all statistically significant indicators of

better postoperative results. The authors concluded that "the overwhelming majority of patients who have proper surgical indications are improved by elective resection for diverticular disease". Stevenson et al.[29] published in 1998 a prospective study on 100 consecutive patients who had laparoscopically assisted anterior resection for diverticular disease. Indications to surgery was proposed to all patients more than 55 years of age who had at least two documented attacks of severe diverticulitis, to any patient who had complicated diverticular disease such as fistula or perforation, and to patients younger than 55 years of age who had at least one attack of diverticulitis. Eighty-two patients had acute episode(s) of diverticulitis, and 18 had complicated diverticular disease (colovesical/vaginal (10 patients) and perforation (8 patients)). At a median time of 37 months, 90 patients were available for follow-up. Eighty-four patients (93%) reported that operation had dramatically improved their symptoms that had been attributed to diverticular disease, while six patients stated that there was little improvement in their symptoms. Sixty-eight percent of patients reported that their bowel habit was more regular, 20% felt that their bowel habits remained unchanged, and 12% complained of worsened bowel habits. Again, it is quite relevant to observe that 18 patients (20%) complained of occasional hypogastric pains or bloating and that all these patients belong to the group of recurrent diverticulitis. Histological results were not reported. Moreaux et al.[30], reviewing 177 patients operated electively, found that sigmoidectomy was beneficial for 82% of the 72 patients who were operated for chronic symptoms, while 96% of the 49 patients who had complicated diverticular disease were free of postoperative complaints. As we can see, the quality of these long-term results, in particular on bowel function, are certainly related to the accuracy of the diagnosis and the pertinence in the indications to surgery where the best results are found in patients with complicated diverticular disease. To our knowledge, our study is the first one exploring functional results after elective laparoscopic sigmoidectomy in patients whose acute diverticulitis was CT-proven in all cases. Histological analysis confirm the accuracy of the diagnosis by finding inflammation in every case. The long-term post-colectomy results after a mean follow-up of 40 months compare quite favorably with the results reported in the literature. The finding that patients with acute inflammation on histology did better than the patients with chronic inflammation is a pure observation and does not have a clear explanation. The shorter delay between the last acute attack of diverticulitis and the greater proportion of patients still reporting occasional abdominal pain at the time of operation might be partially supporting this finding. Finally, it should be added that technical aspects of colonic resection, in particular, complete or partial removal of the sigmoid and anastomosis on the rectum, might probably influence the quality of these results, although these facts have yet never been demonstrated in the literature. Some legitimate fear could be put forward when Thaler et al.[31], comparing laparoscopic to open surgery with 79 patients in each group, found four statistically significant differences between the two procedures. Comparison between laparoscopic and open procedure showed that splenic flexure was less often taken down (24 vs 52%), length of the specimen was shorter (16.1± 5.5 cm vs 18.3±4.1 cm), proximal resection margin was histologically more often inflamed (27 vs 5%), and distal resection margin had less often histological presence of taenia (5 vs 70%). These findings are quite worrying when we observe that 27% of laparoscopically treated patients had incomplete resection of the sigmoid, and 70% of the open treated patients had a colocolic and not a colorectal anastomosis! This incomplete removal of the sigmoid is also reported in the study of Benn et al.[32] on 501 patients operated between 1970 and 1975: in 271 patients (54%), the proximal anastomosis was on the sigmoid colon, and in 321 patients (64%), the distal anastomosis was on the sigmoid colon!

Conclusion

Surgical removal of all the sigmoid and diagnostic accuracy of diverticulitis, which lies on CT-proven demonstration of the diverticular inflammation and secondary well-established indications to elective surgery probably play a major role at reaching the best long-term postoperative results in terms of bowel function, abdominal symptoms, and patients' overall satisfaction.

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Intra-abdominal Esophageal Duplication Cysts: A Review

Niels D. Martin · Judith C. Kim · Sachit K. Verma · Raphael Rubin · Donald G. Mitchell · Diane Bergin · Charles J. Yeo

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Abstract Esophageal duplication cysts (EDCs) are well described within the literature, normally occurring within the mediastinum. Intra-abdominal EDCs are rare and typically occur near the intra-abdominal esophagus. Herein, we describe two cases of intra-abdominal EDCs: a 60-year-old man who was incidentally found to have a retro-duodenal cystic mass and a 50-year-old woman with a cystic lesion near the body and tail of her pancreas causing left flank pain. Both patients underwent enucleation of their respective masses. Pathology revealed ciliated pseudostratified columnar epithelium with scattered mucus-secreting cells and two smooth muscle layers in the cyst wall of both patients, consistent with EDCs. Although intra-abdominal EDCs have been reported in the literature, our two cases and a review of the literature indicate that these lesions are not always adherent to or even near the intra-abdominal esophagus.

Keywords Esophageal duplication cysts · Intra-abdominal EDC · Intra-abdominal esophagus

Introduction

Esophageal duplication cysts (EDCs) are formed by either incomplete embryologic recanalization (coalescence of vacuoles) or atypical blastogenesis of the primitive foregut, usually in the fifth to eighth weeks of gestation.[1–3] In general, they are found adjacent to the thoracic esophagus, the majority being localized to the region around the distal thoracic esophagus. Commonly, most cases are diagnosed in early childhood.[4]

EDCs and bronchogenic cysts are two closely related anomalies both in histology and location. Many early reports of bronchogenic cysts may have actually been EDCs. Both EDCs and bronchogenic cysts contain ciliated columnar epithelium. However, whereas bronchogenic cysts contain cartilage or respiratory glands, EDCs do not contain cartilage or respiratory glands, and are lined with two smooth muscle layers.[5,6] Most literature on the subject of EDCs has focused on mediastinal cysts, which arise in the thorax and tend not to communicate with the esophageal lumen (approximately 90% of cases).[6] In most adult cases of EDCs, the mass is asymptomatic and is usually discovered incidentally.[1] However, when symptoms do exist, the most common are dysphagia and pain.[1] The purpose of this manuscript is to present two new cases of intra-abdominal EDCs and to underscore the observation that these cysts are not always in proximity to the esophagus.

Clinical Material

Case 1 A 60-year-old Caucasian man presented 3 years prior to admission with complaints of occasional nausea and mild diffuse abdominal pain. A CT scan revealed a 7×

N. D. Martin · C. J. Yeo
Department of Surgery, Thomas Jefferson University, Philadelphia, PA, USA

J. C. Kim · R. Rubin
Department of Pathology, Thomas Jefferson University, Philadelphia, PA, USA

S. K. Verma · D. G. Mitchell · D. Bergin
Department of Radiology, Thomas Jefferson University, Philadelphia, PA, USA

C. J. Yeo (✉)
Department of Surgery, Jefferson Medical College, 1015 Walnut St., Suite 620, Philadelphia, PA 19107, USA
e-mail: charles.yeo@jefferson.edu

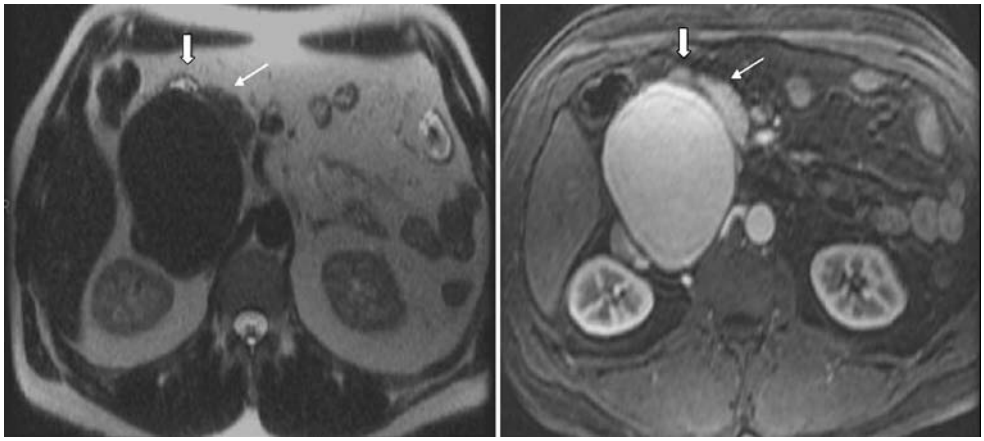

Figure 1 MR images from case 1: Axial T2-weighted (*left*) and contrast-enhanced T1-weighted gradient echo images (*right*) reveal a large atypical retroperitoneal nonenhancing cystic lesion displacing the head of the pancreas (*narrow arrows*) and compressing the second part of duodenum (*wide arrows*) anteriorly.

7-cm cystic mass arising posterior to the duodenum in the retroperitoneum. The lesion was initially observed; however, over the following 3 years, the mass enlarged and the patient developed vague postprandial epigastric pain and symptoms of gastric outlet obstruction. Magnetic resonance imaging (MRI) at that time showed marked compression and displacement of the second part of the duodenum and head of the pancreas anteriorly (Fig. 1). He had no history of jaundice or pancreatitis, but did report a 20-lb weight loss over the past year.

At the time of operation he was found to have a 10-cm cystic lesion in the retro-peritoneum, dorsal to the second portion of the duodenum and the pancreatic head. The duodenum was displaced anteriorly by the mass. With a Kocher maneuver, the mass was separated from the duodenum and pancreatic head. The cystic lesion was easily dissected away from the surrounding structures including the transverse colonic mesentery, Gerota's fascia, and the portal structures. Posteriorly, there were no major attachments to the aorta or vena cava, but the mass did appear to arise from the aorto-caval groove. Small bridging vessels from surrounding soft tissues were noted circumferentially, but no specific blood supply was noted. The cystic mass was removed intact and sent for pathologic evaluation. The patient was discharged on postoperative day 3 and recovered without incident.

Case 2 A 50-year-old, otherwise healthy, woman presented with a several-month history of progressive left-sided flank pain. She denied any history of pancreatitis or prior GI pathology. On contrast-enhanced CT imaging, a 6×5-cm cystic mass was noted either within or adjacent to the body and tail of the pancreas (Fig. 2). With the obvious concern for a cystic neoplasm (potential for premalignancy or actual malignancy), she was brought to surgery.

At celiotomy, she was found to have a 6.5×5.5×4.2-cm mass between and thinly adherent to the inferior portion of

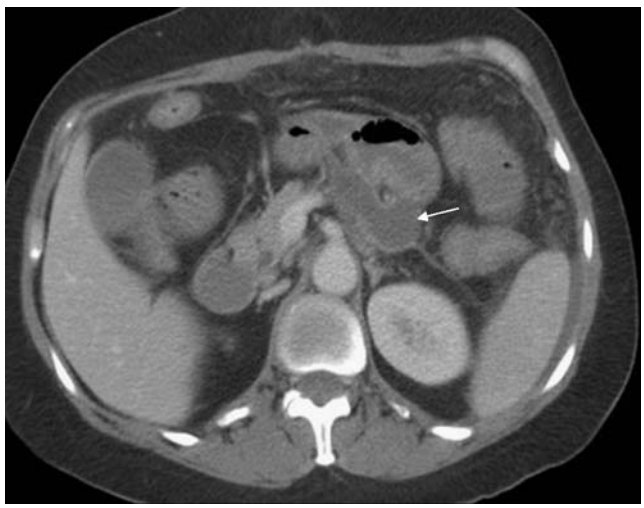

Figure 2 CT images from case 2: Contrast-enhanced CT scan reveals an irregularly shaped, rim-enhancing cystic structure (*arrow*) beneath the body and tail of the pancreas.

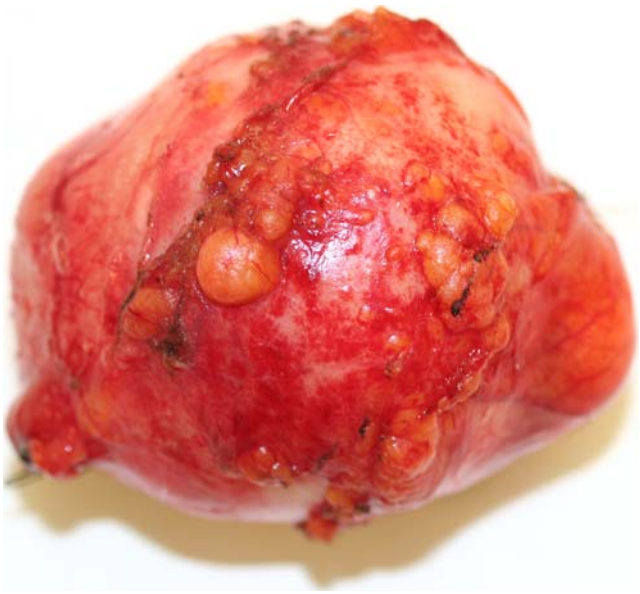

Figure 3 The cyst cavity is filled with abundant viscous, yellow, mucinous material (case 2).

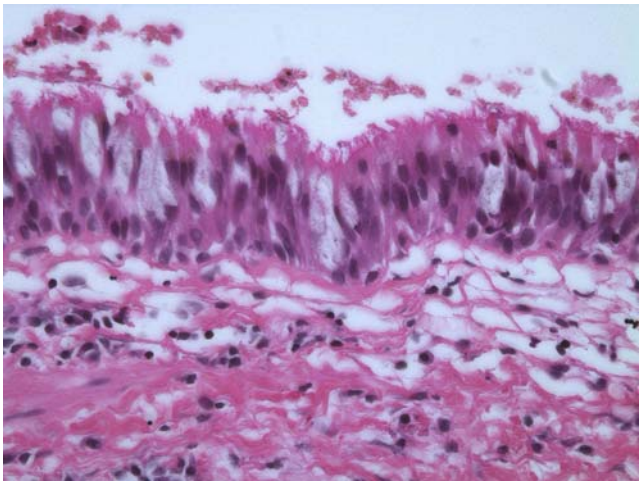

Figure 4 The cyst lining demonstrates ciliated pseudostratified columnar epithelium with scattered mucus-secreting cells (case 1, H+E; magnification=400×).

the pancreatic body/tail and the transverse mesocolon. There was no evidence of any true origin from the pancreas. The mass was enucleated from the surrounding structures, dividing small vascular pedicles, and was sent to pathology. The patient recovered slowly following cyst enucleation and required readmission and laparotomy for a partial mechanical small bowel obstruction. She has subsequently fully recovered.

Pathology The specimens consisted of unilocular, ovoid cystic masses, ranging in size from 6.5 to 8.5 cm in greatest dimensions. The outer surfaces were smooth and pink-tan to red (Fig. 3). In the first case, the cyst contained viscous, brown material, which was adherent to the smooth, tan mucosal lining. The second case revealed abundant, thick, yellow, mucinous cyst contents and mucoid mucosal excrescences on an otherwise smooth, tan mucosa. The cyst walls ranged from 0.1 to 0.5 cm in thickness.

Histologic examination of case 1 demonstrated a ciliated pseudostratified columnar epithelial lining with scattered mucus-secreting cells (Fig. 4). A portion of the epithelium was denuded with associated hemosiderin deposition and chronic inflammation; changes indicative of old hemorrhage, which accounted for the brown appearance of the cyst contents. Ciliated and nonciliated pseudostratified columnar epithelium was seen in case 2. In addition, simple columnar epithelium with more conspicuous mucin was present. Furthermore, partially denuded epithelium, chronic inflammation, and calcifications were identified. There was no evidence of epithelial cytologic atypia or complex architectural patterns in either case. The surrounding cyst walls were composed of two perpendicularly arranged smooth muscle layers (Fig. 5). No cartilage or seromucous glands were identified.

Discussion

Classically, Palmer's pathologic criteria for esophageal cysts were used to differentiate the cysts in this manuscript from other cysts. These criteria included (1) attachment to the esophageal wall, (2) presence of gastrointestinal tract epithelium, and (3) presence of two layers of muscularis propria. It should be noted that intra-abdominal esophageal duplication cysts do not require Palmer's first criterion of attachment to the esophageal wall.[7] In fact, as in both our cases, intra-abdominal EDCs do not need to have contact with any luminal gastrointestinal viscus. Our diagnosis of EDC was based on the classic finding of a ciliated pseudostratified columnar epithelium in association with a two-layer smooth muscle wall as described in the literature.[2,3,5,6,9]

Both computerized tomography (CT) and MRI offer excellent soft tissue contrast and multiplanar imaging capabilities to identify such cysts. MRI may allow for better preoperative evaluation of soft tissue masses to allow for differentiation between benign or malignant tissue and other potential associated abnormalities.[8] However, recent literature has supported the increasing use of endoscopic ultrasound (EUS) for an even higher level of resolution to facilitate diagnosis.[1,6,9,10] In the future, EUS may have even more utility. Imaging is also essential to rule out additional lesions. Complete imaging of the GI tract is recommended (via CT or MRI) so as to avoid a second incidental lesion from going undetected.[3]

The differential diagnosis of intra-abdominal parapancreatic cystic lesions includes pancreatic pseudocyst, serous cystadenoma, cystadenocarcinoma, mucinous cystic neoplasms, retention cysts, dermoid cysts, cysts associated with von-Hippel–Lindau syndrome and polycystic kidney disease, lymphoepithelial cyst, congenital cysts, cystic neuro-

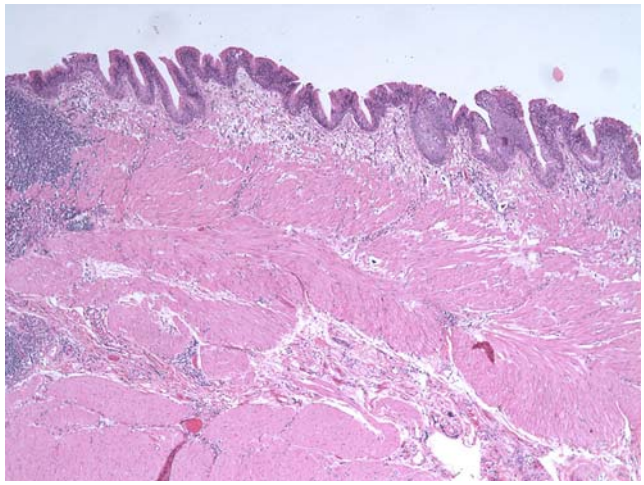

Figure 5 The cyst wall is composed of two smooth muscle layers and is lined by epithelium. Foci of chronic inflammation are present. Cartilage and seromucous glands are not identified (H+E, magnification=40×).

Table 1 Published Case Reports on Intra-Abdominal Esophageal Duplication Cysts

Reference	Year	Age	Sex	Presentation	Location	Size	Operative Procedure
Martin et al.	2007	60	M	gastric outlet obstruction	Retro-duodenal	10 cm×10 cm	Enucleation
Martin et al.	2007	50	F	left flank pain	inferior to pancreatic tail	6.5×5.5×4.2 cm	Enucleation
[6]	2003	51	F	Incedental	diaphragmatic crura	4.5 cm×4 cm× 3.5 cm	Enucleation with esophageal repair
[4]	1998	56	F	Incedental	superior to left kidney	8 cm×6 cm×4.5 cm	Biopsy only*
[5]	1997	51	M	epigastric pain, dysphagia	sub-diaphragmatic	11 cm×9 cm×8 cm	Esophagogastrectomy
[3]	1996	57	F	epigastric pain	near celiac access	2 cm×2 cm	Enucleation
[12]	1989	38	F	epigastric pain, nausea	distal esophagus	4 cm	Enucleation with esophageal repair

*only reported procedure in case report
(The pathology in all the above cases showed ciliated pseudostratified columnar epithelium and a two layer muscular wall)

endocrine neoplasia, and others. EDCs can also be associated with other congenital anomalies. In the chest, cystic lung abnormalities such as intrapulmonary bronchogenic cysts, sequestrations, and bronchiectasis have been described.[11] For all EDCs, appropriate investigations to rule out vertebral anomalies should be initiated upon diagnosis as well. These include scoliosis, hemivertebrae, and spina bifida.[4,8] These all occur as a result of incomplete fusion of the vertebral mesoderm.

Complete surgical excision has been the treatment of choice for all EDCs, whether symptomatic or incidental.[2,3,8] This is based on the potential for compression of adjacent organs, perforation with or without bleeding, and the risk of cancer. In general, the risk of an EDC harboring a malignancy is low, but EDC with cancer has been described in the literature. Tapia and White described a case of squamous cell carcinoma arising from a distal esophageal inclusion cyst.[2]

Table 1 presents a summary of the reported experience with intra-abdominal EDCs including the two present cases. The first reported case was published in 1989. The patients range in age from 38 to 60 years. Five were female and two were male. Two patients presented with incidentally found masses. Three others presented with epigastric pain. Most intra-abdominal EDCs were located near the intra-abdominal esophagus, if not adherent to it. Two actually required esophageal repair after resection and one required esophagogastrectomy. All showed the characteristic ciliated pseudostratified columnar epithelium and a two-layer smooth muscular wall. In addition, one of the present cases demonstrated pseudostratified and simple columnar epithelium with conspicuous mucin. It is known that EDCs may display a variety of epithelial cell types, including squamous or a mixture of any of the above types.[5] EDCs are differentiated from bronchogenic cysts by the absence of cartilage or respiratory glands in EDCs and the presence of two smooth muscle layers.

In conclusion, intra-abdominal EDCs are extremely rare, especially when not in contact with the intra-abdominal esophagus. Diagnosis can be suspected preoperatively based on the use of CT, MRI, or EUS. Moreover, additional duplication cysts and associated malformations can be assessed with these modalities. Complete surgical resection is recommended for all cases to alleviate the risk of compression of adjacent structures, perforation, and the small risk of harboring an occult malignant neoplasm.

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Laparoscopic Medial-to-lateral Colon Dissection: How and Why

Alessio Pigazzi · Minia Hellan · Douglas R. Ewing · Benjamin I. Paz · Garth H. Ballantyne

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Abstract Laparoscopic colectomy is a difficult procedure with a long learning curve. We describe in this study our technique for right- and left-sided laparoscopic medial-to-lateral colectomy. The medial approach involves division of the vascular pedicle first, followed by mobilization of the mesentery toward the abdominal wall, and finally freeing of the colon along the white line of Toldt. This approach allows immediate identification of the plane between the mesocolon and the retroperitoneum and renders the dissection fast and safe. Our series of 50 consecutive laparoscopic colectomies supports this concept. We believe that surgeons familiar with this technique will have an important tool in their armamentarium to circumvent some of the challenges of laparoscopic colectomy.

Keywords Laparoscopic colectomy · Medial approach · Technique

Introduction

Despite its increasing popularity, laparoscopic colectomy is a difficult procedure with a long learning curve.[1] Mastery of different techniques for laparoscopic colon mobilization may help surgeons take on operations of increasing complexity and possibly avoid complications. The medial approach involves division of the vascular pedicle first, followed by mobilization of the mesentery toward the abdominal wall, and finally freeing of the colon along the white line of Toldt. Most surgeons with little experience in laparoscopic colectomy are not familiar with this technique because open colectomies are commonly performed using a lateral-to-medial approach, in which the white line of Toldt is incised first and the vascular pedicles divided last.

Realizing that the medial dissection method has some important potential advantages, an International Consensus Conference sponsored by the European Association of Endoscopic Surgeons (EAES) issued a statement recommending that laparoscopic colectomy be undertaken using the medial-to-lateral method.[2] With the medial approach the dissection is usually very quick, mostly blunt, and greatly aided by CO_2 insufflation. The only retraction needed is the upward elevation of the mesentery. It is quite easy to remain in the proper plane by following the fine areolar tissue, which connects the mesocolon to the retroperitoneum. This, in turn, may help reduce potential injuries to retroperitoneal structures such as ureters and gonadal vessels. Another important advantage of the medial-to-lateral approach is that the tumor-bearing area is manipulated less and only at the end of the procedure after the vascular pedicles have been divided.

Only a few detailed descriptions of laparoscopic medial-to-lateral dissection can be found.[3–5] In this article, we describe our techniques for right- and left-sided laparoscopic medial-to-lateral colectomy. Special emphasis is placed on our left-sided approach involving the inferior mesenteric vein (IMV) as the initial landmark for dissection. We also present our postoperative outcome data since adopting this approach at City of Hope National Cancer Center.

A. Pigazzi (✉) · M. Hellan · B. I. Paz
Department of General and Oncologic Surgery,
City of Hope National Cancer Center,
1500 East Duarte Road, Duarte, CA 91010, USA
e-mail: apigazzi@coh.org

D. R. Ewing · G. H. Ballantyne
Department of Surgery, Hackensack University Medical Center,
30 Prospect Avenue, Hackensack, NJ 07601, USA

Technique

Medial-to-lateral Approach for Right Colectomy

The medial-to-lateral approach for right colectomy takes advantage of the ileocolic pedicle as the landmark under which the mobilization is carried out. Port placement for right colectomy involves a camera port C (10 mm) halfway between the pubic symphysis and the xiphoid. A 10- to 12-mm stapling port (T1) is placed roughly halfway between C and the anterior superior iliac spine in the left lower quadrant. One 5-mm port (T2) is placed approximately 15 cm cephalad of T1 in the left upper abdomen and a second 5-mm port (T3) between C and the pubic symphysis (Fig. 1). The key landmark for medial-to-lateral right colectomy is the ileocolic pedicle, which can be seen in most patients traveling from the superior mesenteric artery medially toward the cecum laterally. When doubt exists as to the exact location of this structure, we find it useful to gently place tension on the mesentery by grasping the fat around the ileocecal area and retracting it anterolaterally. This maneuver usually stretches and elevates the ileocolic vessels (Fig. 2a). To begin the dissection, the peritoneum covering the pedicle is gently scored just under the vessels. Usually cautery is not necessary at this point of the operation and instruments can be used bluntly (Fig. 2b). The areolar plane between the mesocolon and the retroperitoneum is thus exposed and developed for several centimeters. The duodenum should appear in the retroperitoneum just under the elevated ileocolic pedicle. Subsequently, a window is created around the vessels, which can be divided with a stapler, clips, or a bipolar coagulation device. At this point the right mesocolon is held upward by the assistant and the operator uses two instruments to carry out a gentle blunt dissection. The dissection is first carried laterally toward the abdominal wall and then continued superiorly under the transverse mesocolon, over the duodenum and the head of the pancreas. In the majority of patients a right colic branch is not identified when the ileocolic pedicle is divided very near the origin. The middle colic vein and the right branch of the middle colic artery can be identified and divided intracorporeally. The omental attachments are freed along the transverse colon, and the hepatic flexure can be taken down using a combination of medial-to-lateral and lateral-to-medial approaches. After freeing the attachments of the terminal ileum, the proximal and distal bowel may be divided intracorporeally or extracorporeally via a minilaparotomy, and an anastomosis created according to the surgeon's preference.

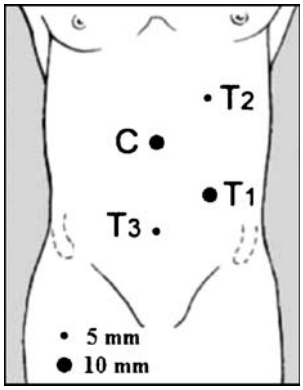

Figure 1 Localization and size of trocars for laparoscopic right colectomy. C = Camera port, T1–T3 = working ports.

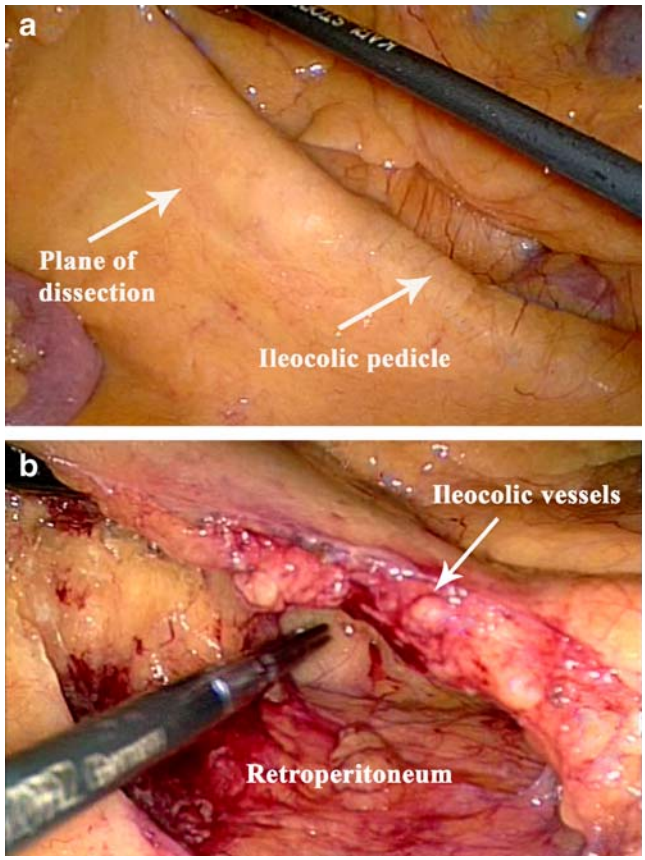

Figure 2 **a** By distracting the mesentery upward and laterally the ileocolic pedicle is easily visible traveling in a diagonal fashion toward the upper cecum (arrow). The second arrow marks the plane where the peritoneum covering the pedicel has to be opened. **b** After incision of the peritoneum along the ileocolic vessels blunt dissection along the areolar plane between mesocolon and retroperitoneum frees the vessel pedicle for division.

Medial-to-lateral Approach for Left and Sigmoid Colectomies

The medial approach to the left and sigmoid colon is usually more difficult. Starting the operation under the origin of the inferior mesenteric artery (IMA) as originally described by Fazio et al.[3] can be difficult because the origin of the IMA is often short and difficult to visualize in dense mesocolic fat. For this reason we favor a different approach utilizing the IMV as the initial anatomic landmark. The

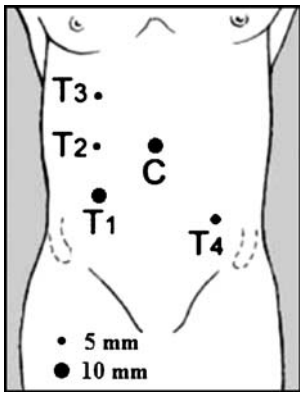

Figure 3 Localization and size of trocars for laparoscopic left or sigmoid colectomy. C = Camera port, T1–T4 = working ports.

main advantage of this method is that the IMV is virtually always visible and provides a very reliable guide for a medial-to-lateral mobilization of the left and sigmoid colon. The principles of this approach have been described in the Italian literature by Sartori and Franzato,[4] but this technique has not been embraced by American surgeons nor ever been described in the English literature.

The camera port C is placed halfway between the xiphoid and the pubic symphysis, and the 10- to 12-mm stapling port T1 is placed roughly halfway between C and the anterior superior iliac spine in the right lower abdomen. One 5-mm port (T2) is placed 10 cm above T1 and the second 5-mm port (T3) 10 cm above T2. An additional port T4 may be placed in the left midabdomen to aid in splenic flexure takedown (Fig. 3). Both the surgeon and the assistant stand on the patient's right side. The surgeon utilizes ports T1 and T2, whereas the assistant will have the camera and T3. With the patient in Trendelenburg position and the left side elevated, the small bowel is moved out of the pelvis. There are three steps in this dissection:

(1) Exposure of the IMV

To expose the IMV the ligament of Treitz and the loose attachments between the proximal jejunum and the transverse mesocolon may have to be divided sharply so that the small bowel can be retracted toward the right upper quadrant (Fig. 4a). Having the patient in a fairly steep Trendelenburg position and with the left side elevated is particularly helpful in this step. A 30° camera is also desirable to obtain adequate exposure.

(2) Development of the medial-to-lateral dissection plane

Next, the peritoneum just under the vein is incised, and the space between the mesocolon and Toldt's fascia is developed toward the abdominal wall (Fig. 4b). At this point the 30° camera is turned to look slightly upward and the tunnel between the mesocolon and Toldt's fascia is easily seen. To avoid traction injuries we recommend early division of the IMV near its insertion posterior to the pancreas where the IMV is azygous, traveling without a paired artery. More distally, the IMV runs parallel to the

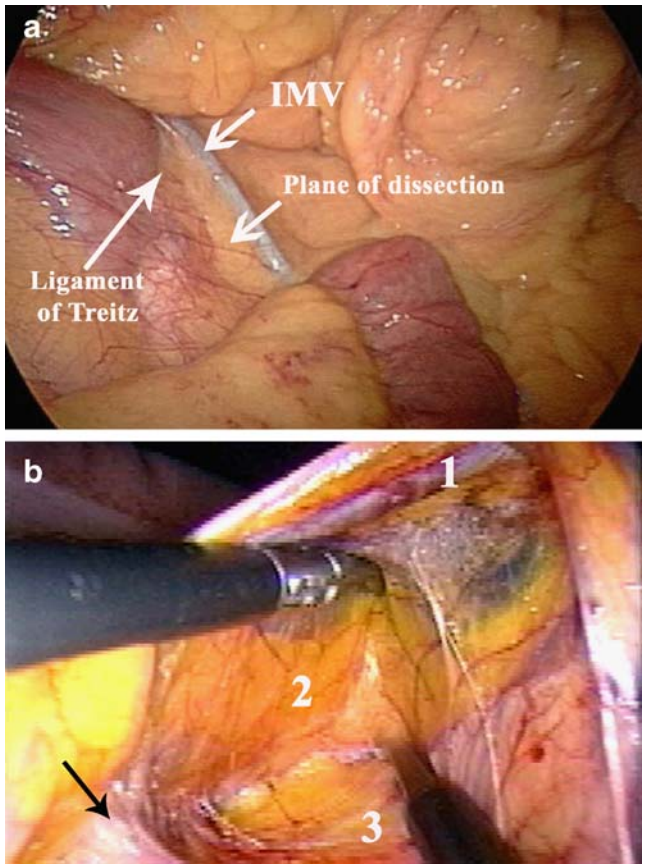

Figure 4 **a** Exposure of the inferior mesenteric vein (IMV) and the ligament of Treitz by retracting the small bowel toward the right upper quadrant and the transverse mesocolon superiorly. The plane of dissection is directly under the IMV as marked by the arrow. **b** After incision of the peritoneum as shown in subpanel **a**, blunt dissection toward the abdominal wall is carried out to free the mesocolon. 1 = IMV, 2 = descending mesocolon, 3 = retroperitoneum with Toldt's fascia, arrow = proximal jejunum.

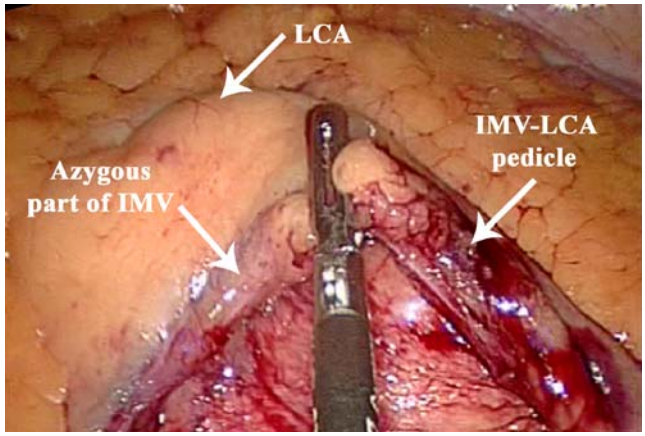

Figure 5 Before the inferior mesenteric vein (IMV) disappears under the pancreas it travels without a paired artery as the azygous part of the IMV. The left colic artery (LCA) has left the IMV to travel laterally.

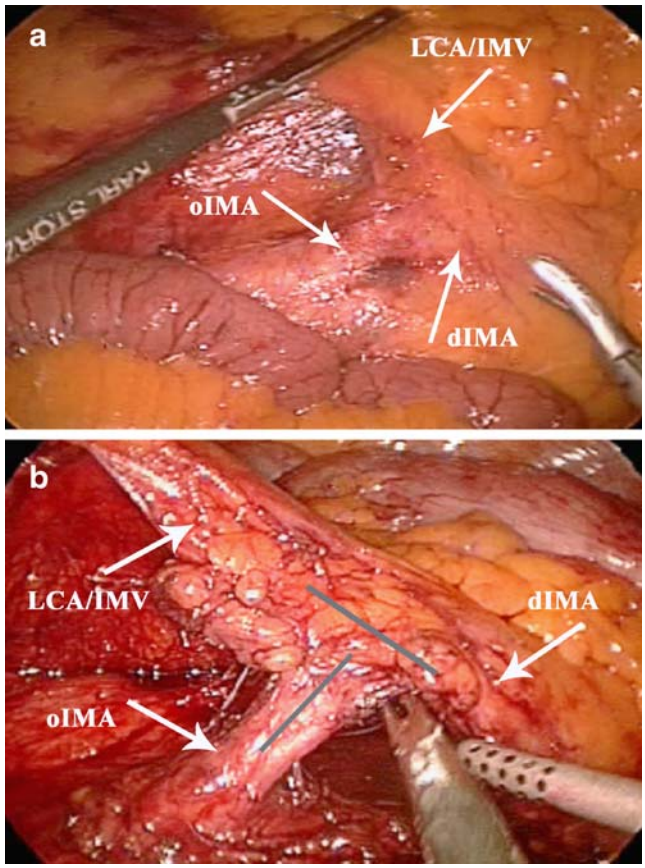

Figure 6 **a** By following the LCA/IMV pedicle caudally the main trunk of the IMA (oIMA) can easily be identified. It divides in a T-shape fashion giving off the LCA and continuing as distal IMA (dIMA). **b** After dissection the T of the IMA becomes even clearer visible and can now be easily and safely divided. LCA = Left colic artery, IMV = inferior mesenteric vein, oIMA = origin of inferior mesenteric artery, dIMA = distal inferior mesenteric artery.

upward traveling left colic artery (Fig. 5). Therefore, the IMV/left colic artery pedicle should be followed inferiorly and freed from its posterior attachments to the aorta until the origin of the IMA is encountered.

3) Division of the IMA

When the IMV/left colic artery pedicle is followed caudally, the origin of the IMA from the aorta is usually easily identified. The origin of the IMA, the left colic artery, and the distal IMA form a characteristic "T-shaped" structure (Fig. 6). Therefore, one can easily divide either the left colic artery or the IMA at the origin or distal to it, depending on the particular case and individual preference. After the medial-to-lateral dissection is completed as far laterally as possible, the white line of Toldt is incised and the colon freed from its attachments to the abdominal wall and medialized. Division of the bowel and anastomosis may now be performed intra- or extracorporeally according to the particular case and surgeon's preference.

Results

At City of Hope National Cancer Center we have adopted the medial-to-lateral dissection for laparoscopic colectomy starting in September 2004 after a trained laparoscopic surgeon (AP) joined our surgical staff and preceptored other surgeons in this technique. We have since offered a laparoscopic approach to all patients regardless of previous surgery, body mass index, or type of pathology. The only contraindications to laparoscopic colectomy were inability to tolerate pneumoperitoneum or a tumor invading adjacent structures. All data were prospectively entered into a colorectal database. For the purpose of this analysis we examined data for all right (N=27), sigmoid (N=16), and left (N=7) colectomies performed between September 2004 and March 2006. Of these 50 patients 21 were female, 19 had previous abdominal surgeries, 35 were operated for cancer, and 15 were operated either for polyps or diverticulosis. The medial-to-lateral technique was successfully applied in all cases. There were 6 conversions out of the 50 cases, for a total conversion rate of 12%. We encountered no mortalities and our total complication rate was 12%. Minor complications included three wound infections. There was only one anastomotic leak in the sigmoid colectomy group, which was treated with reoperation and temporary diversion. Operative times, blood loss, and complications can be seen in Table 1. There is no significant difference in any of the parameters examined between right- or left-sided colectomies.

Table 1 Operative Outcomes

	Right, N=27	Sigmoid, N=16	Left, N= 7
Blood loss (ml)[a]	100 (30–300)	125 (50–600)	200 (100–3,000)
Operative time (min)[a]	180 (60–320)	233 (132–396)	219 (164–269)
Lymph nodes[a]	16 (7–30)	10 (0–30)	12 (6–22)
Hospital stay (days)[a]	3.5 (2–12)	3 (2–6)	4 (3–7)
Minor complications	1	1	1
Major complications	0	2 (1 respiratory failure, 1 leak)	1 (hemorrhage)

[a] Median values

Discussion

Laparoscopic colectomy has many short- and long-term advantages but remains a challenging procedure for inexperienced surgeons. Maneuvers to limit conversions and complications ought to be emphasized and taught to novice laparoscopic surgeons. The medial-to-lateral approach allows immediate identification of the plane between the mesocolon and the retroperitoneum and renders the dissection fast and safe. Our series of 50 consecutive right, left, and sigmoid laparoscopic colectomies supports the concept that this approach results in low conversion rates, blood loss, and overall complication rates.

There is only one randomized prospective trial comparing the medial-to-lateral and the lateral-to-medial technique in patients undergoing laparoscopic rectosigmoid resection for cancer.[5] The authors found that the medial-to-lateral approach resulted in shorter operative times, lower costs, and reduced proinflammatory response parameters such as C-reactive protein and erythrocyte sedimentation rate postoperatively. In addition, complications and recurrence rates were similar in both groups.

With respect to the potential oncologic benefit of a medial-to lateral dissection, the theory that early ligation of the blood supply of the colon may have clinical implication in terms of tumor dissemination dates back over half a century. In 1952 Barnes popularized the "physiologic" resection of the right colon, emphasizing early division of the mesentery and bowel and late handling of the tumor.[6] Subsequently, Turnbull et al.[7] developed the so-called "no-touch technique," which he applied to all segments of the colon stressing the possibly detrimental role played by the surgeon's hands in cancer dissemination. He advocated that the tumor-bearing area should not be manipulated until the lymphovascular pedicles are ligated and the colon is divided. Turnbull et al. reported improved survival for colon cancer patients operated on with his no-touch technique compared with conventional surgery, especially for patients with stage III disease, but his data was entirely retrospective and has been questioned over the years. Currently, the no-touch technique is controversial. A randomized trial comparing no-touch resection with conventional surgery during open resection has failed to show a similar advantage although there was a trend toward shorter time to recurrence and an increase in the number of distant metastases in the conventional surgery group. This was particularly true with advanced tumors.[8] It is interesting that in the laparoscopic literature the randomized prospective trial by Lacy et al.[9] comparing open colectomy to laparoscopic colectomy has shown a statistically significant increase in disease free survival for stage III cancers operated on laparoscopically. Although the survival advantage may be because of a variety of reasons, it is noteworthy that the laparoscopic technique entailed a medial-to-lateral technique, whereas in open surgery a conventional lateral-to-medial technique was employed (A. Lacy, personal communication).

Whether there are any true oncologic advantages to the medial-to-lateral approach in laparoscopic operations for colon cancer still remains to be determined. Nevertheless, we agree with the EAES consensus statement that the medial-to-lateral technique should be the preferred approach for laparoscopic colon dissection. Surgeons familiar with this technique will have an important tool in their armamentarium to circumvent some of the challenges of laparoscopic colectomy.

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Assessment of Pancreatic Neoplasms: Review of Biopsy Techniques

Steven B. Goldin · Michael W. Bradner · Emmanuel E. Zervos · Alexander S. Rosemurgy II

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Abstract Pancreatic cancer is the 4th leading cause of cancer death annually. Recent technological advances in imaging have led to non-uniformity in the evaluation of pancreatic neoplasms. The following article describes the history behind various biopsy techniques and the rationale for obtaining a biopsy of a pancreatic neoplasm and discusses the benefits and disadvantages of the various pancreatic biopsy techniques, including fine needle aspiration biopsy, Tru-cut needle biopsy, endoscopic brushings/cytology, and endoscopic ultrasound guided biopsies. A treatment algorithm for pancreatic neoplasms is then presented.

Keywords Pancreatic neoplasms · Pancreatic cancer · Biopsy

Introduction

Approximately 28,000 people die from pancreatic cancer each year, making this malignancy the fourth leading cause of cancer death.[1] The majority of patients with pancreatic cancer have advanced disease at the time of diagnosis. Unfortunately, the only hope of cure lies with complete surgical resection, which is impossible in most patients. Evaluation of patients with pancreatic neoplasms involves characterizing the lesion and determining resectability by delineating the extent of the tumor. For patients with cancers that involve contiguous spread into adjacent organs, invade or encase major vascular structures, or metastasize, only palliative treatment may be possible.

Patients who have potentially resectable tumors should be assessed for their ability to undergo a major abdominal operation. Given acceptable operative risk, they should then undergo imaging studies aimed at determining the feasibility of resection. The rapid growth of technology has made a wide variety of imaging techniques available for the evaluation of pancreatic tumors and malignancies.[2–9] Treatment algorithms for malignant causes of biliary obstruction, including a pancreatic mass, are straightforward and based on radiographic staging (Fig. 1). Patients with low operative risk and imaging studies suggesting resectable lesions should undergo exploration. No histologic diagnosis is required prior to exploration for patients unless neoadjuvant therapy is considered. Obtaining a preoperative histologic diagnosis may risk or cause dissemination of disease, risk developing complications (e.g., pancreatic leak, pancreatitis), and increase costs. Furthermore, a biopsy not confirming cancer is typically ignored, due to a high false-negative biopsy rate. Operative exploration may begin laparoscopically in an attempt to better stage patients, particularly those with distant metastases. Laparoscopic staging is limited; however, it does not easily allow for evaluation of locally advanced disease. Unresectable disease found at celiotomy changes the operative plan to one of palliation.

Patients with disease initially deemed unresectable based on imaging studies should undergo biopsy if chemotherapy or radiotherapy is planned, as histopathologic diagnosis is required prior to beginning cytotoxic treatment. Biopsies should also be done when patients are suspected of having rare malignancies such as lymphoma, which would be better treated by alternative protocols. Likewise, preoperative biopsy might also be useful in patients with a history of

S. B. Goldin (✉) · M. W. Bradner · E. E. Zervos · A. S. Rosemurgy II
Department of Surgery, Tampa General Hospital, University of South Florida, Davis Island, P.O. Box 1289, Tampa, FL 33601, USA
e-mail: sgoldin@hsc.usf.edu

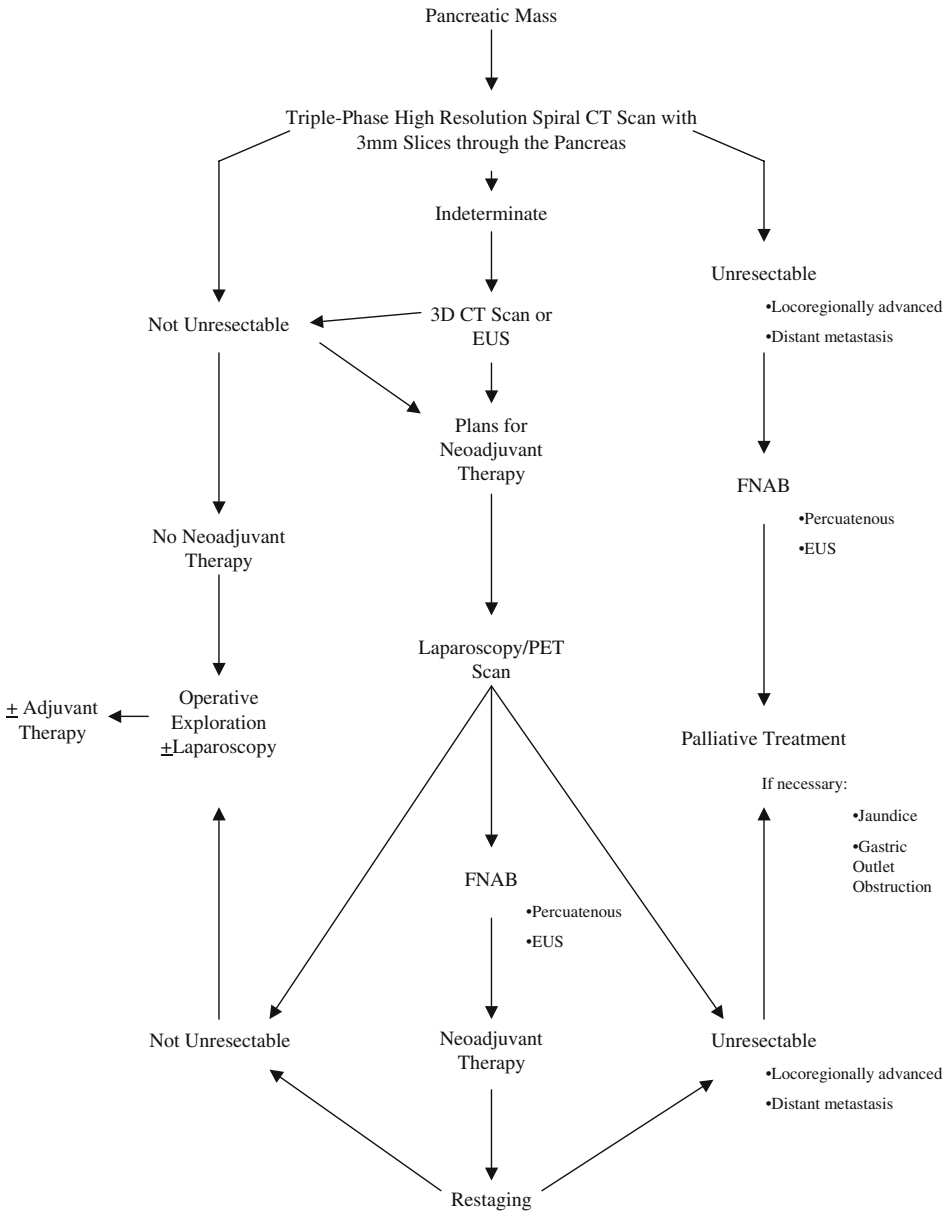

Figure 1 Algorithm for the evaluation of the patient with a pancreatic mass. Protocol treatment may require laparoscopy to stage intraperitoneal disease or PET scan to stage beyond locoregional disease.

Protocol Treatment may require: -Laparoscopy to stage intraperitoneal disease

-PET scan to stage beyond locoregional disease

another malignancy because appropriate treatment for metastatic disease to the pancreas may be nonoperative management. Preoperative biopsy is also warranted, however ill-advised, in patients with a pancreatic neoplasm who refuse surgical resection or exploration, unless there is a positive diagnosis of malignancy. A final group of patients that must undergo preoperative biopsy are those enrolled in neoadjuvant trials.[10,11] In the future, considerations of neoadjuvant therapy might be less of an indication, as other modalities like PET scanning might achieve adequate diagnostic accuracy and sensitivity.

Biopsy Techniques

Tissue for histologic analysis can be obtained by various biopsy techniques.[12] Kirtland first used the Vim–Silverman needle intraoperatively in 1951.[13] The Tru-Cut disposable needle has now replaced the Vim–Silverman needle when obtaining core biopsies. Of note, a core needle biopsy is a more accurate method of obtaining diagnostic tissue than a wedge biopsy of a pancreatic mass.[14] Fine-needle aspiration biopsy (FNAB) of pancreatic lesions was introduced in 1970.[15] FNAB has evolved since that time and can now be

performed percutaneously under ultrasound or CT guidance and, more recently, under the guidance of endoscopic ultrasound (EUS).

Proponents of FNAB suggest that the technique is easy to perform and has reasonable sensitivity and specificity that may prevent major operations for patients with malignancies other than pancreatic cancer, such as metastatic disease or lymphoma. These proponents cite an acceptable sensitivity and specificity for FNAB, with the sensitivity of FNAB ranging between 45 and 100%, and this technique has a specificity of nearly 100% in most studies, with accuracy ranging from 75–95%.[16,20,27–40]

Detractors of FNAB argue that the chance of diagnosing a malignancy other than pancreatic cancer is rare, only 1.6%.[16] They also argue that the sensitivity of FNAB varies widely, that optimal interpretation of the slides requires a pathologist interested and capable in cytology, that FNAB has a high cost of approximately $2,000, and that a negative FNAB result does not rule out cancer and, thereby, does not obviate operative treatment. Opponents also argue that although the mortality and morbidity of the procedure are low, they are measurable and range between 0.006–0.08% and 0.05–0.18%, respectively.[17–19] Complications of FNAB include acute pancreatitis, hemorrhage, pancreatic fistula, pancreatic abscess, pancreatic ascites, sampling error resulting in false negative or positive results (misinterpretation of biopsy slides), which may inappropriately effects treatment and cause intraperitoneal seeding of tumor.[20–25] Detractors of the procedure note that concomitant pancreatitis, cellular debris, necrotic material, blood in the specimen, and the presence of inflammatory cells may lower the sensitivity of the technique. In addition, the desmoplastic reaction surrounding many pancreatic cancers may alter the course of a biopsy needle, produce an acellular aspirate, or lead to a false-negative biopsy. Biliary and pancreatic ductal strictures may also result from extratumoral fibrosis with the majority of the tumor lying outside of the biopsy site. Unusual cytologic features may also make diagnosis by FNAB difficult. Lastly, sampling error is often significantly increased with small tumors; this is likely the most common cause of failure to diagnose malignancy with FNAB.[33] The sensitivity and specificity of FNAB are directly dependent upon tumor size. As well, the complication rate is directly dependent upon tumor size with larger tumors having lower complication rates.[23,26,27] Examining the risks, sensitivity, and specificity of the technique facilitates understanding why patients with resectable disease should not uniformly undergo biopsy prior to resection.

Detractors of FNAB strongly argue that a negative biopsy result does not prevent operative exploration but unnecessarily delays it and potentially complicates it, by dissemination of cancer or by causing pancreatitis or bleeding. A large number of patients with pancreatic cancers would not be eligible for resection if histologic proof of malignancy were a prerequisite. This is due to the relatively low sensitivity of FNAB seen in some of the studies mentioned previously. Tillou et al.[41] noted that 14.4% (14 of 97) of patients with known pancreatic cancer had a negative FNAB result. They also noted that the FNAB results collected on 18% of their patients (21 of 118) were disregarded when making management decisions. This is most notable in patients with smaller cancers where the sensitivity of FNAB is low. Unfortunately, this is when the lesion is more likely resectable and the delay of operative intervention may allow disease progression. Therefore, information gained by FNAB is often disregarded, although the risks and costs of the procedure are still incurred by the patient.

Lastly, one further risk of FNAB is that of seeding the peritoneal cavity or needle tract with malignant cells, eliminating any chance of surgical cure.[42] Prior to the development of the FNAB technique, core needle tract seeding was well documented for a variety of cancers other than pancreatic.[43–46] The first reported case of FNAB needle tract seeding of pancreatic cancer was by Ferrucci et al. in 1979,[47] who observed an abdominal wall implant of pancreatic cancer after the patient had undergone a CT-guided FNAB of his pancreatic lesion with a 22-gauge needle. There have now been multiple case reports of the seeding of FNAB needle tracts following the biopsy of a pancreatic mass (Table 1). The incidence of FNAB needle tract seeding in pancreatic cancer (0.003 and 0.009%) is thought to be higher than for other types of malignancies.[25] However, this quoted rate may be much lower than the true needle-tract-seeding rate for several reasons. First, an average of 4 months elapses between a FNAB and the development of metastases. Second, patients with diffuse metastases are often seriously ill and probably are not observed as closely as others without disseminated disease for the development of subcutaneous nodules. Third, patients with disseminated disease may die before needle tract seeding becomes apparent.[25] Lastly, it is difficult to determine the number of metastases to tissue between the tumor and the subcutaneous tissues because, once apparent, these patients often have disseminated disease not solely attributable to the FNAB procedure. This is important because, in theory, the majority of malignant cells shed from a needle are lost to tissues immediately surrounding the lesion and do not implant within the skin or subcutaneous tissue. Animal studies suggest that needle tract seeding might easily occur and that a single FNAB disseminates between 100 and 10,000 tumor cells along the needle tract.[48] It has been assumed that the majority of the tumor cells released by FNAB are destroyed by the host immune system or by other mechanisms, but this has not

Table 1 Needle Tract Seeding of Pancreatic Cancer Described in the Literature

Reference	Interval and Location of Recurrence	Needle Gauge
Ferrucci[25]	Subcutaneous nodules 3 months later	22 g, 20 needle passes
Smith[61]	Cutaneous nodule 3 months later	22 g, unspecified needle passes
Caturelli[9]	Peritoneal metastasis 2 months later	22 g, two needle passes
Burlefinger[7]	Cutaneous metastasis 6 months	21 g
Rashleigh-Belcher[52]	Cutaneous metastasis 6 months later	22 g, eight passes, and 19 g, one pass
Frohlich[27]	Cutaneous metastasis 2 months	19 g
Gebel,[71] Habscheid[32]	Cutaneous metastasis 5 months later	20 g
Weiss[74]	Unspecified	Unspecified
Weiss[73]	3 months	22 g
Bergenfeldt[3]	Subcutaneous metastasis 3 months	20 g, 2–3 needle passes
Yasuda et al.[80]	Unspecified	Unspecified

been substantiated.[25] The actual number of tumor cells disseminated by a FNAB is dependent upon the number of needle passes required to obtain the specimen, the location of the lesion, and the degree of tumor differentiation. Well-differentiated adenocarcinomas required a significantly higher number of aspirations (5.5) than those that were moderately (2.7), moderately to poorly (3.4), or poorly (2.3) differentiated.[49] Diagnosis of malignancy in lymph nodes and liver metastases on average takes 2–3 passes. When a cytopathologist is present for FNAB, the diagnostic yield increases by 10%. When a cytopathologist is not present, the general recommendation is to perform approximately five needle passes. Unfortunately, anywhere from one to ten passes may be required, with approximately 13% of patients requiring six or more passes. Therefore, to minimize the number of FNAB passes and maximize the histologic yield, a cytopathologist should be immediately available for cytologic review of the specimen.[49] A summary of these points can be found in Table 2.

Research has been undertaken in an attempt to determine whether performing FNAB preoperatively affects patient outcome. Warshaw et al. looked at peritoneal washings in patients with resectable pancreatic lesions based on CT. In this study, 75% of patients that underwent a FNAB had washings positive for malignant cells, whereas only 19% of patients that did not undergo FNAB had positive intraperiotneal washings.[21] Warshaw surmised that preoperative FNAB of potentially resectable lesions predisposed the patient to intraperitoneal spread. He also stated that patients with positive cytology had a significantly lower resection rate and survival than patients with negative washings. Warshaw's data, however, were not supported by his further study,[50] or those of Johnson et al.[42] and Leach et al.[51]. Johnson et al. and Leach et al. found no relation between previous FNAB and positive peritoneal fluid cytology among 32 patients and 60 patients, respectively. In hindsight, it would be doubtful that this methodology would have the sensitivity to detect differences in patients who underwent timely surgical procedures. However, finding no difference does not demonstrate that a small number of viable tumor cells are not disseminated to a new site where they can continue to grow. Whether FNAB actually predisposes a patient to dissemination of disease remains to be determined but may be related to the manner in which the specimen is obtained. While percutaneous FNAB may not predispose to tumor seeding and dissemination, it certainly has no beneficial actions in limiting these occurrences. In other words, it might not be so bad, but it certainly is not good, and the benefit of FNAB must outweigh potential harmful complications if it is to be undertaken.

EUS-guided FNAB has been suggested to be a safer, more accurate, and more sensitive method of obtaining tissue from a pancreatic lesion. EUS-guided FNAB was first reported in 1992[52] and developed to provide cytologic confirmation of malignancy.[53] Indications for EUS-guided FNAB have been summarized by Bhutani et al.[54]. The technique has mainly been used for obtaining a tissue diagnosis in patients with unresectable lesions not amenable to percutaneous biopsy due to tumor location. Others have suggested that EUS-FNAB should be used for

Table 2 Summary of Points Made by Proponents and Detractors of FNAB

Points
Proponents
Easily performed
Reasonable sensitivity and specificity
Prevention of unnecessary operative intervention
Detractors
Negative biopsy does not negate possibility of malignancy
Complications (i.e., acute pancreatitis, hemorrhage, pancreatic fistula)
Dissemination of disease
Cost
Delay of operative intervention
Variable sensitivity
Misinterpretation of biopsy
Necrotic debris
Unusual cell type
Inflammatory cells

lesions suspicious for cancer, which have no primary histopathological diagnosis, and for locoregional staging of confirmed cancer.[55] However, these indications are debatable because local nodal disease is not a contraindication to resection.

The sensitivity and specificity of EUS-guided FNAB of pancreatic lesions has been investigated and seems very operator-dependent. Williams et al. performed EUS-guided FNAB on 144 pancreatic lesions with 113 in the head, 17 in the body, 11 in the tail, and 3 in the ampulla. They noted a sensitivity of 72%, specificity and positive predictive values of 100%, a negative predictive value of 38%, and diagnostic accuracy of 76%. If atypical cytology was considered diagnostic for malignancy, the sensitivity and diagnostic accuracy increased to 82 and 85%, respectively; the specificity and positive predictive value remained at 100%; and the negative predictive value increased to 51%.[55] Others have noted sensitivities and specificities of EUS-guided FNAB of the pancreatic lesions between 64 and 90% and 85 and 100%, respectively.[54,56,57] EUS-guided FNAB assessment of lymph nodes status has also been investigated and has a sensitivity between 84 and 97%, a specificity between 75 and 100%, and an accuracy between 82 and 98%.[58,59] EUS-guided FNAB can be nondiagnostic in approximately 12% of patients,[60] and has an accuracy dependent upon the tumor type. This accuracy is higher for adenocarcinomas (81.4%) than for neuroendocrine (46.7%) tumors or other lesions (75%).[61] The positive predictive value of EUS-guided FNAB has been confirmed at 100% by operative exploration, autopsy, and clinical follow-up, whereas higher negative predictive values, between 67 and 86%, have been observed for lymph nodes and pancreatic lesions, respectively.[60] This casts a shadow over the procedure. The relatively low negative predictive value indicates that a patient in whom there is a high clinical suspicion of a pancreatic carcinoma, even in the face of a negative EUS-guided FNAB, should still undergo resection if able. Lastly, the ability of EUS-guided FNAB to accurately preoperatively stage pancreatic cancers has been evaluated by comparison to the operative stage.[62] Only 44% of patients had similar EUS-guided FNAB stages and pathologic stages, whereas 52% of patients were upstaged and 4% were downstaged as a result of resection. Therefore, although resectability may be determined, the EUS stage is often different from the pathologic stage.

In comparing EUS-guided FNAB to percutaneous FNAB, EUS-guided technique offers several theoretical advantages. EUS-guided FNAB has a shorter distance to the mass, the ability to continuously visualize the needle tip, and the ability to identify vascular structures with Doppler ultrasound. The main disadvantages of EUS-guided FNAB are the risks associated with conscious sedation and endoscopy. Although the benefits seem obvious, the overall complication rate of EUS-guided FNAB of pancreatic lesions appears to be in the range of 1–2%, with solid lesions having a significantly lower complication rate than cystic lesions.[63,64] This rate is higher than that for percutaneous FNAB of pancreatic lesions, although the types of complications seen are similar in both groups. However, it has been suggested that the risk of EUS-guided FNAB needle tract seeding might be lower and would be less consequential than that following percutaneous FNAB.[54] This hypothesis stems from understanding how the biopsy is obtained. During EUS-guided FNAB, a similar number of needle passes (approximately 3.4–4.4) is required when compared to percutaneous FNAB.[54,55,60,62,65] Lesions in the pancreatic head or neck, which are best visualized with the ultrasound transducer in the duodenal bulb, are biopsied through the duodenal wall. Because the duodenum is removed with the operative specimen, needle tract seeding to the duodenum should be inconsequential. Lesions in the pancreatic body or tail and celiac lymph nodes, however, are best visualized with the transducer in the stomach. Therefore, lesions must be sampled via a transgastric approach, often through the proximal stomach. This region is not resected with the specimen and therefore, the same protection afforded in lesions of the head is not present for more distal lesions.

Other methods of obtaining tissue for diagnosis exist. Endoscopic retrograde cholangiopancreatography (ERCP) has come to play a major role in patients with pancreatic cancer, particularly those that present with obstructive jaundice. Debate continues about whether patients with malignant biliary obstruction should be decompressed prior to operative intervention, and its usefulness as a biopsy technique has been questioned. Biopsies during ERCP can be done by multiple modalities, including direct tissue collection with FNA, cytologic brushings, or collection of pancreatic juice. In a study by Ferrari et al. in the early 1990s, the overall results for brush cytology were a sensitivity 56.2% and a specificity 100%.[77] However, in a more recent study by Wakatsuki et al., ERCP was compared with EUS in the evaluation of pancreatic mass without biliary stricture. Those patients that underwent ERCP were evaluated with cytologic brushing. The overall sensitivity of the brushings was 33.3% with a specificity of 100%, as compared to those undergoing EUS-FNA, where the sensitivity was 92.9% and a 100% specificity.[78] Therefore, the use of ERCP to obtain brushings for pathologic diagnosis was not advocated. Also of note, ERCP is not without complications. Post-ERCP is a well recognized complication of this procedure. In the above mentioned study, the incidence of postendoscopic pancreatitis was found to be 33% in the ERCP group compared with 0% in the EUS-FNA group. However, this complica-

tion rate is quite high when compared to other studies, which suggest a post-ERCP pancreatitis rate of 4.3%.[79]

Lastly, the dispute of intraoperative biopsy comes into question. While the intent of this article is to review the role of preoperative biopsy techniques, intraoperative biopsy of pancreatic masses should be addressed. At the time of operative intervention, a thorough search should be undertaken for evidence of locoregionally advanced and/or distant metastatic disease and any suspicious lesions should be biopsied. Schramm et al. have reported that FNAB of pancreatic masses intraoperatively have a sensitivity of 93.1% and specificity of 99.1%.[80] Also, when FNAB was compared with intraoperative excisional biopsy in 262 patients with pancreatic carcinomas, 244 carcinomas (93.1%) could be confirmed by cytologic (FNAB) examination, whereas only 205 carcinomas (78.2%) could be confirmed by histologic (excisional) examination. This demonstrates that intraoperative pancreatic biopsy should be done using FNAB if appropriate cytologic trained personnel are available to evaluate the specimen. In the absence of this, a Tru-Cut needle biopsy would be recommended.

Conclusion

Patients with pancreatic or periampullary masses deserve a thorough evaluation to determine tumor resectability. This proposed algorithm is shown in Fig. 1. Patients who are felt to have resectable disease should undergo operative intervention unless they are being considered for a neo-adjuvant therapy trial. Generally, pancreatic masses should not be biopsied prior to attempted resection. Preoperative biopsy increases risk and cost and delays operative intervention. The risk of disseminating disease is likely also increased by preoperative biopsy. Therefore, preoperative FNAB of pancreatic lesions deemed resectable should be reserved for specific circumstances (e.g., history of other malignancy, reasonable possibility of uncommon cell types such as lymphoma). If the results of FNAB will change the management of the patient, FNAB should be undertaken. However, even if FNAB fails to document malignancy, in the face of a known mass, attempts at resection should be undertaken without delay. It is unacceptable to subject patients to the risks of the FNAB procedure, including dissemination of disease, when they may have potentially curable lesions. Perhaps this will change when the sensitivity of the technique improves to such a level that it will guide surgical treatment. Lastly, if FNAB is to be performed, the EUS-guided FNAB technique may be the safest approach. With EUS-guided FNAB, the distance the needle must travel is much smaller as compared to other biopsy techniques, thus minimizing the chance of dissemination of disease, especially when dealing with lesions in the pancreatic head or neck. The role of ERCP as a biopsy technique has largely been replaced by EUS-FNA. Operative biopsy should obviously be undertaken of suspected metastatic lesions; however, in the absence of such lesions, resection should proceed without biopsy. Finally, patients who are deemed to have unresectable lesions should undergo FNAB to confirm the diagnosis and be entered into clinical trials.

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Surgical Treatment of Crohn's Disease

Alessandro Fichera · Fabrizio Michelassi

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Keywords Crohn's disease · Surgical treatment · Minimally invasive approach

Introduction

Crohn's disease is an entity which comprises a heterogeneous spectrum of intestinal and extraintestinal manifestations, each one requiring individual approaches for diagnosis and management. Medical management has evolved greatly during the last decade: innovations have included the introduction of new therapeutical agents for prophylaxis and for management of complications. Yet, the introduction of new biologic agents, such as anti-TNF antibody,[1,2] or immunomodulators, such as azathioprine/6 mercaptopurine,[3] has not significantly changed the long-term prognosis and natural history of patients with Crohn's disease.[4,5] Patients with Crohn's disease still tend to require surgery as time progresses, and the timing of surgery is critical. This review article will focus on the indications for surgical treatment, on the preoperative evaluation of Crohn's patients, on surgical options specific to different gastrointestinal locations affected by the disease, and on new minimally invasive approaches to this disease.

A. Fichera
Pritzker School of Medicine, University of Chicago,
Chicago, IL, USA

F. Michelassi (✉)
Department of Surgery,
Weill Medical College of Cornell University,
1300 York Avenue, Room F-739,
New York, NY 10021, USA
e-mail: Fam2006@med.cornell.edu

Indications for Surgery in Crohn's Disease

The chronic and unrelenting nature of Crohn's disease brings these patients to the attention of the gastroenterologist during the early phases.[6] The initial management is medical until treatment fails or a complication arises.

Failure to respond to medical treatment or the inability to tolerate effective therapy (Table 1) are the most common indications for surgical treatment of Crohn's disease.[7,8] Some patients may respond to the initial medical therapy only to have the symptoms rapidly recur with the tapering of the medical treatment. For example, some patients respond well to steroid therapy but become steroid-dependent as tapering of the steroid dose results in recurrent symptoms. Due to the severe complications that are virtually inevitable with prolonged steroid treatment, surgery is warranted if the patient cannot be weaned from systemic steroids within 3 to 6 months. The occurrence of complications related to the medical treatment or the progression of disease while on maximal medical treatment represent additional indications to surgical treatment.

More than one in five Crohn's patients present to the surgeon with worsening obstipation.[9] Symptoms are precipitated by a single (Fig. 1) or multiple strictures (Fig. 2) or a lengthy disease segment and differ depending on the location of the disease in the gastrointestinal tract. Even a complete obstruction in Crohn's disease tends to resolve with nasogastric decompression, intravenous hydration, and medical therapy, and surgery should be postponed until resolution of the clinical picture allows for a definitive procedure.

Intestinal fistulae occur in one-third of Crohn's disease patients.[10] Intestinal fistulae, however, are the primary indication for surgery in only a minority of patients. Thus, the presence of an intestinal fistula is not in and of itself an indication for surgery.[11] In general, intestinal fistulae are the primary indication to surgical treatment if they connect

Table 1 Indication for Surgery in Crohn's Disease

Indications
Failure of medical management
Obstruction
Sepsis
Fistulae
Abscesses
Inflammatory mass
Free perforation
Hemorrhage
Dysplasia/cancer
Growth retardation

with the genitourinary tract, if their drainage is cause for personal embarrassment and discomfort, or if they create a bypass of such magnitude as to cause intestinal malabsorption. Enterovesical fistulae occur in 2 to 5% of patients with Crohn's disease[12] and often result in recurrent urinary tract infections including pyelonephritis. While it is not mandatory to operate on all cases of enterovesical fistulae, surgery is warranted to avoid deterioration of renal function. Enterocutaneous fistulae usually drain through a previous abdominal scar or through the umbilicus.[13] At times, they result from surgical incision and drainage of a subcutaneous abscess complicating severe intra-abdominal disease or from percutaneous drainage of an abdominal abscess. Patients may be reluctant to undergo surgical treatment when the enterocutaneous fistula has a minimal output and the underlying disease is under satisfactory control. However, in most cases, the difficulty in maintaining personal hygiene, the fear of social embarrassment, the symptoms associated with the severely diseased segment that led to the formation of the fistula, and the skin excoriation that invariably forms around the cutaneous opening of the fistula, become factors in favoring surgical treatment. Enterovaginal fistulae are rare complications of Crohn's disease and occur only in women who have undergone a previous hysterectomy. The vaginal discharge is cause for discomfort, social and sexual embarrassment, and difficulty in maintaining personal hygiene. A trial of medical therapy may be elected for enterocutaneous and enterovaginal fistulae, but most cases require surgery and most patients readily accept surgical intervention.[14,15] Enteroduodenal,[16] enteroenteric, and enterocolic fistulae (Fig. 3) are usually asymptomatic and often discovered only during a careful abdominal exploration or at examination of the resected specimen. Occasionally, an enteroenteric fistula can result in a significant functional bypass of a major intestinal segment with resulting malabsorption or diarrhea. These fistulae need to be addressed surgically.

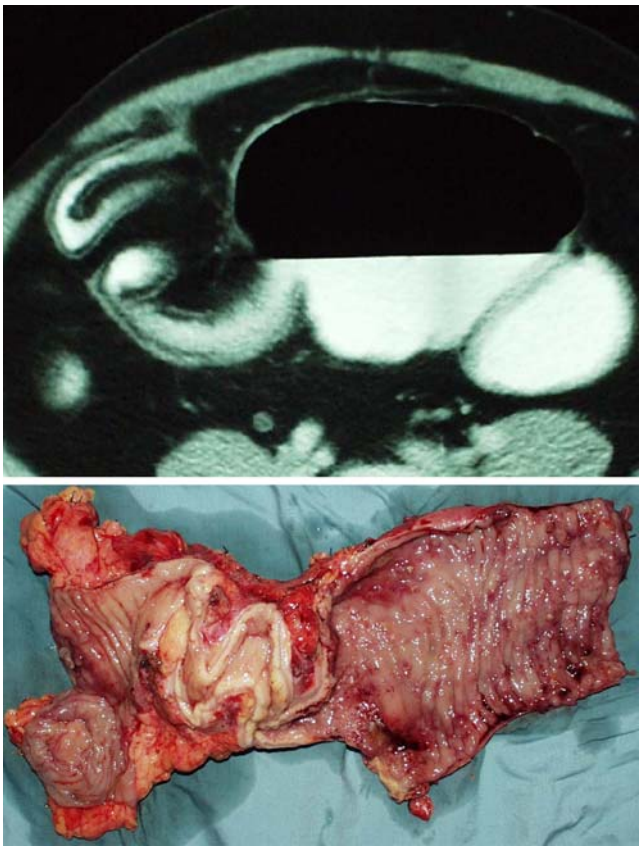

Figure 1 Single small-bowel stricture. *Top panel*: CT scan showing a near complete small-bowel obstruction. *Bottom panel*: surgical specimen after laparoscopic resection. Note the massively dilated proximal bowel and narrow, fibrotic stricture with the typical Crohn's changes.

Intra-abdominal abscesses and inflammatory masses occur less frequently than fistulae but are more often an indication to operative intervention.[8] With the exception of small abscesses which may warrant a trial of antibiotic treatment, almost all intra-abdominal abscesses require drainage, which can be accomplished percutaneously with CT (Fig. 4) or ultrasound guidance.[17,18] Yet, even after successful percutaneous drainage, an abscess is very likely to recur or result in an enterocutaneous fistula due to the severity of the disease in the intestinal segment from which it originated. Hence, surgical resection is often advised.[17] The rare large intraloop abscesses may require open surgical drainage. Inflammatory masses indicate severe disease and often harbor an unrecognized abscess.[8] Thus, inflammatory masses that do not readily respond to antibiotic treatment should be considered for surgical treatment.

Free perforation is a rare complication of Crohn's disease occurring in only about 1% of cases.[19] When this complication occurs, it is an obvious indication for urgent operation. The diagnosis of free perforation is made by detecting a sudden change in the patient's symptoms along with the development of the physical findings of peritonitis or the identification of free intraperitoneal air on plain x-rays or CT scan. The use of immunosuppressant and

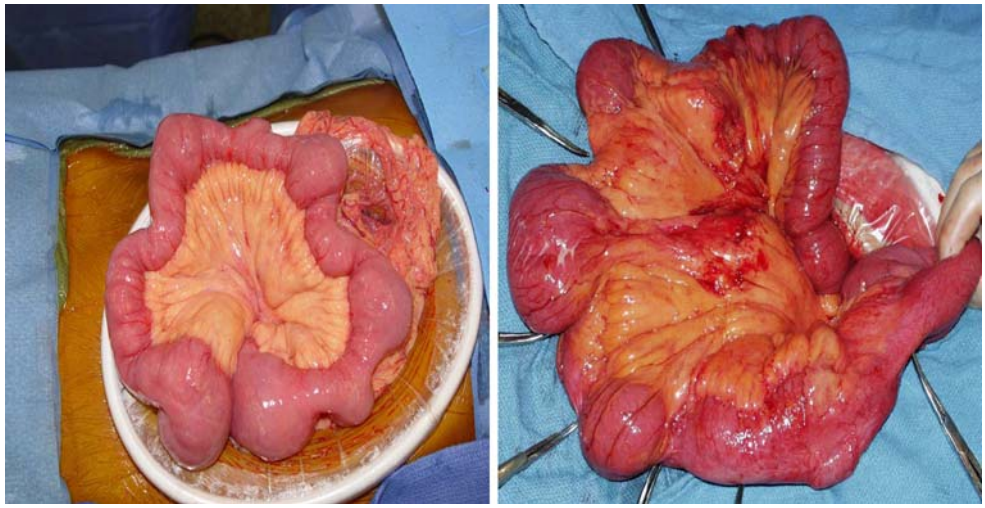

Figure 2 Multiple small bowel strictures. Serial short strictures involving long segments of jejunum (*left panel*) and ileum (*right panel*).

glucocorticosteroids can blunt many of the physical findings of acute perforation; therefore, the index of suspicion for perforation must be higher in immunocompromised patients who complain of worsening symptoms or show early signs of sepsis.

Hemorrhage is an uncommon complication in Crohn's disease. A thorough diagnostic work up is essential to identify the source of bleeding as many times it may be unrelated to the baseline inflammatory bowel disease. As an example, patients on chronic steroids may develop peptic ulcer disease. Hemorrhage from small bowel disease tends to be indolent with chronic bleeding causing anemia, but rarely requiring emergent surgery. Massive gastrointestinal hemorrhage occurs more frequently in colitis. Localization of the site of bleeding is accomplished by angiography in the presence of brisk bleeding; otherwise, upper endoscopy and capsule endoscopy can be used to localize the bleeding source in the duodenum and small bowel, whereas colonoscopy can be employed for large bowel. Intraoperative localization can be aided by enteroscopy or colonoscopy. When severe hemorrhage occurs in Crohn's disease, it is usually due to the erosion of a single vessel by a deep ulcer or fissure. Recurrent bleeding in an area of small bowel disease is a common phenomenon and it has been argued that even after the control of hemorrhage with conservative management, elective resection of the areas of Crohn's disease should be undertaken to prevent recurrent bleeding.[20,21] The possibility of a life-threatening hemorrhage in a Crohn's disease patient should not be underestimated because five cases of exsanguinating gastrointestinal hemorrhage have been reported in patients with Crohn's disease.[22]

Crohn's disease is a preneoplastic condition with increased risk for adenocarcinoma of the affected intestinal segment.[23–25] The risk of colorectal cancer in Crohn's colitis is 4 to 20 times[26] higher than that of the control population, with an incidence between 1.4 and 1.8%.[27] The preoperative diagnosis of adenocarcinoma of the small bowel is difficult to achieve because symptoms and

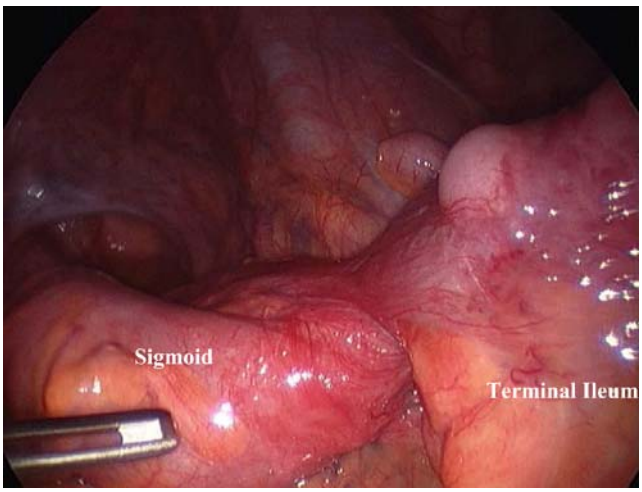

Figure 3 Intestinal fistulae. Laparoscopic view of an ileal sigmoid fistula, originating from a diseased segment of terminal ileum and involving the sigmoid.

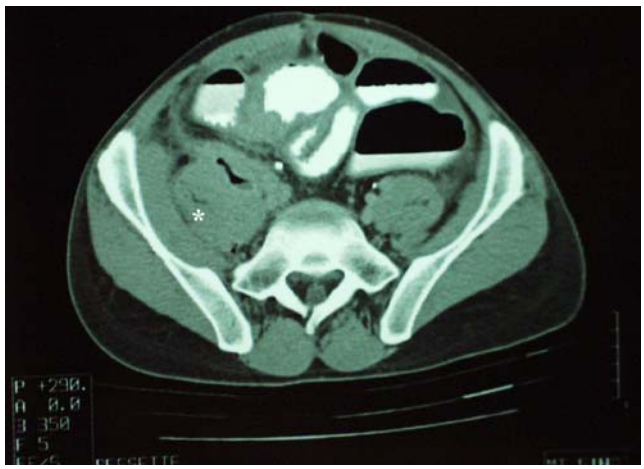

Figure 4 Psoas abscess. Large right psoas abscess (*asterisk*) secondary to a localized perforation of terminal ileal disease.

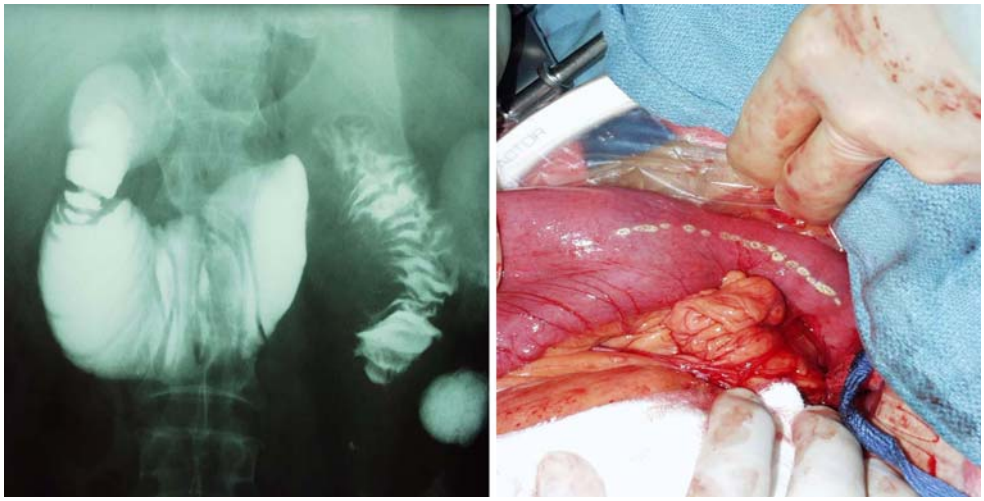

Figure 5 Duodenal obstruction. *Left panel*: upper GI contrast study showing a high grade duodenal obstruction. Note the dilated duodenum with contrast slowly passing in the jejunum. *Right panel*: surgical view showing the stricture at the distal duodenum.

radiographic findings of small bowel malignancy can be similar to those of the underlying Crohn's disease. Small bowel adenocarcinoma should be suspected in any patient presenting with a complete bowel obstruction that does not respond to bowel decompression and steroid therapy. Male patients and patients with long-standing disease appear to be at increased risk for small bowel adenocarcinoma.[28] Defunctionalized segments of bowel also seem to be at particular risk for malignancy.[29] For this reason, bypass surgery should be avoided and defunctionalized rectal stumps should either be restored to their function or excised.[30] Surveillance for colonic malignancies can be undertaken by colonoscopy with random mucosal biopsy. Carcinoma can arise in long-standing benign stricture, probably due to chronic inflammation.[31] These strictures should be closely examined and biopsied. If dysplasia is diagnosed, then resection of the affected area should be considered.[32] Strictures that are too narrow to allow passage of the colonoscope or cannot be adequately assessed endoscopically should be resected.

Growth retardation occurs in a quarter of all children affected by Crohn's disease. Although steroid treatment may delay growth in children, the major cause of growth retardation in Crohn's disease patients is due to the malnutrition associated with active intestinal disease.[33] It is important that optimal control of Crohn's disease with adequate nutrition is maintained during critical growth periods and puberty, as significant growth will not occur after closure of the epiphyseal plates. Persistent growth retardation in the face of adequate medical and nutritional therapy is an indication for surgical intervention.

Preoperative Evaluation and Preparation

Elective abdominal surgery for Crohn's disease should be preceded by a complete evaluation of the gastrointestinal tract. Conventional double contrast enteroclysis or computed tomography enteroclysis are best to study the small bowel.[34] Capsule endoscopy, indicated for the diagnosis of Crohn's disease, should be employed only after a contrast study has eliminated the presence of severe strictures that may prevent capsule passage.[35] Colonoscopy affords the best view for the large bowel and allows for biopsies of the terminal ileum. Computed tomography scanning of the abdomen and pelvis may be necessary to validate a clinical suspicion of an abdominal abscess, inflammatory mass, or obstructive uropathy.[36]

If feasible, well-contained intra-abdominal abscesses should be drained percutaneously prior to surgery.[17,18] If an abdominal stoma is contemplated, then the optimal site for the stoma location should be identified and marked preoperatively. In cases where preoperative CT scan suggests significant inflammation in proximity to the ureters, preoperative ureteral stenting can be helpful.

Meticulous mechanical preparation of the small and large bowel should be undertaken in all patients before abdominal surgery for Crohn's disease. Even in cases thought to be limited to the small bowel, the surgeon must always be prepared to perform surgery on the large bowel due to secondary involvement of the colon by fistulae or by an adherent inflammatory mass or abscess.

Surgical Strategy

Once the need for surgical intervention has been established, surgical strategy will vary depending on the intestinal district affected by Crohn's disease.

Gastroduodenal Crohn's Disease

About 2 to 4% of Crohn's disease patients present with involvement of the stomach or duodenum.[9,37] The most

common indication for surgery in gastroduodenal Crohn's disease is duodenal obstruction[38] (Fig. 5). In a recent review of 108 patients, 83% underwent surgery for obstruction.[39] Multiple surgical procedures have been advocated for the treatment of gastroduodenal Crohn's disease. Gastrojejunostomy with or without vagotomy has been the procedure most often used in the past. Based on the location of the disease, gastroduodenostomy or duodenojejunostomy have also been used as bypass procedures. Resectional antiulcer procedures have been associated with high morbidity and mortality rates and have been performed mostly in situations in which an ulcer was misdiagnosed.[37]

By-pass procedures are associated with acceptable perioperative morbidity but carry a significant risk of long-term complications, including delayed gastric emptying in up to 24% of patients and marginal ulceration after gastrojejunostomy, occasionally requiring the need for additional surgery. In view of this, strictureplasty has been advocated as an alternative to bypass procedures in selected patients. The Heineke–Mikulicz piloroplasty can be used in patients with short Crohn's strictures of the first, second, and third portion of the duodenum; the Finney strictureplasty lends itself better to longer strictures in the first and fourth portion of the duodenum.[40,41]

Jejunoileal Crohn's Disease

The jejunum and ileum are affected by Crohn's disease in 3 to 10% of patients.[9,42] The two most common indications for surgical treatment are obstruction and sepsis; massive hemorrhage and carcinoma are much less common. Chronic, high-grade, small-bowel obstruction may be caused by single or multiple short or long strictures. These patients present with postprandial abdominal cramps, nausea, and vomiting and often progress to a complete obstruction. When multiple tight strictures are present, the small bowel is transformed into a sequence of dilated saccular segments separated by tight, ring-like strictures. The dilated segments, which contain partially digested food particles, become the ideal environment for bacterial overgrowth. Patients report diarrhea secondary to bacterial overgrowth and stagnation. Malabsorption and vitamin B12 deficiency may also occur.

Small-bowel Crohn's disease has been traditionally treated with a resection. Due to the need for a second operation in as many as 30% of patients, short bowel syndrome has occurred in the past in up to 12.6% of cases.[43,44] In an attempt to preserve bowel function, Lee and Papaioannou in 1982[45] and, subsequently, Alexander-Williams and Haynes in 1985[46] described the use of strictureplasty techniques, which had been previously described in India to correct tubercular stricture of the terminal ileum and cecum.[47] Currently, the three most commonly performed strictureplasty techniques are the Heineke–Mikulicz (Fig. 6), the Finney, and the side-to-side isoperistaltic strictureplasties[48,49] (Fig. 7). In general, a Heineke–Mikulicz strictureplasty is used for short strictures (up to 7 cm in length), a Finney strictureplasty is used for longer strictures (up to 10–12 cm), and a side-to-side isoperistaltic strictureplasty is used for multiple sequential strictures. Strictureplasty is contraindicated in the presence of active sepsis when the bowel wall is thick and unyielding or in patients with severe weight loss and marked hypoalbuminemia.[50]

Surgeons were initially concerned that strictureplasties, performed on diseased intestine, would carry a disproportionate risk of perioperative complications and disease recurrence. Many groups have since demonstrated that this is not the case. The Cleveland Clinic group reviewed their experience with 1,124 stricturoplasties in 314 patients with a median follow up of 7.5 years.[50] The overall morbidity rate was 18%, including 2% dehiscence rate and 7% incidence of anastomotic line hemorrhage treated with transfusions and supportive measures.[51] They reported 34% surgical recurrence rate: interestingly, most of these recurrences occurred away from the strictureplasty site, an observation confirmed in a meta-analysis by Tichansky, where the recurrence rate on strictureplasty site was found to be 0–8%.[52]

Recently, several studies have provided compelling evidence that active Crohn's disease regresses to quiescent disease at the site of a strictureplasty.[53] These observations provide further support to bowel-sparing procedures in Crohn's disease and offer hope that regression from active to quiescent disease may translate in return of intestinal absorptive function.

Small bowel carcinoma in Crohn's disease is treated with a radical segmental resection when feasible. The prognosis is poor, with survival rates of 23% at 3 years[28] and 5% at 5 years.[54] Cancers in bypassed loops or in defunctionalized stumps can grow to advanced stages before they become symptomatic. The prognosis for these patients is usually poor, with most of them not surviving longer than 18 months[28] due to the advanced stage of their cancer at the time of surgical intervention. Fazio reported one patient who developed an adenocarcinoma at a strictureplasty site 7 years after the index operation. Negative biopsies of the stricture had been obtained at the time of the index operation.[55] A similar case has been reported by Jaskowiak and Michelassi.[56] At the time of strictureplasty, all suspicious lesions should be biopsied.

Terminal Ileal Crohn's Diseases

The terminal ileum is the most common Crohn's affected site requiring surgery and accounts for approximately 40–

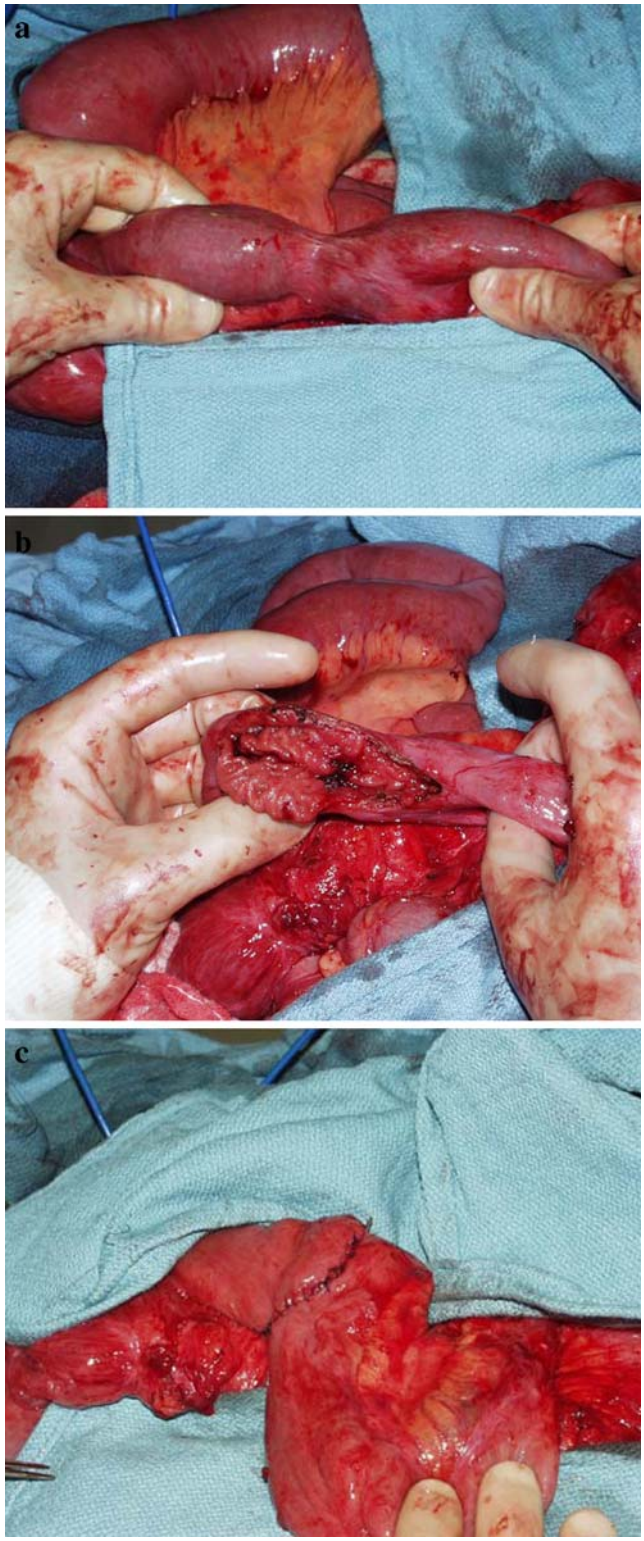

Figure 6 Heineke–Mikulicz strictureplasty. **a** Short small bowel stricture, amenable to a Heineke–Mikulicz strictureplasty. **b** The longitudinal enterotomy has been performed extending for 2 cm into normal bowel proximally and distally. **c** The enterotomy has been closed transversally.

50% of Crohn's disease patients referred to the surgeon.[6,9] Commonly, patients present with obstructive symptoms or with septic features suggesting either a contained perforation or an abscess with or without a fistula.

For obstructive primary disease involving exclusively the terminal ileum without septic complication, the treatment is resection (Fig. 8), either in the form of an ileocolic resection or a formal right hemicolectomy if there is significant involvement of the ascending colon. Results of resection indicate a surgical recurrence rate between 31 and 36% at 10 years, with 69% of patients requiring only one resection.[9,57,58] Recurrence rate after ileocolic resection is significantly higher in patients with multiple site involvement and cigarette smoking.[9,57–59]

Crohn's disease complicated by abscess formation requires special consideration regarding method and timing of intervention. As previously mentioned, resection should be preceded by a trial of antibiotics for small abscesses or an attempt at percutaneous drainage under CT or ultrasound guidance.[17,18] Percutaneous drainage successfully avoids early surgery and shortens hospital stay in approximately 50% of patients.[60] Large intraloop abscesses may require open surgical drainage, as they are not readily approachable percutaneously. Psoas abscesses, resulting from a retroperitoneal perforation of the ileocecal region, can create a chronic inflammatory reaction at the pelvic brim with stenosis of the ureter and right hydronephrosis. Drainage of the abscess and resection of the diseased terminal ileum usually relieves the compression on the ureter and resolves the hydronephrosis.

If percutaneous drainage is not successful or in the presence of secondary free rupture of the abscess, open surgical exploration is then warranted. The extent of the procedure should take in consideration the degree of acute inflammatory reaction: if this is limited, the abscess can usually be completely resected with the diseased intestinal segment and a primary anastomosis can be performed; if it is extensive, the surgical intervention should be limited to incision and drainage of the abscess, clearance of the sepsis, and temporary diversion. Emergency resections should be avoided at any cost, as they usually end up sacrificing much more bowel than necessary.

Strictureplasty has been used for the treatment of anastomotic stricture secondary to recurrent Crohn's disease after entero-enteric and ileocolic resections, with excellent results.[61]

Crohn's Colitis

The colon is affected by Crohn's disease in up to 30% of patients.[6,7,9] The involvement can be limited to a segment or extend to the entire colon and rectum. In the presence of pancolitis, the differential diagnosis between Crohn's

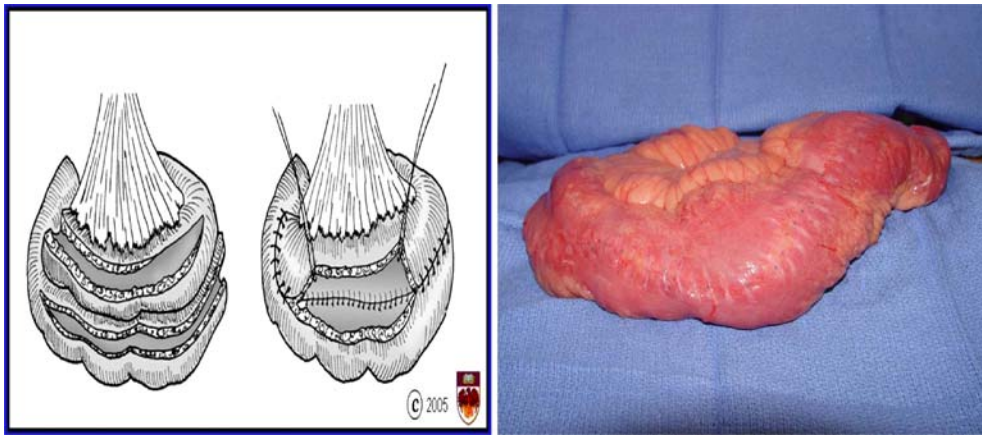

Figure 7 Side-to-side isoperistaltic strictureplasty. *Left panel*: The drawing shows the two loops containing the long strictures being approximated, open longitudinally, and sewn together in a side-to-side fashion. *Right panel*: surgical view of a well-healed and well-functioning strictureplasty in a patient operated on for a Crohn's disease recurrence elsewhere.

disease and ulcerative colitis may be difficult and as many as 10–20% of patients end up carrying a diagnosis of indeterminate colitis[62] or the wrong diagnosis.[63–65] With the advent of ileoanal pouch procedures, this differentiation is crucial because pouch reconstruction in patients with Crohn's disease has a pouch failure rate of up to 40%.[63–66]

The most common indication for surgery in patients with disease localized primarily to the colon is failure of medical therapy.[9,67] These patients present with persistent, often bloody, diarrhea and abdominal pain not responding to medical therapy. The surgical plan depends on the extent of the disease, the urgency of intervention, the quality of the anorectal function, and the general condition of the patient. In the elective situation and in the absence of significant perineal involvement and anorectal incontinence, if the disease is confined to the right colon, a right hemicolectomy will suffice; if the disease involves the transverse colon or extends to the descending colon, an extended right hemicolectomy or an abdominal colectomy will be needed; in the presence of pancolitis, a proctocolectomy with end ileostomy is the procedure of choice.

For left side segmental disease, the appropriate surgery is more controversial. Studies have indicated that segmental colonic resection with colocolonic anastomosis for sigmoid disease or abdominoperineal resection with left-sided colostomy for proctitis can be performed with overall good results.[68,69] However, such strategy may place the patient at higher risk for early recurrence of disease within the colon.[70] After segmental colectomy, the risk of recurrence and additional surgery has been reported to be 62% at 5.5 years,[71] although up to 86% of patients maintain bowel continuity at 14 years.[72] Yet, sacrifice of the normal proximal colon is controversial. The benefits of preserving the absorptive capacity of the ascending colon in appropriately selected cases may outweigh the higher risk of recurrence. Furthermore, the recurrence of Crohn's disease

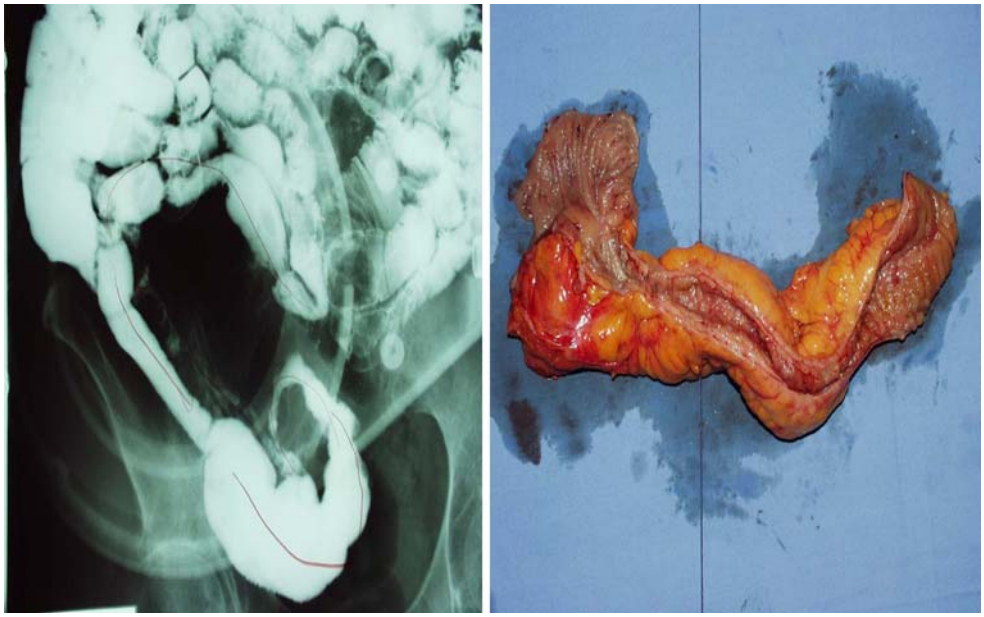

Figure 8 Terminal ileal stricture. *Left panel*: GI contrast study showing terminal ileal disease with narrowing of the lumen and obstruction. *Right panel*: surgical specimen after laparoscopic resection.

in the small bowel after total proctocolectomy has been reported between 3 and 46%[73,74] and it involves the distal 25 cm of ileum in up to 90% of patients.[75] Thus, the more extensive resections may be of greater value in patients who have no history of small bowel Crohn's disease, as it appears that colorectal Crohn's disease without small bowel involvement is unlikely to result in recurrence within the small bowel once a proctocolectomy is performed.[70] In patients with prior small bowel resections, preservation of colonic absorptive capacity may be beneficial; thus, these patients may be better managed with a segmental resection.

Most surgeons believe that ileal pouch surgery is contraindicated for Crohn's disease patients[64,66] because of the recurrent nature of Crohn's disease. This attitude is based on experience accrued in patients whose diagnosis of Crohn's disease was made only after the restorative proctocolectomy had been performed. Sagar et al.[76] and Deutch et al.[63] in two separate unselected series reported a pouch failure rate of 45% at 10 years in 46 patients. Hyman et al.[65] analyzed the outcome of this procedure on 25 patients with a preoperative diagnosis of ulcerative colitis who were subsequently proven to have Crohn's disease. Sixteen patients, at a mean follow up of 38 months, had a functioning pouch, seven had required pouch excision, one was diverted, and one had died. Only one of nine patients in whom there was a preoperative clinical feature suggestive of Crohn's disease had a functioning pouch, with complications uniformly occurring within months of ileostomy closure. In contrast, 15 of 16 patients without preoperative features of Crohn's disease had maintained their pouch, generally with good results.

This concept has been recently challenged by Panis et al.[77], who reported on the long-term results of Crohn's disease patients with no evidence of perineal or small-bowel disease undergoing an elective ileo-anal pouch procedure. Six of 31 Crohn's disease patients (19%) experienced specific complications 9 months to 6 years after surgery. Three of these six patients had pouch-perineal fistulae, which required pouch excision in two cases. In the remaining patients, there were no significant differences between Crohn's disease patients with a functioning pouch and matched ulcerative colitis patients in respect to stool frequency, continence, gas/stool discrimination, leak or need for protective pads, and sexual activity at 5 years from the procedure. This particular pattern of Crohn's disease, however, is rare as most patients with Crohn's proctocolitis will have some degree of small bowel involvement or perineal manifestations and, thus, would not be considered candidates for the ileoanal procedure.

Toxic colitis with or without megacolon is a complication less frequently associated with Crohn's disease than ulcerative colitis, but it carries the same mortality in both diseases (16 and 14%). Initial therapy consists of high-dose steroids, bowel rest, and antibiotics. Lack of improvement over a short period of time or signs of worsening medical conditions are indications for an urgent operation to avoid the occurrence of colonic perforation. Factors affecting mortality include age (30% for patients over 40 years old vs 5% for those younger than 40), gender (21% in women vs 13% in men), and the occurrence of colonic perforation (44% for cases with perforation vs only 2% in those without).[78]

Patients requiring a proctectomy in the presence of severe perianal sepsis are at risk of developing postoperative perineal septic wound complications. An alternative approach consists of an abdominal colectomy with an end ileostomy or a left-sided colostomy, depending on the proximal extent of the disease and closure of the rectal stump as first stage. This strategy allows decreasing the active perineal sepsis prior to a completion proctectomy at a later date. An abdominal colectomy with ileostomy is also indicated in patients too ill to tolerate definitive surgery or with indeterminate colitis. In these cases, an abdominal colectomy allows minimizing morbidity and establishing the diagnosis between ulcerative and Crohn's colitis. Patients who are not even fit for an abdominal colectomy should be offered a diverting ileostomy as a first-stage procedure.

Perianal Crohn's Disease

The reported incidence of perianal Crohn's disease requiring surgery varies between 25 and 30%.[9,79] Risk factors associated with perineal disease include the concurrence of Crohn's rectal disease and smoking. Anorectal Crohn's disease may manifest with edematous skin tags; fissures; ulcers; abscesses; fistulae; strictures; and, as a manifestation of chronic, long-standing inflammation, anal cancer. The most common indications for surgery in perianal Crohn's disease are septic in nature (abscesses and fistulae) (Fig. 9), followed by strictures and cancer. A treatment plan should follow careful assessment of the magnitude and severity of the perianal manifestations based on assessment of sphincter function and continence, presence of concomitant rectal disease, presence of associated complications, number and complexity of tracts, patient's nutritional state, and impact of symptoms on quality of life.

Anal stenosis can be dilated under anesthesia: although they frequently recur, anal stenoses are rarely the cause for a proctectomy. Superficial perirectal abscesses require incision and drainage as close as possible to the anal verge; with a deep ischiorectal abscess, drainage may need to be facilitated by placement of a drainage catheter percutaneously under CT guidance or at surgery. The most superficial fistulae-in-ano (class A in Park's classification)[80] can be safely handled with a fistulotomy,[81] with healing rates up to 85%;[82,83] all other fistulae-in-ano

should be treated with a combination approach based on the placement of a noncutting seton and medical treatment. Setons keep tracts open, eliminate the accumulation of pus, and foster tract quiescence. Therapeutic efficacy has been proven for infliximab and tacrolimus and suggested for antibiotics and immunomodulators (6-MP, cyclosporine, and methotrexate).[84] Combination treatment has a higher response rate (100 vs 83%) and a lower recurrence rate (79 vs 44%) than medical treatment alone; furthermore, when a recurrence occurs, the time to recurrence is longer in the combination-treatment group (13.5 vs 3.6 months).[85]

Rectovaginal fistulae occur as a complication of anorectal Crohn's disease in about 10% of patients[86,87] and require special mention. Most fistulae are truly anointroital, with the internal opening in the anal canal and the external opening at the base of the introitus. They are typically associated with a deep rectal ulceration.[88] In selected patients, these fistulae can be closed by performing a mucosal advancement flap.[89,90] The procedure entails performing a semicircular incision at the dentate line, with the internal opening of the fistula in the center. A 4–5-cm flap of mucosa, submucosa, and smooth muscle is elevated and its tip, inclusive of the fistulous opening, is debrided. The anovaginal tract is curetted and sutured. The flap is advanced to the anoderm and sutured without tension. Several variations have been proposed when the rectal mucosa is significantly diseased, including performing the repair from the vaginal side[91] and using an ano cutaneous flap from the perineum.[92] In patients with associated severe perineal sepsis, surgical repair may need to be staged with temporary diversion of the fecal stream.[93] Success rates with this approach have been reported around 70 to 75% in relatively small series.[89,90,94] In the event of failure, the advancement flap can be repeated as reported by Joo et al.[89] and by us.[94] In our series, the majority of patients who did not heal with the first procedure were successfully closed after a second attempt.

An aggressive surgical and medical approach should allow perineal wound healing and sphincter preservation in 62 to 86% of Crohn's disease patients[86,94] in the long term. Proctectomy becomes necessary when quality of life is severely affected by symptoms and complications, when fecal incontinence has occurred and is not manageable, or in the presence of severe rectal disease or neoplastic transformation. In our experience,[94] the most common reasons for proctectomy included aggressive, concomitant rectal disease not responding to conservative measures and extensive perineal disease. We found that patients with rectal disease had a significantly higher rate of proctectomy than patients with rectal sparing (77.6 vs 13.6%) and that, in the absence of rectal involvement, patients with multiple complications had a significantly higher rate of proctectomy than patients with single complications (23 vs 10%).

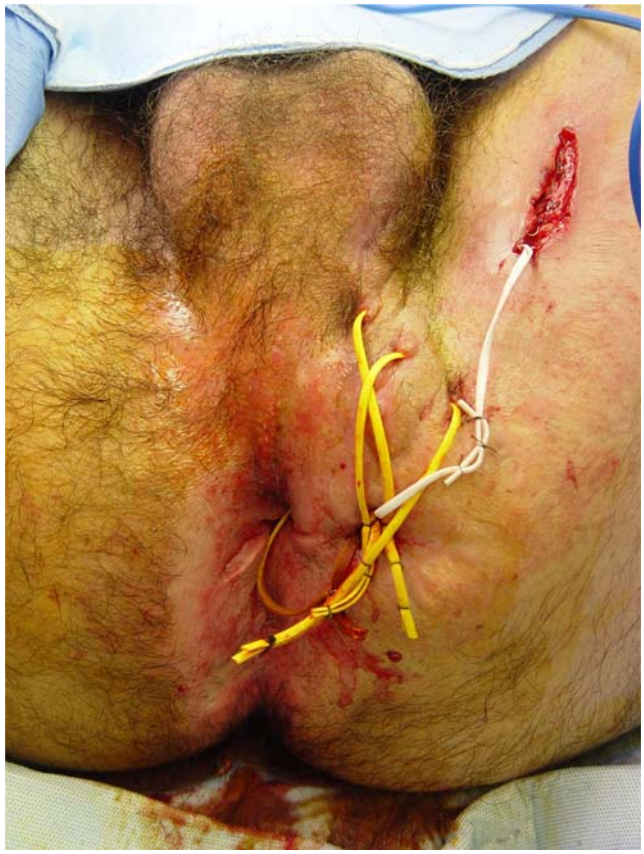

Figure 9 Perianal Crohn's disease. Severe disease treated conservatively in preparation for proctectomy.

Laparoscopic Surgery for Crohn's Disease

Over the past 15 years, laparoscopy has been advocated for Crohn's disease and has been shown to improve cosmetic results and potentially reduce postoperative ileus and hospital stay.[95–97] However, many of the unique features of Crohn's disease, such as intense inflammation, thickened mesentery, enteric fistulae, inflammatory masses or phlegmon, and skip areas, make the laparoscopic approach technically demanding. Thus, the role of laparoscopy in Crohn's disease is still evolving and debated.

Several studies have compared laparoscopy to open surgery for Crohn's disease.[95,96,98–102] Unfortunately, most of these studies have reported on relatively small numbers of subjects with very short follow-ups, resulting in limited power to evaluate significant outcome measures. Furthermore, some of these studies have reported conflicting results. A meta-analysis of the currently available published trials has recently shown that laparoscopic surgery in Crohn's disease is associated with prolonged operative time, shorter duration of postoperative ileus, shorter hospital stay, lower incidence of early postoperative complications, and postoperative small-bowel obstruction. Furthermore, due to the significantly shorter length of stay,

a trend towards lower overall cost was noted with laparoscopic surgery.[103]

Indication to surgical treatment and surgical strategy when using the laparoscopic approach are identical to the open approach. Current contraindications to a laparoscopic approach include patients who are critically ill and unable to tolerate the pneumoperitoneum due to hypotension or hypercarbia, patients with dense adhesions or extensive intra-abdominal sepsis (abscess, free perforation, complex fistula), and difficulty in identifying the anatomy (previous surgery, obesity, adhesions). With the advent of hand-assisted techniques,[104] most of these contraindications have become relative. The availability of hand-access devices has allowed the surgeon to minimize conversion rates while tackling more complex procedures.

Laparoscopy offers great advantages to patients in need of fecal diversion or an isolated small-bowel resection or strictureplasty. In these patients, laparoscopy may obviate a laparotomy, laparoscopy still allows for a full evaluation of the gastrointestinal tract, and the involved area or areas can be easily exteriorized through a small incision for the extracorporeal performance of a bowel anastomosis or strictureplasty.[105]

Segmental or total colectomies with or without anastomosis are feasible by laparoscopy-assisted or hand-assisted methods. Few series have reported favorable results in a small number of cases[106,107] yet, some authors still do not consider laparoscopic colon resection for Crohn's disease to be advantageous.[108]

Laparoscopic assisted ileocolic resection for Crohn's disease is currently the most commonly performed laparoscopic procedure for Crohn's disease.[106] The only prospective randomized trial available in laparoscopy for Crohn's disease focused on this specific procedure.[109] It showed faster postoperative recovery of respiratory function and fewer minor complications in the laparoscopic group. Bemelman et al.[95] compared 48 open with 30 laparoscopic assisted ileocolic resections. They showed that laparoscopic ileocolic resection for Crohn's disease is associated with similar morbidity rates, a shorter hospital stay, and improved cosmetic results. Alabaz et al.[96] compared 48 open with 26 laparoscopic assisted ileocolic resections. Patients in the laparoscopic assisted group returned to work more quickly, had better cosmetic results, and were more likely to have improved social and sexual lives.

Conclusion

The last quarter of a century has witnessed great progress in the medical and surgical treatment of Crohn's disease and its complications. Surgeons have accepted bowel-sparing procedures as superior to ablative procedures for Crohn's disease of the small bowel, and minimally invasive procedures are slowly but surely demonstrating their superiority over open procedures in terms of allowing patients a more rapid recovery. Combination treatment has been refined for perineal complications of Crohn's disease to the point of assuring the best palliation possible and the avoidance of abdomino-perineal resections. Controversy still exists on the best surgical approach to segmental colitis and whether patients with Crohn's colitis should be offered a restorative proctocolectomy with ileal pouch anal anastomosis. Surgery continues to play an important role in the treatment of Crohn's disease.

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Giant Gastrointestinal Stromal Tumor of the Stomach in An Elderly Patient

Herbert Maria Dal Corso · Mario Solej · Mario Nano

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Abstract We report a case of giant gastrointestinal stromal tumor (GIST) of the stomach of 17 cm in diameter detected in an 88-year-old Caucasian female. An en-block resection of the mass requiring gastric and transverse colon resection was carried out. Pathological examination evidenced a smooth multycistic giant gastric GIST measuring 17×13×9 and weighing 1,630 g. At immunohistochemistry, the specimen was c-kit positive, CD34-positive, SMA-negative S100-negative, desmin-negative, CD31-negative, HMB45-negative, and calponin-negative. It was diagnosed as an uncommitted GIST at high risk for malignancy.

Keywords GIST · Elderly patient · Stomach

Case Report

An 88-year-old lady presented with a complaint of a remarkable increase of her abdominal diameter. On clinical examination, a movable painless abdominal mass was appreciable in the higher abdominal quadrants, measuring approximately 20 cm in length. She had a normal diet and regular bowel movements with normal stools. A complete blood test examination showed only a macrocytic normocromic anaemia (HGB 8.3 g/dl). Preoperative investigation included gastroscopy and superficial biopsies, colonoscopy, computed tomography (CT) scan and angiograpy (Figs. 1, 2).

H. M. Dal Corso
Department of General Surgery, ASO S. Croce e Carle,
Cuneo, Italy

M. Solej · M. Nano
Department of Clinical Pathophisiology, School of Medicine,
Turin, Italy

M. Nano (✉)
Dipartimento di Fisiopatologia Clinica,
Via Genova 3, 10126 Turin, Italy
e-mail: mario.nano@unito.it

At gastroscopy, the mucosal lining was normal, although massively compressed by a mass apparently originating from the gastric wall of the lesser curve. Several biopsies have been taken, with evidence of mild chronic gastritis and foci of complete intestinal metaplasia. A CT scan of the whole abdomen evidenced a giant mass compressing the stomach with possible infiltration of the transverse colon, posing a diagnosis of invasive gastric gastrointestinal stromal tumor (GIST). Liver, pancreas, kidneys, bladder were normal, and no sign of lymph node packages could be detected in the abdomen. Colonoscopy, performed to rule out a possible invasion at the transverse colon did not show lesions invading the lumen. At the intervent, the mass has been mobilized posteriorly from the anterior aspect of the pancreas and the superior mesenteric vessels. An en-block resection of the stomach, together with a segment of transverse colon that could not be separated from the mass, has been carried out (Fig. 3). Gross pathology described a solid mass 17×13×9 cm with cysts and hemorrhagic areas. The mass adhered to but was not infiltrating the bowel wall. Immunohistochemistry was performed, resulting positive for CD 117 (Fig. 4) and CD 34 and for desmin, smooth muscle actin (SMA), citocheratine KL1, CD 31, HMB45, S100, and calponine. Mitotic count was 4/50 high-power field, and proliferation index using MIBI-Ab was 5%. The mass was diagnosed an as an uncommitted type gastric GIST with high risk of malignancy[1].

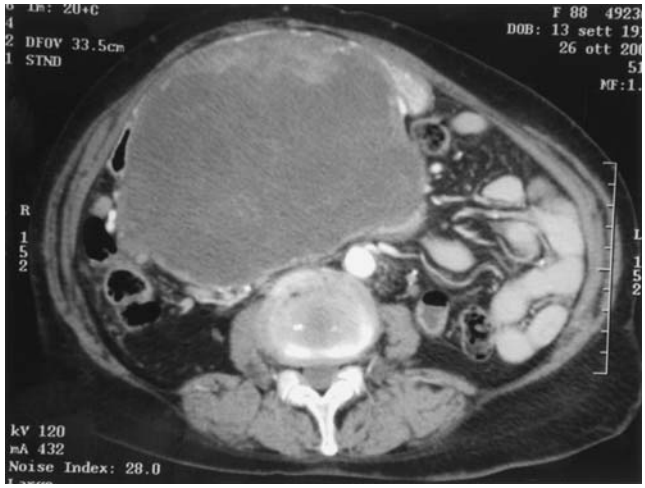

Figure 1 CT scan of the abdomen. The dimension of the mass is clearly evident.

Discussion

The size of the GIST is claimed by the majority of authors as an independent factor for malignancy and distant spread. Most GISTs are larger than 5 cm in diameter, and a diameter of 10 cm is associated with a higher risk of distant spread, but only a few papers report cases of GIST bigger than 15 cm, all in elderly patients without mention of distant metastasis[2]. Special considerations about this case: despite its size, this gastric GIST did not cause alarming symptoms to the patient. Symptoms like pain and weakness are somehow considered by the elderly as problems related to their age that should be either accepted, or at most, treated with a few tablets, thus, seeking medical advice only when their problem cannot be managed otherwise, leaving enough time for the tumor to grow to enormous dimensions. Furthermore,

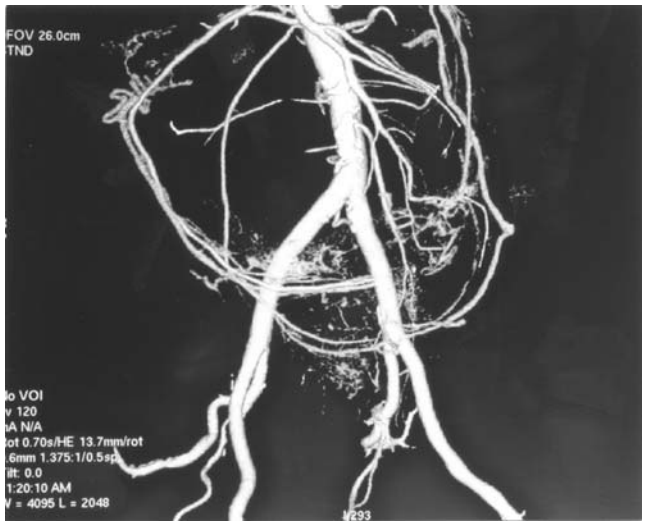

Figure 2 Angio CT. Vasculature of the mass originating from the left gastric artery and gastroepiploic artery. It is evident how the core is not perfused.

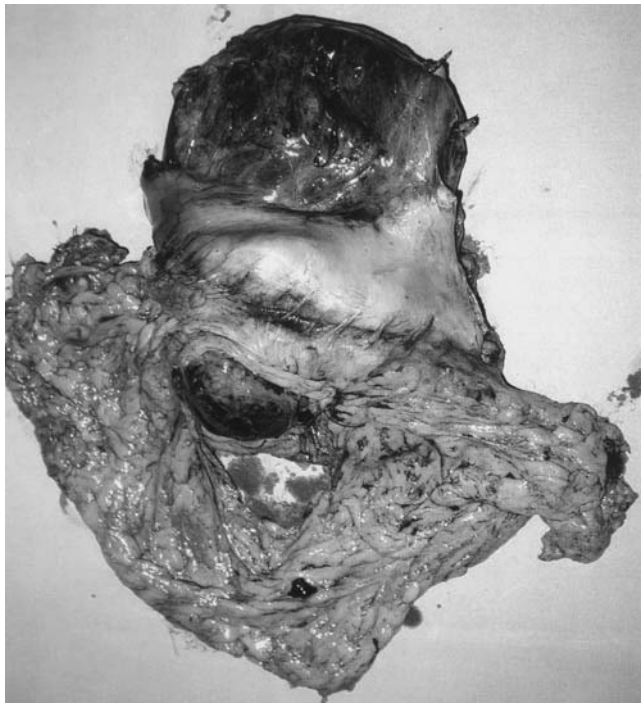

Figure 3 En-block resection.

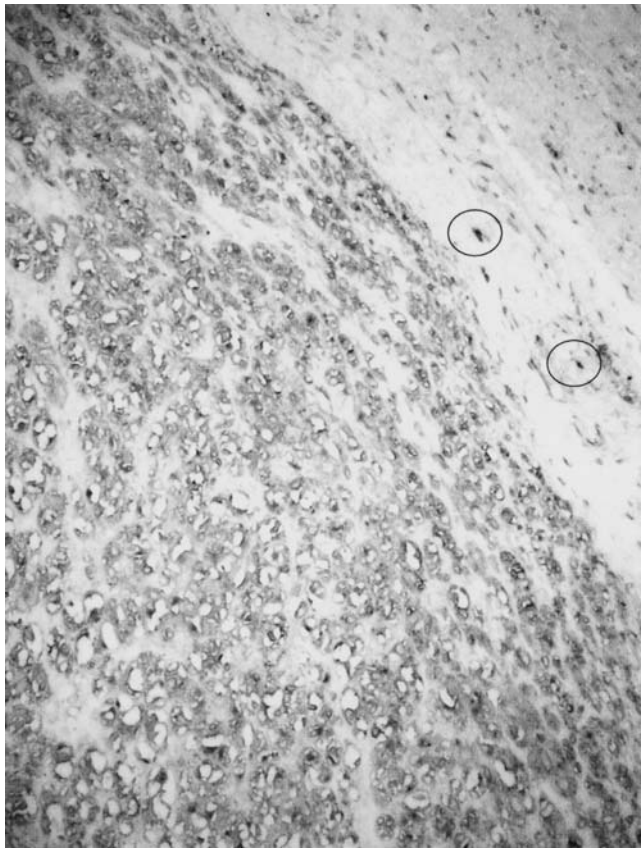

Figure 4 C-kit positivity as shown by immunohistochemistry (mastocytes of the mucosa are *encircled*).

some doctors tend to spare their elderly patients "complicated and painful" investigations, leaving them to live peacefully, which is certainly the best choice. We think that there is the indication, in the surgical treatment of gastric GIST, of a smaller size even in very old patients, as the tumor grows as rapidly as in younger patients. Besides, if the diagnosis is obtained once the mass has grown to enormous dimensions, surgery is necessarily extended and usually not well tolerated by the elderly.

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